CLINICAL REVIEW

Application Type	NDA
Submission Number	20-236, (b) (4)
Submission Code	(b) (4)
Letter Date	December 21, 2005
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Reviewer Name	Sally Seymour, M.D.
Review Completion Date	May 30, 2006
Established Name	Salmeterol Xinafoate
(Proposed) Trade Name	Serevent Inhalation Aerosol
Therapeutic Class	Long acting $beta_2$-adrenergic agonist
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Inhalation Aerosol
Dosing Regimen	None proposed
Indication	Asthma, reactive airways disease
Intended Population	Children 6 months to < 4 years

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

(b) (4)

1.2 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

1.2.1 Risk Management Activity

There are no postmarketing risk management activities recommended.

1.2.2 Required Phase 4 Commitments

There are no recommendations for required phase 4 commitments.

1.2.3 Other Phase 4 Requests

There are no recommendations for additional phase 4 requests.

1.3 Summary of Clinical Findings

Before addressing the results of the clinical studies, it is important to note that the inadequate in vitro characterization of salmeterol xinafoate inhalation aerosol with valved holding chambers limits interpretation of the safety and efficacy data from the clinical studies. That being said, the safety and efficacy data from the clinical studies were reviewed in detail and are discussed in this review. However, no conclusions can be drawn regarding the safety and efficacy of salmeterol xinafoate with valved holding chambers in children < 4 years of age.

(b) (4), the Applicant submitted data from four clinical studies with salmeterol xinafoate inhalation aerosol with valved holding chambers in children < 4 years of age. The efficacy data do not establish the superiority of salmeterol xinafoate inhalation aerosol over placebo in children ≤ 4 years of age. In general, the safety data shows that adverse events (AEs) were more common in children 6 to 23 months of age than in children 24 months to < 4 years of age. Many of the AEs reported were consistent with AEs reported in clinical studies with salmeterol inhalation aerosol in adults and adolescents > 12 years of age. In general, there were no clinically significant differences between treatment groups in terms of vital signs, ECGs, and laboratories.

1.3.1 Brief Overview of Clinical Program

The clinical program included four clinical studies in children < 4 years of age: two dose ranging studies and two 4-week safety and efficacy studies. Each of the studies is briefly described below.

- **Study SMS20010** was a randomized, double-blind, double-dummy, placebo-controlled, two-period, crossover, study of 3 doses of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 21 children with asthma aged 24 to 47 months.
- **Study SMS20011** was a randomized, double-blind, double-dummy, placebo-controlled, two-period, crossover, study of 3 doses of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 21 children with asthma aged 6 to 23 months.
- **Study SMS30076** was a 4-week, randomized, double-blind, double-dummy, placebo-controlled, parallel group safety and efficacy clinical study of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 338 children with asthma aged 24 to 47 months.

- **Study SMS30077** was a 4-week, randomized, double-blind, double-dummy, placebo-controlled, parallel group safety and efficacy clinical study of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 167 children with asthma aged 6 to 23 months.

1.3.2 Efficacy

The efficacy data in this supplement do not establish the efficacy superiority of salmeterol xinafoate inhalation aerosol over placebo in children ≤ 4 years of age. The primary source of the efficacy data were the two 4-week clinical studies, Studies SMS30076 and SMS30077, and the primary efficacy endpoint was the change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores during the treatment period. There was no significant difference between the salmeterol treatment groups and placebo with respect to the change from baseline in asthma symptom scores. In addition, the secondary endpoints (peak expiratory flow, asthma symptom-free days, rescue medication use, treatment failures, and subject discontinuations) do not support the efficacy superiority of salmeterol xinafoate inhalation aerosol over placebo.

1.3.3 Safety

The safety data in this supplement show that adverse events (AEs) were more common in children 6 to 23 months of age than in children 24 months to < 4 years of age. Many of the AEs reported were consistent with AEs reported in clinical studies with salmeterol inhalation aerosol in adults and adolescents > 12 years of age. Fever was the most common AE in all treatment groups. AEs reported more frequently in one of the salmeterol treatment groups than in the placebo group included the following: rhinorrhea, rhinitis, irritability, ENT infection, viral URTI, bronchitis, keratitis/conjunctivitis, psychomotor disorders, and pharyngotonsillitis/upper respiratory inflammation/throat irritation.

In general, there were no clinically significant differences between treatment groups in terms of vital signs, ECGs, and laboratories. In the dose ranging studies, Holter monitors were performed at baseline and the end of each treatment period. There was no clinically significant change from baseline in 24 hour heart rates, supraventricular ectopic (SVE) or single ventricular ectopic events between treatment groups. In Study SMS20011, one subject in the salmeterol 25mcg TID treatment group was withdrawn due to abnormal Holter findings (increase from 1 SVE at baseline to 24 SVEs in 23 hours).

Two specific safety assessments are worth noting. Investigators specifically assessed for tremors in all four clinical studies. No tremor was noted in the majority of subjects. In subjects in which tremor was noted, the tremor was generally mild in severity. In one study, tremor was noted more frequently in the salmeterol treatment groups than in the placebo group at Week 4. Dedicated nasopharyngeal examinations were performed in Study SMS30077 at each clinic visit. Overall, there were more subjects in the salmeterol 25mcg treatment group (29%) with a shift from normal to abnormal nasal findings compared to the other groups (16-17%). The majority of changes were related to nasal secretions – quantity, consistency, and color.

1.3.4 Dosing Regimen and Administration

The Applicant does not seek an indication in children < 4 years of age.

1.3.5 Drug-Drug Interactions

There were no important drug-drug interactions noted in the clinical studies in this supplement.

1.3.6 Special Populations

The clinical studies in this submission were performed in children < 4 years of age. There were no additional special population considerations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Serevent Inhalation Aerosol is a long acting beta$_2$-adrenergic agonist that was approved on February 4, 1994, for the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease. (b) (4) Serevent Diskus was approved on September 19, 1997, for the same indication in children 4 years of age and older. Because children < 4 years of age may not be able to use the Diskus properly, the Agency issued a WR to study Serevent Inhalation Aerosol administered with a holding chamber and facemask in children < 4 years of age.

It should be noted that Serevent Inhalation Aerosol is no longer marketed in the United States.

2.5 Presubmission Regulatory Activity

The following is a brief summary of the regulatory history relevant to this (b) (4) supplement [N20236/2005-12-21/pedstudyrequest.pdf, pg 1-25; 2-5-clin-ov.pdf, pg 6-11].

- February 19, 1999 Proposed Pediatric Study Request submitted
- May 20, 1999, Written Request issued by Agency (full WR not reproduced)
  - **Study 1:** Dose-ranging safety of salmeterol xinafoate for treatment of asthma in children between the ages of 2 years to <4 years.
  - **Study 2:** Efficacy and safety of salmeterol xinafoate for treatment of asthma in children between the ages of 2 years to <4 years.
  - **Study 3:** Dose-ranging safety of salmeterol xinafoate for treatment of asthma in children between the ages of 6 months to <2 years.
  - **Study 4:** Efficacy and safety of salmeterol xinafoate for treatment of asthma in children between the ages of 6 months to <2 years.
- August 23, 1999, In vitro data with valved holding chambers submitted
  - The Applicant submitted a summary of the particle size distribution in vitro data to characterize the dose delivery of salmeterol with a holding chamber.
- February 9, 2000, Amended Written Request issued by Agency
  - **Rational/Objective**
    - Added the requirement to have salmeterol xinafoate delivered with a facemask in all 4 studies
    - For studies 3 and 4, the use of "two different spacers" to deliver the doses for salmeterol xinafoate inhalation aerosol was amended *to* the use of "one spacer" to deliver the doses of salmeterol xinafoate.
    - Change in the age range throughout the Written Request in studies 1 and 2 ***from*** 2 years and <4 years ***to*** ≥2 years to <4 years and in studies 3 and 4 ***from*** 6 months and <2 years ***to*** ≥6 months to <2 years

- **Study Design**
  - For studies 1 and 3, the elimination of the highest dose (50 mcg TID)
  - For study 1, the evaluation of the salmeterol dose emitted from the spacers' mouthpieces was amended ***from*** "deemed equivalent" to the adult dose of salmeterol on a twice daily schedule, the same dose on a three times daily schedule, and a lower dose on twice and three times schedules ***to*** "deemed comparable" to the adult dose of salmeterol on a twice daily schedule, the same dose on a three times daily schedule, and a lower dose on twice and three times schedules
- **Number of Patients**
  - For studies 1 and 3, reduction of the number of completed patients per group from 20 to 18 and the reduction in the number of groups from 5 groups to 4 groups. The elimination of the requirement for ten patients in each group must use one type of spacer and the other 10 patients must use a different type of spacer.
  - For study 2, the criteria for one-half of the study patients must use one type of spacer, and the other half must use a different type of spacer was loosened to "approximately" one-half of the study patients must use one type of spacer, and the other half must use a different type of spacer.
  - For Study 4, the number of completed patients per group was reduced from 100 to 50 patients and patients can use the same type of spacer
- **Clinical Endpoints**
  - For studies 1 and 3, provided option to evaluate 24-hour Holter monitoring as opposed to ECG as a safety endpoint
- **Study Evaluations**
  - For studies 1 and 3, 24-hour Holter monitoring was added as an evaluation
  - For studies 1 and 3, the addition of the provision for the use of laboratory assessments within 3 months of baseline.
  - For Studies 2 and 4, the requirements for ECG and physical examinations were amended *from* assessments at every clinic visit *to* assessments at screening (baseline) and at the completion of the treatment period (end of study).
- **Drug Information**
  - Revised requirement that all studies use 2 different US-marketed spacers ***to*** Studies 1 and 2 use salmeterol xinafoate inhalation aerosol in conjunction with two difference US-marketed spacers and Studies 3 and 4 to use salmeterol xinafoate inhalation aerosol in conjunction with 1 type of US-marketed spacer.
  - Revised the requirement that one-half of patients in the "whole program" must use one kind of spacer and the other half to use a different kind of spacer ***to*** "approximately" one-half of patients in "studies 1 and 2" must use one kind of spacer and the other half to use a different kind of spacer.
  - In addition to studies 3 and 4, added the requirement that Studies 1 and 2 to use facemasks with the spacers to optimize drug delivery
- **Timeframe**

        - The agency removed the statements requiring the clinical program to be completed in sequence, so the clinical studies could be started in overlapping fashion and the agency agreed to change the timeframe for the full study reports to be submitted ***from*** December 31, 2001 ***to*** December 31, 2005.
    - The elimination of the following text, "We recommend you seek a written agreement, as described in the guidance to industry (Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act), with FDA before developing pediatric protocols."
    - The elimination of the following text, "Perform the clinical program in sequence, so that the studies on the older children are completed before the younger children. This will help you in dose selection for the younger children from the results of the older children, and give you time to complete the necessary juvenile animal studies."
- <u>May 2, 2000, Amended Written Request issued by Agency</u>
    - **Age group in which studies will be performed**
        - In studies 3 and 4, changed from approximately half of the study patients in each treatment group must be below 1 year of age **to** approximately one third of the study patients in each treatment group must be below 1 year of age
    - **Study Evaluations**
        - The evaluation for studies 1 and 3 was changed ***from*** "Record heart rate and assess for adrenergic stimulation at least twice daily. Perform ECG or 24-hour Holter monitoring and laboratory measures during treatment and after the 7 days of treatment. Laboratory assessments within 3 months of baseline will be acceptable. In study 1, attempt to record peak expiratory flow rate twice daily ***to*** "Record heart rate and assess for adrenergic stimulation. Perform ECG or 24- hour Holter monitoring and laboratory measures at baseline and in the latter part of each treatment period, while the patient is still on treatment. Laboratory assessment within 3 months of baseline will be acceptable. In study 1, attempt to record peak expiratory flow rate twice daily."
        - The evaluation for studies 2 and 4 was changed ***from*** "Instruct patients and caregivers of the patients to record symptom scores, adverse events, and assess for adrenergic stimulation twice daily on diary cards. Conduct clinic visits every week. During the clinic visits, record vital signs, assess for adverse experience, and assess for adrenergic stimulation. Perform physical examination, ECG, and clinical laboratory measures before treatment and at the completion of the treatment. In study 2, attempt to record peak expiratory flow rate twice daily on diary cards." ***to*** "Instruct parents and caregivers of the patients to record symptom scores, adverse events, and assess for adrenergic stimulation. Conduct clinic visits approximately weekly. During the clinic visits, record vital signs, assess for adverse experience, and assess for adrenergic stimulation. Perform physical examination, ECG, and clinical laboratory measures before

treatment and at the completion of the treatment. In study 2, attempt to record peak expiratory flow rate twice daily on diary cards."

- May 21, 2001, Summary of 13 Week Dog Toxicity Study submitted
  - The Applicant submitted the summary results from the 13 week juvenile dog toxicity study
- September 21, 2001, Final nonclinical study reports submitted by Applicant
  - The Applicant submitted the final study reports for the 5 day and 13 week juvenile dog toxicity studies
- July 3, 2002, Amended Written Request issued by Agency
  - WR reissued because of passage of Best Pharmaceuticals for Children Act (BPCA)
- July 16, 2002, Teleconference with Applicant
  - Teleconference held with Applicant to discuss findings of juvenile dog toxicity study
  - Applicant offered to perform nasal passage examinations in Study SMS30077.
- May 7, 2004, Amended Written Request issued by Agency
  - **Formats of reports to be submitted**
    - amended to specify more information on racial and ethnic minorities (BCPA)
  - Reminder that a summary of medical and clinical pharmacology reviews of a pediatric supplement response to WR will be made public (posted on FDA website)
- November 18, 2004, Amended Written Request #5 issued by Agency
  - **Timeframe for submitting reports of the studies**
    - Full study reports must be submitted by March 31, 2006
  - **Number of patients to be studied**
    - In Study 4, changed from a minimum of 50 completers to a minimum of 45 patients per group (3 groups) must complete the study
- December 21, 2005, Complete response to Written Request submitted
- February 21, 2006, Request for Information conveyed to Applicant
  - The Division conveyed a request for additional information regarding the CMC in vitro characterization of the dose delivery of salmeterol xinafoate inhalation aerosol using various holding chambers.

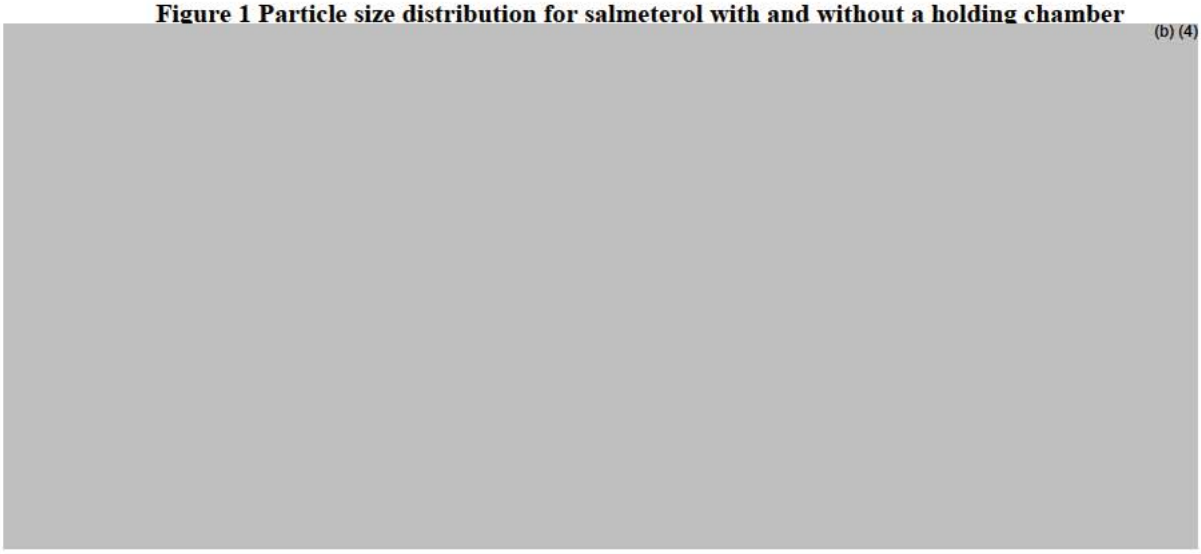
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The Applicant submitted in vitro particle size distribution data to characterize the dose delivery of salmeterol with the following valved holding chambers: (b) (4)

(b) (4). The Applicant determined that the difference in FPM was not significant enough to change the dose of salmeterol xinafoate inhalation aerosol for the clinical trials. The figure below shows the particle size distribution comparison for salmeterol xinafoate inhalation aerosol without and with various holding chambers.

Figure 1 Particle size distribution for salmeterol with and without a holding chamber



Source: N20236/2005-12-21/3-2-p-2.pdf, pg 30

In the Written Request, the Agency did not specify which in vitro tests should be performed to characterize the dose delivery of salmeterol xinafoate inhalation aerosol with various holding chambers. Therefore, the data submitted by the Applicant is sufficient to fulfill the WR with regards to the CMC in vitro characterization. However, since the issuance of the Written Request, the Division has noted that additional information is necessary to adequately characterize the dose delivery of an MDI using a holding chamber for the pediatric population. For example, the effect of the following variables on dose delivery should be considered: inspiratory flow rates appropriate for the pediatric population, time delay between actuation and collection of dose, tidal breathing, changes in priming requirements, and cleaning of the holding chamber.

In an Information Request dated February 21, 2006, the Division requested additional in vitro characterization data, if available. In a response, the Applicant indicated that additional in vitro characterization data was not available. Without adequate in vitro characterization of dose delivery of salmeterol xinafoate inhalation aerosol with a holding chamber, interpretation of the safety and efficacy data from the clinical studies is limited.
Reviewer's Comment: It is important to know the dose delivery with a holding chamber with flow rates appropriate for the pediatric population or with a time delay. If there is a significant decrease in dose delivery, this would influence the results of the study. The lack of adequate in vitro characterization of salmeterol xinafoate inhalation aerosol with a holding chamber limits interpretation of the clinical studies.

Reviewer's Comment: For a detailed review of the CMC data, refer to Dr. Stuart Zimmerman's CMC review.

3.2 Animal Pharmacology/Toxicology

To support clinical studies in pediatric subjects, the Applicant conducted two nonclinical studies: 1) a 5-day dose ranging toxicity study in juvenile dogs; and 2) a 13 week toxicity study in juvenile dogs. The study reports for these toxicology studies were submitted to the Agency in September 2001. The reports were reviewed by the Division's pharmacology/toxicology reviewer, Dr. Lawrence Sancilio in 2002. The 13 week dog toxicity study identified the nasal cavity as the target organ. Nasal cavity findings included: suppurative exudate, subacute inflammation, and hyperplasia of the goblet cells.

Based upon the juvenile dog study, the Division held a teleconference with the Sponsor on July 16, 2002, to discuss the findings of the juvenile animal study. To monitor for the nasal toxicities in the clinical setting, the Sponsor proposed to perform nasal passage and oropharyngeal examinations in Study SMS30077.
Reviewer's Comment: For a detailed review of the 13 week dog toxicity study, refer to Dr. Lawrence Sancilio's pharmacology/toxicology review dated June 12, 2002.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data for this clinical review are the clinical studies conducted by the Applicant, which were submitted in this (b) (4) supplement.

4.2 Table of Clinical Studies

Table 1 displays the four clinical studies submitted in this (b) (4) supplement.

Table 1 Clinical Studies with Salmeterol Xinafoate in Subjects 6 to 47 Months of Age

Study	Study Purpose	Subjects	Design	Treatment Groups	Endpoints
SMS20010 United States US	Safety, Dose Ranging	24-47 Months N=42	R, DB, PC, DD, Two Period, Four Treatment XO	- Serevent 25mcg BID (CFC) - Serevent 25mcg TID (CFC) - Serevent 50mcg BID (CFC) - Placebo CFC (b) (4) and facemask	Safety – HR, Holter monitoring, ECGs, glucose, potassium, adrenergic stimulation Efficacy – asthma symptoms, PEF
SMS20011 United States	Safety, Dose Ranging	6-23 Months N=45	R, DB, PC, DD, Two Period, Four Treatment XO	- Serevent 25mcg BID (CFC) - Serevent 25mcg TID (CFC) - Serevent 50mcg BID (CFC) - Placebo CFC (b) (4) and facemask	Safety – HR, Holter monitoring, ECGs, glucose, potassium, adrenergic stimulation Efficacy – asthma symptoms
SMS30076 United States Mexico Costa Rica	Efficacy, Safety	24-47 Months N=338	R, DB, DD, PC, //, 30 day	- Serevent 25mcg BID (CFC) - Serevent 50mcg BID (CFC) - Placebo CFC (b) (4) and facemask	Efficacy – asthma symptom scores, PEF, rescue medication use, exacerbations Safety – ECG, VS, adrenergic stimulation
SMS30077 United States Costa Rica	Efficacy, Safety	4-23 Months N=167	R, DB, DD, PC, //, 30 day	- Serevent 25mcg BID (CFC) - Serevent 50mcg BID (CFC) - Placebo CFC (b) (4) and facemask	Efficacy – asthma symptom scores, PEF, rescue medication use, exacerbations Safety – ECG, VS, adrenergic stimulation

R – randomized; DB-double blind; DD- double dummy; PC – placebo controlled; // - parallel group; XO – cross over, HR – heart rate; PEF – peak expiratory flow rate; VS – vital signs

4.3 Review Strategy

The general strategy for this review was a thorough review of the four clinical studies submitted (b) (4) Studies SMS30076 and SMS30077 were the primary sources of efficacy data discussed in the integrated efficacy review because these studies were 30 days duration and enrolled more subjects than Studies SMS20010 and SMS20011. The data from all four clinical studies were included in the integrated safety review.

4.4 Data Quality and Integrity

The Division of Scientific Investigations was not consulted to audit the Applicant's data primarily because the Applicant was not seeking an indication based upon the submitted clinical studies.

4.5 Compliance with Good Clinical Practices

Informed consent was obtained from each subject prior to performing any study procedures. The studies were performed in accordance with the Declaration of Helsinki and complied with the principles of Good Clinical Practice. The Applicant submitted a debarment certification stating it did not use the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the Application [N20236\2005-12-21\2-5-clin-ov.pdf, pg 6; N20236\2005-12-21\debar.pdf. pg 1-91].

4.6 Financial Disclosures

The Applicant submitted financial disclosure information for the clinical investigators who participated in the clinical studies to support this (b) (4) supplement. The following are notable disclosures [N20236\2005-12-21\financial.pdf].

- One subinvestigator in Study SMS30077 reported >$25,000 payments of other sorts. The subinvestigator was (b) (6) (Study Center (b) (6) (b) (6) reported $628,450 in honoraria.
  - This site contributed only (b) (6) subjects of the 167 subjects in Study SMS30077 and is unlikely to affect the results of Study SMS30077.
- One investigator reported >$50,000 equity interest. The investigator was (b) (6) (Study Center (b) (6). (b) (6) reported $75,000 in equity interest.
  - This site contributed only (b) (6) subjects of the 167 subjects in Study SMS30077 and is unlikely to affect the results of Study SMS30077.

It should be noted that the Applicant was not able to obtain updated financial disclosure information from all of the investigators in a timely manner. Investigators were to update their financial disclosure information 1 year following study completion. The Applicant supplied a list of 9 investigators/subinvestigators in SMS20011, 26 investigators/subinvestigators in SMS 30076, and 1 investigator/subinvestigator in SMS30077 for whom updated financial disclosure information was not available.

The Applicant has adequately disclosed available financial arrangements with the clinical investigators. The two investigators discussed above are unlikely to affect the results of Study SMS30077 because of the few number of subjects they enrolled.

5 CLINICAL PHARMACOLOGY

This section is not applicable because pharmacokinetic parameters were not collected in the four clinical studies in this (b) (4) supplement.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Serevent Inhalation Aerosol is currently approved for the maintenance treatment of asthma and prevention of bronchospasm in patients 12 years of age and older. The Applicant does not seek an indication in children ≤ 4 years of age based upon the clinical studies in this submission.

6.1.1 Methods

All four clinical studies in this submission were reviewed individually. Studies SMS20010 and SMS20011 were primarily dose ranging, safety studies and will not be included in this integrated

review of efficacy. Studies SMS30076 and SMS30077 were 4 week safety and efficacy studies and the efficacy endpoints from these studies will be discussed in this integrated review of efficacy.

6.1.2 General Discussion of Endpoints

In the Written Request, the Agency requested that the Applicant measure asthma symptom scores as the primary endpoint and include peak expiratory flow, asthma symptom-free days, rescue medication use, treatment failures, and subject discontinuations as secondary endpoints.

In Studies SMS30076 and SMS30077, the primary efficacy endpoint was the change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores during the treatment period. Asthma symptom scores assessed symptoms of wheeze, cough, and shortness of breath based upon the parent/guardian's rating of the symptoms twice daily in the diary. The following is the scoring system.

- **Asthma symptoms scores**
  - **Night symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with sleep
    - 2 Moderate; awakened once or more because of asthma symptoms
    - 3 Severe; awake most of the night due to asthma symptoms
  - **Day symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with daily activities
    - 2 Moderate; symptoms present often, causing some interference with daily routine and activities
    - 3 Severe; symptoms continuous or present most of the day, restricting daily routine and activities severely

The following is a list of the pertinent secondary endpoints and included in Studies SMS30076 and SMS30077:

- Percentage of symptom-free 24 hour days
  - Symptom free day is a day in which subject has a nighttime & daytime score of 0
- Rescue albuterol use
  - Recorded by the parent/guardian in the diary
- Percentage of symptom-free and albuterol-free 24 hour days
- Individual daytime and nighttime asthma symptom scores
- Number of asthma exacerbations
  - An asthma exacerbation (treatment failure) was defined as an increase in signs or symptoms of asthma, not controlled by as needed albuterol and requiring asthma medications not allowed by the protocol
- Subject discontinuations
- Child health status as assessed by the Functional Status II-(R)
- Percentage of nights with no awakenings

- Peak expiratory flow (PEF) (Study SMS30076 only)
  - In subjects able to perform maneuver, PEF were collected using a PEF meter each morning and evening. Duplicate measurements were obtained with highest PEF value recorded in the diary.

6.1.3 Study Design

Studies SMS30076 and SMS3007 were randomized, double-blind, double-dummy, placebo controlled, parallel group, 4 week trials. In general, the design of these studies is acceptable to assess some efficacy endpoints; however, neither of these studies were adequately powered to establish efficacy.

6.1.4 Efficacy Findings

In Studies SMS30076 and SMS30077, the primary efficacy endpoint was the change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores during the treatment period. As shown below in Table 2, there was no significant difference between the salmeterol treatment groups and placebo with respect to the change from baseline in composite asthma symptom scores. Baseline scores were similar between treatment groups and all treatment groups demonstrated a small improvement in symptom scores during the study.

Table 2 Composite* Asthma Symptom Scores
Studies SMS30076 and SMS30077 - ITT Population

	Placebo	Salmeterol 25mcg BID	Salmeterol 50mcg BID
Study SMS30076 (24 to 47 months of age)	**n=113**	**n=112**	**n=113**
Baseline mean score (SE)	1.2 (0.05)	1.2 (0.05)	1.2 (0.05)
Week 1-4			
Adjusted mean score (SE)	0.8 (0.10)	0.9 (0.10)	0.8 (0.10)
Adjusted mean change (SE)	-0.3 (0.10)	-0.3 (0.10)	-0.4 (0.10)
Treatment group difference vs. placebo		0 (0.06)	0.1 (0.06)
95% CI vs. placebo		-0.1, 0.1	0, 0.2
p-value vs. placebo		0.75	0.17
Study SMS30077 (6 to 23 months of age)	**n=55**	**n=56**	**n=5**
Baseline mean score (SD)	1.3 (0.5)	1.0 (0.5)	1.2 (0.6)
Week 1-4			
Adjusted mean score (SE)	0.8 (0.10)	0.8 (0.10)	0.8 (0.10)
Adjusted mean change (SE)	-0.4 (0.10)	-0.4 (0.10)	-0.4 (0.10)
Treatment group difference vs. placebo		0 (0.09)	0 (0.09)
95% CI vs. placebo		-0.2, 0.2	-0.2, 0.2
p-value vs. placebo		0.932	0.954

* Composite Symptom Score = (daytime score + nighttime score)/2
Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 60; N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 67

Similarly, for the following secondary endpoints: percent symptom free days, percent symptom and albuterol free days, albuterol use, and percent nights without awakenings, there was no significant difference in change from baseline among the treatment groups. Baseline values were

similar among the treatment groups and each treatment group showed improvement in each of the secondary endpoints. However, the difference between groups was not significant. *Reviewer's Comment: For details of the secondary endpoints in Studies SMS30076 and SMS30077, refer to Table 40 and Table 49 in the Appendices.*

Asthma exacerbations were considered treatment failures. In Study SMS30076, there was no significant differences between treatment groups in the number of subjects experiencing an asthma exacerbation; however, in Study SMS30077, there were more subjects in the salmeterol 25mcg group (5) who experienced an asthma exacerbation compared to 1 in the placebo group and 1 in the salmeterol 50mcg group [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 73, 226-227].

In terms of subject discontinuations, in Study SMS30076, there were more subjects who discontinued the salmeterol 50mcg treatment group (12) than the placebo group (6) or the salmeterol 25mcg treatment group (5). In Study SMS30077 there were a similar number of subjects who discontinued each treatment group (3-6) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 67].

The Applicant measured peak expiratory flow in a subset of patients in Study SMS30076. In subjects able to perform the PEF maneuver, PEF measurements were recorded in the patient diary twice daily. Approximately one third of the subjects in each treatment group were able to perform the PEF maneuver. The mean change from baseline AM and PM PEF were similar among the treatment groups.

In Studies SMS30076 and SMS30077, patient's health status was assessed by the parent/guardian using the FSII(R) during Baseline and Weeks 1, 2, 3, and 4. Baseline total scores were similar between treatment groups. Mean scores improved in all groups during the treatment period. In general, there were no significant differences between treatment groups for the mean change from baseline in the total FSII(R) scores; however, the salmeterol 25mcg treatment group had a numerically smaller increase (improvement) in FSII(R) score compared to the other treatment groups.

6.1.5 Clinical Microbiology

There was no clinical microbiology in this (b) (4) supplement.

6.1.6 Efficacy Conclusions

The efficacy data from the clinical studies in this supplement do not establish the efficacy superiority of salmeterol xinafoate inhalation aerosol over placebo in children ≤ 4 years of age. The primary source of the efficacy data were the two 4-week clinical studies, Studies SMS30076 and SMS30077. As specified in the Written Request, the Applicant utilized asthma symptom scores as the primary endpoint and included peak expiratory flow, asthma symptom-free days, rescue medication use, treatment failures, and subject discontinuations as secondary endpoints.

In Studies SMS30076 and SMS30077, the primary efficacy endpoint was the change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores during the treatment period. There was no significant difference between the salmeterol treatment groups and placebo with respect to the change from baseline in asthma symptom scores. In addition, the secondary endpoints did not support the efficacy superiority of salmeterol xinafoate inhalation aerosol over placebo.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The sources of data for the integrated safety review were the four clinical studies submitted in this (b) (4) supplement. The four clinical studies were reviewed individually and the reviews are located in the Appendix. The Applicant did not provide an integrated safety summary; however, this reviewer summarized the safety data from the two efficacy and safety studies, Studies SMS30076 and SMS30077, in this integrated safety review. Any important safety signals noted in the two dose ranging studies, Studies SMS20010 and SMS20011 are also noted in this safety review.

7.1.1 Deaths

There were no deaths in any of the clinical studies in this Application.

7.1.2 Other Serious Adverse Events

In the two four week efficacy and safety studies, there were five subjects with SAEs. The most common SAEs were respiratory related. There was a similar number of subjects with SAEs in each treatment group.

In the salmeterol 25mcg bid treatment group, there were two subjects with SAEs: 1) ectopic atrial beat on Week 4 ECG; and 2) pneumonia. In the salmeterol 50mcg bid treatment group there was one subject with an SAE: cough/ wheezing/hypoxia. In the placebo treatment group, there were two SAEs: 1) wheezing/dyspnea; and 2) bronchospasm. It should be noted that there was one additional SAE (gastroenteritis); however, this SAE occurred during the screening period.

In the two 7 day dose ranging studies, there was only one subject with an SAE. One subject in the salmeterol 25mcg BID treatment group in Study SMS20010 was hospitalized for wheezing and cough two days after completing treatment.

7.1.3 Dropouts and Other Significant Adverse Events

In the four week safety and efficacy studies, there were eight subjects who discontinued secondary to adverse events. More subjects discontinued due to AEs in the placebo treatment

group (4) than in either of the salmeterol treatment groups (2). The AEs leading to discontinuation were varied, but the most common AEs leading to discontinuation were respiratory related.

7.1.3.1 Overall profile of dropouts

The majority of the subjects who discontinued secondary to AEs were in Study SMS30076 and thus were age 24 to < 47 months.

7.1.3.2 Adverse events associated with dropouts

The following is a list of the AEs associated with dropouts arranged by treatment groups:

- Placebo (4)
  - Bronchospasm – Study SMS30076
  - Wheezing and dyspnea – Study SMS30076
  - Headaches – Study SMS30076
  - Rash – Study SMS30077
- Salmeterol 25mcg (2)
  - Elevated alkaline phosphatase on screening – Study SMS30076
  - Pneumonia – Study SMS30077
- Salmeterol 50mcg (2)
  - Hyperactivity – Study SMS30076
  - Cough, wheezing, and hypoxia – Study SMS30076

In the 7 day dose ranging studies, there was once subject who discontinued secondary to an adverse event. In Study SMS20011, one subject in the salmeterol 25mcg TID treatment group was withdrawn due to abnormal Holter findings. The subject had one supraventricular ectopic event (SVE) at baseline and 24 SVEs in 23 hours

7.1.3.3 Other significant adverse events

There were no other significant adverse events noted in the four clinical studies in this supplement.

7.1.4 Other Search Strategies

This section is not applicable as there were no special algorithms used to review the safety data.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Parents/guardians were given diary cards and instructed to record any medical problems. The diary cards were reviewed at each study visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In Study SMS30076, the case report form text for AEs was coded using the GOLD MIDAS dictionary and were grouped into common terms and body systems using a respiratory specific dictionary. The case report form text for AEs was coded using the Medical Dictionary for Regulatory Activities (MedDRA). The AEs were reported using the primary system organ class and the preferred term.
Reviewer's Comment: The AE categorization and preferred terms are acceptable.

7.1.5.3 Incidence of common adverse events

The AE data from the two 4-week safety and efficacy studies could not be combined since the Applicant utilized two different dictionaries of preferred terms. The majority of subjects (>60%) in Studies SMS30076 and SMS30077 reported at least one AE during the treatment period. More subjects reported AEs in Study SMS30077 (6-23 months of age) than in Study SMS30076. Of interest are the AEs reported with greater frequency in the salmeterol groups than in the placebo groups. The results from the individual studies are shown in the tables below.

Table 3 Adverse Events >3% Incidence and More Common than Placebo during the Treatment Period in Study SMS30076

Number of Subjects with AE	Placebo N=113 n (%)	Salmeterol 25mcg BID N=112 n (%)	Salmeterol 50mcg BID N=113 n (%)
Any Event	68 (60)	72 (64)	76 (67)
Fever	18 (16)	20 (18)	23 (20)
Rhinorrhea/post nasal drip	4 (4)	3 (3)	13 (12)
ENT infections	6 (5)	9 (8)	6 (5)
Skin rashes	4 (4)	2 (2)	6 (5)
Sinusitis	5 (4)	6 (5)	4 (4)
Mood disorders	3 (3)	5 (4)	4 (4)
Epistaxis	3 (3)	4 (4)	2 (2)
Rhinitis	2 (2)	4 (4)	2 (2)
GI discomfort & pain	2 (2)	2 (2)	4 (4)
Throat irritation	1 (<1)	4 (4)	3 (3)
Upper respiratory inflammation	1 (<1)	1 (<1)	6 (5)
Keratitis & conjunctivitis	1 (<1)	4 (4)	2 (2)
Psychomotor disorders	0	2 (2)	4 (4)

Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 74

With regards to the above table, the following was noted. Fever was the most common AE. Rhinorrhea/PND and upper respiratory inflammation were reported more frequently in the salmeterol 50mcg treatment group compared to the other treatment groups. Psychomotor disorders (hyperactivity) were only reported in the salmeterol treatment groups. Other notable AEs more common in the salmeterol treatment groups included: throat irritation and keratitis/conjunctivitis.

Table 4 Adverse Events >3% Incidence and More Common than Placebo during the Treatment Period in Study SMS30077

Number of Subjects with AE	Placebo N=55 n (%)	Salmeterol 25mcg BID N=56 n (%)	Salmeterol 50mcg BID N=56 n (%)
Any Event	47 (85)	44 (79)	48 (86)
Pyrexia	16 (29)	19 (34)	18 (32)
Diarrhea	7 (13)	9 (16)	6 (11)
Rhinorrhea	4 (7)	6 (11)	8 (14)
Rhinitis	3 (5)	6 (11)	3 (5)
Irritability	0	5 (9)	4 (7)
Ear infection	1 (2)	5 (9)	2 (4)
Influenza	2 (4)	4 (7)	2 (4)
Viral URTI	1 (2)	4 (7)	0
Rash	2 (4)	4 (7)	1 (2)
Conjunctivitis	2 (4)	4 (7)	2 (4)
Bronchitis	0	3 (5)	1 (2)
Otitis media	2 (4)	2 (4)	4 (7)
Pneumonia	0	2 (4)	0
Pharyngotonsilitis	1 (2)	1 (2)	4 (7)
Gastroenteritis	0	0	2 (4)
Sinus tachycardia	1 (2)	1 (2)	3 (5)
Tachycardia	1 (2)	1 (2)	2 (4)
Headache	1 (2)	0	2 (4)

Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 77

With regards to the above table, the following was noted. Fever and diarrhea were the most common AEs. Rhinorrhea, rhinitis, irritability, ear infection, influenza, viral URTI, rash, conjunctivitis, otitis media, and pharyngotonsilitis were reported at a higher incidence in one of the salmeterol groups compared to placebo.

In the two 7-day dose ranging studies, there were only approximately 20 subjects in each treatment group in each study. The AE data was not combined; however, in the individual studies, AEs that were reported in at least two more subjects in one of the salmeterol treatment groups compared to placebo were the following: URI, ENT infections, GI discomfort and pain, appetite disturbances, fever, and diarrhea.

Tremor

In each clinical study, physicians specifically assessed for tremor. In the four week clinical studies, tremor was assessed each week pre-dose and post-dose. No tremor was noted in the majority of subjects. In general, the tremor that was noted was mild in severity. In Study SMS30076, post-dose tremor was noted more frequently in the salmeterol treatment groups than in the placebo group at Week 4.

Nasopharyngeal Examinations

Because of the findings in the juvenile animal study, dedicated nasopharyngeal examinations were performed in Study SMS30077 at each clinic visit. Overall, there were more subjects in the salmeterol 25mcg treatment group (29%) with a shift from normal to abnormal nasal findings compared to the other groups (16-17%). The majority of changes were related to nasal secretions – quantity, consistency, and color. The Sponsor performed additional analyses of the data and noted that ~60-70% of subjects with abnormal changes in nasal exam had a history of allergies. Some of the changes were observed close to URTI, sinusitis, ear infections, and other URT AEs. In terms of oropharyngeal examinations, there were a similar percentage of subjects in each treatment group (4-5%) with shift from normal to abnormal from baseline to the end of treatment. The majority of the changes were change in tonsil size/color and change in posterior pharyngeal wall.

Functional Status II-(R) Scores
Subject's health status was assessed by the parent/guardian at baseline and each clinic visit. Individual items from the FSII(R) questionnaire were selected to evaluate potential signs and symptoms of adrenergic stimulation: sleep well; content/cheerful; act moody; unusually irritable; sleep thru night; unusually difficult; and react by crying. Individual item scores were on a 0-2 scale, with higher numbers indicating better functioning. Mean scores were similar at baseline and end of study and in general, scores increased slightly for most of the items in each treatment group.

7.1.5.4 Common adverse event tables

As discussed above, Table 3 and Table 4 display the AEs which were reported with >3% incidence in any treatment group and with a greater incidence in one of the salmeterol groups compared to the placebo group in Studies SMS30076 and SMS30077, respectively.

7.1.5.5 Identifying common and drug-related adverse events

The Applicant presented the AEs attributed to study medications. The drug-related AEs included: mood disorders, headaches, sleep disorders, and psychomotor disorders, tachycardia, irritability, increased alkaline phosphatase, abnormal QRS axis, cough, dysphagia, psychomotor hyperactivity, tremor, muscle twitching, and rash. Many of the drug related AEs are what would be expected for a beta adrenergic agonist.

7.1.5.6 Additional analyses and explorations

Of the AEs shown in Table 3 and Table 4, none of the AEs have a clear dose response relationship.

7.1.6 Less Common Adverse Events

The AE data in this (b) (4) supplement is not sufficient to identify less common adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the four-week clinical studies, laboratories (hematology and chemistry) were drawn at baseline and at the end of the study (Week 4). In the one-week clinical studies, laboratories (hematology and chemistry) were drawn at baseline and at the end of each treatment period.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

All four clinical studies were placebo controlled. The laboratory data from each study were reviewed.

7.1.7.3 Standard analyses and explorations of laboratory data

The Applicant presented the laboratory data in shift tables. In terms of laboratory assessments, the majority of subject had no shift from normal or shifted to normal range. Although there were some shifts to low or high noted in some of the laboratory parameters, the majority of the shifts were not outside the Applicant's predefined threshold levels and there was no consistent pattern noted in the treatment groups between the two four week studies.

The glucose and potassium data are of interest because of the known effect of beta adrenergic stimulation on these laboratory parameters. There was little change from baseline in median serum potassium or glucose among the treatment groups. More subjects in the salmeterol treatment groups were noted to have a shift to low potassium; however, none of the potassium levels were below the predefined threshold of < 3.5mEq/L. In terms of glucose, one subject in the placebo group and one in the salmeterol 50mcg group had shifts to glucose values above the threshold (140mg/dL) and no subjects had decrease below the threshold (45mg/dL).

7.1.7.4 Additional analyses and explorations

There was no consistent laboratory safety signal noted in the four-week clinical studies; therefore, there were no additional analyses or explorations performed for the laboratory data.

7.1.7.5 Special assessments

Glucose and potassium levels are of particular interest in studies with beta adrenergic agonists and were discussed above in Section 7.1.7.2.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were performed at the baseline and end of each treatment period in the two dose ranging studies and at baseline and each week in the two four week studies.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

All four clinical studies were placebo controlled. The vital sign data from each study were reviewed individually.

7.1.8.3 Standard analyses and explorations of vital signs data

The Applicant presented the mean systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and respiratory rate data for baseline, end of treatment period, and change from baseline. In general there were no clinically significant differences between treatment groups for mean change from baseline.

7.1.8.4 Additional analyses and explorations

There was no consistent vital sign safety signal noted in the four-week clinical studies; therefore, there were no additional analyses or explorations performed for the vital sign data.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were performed at baseline and at the end of the treatment period in all four clinical studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

All four clinical studies were placebo controlled. The ECG data from each study were reviewed individually.

7.1.9.3 Standard analyses and explorations of ECG data

The majority of subjects had normal ECGs. In Study SMS30076, two subjects were noted to have unfavorable changes from baseline at Week 4: increased heart rate (salmeterol 50mcg group) and increased QTc interval (salmeterol 25mcg group). In Study SMS30077, one subject in the placebo group was discontinued from the study for an unfavorable clinically significant

change from baseline ECG (sinus tachycardia and left axis deviation). In both studies, there were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF intervals. No subject had a QTcF interval ≥ 440msec at the end of the treatment period.

In terms of outliers, there were four subjects in Study SMS30077 who had a significant increase in QT_c: 3 subjects in the salmeterol 50mcg treatment group with and increase from baseline of 81, 50, and 40msec, respectively; and one subject in the placebo group who had an increase of 37msec

7.1.9.4 Additional analyses and explorations

In the dose ranging studies, Holter monitors were performed at baseline and the end of each treatment period. The heart rate data and ectopic events were analyzed. There was no clinically significant change from baseline in 24 hour heart rates between treatment groups. There was no increase in supraventricular ectopic or single ventricular ectopic events during the treatment period. However, in Study SMS30077, there were 4 subjects with ventricular ectopic couplets in the salmeterol treatment groups compared to none in the placebo group at the end of the treatment period.

7.1.10 Immunogenicity

This section is not applicable because salmeterol is a small synthetic molecule and is not suspected to elicit an immune response.

7.1.11 Human Carcinogenicity

There were no malignancies reported in the four clinical studies in this (b) (4) supplement. Nonclinical carcinogenicity studies have been conducted with salmeterol in CD-mice and Sprague Dawley rats. In CD-mice salmeterol at 9 times the maximum recommended daily dose in adults (based on AUCs) caused dose-related increases in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumors were noted at a dose comparable to the maximum recommended human daily inhalation dose in adults (based on AUCs). In Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at approximately 55 times the maximum recommended daily dose in adults (based on mg/m^2). No tumors were noted at approximately 15 times the maximum recommended daily dose in adults (based on mg/m^2) [Serevent Inhalation Aerosol package insert].

7.1.12 Special Safety Studies

There were no special safety studies in this (b) (4) supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This section is not applicable as beta adrenergic agonists do not have a history of abuse potential or withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

There was no human reproduction or pregnancy data submitted in this (b) (4) supplement as all the clinical studies were conducted in the pediatric population. Similar to other beta adrenergic agonists, salmeterol is a Pregnancy Category C [Serevent Inhalation Aerosol package insert].

7.1.15 Assessment of Effect on Growth

This section is not applicable as clinical studies to evaluate the effect on growth were not submitted with this (b) (4) supplement.

7.1.16 Overdose Experience

There was no specific cumulative dose study in this (b) (4) supplement; however, the symptoms expected with overdose of salmeterol are those of excessive beta-adrenergic receptor stimulation, such as tachycardia, nervousness, tremor, palpitations, hypokalemia, and arrhythmias. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_c interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia [Serevent Inhalation Aerosol package insert].

7.1.17 Postmarketing Experience

Salmeterol has extensive US and worldwide postmarketing experience and serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating, but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol xinafoate inhalation aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

The following events have also been identified during postapproval use of salmeterol in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to salmeterol [Serevent Inhalation Aerosol package insert].

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Table 1 in Section 4.2 contains an overview of the four clinical studies which were the primary sources of data to evaluate safety.

7.2.1.1 Study type and design/patient enumeration

Table 1 in Section 4.2 displays an overview of the study type and design in this (b) (4) supplement. Table 5 below shows the number of subjects randomized to each treatment group in each study.

Table 5 Patient Enumeration

Study Number	Salmeterol 25mcg BID	Salmeterol 25mcg TID	Salmeterol 50mcg BID	Placebo
SMS20010	21	19	19	20
SMS20011	21	21	20	20
SMS30076	112	0	113	113
SMS30077	56	0	56	55
Total	210	40	208	208

7.2.1.2 Demographics

In Studies SMS20010 and SMS30076, the mean age for subjects was 35.3 to 36 months with a minimum age of 22 months and a maximum age of 47 months. Approximately half of the children were 24-36 months and the other half were 37-47 months. There were more males (64-67%) than females (33-36%). In Study SMS20010, the majority of subjects were White (69%) and the remainder were 10% Asian, 12% Black, and 10% Hispanic. In Study SMS30076, the majority of subjects were White (46%) and the remainder were 2% Asian, 22% Black, 26% Hispanic, and 4% Other.

In Studies SMS20011 and SMS30077, the mean age for subjects was 14.6 -15.2 months with a minimum age of 4 months and a maximum age of 23 months. Approximately one third of the children were 6 to 11 months and the other two thirds were 12-23 months. One subject (<1%) was 4 months of age. There were more males (66-76%) than females (24-36%). In Study SMS20011, the majority of subjects were White (51%) with the remainder 31% Black, 11% Hispanic, and 7% other ethnic origin. In Study SMS30076, the majority of subjects were White (54%), while 46% were American Hispanic, and <1% were Other.

7.2.1.3 Extent of exposure (dose/duration)

In Studies SMS30076 and SMS30077, the majority of subjects (>89%) had > 28 days exposure of study medication and in Studies SMS20010 and SMS20011, the majority (>89%) of subjects had ≥ 7 days of study medication exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The four clinical studies described above (Studies SMS2001, SMS20011, SMS30076, SMS30077) contributed to the safety data in this supplement. No additional clinical studies were conducted.

7.2.2.2 Postmarketing experience

Although salmeterol has extensive US and worldwide postmarketing experience, the postmarketing experience did not contribute to the safety data in this (b) (4) supplement because the postmarketing experience is presumed to be from salmeterol use without a holding chamber. In the clinical studies in this supplement, salmeterol was administered with a holding chamber and facemask; therefore, the postmarketing experience may not be applicable.

7.2.2.3 Literature

Published literature did not contribute to the safety review in this (b) (4) supplement.

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Applicant performed in vitro testing of salmeterol xinafoate inhalation aerosol with valved holding chambers. However, the Applicant did not test factors that may be relevant in the pediatric population, such as lower flow rates or the effects of a time delay. Therefore, the in vitro testing is deemed not adequate to fully characterize the dose delivery of salmeterol xinafoate inhalation aerosol in pediatric subjects < 4 years of age. Thus, interpretation of the results of the clinical studies is limited.

The Applicant performed two juvenile dog studies to support conducting clinical studies in pediatric subjects. Refer to Section 3.2 for a brief overview of the pharmacology/toxicology program and findings.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical monitoring in the four clinical studies was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This section is not applicable as there were no pharmacokinetic data collected in the clinical studies.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

In all four clinical studies, the Applicant specifically monitored for beta adrenergic adverse events, such as tremor, irritability, and increased heart rate.

7.2.8 Assessment of Quality and Completeness of Data

The Applicant did not adequately characterize the in vitro dose delivery of salmeterol inhalation aerosol with valved holding chamber and facemask for use in children < 4 years of age. Therefore, interpretation of the safety and efficacy results of the four clinical studies in this supplement is limited.

7.2.9 Additional Submissions, Including Safety Update

The Applicant did not provide additional submissions or safety update during the review period.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The Applicant did not adequately characterize the in vitro dose delivery of salmeterol inhalation aerosol with valved holding chamber and facemask for use in children < 4 years of age. Therefore, interpretation of the safety and efficacy results of the four clinical studies in this supplement is limited.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The individual studies were reviewed in detail in the Appendices. The safety data from the two 4-week clinical studies were described together; however, the safety data was not combined for analysis. The rationale for not combining the safety data was because the Applicant utilized two different medical dictionaries to code adverse events. In addition, the studies enrolled children in two different age groups.

7.4.1.2 Combining data

As discussed above, the safety data from the two 4-week clinical studies were described together; however, the safety data was not combined for analysis.

7.4.2 Explorations for Predictive Factors

Explorations for predictive factors were not performed in this review. Although the safety data was reviewed and the results described in Section 7.1, interpretation of the results of the clinical studies is limited because the Applicant did not provide adequate in vitro characterization of salmeterol xinafoate inhalation aerosol with valved holding chambers for children < 4 years of age.

7.4.3 Causality Determination

Assessment of causality in this supplement is limited because the Applicant did not provide adequate in vitro characterization of salmeterol xinafoate inhalation aerosol with valved holding chambers for children < 4 years of age. Therefore, the interpretation of the results of the clinical studies is limited.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant conducted 4 clinical studies in children 6 months to < 47 months of age with salmeterol xinafoate inhalation aerosol and two different valved holding chambers. In terms of efficacy, the clinical studies did not demonstrate that salmeterol xinafoate inhalation aerosol was superior to placebo. In terms of safety, there were some differences noted between treatment groups, primarily with respect to AEs.

In order to interpret the safety and efficacy data from the clinical studies, it is important to understand how the delivery of salmeterol xinafoate inhalation aerosol is affected by the use of a valved holding chamber. In addition, since this is a pediatric population, other factors need to be considered. For example, children < 4 years of age are unlikely to be able to generate inspiratory flow rates of approximately 30L/min, which is a standard flow rate utilized for in vitro testing. Children in this age group may not be able to cooperate fully and there may be a time delay after actuation before the child inhales from the holding chamber. To interpret the clinical studies, it is important to know that the children received medication. The Applicant did perform in vitro testing of salmeterol xinafoate inhalation aerosol with valved holding chambers. However, because the Applicant did not test factors such as lower flow rates or the effects of a time delay, the in vitro testing is deemed not adequate to fully characterize the in vitro delivery. Therefore, interpretation of the results of the clinical studies is limited. In addition, the lack of evidence of efficacy with salmeterol and lack of PK data cannot assure drug delivery.

9.2 Recommendation on Regulatory Action

(b) (4)

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing studies.

9.3.1 Risk Management Activity

There are no postmarketing risk management activities recommended.

9.3.2 Required Phase 4 Commitments

There are no required phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no additional phase 4 requests.

9.4 Labeling Review

(b) (4)

9.5 Comments to Applicant

(b) (4)

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study SMS20010

A Five-Week, Randomized, Double-Blind, Double-Dummy, Two-Period, Four-Treatment Crossover, Placebo-Controlled, Balanced Incomplete Block Design, Multi-Center Study of Salmeterol Xinafoate Inhalation Aerosol and Placebo Administered via a Holding Chamber with Facemask in Subjects with Asthma Aged 24 to 47 Months

10.1.1.1 Protocol

Objective
The objective of Study SMS20010 is to evaluate the safety of 3 doses of salmeterol xinafoate inhalation aerosol over a 1-week treatment period in subjects with mild to moderate asthma aged 24 to 47 months.

Study Design
Study SMS20010 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, two-period, four-treatment crossover incomplete block design study of 3 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 24 to 47 months. Eligible subjects underwent a 7 day screening period at Visit 1. Subjects meeting entry criteria were randomized at Visit 2 to one of the following treatment groups for the first 7 day double-blind treatment period.

- Salmeterol xinafoate inhalation aerosol 25mcg BID
- Salmeterol xinafoate inhalation aerosol 25mcg TID
- Salmeterol xinafoate inhalation aerosol 50mcg BID
- Placebo MDI BID.

At Visit 3, subjects entered a 5 day washout period before Visit 4 when they received the second randomized treatment for 7 days. Subjects returned for Visit 5 to enter another 5 day washout period, followed by Visit 6 for end of study assessments [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 14].

Study Population
The following is a list of the pertinent inclusion criteria for the screening phase of SMS20010:

- Male or females 24 to 47 months of age
- At least 2 exacerbations of wheeze and cough within the preceding 12 months. In addition, subjects must also fulfill the following criteria prior to Visit 1
    - Have required therapy with a maintenance asthma medication (other than systemic corticosteroid) on a regular basis for the preceding 6 weeks **and/or**

- Have required therapy with a short-acting beta-agonist for relief of respiratory symptoms at least twice per week over the preceding 3 weeks.

The following is a list of the pertinent inclusion criteria for the treatment phase of SMS20010:

- Parents/guardians comply with use of diary card on at least 80% of the days during the screening period
- Subject is able to use the MDI with holding chamber and facemask
- Subject has not experience a severe exacerbation during the screening period (ER visit or systemic corticosteroid use)
- Parent/guardian capable of supervising the Holter monitor.

The following is a list of the pertinent exclusion criteria for SMS20010:

- Life-threatening asthma (ICU admission) within previous 6 months
- Subjects treated in the ER or admitted to the hospital for airway obstruction on two more occasions within the previous 6 months
- Acute systemic corticosteroid therapy within 14 days of screening
- Chronic systemic corticosteroid therapy for > 8 weeks within 12 weeks of screening
- Concurrent significant disease including the following: CF, bronchiectasis, BPD, pneumonia (3 months), ENT disorders requiring surgery (12 months), seizure disorder, reflux esophagitis (3 months), Cushing's Syndrome, renal disease, hematological disease, hepatic disease, malignancy, cellular or humoral immunity disorder, JRA, SLE, or other collagen vascular disease, inadequately controlled psychiatric disorder, DM, pan-hypopituitarism, hyperthyroidism, glaucoma
- Hypersensitivity to beta-agonists, component of MDI formulation, facemask, or adhesives
- Clinically significant laboratories
- Recent bacterial or viral URI, LRI, sinus, or middle ear infection that is not resolved within 2 weeks prior to screening

[N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 15-18].

Materials

The parent/guardian for each subject received 3 canisters (A, B, and C). They were instructed to administer one inhalation from canister A and B in the AM and at bedtime, and one inhalation from canister C at mid-day as shown below [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 19]:

- Salmeterol xinafoate inhalation aerosol 25mcg BID
  - One inhalation 25mcg (canister A or B) in AM and at bedtime
  - One inhalation placebo (canister A or B) in AM and at bedtime
  - One inhalation of placebo (canister C) at mid afternoon
- Salmeterol xinafoate inhalation aerosol 25mcg TID
  - One inhalation 25mcg (canister A or B) in AM and at bedtime
  - One inhalation placebo (canister A or B) in AM and at bedtime
  - One inhalation of 25mcg (canister C) at mid afternoon
- Salmeterol xinafoate inhalation aerosol 50mcg BID

    - One inhalation 25mcg (canister A or B) in AM and at bedtime
    - One inhalation 25mcg (canister A or B) in AM and at bedtime
    - One inhalation of placebo (canister C) at mid afternoon
- Placebo MDI BID
    - One inhalation placebo (canister A or B) in AM and at bedtime
    - One inhalation placebo (canister A or B) in AM and at bedtime
    - One inhalation of placebo (canister C) at mid afternoon

All study medication was administered via holding chamber and facemask. Approximately half of the subjects were assigned to use holding chamber "A" and the other half assigned to holding chamber "B". The assigned chambers were used for the duration of the study. The (b) (4) was holding chamber "A" and the (b) (4) was holding chamber "B".

Rescue medication was supplied as Ventolin MDI and nebules.

Concomitant Therapy

The following medications were prohibited during the course of the study [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 21-22]:

- Beta-adrenergic agonists
- Systemic corticosteroids
- Beta-adrenergic antagonists
- Anti-cholinergics e.g. (ipratropium bromide)
- Theophylline or aminophylline
- Leukotriene antagonists
- Antiarrythmics
- Anticonvulsants
- CNS stimulants
- Oral antihistamines
- Systemic decongestants
- Narcotic or non-narcotic cough suppressants
- Immunosuppressives

Study Conduct

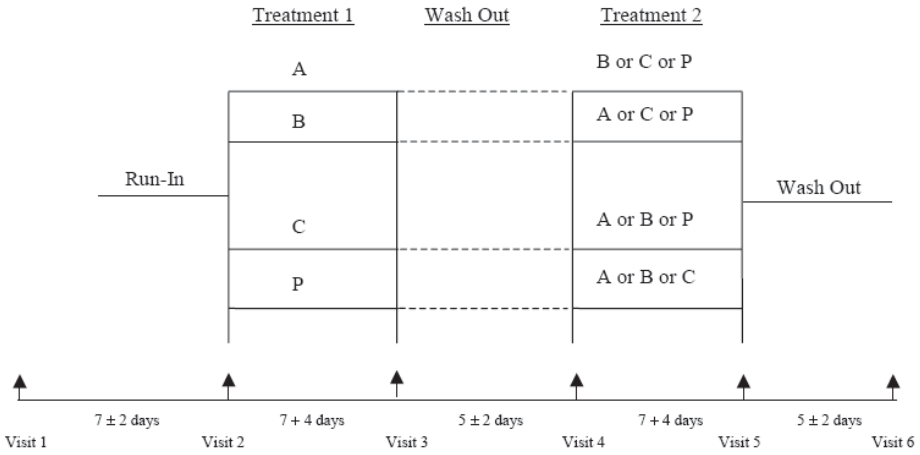
Informed consent was obtained prior to any screening or treatment study procedures being performed. Screening evaluations were performed at Visit 1. Subjects and guardians/parents were instructed on the proper completion of the diary card, proper use of the peak flow meter, and proper administration of the MDI and nebules. Subjects underwent a 7 (+/- 2) day run-in period.

At Visit 2, eligibility criteria were reviewed and if subjects were eligible, they were randomized in a 1:1:1:1 fashion to one of the four treatment groups for a 7 day double-blind treatment period. At Visit 3, subjects entered a 5 day washout period before Visit 4 when they received the second randomized treatment for 7 days. Subjects returned for Visit 5 to enter another 5 day washout period, followed by Visit 6 for end of study assessments. Throughout the treatment period,

parents/guardians completed diary cards (symptoms and PEF) and recorded rescue medication use. Study medication was administered in the clinic during Visits 2 and 4.

Figure 2 displays the study design followed by Table 6, which displays the study assessments performed at each clinic visit [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 14].

Figure 2 Schematic of Balanced Incomplete Block Crossover Study Design



Treatments

A = 25mcg BID B = 50mcg BID C = 25mcg TID P = Placebo

Source: N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 58

Table 6 SMS 20010 Study Assessments

Visit	1	2	3	4	5	6	
Days since prior Visit		7 ±2 days	7 +4 days	5 ±2 days	7 +4 days	5 ±2 days	Premature Discontinuation
Procedure							
Informed Consent	X						
Review Holter data		X	X		X		
AE assess		X	X	X	X	X	X
Administer FSII(R)		X	X		X		X[d]
Med History	X						
Con Meds	X	X	X	X	X	X	X
Tremor Assess	X	X[a]	X	X[a]	X	X	X
Physical	X					X	X
Vital signs	X	X	X	X	X	X	X
ECG	X		X		X		X
PEF (In clinic)	X[b]	X[b]					
Review Diary Assessments		X	X	X	X	X	X
Dispense/collect diary cards and review instructions	X	X	X	X	X	X	X
Review MDI technique	X	X		X			
Dispense/collect **VENTOLIN**	X	X	X	X	X	X	X
Dispense/collect double blind study medication		X	X	X	X		X
24 hr Holter monitoring	Day prior to Visit 2	Day prior to Visit 3		Day prior to Visit 5			
Lab Tests	X[c]		X		X		X

a. Evaluated pre-dose and one hour post dosing of study medication.
b. Subjects who provide technically acceptable maneuvers will continue to record PEF twice-daily on dairy cards.
c. Subjects will have a lab assessment at Visit 1 unless there is historical evidence of a normal lab assessment within 3 months of Visit 1 that includes both blood glucose and serum potassium and the subject has had no change in medical status since that assessment.
d. Administer FSII(R) at premature discontinuation only if the premature discontinuation occurs between Visit 2 and Visit 3 or between Visit 4 and Visit 5.

Source: N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 57

If subjects discontinued the study early, the investigator was to make an effort to perform the end of study evaluations.

Efficacy

Some efficacy measures were specified in the protocol. Efficacy measures included individual daytime and night-time asthma symptom scores, PEF, withdrawals due to asthma exacerbations, and rescue medication use. Each efficacy measure will be briefly discussed [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 29-31].

- **Asthma symptoms scores**
  - Endpoint – change from baseline in individual daytime and night-time asthma symptom scores over each treatment period
  - Based upon parent/guardian's rating of subject's symptoms on diary card recorded twice daily using the following scale
  - **Night symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with sleep
    - 2 Moderate; awakened once or more because of asthma symptoms
    - 3 Severe; awake most of the night due to asthma symptoms

  - **Day symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with daily activities
    - 2 Moderate; symptoms present often, causing some interference with daily routine and activities
    - 3 Severe; symptoms continuous or present most of the day, restricting daily routine and activities severely
- **Peak expiratory flow (PEF)**
  - In subjects able to perform maneuver, PEF were collected using the MiniWright^{TM} PEF meter each morning and evening.
  - Triplicate measurements obtained with highest PEF value recorded
- **Rescue medication use (Ventolin use)**
  - As recorded on diary card
- **Withdrawal due to asthma exacerbation**
  - Asthma exacerbation defined as an increase in asthma signs and symptoms that, in the opinion of the investigator, require an excluded medication including a course of systemic corticosteroids or the subject's disease is unstable and the study drug is not efficacious

In addition the Functional Status II(R) questionnaire (FSII(R)) was utilized to assess the health status of the subjects. The FSII(R) is an interviewer administered questionnaire which contains 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention during the previous two-week period. The FSII(R) was modified to assess the behavior during the previous week. Each item was scored on a three-point scale indicating the frequency with which a child exhibits the specified behavior or performs the specified activity. A second level of responses evaluated to what extent poor functioning indicated in the first level of questioning is related to the child's illness. The items are summed and a total score is calculated as the percent of total possible scores. Higher scores reflect a better functional status. The FSII(R) was administered at baseline and following each 7 day treatment period [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 31].

Safety

Safety assessments included Holter monitoring (heart rate), adverse events, physical examination, laboratories, ECGs, physician's assessment of tremor and symptoms of adrenergic stimulation (irritability and lack of sleep) from the FSII(R) questionnaire. Each safety measure will be briefly discussed [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 32-36].

- **Holter monitoring**
  - A 24 hour Holter monitor was conducted prior to randomization at Visit 2. Repeat Holter monitors were conducted one day prior to the completion of each treatment period (i.e. one day prior to Visit 3 and 5). If the Holter monitor was inadequate (<12 hours of recording), a single repeat attempt was initiated.
  - If the subject developed a fever, the baseline Holter session was repeated. However, the Holter sessions at the end of the treatment periods were not repeated. The fever was noted as an AE.

- **Physical examination**
  - A physical exam was performed at screening (Visit 1) and end of study (Visit 6)
- **Vital signs**
  - A set of vital signs (HR, BP, T, RR) was measured at each study visit
- **Adverse Events**
  - Adverse events were collected via the diary card and were reviewed at each study visit
- **ECG**
  - A 12 lead ECG was recorded at screening (Visit 1) and at the end of each of the treatment periods (Visits 3 and 5).
  - An independent electrocardiographer, blinded to treatment assignment, provided measurements of heart rate, PR interval, QTc interval, QRS duration, and an overall interpretation of each ECG collected
  - Criteria were specified in the protocol for an abnormal ECG. Inclusion criteria specified subjects must have a normal screening ECG
  - The ECGs collected at Visits 3 and 5 were compared to the screening ECG to determine if a clinically significant change occurred.
- **Laboratories**
  - Chemistry, hematology, and electrolytes were performed at Visit 1 (if indicated), Visit 3, and Visit 5
  - Baseline labs within previous 3 months were acceptable
- **Tremor assessments**
  - Tremor was evaluated by the investigator at each visit. When study drug was administered during Visits 2 and 4, tremor was assessed pre-dose and one hour post-dose.
  - Tremor was graded on the following scale
    - 0 – no tremor present
    - 1 – mild tremor present
    - 2 – moderate tremor present
    - 3 - severe tremor present

Data Analysis

According to the protocol, Thirty-six (36) completed subjects (three replicates of a balanced, incomplete block design) ensured that each treatment was represented within 18 of the 36 subjects. The subjects were recruited at nine study sites in the United States. One block contained four subjects, therefore the planned number of subjects per site was four to eight. In an effort to ensure treatment balance within the two age ranges: 24-36 months old and 37-47 months old, the randomization was stratified at a ratio of 1:1 into these two groups.

Efficacy measures were specified as follows; however, no statistical analyses were specified [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 38-39].

- **Asthma symptoms scores** - change from baseline in individual daytime and night-time asthma symptom scores over each treatment period. Baseline was defined as the average of the values during the run-in period.

- **Peak expiratory flow (PEF)** – change from baseline in PEF in subjects capable of performing the maneuver. Baseline was defined as the average of the values during the run-in period.
- **Rescue medication use (Ventolin use) –** change from baseline in Ventolin use
- **FSII(R) –** change from baseline in total scores at Visits 3 and 5. Baseline was defined as the assessment at Visit 2.

The primary endpoint was the effect of study drug following 7(+4) days of therapy on 24 hour heart rate, obtained via Holter monitoring, including mean, peak, and trough heart rate. Baseline was defined as the measurement from Visit 2.

Amendments

Two amendments were made to the original protocol (October 5, 1999 and December 17, 1999). The following is a brief summary of the amendments [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 61-63].

- Addition of exclusion criteria regarding asthma history to exclude subjects who were treated in the ER or admitted to the hospital on two or more occasions with the previous 6 months
- Switched from (b) (4) as holding chamber "A" to (b) (4)
- Addition of Ventolin use as an efficacy endpoint
- Changed the treatment period from 7 (+/-2) days to 7 (+/-4) days
- Changed acceptable criteria for Holter from 12 continuous hours to 12 hours of data
- Addition of requirement for baseline afebrile Holter monitor
- Changed recording of ECG from Visit 1 and Visit 6 to Visits 1, 3, and 5
- Changed laboratories from Visits 1 and Visit 6 to Visits 1, 3, and 5

10.1.1.2 Results

Study SMS20010 was initiated October 29, 1999, and completed July 25, 2000. The final study report is dated April 17, 2001. The drug supplies for the study were salmeterol xinafoate inhalation aerosol 25mcg from batch identification number 8ZM1229 and placebo inhalation aerosol from batch identification number 8ZM0902 [N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 1 & 25].

10.1.1.2.1 Subject Disposition

Forty-four subjects were screened at 10 investigational sites. Forty-two subjects were randomized and 37 subjects (88%) completed treatment. Five subjects were discontinued from the study for protocol violation, withdrawn consent, and other. The disposition of the subjects enrolled in Study SMS20010 with explanation of the protocol violations and 'other' reasons are shown below in Table 7.

Table 7 Subject Disposition for Study SMS20010

	Salmeterol 25mcg BID	Salmeterol 25mcg TID	Salmeterol 50mcg BID	Placebo
Randomized (N=42)				
Completed (N=37)				
Discontinued (N=5)				
AE (N=0)	0	0	0	0
Protocol Violation (N=2)	2*	0	0	0
Consent withdrawn (N=1)	0	0	1	0
Lost to follow-up (N=0)	0	0	0	0
Other (N=2)	0	1**	0	1**

*abnormal baseline ECG; concomitant medication violation
**inadequate Holter data
Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 52, 100

10.1.1.2.2 Protocol Violations

Twenty-four percent (N=10) of subjects reported at least one protocol violation. The most common protocol violation was concurrent medication violation (N=4). Other protocol violations included: abnormal baseline ECG, Holter monitor violation (2); no washout between Visit 3 and Visit 4, Visit 5 ECG not done, and unable to get labs at Visit 3 and Visit 5 [N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 219-220].

10.1.1.2.3 Demographics and Baseline Characteristics

The mean age for subjects was 35.3 months with a minimum age of 24 months and a maximum age of 47 months. Fifty percent of the children were 24-36 months and the other 50% were 37-47 months. There were more males (67%) than females (33%). The majority of subjects did not use ICS (76%). The majority of subjects were White (69%) and 10% Asian, 12% Black, and 10% Hispanic. Fifty-two percent of the subjects were assigned to the (b) (4) while 48% were assigned to the (b) (4) [N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 107-108].
Reviewer's Comment: The above age data were based upon screening data. The Applicant also presented the age data at time of randomization. One subject moved from the 24-36 month age group to the 37-47 month age group.

The most common concurrent medical conditions were in the allergies (40%), skin (26%) and ENT (19%) body systems. Twenty-six (62%) of subjects reported concurrent asthma medication use: 15 (36%) sodium cromoglycate, 12 (29%) corticosteroid, and 2 (5%) expectorants. Eight subjects (19%) used corticosteroids for reasons other than asthma (e.g. exzema or allergic rhinitis) [N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 118].

10.1.1.2.4 Efficacy

Efficacy was a secondary objective of Study SMS20010. However, some efficacy variables were measured – asthma symptom scores, PEF, rescue medication use. The study was not powered to demonstrate efficacy. The results for the efficacy variables will be briefly described. In general, treatment compliance was high and similar across treatments with the mean

compliance ranging from 92.3% to 97.7% compliance [N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 123].

Asthma Symptom Scores

Asthma symptom scores were recorded by the guardian/parent on the diary card twice daily using a four point symptom scale that ranged from 0 (no symptoms) to 3 (severe symptoms). Baseline symptoms scores were defined as the average of the values during the run-in period. The specified asthma symptom score endpoint was the change from baseline in individual daytime and night-time asthma symptom scores over each treatment period. Changes in asthma symptoms were minimal. The placebo group demonstrated the largest decrease (improvement) in daytime asthma symptoms, while the salmeterol 25mcg TID group demonstrated the largest decrease (improvement) in nighttime asthma symptoms; however, it should be noted that the placebo group had a similar improvement in nighttime asthma symptoms. The results are shown below in Table 8.

Table 8 Mean Daytime and Nighttime Asthma Symptom Scores, Study SMS20010

	Salmeterol 25mcg BID (n=21)	Salmeterol 25mcg TID (n=19)	Salmeterol 50mcg BID (n=19)	Placebo (n=20)
Baseline				
Daytime	0.73	0.81	0.64	0.96
Nighttime	0.58	1.01	0.44	0.75
During Treatment				
Daytime	0.50	0.76	0.59	0.55
Nighttime	0.41	0.79	0.51	0.57
Change from Baseline				
Daytime	-0.23	-0.05	-0.06	-0.42
Nighttime	-0.17	-0.22	0.07	-0.19

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 55

Reviewer's Comment: Based on the mean asthma symptom scores, the placebo group showed a numerically greater improvement in asthma symptom scores than the salmeterol treatment groups. Of the three salmeterol treatment groups, the salmeterol 25mcg BID group showed a numerically greater improvement in asthma symptom scores than the other two treatment groups. However, it should be noted that the study was not powered to show a difference between treatment groups. In addition, it is unclear what effect the baseline values have on the change from baseline.

Peak Expiratory Flow

PEF were recoded by the parent/guardian in the patient diary twice daily. The efficacy endpoint was the change from baseline in PEF in subjects capable of performing the maneuver, where baseline was defined as the average of the PEF values during the run-in period. Similar to the asthma symptom scores, there were minimal changes in PEF between treatment groups. As shown below in Table 9, the placebo and 25 mcg salmeterol BID group demonstrated the largest increase (10 to 14 L/min) in mean morning and evening PEF.

Table 9 Mean Morning and Evening PEF (L/min), Study SMS20010				
	Salmeterol 25mcg BID (n=13)	Salmeterol 25mcg TID (n=8)	Salmeterol 50mcg BID (n=12)	Placebo (n=9)
Baseline				
Morning	94	88	93	114
Evening	98	90	100	119
During Treatment				
Morning	106	90	100	127
Evening	112	99	102	129
Change from Baseline				
Morning	12	2	7	14
Evening	14	10	2	10
Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 56				

Reviewer's Comment: Based on the mean PEF, the placebo group showed a similar numerical increase in PEF as the salmeterol 25mcg BID treatment group. However, it should be noted that the study was not powered to show a difference between treatment groups. In addition, it is unclear what effect the baseline values have on the change from baseline.

Rescue Medication use

Rescue medication use was recorded in the patient diary by the parent/guardian. The efficacy endpoint was the change from baseline in rescue medication use. The change from baseline in rescue medication use was small. The largest decrease in rescue medication use was in the placebo group.

Table 10 Mean Daily Albuterol Use (Number of Puffs), Study SMS20010				
	Salmeterol 25mcg BID (n=21)	Salmeterol 25mcg TID (n=19)	Salmeterol 50mcg BID (n=19)	Placebo (n=20)
Baseline	1.07	1.46	0.93	1.78
During Treatment	0.54	1.27	0.57	0.67
Change from Baseline	-0.53	-0.19	-0.36	-1.10
Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 56				

Reviewer's Comment: Based on rescue medication use, the placebo group showed a numerically greater decrease in rescue medication use than the salmeterol treatment groups. Of the three salmeterol treatment groups, the salmeterol 25mcg BID group showed a numerically greater decrease in rescue medication use than the other two treatment groups. However, it should be noted that the study was not powered to show a difference between treatment groups. In addition, it is unclear what effect the baseline values have on the change from baseline.

Functional Status II (R) Questionnaire (FSII(R))

The FSII(R) was utilized to assess the health status of the subjects. The FSII(R) was administered at baseline and following each 7 day treatment period. The FSII(R) was scored by summing the item scores and normalizing on a scale of 0 (worst functioning) to 100 (best functioning). As shown below in Table 11, there was a high pre-treatment baseline FSII(R)

score and minimal change from baseline in FSII(R) Scores following treatment [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 58].

Table 11 Baseline, Treatment, and Change from Baseline Total Scores for FSII(R) Questionnaires

	Salmeterol 25mcg BID		Salmeterol 25mcg TID		Salmeterol 50mcg BID		Placebo	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline								
All subjects	21	92	19	87	19	95	20	90
Same parent/guardian	18	93	16	87	15	95	17	88
Treatment (Actual value)								
All subjects	21	92	19	91	18	96	20	92
Same parent/guardian	18	92	16	89	15	96	17	93
Treatment (Change from Baseline)								
All subjects	21	-0.3	19	4	18	1	20	2
Same parent/guardian	18	-0.8	16	3	15	0.7	17	5

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 59

Reviewer's Comment: The results above are shown for the total group and the same-parent subset (same parent/guardian completing the FSII(R) at each visit). In general, the results for the two populations were similar with the exception of the placebo group, in which the same-parent subset had a numerically greater change from baseline FSII(R) score.

The Applicant also looked at individual item scores to assess for potential beta mediated effects. Item scores that could suggest signs and symptoms of adrenergic stimulation included: "sleep well", "act moody", "unusually irritable", "sleep through the night", and "react by crying". In general, most of these item scores showed a numerical increase (improvement) during treatment in the placebo and salmeterol treatment groups [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 58, 136, 137].

Efficacy Conclusion

Study SMS20010 was not powered to demonstrate efficacy, thus no inferential statistics were performed by the Applicant. The results for asthma symptom scores, PEF and rescue medication use were briefly described. In general, the changes in asthma symptom scores, PEF, and rescue albuterol use were minimal and likely not clinically meaningful. The asthma symptom scores and rescue medication use data appeared to favor the placebo group; however, because the study was not powered to demonstrate efficacy and because the effect of baseline values were not accounted for, no definitive conclusions can be made regarding efficacy in Study SMS20010.

10.1.1.2.5 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A summary of the safety findings from this study follows.

Exposure

As shown below in Table 12, study medication exposure was similar between treatment groups.

Table 12 Study Medication Exposure				
	Salmeterol 25mcg BID (n=21)	Salmeterol 25mcg TID (n=19)	Salmeterol 50mcg BID (n=19)	Placebo (n=20)
Number of Days				
<7	0	0	1 (5%)*	0
7-11	19 (90%)	18 (95%)	17 (89%)	20 (100%)
>11	2 (10%)	1 (5%)	1 (5%)	0

*Subject withdrew consent and did not complete treatment
Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 64

24 –Hour Heart Rates

Heart rates were analyzed from the Holter monitor data performed at baseline and at the end of each treatment period. The heart rate data for 6 hour intervals were analyzed in addition to the 24 hour overall period. Table 13 below summarizes the 24 hour mean heart rate data at baseline and during treatment. There were no clinically significant changes in mean heart rate from baseline. The salmeterol 50mcg BID treatment group demonstrated the greatest numerical increase from baseline at 2.2 beats per minute

Table 13 Mean 24-Hour Heart Rates – Holter Monitoring (beats/min)									
Treatment	Baseline			During Treatment			Change from Baseline		
	N	Mean	Min; Max	N	Mean	Min; Max	N	Mean	Min; Max
Placebo	19	109	63;184	19	105	61;182	19	-4.6	-2.1;-2.3
Salmeterol 25mcg BID	21	109	65;182	19	110	66;181	19	0.4	0.6; -1.7
Salmeterol 25mcg TID	19	111	64; 188	18	110	65; 191	18	-0.7	1.0; 2.3
Salmeterol 50mcg BID	19	107	62; 181	15	109	64; 182	15	2.2	2.6; 0.3

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 60

Reviewer's Comment: Data for subjects with fever during the Holter monitoring were not included above (n=5).

In general, the number of subjects with ectopic ventricular events at baseline was low and varied between treatment groups from 1 to 4. There was no significant increase in the number of subjects with single ventricular ectopic events during treatment. However, there were four subjects with ventricular ectopic couplets on treatment in the salmeterol treatment groups as shown below in Table 14. There were no subjects with runs of ventricular ectopic events in any treatment group.

Table 14 Number of Subjects with Ventricular Ectopic (VE) Events – Holter Monitoring								
	Baseline				During Treatment			
	N	Single VEs	VE couplets	VE Runs	N	Single VEs	VE couplets	VE Runs
Placebo	19	4	0	0	19	6	0	0
Salmeterol 25mcg BID	21	2	0	0	19	2	1	0
Salmeterol 25mcg TID	19	4	0	0	18	5	1	0
Salmeterol 50mcg BID	19	1	0	0	15	1	2	0
Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 61								

Reviewer's Comment: The change from baseline in number of VEs in 24 hours ranged from -2 to 6 in the placebo group; -1 to 10 in the salmeterol 25mcg BID group; -1 to 3 in the salmeterol 25mcg TID treatment group; and 0 to 13 in the salmeterol 50mcg BID treatment group [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 147].

The number of supraventricular ectopic events was low at baseline and did not increase during treatment as shown below in Table 15.

Table 15 Median Number of Supraventricular Ectopic Events – Holter Monitoring									
Treatment	**Baseline**			**During Treatment**			**Change from Baseline**		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	19	1	0;6	19	0	0;1	19	-1	-5; 1
Salmeterol 25mcg BID	21	0	0; 5	19	1	0; 4	19	0	-5; 3
Salmeterol 25mcg TID	19	1	0; 6	18	0	0; 4	18	-1	-6; 3
Salmeterol 50mcg BID	19	1	0; 5	15	1	0; 3	15	-1	-3; 1
Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 61									

Reviewer's Comment: The Applicant also analyzed the data for the subset of subjects with > 18 hours of Holter monitoring data and the results are similar to what is shown above for heart rate, ventricular ectopic events, and supraventricular ectopic events.

Electrocardiograms (ECGs)

A 12 lead ECG was recorded at screening (Visit 1) and at the end of each of the treatment periods (Visits 3 and 5). No abnormal ECGs were reported during the treatment period. There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval as shown below in Table 16. No QTcF intervals were ≥ 440msec and no subject had an increase in QT interval >30msec. One subject in the placebo group had an increase in QTcF >30msec [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 160-166].

Table 16 Mean QT, QTcF, QRS Duration, PR Intervals at Baseline, During Treatment, and Change from Baseline (msec)

	Placebo		Salmeterol 25mcg BID		Salmeterol 25mcg TID		Salmeterol 50mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
QT Interval								
Screening	20	302	21	299	19	304	19	303
End of Treatment	18	298	19	300	18	289	16	293
Change from Baseline	18	-4.2	19	1.6	18	-14.3	16	-11.3
QTcF Interval								
Screening	20	366	21	366	19	367	19	363
End of Treatment	18	363	19	366	18	359	16	358
Change from Baseline	18	-3.5	19	-0.1	18	-8.2	16	-5.1
QRS Duration								
Screening	20	66	21	63	19	64	19	63
End of Treatment	18	67	19	64	18	66	16	64
Change from Baseline	18	0.7	19	1.4	18	2.4	16	0.9
PR Intervals								
Screening	20	121	21	114	19	121	19	114
End of Treatment	18	122	19	113	18	115	16	112
Change from Baseline	18	-0.6	19	-0.1	18	-5.2	16	-3.9

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 63

Mean heart rate values as measured via ECGs were similar at baseline across treatment groups (108-111bpm). Both the salmeterol 25mcg TID and salmeterol 50mcg BID demonstrated slight increases in mean heart rate at the end of treatment with 118bpm and 112bpm, respectively [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 64].

Adverse Events

There were no deaths or SAEs in this study. No subjects discontinued due to AEs. Thirty subjects reported at least one AE during the study for a total of 66 AEs. Adverse events that occurred during the washout period were assigned to the treatment received during the preceding treatment period. The most frequently reported AEs were URI and tremors and both were more common in the salmeterol treatment groups. Ear, nose, and throat infections, appetite disturbance, and gastrointestinal discomfort were also reported in two or more subjects in the salmeterol groups and no subjects in the placebo group. Table 17 displays a summary of adverse events reported in >3% of subjects in each of the treatment groups and more common in the salmeterol treatment groups than in the placebo group.

Table 17 Adverse Events >3% Incidence and More Common than Placebo

Number of Subjects with Adverse Event	Placebo (N=20) n(%)	Salmeterol 25mcg BID (N=21) n(%)	Salmeterol 25mcg TID (N=19) n(%)	Salmeterol 50mcg BID (N=19) n(%)
Any Event	11 (55)	11(52)	7 (37)	11 (58)
URI	1 (5)	2 (10)	2 (11)	4 (21)
Tremors	1 (5)	2 (10)	0	2 (11)
Epistaxis	1 (5)	1 (5)	1 (5)	0
Ear, nose, & throat infections	0	1 (5)	1 (5)	2 (11)
Gastrointestinal discomfort & pain	0	0	1 (5)	2 (11)
Rhinorrhea/PND	1 (5)	0	0	1 (5)
Appetite disturbances	0	0	1 (5)	2 (11)
Larynx disorders	0	0	0	1 (5)
Nasal congestion/blockage	0	1 (5)	0	0
Pharyngitis/throat infection	0	1 (5)	0	0
Sinusitis	0	0	1 (5)	0
Headaches	0	1 (5)	0	0
Hypnagogic effects	0	0	1 (5)	0
Psychomotor restlessness	0	0	0	1 (5)
Sleep disorders	0	1 (5)	0	0
Nausea & vomiting	1 (5)	0	1 (5)	0
Skin rashes	0	1 (5)	0	1 (5)
Photodermatitis	0	0	0	1 (5)
Musculoskeletal	0	0	0	1 (5)

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 66

Reviewer's Comment: The Applicant also presented the AEs attributed to study medication. The only AE reported in more than one subject and attributed to study medication was tremor. Three tremor AEs were reported in 2 subjects, 1 in the placebo group and 2 in the salmeterol 25mcg BID treatment group. The tremor intensity was mild [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 67].

Laboratory Evaluations

Laboratories were drawn at baseline and post-treatment during Visits 3 and 5. Shift table data were presented and reviewed. For hematology parameters, the majority of subjects had no shift or shifted to normal range for hemoglobin, hematocrit, WBC, or platelets. Two subjects were noted to have a change in hematocrit from normal to low (1 placebo, 1 salm 25mcg TID). Four subjects were noted to have a change in platelets from normal to low (1 placebo, 2 salm 25mcg BID, 1 salm 25mcg TID). One subject was noted to have a decrease in WBC from normal to low (salm 50mcg BID). The Applicant defined thresholds for laboratory values and reported the incidence of hematology parameters outside the thresholds as shown below [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 68, 191].

Table 18 Incidence of Hematology Parameters Outside Defined Threshold Values at Any Visit Post-Baseline

Hematology Parameter	Placebo (N=20) n(%)	Salmeterol 25mcg BID (N=21) n(%)	Salmeterol 25mcg TID (N=19) n(%)	Salmeterol 50mcg BID (N=19) n(%)
Hemoglobin	1/16 (6)	1/14 (7)	0	0
RBC	1/16 (6)	0	1/16 (6)	1/17 (6)
Platelets	0	0	1/16 (6)	0
Neutrophils	1/16 (6)	1/14 (7)	0	1/16 (6)
Lymphocytes	1/16 (6)	0	0	0
Monocytes	0	1/14 (7)	2/16 (13)	0
Eosinophils	3/16 (19)	1/14 (7)	4/16 (25)	0

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 68, 258-261

Reviewer's Comment: Eosinophil count was the hematology parameter that was most frequently noted outside the pre-specified threshold value. It should be noted that five subjects had elevated eosinophil counts outside the pre-specified threshold value. Four of these subjects were noted to have an eosinophil count outside the threshold value at screening or following placebo.

Reviewer's Comment: The hematology data does not suggest a safety signal.

For chemistry, the majority of subjects had no shift or shifted to normal range for the chemistry parameters. The following shifts are worth noting: a) a shift to low bicarbonate was noted once in each of the salmeterol treatment groups; and b) a shift to high AST was noted in 4 subjects in the placebo group, 2 subjects in the salmeterol 25mcg TID group and in 1 subject in the salmeterol 50mcg BID group. Although some subjects had a shift to the low or high range for chemistry parameters, very few of these chemistry parameters were outside the pre-defined thresholds. Most chemistry parameters did not have any values outside the pre-defined threshold. The incidence of chemistry parameters outside the thresholds are shown below. The placebo group had the most chemistry parameters outside the pre-defined threshold [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 69, 187-191].

Table 19 Incidence of Chemistry Parameters Outside Defined Threshold Values at Any Visit Post-Baseline

Chemistry Parameter	Placebo (N=20) n(%)	Salmeterol 25mcg BID (N=21) n(%)	Salmeterol 25mcg TID (N=19) n(%)	Salmeterol 50mcg BID (N=19) n(%)
Bicarbonate	0	1/15 (7)	0	0
Albumin	1/16 (6)	0	0	1/17 (6)
Alkaline phosphatase	2/16 (13)	1/13 (8)	0	0
Uric acid	2/16 (13)	0	2/16 (13)	0

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 69

The Applicant further analyzed the glucose data. Although 16 subjects had glucose values outside the normal range, none of the values met the pre-defined threshold values (<45 mg/dL,

>300 mg/dL). Nine subjects had a low glucose value (3 at screening or placebo, 2 salmeterol 25mcg BID, 3 with salmeterol 25mcg TID, and 1 with salmeterol 50mcg BID). Seven subjects had a high glucose (2 at screening or placebo, 2 salmeterol 25mcg BID, 1 salmeterol 25mcg TID, 2 with salmeterol 50mcg BID). The glucose values were reviewed. Four subjects had glucose values ≥ 120mg/dL [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 69, 264-267]:

- 137mg/dL in subject 4032 – salmeterol 25mcg BID
- 120mg/dL in subject 4034 – salmeterol 25mcg BID
- 128mg/dL in subject 3981 – salmeterol 50mcg BID
- 123mg/dL in subject 4042 – salmeterol 50mcg BID.

The Applicant further analyzed the potassium data. No episodes of hypokalemia were observed. One subject was noted to have a high potassium at Visit 5 of 5.5mEq/L [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 69, 267].

Vital Signs and Physical Examinations

No significant changes in heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment as shown below in Table 20.

Table 20 Summary of Vital Signs

	Placebo		Salmeterol 25mcg BID		Salmeterol 25mcg TID		Salmeterol 50mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Systolic BP (mmHg)								
Prior to Start of Treatment	20	87	21	91	18	92	19	94
End of Treatment	18	90	19	88	18	92	18	94
Diastolic BP (mmHg)								
Prior to Start of Treatment	20	56	21	57	18	59	19	59
End of Treatment	18	57	20	55	18	56	18	57
Pulse Rate (bpm)								
Prior to Start of Treatment	20	95	21	99	19	103	19	104
End of Treatment	18	96	20	97	19	105	18	106
Temperature (C)								
Prior to Start of Treatment	20	36	21	36	18	36	19	36
End of Treatment	18	36	20	37	19	36	18	37
Respiratory Rate (breaths/min)								
Prior to Start of Treatment	20	24	21	22	19	23	19	23
End of Treatment	18	23	20	22	19	23	18	23

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 70

Physical examinations were performed at baseline and end of study. Abnormalities in physical examination (excluding asthma and asthma related symptoms) were noted in two subjects and were URI and bronchitis. [N20236\2005-12-21\sms20010-03-protocol-amend-2.pdf, pg 70].

Physicians specifically assessed for tremor. Only four incidences of tremor were noted post-dose as shown below in Table 21. One of the post-dose tremors was in the placebo group. All the tremors were noted to be mild in severity.

Table 21 Summary of Physician's Assessment of Tremor

	Placebo (N=20) n(%)	Salmeterol 25mcg BID (N=21) n(%)	Salmeterol 25mcg TID (N=19) n(%)	Salmeterol 50mcg BID (N=19) n(%)
Start of Treatment Period				
Pre-dose				
No tremor present	20 (100)	21(100)	19 (100)	17 (89)
Mild tremor present	0	0	0	2 (11)
Post-dose				
No tremor present	19 (95)	20 (95)	19 (100)	18 (95)
Mild tremor present	1 (5)	1 (5)	0	1 (5)
End of Treatment Period				
No tremor present	19 (100)	19 (95)	19 (100)	18 (100)
Mild tremor present	0	1 (5)	0	0

Source: N20236\2005-12-21\sms20010-01-body-csr.pdf, pg 71

Safety Conclusions

In general, the safety data from Study SMS20010 do not suggest a new safety signal for any of the doses of salmeterol administered in this study.

In terms of cardiovascular safety, the Holter monitor data showed that there no clinically significant changes in mean heart rate, single ventricular ectopic or supraventricular ectopic events during treatment. However, there were 4 subjects with ventricular ectopic couplets on treatment in the salmeterol treatment groups and none in the placebo group. There were no subjects with runs of ventricular ectopic events in any treatment group. No abnormal ECGs were reported during the treatment period. There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval.

There were no deaths or SAEs in this study. No subjects discontinued due to AEs. Thirty subjects reported at least one AE during the study for a total of 66 AEs. The most frequently reported AEs were URI and tremors and both were more common in the salmeterol treatment groups. Two-four subjects reported URI in the salmeterol group compared to one subject in the placebo group. Two subjects reported tremors in the salmeterol 25mcg BID and 50mcgBID treatment group compared to one subject in the placebo group. Ear, nose, and throat infections, appetite disturbance, and gastrointestinal discomfort were also reported in two subjects in the salmeterol groups and no subjects in the placebo group.

In terms of laboratory assessments, although 16 subjects had glucose values outside the normal range, none of the values met the pre-defined threshold values (<45 mg/dL, >300 mg/dL). Four subjects in the salmeterol treatment groups had glucose values ≥ 120mg/dL. No episodes of hypokalemia were observed.

No significant changes in heart rate, blood pressure, temperature, or respiratory rate were noted. Abnormalities in physical examination were noted in two subjects (URI and bronchitis). Only

four incidences of tremor were noted post-study medication. One of the post-dose tremors was in the placebo group. All the tremors were noted to be mild in severity.

10.1.1.2.6 Discussion and Conclusions

StudySMS20010 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, two-period, four-treatment crossover study of 3 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 24 to 47 months to primarily assess safety.

Study SMS20010 was not powered to demonstrate efficacy, thus no inferential statistics were performed by the Applicant. The results for asthma symptom scores, PEF and rescue medication use were briefly described. In general, the changes in asthma symptom scores, PEF, and rescue albuterol use were minimal and likely not clinically meaningful. The asthma symptom scores and rescue medication use data appeared to favor the placebo group; however, because the study was not powered to demonstrate efficacy and because the effect of baseline values were not accounted for, no definitive conclusions can be made regarding efficacy in Study SMS20010.

In general, the safety data from Study SMS20010 do not suggest a new safety signal for any of the doses of salmeterol administered in this study. In terms of cardiovascular safety, the Holter monitor data showed that there no clinically significant changes in mean heart rate, single ventricular ectopic or supraventricular ectopic events during treatment. However, there were 4 subjects with ventricular ectopic couplets on treatment in the salmeterol treatment groups and none in the placebo group. There were no subjects with runs of ventricular ectopic events in any treatment group. No abnormal ECGs were reported during the treatment period. There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval.

There were no deaths or SAEs in this study. No subjects discontinued due to AEs. Thirty subjects reported at least one AE during the study for a total of 66 AEs. The most frequently reported AEs were URI and tremors and both were more common in the salmeterol treatment groups. Two-four subjects reported URI in the salmeterol group compared to one subject in the placebo group. Two subjects reported tremors in the salmeterol 25mcg BID and 50mcgBID treatment group compared to one subject in the placebo group. Ear, nose, and throat infections, appetite disturbance, and gastrointestinal discomfort were also reported in two subjects in the salmeterol groups and no subjects in the placebo group.

In terms of laboratory assessments, although 16 subjects had glucose values outside the normal range, none of the values met the pre-defined threshold values (<45 mg/dL, >300 mg/dL). Four subjects in the salmeterol treatment groups had glucose values ≥ 120mg/dL. No episodes of hypokalemia were observed. No significant changes in heart rate, blood pressure, temperature, or respiratory rate were noted. Abnormalities in physical examination were noted in two subjects (URI and bronchitis). Only four incidences of tremor were noted post-study medication. One of the post-dose tremors was in the placebo group. All the tremors were noted to be mild in severity.

One issue to note is that although two holding chambers were utilized in this study, the results were not presented for the two holding chamber subpopulations.

10.1.2 Study SMS20011

A Five-Week, Randomized, Double-Blind, Double-Dummy, Two-Period, Four-Treatment Crossover, Placebo-Controlled, Balanced Incomplete Block Design, Multi-Center Study of Salmeterol Xinafoate Inhalation Aerosol and Placebo Administered via a Holding Chamber with Facemask in Subjects with Asthma Aged 6 to 23 Months

10.1.2.1 Protocol

The protocol for Study SMS20011 is very similar to the protocol for Study SMS20010 described in detail in Section 10.1.2.1.

Objective
The objective of Study SMS20011 is to evaluate the safety of 3 doses of salmeterol xinafoate inhalation aerosol over a 1-week treatment period in subjects with mild to moderate asthma aged 6 to 23 months.

Study Design
Study SMS20011 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, two-period, four-treatment crossover incomplete block design study of 3 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 24 to 47 months. Eligible subjects underwent a 7 day screening period at Visit 1. Subjects meeting entry criteria were randomized at Visit 2 to one of the following treatment groups for the first 7 day double-blind treatment period.

- Salmeterol xinafoate inhalation aerosol 25mcg BID
- Salmeterol xinafoate inhalation aerosol 25mcg TID
- Salmeterol xinafoate inhalation aerosol 50mcg BID
- Placebo MDI BID.

At Visit 3, subjects entered a 5 day washout period before Visit 4 when they received the second randomized treatment for 7 days. Subjects returned for Visit 5 to enter another 5 day washout period, followed by Visit 6 for end of study assessments [N20236\2005-12-21\20011_04protocol.pdf, pg 13].

Study Population
The following is a list of the pertinent inclusion criteria for the screening phase of SMS20011:

- Male or females 6 to 23 months of age
- An exacerbation of wheeze and cough within the preceding 6 months. In addition, subjects must also fulfill the following criteria prior to Visit 1
    - Have required therapy with a maintenance asthma medication (other than systemic corticosteroid) **and/or**

- Have required therapy with a short-acting beta-agonist for relief of respiratory symptoms at least twice per week over the preceding 3 weeks.

The following is a list of the pertinent inclusion criteria for the treatment phase of SMS20011:

- Parents/guardians comply with use of diary card on at least 80% of the days during the screening period
- Subject is able to use the MDI with holding chamber and facemask
- Subject has not experience a severe exacerbation during the screening period (ER visit or systemic corticosteroid use)
- Parent/guardian capable of supervising the Holter monitor.

The following is a list of the pertinent exclusion criteria for SMS20011:

- Life-threatening asthma (ICU admission) within previous 3 months
- Subjects treated in the ER or admitted to the hospital for airway obstruction on two more occasions within the previous 3 months
- Acute systemic corticosteroid therapy within 14 days of screening
- Chronic systemic corticosteroid therapy for > 4 weeks within 12 weeks of screening
- Use of methylphenidate/pemoline within 30 days prior to Visit 1
- Concurrent significant disease including the following: CF, bronchiectasis, BPD, pneumonia (3 months), ENT disorders requiring surgery (12 months), seizure disorder, reflux esophagitis (3 months), Cushing's Syndrome, renal disease, hematological disease, hepatic disease, malignancy, cellular or humoral immunity disorder, JRA, SLE, or other collagen vascular disease, inadequately controlled psychiatric disorder, DM, pan-hypopituitarism, hyperthyroidism, glaucoma, congenital heart disease
- Hypersensitivity to beta-agonists, component of MDI formulation, facemask, or adhesives
- Clinically significant laboratory abnormalities
- Recent bacterial or viral URI, LRI, sinus, or middle ear infection that is not resolved within 2 weeks prior to screening
- CXR abnormality not consistent with asthma

[N20236\2005-12-21\20011_04protocol.pdf, pg 13-17].

Materials

The parent/guardian for each subject received 3 canisters (A, B, and C). They were instructed to administer one inhalation from canister A and B in the AM and at bedtime, and one inhalation from canister C at mid-day as shown below [N20236\2005-12-21\20011_04protocol.pdf, pg 18-19].

- Salmeterol xinafoate inhalation aerosol 25mcg BID
  - One inhalation 25mcg (canister A or B) in AM and at bedtime
  - One inhalation placebo (canister A or B) in AM and at bedtime
  - One inhalation of placebo (canister C) at mid afternoon
- Salmeterol xinafoate inhalation aerosol 25mcg TID
  - One inhalation 25mcg (canister A or B) in AM and at bedtime
  - One inhalation placebo (canister A or B) in AM and at bedtime

    - One inhalation of 25mcg (canister C) at mid afternoon
- Salmeterol xinafoate inhalation aerosol 50mcg BID
    - One inhalation 25mcg (canister A or B) in AM and at bedtime
    - One inhalation 25mcg (canister A or B) in AM and at bedtime
    - One inhalation of placebo (canister C) at mid afternoon
- Placebo MDI BID
    - One inhalation placebo (canister A or B) in AM and at bedtime
    - One inhalation placebo (canister A or B) in AM and at bedtime
    - One inhalation of placebo (canister C) at mid afternoon

All study medication was administered via holding chamber and facemask. All subjects were administered treatments via the (b) (4) holding chamber. Rescue medication was supplied as albuterol MDI and nebules.

Concomitant Therapy

The following medications were prohibited during the course of the study [N20236\2005-12-21\20011_04protocol.pdf, pg 20-21]:

- Beta-adrenergic agonists
- Systemic corticosteroids
- Beta-adrenergic antagonists
- Anti-cholinergics e.g. (ipratropium bromide)
- Theophylline or aminophylline
- Leukotriene antagonists
- Antiarrythmics
- Anticonvulsants
- CNS stimulants
- Oral antihistamines
- Systemic decongestants
- Narcotic or non-narcotic cough suppressants
- Immunosuppressives

Study Conduct

Informed consent was obtained prior to any screening or treatment study procedures being performed. Screening evaluations were performed at Visit 1. Subjects and guardians/parents were instructed on the proper completion of the diary card and proper administration of the MDI and nebules. Subjects underwent a 7 (+/- 2) day run-in period. During the 7 day run-in period, all SABA were discontinued and replaced with albuterol MDI or nebules.

At Visit 2, eligibility criteria were reviewed and if subjects were eligible, they were randomized in a 1:1:1:1 fashion to one of the four treatment groups for a 7 day double-blind treatment period. At Visit 3, subjects entered a 5 day washout period before Visit 4 when they received the second randomized treatment for 7 days. Subjects returned for Visit 5 to enter another 5 day washout period, followed by Visit 6 for end of study assessments. Throughout the treatment period, parents/guardians completed diary cards (symptoms) and recorded rescue medication use. Study medication was administered in the clinic during Visits 2 and 4. Table 22 displays the study assessments performed at each clinic visit. If subjects discontinued the study early, the investigator was to make an effort to perform the end of study evaluations [N20236\2005-12-21\20011_04protocol.pdf, pg 52].

Table 22 SMS 20011 Study Assessments

Visit	1	2	3	4	5	6	
Days since prior Visit		7 ±2 days	7 +4 days	5 ±2 days	7 +4 days	5 ±2 days	Premature Discontinuation
Procedure							
Informed Consent	X						
Review Holter data		X	X		X		
AE assess		X	X	X	X	X	X
Administer FSII(R)		X	X		X		X[c]
Med History	X						
Con Meds	X	X	X	X	X	X	X
Tremor Assess	X	X[a]	X	X[a]	X	X	X
Physical exam	X					X	X
Vital signs	X	X	X	X	X	X	X
ECG	X		X		X		X
Review Diary Assessments		X	X	X	X	X	X
Dispense/collect diary cards and review instructions	X	X	X	X	X	X	X
Review MDI technique	X	X		X			
Dispense/collect albuterol	X	X	X	X	X	X	X
Dispense/collect double blind study medication		X	X	X	X		X
24 hr Holter monitoring	Day prior to Visit 2	Day prior to Visit 3		Day prior to Visit 5			
Lab Tests	X[b]		X		X		X

a. Evaluated pre-dose and one hour post dosing of study medication.
b. Subjects will have a lab assessment at Visit 1 unless there is historical evidence of a normal lab assessment within 3 months of Visit 1 that includes both blood glucose and serum potassium and the subject has had no change in medical status since that assessment.
c. Administer FSII(R) at premature discontinuation only if the premature discontinuation occurs between Visit 2 and Visit 3 or between Visit 4 and Visit 5.

Source: N20236\2005-12-21\20011_04protocol.pdf, pg 52

Efficacy

Some efficacy measures were specified in the protocol. Efficacy measures included individual daytime and night-time asthma symptom scores, withdrawals due to asthma exacerbations, and

rescue medication use. Each efficacy measure will be briefly discussed [N20236\2005-12-21\20011_04protocol.pdf, pg 28-29].

- **Asthma symptoms scores**
  - Endpoint – change from baseline in individual daytime and night-time asthma symptom scores over each treatment period
  - Based upon parent/guardian's rating of subject's symptoms on diary card recorded twice daily using the following scale
  - **Night symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with sleep
    - 2 Moderate; awakened once or more because of asthma symptoms
    - 3 Severe; awake most of the night due to asthma symptoms
  - **Day symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with daily activities
    - 2 Moderate; symptoms present often, causing some interference with daily routine and activities
    - 3 Severe; symptoms continuous or present most of the day, restricting daily routine and activities severely
- **Rescue medication use (Ventolin use)**
  - As recorded on diary card
- **Withdrawal due to asthma exacerbation**
  - Asthma exacerbation defined as an increase in asthma signs and symptoms that, in the opinion of the investigator, require an excluded medication including a course of systemic corticosteroids or the subject's disease is unstable and the study drug is not efficacious

In addition the Functional Status II(R) questionnaire (FSII(R)) was utilized to assess the health status of the subjects. The FSII(R) is an interviewer administered questionnaire which contains 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention during the previous two-week period. The FSII(R) was modified to assess the behavior during the previous week. Each item was scored on a three-point scale indicating the frequency with which a child exhibits the specified behavior or performs the specified activity. A second level of responses evaluated to what extent poor functioning indicated in the first level of questioning is related to the child's illness. The items are summed and a total score is calculated as the percent of total possible scores. Higher scores reflect a better functional status. The FSII(R) was administered at baseline and following each 7 day treatment period [N20236\2005-12-21\20011_04protocol.pdf, pg 29-30].

Safety

Safety assessments included Holter monitoring (heart rate), adverse events, physical examination, laboratories, ECGs, physician's assessment of tremor and symptoms of adrenergic stimulation (irritability and lack of sleep) from the FSII(R) questionnaire. Each safety measure will be briefly discussed [N20236\2005-12-21\20011_04protocol.pdf, pg 30-34].

- **Holter monitoring**

  - A 24 hour Holter monitor was conducted prior to randomization at Visit 2. Repeat Holter monitors were conducted one day prior to the completion of each treatment period (i.e. one day prior to Visit 3 and 5). If the Holter monitor was inadequate (<12 hours of recording), a single repeat attempt was initiated.
  - If the subject developed a fever, the baseline Holter session was repeated. However, the Holter sessions at the end of the treatment periods were not repeated. The fever was noted as an AE.
- **Physical examination**
  - A physical exam was performed at screening (Visit 1) and end of study (Visit 6)
- **Vital signs**
  - A set of vital signs (HR, BP, T, RR) was measured at each study visit
- **Adverse Events**
  - Adverse events were collected via the diary card and were reviewed at each study visit
- **ECG**
  - A 12 lead ECG was recorded at screening (Visit 1) and at the end of each of the treatment periods (Visits 3 and 5).
  - An independent electrocardiographer, blinded to treatment assignment, provided measurements of heart rate, PR interval, QTc interval, QRS duration, and an overall interpretation of each ECG collected
  - Criteria were specified in the protocol for an abnormal ECG. Inclusion criteria specified subjects must have a normal screening ECG
  - The ECGs collected at Visits 3 and 5 were compared to the screening ECG to determine if a clinically significant change occurred.
- **Laboratories**
  - Chemistry, hematology, and electrolytes were performed at Visit 1 (if indicated), Visit 3, and Visit 5
  - Baseline labs within previous 3 months were acceptable
- **Tremor assessments**
  - Tremor was evaluated by the investigator at each visit. When study drug was administered during Visits 2 and 4, tremor was assessed pre-dose and one hour post-dose.
  - Tremor was graded on the following scale
    - 0 – no tremor present
    - 1 – mild tremor present
    - 2 – moderate tremor present
    - 3 - severe tremor present

Data Analysis

According to the protocol, Thirty-six (36) completed subjects (three replicates of a balanced, incomplete block design) ensured that each treatment was represented within 18 of the 36 subjects. The subjects were recruited at ten study sites in the United States. One block contained three subjects, therefore the planned number of subjects per site was 3 to 6. In an effort to ensure treatment balance within the two age ranges: 6-11 months old and 12-23 months old, the

randomization was stratified at a ratio of 1:2 into these two groups [N20236\2005-12-21\20011_04protocol.pdf, pg 35].

Efficacy measures were specified as follows; however, no statistical analyses were specified [N20236\2005-12-21\20011_04protocol.pdf, pg 37].

- **Asthma symptoms scores** - change from baseline in individual daytime and night-time asthma symptom scores over each treatment period. Baseline was defined as the average of the values during the run-in period.
- **Rescue medication use –** change from baseline in rescue medication use
- **FSII(R) –** change from baseline in total scores at Visits 3 and 5. Baseline was defined as the assessment at Visit 2.

The primary endpoint (safety) was the effect of study drug following 7(+4) days of therapy on 24 hour heart rate, obtained via Holter monitoring, including mean, peak, and trough heart rate. Baseline was defined as the measurement from Visit 2. Secondary safety endpoints included ECGs, AEs, vital signs, laboratories, and physician's assessment of tremor.

Amendments

One amendment was made to the original protocol (March 14, 2002). The following is a brief summary of the amendment [N20236\2005-12-21\20011_04protocol.pdf, pg 110].

- Increase participating centers from 10 to 20
- Amend exclusion criteria to allow subjects with reflux esophagitis who are well controlled and no longer contributing to subject's asthma symptoms
- Allow study visits to be conducted outside the 6-10AM window as long as they occur at a consistent time with regard to Visit 1
- Amend the requirement of 12 lead ECG with a one minute rhythm strip to recording of 12-lead ECG with a 30 second rhythm strip

10.1.2.2 Results

Study SMS20011 was initiated August 1, 2001, and completed September 27, 2002. The final study report is dated April 28, 2003. The drug supplies for the study were salmeterol xinafoate inhalation aerosol 25mcg from batch identification numbers 9ZP1830 and 0ZM2891 and placebo inhalation aerosol from batch identification numbers 9ZP1829 and 0ZM2887. Ventolin CFC MDI was from batch 0ZP0115 and the albuterol nebules were from batch 2A31. Proventil was from batches 0MYW610 and 1MYW565 [N20236\2005-12-21\20011_02csr.pdf, pg 1 & 22].

10.1.2.2.1 Subject Disposition

Forty-four subjects were screened at 10 investigational sites. Forty-five subjects were randomized and 35 subjects (78%) completed treatment. Ten subjects were discontinued from the study for AE, protocol violation, withdrawn consent, lack of efficacy, and other. The disposition of the subjects enrolled in Study SMS20011 with explanation of the protocol violations and 'other' reasons are shown below in Table 23.

Table 23 Subject Disposition for Study SMS20011

	Salmeterol 25mcg BID	Salmeterol 25mcg TID	Salmeterol 50mcg BID	Placebo
Randomized (N=45)				
Completed (N=35)				
Discontinued (N=10)				
AE (N=1)	0	1	0	0
Protocol Violation (N=1)	0	1*	0	0
Lack of efficacy (N=1)	0	0	0	1
Consent withdrawn (N=4)	2	1	1	1
Lost to follow-up (N=1)	0	1	1	0
Other (N=2)	1**	0	1***	0

* concomitant medication violation; **abnormal laboratory; ***noncompliance with study visit attendance
Source: N20236\2005-12-21\20011_02csr.pdf, pg 46, 84-89

10.1.2.2.2 Protocol Violations

Thirty-one percent (N=14) of subjects reported at least one protocol violation. The most common protocol violations were concurrent medication violation (N=7) and other (N=6). Other protocol violations included: use of own supply of albuterol, did not meet exclusion criteria for recent infection, less than 12 hours of Holter monitoring data, treatment duration > 20 days, and Visit 5 out of specified window [N20236\2005-12-21\20011_02csr.pdf, pg 47].

Treatment blind was broken for two subjects (Inv 50645/Subject 13410, Salm 25mcg TID treatment and Inv 7059/Subject13343), placebo/Salm 25mcg TID treatments). Subject 13410 had an abnormal Holter recording and was withdrawn from the study. The blinding label flaked off for Subject 13343 [N20236\2005-12-21\20011_02csr.pdf, pg 47].
Reviewer's Comment: The broken blind of two subjects is unlikely to affect the results of the study.

10.1.2.2.3 Demographics and Baseline Characteristics

The mean age for subjects was 14.6 months with a minimum age of 6 months and a maximum age of 23 months. Forty percent of the children were 6 to 11 months and the other 60% were 12-24 months. There were more males (76%) than females (24%). The majority of subjects did not use ICS (76%). The majority of subjects were White (51%) with 31% Black, 11% Hispanic, and 7% other ethnic origin [N20236\2005-12-21\20011_02csr.pdf, pg 48, 94].

The most common concurrent medical conditions were in the allergies (24%), skin (24%) and ENT (44%) body systems. Thirty-one (69%) of subjects reported concurrent asthma medication use: 17 (38%) salbutamol, 7 (16%) sodium cromoglycate, and 14 (31%) corticosteroid. Seven subjects (18%) used corticosteroids for reasons other than asthma (e.g. exzema or allergic rhinitis) [N20236\2005-12-21\20011_02csr.pdf, pg 48, 96, 101].

10.1.2.2.4 Efficacy

Efficacy was a secondary objective of Study SMS20011. However, some efficacy variables were measured – asthma symptom scores and rescue medication use. The study was not powered to demonstrate efficacy. The results for the efficacy variables will be briefly described. In general, treatment compliance was high and similar across treatments with the mean compliance ranging from 85% to 91% compliance [N20236\2005-12-21\20011_02csr.pdf, pg 48].

Asthma Symptom Scores

Asthma symptom scores were recorded by the guardian/parent on the diary card twice daily using a four point symptom scale that ranged from 0 (no symptoms) to 3 (severe symptoms). Baseline symptoms scores were defined as the average of the values during the run-in period. The specified asthma symptom score endpoint was the change from baseline in individual daytime and night-time asthma symptom scores over each treatment period. Changes in asthma symptoms were minimal. The salmeterol 25mcg BID and 25mg TID treatment groups demonstrated the largest decrease (improvement) in asthma symptoms; however, it should be noted that the placebo group had a similar improvement in daytime asthma symptoms. The results are shown below in Table 24.

Table 24 Mean Daytime and Nighttime Asthma Symptom Scores, Study SMS20011

	Salmeterol 25mcg BID (n=21)	Salmeterol 25mcg TID (n=21)	Salmeterol 50mcg BID (n=20)	Placebo (n=20)
Baseline				
Daytime	1.05	0.77	0.94	0.72
Nighttime	0.89	0.73	0.76	0.61
During Treatment				
Daytime	0.83	0.64	0.82	0.55
Nighttime	0.81	0.57	0.73	0.53
Change from Baseline				
Daytime	-0.20	-0.16	-0.12	-0.17
Nighttime	-0.16	-0.18	-0.03	-0.08

Source: N20236\2005-12-21\20011_02csr.pdf, pg 49

Reviewer's Comment: It is unclear what effect the baseline values have on the change from baseline.

Rescue Medication use

Rescue medication use was recorded in the patient diary by the parent/guardian. The efficacy endpoint was the change from baseline in rescue medication use. Baseline rescue medication use differed between treatment groups and the change from baseline in rescue medication use varied between treatment groups. All 3 salmeterol treatment groups demonstrated a numerically greater decrease in rescue medication use compared to the placebo group as shown in the table below.

Table 25 Mean Daily Albuterol Use (Number of Puffs), Study SMS20011				
	Salmeterol 25mcg BID (n=21)	Salmeterol 25mcg TID (n=21)	Salmeterol 50mcg BID (n=20)	Placebo (n=20)
Baseline	2.62	2.11	2.70	1.70
During Treatment	1.31	1.40	1.29	1.28
Change from Baseline	-1.31	-0.90	-1.40	-0.42
Source: N20236\2005-12-21\20011_02csr.pdf, pg 49-50				

Reviewer's Comment: It should be noted that the study was not powered to show a difference between treatment groups. In addition, it is unclear what effect the baseline values have on the change from baseline.

Functional Status II (R) Questionnaire (FSII(R))

The FSII(R) was utilized to assess the health status of the subjects. The FSII(R) was administered at baseline and following each 7 day treatment period. The FSII(R) was scored by summing the item scores and normalizing on a scale of 0 (worst functioning) to 100 (best functioning). As shown below in Table 26, there was a high pre-treatment baseline FSII(R) score and minimal change from baseline in FSII(R) Scores following treatment. The placebo group had a greater increase from baseline than all of the salmeterol groups [N20236\2005-12-21\20011_02csr.pdf, pg 48].

Table 26 Baseline, Treatment, and Change from Baseline Total Scores for FSII(R) Questionnaires								
	Salmeterol 25mcg BID		Salmeterol 25mcg TID		Salmeterol 50mcg BID		Placebo	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline								
All subjects	21	88	21	89	19	88	20	88
Same parent/guardian	16	88	19	89	19	88	16	89
Treatment (Actual value)								
All subjects	19	90	21	92	19	86	18	97
Same parent/guardian	16	90	19	91	19	86	16	97
Treatment (Change from Baseline)								
All subjects	19	1.6	21	3.2	19	-2.0	18	8.1
Same parent/guardian	16	2.1	19	2.1	19	-2.0	16	8.4
Source: N20236\2005-12-21\20011_02csr.pdf, pg 68								

Reviewer's Comment: The results above are shown for the total group and the same-parent subset (same parent/guardian completing the FSII(R) at each visit). In general, the results for the two populations were similar.

Efficacy Conclusion

Study SMS20011 was not powered to demonstrate efficacy, thus no inferential statistics were performed by the Applicant. The salmeterol 25mcg BID and 25mg TID treatment groups demonstrated the largest decrease (improvement) in nighttime asthma symptoms. There was no significant change in daytime asthma symptoms. In terms of rescue medication use, all 3 salmeterol treatment groups demonstrated a numerically greater decrease in rescue medication use compared to the placebo group. Because the study was not powered to demonstrate efficacy

and because the effect of baseline values were not accounted for, no definitive conclusions can be made regarding efficacy in Study SMS20011.

10.1.2.2.5 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A summary of the safety findings from this study follows.

Exposure

As shown below in Table 27, study medication exposure was similar between treatment groups with the exception of a higher percentage of subjects with >11 days of exposure in the salmeterol 50mcg BID treatment group. The median exposure was 8 or 9 days in each of the treatment groups.

Table 27 Study Medication Exposure

	Salmeterol 25mcg BID (n=21)	Salmeterol 25mcg TID (n=21)	Salmeterol 50mcg BID (n=20)	Placebo (n=20)
Number of Days – n (%)				
<7	1 (5)	0	0	2 (10)
7-11	19 (90)	20 (95)	15 (75)	15 (75)
>11	1 (5)	1 (5)	5 (25)	3 (15)

Source: N20236\2005-12-21\20011_02csr.pdf, pg 57-58

24 –Hour Heart Rates

Heart rates were analyzed from the Holter monitor data performed at baseline and at the end of each treatment period. The heart rate data for 6 hour intervals were analyzed in addition to the 24 hour overall period. Table 28 below summarizes the 24 hour mean heart rate data at baseline and during treatment. There were no clinically significant changes in mean heart rate from baseline. The salmeterol 50mcg BID treatment group demonstrated the greatest numerical increase from baseline with a mean change from baseline of 2.2 beats per minute

Table 28 Mean 24-Hour Heart Rates – Holter Monitoring (beats/min)

Treatment	Baseline			During Treatment			Change from Baseline		
	N	Mean	Min; Max	N	Mean	Min; Max	N	Mean	Min; Max
Placebo	20	122	73; 185	18	121	75; 188	18	-1.0	1.9, 2.2
Salmeterol 25mcg BID	21	127	76; 193	18	127	73; 193	18	-0.5	-2.9; -0.6
Salmeterol 25mcg TID	21	125	78; 189	20	125	79; 190	20	-1.4	1.3, 0.6
Salmeterol 50mcg BID	20	125	76; 192	19	127	76; 188	19	2.2	0.5; -2.1

Source: N20236\2005-12-21\20011_02csr.pdf, pg 51

Reviewer's Comment: Data for subjects with fever during the Holter monitoring were not included above (n=5).

In general, the number of subjects with ectopic ventricular events at baseline was low and varied between treatment groups from 3 to 6. There was no significant increase in the number of

subjects with single ventricular ectopic events in the active treatment groups during treatment. No subjects had ventricular couplets or runs in any treatment group as shown below in Table 29.

Table 29 Number of Subjects with Ventricular Ectopic (VE) Events – Holter Monitoring

	Baseline				During Treatment			
	N	Single VEs n (%)	VE couplets	VE Runs	N	Single VEs n (%)	VE couplets	VE Runs
Placebo	20	3 (15)	0	0	18	5 (28)	0	0
Salmeterol 25mcg BID	21	3 (14)	0	0	19	2 (11)	0	0
Salmeterol 25mcg TID	21	6 (29)	0	0	20	2 (10)	0	0
Salmeterol 50mcg BID	20	2 (10)	0	0	19	3 (16)	0	0

Source: N20236\2005-12-21\20011_02csr.pdf, pg 53

The number of supraventricular ectopic events was low at baseline and did not increase during treatment as shown below in Table 30. It should be noted that one subject (Inv50645/Subject13410) had 24 supraventicular ectopic events in the salmeterol 25mcg TID treatment group and was withdrawn from the study.

Table 30 Median Number of Supraventricular Ectopic Events – Holter Monitoring

Treatment	Baseline			During Treatment			Change from Baseline		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	20	0	0;4	18	0	0;5	18	0	-4; 3
Salmeterol 25mcg BID	21	0	0;8	19	1	0 ;4	19	0	-6; 4
Salmeterol 25mcg TID	21	0	0;2	20	0	0;24	20	0	-2; 23
Salmeterol 50mcg BID	20	1	0;8	19	0	0;3	19	0	-8; 3

Source: N20236\2005-12-21\20011_02csr.pdf, pg 53, 132-134

Reviewer's Comment: The Applicant also analyzed the data for the subset of subjects with > 18 hours of Holter monitoring data and the results are similar to what is shown above for heart rate, ventricular ectopic events, and supraventricular ectopic events [N20236\2005-12-21\20011_02csr.pdf, pg 54].

Electrocardiograms (ECGs)

A 12 lead ECG was recorded at screening (Visit 1) and at the end of each of the treatment periods (Visits 3 and 5). No abnormal ECGs were reported during the treatment period. In general, the salmeterol treatment groups demonstrated greater increase from baseline in mean PR, QRS duration, QT interval, or QTcF interval than the placebo treatment group as shown below in Table 31. However, the changes in PR, QRS, QT, and QTcF are unlikely to be clinically significant. No QTcF intervals were ≥ 440msec [N20236\2005-12-21\20011_02csr.pdf, pg 55-56].

Table 31 Mean QT, QTcF, QRS Duration, PR Intervals at Baseline, During Treatment, and Change from Baseline (msec)

	Placebo		Salmeterol 25mcg BID		Salmeterol 25mcg TID		Salmeterol 50mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
QT Interval								
Screening	20	266	21	258	21	264	20	263
End of Treatment	18	263	18	264	20	268	16	268
Change from Baseline	18	-0.5	18	5.7	20	5.4	16	-0.5
QTcF Interval								
Screening	20	336	21	334	21	338	20	338
End of Treatment	18	331	18	338	20	342	16	348
Change from Baseline	18	-3.7	18	4.2	20	5.4	16	5.2
QRS Duration								
Screening	20	66	21	67	21	69	20	66
End of Treatment	18	68	18	69	20	71	16	68
Change from Baseline	18	1.1	18	3.1	20	2.1	16	-0.3
PR Intervals								
Screening	20	121	21	112	21	120	20	114
End of Treatment	18	120	18	117	20	122	16	115
Change from Baseline	18	-1.1	18	6.7	20	2.1	16	1.3

Source: N20236\2005-12-21\20011_02csr.pdf, pg 55-56

Mean heart rate values as measured via ECGs were similar at baseline across treatment groups (129-132bpm). The salmeterol 50mcg BID demonstrated a slight increase in mean heart rate at the end of treatment with 137bpm. The other treatment groups did not demonstrate an increase in heart rate during the treatment period [N20236\2005-12-21\20011_02csr.pdf, pg 57].

Adverse Events

There were no deaths in this study. One subject experienced two SAEs, wheezing and cough, two days after completing treatment with salmeterol 25mcg BID. The SAEs led to hospitalization for one day. One subject (Inv50645/Subject13410) in the salmeterol 25mcg TID treatment group was withdrawn due to abnormal Holter findings. The subject had one supraventricular ectopic event (SVE) at baseline and 24 SVEs in 23 hours [N20236\2005-12-21\20011_02csr.pdf, pg 60].

Twenty-four subjects reported at least one AE during the study for a total of 34 AEs. Adverse events that occurred during the washout period were assigned to the treatment received during the preceding treatment period. AEs were more common in the salmeterol treatment group. The most frequently reported AEs were ear, nose, and throat infections and fever, and diarrhea and were reported in more subjects in the salmeterol treatment groups than in the placebo group. Table 32 displays a summary of adverse events reported in >3% of subjects in each of the treatment groups and more common in the salmeterol treatment groups than in the placebo group.

Table 32 Adverse Events >3% Incidence and More Common than Placebo				
Number of Subjects with Adverse Event	**Placebo (N=20) n (%)**	**Salmeterol 25mcg BID (N=21) n (%)**	**Salmeterol 25mcg TID (N=21) n (%)**	**Salmeterol 50mcg BID (N=20) n (%)**
Any Event	5 (25)	15 (71)	8 (38)	6 (30)
ENT infections	1 (5)	4 (19)	0	1 (5)
Fever	0	2 (10)	1 (5)	2 (10)
Diarrhea	0	2 (10)	2 (10)	0
Normal tooth eruption	0	1 (5)	1 (5)	1 (5)
Nasal congestion/blockage	0	1 (5)	1 (5)	0
Cough	0	1 (5)	1 (5)	0
Skin erythema	0	1 (5)	0	1 (5)
Ear signs/symptoms	0	1 (5)	0	0
Otitis	0	0	1 (5)	0
Sinusitis	0	0	0	1 (5)
Candidiasis mouth/throat	0	0	1 (5)	0
Gastroenteritis	0	1 (5)	0	0
Eczema	0	0	0	1 (5)
Fungal skin infections	0	1 (5)	0	0
Photodermatitis	0	0	0	1 (5)
Skin disorders	0	0	0	1 (5)
Skin rashes	0	0	1 (5)	0
Candidiasis, unspecified	0	1 (5)	0	0
Contusions/hematomas	0	1 (5)	1 (5)	1 (5)
Chest sounds	0	1 (5)	0	0
Viral respiratory infections	0	0	0	1 (5)
Appetite disturbances	0	0	1 (5)	0
Mood disorders	0	1 (5)	0	0
Muscle twitching and fasciculation	0	1 (5)	0	0
Cardiovascular test findings	0	0	1 (5)	0
Source: N20236\2005-12-21\20011_02csr.pdf, pg 59				

Reviewer's Comment: The Applicant also presented the AEs attributed to study medication. The only AEs attributed to study medication were mood disorder (fussiness) and muscle twitching (during nap). Both of these AEs occurred in the salmeterol 25mcg BID treatment group [N20236\2005-12-21\20011_02csr.pdf, pg 60].

Laboratory Evaluations

Laboratories were drawn at baseline and post-treatment during Visits 3 and 5. Shift table data were presented and reviewed. The majority of subjects had no shift or shifted to normal range for hemoglobin, hematocrit, or platelets. In terms of WBC count, 2-4 subjects in each treatment group were noted to shift to a high WBC, however, the increase in WBC count was not outside the defined threshold values. More subjects treated with salmeterol 50mcg BID had shifts to low in neutrophils, one of which was below the threshold defined value. The Applicant defined thresholds for laboratory values and reported the incidence of hematology parameters outside the thresholds as shown below [N20236\2005-12-21\20011_02csr.pdf, pg 185-189].

Table 33 Incidence of Hematology Parameters Outside Defined Threshold Values at Any Visit Post-Baseline

Hematology Parameter	Placebo n (%)	Salmeterol 25mcg BID n (%)	Salmeterol 25mcg TID n (%)	Salmeterol 50mcg BID n (%)
Hemoglobin	3/19 (16)	3/16 (19)	2/17 (12)	0
RBC	0	0	1/17 (6)	0
Platelets	1/19 (6)	0	0	1/19 (6)
WBC	0	0	0	0
Neutrophils	0	0	1/17 (6)	0
Lymphocytes	0	0	0	0
Monocytes	3/19 (16)	1/16 (6)	1/17 (6)	3/19 (16)
Eosinophils	4/19 (21)	2/16 (13)	0	2/19 (11)

Source: N20236\2005-12-21\20011_02csr.pdf, pg 192

Reviewer's Comment: Hemoglobin and eosinophil counts were the hematology parameters that were most frequently noted outside the pre-specified threshold value; however, the placebo group had similar frequency of values outside the threshold as the active treatment groups.

Reviewer's Comment: The hematology data does not suggest a safety signal.

In terms of chemistry parameters, 2-5 subjects in each treatment group had shifts to high calcium, more subjects treated with salmeterol 50mcg BID had shift to low bicarbonate, and more subjects had a shift to high range for creatinine in the salmeterol 25mcg TID and 50mcg BID treatment groups. Although some subjects had a shift to the low or high range for chemistry parameters, very few of these chemistry parameters were outside the pre-defined thresholds. The incidence of chemistry parameters outside the thresholds are shown below. Chemistry parameters most frequently noted to be outside the defined threshold values were decreased total bilirubin, uric acid, and bicarbonate and increased phosphorus. Decreased bicarbonate below the threshold value (<15mEq/L) was only noted in the salmeterol treatment groups [N20236\2005-12-21\20011_02csr.pdf, pg 64].

Table 34 Incidence of Chemistry Parameters Outside Defined Threshold Values at Any Visit Post-Baseline

Chemistry Parameter	Placebo n (%)	Salmeterol 25mcg BID n (%)	Salmeterol 25mcg TID n (%)	Salmeterol 50mcg BID n (%)
Bicarbonate	0	1/17 (6)	1/18 (6)	3/19 (16)
Albumin	0	1/17 (6)	1/18 (6)	1/16 (5)
Uric acid	2/19 (11)	1/17 (6)	4/18 (22)	1/16 (5)
Urea nitrogen	0	0	0	1/16 (5)
Total Bili	6/19 (32)	6/17 (35)	7/18 (39)	6/19 (32)
Alkaline phosphatase	2/19 (11)	0	1/18 (6)	0
Phosphorus	1/19 (5)	3/17 (18)	2/18 (11)	0

Source: N20236\2005-12-21\20011_02csr.pdf, pg 64, 193

The Applicant further analyzed the glucose and potassium data. One subject had a shift to high glucose in the placebo group, but the value was not outside the pre-defined threshold value. No shifts to low potassium were noted and no episodes of hypokalemia were observed [N20236\2005-12-21\20011_02csr.pdf, pg 187].

Vital Signs and Physical Examinations

No significant changes in heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment as shown below in Table 35.

Table 35 Summary of Vital Signs

	Placebo		Salmeterol 25mcg BID		Salmeterol 25mcg TID		Salmeterol 50mcg BID	
	N	Mean	N	Mean	N	Mean	N	Mean
Systolic BP (mmHg)								
Prior to Start of Treatment	20	96	21	94	21	95	19	94
End of Treatment	18	96	18	97	21	92	19	96
Diastolic BP (mmHg)								
Prior to Start of Treatment	20	62	21	60	21	61	19	59
End of Treatment	18	57	18	61	21	58	19	61
Pulse Rate (bpm)								
Prior to Start of Treatment	20	122	21	120	21	121	19	117
End of Treatment	18	121	19	122	21	121	19	121
Temperature (C)								
Prior to Start of Treatment	20	37	21	37	21	37	19	36
End of Treatment	18	37	19	37	21	36	19	37
Respiratory Rate (breaths/min)								
Prior to Start of Treatment	20	25	21	26	21	28	19	26
End of Treatment	18	24	19	24	21	27	19	26

Source: N20236\2005-12-21\20011_02csr.pdf, pg 65

Physical examinations were performed at baseline and end of study. There were less abnormalities in physical examination noted at the end of study than at baseline. Common abnormalities included the ear, nose, and throat or the hair and skin [N20236\2005-12-21\20011_02csr.pdf, pg 65, 201].

Physicians specifically assessed for tremor at screening, end of study, pre-dose, 1 hour post-dose, and end of treatment period. Nine incidences of mild tremor were noted in 4 subjects (3 of which were at the same site). Mild tremor was noted more frequently in the salmeterol treatment groups at the end of the treatment period as shown below in Table 36. No tremors were moderate or severe.

Table 36 Summary of Physician's Assessment of Tremor				
	Placebo (N=20) n (%)	Salmeterol 25mcg BID (N=21) n (%)	Salmeterol 25mcg TID (N=21) n (%)	Salmeterol 50mcg BID (N=20) n (%)
Start of Treatment Period				
Pre-dose				
No tremor present	20 (100)	21(100)	21 (100)	18 (95)
Mild tremor present	0	0	0	1 (5)
Post-dose				
No tremor present	19 (95)	19 (90)	21 (100)	18 (95)
Mild tremor present	1 (5)	2 (10)	0	1 (5)
End of Treatment Period				
No tremor present	18 (100)	17 (89)	20 (95)	18 (95)
Mild tremor present	0	2 (11)	1 (5)	1 (5)
Source: N20236\2005-12-21\20011_02csr.pdf, pg 66				

Symptoms of adrenergic stimulation were addressed by several questions from the FSII(R). The Applicant also looked at individual item scores to assess for potential beta mediated effects. Item scores that could suggest signs and symptoms of adrenergic stimulation included: "sleep well", "act moody", "unusually irritable", "sleep through the night", and "react by crying". In general, most of these item scores showed little change during treatment compared to baseline in all of the treatment groups [N20236\2005-12-21\20011_02csr.pdf, pg 69].

Safety Conclusions

In general, the safety data from Study SMS20011 do not suggest a new safety signal for any of the doses of salmeterol administered in this study.

In terms of cardiovascular safety, the Holter monitor data showed that there were no clinically significant changes in mean heart rate, ventricular ectopic or supraventicular ectopic events during treatment. However, one subject was noted to have 24 supraventicular ectopic events in the salmeterol 25mcg TID treatment group and was withdrawn from the study. No abnormal ECGs were reported during the treatment period. There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval.

There were no deaths in this study. One subject experienced two SAEs (wheezing and cough) two days after completing treatment with salmeterol 25mcg BID. As mentioned above, one subject in the salmeterol 25mcg TID treatment group was withdrawn due to abnormal Holter findings. AEs were more common in the salmeterol treatment group. The most frequently reported AEs more common in the salmeterol treatment groups were ear, nose, and throat infections and fever, and diarrhea.

In terms of laboratory assessments, no incidences of hypokalemia or hyperglycemia were noted in the salmeterol treatment groups. more subjects treated with salmeterol 50mcg BID had shift to low bicarbonate, and more subjects had a shift to high range for creatinine in the salmeterol 25mcg TID and 50mcg BID treatment groups. Although some subjects had a shift to the low or

high range for chemistry parameters, very few of these chemistry parameters were outside the pre-defined thresholds. Decreased bicarbonate below the threshold value (<15mEq/L) was only noted in the salmeterol treatment groups.

No significant changes in heart rate, blood pressure, temperature, or respiratory rate were noted. Mild tremor was noted more frequently in the salmeterol treatment groups at the end of the treatment period. Symptoms of adrenergic stimulation were addressed by several questions from the FSII(R). Individual item scores to assess for potential beta mediated effects showed little change during treatment compared to baseline in all of the treatment groups.

10.1.2.2.6 Discussion and Conclusions

Study SMS20011 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, two-period, four-treatment crossover study of 3 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 6 to 23 months to primarily assess safety.

Study SMS20011 was not powered to demonstrate efficacy, thus no inferential statistics were performed by the Applicant. The salmeterol 25mcg BID and 25mg TID treatment groups demonstrated the largest decrease (improvement) in nighttime asthma symptoms. There was no significant change in daytime asthma symptoms. In terms of rescue medication use, all 3 salmeterol treatment groups demonstrated a numerically greater decrease in rescue medication use compared to the placebo group. Because the study was not powered to demonstrate efficacy and because the effect of baseline values were not accounted for, no definitive conclusions can be made regarding efficacy in Study SMS20011.

In general, the safety data from Study SMS20011 do not suggest a new safety signal for any of the doses of salmeterol administered in this study. Many of the notable findings from the safety data are consistent with AEs associated with beta adrenergic agonists. Notable findings include the following: (1) one subject with 24 supraventicular ectopic events in the salmeterol 25mcg TID treatment group; (2) AEs more common with salmeterol use were ear, nose, and throat infections, fever, and diarrhea; (3) more subjects treated with salmeterol had a decrease in bicarbonate (salmeterol 50mcg BID) or an increase in creatinine (salmeterol 25mcg TID and 50mcg BID); and (4) mild tremor was noted more frequently in the salmeterol treatment groups.

10.1.3 Study SMS30076

A Four-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group Clinical Study of Salmeterol Xinafoate Inhalation Aerosol and Placebo Administered via a Holding Chamber with Facemask in Subjects with Asthma Aged 24 to 47 Months

10.1.3.1 Protocol

Objective

The objective of Study SMS30076 is to evaluate the efficacy and safety of salmeterol xinafoate inhalation aerosol 25mcg BID and 50mcg BID administered via 2 different holding chambers

with facemask over a 4-week treatment period in pediatric subjects with asthma aged 24 to 47 months.

Study Design
Study SMS30076 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, parallel group study of 2 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 24 to 47 months. Eligible subjects underwent a 7-28 day screening period following Visit 1. Subjects meeting entry criteria were randomized at Visit 2 to one of the following treatment groups for the 28 day double-blind treatment period.

- Salmeterol xinafoate inhalation aerosol 25mcg BID
- Salmeterol xinafoate inhalation aerosol 50mcg BID
- Placebo MDI BID.

Study medication was administered via a valved holding chamber with facemask. Subjects were followed a weekly clinical visits (Visits 3, 4, 5, and 6). Study medication was discontinued at Visit 6. A follow up phone call was made approximately one week later (Visit 7) [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 15].

Study Population [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 16-19]
The following is a list of the pertinent inclusion criteria for the screening phase of SMS30076:

- Male or females 24 to 47 months of age
- A history of symptomatic asthma and at least 2 exacerbations of increased symptoms of asthma requiring medical attention and pharmacotherapy within the preceding 12 months. In addition, subjects must also fulfill the following criteria prior to Visit 1
    - Have required therapy with a maintenance asthma medication (other than systemic corticosteroid) on a regular basis for the preceding 4 weeks **and/or**
    - Have required therapy with a short-acting beta-agonist for relief of respiratory symptoms at least twice per week over the preceding 3 weeks.

The following is a list of the pertinent inclusion criteria for the treatment phase of SMS30076:

- Symptoms of asthma (a score ≥ 1 on either or both daytime and nighttime asthma symptom scales) must have been demonstrated and recorded on the diary record on at least 5 of the last 7 days of the 7 to 28 day treatment period.
- Albuterol use documented on the diary record on at least 2 days during the 5 symptomatic screening days
- Parents/guardians comply with use of diary card on at least 80% of the days during the screening period
- Subject is able to use the MDI with holding chamber and facemask
- Subject has not experienced an asthma exacerbation during the screening period
- Parent/guardian capable of supervising the Holter monitor.

The following is a list of the pertinent exclusion criteria for SMS30076:

- Life-threatening asthma (ICU admission) within previous 6 months
- Acute systemic corticosteroid therapy within 4 weeks of screening
- Chronic systemic corticosteroid therapy for > 4 weeks within 6 months of screening

- Use of CNS stimulants (methylphenidate, pemoline, Dexedrine) within 30 days prior to screening
- Concurrent use of prohibited medications (see Concomitant Therapy, below)
- Concurrent significant disease including the following: CF, bronchiectasis, BPD, pneumonia (3 months), ENT disorders likely to require surgery during the treatment period, congenital heart disease that required therapy/surgery within previous 12 months, seizure disorder, reflux esophagitis not controlled by pharmacotherapy, Cushing's Syndrome, renal disease, hematological disease, hepatic disease, malignancy, cellular or humoral immunity disorder, JRA, SLE, or other collagen vascular disease, inadequately controlled psychiatric disorder, DM, pan-hypopituitarism, hyperthyroidism, glaucoma
- Hypersensitivity to beta-agonists, component of MDI formulation, facemask, or adhesives
- Clinically significant laboratory, ECG, or CXR abnormalities
- Recent bacterial or viral URI, LRI, sinus, or middle ear infection that is not resolved within 2 weeks prior to screening or during the screening period

Materials

The parent/guardian for each subject received 2 canisters (A and B) at Visit 2 and 4. They were instructed to administer one inhalation from canisters A and B in the AM (0600-0800 hrs) and in the PM (1800-2000 hrs) [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 20-21]:

- Salmeterol xinafoate inhalation aerosol 25mcg BID
  - One inhalation 25mcg (canister A) in AM and in the PM
  - One inhalation placebo (canister B) in AM and in the PM
- Salmeterol xinafoate inhalation aerosol 50mcg BID
  - One inhalation 25mcg (canister A) in AM and in the PM
  - One inhalation 25mcg (canister B) in AM and in the PM
- Placebo MDI BID
  - One inhalation placebo (canister A) in AM and in the PM
  - One inhalation placebo (canister B) in AM and in the PM

Reviewer's Comment: The protocol did not include a rationale utilizing the in vitro data or the results of Study SMS20010 for the choice of salmeterol doses. However, it should be noted that the choice of doses is somewhat limited.

All study medication was administered via holding chamber and facemask. Approximately half of the subjects were assigned to use the (b) (4) and the other half assigned to the (b) (4) Rescue medication was supplied as Ventolin MDI and albuterol nebules.

Concomitant Therapy

The following medications were prohibited during the course of the study [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 23-25]:

- Beta-adrenergic agonists
- Systemic corticosteroids
- Inhaled corticosteroids unless started four weeks prior to screening and continued during the treatment period

- Cromolyn or nedocromil unless started four weeks prior to screening and continued during the treatment period
- Anti-cholinergics e.g. (ipratropium bromide)
- Theophylline or aminophylline
- Leukotriene antagonists, unless started four weeks prior to screening and continued during the treatment period
- Antiarrythmics
- Anticonvulsants
- CNS stimulants
- Beta adrenergic antagonists
- Oral antihistamines, unless started four weeks prior to screening and continued during the treatment period
- Systemic decongestants, unless started four weeks prior to screening and continued during the treatment period
- Narcotic or non-narcotic cough suppressants
- Immunosuppressives

Study Conduct

Informed consent was obtained prior to any screening or treatment study procedures being performed. Screening evaluations were performed at Visit 1. Subjects and guardians/parents were instructed on the proper completion of the diary card, proper use of the peak flow meter, and proper administration of the MDI and nebules. Subjects underwent a 7 to 28 day screening period.

At Visit 2, eligibility criteria were reviewed and if subjects were eligible, they were randomized in a 1:1:1 fashion to one of the three treatment groups for a 28 day double-blind treatment period. Treatments were stratified by age at randomization: 24 to < 36 months and 36 to 47 months. Study medication was administered via a valved holding chamber with facemask as described in the Materials Section above. Subjects were followed a weekly clinical visits (Visits 3, 4, 5, and 6). Study medication was discontinued at Visit 6. A follow up phone call was made approximately one week later (Visit 7). Throughout the treatment period, parents/guardians completed diary cards (symptoms and PEF) and recorded rescue medication use. On the diary cards, parents/guardians of the subjects were instructed to record any medical problems, including signs and symptoms of adrenergic stimulation, such as feelings of nervousness, anxiety, irritability, lack of sleep, etc. The diary cards were reviewed at each study visit. Table 37 displays the study assessments performed at each clinic visit.

Table 37 SMS30076 Study Assessments

Visit	1	Phone	2	3	4	5	6	Premature D/C	7 (Phone)
Day	-28 to -7 days	At least weekly	1	8 (+5 days)	15 (+5 days)	22 (+5 days)	29 (+5 days)		36 (±2 days)
Procedure									
Informed Consent	x								
Med history	x								
AE assess	x[a]		x	x	x	x	x	x	x
Con meds	x		x	x	x	x	x	x	
Check symptom scores		x							
Review/dispense diary	x		x	x	x	x	x	x	
Administer FSII(R)			x	x	x	x	x	x	
Tremor assessment	x		x[b]	x	x	x	x	x	
Physical exam	x						x	x	
Vital signs	x		x[b]	x	x	x	x	x	
ECG	x						x	x	
PEF (In-clinic)	x[c]		x[c]						
Check MDI/holding chamber use	x		x	x	x	x			
Dispense/collect Study Med			x		x		x	x	
Dispense/ collect albuterol	x		x		x		x	x	
Lab tests	x						x	x	

a Assessment of adverse events begins when the informed consent form is signed.
b Evaluated pre-dose and one hour post dosing of study medication.
c Subjects who provide technically acceptable maneuvers will continue to record PEF twice-daily on diary record.

Source: N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 64

If subjects discontinued the study early, the investigator was to make an effort to perform the end of study evaluations. I

If subjects experienced an asthma exacerbation during the treatment period, subjects were withdrawn from the study. The protocol definition of asthma exacerbation (treatment failure) is increasing signs or symptoms of asthma, not controlled by as needed albuterol and requiring asthma medications not allowed by the protocol [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 16].

Efficacy [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 34-36]
The primary efficacy endpoint was the average of the change from baseline in daytime asthma symptom scores and the change from baseline in nighttime asthma symptom scores during the treatment period. Each subject's parent/guardian was instructed to assess symptoms twice daily and record in the diary. The following is the scoring system.

- **Asthma symptoms scores**
  - **Night symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with sleep
    - 2 Moderate; awakened once or more because of asthma symptoms
    - 3 Severe; awake most of the night due to asthma symptoms

Reviewer's Comment: According to the protocol, a nighttime symptom score of 2 or 3 indicated that the subject was awakened during the night due to asthma symptoms.

  - **Day symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with daily activities

  - 2 Moderate; symptoms present often, causing some interference with daily routine and activities
  - 3 Severe; symptoms continuous or present most of the day, restricting daily routine and activities severely

Secondary efficacy endpoints include the following:

- Percentage of symptom-free 24 hour days
- Percentage of symptom-free and albuterol-free 24 hour days
- Individual daytime and nighttime asthma symptom scores
- Number of asthma exacerbations
- Subject discontinuations
- Albuterol use
- Child health status as assessed by the Functional Status II-(R)
- Percentage of nights with no awakenings

Other efficacy measures include the following:

- Diary AM and PM PEF in subjects capable of performing the maneuver
- Time to first asthma exacerbation
- Measures of pulmonary function via oscillometry (selected sites)

The following is a brief description of the details of the secondary and other endpoints.

- **Peak expiratory flow (PEF)**
  - In subjects able to perform maneuver, PEF were collected using a PEF meter each morning and evening.
  - Duplicate measurements obtained with highest PEF value recorded
- **Rescue medication use (Ventolin use)**
  - Recorded by the parent/guardian in the diary as the number of puffs of MDI used over the preceding 24 hours
- **Asthma exacerbations**
  - An asthma exacerbation (treatment failure) was defined as an increase in signs or symptoms of asthma, not controlled by as needed albuterol and requiring asthma medications not allowed by the protocol
- **Oscillometry** [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 70-73].
  - Selected sites measured pulmonary function via the forced oscillometry technique in ~40 subjects
  - Oscillometry was measured at Visits 2 and 6 pre and post study drug administration

Reviewer's Comment: According to the protocol, oscillometry requires only passive cooperation by the subject. The device applies small pressure impulses to a tube through which the subject breaths. The forces in the respiratory system that resist oscillatory airflow are measured.

In addition, the Functional Status II(R) questionnaire (FSII(R)) was utilized to assess the health status of the subjects. The FSII(R) is an interviewer administered questionnaire which contains 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention during the previous two-week period. The FSII(R) was modified to assess the behavior during

the previous week. Each item was scored on a three-point scale indicating the frequency with which a child exhibits the specified behavior or performs the specified activity. A second level of responses evaluated to what extent poor functioning indicated in the first level of questioning is related to the child's illness. The items are summed and a total score is calculated as the percent of total possible scores. Higher scores reflect a better functional status. The FSII(R) was administered at all Visits 2-6 [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 36].

Safety

Safety assessments included adverse events, physical examination, laboratories, ECGs, physician's assessment of tremor and symptoms of adrenergic stimulation (irritability and lack of sleep) from the FSII(R) questionnaire. Each safety measure will be briefly discussed [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 37-39].

- **Physical examination**
  - A physical exam was performed at screening (Visit 1) and end of study (Visit 6)
- **Vital signs**
  - A set of vital signs (HR, BP, T, RR) was measured at each study visit
- **Adverse Events**
  - Adverse events were collected via the diary card and were reviewed at each study visit
- **ECG**
  - A 12 lead ECG was recorded at screening (Visit 1) and at the end of the treatment period (Visit 6)
  - An independent electrocardiographer, blinded to treatment assignment, provided measurements of heart rate, PR interval, QTc interval, QRS duration, and an overall interpretation of each ECG collected
  - Criteria were specified in the protocol for an abnormal ECG. Inclusion criteria specified subjects must have a normal screening ECG
  - The ECG collected at Visit 6 were compared to the screening ECG to determine if a clinically significant change occurred.
- **Laboratories**
  - Chemistry, hematology, and electrolytes were performed at Visit 1 (if indicated) and Visit 6
  - Baseline labs within previous 3 months of Visit 1 were acceptable
- **Tremor assessments**
  - Tremor was evaluated by the investigator at each visit. When study drug was administered during Visits 2, tremor was assessed pre-dose and one hour post-dose.
  - Tremor was graded on the following scale
    - 0 – no tremor present
    - 1 – mild tremor present
    - 2 – moderate tremor present
    - 3 - severe tremor present

Data Analysis

A minimum of 100 completed subjects per treatment group was requested by the FDA. The dropout rate was estimated to be 20%. Approximately 390 subjects (130 per treatment group) were to be randomized. The Sponsor estimated that 100 subjects per treatment group would provide at least 90% power to detect a difference of 0.3 between treatment groups (change from baseline in daily asthma symptom scores). No imputations of missing data were planned [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 41].

The primary efficacy endpoint was the average of the change from baseline in daytime asthma symptom scores and the change from baseline in nighttime asthma symptom scores during the treatment period. The Composite Symptom Score = (change from baseline in daytime score + change from baseline in nighttime score)/2. Two pairwise comparisons between placebo and the active groups were the primary contrasts of interest. The ANCOVA using baseline as the covariate and controlling for region was the primary analysis method. Baseline was defined as the average of the daytime and nighttime scores recorded during the last 7 days of the screening period immediately prior to randomization [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 41].

The following are details of some of the secondary endpoints [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 41-46].

- **Peak expiratory flow (PEF)** – change from baseline (AM and PM) in PEF in subjects capable of performing the maneuver.
- **Percentage of symptom free days**
  - P = 100* (# of symptom-free days)/(# of days in treatment period)
  - Symptom free day is a day in which subjects has a nighttime and daytime score of 0
- **Percentage of symptom free days and albuterol free days**
  - P = 100* (# of symptom-free days and albuterol free days)/(# of days in treatment period)
- **FSII(R) –** Total scores and individual item scores were to be summarized by treatment group and study visit

Amendments

Two amendments were made to the original protocol (February 19, 2001 and January 7, 2002). The following is a brief summary of the amendments [N20236\2005-12-21\sms30076-03-protocol-amend-2.pdf, pg 79-102].

- Clarified dosing instructions (specifically priming)
- Minimum time for treatment period
- Relationship of health status questionnaires to AEs
- Clarified ECG interpretations and oscillometry measures
- Expanded from US study to Global study (increased number of study sites)
- Changed the time for acceptable visit window
- Allowed use of leukotriene antagonists

10.1.3.2 Results

Study SMS30076 was initiated March 12, 2001, and completed July 02, 2002. The final study report is dated June 17, 2005. The drug supplies for the study were salmeterol xinafoate inhalation aerosol 25mcg from batch identification numbers 9ZP1830 & 02M2891 and placebo inhalation aerosol from batch identification numbers 9ZP1829 & 02M2887 [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 1 & 3].

Prior to discussion of the results of the study, it should be noted that two investigative sites (Dr. Sauceda and Dr. Luber) had GCP violations. Dr. Sauceda (Inv. # 99420) was serving a 5-year probation of his medical license and Dr. Luber (Inv. #74170) had study conduct irregularities. Dr. Sauceda enrolled 3 subjects and Dr. Luber enrolled 8 subjects. The Applicant presented the results for the ITT population as well as the ITT population excluding the 11 subjects from the two GCP non-compliant investigator sites [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 40].

10.1.3.2.1 Subject Disposition

Five hundred twenty-three subjects were screened at 117 investigational sites. Three hundred thirty-eight subjects were randomized and 315 subjects (93%) completed treatment. Twenty-three subjects were discontinued from the study as shown below in Table 38. More subjects discontinued from the salmeterol 50mcg BID treatment group primarily due to protocol violation, lost to follow-up, and other.

Table 38 Subject Disposition for Study SMS30076

	Placebo n (%)	Salmeterol 25mcg BID n (%)	Salmeterol 50mcg BID n (%)
Randomized (N=338)	113	112	113
Completed (N=315)	107 (95)	107 (96)	101 (89)
Discontinued (N=23)	6 (5)	5 (4)	12 (11)
AE	3 (3)	1 (<1)	2 (2)
Protocol Violation	1 (<1)	1 (<1)	3 (3)
Lost to follow-up	0	1 (<1)	3 (3)
Lack of efficacy	2 (2)	0	2 (2)
Consent withdrawn	0	1 (<1)	0
Other	0	1 (<1)	2 (2)

Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 56

10.1.3.2.2 Protocol Violations

Approximately 37% of subjects had protocol violations. More subjects in the salmeterol treatment groups had protocol violations than the placebo group. The most common protocol violation was concurrent medication violation and other. Other protocol violations included: ECG rhythm strip not done and visit date or time outside the specified window [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 57].

10.1.3.2.3 Demographics and Baseline Characteristics

The mean age for subjects was approximately 36 months with a minimum age of 22 months and a maximum age of 47 months. Approximately forty-eight percent of the children were 24-35 months and 52% were 36-47 months. There were more males (64%) than females (36%). The majority of subjects were White (46%) and 2% Asian, 22% Black, 26% Hispanic, and 4% Other. Fifty percent of the subjects were assigned to the (b) (4) while 50% were assigned to the (b) (4) The treatment groups were similar in terms of age and race; however, the salmeterol 50mcg group had more males (72%) than the other treatment groups (40%) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 58, 163].

The most common concurrent medical conditions were in the allergies, skin, and ENT body systems. The incidence was similar among the treatment groups except the salmeterol 25mcg group had more ENT conditions (43%) compared to the other treatment groups (30-33%). Approximately 54-59% of subjects used concurrent asthma medications during the treatment period, with 45-48% using corticosteroids. The use of concurrent asthma medications was similar among treatment groups [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 59].

Mean treatment compliance was high and similar among treatment groups (90-93%). The salmeterol 50mcg treatment group had more subjects with <80% compliance (12%) compared to 6-7% in the other treatment groups [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 187].

10.1.3.2.4 Efficacy

Primary Endpoint

The primary efficacy endpoint was the average of the change from baseline in daytime asthma symptom scores and the change from baseline in nighttime asthma symptom scores during the treatment period (i.e. the change from baseline Composite Symptom Score). The Composite Symptom Score = (change from baseline in daytime score + change from baseline in nighttime score)/2. Baseline was defined as the average of the daytime and nighttime scores recorded during the last 7 days of the screening period immediately prior to randomization. Each subject's parent/guardian was instructed to assess symptoms twice daily and record in the diary.

Baseline mean composite asthma symptom scores were similar between treatment groups. The mean composite asthma symptom scores improved in each treatment group during the treatment period. The mean change from baseline was not significantly different in the salmeterol treatment groups compared to placebo as shown in the table below [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 60].

Table 39 Composite* Asthma Symptom Scores in Study SMS30076

ITT Population

	Placebo n=113	Salmeterol 25mcg BID n=112	Salmeterol 50mcg BID n=113
Baseline mean score (SE)	1.2 (0.05)	1.2 (0.05)	1.2 (0.05)
Week 1-4			
Adjusted mean score (SE)	0.8 (0.10)	0.9 (0.10)	0.8 (0.10)
Adjusted mean change (SE)	-0.3 (0.10)	-0.3 (0.10)	-0.4 (0.10)
Treatment group difference vs. placebo		0 (0.06)	0.1 (0.06)
95% CI vs. placebo		-0.1, 0.1	0, 0.2
p-value vs. placebo		0.75	0.17

* Composite Symptom Score = change from baseline in daytime score + change from baseline in nighttime score)/2
Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 60

Reviewer's Comment: The results for the ITT population excluding the two noncompliant GCP investigators were similar.

The Applicant analyzed the primary endpoint for subgroups based upon concurrent asthma medication use and by holding chamber use. For the concurrent asthma medication subpopulations, the subjects with concurrent ICS use are of interest. For subjects who used ICS and subjects who did not use concurrent asthma medication, the baseline composite asthma symptom scores were similar and the decline from baseline were similar across treatments and between subgroups. For the holding chamber subpopulations ((b) (4) and (b) (4) the baseline composite asthma symptom scores were similar and the decline from baseline were similar across treatments and between subgroups [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 62-63].

The Applicant analyzed the composite asthma symptom scores for the individual weeks. Again there was no significant difference between treatment groups for the mean asthma symptom scores or change from baseline at the individual weeks [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 64].

Secondary Endpoints

The pre-specified secondary efficacy endpoints will be briefly discussed.

Individual Daytime and Nighttime Asthma Symptom Scores

The baseline mean daytime and nighttime asthma symptom scores and the mean decline from baseline were similar across treatment groups. There was no significant difference between treatment groups for the individual daytime and nighttime asthma symptom scores for Weeks 1-4 [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 65].

Table 40 displays additional secondary efficacy variables: percent symptom free days, percent symptom and albuterol free days, albuterol use, and percent nights without awakenings. The percent of symptom free days and percent of symptom, albuterol free days, and the percent of nights without awakenings increased in all 3 treatment groups during the treatment period. Albuterol use decreased in all 3 treatment groups during the treatment period. There were no

significant differences in the salmeterol treatment groups compared to the placebo group for any of these secondary efficacy variables. However, the salmeterol 50mcg treatment group did have a numerically greater increase in percent symptom free days, percent symptom and albuterol free days, and percent of nights without awakenings.

Table 40 Secondary Efficacy Measures in Study SMS30076

ITT Population

	Placebo n=113	Salmeterol 25mcg BID n=112	Salmeterol 50mcg BID n=113
Percent Symptom Free Days*			
Baseline Mean (SE)	7.9 (1.25)	8.5 (1.10)	7.2 (1.17)
Week 1-4			
Mean (SE)	30.4 (2.86)	28.1 (2.63)	34.6 (2.97)
Mean change (SE)	22.4 (2.73)	19.2 (2.47)	27.1 (2.68)
p-value vs. placebo		0.58	0.12
Percent Symptom and Albuterol Free Days**			
Baseline Mean (SE)	5.0 (1.11)	5.6 (0.86)	4.4 (0.92)
Week 1-4			
Mean (SE)	21.7 (2.56)	20.5 (2.44)	25.0 (2.79)
Mean change (SE)	16.5 (2.63)	15.0 (2.24)	20.3 (2.61)
p-value vs. placebo		0.92	0.50
Albuterol Use (puffs/24 hours)			
Baseline Mean (SE)	2.7 (0.21)	2.9 (0.21)	2.8 (0.19)
Week 1-4			
Mean (SE)	1.4 (0.14)	1.8 (0.18)	1.6 (0.17)
Mean change (SE)	-1.1 (0.16)	-1.1 (0.18)	-1.1 (0.21)
p-value vs. placebo		0.52	0.96
Percent Nights No Awakenings***			
Baseline Mean (SE)	69.4 (3.10)	68.6 (2.96)	70.8 (2.84)
Week 1-4			
Mean (SE)	80.2 (2.39)	80.6 (2.32)	83.1 (2.17)
Mean change (SE)	10.8 (2.51)	11.9 (2.32)	12.9 (2.63)
p-value vs. placebo		0.81	0.48

* **Percentage of symptom free days** = 100* (# of symptom-free days)/(# of days in treatment period); symptom free day is a day in which subjects has a nighttime and daytime score of 0
Percentage of symptom free days and albuterol free days = 100* (# of symptom-free days and albuterol free days)/(# of days in treatment period)
***Percent Nights No Awakenings** = 100*(# nights with nighttime symptom score of 0 or 1)/(# of days in treatment period)
Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 66

Asthma Exacerbations

An asthma exacerbation (treatment failure) was defined as an increase in signs or symptoms of asthma, not controlled by as needed albuterol and requiring asthma medications not allowed by the protocol. No significant differences were noted between treatment groups in the number of subjects experiencing an asthma exacerbation (2 in the placebo group, none in the salmeterol 25mcg group, and 2 in the salmeterol 50mcg group) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 67].

Subject Discontinuations

More subjects discontinued from the salmeterol 50mcg treatment group (12) than the placebo group (6) or the salmeterol 25mcg treatment group (5) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 67].

Functional Status II-(R) Scores

Subject's health status was assessed by the parent/guardian at Baseline and Weeks 1, 2, 3, and 4. Baseline total scores were similar between treatment groups. Mean scores improved in all groups during the treatment period. In general, there were no significant differences between treatment groups for the mean change from baseline in the total FSII(R) scores. However, at Week 4, the salmeterol 25mcg treatment group had a numerically smaller (and statistically significant) increase in FSII(R) score compared to placebo [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 272-278].

Other Efficacy Measures: AM and PM PEF

In subjects able to perform the PEF maneuver, PEF measurements were recorded in the patient diary twice daily. Mean baseline AM and PM PEF were slightly higher in the salmeterol 25mcg treatment group and the change from baseline was slightly lower in this treatment group. However, the mean AM and PM PEF were similar between the treatment groups during the treatment period as shown below in Table 41.

Table 41 Peak Expiratory Flow in Study SMS30076

	Placebo n=113	Salmeterol 25mcg BID n=112	Salmeterol 50mcg BID n=113
AM PEF (L/min)			
Baseline (n)	39	39	33
Mean (SE)	86.4 (4.18)	90.1 (3.36)	84.5 (4.40)
Week 1-4 (n)	37	38	29
Mean (SE)	97.8 (4.69)	96.9 (3.62)	96.9 (5.03)
Mean change (SE)	10.1 (2.11)	6.0 (1.71)	10.7 (3.12)
PM PEF (L/min)			
Baseline (n)	38	39	30
Mean (SE)	89.1 (4.22)	91.9 (3.47)	86.7 (3.84)
Week 1-4 (n)	37	38	26
Mean (SE)	101.0 (4.72)	99.5 (3.67)	100.4 (5.41)
Mean change (SE)	11.4 (2.41)	6.6 (1.79)	8.8 (4.10)

Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 68

Other Efficacy Measures: Time to first asthma exacerbation

Subjects were withdrawn for asthma exacerbations. As discussed above, very few subjects experienced an asthma exacerbation and no significant differences were noted between treatment groups in the number of subjects experiencing an asthma exacerbation. The mean time to asthma exacerbation was similar between the placebo group and the salmeterol 50mcg treatment group (approximately 16 days) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 287].

Other Efficacy Measures: Oscillometry

The study included an exploratory assessment of pulmonary function in a subset of 17 subjects using oscillometry. According to the Applicant, oscillometry requires only passive cooperation by the subject. The device applies small pressure impulses to a tube through which the subject breaths. The forces in the respiratory system that resist oscillatory airflow were measured. Measurements were taken pre-dose and 2 hours post-dose on Day 1 and Week 4. The following parameters were collected: inspiration/expiration (whole breath) and inspiration and expiration separately: total respiratory resistance at 5Hz (R5), frequency-dependence of resistance between R5 and R15 (R5-R15), reactance at 5Hz (X5), resonant frequency (F_{res}), and area of X integrated from 5Hz up to F_{res} (AX). The Applicant suggests that since there is wide variability in X5 and relative stability in F_{res}, the parameters most useful for evaluation of pulmonary function (peripheral airways) are R5, R5-R15, and AX [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 72].

Reviewer's Comment: The oscillometry measurements are exploratory and there were too few subjects with acceptable data (14) to draw any definitive conclusions. The following is a brief description of some of the oscillometry measures. R is the total respiratory resistance. In patients with chronic airflow obstruction, R is generally increased and decreases as oscillation frequency increases. X is reactance which is the sum of respiratory elastance and inertance pressures. The resonant frequency F_{res} is reached when X=0 which occurs when inertial pressures equal elastic pressures. In patients with asthma, R5, AX, and F_{res} are often increased.

Of the 19 subjects with oscillometry measurement, one was used for preliminary test data and four had unacceptable measurements. The baseline measurement for R5, R5-15, and AX were similar between treatment groups. In general, the salmeterol treatment groups had greater decreases in R5, R15, and AX than the placebo group; however, the sample size was too small to make definitive conclusions [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 71-72, 287].

Efficacy Conclusion

Study SMS30076 did not demonstrate that salmeterol 25mcg BID or 50mcg BID were superior to placebo with regards to the primary endpoint, composite asthma symptom scores. Results were comparable between subjects using the (b) (4) and subjects using the (b) (4) holding chamber. In general, subgroup analyses and secondary endpoints did not suggest that the salmeterol treatment groups were superior to placebo.

10.1.3.2.5 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A summary of the safety findings from this study follows.

Exposure

As shown below in Table 42, study medication exposure was similar between treatment groups. The majority of subjects received more than 28 days of treatment.

Table 42 Study Medication Exposure			
	Placebo n=113	Salmeterol 25mcg BID n=112	Salmeterol 50mcg BID n=113
Exposure (days) Median	30	30	30
Range (days)	2-45	1-41	1-43
Length of treatment – n (%)			
<= 7 days	2 (2)	2 (2)	2 (2)
8-14 days	2 (2)	0	1 (<1)
15-21 days	2 (2)	2 (2)	3 (3)
22-28 days	0	4 (4)	5 (4)
>28 days	107 (95)	104 (93)	102 (90)
Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 73			

Adverse Events

There were no deaths in this study. There were four subjects with SAEs as described below [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 76]:

- Placebo (2)
  - Subject #24633: 2 year old male hospitalized for wheezing and dyspnea one day after starting study medication. Subject withdrawn from the study.
  - Subject #24816: 3 year old male hospitalized for bronchospasm one week after initiating treatment. Subject withdrawn from the study.
- Salmeterol 25mcg (1)
  - Subject #24696: 2 year old female with sinus tachycardia (141 bpm) with aberrantly conducted ectopic atrial beats on the final (Week 4) ECG. Follow up ECG showed normal sinus rhythm.
- Salmeterol 50mcg (1)
  - Subject #23847: 2 year old male hospitalized for cough, wheezing, and hypoxia 3 weeks after initiating study medication. Subject withdrawn from the study.

Six subjects discontinued due to AEs. Three of the subjects and AEs were described above. The other 3 subjects who discontinued due to AEs are as follows [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 77]:

- Placebo (3)
  - Subject# 24219: 4 year old male with headaches during first 6 days of treatment
- Salmeterol 25mcg (1)
  - Subject# 24065: 2 year old male with elevated alkaline phosphatase on screening and enrolled in error
- Salmeterol 50mcg (2)
  - Subject# 11649: 2 year old male with hyperactivity after one day of study treatment

The majority of subjects (>60%) reported at least one AE during the treatment period. Rhinorrhea/PND and upper respiratory inflammation were reported more frequently in the salmeterol 50mcg treatment group compared to the other treatment groups. Psychomotor

disorders (hyperactivity) were only reported in the salmeterol treatment groups. Other notable AEs more common in the salmeterol treatment groups included: throat irritation and keratitis/conjunctivitis. Table 43 displays a summary of adverse events reported in >3% of subjects in each of the treatment groups and more common in the salmeterol treatment groups than in the placebo group.

Table 43 Adverse Events >3% Incidence and More Common than Placebo during the Treatment Period

Number of Subjects with AE	Placebo N=113 n (%)	Salmeterol 25mcg BID N=112 n (%)	Salmeterol 50mcg BID N=113 n (%)
Any Event	68 (60)	72 (64)	76 (67)
Fever	18 (16)	20 (18)	23 (20)
Rhinorrhea/post nasal drip	4 (4)	3 (3)	13 (12)
ENT infections	6 (5)	9 (8)	6 (5)
Skin rashes	4 (4)	2 (2)	6 (5)
Sinusitis	5 (4)	6 (5)	4 (4)
Mood disorders	3 (3)	5 (4)	4 (4)
Epistaxis	3 (3)	4 (4)	2 (2)
Rhinitis	2 (2)	4 (4)	2 (2)
GI discomfort & pain	2 (2)	2 (2)	4 (4)
Throat irritation	1 (<1)	4 (4)	3 (3)
Upper respiratory inflammation	1 (<1)	1 (<1)	6 (5)
Keratitis & conjunctivitis	1 (<1)	4 (4)	2 (2)
Psychomotor disorders	0	2 (2)	4 (4)

Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 74

Reviewer's Comment: The Applicant further analyzed the rhinorrhea data since there was an imbalance in the salmeterol 50mcg treatment group versus the other treatment groups. In general, the rhinorrhea was mild in severity, occurred in both male and females, and all racial subgroups. None of the rhinorrhea was considered to be related to study medication. None of the subjects had concurrent URI, but approximately half of the subjects had concurrent allergic and/or ENT conditions.

Reviewer's Comment: The Applicant also presented the AEs attributed to study medication. The drug-related AEs included mood disorders, headaches, and psychomotor disorders. As stated above, psychomotor disorders were only reported in the salmeterol treatment groups. Mood disorders and headaches were reported in the placebo group with approximately the same frequency as the salmeterol treatment groups.

Reviewer's Comment: The Applicant also presented the AEs possibly related to adrenergic stimulation. Similar to above, the most commonly reported were headache, mood disorders, sleep disorders, and psychomotor disorders. Psychomotor disorders were only reported in the salmeterol treatment groups. Mood disorders and headaches were reported in the placebo group with approximately the same frequency as the salmeterol treatment groups. [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 76].

The AE data does not suggest a new safety signal for salmeterol. Many of the AEs noted in the salmeterol group are consistent with symptoms of beta adrenergic stimulation, such as

tachycardia and hyperactivity. Other AEs more common in the salmeterol groups included rhinorrhea, throat irritation, upper respiratory inflammation and keratitis/conjunctivitis.

Electrocardiograms (ECGs)

The ECG data does not suggest a new safety signal. A 12 lead ECG was recorded at screening (Visit 1) and at the end of the treatment period (Visit 6). Most subjects had normal ECGs. Four subjects had an abnormal ECG at baseline, but were enrolled in the study. Two subjects were noted to have unfavorable changes from baseline at Week 4: Subject 11488 in the salmeterol 50mcg group with increased heart rate and Subject 24696 with increased QTc interval in the salmeterol 25mcg group. There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval as shown below in Table 44. No subject had a QTcF interval ≥ 440msec at the end of the treatment period [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 81, 503].

Table 44 Mean QT, QTcF, QRS Duration, PR Intervals at Baseline, During Treatment, and Change from Baseline (msec)

	Placebo N=113		Salmeterol 25mcg BID N=112		Salmeterol 50mcg BID N=113	
	N	Mean	N	Mean	N	Mean
QT Interval						
Screening	113	302.7	112	301.3	113	301.7
End of Treatment	105	308.1	107	306.3	101	304.1
Change from Baseline	105	4.9	107	4.9	101	4.0
QTcF Interval						
Screening	113	368.2	112	367.5	113	369.9
End of Treatment	105	371.0	107	371.7	101	370.9
Change from Baseline	105	3.0	107	4.3	101	2.2
QRS Duration						
Screening	113	70.1	112	69.5	113	70.5
End of Treatment	105	71.5	107	70.0	101	75.6
PR Intervals						
Screening	113	123.6	112	124.2	113	124.8
End of Treatment	105	124.3	107	124.1	101	124.2

Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 81

Reviewer's Comment: The Applicant did not provide the change from baseline for QRS and PR intervals. However, there was minimal difference in the mean values for the intervals from screening to end of treatment except the salmeterol 50mcg treatment group, which showed an increase in QRS duration of approximately 5msec.

Mean heart rate values as measured via ECGs were similar at baseline across treatment groups (112-113bpm). The mean heart rate decreased from baseline in all 3 treatment groups at the end of the treatment period (Week 4) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 81].

Laboratory Evaluations

Laboratories were drawn at baseline and end of study (Visit 6). Shift table data were presented and reviewed. For hematology parameters, the majority of subjects had no shift or shifted to normal range for hemoglobin, hematocrit, WBC, or platelets. In general, the number of subjects with shifts from normal were similar among the treatment groups; however, the following were noted: a) there were more subjects who shifted to low hemoglobin in the salmeterol 50mcg treatment group (4%) versus < 1% in the placebo group; and b) there were more subjects in the salmeterol 25mcg group who shifted to high WBC (11%) than in the placebo group (4%) or the salmeterol 50mcg treatment group (6%). The Applicant defined thresholds for laboratory values and reported the incidence of hematology parameters outside the thresholds. In general, the number of subjects with laboratory values above or below threshold levels was similar across treatment groups [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 80, 484-485].
Reviewer's Comment: The hematology data does not suggest a safety signal.

For chemistry, again the majority of subjects had no shift or shifted to normal range for the chemistry parameters. In general, the number of subjects with a shift to high or low range were similar among the treatment groups; however, the following was noted. There were more subjects in the salmeterol 25mcg treatment group (29%) with shift to high total protein compared to placebo (13%) and salmeterol 50mcg group (16%). However, the majority of these subjects did not have total protein above the pre-defined threshold of 7.7g/dL (4% placebo, 2% salmeterol 25mcg, 5% salmeterol 50mcg). Most subjects did not have chemistry values outside the pre-defined threshold and in general, the number of subjects with laboratory values above or below threshold levels was similar across treatment groups; however, there were more subjects in the salmeterol 25mcg group with an albumin above the threshold (6%) versus 2% in the placebo and salmeterol 50mcg group [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 80, 486-493].

Reviewer's Comment: In Table 15 of the study report, it appears that the columns labeled "above" and "below" have been transposed. The columns do not reconcile with the source tables 13.16 and 13.17.

In a response to request for information, the Sponsor clarified that there is an error in Table 15 and the columns were mislabeled. Tables 13.16 and 13.17 are correct.

The glucose and potassium data are of interest because of the known effect of beta adrenergic stimulation on these laboratory parameters. There was little change from baseline in median serum potassium or glucose among the treatment groups. There were no subjects with shift to low potassium or below the threshold level. One subject in each treatment group had a decline from baseline potassium of >1mEq/L. There were no subjects with shift in glucose above the threshold level and more subjects in the placebo group with increase in glucose > 50mg/dL [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 79-80].

Vital Signs

Vital signs were measured at Screening, Day 1 (pre and post-dose), and Weeks 2, 3, 4. No significant changes in mean heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment as shown below in Table 45.

Table 45 Summary of Vital Signs

	Placebo N=113		Salmeterol 25mcg BID N=112		Salmeterol 50mcg BID N=113	
	N	Mean	N	Mean	N	Mean
Systolic BP (mmHg)						
Baseline	112	91.5	111	95.0	110	91.7
Week 4	106	91.9	107	93.6	101	91.4
Change from Baseline	105	0.5	107	-0.8	98	-0.0
Diastolic BP (mmHg)						
Baseline	112	57.6	111	58.9	110	57.2
Week 4	106	57.9	107	57.7	101	56.7
Change from Baseline	105	0.6	107	-1.1	98	-0.4
Pulse Rate (bpm)						
Baseline	113	98.6	112	103.2	111	103.7
Week 4	106	99.3	106	100.3	101	101.7
Temperature (C)						
Baseline	113	36.3	111	36.4	111	36.5
Week 4	106	36.4	107	36.4	100	36.4
Respiratory Rate (breaths/min)						
Baseline	113	22.6	112	23.1	111	23.9
Week 4	106	22.4	107	22.6	101	22.7

Source: N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 83

Reviewer's Comment: The post-dose blood pressure, heart rate, temperature and respiratory rate were also similar to pre-dose values.

Tremor Assessment

Physicians specifically assessed for tremor at each clinic visit. During Visit 1, physicians assessed for tremor pre and post-dose of study medication. Tremor severity was assessed as mild, moderate, or severe. Most subjects had no tremor present. Mild tremor was noted in all treatment groups at each clinic visit. The percentage of subjects with mild tremor was similar between treatment groups except for Week 3 and 4, in which more subjects in the salmeterol treatment groups were noted to have mild tremor than in the placebo group (9-15% in salmeterol groups vs. 7% in placebo at Week 3 and 10-11% in the salmeterol groups vs. 3% in placebo at Week 4) [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 83-84, 522-523].

On Day 1 post-study medication, moderate tremor was noted in 4 subjects (1 placebo, 2 salmeterol 25mcg, and 1 salmeterol 50mcg). At Week 4, there were more subjects with moderate tremor in the salmeterol groups (2 in each group) compared to none in the placebo group [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 83-84, 522-523].

Functional Status II-(R) Scores

Subject's health status was assessed by the parent/guardian at Baseline and Weeks 1, 2, 3, and 4. The Sponsor selected individual items from the FSII(R) questionnaire to evaluate potential signs and symptoms of adrenergic stimulation: sleep well; content/cheerful; act moody; unusually irritable; sleep thru night; unusually difficult; and react by crying. Individual item scores were

on a 0-2 scale, with higher numbers indicating better functioning. In general, mean scores increased for all the items in all treatment groups. Mean scores were similar at baseline and end of study [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 84].

Physical examinations were performed at baseline and end of study. More subjects in the salmeterol treatment groups (54%) had abnormal physical examination findings at baseline compared to the placebo group (41%). More subjects in the salmeterol groups (14-17%) had detrimental changes in physical examination findings compared to the placebo group (8%). The primary physical examination findings accounting for the difference had to do with the ears, nose, and throat system [N20236\2005-12-21\sms30076-01-body-csr.pdf, pg 85-86].

Safety Conclusions

In general, the safety data from Study SMS30076 do not suggest a new safety signal for the two doses of salmeterol administered in this study.

The AEs more common in the salmeterol groups, such as tachycardia and hyperactivity, were consistent with symptoms of beta adrenergic stimulation. Other AEs more common in the salmeterol groups included rhinorrhea, throat irritation, upper respiratory inflammation and keratitis/conjunctivitis.

There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval. Two subjects were noted to have unfavorable changes from baseline at Week 4: Subject 11488 in the salmeterol 50mcg group with increased heart rate and Subject 24696 with increased QTc interval in the salmeterol 25mcg group.

In terms of laboratory assessments, in general there were no safety signals identified. There were more subjects in the salmeterol 25mcg treatment group (29%) with shift to high total protein compared to placebo (13%) and salmeterol 50mcg group (16%). However, the majority of these subjects did not have total protein above the pre-defined threshold of 7.7g/dL (4% placebo, 2% salmeterol 25mcg, 5% salmeterol 50mcg). The change in total protein noted is not likely to be clinically significant.

No significant changes in mean heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment. Mild tremor was noted in all treatment groups at each clinic visit. The percentage of subjects with mild tremor was similar between treatment groups except for Week 3 and 4, in which more subjects in the salmeterol treatment groups were noted to have mild tremor than in the placebo group. At Week 4, there were more subjects with moderate tremor in the salmeterol groups (2 in each group) compared to none in the placebo group. In general, mean FS(II)R scores improved for potential adrenergic signs and symptoms in all treatment groups and were similar at baseline and end of study.

More subjects in the salmeterol treatment groups (54%) had abnormal physical examination findings at baseline compared to the placebo group (41%). More subjects in the salmeterol groups (14-17%) had detrimental changes in physical examination findings compared to the

placebo group (8%). The primary physical examination findings accounting for the difference had to do with the ears, nose, and throat system.

10.1.3.2.6 Discussion and Conclusions

Study SMS30076 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, parallel group study of 2 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 24 to 47 months.

Study SMS30076 did not demonstrate that salmeterol 25mcg BID or 50mcg BID were superior to placebo with regards to the primary endpoint, composite asthma symptom scores. Results were comparable between subjects using the (b) (4) and subjects using the (b) (4) holding chamber. In general, subgroup analyses and secondary endpoints did not suggest that the salmeterol treatment groups were superior to placebo.

In general, the safety data from Study SMS30076 do not suggest a new safety signal for the two doses of salmeterol administered in this study. The AEs more common in the salmeterol groups, such as tachycardia and hyperactivity, were consistent with symptoms of beta adrenergic stimulation. Other AEs more common in the salmeterol groups included rhinorrhea, throat irritation, upper respiratory inflammation and keratitis/conjunctivitis.

There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval. Two subjects were noted to have unfavorable changes from baseline at Week 4: Subject 11488 in the salmeterol 50mcg group with increased heart rate and Subject 24696 with increased QTc interval in the salmeterol 25mcg group. In terms of laboratory assessments, in general there were no clinically significant safety signals identified.

No significant changes in mean heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment. Mild tremor was noted in all treatment groups at each clinic visit. The percentage of subjects with mild tremor was similar between treatment groups except for Week 3 and 4, in which more subjects in the salmeterol treatment groups were noted to have mild tremor than in the placebo group. At Week 4, there were more subjects with moderate tremor in the salmeterol groups (2 in each group) compared to none in the placebo group.

More subjects in the salmeterol treatment groups (54%) had abnormal physical examination findings at baseline compared to the placebo group (41%). More subjects in the salmeterol groups (14-17%) had detrimental changes in physical examination findings compared to the placebo group (8%). The primary physical examination findings accounting for the difference had to do with the ears, nose, and throat system.

It should be noted that the results were not presented for the two holding chamber subpopulations.

10.1.4 Study SMS30077

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel Group, Multi-Center Clinical Trial of Four-Week, Four-Week Treatment with Salmeterol Xinafoate Inhalation Aerosol 25mcg BID, 50mcg BID, and Placebo Administered via a Holding Chamber with Facemask in Subjects with Symptoms of Asthma or Reactive Airways Disease Aged 6 to 23 Months

10.1.4.1 Protocol

Objective
The objective of Study SMS30077 is to evaluate the efficacy and safety of salmeterol xinafoate inhalation aerosol 25mcg BID and 50mcg BID administered via a holding chamber with facemask over a 4-week treatment period in pediatric subjects with symptoms of asthma or reactive airways disease aged 6 to 23 months.

Study Design
Study SMS30077 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, parallel group study of 2 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 6 to 23 months. Eligible subjects underwent a 7-28 day screening period during which parents/guardians recorded asthma symptom scores. Subjects meeting entry criteria were randomized at Visit 2 to one of the following treatment groups for the 29 day double-blind treatment period.

- Salmeterol xinafoate inhalation aerosol 25mcg BID
- Salmeterol xinafoate inhalation aerosol 50mcg BID
- Placebo MDI BID.

Study medication was administered via the (b) (4) valved holding chamber with facemask. Subjects were followed a weekly clinical visits (Visits 3, 4, 5, and 6). Study medication was discontinued at Visit 6. A follow up phone call was made approximately one week later (Visit 7) [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 19].

Study Population [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 20-24]
The following is a list of the pertinent inclusion criteria for the screening phase of SMS30077:

- Male or females 6 to 23 months of age
- A history of symptomatic asthma or reactive airways disease (RAD) and at least 1 exacerbation of increased symptoms of asthma/reactive airways disease requiring medical attention and pharmacotherapy within the preceding 3 months. In addition, subjects must also fulfill the following criteria prior to Visit 1
    - Have required therapy with a maintenance asthma medication (other than systemic corticosteroid) on a regular basis for the preceding 3 weeks **and/or**
    - Have required therapy with a short-acting beta-agonist for relief of respiratory symptoms at least three times per week over the preceding 3 weeks.

The following is a list of the pertinent inclusion criteria for the treatment phase of SMS30077:

- Symptoms of asthma/RAD (a score ≥ 1 on either or both daytime and nighttime asthma symptom scales) must have been demonstrated and recorded on the diary record on at least 5 of any 7 consecutive days of the 7 to 28 day treatment period.
- Albuterol use documented on the diary record on at least 2 days during the 5 of the 7 consecutive symptomatic screening days
- Parents/guardians comply with use of diary card on at least 80% of the days during the screening period
- Subject has not experienced an asthma exacerbation during the screening period

The following is a list of the pertinent exclusion criteria for SMS30077:

- African American descent

Reviewer's Comment: It is unclear why African American children were excluded from this study.

- Life-threatening asthma (ICU admission) within previous 3 months
- Treatment in the ER or hospital admission for airway obstruction on two or more occasions within the previous 3 months
- Acute systemic corticosteroid therapy within 2 weeks of screening
- Chronic systemic corticosteroid therapy for > 4 weeks within 3 months of screening
- Use of CNS stimulants (methylphenidate, pemoline, Dexedrine) within 30 days prior to screening
- Concurrent use of prohibited medications (see Concomitant Therapy, below)
- Concurrent significant disease including the following: CF, bronchiectasis, BPD, pneumonia (3 months), ENT disorders likely to require surgery during the treatment period, cardiovascular disease, congenital heart disease that required therapy/surgery within previous 12 months, seizure disorder, reflux esophagitis not controlled by pharmacotherapy, Cushing's Syndrome, renal disease, hematological disease, hepatic disease, malignancy, cellular or humoral immunity disorder, JRA, SLE, or other collagen vascular disease, inadequately controlled psychiatric disorder, DM, pan-hypopituitarism, hyperthyroidism, glaucoma, chickenpox
- Hypersensitivity to beta-agonists, component of MDI formulation, facemask, or adhesives
- Clinically significant laboratory, ECG, or CXR abnormalities
- Recent bacterial or viral URI, LRI, sinus, or middle ear infection that is not resolved within 2 weeks prior to screening or during the screening period

Materials

The parent/guardian for each subject received 2 canisters (A and B) at Visit 2 and 4. They were instructed to administer one inhalation from canisters A and B in the AM (0600-0800 hrs) and in the PM (1800-2000 hrs) [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 43]:

- Salmeterol xinafoate inhalation aerosol 25mcg BID
  - One inhalation 25mcg (canister A) in AM and in the PM
  - One inhalation placebo (canister B) in AM and in the PM
- Salmeterol xinafoate inhalation aerosol 50mcg BID
  - One inhalation 25mcg (canister A) in AM and in the PM

    - One inhalation 25mcg (canister B) in AM and in the PM
- Placebo MDI BID
    - One inhalation placebo (canister A) in AM and in the PM
    - One inhalation placebo (canister B) in AM and in the PM

Reviewer's Comment: The protocol did include a rationale utilizing the results of Study SMS20011 for the choice of salmeterol doses. According to the Sponsor, Study SMS20011 showed that salmeterol 25mcg BID and 50mcg BID are well-tolerated and safe for use in subjects age 6 to 23 months.

All study medication was administered via the (b) (4) chamber and facemask. Rescue medication was supplied as Ventolin MDI and albuterol nebules.

Concomitant Therapy

The following medications were prohibited during the course of the study [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 49]:

- Beta-adrenergic agonists other than study supplied albuterol
- Systemic corticosteroids
- Inhaled corticosteroids unless started at least 3 weeks prior to screening and continued during the treatment period
- Cromolyn or nedocromil unless started at least 3 weeks prior to screening and continued at stable dose during the treatment period
- Anti-cholinergics e.g. (ipratropium bromide)
- Theophylline or aminophylline
- Leukotriene antagonists, unless started 3 weeks prior to screening and continued during the treatment period
- Antiarrythmics
- Anticonvulsants
- CNS stimulants
- Beta adrenergic antagonists
- Nasal decongestants
- Narcotic or non-narcotic cough suppressants
- Immunosuppressives

Study Conduct

Informed consent was obtained prior to any screening or treatment study procedures being performed. Screening evaluations were performed at Visit 1. Subjects and guardians/parents were instructed on the proper completion of the diary card and proper administration of the MDI and nebules. Subjects underwent a 7 to 28 day screening period.

At Visit 2, eligibility criteria were reviewed and if subjects were eligible, they were randomized in a 1:1:1 fashion to one of the three treatment groups for a 28 day double-blind treatment period. Treatments were stratified by age at randomization: 6 to < 12 months and 12 to < 24 months. Study medication was administered via a valved holding chamber with facemask as described in the Materials Section above. Subjects were followed a weekly clinical visits (Visits 3, 4, 5, and

6). Study medication was discontinued at Visit 6. A follow up phone call was made approximately one week later (Visit 7). Throughout the treatment period, parents/guardians completed diary cards and recorded rescue medication use. Table 46 displays the study assessments performed at each clinic visit.

Table 46 SMS30077 Study Assessments

	Screening		Double Blind Treatment Phase						Post -Tx
Visit	1	Phone	2	3	4	5	6	Premature D/C	Follow-Up (Phone)
Day[5]	-28 to -7 days	At least weekly	1	8 (+5 days)[5]	15 (+5 days)[5]	22 (+5 days)[5]	29 (+5 days)[5]		36 (±2 days)[5]
Informed Consent	X								
Medical History	X								
Adverse Event assessment	X[1]	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Review Symptom Scores		X	X	X	X	X	X	X	
Review/dispense diary	X		X	X	X	X	X	X	
Administer FSII(R)			X	X	X	X	X	X	
Tremor assessment	X		X[2]	X	X	X	X[2]	X	
Physical exam	X						X	X	
Vital signs	X		X[2]	X	X	X	X[2]	X	
12-lead ECG	X						X[3]	X	
Nasal passage and Oropharyngeal exams	X		X	X	X	X	X	X	
Check MDI/holding chamber use	X		X	X	X	X			
Dispense/collect Study Med			X		X		X	X	
Dispense/collect albuterol	X		X		X		X	X	
Laboratory tests	X[4]						X	X	
Phone call to parent/guardian		X							X

1. Assessment of adverse events begins at Visit 1. Assessment of Serious Adverse Events begins when the informed consent is signed.
2. Evaluated pre-dose and one hour post dosing of study medication.
3. 12-lead ECGs at Visit 6 is to be conducted approximately 30 to 90 minutes after the administration of study drug.
4. Historical evidence of a normal laboratory assessment except for electrolytes (sodium, potassium, chloride, and bicarbonate) and glucose within 2 months of Visit 1 is acceptable provided there is no change in medical status since the last assessment. Historical evidence of normal electrolytes and glucose within one week of Visit 1 is acceptable provided there is no change in medical status since the last assessment (see Section 6.3.7).
5. Days during the double blind Treatment phase represent the number of days after the randomization Visit 2 where Day 1/Randomization is defined as the start of double blind treatment administration. The visit windows are to provide flexibility in scheduling visits. Subjects are to be treated for a minimum of 29 days and visits should be scheduled in such a manner to ensure treatment duration.

Source: N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 79

If subjects discontinued the study early, the investigator was to make an effort to perform the end of study evaluations.

Subjects were withdrawn due to worsening asthma. The protocol definition of asthma exacerbation is worsening asthma requiring emergency intervention, hospitalization, or treatment with an asthma medications not allowed by the protocol [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 38-39].

Efficacy [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 17]
The primary efficacy endpoint was the mean change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores (composite) during the 4 week treatment period. Each subject's parent/guardian was instructed to assess symptoms twice daily and record in the diary. The following is the scoring system.

- **Asthma symptoms scores**
  - **Night symptoms scores**
    - 0 None; no asthma symptoms (cough, wheeze, SOB)
    - 1 Mild; noticeable symptoms but not interfering with sleep
    - 2 Moderate; awakened once or more because of asthma symptoms

        - 3 Severe; awake most of the night due to asthma symptoms
    - **Day symptoms scores**
        - 0 None; no asthma symptoms (cough, wheeze, SOB)
        - 1 Mild; noticeable symptoms but not interfering with daily activities
        - 2 Moderate; symptoms present often, causing some interference with daily routine and activities
        - 3 Severe; symptoms continuous or present most of the day, restricting daily routine and activities severely

Secondary efficacy endpoints include the following:

- Average of the change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores (composite), Wk 1, Wk 2, Wk 3, Wk 4, Wk 1-4
- Percentage of symptom-free 24 hour days, Wk 1, Wk 2, Wk 3, Wk 4, Wk 1-4
    - A symptom free day is a day with a nighttime and daytime symptom score of 0
- Percentage of symptom-free and albuterol-free 24 hour days, Wk 1, Wk 2, Wk 3, Wk 4, Wk 1-4
- Percentage of nights with no awakenings, Wk 1, Wk 2, Wk 3, Wk 4, Wk 1-4
    - A night with no awakenings due to asthma is defined as a night with a symptom score of 0 or 1
- Individual daytime and nighttime asthma symptom scores, Wk 1, Wk 2, Wk 3, Wk 4, Wk 1-4
- Albuterol use
- Number of asthma exacerbations
- Subject discontinuations
- Child health status as assessed by the Functional Status II-(R)

The following is a brief description of the details of the secondary and other endpoints.

- **Rescue medication use (Ventolin use)**
    - Recorded by the parent/guardian in the diary as the number of puffs of MDI used over the preceding 24 hours
- **Asthma exacerbations**
    - An asthma exacerbation (treatment failure) was defined as an increase in signs or symptoms of asthma, not controlled by as needed albuterol and requiring asthma medications not allowed by the protocol

In addition, the Functional Status II(R) questionnaire (FSII(R)) was utilized to assess the health status of the subjects. The FSII(R) is an interviewer administered questionnaire which contains 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention during the previous two-week period. The FSII(R) was modified to assess the behavior during the previous week. Each item was scored on a three-point scale indicating the frequency with which a child exhibits the specified behavior or performs the specified activity. A second level of responses evaluated to what extent poor functioning indicated in the first level of questioning is related to the child's illness. The items are summed and a total score is calculated as the percent of total possible scores. Higher scores reflect a better functional status. The FSII(R) was administered at all Visits 2-6 [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 41].

Safety

Safety assessments included adverse events, physical examination, laboratories, ECGs, physician's assessment of tremor and symptoms of adrenergic stimulation (irritability and lack of sleep) from the FSII(R) questionnaire. Each safety measure will be briefly discussed [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 79].

- **Physical examination**
  - A physical exam was performed at screening (Visit 1) and end of study (Visit 6)
- **Oropharyngeal and Nasal examination**
  - A nasal and oropharyngeal examination was performed at each study visit
- **Vital signs**
  - A set of vital signs (HR, BP, T, RR) was measured at each study visit
- **Adverse Events**
  - Adverse events were collected via the diary card and were reviewed at each visit
- **ECG**
  - A 12 lead ECG was recorded at screening (Visit 1) and at the end of the treatment period (Visit 6)
  - An independent electrocardiographer, blinded to treatment assignment, provided measurements of heart rate, PR interval, QTc interval, QRS duration, and an overall interpretation of each ECG collected
  - Criteria were specified in the protocol for an abnormal ECG. Inclusion criteria specified subjects must have a normal screening ECG
  - The ECG collected at Visit 6 were compared to the screening ECG to determine if a clinically significant change occurred.
- **Laboratories**
  - Chemistry, hematology, and electrolytes were performed at Visit 1 (if indicated) and Visit 6
  - Baseline labs within previous 3 months of Visit 1 were acceptable
- **Tremor assessments**
  - Tremor was evaluated by the investigator at each visit. When study drug was administered during Visits 2 and 6, tremor was assessed pre-dose and one hour post-dose.
  - Tremor was graded on the following scale
    - 0 – no tremor present
    - 1 – mild tremor present
    - 2 – moderate tremor present
    - 3 - severe tremor present

Data Analysis

A minimum of 45 completed subjects per treatment group was requested by the FDA. The dropout rate was estimated to be 20%. Approximately 180 subjects (60 per treatment group) were to be randomized.

The primary efficacy endpoint was the average of the change from baseline in daytime asthma symptom scores and the change from baseline in nighttime asthma symptom scores during the

treatment period. The Composite Symptom Score = (change from baseline in daytime score + change from baseline in nighttime score)/2. Two pairwise comparisons between placebo and the active groups were the primary contrasts of interest. The ANCOVA using baseline as the covariate and controlling for region was the primary analysis method. Baseline was defined as the average of the daytime and nighttime scores recorded during the last 7 days of the screening period immediately prior to randomization [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 66].

The following are details of some of the secondary endpoints [N20236\2005-12-21\sms30077-03-protocol-amend-2.pdf, pg 64-68].

- **Percentage of symptom free days**
  - P = 100* (# of symptom-free days)/(# of days in treatment period)
  - Symptom free day is a day in which subjects has a nighttime & daytime score of 0
- **Percentage of symptom free days and albuterol free days**
  - P = 100* (# of symptom-free days and albuterol free days)/(# of days in treatment period)
- **FSII(R) –** Total scores and individual item scores were to be summarized by treatment group and study visit

Amendments

Three amendments were made to the original protocol (May 6, 2003, August 13, 2003, and June 14, 2005). The following is a brief summary of the amendments [N20236\2005-12-21\sms30077-03-protocol-amend-3.pdf, pg 2-3].

- Clarified abnormal ECG criteria, laboratory threshold values, sample size assumptions
- Added reactive airways disease as the clinical presentation
- Number of subjects enrolled amended from 165 to 180
- Clarified exclusion criteria
  - Clinically significant laboratories
  - African American children
- Change in minimum number of completed subjects from 50 to 45 per treatment group
- Nasal examination population and oropharyngeal population added

10.1.4.2 Results

Study SMS30077 was initiated November 8, 2003, and completed June 10, 2005. The final study report is dated October 2005. The drug supplies for the study were salmeterol xinafoate inhalation aerosol 25mcg from batch identification numbers 3ZP1418 and 1ZP0573 and placebo inhalation aerosol from batch identification number 2ZP2094 [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 1 &5].

10.1.4.2.1 Subject Disposition

Two hundred fifty-six subjects were screened at 43 investigational sites. One hundred sixty seven subjects were randomized and 153 subjects (92%) completed treatment. Fourteen subjects

were discontinued from the study as shown below in Table 47. The common reason for discontinuation was lack of efficacy.

Table 47 Subject Disposition for Study SMS30077

	Placebo n (%)	Salmeterol 25mcg BID n (%)	Salmeterol 50mcg BID n (%)
Randomized (N=167)	55	56	56
Completed (N=153)	50 (91)	50 (89)	53 (95)
Discontinued (N=14)	5 (9)	6 (11)	3 (5)
AE	1 (2)	1 (2)	0
Protocol Violation	1 (2)	0	1 (2)
Lost to follow-up	1 (2)	1 (2)	0
Lack of efficacy	2 (4)	3 (5)	1 (2)
Consent withdrawn	0	1 (2)	0
Other	0	0	1 (2)

Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 63

10.1.4.2.2 Protocol Violations

Approximately 43% of subjects had protocol violations. The salmeterol 50mcg treatment group had the lowest percentage of subjects with protocol violations (38%). The most common protocol violations were non-compliance with study procedures, prohibited concurrent medications, and other [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 139].
Reviewer's Comment: There were 5 subjects with affiliation to the investigational site (3 placebo and one in each salmeterol treatment group).

10.1.4.2.3 Demographics and Baseline Characteristics

The mean age for subjects was approximately 15.2 months with a minimum age of 4 months and a maximum age of 23 months. Approximately 30% percent of the children were 6-11 months 69% were 12-23 months, and <1% were <6 months. There were more males (66%) than females (34%). The majority of subjects were White (54%), while 46% were American Hispanic, and <1% were Other. All subjects were assigned to the (b) (4) The placebo group had a more even mix of males and females (53% and 47%, respectively) compared to the other treatment groups (70-77% males and 23-34% females) [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 65].
Reviewer's Comment: The age stratification was similar among the treatment groups.

The most common concurrent medical conditions were in the allergies, skin, musculoskeletal, GI, and ENT body systems. Approximately 70% of subjects used concurrent asthma medications during the treatment period, with inhaled corticosteroids being the most frequently used asthma medication [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 161].

Mean treatment compliance was high and similar among treatment groups (92-93%). Five subjects in each treatment group were <80% compliant [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 174].

10.1.4.2.4 Efficacy

Primary Endpoint

The primary efficacy endpoint was the average of the change from baseline in daytime asthma symptom scores and the change from baseline in nighttime asthma symptom scores during the treatment period (i.e. the change from baseline Composite Symptom Score). The Composite Symptom Score = (mean daytime score + mean nighttime score)/2. Baseline was defined as the average of the daytime and nighttime scores recorded during the last 7 days of the screening period immediately prior to randomization. Each subject's parent/guardian was instructed to assess symptoms twice daily and record in the diary. Change from Baseline Composite Asthma Symptoms Score = (mean change from baseline daytime score + mean change from baseline nighttime score)/2.

Baseline mean composite asthma symptom scores were similar between treatment groups. The mean composite asthma symptom scores improved in each treatment group during the treatment period. The mean change from baseline was similar between treatment groups as shown in the table below [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 67].

Table 48 Composite* Asthma Symptom Scores in Study SMS30077 ITT Population

	Placebo n=55	Salmeterol 25mcg BID n=56	Salmeterol 50mcg BID n=56
Baseline mean score (SD)	1.3 (0.5)	1.0 (0.5)	1.2 (0.6)
Week 1-4			
Adjusted mean score (SE)	0.8 (0.10)	0.8 (0.10)	0.8 (0.10)
Adjusted mean change (SE)	-0.4 (0.10)	-0.4 (0.10)	-0.4 (0.10)
Treatment group difference vs. placebo		0 (0.09)	0 (0.09)
95% CI vs. placebo		-0.2, 0.2	-0.2, 0.2
p-value vs. placebo		0.932	0.954

* Composite Symptom Score = (mean daytime score + mean nighttime score)/2
** Change from Baseline Composite Asthma Symptoms Score = (mean change from baseline daytime score + mean change from baseline nighttime score)/2
Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 67

The Applicant analyzed the primary endpoint for subgroups based upon concurrent asthma medication use. For the concurrent asthma medication subpopulations, the subjects with concurrent ICS use are of interest. For subjects who used ICS and subjects who did not use concurrent asthma medication, the baseline composite asthma symptom scores were similar and the decline from baseline were similar across treatments and between subgroups [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 68].

The Applicant analyzed the composite asthma symptom scores for the individual weeks. Again there was no significant difference between treatment groups for the composite asthma symptom scores or change from baseline at the individual weeks [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 70].

Secondary Endpoints

The pre-specified secondary efficacy endpoints will be briefly discussed.

Individual Daytime and Nighttime Asthma Symptom Scores

The baseline mean daytime and nighttime asthma symptom scores and the mean decline from baseline were similar across treatment groups. There was no significant difference between treatment groups for the individual daytime and nighttime asthma symptom scores for Weeks 1-4 [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 71].

Table 49 displays additional secondary efficacy variables: percent symptom free days, percent symptom and albuterol free days, albuterol use, and percent nights without awakenings. The percent of symptom free days and percent of symptom, albuterol free days, and the percent of nights without awakenings increased in all 3 treatment groups during the treatment period. Albuterol use decreased in all 3 treatment groups during the treatment period. There were no statistically significant differences in the salmeterol treatment groups compared to the placebo group for any of these secondary efficacy variables.

Table 49 Secondary Efficacy Measures in Study SMS30077 ITT Population

	Placebo n=55	Salmeterol 25mcg BID n=56	Salmeterol 50mcg BID n=56
Percent Symptom Free Days*			
Baseline Mean (SE)	6.8 (1.92)	9.7 (2.44)	6.5 (1.77)
Week 1-4			
Mean (SE)	27.9 (4.09)	34.2 (4.22)	29.9 (4.07)
Mean change (SE)	20.0 (4.04)	25.3 (3.76)	23.8 (3.94)
p-value vs. placebo		0.218	0.942
Percent Symptom and Albuterol Free Days**			
Baseline Mean (SE)	6.5 (1.91)	8.4 (2.38)	4.5 (1.28)
Week 1-4			
Mean (SE)	23.7 (3.72)	32.5 (4.26)	27.9 (3.96)
Mean change (SE)	16.8 (4.08)	25.0 (3.90)	23.9 (3.77)
p-value vs. placebo		0.110	0.491
Albuterol Use (puffs/24 hours)			
Baseline Mean (SE)	3.9 (0.42)	3.6 (0.33)	3.8 (0.29)
Week 1-4			
Mean (SE)	2.3 (0.33)	1.7 (0.25)	1.7 (0.21)
Mean change (SE)	-1.6 (0.34)	-1.9 (0.29)	-2.1 (0.31)
p-value vs. placebo		0.943	0.489
Percent Nights No Awakenings***			
Baseline Mean (SE)	64.7 (4.10)	75.3 (3.98)	67.7 (4.51)
Week 1-4			
Mean (SE)	80.3 (2.72)	82.1 (2.70)	78.5 (3.41)
Mean change (SE)	15.4 (3.91)	7.3 (3.34)	11.0 (4.04)
p-value vs. placebo		0.107	0.407

* **Percentage of symptom free days** = 100* (# of symptom-free days)/(# of days in treatment period); symptom free day is a day in which subjects has a nighttime and daytime score of 0
Percentage of symptom free days and albuterol free days = 100* (# of symptom-free days and albuterol free days)/(# of days in treatment period)
***Percent Nights No Awakenings** = 100*(# nights with nighttime symptom score of 0 or 1)/(# of days in treatment period)
Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 72

Asthma Exacerbations

An asthma exacerbation (treatment failure) was defined as an increase in signs or symptoms of asthma, not controlled by as needed albuterol and requiring asthma medications not allowed by the protocol. Seven subjects experienced an asthma exacerbation during the study. More subjects in the salmeterol 25mcg group (5) experienced an asthma exacerbation compared to 1 in the placebo group and 1 in the salmeterol 50mcg group. Most of the exacerbations were moderate in severity. The mean time to onset of first exacerbation was 12 days in the placebo group versus 17 days in the salmeterol treatment groups [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 73, 226-227].

Functional Status II-(R) Scores

Subject's health status was assessed by the parent/guardian at Baseline and Weeks 1, 2, 3, and 4. Baseline total scores were similar between treatment groups. Mean scores improved in all

groups during the treatment period. There was no statistical difference in the mean change FSII(R) score between treatment groups; however, the salmeterol 25mcg group had the smallest numerical improvement in the FSII(R) score [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 74].

Efficacy Conclusion

Study SMS30077 did not demonstrate that salmeterol 25mcg BID or 50mcg BID were superior to placebo with regards to the primary endpoint, composite asthma symptom scores. Results were comparable between treatment groups. In general, secondary endpoints did not suggest that the salmeterol treatment groups were superior to placebo.

10.1.4.2.5 Safety

The safety findings from this study, along with the safety data from the other clinical studies, will be reviewed in depth in the Integrated Review of Safety section of this review. A summary of the safety findings from this study follows.

Exposure

As shown below in Table 50, study medication exposure was similar between treatment groups. The majority of subjects received more than 28 days of treatment.

Table 50 Study Medication Exposure in SMS30077

	Placebo n=55	Salmeterol 25mcg BID n=56	Salmeterol 50mcg BID n=56
Exposure (days) Median	30	30	31
Range (days)	2-41	5-57	8-48
Length of treatment – n (%)			
<= 7 days	1 (2)	1 (2)	0
8-14 days	1 (2)	2 (4)	1 (2)
15-21 days	2 (4)	1 (2)	1 (2)
22-28 days	2 (4)	2 (4)	2 (4)
>28 days	49 (89)	50 (89)	52 (93)

Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 75

Adverse Events

The AE data suggest that irritability is more common with salmeterol use. Irritability, is a possible symptom of beta adrenergic stimulation. Other AEs reported were not unexpected in the patient population.

There were no deaths in this study. There were two subjects with SAEs, one of which occurred during the screening period (gastroenteritis). The other SAE was reported by a 21 month old female in the salmeterol 25mcg group. The subject was hospitalized for pneumonia 27 days following the start of study medication [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 79].

Two subjects discontinued due to AEs. One of the discontinuations was the subject with the SAE described above. In addition, a 13 month old male in the placebo group was discontinued from the study for a rash.

The majority of subjects (>60%) reported at least one AE during the treatment period. The incidence of AEs was similar between treatment groups. Rhinorrhea, rhinitis, irritability, ear infection, influenza, viral URTI, rash, conjunctivitis, otitis media, and pharyngotonsilitis were reported at a higher incidence in one of the salmeterol groups compared to placebo as shown in the table below.

Table 51 Adverse Events >3% Incidence and More Common than Placebo during the Treatment Period

Number of Subjects with AE	Placebo N=55 n (%)	Salmeterol 25mcg BID N=56 n (%)	Salmeterol 50mcg BID N=56 n (%)
Any Event	47 (85)	44 (79)	48 (86)
Pyrexia	16 (29)	19 (34)	18 (32)
Diarrhea	7 (13)	9 (16)	6 (11)
Rhinorrhea	4 (7)	6 (11)	8 (14)
Rhinitis	3 (5)	6 (11)	3 (5)
Irritability	0	5 (9)	4 (7)
Ear infection	1 (2)	5 (9)	2 (4)
Influenza	2 (4)	4 (7)	2 (4)
Viral URTI	1 (2)	4 (7)	0
Rash	2 (4)	4 (7)	1 (2)
Conjunctivitis	2 (4)	4 (7)	2 (4)
Bronchitis	0	3 (5)	1 (2)
Otitis media	2 (4)	2 (4)	4 (7)
Pneumonia	0	2 (4)	0
Pharyngotonsillitis	1 (2)	1 (2)	4 (7)
Gastroenteritis	0	0	2 (4)
Sinus tachycardia	1 (2)	1 (2)	3 (5)
Tachycardia	1 (2)	1 (2)	2 (4)
Headache	1 (2)	0	2 (4)

Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 77

Reviewer's Comment: The Applicant also presented the AEs attributed to study medication. The drug-related AEs included tachycardia, irritability, increased alkaline phosphatase, abnormal QRS axis, cough, dysphagia, psychomotor hyperactivity, and rash. Overall, drug-related AEs were more common in the placebo group with the exception of irritability, which was more common in the salmeterol groups.

The Applicant presented the data for AEs possibly related to adrenergic stimulation. The incidence of these particular AEs were similar across treatment groups. The most common noted AEs were irritability, tachycardia, and headache. As noted above, irritability was more common in the salmeterol groups.

Electrocardiograms (ECGs)

The ECG data suggest a slight increase in QT interval with salmeterol use. A 12 lead ECG was recorded at screening (Visit 1) and at the end of the treatment period (Visit 6). Most subjects had normal ECGs at baseline; however, four subjects had an abnormal ECG at baseline that were deemed not clinically significant and were enrolled in the study. A similar number of subjects in each treatment group had an unfavorable clinically significant change from baseline, the majority of which were sinus tachycardia noted at Week 4. One subject in the placebo group was discontinued from the study for an unfavorable clinically significant change from baseline ECG (sinus tachycardia and left axis deviation). There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF intervals. However, a mean increase in QT interval of 5msec in the salmeterol 25mcg BID and a mean increase of 3msec in QRS in the salmeterol 50mcg BID group were noted. No subject had a QTcF interval ≥ 440msec at the end of the treatment period [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 86].

Table 52 Mean QT, QTcF, QRS Duration, PR Intervals at Baseline, During Treatment, and Change from Baseline (msec)

	Placebo N=55		Salmeterol 25mcg BID N=56		Salmeterol 50mcg BID N=56	
	N	Mean	N	Mean	N	Mean
Heart Rate (bpm)						
Baseline	55	130.4	56	126.8	56	133.6
Week 4	51	129.2	50	126.1	53	130.6
Change from Baseline	51	-1.5	50	-0.3	53	-2.2
QT Interval						
Baseline	55	283.9	56	301.3	56	301.7
Week 4	51	284.3	50	306.3	53	304.1
Change from Baseline	51	0.2	50	4.9	53	4.0
QTcF Interval						
Baseline	55	366.8	56	366.8	56	361.7
Week 4	51	365.9	50	368.1	53	365.5
Change from Baseline	51	-1.4	50	1.9	53	3.5
QRS Duration						
Baseline	55	112.5	56	108.8	56	104.8
Week 4	51	112.6	50	107.0	53	107.8
PR Intervals						
Baseline	55	67.6	56	68.4	56	67.6
Week 4	51	66.6	50	67.1	53	66.9

Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 86

There were a similar number of subjects in each treatment group whose change from baseline in QTc were outliers. Of note are the subjects who had an increase from baseline QTc: in the salmeterol 50mcg treatment group 3 subjects had an increase from baseline QTc of 81, 50, and 40msec, respectively; and one subject in the placebo group had an increase of 37msec [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 87-88].

Laboratory Evaluations

The laboratory data do not identify a new safety signal for salmeterol. Laboratories were drawn at baseline and end of study (Visit 6). Shift table data were presented and reviewed. For hematology parameters, the majority of subjects had no shift or shifted to normal range for hemoglobin, hematocrit, WBC, or platelets. In general, the number of subjects with shifts from normal were similar among the treatment groups; however, there were more subjects who shifted to low hematocrit in the salmeterol treatment groups (6-7%) versus 0% in the placebo group. The Applicant defined thresholds for laboratory values and reported the incidence of hematology parameters outside the thresholds. In general, the number of subjects with hematology laboratory values above or below threshold levels was similar across treatment groups [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 81, 438-440].

For chemistry, again the majority of subjects had no shift or shifted to normal range for the chemistry parameters. In general, the number of subjects with a shift to high or low range were similar among the treatment groups; however, there were more subjects in the salmeterol treatment groups with shift to low potassium. Most subjects did not have chemistry values outside the pre-defined threshold and in general, the number of subjects with laboratory values above or below threshold levels was similar across treatment groups [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 81, 441-444].

The glucose and potassium data are of interest because of the known effect of beta adrenergic stimulation on these laboratory parameters. There was little change from baseline in median serum potassium or glucose among the treatment groups. There were seven subjects (2 salmeterol 25mcg and 5 salmeterol 50mcg) with shift to low potassium; however, none of the decreases were below the threshold level (< 3mEq/L). Upon review of the individual data, no subject had a decline in potassium to < 3.5meq/L. Outlier analyses identified two subjects in the placebo group and two subjects in the salmeterol 25mcg group whose change from baseline potassium were outliers. One subject in the placebo and salmeterol 25mcg group had increase in potassium of 1.2mEq/L and 1.4mEq, respectively. One subject in the placebo and salmeterol 25mcg group had decrease in potassium of 1.2mEq/L and 2.2mEq, respectively.

In terms of glucose, one subject in the placebo group and one in the salmeterol 50mcg group had shifts to glucose values above the threshold (140mg/dL) and no subjects had decrease below the threshold (45mg/dL). Outlier analyses identified three subjects in the salmeterol 25mcg group (increase of 59mg/dL, decrease 46mg/dL, and decrease 131mg/dL) and three subjects in the salmeterol 50mcg group (increase 123mg/dL, decrease 45mg/dL (2)) whose change from baseline glucose were outliers [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 84-85].

Vital Signs

Vital signs were measured at Screening, Day 1 (pre and post-dose), and Weeks 2, 3, 4 (pre and post-dose). No clinically significant changes in mean heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment as shown below. However, it was noted that the salmeterol groups did show a slight increase in mean pulse of approximately 7 and 4 beats per minute.

Table 53 Summary of Vital Signs

	Placebo N=55		Salmeterol 25mcg BID N=56		Salmeterol 50mcg BID N=56	
	N	Mean	N	Mean	N	Mean
Systolic BP (mmHg)						
Baseline	55	88.9	56	88.4	54	88.5
Week 4	50	91.4	49	92.6	53	88.2
Change from Baseline	50	2.0	49	4.0	52	-0.1
Diastolic BP (mmHg)						
Baseline	55	54.4	56	54.7	54	54.9
Week 4	50	54.7	49	54.2	53	56.1
Change from Baseline	50	0.4	49	2.1	52	1.3
Pulse Rate (bpm)						
Baseline	55	118.7	56	115.6	56	117.5
Week 4	50	118.1	49	122.8	63	121.9
Temperature (C)						
Baseline	55	36.5	56	36.4	56	36.5
Week 4	50	36.5	49	36.5	63	36.6
Respiratory Rate (breaths/min)						
Baseline	55	27.0	56	26.5	56	26.2
Week 4	50	26.3	49	25.9	63	25.1

Source: N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 88

Reviewer's Comment: The post-dose blood pressure, heart rate, temperature and respiratory rate were also similar to pre-dose values.

Tremor Assessment

Physicians specifically assessed for tremor at each clinic visit. During Visit 1, physicians assessed for tremor pre and post-dose of study medication. Tremor severity was assessed as mild, moderate, or severe. Most subjects had no tremor present. Mild tremor was noted in one subject in the salmeterol 50mcg treatment group pre-dose on Day1 and moderate tremor post dose on Day 1. Mild tremor was noted in one subject in the placebo group at Week 1 [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 94, 962-965].

Functional Status II-(R) Scores

Subject's health status was assessed by the parent/guardian at Baseline and Weeks 1, 2, 3, and 4. The Sponsor selected individual items from the FSII(R) questionnaire to evaluate potential signs and symptoms of adrenergic stimulation: sleep well; content/cheerful; act moody; unusually irritable; sleep thru night; unusually difficult; and react by crying. Individual item scores were on a 0-2 scale, with higher numbers indicating better functioning. Mean scores were similar at baseline and end of study and in general, scores increased slightly for most of the items in each treatment group [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 95].

Physical Examinations Including Oral and Nasopharyngeal Examinations

Physical examinations were performed at baseline and end of study. A similar percentage of subjects in each treatment group had abnormal physical examination findings at baseline. More

subjects in the salmeterol 25mcg treatment group (32%) had detrimental changes in physical examination findings compared to the other groups (20%). The primary physical examination findings accounting for the difference had to do with the ears, nose, and throat system [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 89, 588].

Dedicated nasal examinations were significant for more subjects in the salmeterol 25mcg treatment group with shifts from normal to abnormal nasal findings compared to the other treatment groups. The Sponsor amended the study to include nasal pharyngeal examinations because of findings in the preclinical juvenile dog studies. Nasal examinations were performed at each clinic visit. Overall, there were more subjects in the salmeterol 25mcg treatment group (29%) with a shift from normal to abnormal nasal findings compared to the other groups (16-17%). The majority of changes were related to nasal secretions – quantity, consistency, and color. The Sponsor performed additional analyses of the data and noted that ~60-70% of subjects with abnormal changes in nasal exam had a history of allergies. Some of the changes were observed close to URTI, sinusitis, ear infections, and other URT AEs [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 90-91].

In terms of oropharyngeal examinations, there were a similar percentage of subjects in each treatment group (4-5%) with shift from normal to abnormal from baseline to the end of treatment. The majority of the changes were change in tonsil size/color and change in posterior pharyngeal wall [N20236\2005-12-21\sms30077-01-body-csr.pdf, pg 9-94].

Safety Conclusions

In general, the safety data from Study SMS30077 do not suggest a new safety signal for salmeterol.

The AE data suggest that irritability is more common with salmeterol use. Irritability is a symptom of beta adrenergic stimulation. Other AEs reported were not unexpected in the patient population. There were no clinically significant changes from baseline in mean PR, QRS duration, QT interval, or QTcF interval; however, the ECG data suggest an increase in the mean QT interval of 3-5msec with salmeterol use. In terms of laboratory assessments, in general there were no safety signals identified.

No clinically significant changes in mean heart rate, blood pressure, temperature, or respiratory rate were noted from the start of treatment to the end of treatment as shown below. However, it was noted that the salmeterol groups did show a slight increase in mean pulse of approximately 7 and 4 beats per minute. Mean FSII(R) scores were similar at baseline and end of study and in general, scores increased slightly for most of the items in each treatment group. The tremor data did not suggest an increase in tremor with salmeterol use.

More subjects in the salmeterol 25mcg treatment group (32%) had detrimental changes in physical examination findings compared to the other groups (20%). The primary physical examination findings accounting for the difference had to do with the ears, nose, and throat system. Dedicated nasal examinations were significant for more subjects in the salmeterol 25mcg treatment group with shifts from normal to abnormal nasal findings compared to the other

treatment groups. The majority of changes were related to nasal secretions – quantity, consistency, and color. In terms of oropharyngeal examinations, there were a similar percentage of subjects in each treatment group (4-5%) with shift from normal to abnormal from baseline to the end of treatment.

10.1.4.2.6 Discussion and Conclusions

Study SMS30077 was a double-blind, randomized, double-dummy, placebo-controlled, multicenter, parallel group study of 2 doses of salmeterol xinafoate inhalation aerosol in subjects with asthma aged 6 to 23 months.

Study SMS30077 did not demonstrate that salmeterol 25mcg BID or 50mcg BID were superior to placebo with regards to the primary endpoint, composite asthma symptom scores. In general, subgroup analyses and secondary endpoints did not suggest that the salmeterol treatment groups were superior to placebo.

In general, the safety data from Study SMS30077 do not suggest a new safety signal for the two doses of salmeterol administered in this study. One notable AE more common in the salmeterol groups, irritability, is a symptom of beta adrenergic stimulation. The ECG data was notable for an increase in the mean QT interval of 3-5msec with salmeterol use. The laboratory assessments and tremor assessments did not suggest a signal. Changes in mean vital sign measurement were similar among the treatment groups; however, it was noted that the salmeterol groups did show a slight increase in mean pulse of approximately 7 and 4 beats per minute.

More subjects in the salmeterol 25mcg treatment group (32%) had detrimental changes in physical examination findings compared to the other groups (20%). The primary physical examination findings accounting for the difference had to do with the ears, nose, and throat system. Dedicated nasal examinations were significant for more subjects in the salmeterol 25mcg treatment group with shifts from normal to abnormal nasal findings compared to the other treatment groups. The majority of changes were related to nasal secretions – quantity, consistency, and color. In terms of oropharyngeal examinations, there were a similar percentage of subjects in each treatment group (4-5%) with shift from normal to abnormal from baseline to the end of treatment.

10.2 Line-by-Line Labeling Review

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