CLINICAL REVIEW

Application Type	NDA
Submission Number	20-983
Submission Code	(b) (4)
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Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	2/22/08
Established Name	Albuterol Sulfate HFA Inhalation Aerosol
(Proposed) Trade Name	Ventolin HFA
Therapeutic Class	β-2 agonist bronchodilator
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Oral Inhalation Aerosol
Dosing Regimen	Albuterol 180 mcg (2 inhalations) every 4 to 6 hours; in some patients, 90 mcg (1 inhalation) every 4 hours may be sufficient
Indication	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older
Intended Population	Pediatric patient population from birth to less than 4 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

(b) (4)

The Applicant conducted three pediatric clinical studies to evaluate the efficacy and safety of Ventolin HFA in patients from birth to less than 4 years of age with reversible airway disease. The pediatric clinical studies failed to demonstrate the efficacy of Ventolin HFA in the study patient population. There were no new safety signals revealed from the three pediatric clinical studies. Results from *in vitro* and clinical studies should be added to the labeling for the product, as it represents important information for the practitioner.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific risk management /minimization activities are proposed or are necessary for this application.

1.2.2 Required Phase 4 Commitments

There are no Phase 4 commitments required for this application.

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

There are three pediatric clinical studies in this supplemental NDA submission. Clinical studies 1 and 2 were to assess the safety and efficacy of Ventolin HFA delivered with facemask spacers in children with obstructive airway disease between the ages of 2 to <4 years and from birth to <2 years, respectively. Clinical study 3 was to assess the safety and efficacy of cumulative-dose administration of either albuterol sulfate inhalation solution delivered via nebulization or albuterol sulfate HFA MDI with a valve holding chamber with attached facemask, in an acute bronchodilation setting in children from birth to <2 years of age with obstructive airway disease.

The Applicant also conducted the *in vitro* studies to characterize the dose delivery from the Ventolin HFA inhaler with two different U.S.-marketed spacers.

1.3.2 Efficacy

The efficacy review is based on the three pediatric efficacy and safety studies in the submission. Study SB020001 was a 4-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of Ventolin HFA delivered with facemask and two different valved holding chambers in subjects aged 24 to <48 months with asthma symptoms (i.e. wheeze, cough, dyspnea or chest tightness) or consistent with asthma or obstructive airway disease or bronchospasm. Study SB030001 had a same study design with the study SB020001, except that the study subjects were pediatric population from birth to <24 months old and one valved holding chamber was used to deliver the test drug. Study SB030002 was a one-day cumulative dose study of Ventolin HFA delivered with one valved holding chamber in pediatric population from birth to <24 months old.

The study SB020001 and SB030001 demonstrated that Ventolin HFA 180 mcg and 360 mcg MDI inhalation delivered through a facemask and valved holding chambers had no significant effect on asthma symptom scores in pediatric patients from birth to <4 years old. In study SB030002, a cumulative dose of Ventolin HFA inhalation in 3-hour treatment period decreased modified Tal asthma symptom scores 49.8% and 48.4% comparing to baseline in Ventolin HFA 180 mcg and 360 mcg groups, respectively. However, there was no placebo group in study SB030002. In all three studies, there were no differences between Ventolin HFA 180 mcg and 360 mcg groups.

1.3.3 Safety

The safety data from the three clinical studies in pediatric patients from birth to <4 years old did not identify new safety signals. A total of 250 subjects were exposed to investigational drug, Ventolin HFA (albuterol sulfate inhalation aerosol), in three pediatric clinical studies in subjects aged from birth to <48 months. The study subjects were exposed from three hours to 4 weeks. In two of the clinical studies 163 subjects were dosed three times daily for 4 weeks. One study was a cumulative dose study, in which 87 subjects were exposed to a maximum of 6 doses of the drug in 3 hours. The adverse event data from the three clinical studies in subjects aged from birth to <48 months did not identify new safety signals. The reported adverse events were common symptoms in pediatric population, including upper respiratory infection, diarrhea, cough, diarrhea, vomiting, fever, sinus tachycardia, skin disorder, and others.

There were no deaths. A total of 4 non-fatal serious adverse events (SAEs) were reported in the three clinical studies. There were two cases of asthma exacerbation during the studies SB20001 and SB 30001, one case of fever, and one case of RSV infection after completing the study SB030002. None of the serious adverse events were considered by the investigators to be related to study medication. There was one dropout from the three clinical studies due to an SAE. This subject was in placebo group and withdrew from the study after experiencing an asthma exacerbation. Laboratory studies, vital signs, and ECG in the three clinical studies in subjects aged from birth to <48 months did not identify a safety signal.

The Applicant searched the company safety database for postmarketing adverse events reported for Ventolin HFA. In the albuterol HFA <4 years age group, 13 cases were identified as serious

adverse events (12 spontaneous reports and one from a clinical trial). The postmarketing adverse events in children <4 years old did not raise new concerns regarding a safety signal.

1.3.4 Dosing Regimen and Administration

(b) (4)

Ventolin HFA (albuterol sulfate inhalation aerosol) was approved for treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The Applicant conducted three pediatric clinical studies to evaluate the efficacy and safety of Ventolin HFA in patients from birth to less than 4 years of age with reversible airway disease.

The data from the clinical and in vitro studies suggest that the dose chosen for the clinical studies is not optimal. Efficacy may not be extrapolated from previously conducted clinical studies in patients 4 years of age and greater because the previously conducted studies did not use a valved holding chamber and facemask and because in vitro studies and clinical studies in children less than 4 years of age suggest that the optimal dose of Ventolin HFA has not been defined.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were conducted with Ventolin HFA (albuterol sulfate inhalation aerosol). In the original NDA submission, the drug-drug interaction between the use of inhaled corticosteroids (ICS) and Ventolin HFA was evaluated. No trends were identified in adverse events related to ICS use in adults, adolescents, and children aged ≥4 years. Prior studies showed the effects of albuterol on monoamine oxidase inhibitors or tricyclic antidepressants, β-adrenergic receptor blocking agents, and digoxin. The action of albuterol on the vascular system may be potentiated by co-administering monoamine oxidase inhibitors or tricyclic antidepressants. β-adrenergic receptor blocking agents may produce severe bronchospasm in patients with asthma by blocking the effect of Ventolin HFA. Although the effect of inhaled albuterol on the clearance of digoxin is unclear, a single dose intravenous and oral administration of albuterol decreases serum digoxin level by 16 to 22% in normal volunteers who had received digoxin for 10 days. The product label for Ventolin HFA appropriately addresses the potential of these drug-drug interactions.

1.3.6 Special Populations

The clinical studies in this supplemental NDA are conducted in pediatric population from birth to <4 years old and designed to assess the efficacy of the product in this special population. Both genders and race/ethnicity groups were adequately represented in the study population. There were no significant differences in efficacy and safety assessment among gender and race/ethnicity groups. There were no other special populations studied in this NDA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Ventolin HFA was developed as an alternative to CFC-driven pressurized metered dose Ventolin. The HFA propellant 1,1,1,2-tetrafluoroethane (HFA134a, Norflurane, Glaxo Wellcome code GRX106642X) has been adopted as a replacement propellant for use in medical products because it is chemically inert, non-flammable, of low toxicity, and does not contribute to depletion of the ozone layer.

Ventolin HFA is designed to deliver 90mcg of albuterol (as 108mcg of albuterol sulfate) per actuation from the actuator, and 200 actuations per inhaler. The dosing regimen and administration of Ventolin HFA (albuterol sulfate inhalation aerosol) is albuterol base 180 mcg (two inhalations) every 4 to 6 hours; in some patients, 90 mcg (one inhalation) every 4 hours may be sufficient. In clinical practice often a spacer with facemask is needed to deliver inhaled drugs in young children. The Agency requested in the Written Request *in vitro* studies to characterize the dose delivery from the Ventolin HFA inhaler with two different U.S.-marketed spacers. The Applicant conducted the *in vitro* studies, as requested. The *in vitro* studies indicated that at various flow rates and delay times the content of albuterol per actuation was reduced compared with the label claim. The dose delivered by the inhaler with spacers and masks were weight-proportional with that delivered by the inhaler without a spacer or facemask to a 70-kg adult, however.

2.2 Currently Available Treatment for Indications

Ventolin HFA is a short acting β-2 agonist bronchodilator approved for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease in patients 4 years of age and older. An albuterol inhalation solution, AccuNeb (albuterol sulfate inhalation solution, NDA 20-9(b) (4)) was approved April 30, 2001 for the treatment of asthma in patients 2 years of age and older. Various other brand name and generic albuterol sulfate inhalation solutions are also approved.

2.3 Availability of Proposed Active Ingredient in the United States

Ventolin HFA is currently available in the market for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease in patients 4 years of age and older. (b) (4) Ventolin HFA has never been withdrawn from the U.S. market.

2.4 Important Issues With Pharmacologically Related Products

There were no important issues with pharmacologically related products. Clogging of the MDI orifice has been a problem with Proventil HFA and Pro-Air HFA. The clinical data in this submission do not suggest a similar problem with Ventolin HFA.

2.5 Presubmission Regulatory Activity

The original NDA for Ventolin HFA was approved in the United States April 19, 2001. The approved indications are for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The FDA issued a Written Request (WR) December 31, 2001 for the pediatric drug development for the approved NDA product. After being amended six times, the last and final WR was issued December 7, 2005.

(b) (4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Applicant conducted *in vitro* study to measure the particle size of Ventolin HFA delivered through the combination of valved holding chambers and a facemask with the MDI actuator. The fine particle mass represented between (b) (4) of the delivered dose. Fine particles were defined as the particles in approximate size of (b) (4) The Applicant stated that for the MDI alone the fine particle mass for Ventolin HFA represented (b) (4) of the delivered dose. The results showed that valved holding chambers (b) (4) of the delivered dose and (b) (4) the proportion of the fine particle mass.

The Applicant also conducted *in vitro* studies to evaluate the delivered dose for Ventolin HFA through a valved holding chamber, AeroChamber Plus, and a facemask with the MDI actuator at different air flow rates and holding times. The airflow rates of 4.9, 8.0, and 12 L/min were considered representative of the average inspiratory flow rates of children age groups of 6-12 months, 2-5 years, and above 5 years, respectively. The data in Table 1 showed that the *in vitro* delivered doses of Ventolin HFA were consistent with small and medium facemasks and at different air flow rates and holding times.

Table 1 *In vitro* medication delivery of Ventolin HFA through AeroChamber Plus valved holding chamber with a facemask

Age	Facemask	Flow rate (L/min)	Hold (second)	Medication delivered mcg/act	mcg/kg*
6 to 12 months	small	4.9	0	18.2	1.8-2.4
			2	19.8	2.0-2.6
			5	13.8	1.4-1.8
			10	15.4	1.6-2.1
2 to 5 years	Small	8.0	0	17.8	1.0-1.4
			2	16.0	0.9-1.3
			5	16.3	0.9-1.3
			10	18.3	1.0-1.5
>5 years	small	12.0	0	25.2	1.4
			2	24.4	1.4
			5	22.5	1.3
			10	21.3	1.2
6 to 12 months	medium	4.9	0	13.5	1.4-1.8
			2	14.2	1.4-1.9
			5	12.5	1.3-1.6
			10	14.6	1.5-1.9
2 to 5 years	Medium	8.0	0	21.1	1.2-1.7
			2	15.3	0.8-1.2
			5	18.3	1.0-1.5
			10	18.2	1.0-1.5
>5 years	medium	12.0	0	26.8	1.5
			2	20.9	1.2
			5	19.6	1.1
			10	20.3	1.1

* In adult studies, Ventolin HFA inhalation without a spacer and a facemask delivers approximately dose of1.3 mcg/kg.

The drug material and the excipients had been reviewed in the original NDA. There is no new data in this supplemental NDA submission. Additional CMC information may be found in Dr. Chong Ho Kim's review. [C. Kim, Ph.D., CMC Review, NDA 22-983, (b) (4) , 9/28/07]

Reviewer comment:
The in vitro study results showed that delivered dose for Ventolin HFA through a valved holding chamber and facemask in children from 6 months to >5 years old was comparable to the delivered dose in adults without a spacer and a facemask per kilogram of body weight. However, the in vitro study data only verified that the test drug was delivered to the space of the facemask, but cannot determine if the dose is delivered into the respiratory system in patients.

3.2 Animal Pharmacology/Toxicology

No new non-clinical toxicology studies were required or performed for this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

(b) (4) The original NDA for Ventolin HFA was approved on April 19, 2001. The approved indications are for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The FDA issued a Written Request (WR) on December 31, 2001 for the pediatric drug development for the approved NDA product. After being amended several times upon requests from the Applicant, the last and final WR was issued on December 7, 2005. (b) (4)

The Applicant's submission includes reports of 3 clinical efficacy and safety studies and summaries of two clinical studies that have been reviewed in original NDA. Data from postmarketing surveillance, literature reports referenced by the Applicant, were also included.

This submission refers to three pediatric clinical studies that summarized in Table 2.

Table 2 Summary of clinical studies

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Subjects	Diagnosis, age of subjects
SB020001	Pivotal safety and efficacy study	Ventolin HFA 90 mcg TID for 4 weeks Ventolin HFA 180 mcg TID for 4 weeks Placebo HFA TID for 4 weeks	Three times daily for 4 weeks	Randomized, double-blind, placebo-control, parallel group, multi-center	77 male and female	subjects aged 24 to <48 months with asthma symptoms
SB030001	Pivotal safety and efficacy study	Ventolin HFA 90 mcg TID for 4 weeks Ventolin HFA 180 mcg TID for 4 weeks Placebo HFA TID for 4 weeks	Three times daily for 4 weeks	Randomized, double-blind, placebo-control, parallel group, multi-center	86 male and female	subjects aged from birth to <24 months with asthma symptoms

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Subjects	Diagnosis, age of subjects
SB030002	Pivotal safety and efficacy study	Ventolin HFA 180 mcg every 20 minutes for the fist hour, then hourly for next 2 hours Ventolin HFA 360 mcg every 20 minutes for the fist hour, then hourly for next 2 hours	3 hours	Randomized, double-blind, cumulative dose, parallel group, multi-center	87 male and female	subjects aged from birth to <24 months with asthma symptoms

4.3 Review Strategy

The three pediatric clinical studies presented in the Table 2 were reviewed, with emphasis on whether the application has met the terms specified by the Written Request. The Applicant's summary data tables were reviewed in detail. Appendix tables and data listings were also reviewed in varying amounts of detail, depending upon the endpoint and review issue. Case report forms (CRF) of patients with Serious Adverse Events (SAE) were reviewed. Postmarketing safety data from Ventolin HFA was provided by the Applicant and was reviewed.

4.4 Data Quality and Integrity

No DSI clinical audit was planned and requested for clinical studies in this supplemental NDA.

4.5 Compliance with Good Clinical Practices

The three pediatric clinical studies in this application were conducted in accordance with Good Clinical Practices and all applicable regulations, including, where applicable, the Declaration of Helsinki, June 1964, as modified by the 48th World Medical Association, Republic of South Africa, and October 1996. The applicant certified that they did not use and would not use in any capacity the services of any person debarred under to Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with their application.

4.6 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The applicant stated that the clinical investigators in the pivotal studies in this application certified that they did not have a proprietary interest in the proposed product or a significant equity in the applicant. The clinical investigators also certified that they were not a recipient of significant payments. Form FDA 3454 was included in the submission.

5 CLINICAL PHARMACOLOGY

No clinical pharmacology studies with Ventolin HFA were included in this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The approved indications for the drug are for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The FDA issued a Written Request (WR) on December 31, 2001 for the pediatric drug development for the approved NDA product. After being amended several times upon requests from the Applicant, the last and final WR was issued on December 7, 2005. (b) (4)

6.1.1 Methods

The efficacy review is based on the three pediatric efficacy and safety studies in the submission. Study SB020001 was a 4-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of Ventolin HFA delivered with facemask and two different valved holding chambers in subjects aged 24 to <48 months with asthma symptoms (i.e. wheeze, cough, dyspnea or chest tightness) or consistent with asthma or obstructive airway disease or bronchospasm. Study SB030001 had same study design with the study SB020001, except that the study subjects were pediatric population from birth to <24 months old and one valved holding chamber was used to deliver the test drug. Study SB030002 was a one-day cumulative dose study of Ventolin HFA delivered with one valved holding chamber in pediatric population from birth to <24 months old. Detailed reviews of the individual studies are provided in the Appendix.

The Applicant provided summaries of two clinical studies (SALT05 and SALA3006) that had been reviewed in original NDA. These two studies conducted in subjects aged 6-14 and 4-11 years of age, respectively. The applicant stated that these two studies provided evidence of efficacy for Ventolin HFA in the treatment of bronchospasm and the results were extrapolated to children less than 4 years of age in this supplemental NDA.

6.1.2 General discussion of endpoints

In study SB020001 and SB030001, the primary efficacy endpoint was the mean change from baseline to endpoint in 24-hour daily asthma symptom scores. Daily symptom scores were defined as the maximum value recorded for the daytime and nighttime individual symptom

scores. Baseline was the average of the non-missing values recorded on the last 7 days of the screening period. Endpoint was the average of the non-missing values during the 29-day treatment period. Asthma symptom scores were determined based upon the parent/guardian's rating of the subject's daytime and nighttime asthma symptoms (cough, wheeze and shortness of breath) recorded on the daily diary card over the treatment period. Secondary endpoints for both studies included percent change in daytime and nighttime asthma symptom scores, change in percentage of symptom-free 24-hour days, change in 24-hour rescue albuterol use, change in percentage of nights with no awakenings due to asthma, use of rescue systemic and/or inhaled corticosteroids (ICS), time to treatment failure, and change peak expiratory flow (PEF) for subjects who were capable of performing the maneuver.

In study SB030002, the primary efficacy measure was the percent change from baseline over the entire treatment period in the Modified Tal Asthma Symptoms Score, which included components of respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization as assessed by the investigator. Secondary efficacy endpoint was the rescue albuterol use during the study.

6.1.3 Study design

6.1.3.1 Study SB020001

Study SB020001 was a four-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of Ventolin HFA delivered with facemask and two different holding chambers in subjects aged 24 to <48 months with asthma symptoms (i.e. wheeze, cough, dyspnea or chest tightness) or consistent with asthma or obstructive airway disease or bronchospasm. A total of 77 male and female subjects aged 24 to <48 months were randomized into 3 study arms, 26 to Ventolin HFA 90mcg, 25 to Ventolin HFA 180mcg and 26 to placebo HFA. Most subjects completed the study (>88%). To be eligible for randomization, subjects had to: 1) demonstrate asthma symptoms recorded on the diary record on 2 of the 7 consecutive days of the 7 to 28 days Screening Period, and 2) demonstrate albuterol use documented on the diary record on at least 2 of 7 consecutive days in the 7-28 day screening period. Subjects who experienced an asthma exacerbation during the screening period were not eligible. Four weeks of Ventolin HFA 90 mcg or 180 mcg TID inhalation were given via MDI and with either an AeroChamber or Optichamber valved holding chamber using HFA propellant. Matching placebo was given by the same route. The safety measures included the assessment of adverse events, signs and symptoms of adrenergic stimulation, the diary record and the physician's assessment of tremor, clinical laboratory assessments, ECG, physical examination, including vital signs and twice daily peak expiratory flow measurements in subjects capable of performing this maneuver.

6.1.3.2 Study SB030001

Study SB030001 was a four-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of Ventolin HFA delivered TID with facemask and a valved holding chamber AeroChamber Plus in subjects between birth to <24 months of age with symptoms of bronchospasm (i.e. wheeze, cough, dyspnea or chest tightness) or consistent with obstructive airway disease. A total of 86 male and female subjects aged <24 months were randomized into 3

study arms, 29 subjects to the Ventolin HFA 90mcg, 29 to the Ventolin HFA 180mcg, and 28 to placebo HFA. Most subjects completed the study (>81%). Twenty-two subjects below 24 months of age were included. To be eligible for randomization, subjects had to: 1) demonstrate asthma symptoms recorded on the diary record on 2 of the 7 consecutive days of the 7 to 28 days Screening Period, and 2) demonstrate albuterol use documented on the diary record on at least 2 of 7 consecutive days in the 7-28 day screening period. Subjects who experienced an asthma exacerbation during the screening period were not eligible. Four weeks of Ventolin HFA 90 mcg or 180 mcg TID inhalation were given via MDI and with a valved holding chamber (AeroChamber Plus). Matching placebo was given by the same route. The safety measures included the assessment of adverse events, signs and symptoms of adrenergic stimulation, as assessed by the diary record, heart rate and certain questions of the FSII (R) health status questionnaire, clinical laboratory assessments, ECG, and physical examination, including vital signs.

6.1.3.3 Study SB030002

Study SB030002 was a randomized, double-blind, parallel-group, multi-center study of albuterol sulfate HFA inhalation aerosol delivered cumulatively with a valved holding chamber and an attached facemask in subjects between birth to 23 months of age with acute wheezing due to obstructive airway disease. A total of 87 male and female subjects aged <24 months were randomized into 2 treatment arms, 43 subjects to the Ventolin HFA 180mcg, 44 to the Ventolin HFA 360mcg. A subject was eligible when having a documented history of acute wheezing consistent with reversible obstructive airway disease, an asthma symptoms score between 4-9 based on the Modified Tal Asthma Symptoms Score and pulse oximetry greater than 88% taken at Screening while the subject was breathing room air. Subjects who experienced an asthma exacerbation during the screening period were not eligible. Eligible subjects received either Ventolin HFA 180 mcg or 360 mcg inhalation aerosol via MDI, administered every 20 (+5 minutes) for the first hour and then hourly (60+5 minutes) for the next two hours: 1) Ventolin HFA 180mcg: 2 inhalations of albuterol sulfate HFA 90 mcg and 2 inhalations of placebo; 2) Ventolin HFA 360 mcg: 2 inhalations of albuterol sulfate HFA 90 mcg and 2 inhalations of albuterol sulfate HFA 90 mcg. The safety measures included adverse events, continuous ECG monitoring, pulse oximetry, vital signs, physical examination, clinical laboratory tests for blood glucose and serum potassium, and adrenergic stimulation.

6.1.4 Efficacy findings

6.1.4.1 Study subjects demographics and disposition

Table 3 shows the demographics of in each of the 3 pediatric efficacy and safety studies for Ventolin HFA. A total of 196 patients received Ventolin HFA and 54 patients received placebo in the three pediatric efficacy and safety studies. Both genders were adequately represented in the studies. All ages were adequately represented in these studies, with the exception of patients 0-1 month of age. Patients of Asian origin were represented less well than other ethnic origins. Table 4 shows the enrollment and patient disposition in each of the 3 pediatric efficacy and safety studies for Ventolin HFA.

Table 3 Demographics of subjects in 3 pediatric studies for Ventolin HFA

	Study SB020001			Study SB030001			Study SB030002	
Demographics	**Placebo**	**Ventolin 90**	**Ventolin 180**	**Placebo**	**Ventolin 90**	**Ventolin 180**	**Ventolin 180**	**Ventolin 360**
Randomized	26	26	25	28	29	29	43	44
Gender								
Male	16(62%)	21(81%)	13(52%)	19(68%)	19(66%)	21(72%)	30(70%)	27(61%)
Female	10(38%)	5 (19%)	12(48%)	9(32%)	10(34%)	8 (28%)	13(30%)	17(39%)
Age (month)								
Mean	35.7	36.4	35.8	13.9	14.1	16.3	10.9	10.5
Range	24-47	24-47	24-47	3-23	2-22	6-23	1-23	2-21
Age range								
36-47 months	13(50%)	13(50%)	12(48%)					
24-35 months	13(50%)	13(50%)	13(52%)					
12-23 months				18(64%)	22(76%)	24(83%)	19(44%)	19(43%)
0-11 months				10(36%)	7 (24%)	5 (17%)	24(56%)	25(57%)
(0-1 month)				0	0	0	1	0
Ethnic origin								
White	16(62%)	16(62%)	10(40%)	15(54%)	17(59%)	13(45%)	19(44%)	20(45%)
Hispanic	6 (23%)	4 (15%)	4 (16%)	6 (21%)	7 (24%)	9 (31%)	9 (21%)	10(23%)
Black	3 (12%)	6 (23%)	9 (36%)	7 (25%)	5 (17%)	6 (21%)	10(23%)	11(25%)
Asian	1 (4%)	0	0	0	0	0	0	0
Other	0	0	2 (8%)	0	0	1 (3%)	5 (12%)	3 (7%)

Table 4 Enrollment and disposition in 3 pediatric studies for Ventolin HFA

	Study SB020001			Study SB030001			Study SB030002	
Disposition	Placebo	Ventolin 90	Ventolin 180	Placebo	Ventolin 90	Ventolin 180	Ventolin 180	Ventolin 360
Randomized	26	26	25	28	29	29	43	44
Completed*	23 (88%)	24 (92%)	23 (92%)	24 (86%)	28 (97%)	26 (90%)	35 (81%)	31 (70%)

* Study SB030002 was a cumulative dose study. In the study, a subject was discharged if his or her acute respiratory symptoms improved and required no further dosing. Subjects who received minimum three doses of treatment were counted as completed.

6.1.4.2 Primary efficacy finding: Study SB020001 and Study SB030001

The primary efficacy endpoint of the studies SB 020001 and SB030001 was the mean change from baseline to endpoint in 24-hour daily asthma symptom scores. Table 5 summarized the primary efficacy findings in the two studies. Over 4 weeks of treatment, a slight decline in mean asthma symptom scores was noted in each of the treatment groups. No significant differences between the Ventolin HFA treatment groups and the placebo group were observed and no differences in mean changes from baseline in 24-hour asthma symptom scores between the Ventolin HFA groups and the placebo group were noted in the two studies.

Table 5 Primary efficacy findings in Study SB020001 and Study SB 030001

	Study SB020001			Study SB030001		
	Placebo (N=26)	**Ventolin 90 (N=26)**	**Ventolin 180 (N=25)**	**Placebo (N=28)**	**Ventolin 90 (N=29)**	**Ventolin 180 (N=29)**
Baseline ASS[a] (SE)	1.3 (0.12)	1.4 (0.10)	1.6 (0.14)	1.3 (0.11)	1.5 (0.11)	1.3 (0.10)
Endpoint ASS (SE)	1.2 (0.12)	1.1 (0.12)	1.1 (0.12)	1.0 (0.15)	1.2 (0.14)	1.0 (0.13)
Baseline to endpoint change ASS (SE)	-0.3 (0.12)	-0.4 (0.12)	-0.4 (0.12)	-0.4 (0.15)	-0.2 (0.14)	-0.3 (0.13)
Comparison (to Placebo) ASS (SE) 95% CI p-value		-0.1 (0.16) -0.4 to 0.2 0.406	-0.1 (0.16) -0.4 to 0.2 0.467		0.2 (0.20) -0.2 to 0.6 0.334	0.0 (0.19) -0.4 to 0.4 0.978
Comparison (to Ventolin 90) ASS (SE) 95% CI p-value			0 (0.16) -0.3 to 0.3 0.933			-0.2 (0.20) -0.6 to 0.2 0.345

a. Asthma symptom score

6.1.4.3 Primary efficacy finding: Study SB030002

The primary efficacy endpoint was the mean percent change from baseline over the entire treatment period in Modified Tal Asthma Symptoms Score, which includes respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization as assessed by the investigator. Table 6 summarized the primary efficacy finding in the study. At the endpoint, mean percent changes from the baseline were -49.8 and -48.4 in Ventolin 180 mcg and 360 mcg groups, respectively. No significant differences were observed between the Ventolin 180 mcg and 360 mcg groups in Modified Tal asthma symptom scores and the percent change from the baseline. There was no placebo control in the study SB030002.

Table 6 Primary efficacy finding of Study SB030002

	Ventolin 180 (N=43)	**Ventolin 360 (N=44)**
Baseline mean Tal score (SE)	5.7 (0.19)	5.8 (0.19)
Endpoint mean Tal score (SE)	2.9 (0.23)	3.2 (0.18)
Mean percent change (SE)	-49.8 (3.39)	-48.4 (3.68)
Treatment comparison Mean percent difference 95% CI p-value		1.4 -7.1 to 10.0 0.739

6.1.4.4 Secondary efficacy findings

Secondary efficacy endpoints for study SB020001 and study SB030001 included percent change in daytime and nighttime asthma symptom scores, change in percentage of symptom-free 24-

hour days, change in 24-hour rescue albuterol use, change in percentage of nights with no awakenings due to asthma, use of rescue systemic and/or inhaled corticosteroids (ICS), time to treatment failure, and change peak expiratory flow (PEF) for subjects who were capable of performing the maneuver. None of these secondary efficacy endpoints had shown significant difference between placebo and treatment groups.

In study SB030002, secondary efficacy endpoint was the rescue albuterol use during the study. There were 4 and 3 subjects used rescue albuterol during the study in Ventolin 180 mcg and 360 mcg groups, respectively.

6.1.4.5 Efficacy findings in study SALT05

Study SALT05 was a randomized, double-blind, cross-over study in subjects 6 to 14 years of age (n=25) with histamine-induced bronchoconstriction with reversible airway obstruction. Treatment groups included 200µg albuterol HFA, 200µg albuterol CFC, and placebo HFA delivered by a pressurized inhaler on three separate days. Valved holding chambers were not used in this study. The study was conducted in the UK. The objective of the study was to demonstrate equivalence in terms of efficacy and tolerability of a single dose of albuterol 200µg administered by a pressurized inhaler propelled by HFA or CFC in the protection from histamine induced bronchoconstriction in pediatric patients with reversible airways obstruction.

The primary efficacy variable was the response to an inhaled dose of histamine (PD20: the dose of histamine producing a 20% fall in FEV1 from saline baseline) administered 30 minutes following inhalation of study treatment. The PD20 geometric mean values for placebo were lower than those for albuterol values. The differences in PD20 between each of the albuterol groups and placebo were statistically significant ($p<0.001$ in both cases). Analysis also indicated that the two albuterol formulations were equivalent.

The secondary efficacy endpoints were FEV1 and FVC. The study results showed that the both albuterol formulations increased FEV1 compared to the baseline value and the value in placebo group. Mean FVC values were approximately equal foe each treatments. No statistical analysis was performed.

6.1.4.6 Efficacy findings in study SALA3006

Study SALA3006 was a randomized, double blind, placebo-controlled, parallel-group, 2-week safety and efficacy study in 4 to 11 year old subjects (n=135) with asthma. Treatment groups included 200µg (180µg ex-actuator) albuterol HFA (N=46), 200µg (180µg ex-actuator) albuterol CFC (N=46), and placebo HFA (N=43) administered via the metered dose inhaler (MDI). Valved holding chambers were not used in this study. The objective of the study was to compare the efficacy and safety of albuterol 200µg in CFC propellant given QID to albuterol 200µg in HFA propellant given QID with placebo HFA via the MDI when administered for 2 weeks in pediatric subjects with asthma.

The primary efficacy endpoints were serial FEV1 measurements (for 6-11 year olds and 4-5 year olds who could perform spirometry) and Peak Expiratory Flow (PEF) at Treatment Day 1 and

Week 2. The results showed that both albuterol groups had significantly better PEF measurements in the 2 treatment visits ($p \leq 0.006$). There was no significant difference between 2 albuterol groups.

The secondary efficacy endpoints in the study included mean change from baseline PEF, analysis of functions of serial PEF, subjects with ≥15% increase in PEF over time, mean change from baseline FEV1, analysis of functions of serial FEV1, and subjects with ≥15% increase in FEV1 over time, rescue albuterol use, subjects-rated asthma symptom scores, frequency of nighttime awakenings, and frequency of asthma exacerbations. The functions of serial PEF and serial FEV1 included percentage of subjects achieving effect (≥15% increase), onset of effect, offset of effect, maximum effect, time of maximum effect, duration of effect, and AUC. In general, the two albuterol treatment groups had significant improvements in these secondary efficacy endpoints. There were no significant differences between the two albuterol formulations.

The Applicant concluded that albuterol in propellants HFA and CFC significantly improved lung function and decreased the need for use of rescue albuterol in this 2-week study in the pediatric subjects (4 to 11 years old) with asthma.

Reviewer comment:
The study SALA3006 report was submitted and reviewed in the original NDA. For detailed review of the study, refer to Medical Officer Review, NDA 20-983, A. Trontell, M.D., 6/23/1999.

6.1.5 Efficacy conclusion

The study SB020001 and SB030001 demonstrated that albuterol HFA 180 mcg and 360 mcg MDI inhalation delivered through a facemask and valved holding chambers had no significant effect on asthma symptom scores in pediatric patients from birth to <4 years old. In study SB030002, a cumulative dose of albuterol HFA inhalation in 3-hour treatment period decreased modified Tal asthma symptom scores 49.8% and 48.4% comparing to baseline in Ventolin HFA 180 mcg and 360 mcg groups, respectively. However, there was no placebo control in study SB030002. In all three studies, there were no differences between different albuterol HFA dose groups.

Reviewer comment:
(b) (4)

. The 3 pivotal pediatric clinical studies failed to demonstrate the efficacy of Ventolin HFA in the study patient population. In vitro data suggest that the dose delivered by Ventolin HFA through a valved holding chamber and facemask in children from 6 months to >5 years old was comparable on a per kilogram basis to the dose delivered to adults without a spacer and a facemask. The data from the in clinical and in vitro studies suggest that the dose chosen for the clinical studies is not optimal. Efficacy may not be

extrapolated from previously conducted clinical studies in patients 4 years of age and greater because the previously conducted studies did not use a valved holding chamber and facemask and because in vitro studies and clinical studies in children less than 4 years of age suggest that the optimal dose of Ventolin HFA has not been defined.

7 INTEGRATED REVIEW OF SAFETY

The applicant's Integrated Summary of Safety (ISS) consisted of a summary of safety information from the three pediatric clinical studies. The safety information from the clinical studies included adverse event data and withdrawal information, clinical laboratory tests, vital signs, and ECG. The Applicant searched their safety database for postmarketing and spontaneous adverse event reports for albuterol HFA. The database includes cases from clinical trials and spontaneous adverse event reports. The search covered the period from 1997 to March 31, 2007.

The safety data from the clinical studies in pediatric patients from birth to less than 4 years of age did not identify a safety signal. The adverse event data from the pediatric clinical studies not suggest an association of adverse events and race/ethnicity. Given the extensive exposure to Ventolin HFA in adults and pediatric population, the safety data in this submission did not raise new concerns regarding a safety signal.

A detailed review of the Applicant's Integrated Summary of Safety follows below.

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in the 3 clinical studies in this application.

7.1.2 Other Serious Adverse Events

A total of 4 non-fatal SAEs were reported across the three pediatric studies in subjects from birth to <4 years old. None of the serious adverse events were considered by the investigators to be related to study medication. One non-fatal serious adverse event was reported in study SB020001: a 33-month old subject in Ventolin 90 group experienced an asthma exacerbation three weeks after the study. One non-fatal serious adverse event was reported in study SB030001: a 9-month old subject in placebo group experienced an asthma exacerbation during the study. The patient withdrew from the study. There were two non-fatal serious adverse events reported in study SB030002. Both cases were received Ventolin HFA 360 mcg. One case was one-year old and developed a fever of 102 F and worsening of wheezing after completing the study. The subject was hospitalized for 4 days with a full recovery. Another case was 6-month old and developed cough and wheezing after completing the study. The subject was diagnosed having an RSV bronchiolitis and fully recovered.

In the supportive studies, no serious adverse events occurred in study SALT05, and two serious adverse events of asthma exacerbation occurred (one during run-in and one during the treatment phase) in study SALA3006 with subjects aged 4 to 11 years.

GSK conducted a search of their safety database for SAEs. In the albuterol HFA < 4 years age group, thirteen cases were identified on the company safety database as fulfilling regulatory criteria for serious adverse events (12 spontaneous reports and one from a clinical trial). Five of the serious spontaneous cases refer to hospitalization or intervention for respiratory symptoms, and the applicant considered the majority of these to be related to the patient's underlying disease. A further four of the cases describing aggression (n=1), convulsion (n=1), periventricular leukomalacia, cerebral palsy, diplegia, cerebral atrophy (n=1) and hyperamylasemia, vomiting, nausea, abdominal distension and abnormal bowel sounds (n=1) were considered by the applicant to be confounded by co-suspect medication. Of the remaining three cases, one reported events associated with a hypersensitivity reaction, one describing blistering was poorly documented and one reported asymptomatic intentional overdose. The final serious case was a report from a clinical trial and described an asthma exacerbation three weeks after discontinuation of albuterol HFA (SB020001).

Reviewer comment:
These data do not identify a new safety signal.

7.1.3 Dropouts and Other Significant Adverse Events

There was one dropout from the three clinical studies in subjects less than 4 years of age due to adverse events. In study SB030001, one subject in placebo group experienced an asthma exacerbation and withdrew from the study. This case was considered not study drug related by the investigator.

In the supportive study SALA3006, one subject was withdrawn due to an SAE of asthma exacerbation.

Reviewer comment:
These data do not identify a safety signal.

7.1.4 Other Search Strategies

No other search strategies were used in this application.

7.1.5 Common Adverse Events

Common adverse events are discussed in the following section.

In study SB020001 a total of 33 subjects (43%) reported AE during treatment: 11 subjects (42%) in the placebo group, 9 subjects (35%) in the Ventolin HFA 90mcg group, and 13 subjects (52%) in the Ventolin HFA 180 mcg group. The reported adverse events were common symptoms in pediatric population, including upper respiratory infection, diarrhea, cough, skin disorder, and

others. The adverse events occurring in more than one subject are listed in Table 7. The most frequently reported adverse event (4 cases) was ECG QT prolongation. Three of the four cases had a prolonged QT interval (ranging from 311 to 389 msec) prior to the start of the study drug and in two cases the prolonged QT interval resolved during the study. One subject in the Ventolin 90 mcg group (Subject 011922-0110) with a normal QTc interval at baseline had a prolonged QTc interval post-dose at Week 4. This patient's QTc was 375 msec at baseline, 451 msec pre-dose at Week 4 and 457 msec post-dose at Week 4. This subject did not report any other symptoms and the QTc prolongation resolved with a value of 392 msec when the ECG was repeated within a week. None of the QT prolongation events were considered by the investigators to be related to the study drug.

Table 7 Adverse events occurring in more than one subject, Study SB020001

Adverse event	Placebo (N=26) n (%)	Ventolin 90 (N=26) n (%)	Ventolin 180 (N=25) n (%)
All subjects with adverse events	11 (42)	9 (35)	13 (52)
Diarrhea	0	0	2 (8.0)
ECG QT prolonged	0	1 (4.0)	3 (12)

In study SB030001, a total of 50 subjects (58%) reported AE during treatment: 12 subjects (43%) in the placebo group, 16 subjects (55%) in the Ventolin HFA 90mcg group, and 22 subjects (76%) in the Ventolin HFA 180 mcg group. The reported adverse events were common symptoms in pediatric population, including fever, sinus tachycardia, upper respiratory infection, diarrhea, vomiting, skin disorder, and others. The adverse events occurring in more than one subject are listed in Table 8.

Table 8 Adverse events occurring in more than one subject, Study SB030001

Adverse event	Placebo (N=28) n (%)	Ventolin 90 (N=29) n (%)	Ventolin 180 (N=29) n (%)
All subjects with adverse events	12 (43)	16 (55)	22 (76)
Pyrexia	3 (11)	2 (7)	7 (24)
Sinus tachycardia	2 (7)	2 (7)	5 (17)
UR tract infection	3 (11)	0	5 (17)
Nasopharyngitis	3 (11)	2 (7)	4 (14)
Teething	3 (11)	4 (14)	1 (3)
Nasal congestion	1 (4)	3 (10)	1 (3)
Ear infection	0	1 (3)	2 (7)
Diarrhea	1 (4)	2 (7)	1 (3)
Vomiting	0	1 (3)	2 (7)
Rash	1 (4)	1 (3)	2 (7)
Dermatitis diaper	0	1 (3)	2 (7)
Eczema	0	0	2 (7)
Ventricular hypertrophy	0	2 (7)	0
Body temperature increased	0	2 (7)	0

In study SB030002, a total of 7 subjects (8%) reported adverse events during the study: 4 subjects (9%) in the Ventolin 180 mcg group and 3 subjects (7%) in the Ventolin 360 mcg group. The reported adverse events were nasal congestion, rhinorrhea, ventricular extrasystoles, pyrexia, bronchial hyperactivity, tachycardia, RSV infection, and electrocardiogram QT prolongation. The adverse event of QT prolongation was in the Ventolin 360 mcg group. The subject (009220-657) had a sinus rhythm and prolonged QT (up to 304 msec) and QTc (up to 392 msec) intermittently, which resolved after the 180 minutes post-dose assessment. The investigator did not consider this QT prolongation a SAE and a study drug related case. Two subjects reported pyrexia. All other adverse events occurred in one subject.

In the supportive study SALT05, all subjects reported wheezing post histamine challenge during the study. Flushing and cough were reported by 20% of patients or more with a similar incidence in both albuterol HFA and CFC treatment groups but not with placebo. Other adverse events in this study included headache, 2 cases of eye disorders, and 1 case of nausea and vomiting.

In supportive study SALA3006, the number of patients who experienced at least one adverse event ranged from 14 (30%) in the albuterol HFA group, to 15 (35%) in the placebo HFA group, to 16 (35%) in the albuterol CFC group. The most common adverse event was upper respiratory tract infection, headache, gastrointestinal symptoms, and fever.

7.1.5.1 Incidence of adverse events in subgroups—Race

In the combined study population (Table 1), a half of the subjects were Caucasian (126 out of 250). Black (57 out of 250) and Hispanic (55 out of 250) counted for about one fourth of the study population, respectively. The applicant found no meaningful differences between racial and ethnic subgroups and could not draw conclusions regarding the distribution of adverse events.

Reviewer comments:
The reviewer concurs that it is not possible to draw conclusions on the association of adverse events with race in these studies.

7.1.5.2 Incidence of adverse events in subgroups—Age

The study subjects were from birth to less than 4 years of age. The age distribution was listed in Table 1. For the age subgroups, the applicant found no trends or clinically significant differences were found when compared with the combined study populations.

Reviewer comments:
The reviewer concurs that it is not possible to draw conclusions on the association of adverse events with age in these studies.

7.1.6 Less Common Adverse Events

Adverse events occurring in the three clinical studies in adults are reviewed in Section 7.1.5. Adverse events were fairly uncommon, overall. Less common adverse events did not suggest a safety signal.

7.1.7 Laboratory Findings

Laboratory tests included hematology and clinical chemistry panel in study SB020001. There were no meaningful or apparent changes and differences between the treatment and placebo groups. For studies SB030001 and SB030002, laboratory tests only included serum potassium and blood glucose. Serum potassium and blood glucose measurements remained fairly consistent across the treatment groups over the course of the study SB030001. In study SB030002, the serum potassium values remained fairly consistent across the treatment groups, and the blood glucose values were increased in 6 subjects (18%) and 7 subjects (18%) in Ventolin HFA 180 mcg and 360 mcg groups, respectively. The mean increase of blood glucose level was 13.6 mg/dL and 21.1 mg/dL for the Ventolin 180 mcg and 360 mcg groups, respectively. The increase in glucose values were deemed by the study site investigators as not clinically significant and were attributed to high glucose meal consumption or concomitant corticosteroid use by the respective subjects during the study. No adverse events of hypokalemia or hyperglycemia were reported.

Reviewer comment:
The study subjects received repeated large doses of albuterol inhalation within 3 hours, which was most likely the cause of the increased blood glucose level in the study subjects.

7.1.8 Vital Signs

Vital sign assessments were conducted in the screening and at each clinical visit during the studies. No clinically significant changes from baseline data were noted.

7.1.9 Physical Examination

Physical examination was performed in the screening and at the end of the studies. Physical examination abnormalities during the studies were recorded as adverse events that were described in Section 7.1.5. No significant abnormalities of physical examination were noted.

7.1.10 Electrocardiograms and Holter Monitoring

In study SB020001, a 12-lead ECG with a 30-second rhythm strip was recorded at pre and one hour post dose at visit 2 and visit 5. No subjects had unfavorable clinically significant changes in ECG during the study.

There were 4 cases of ECG QT prolongation. Three of the four cases had a prolonged QT interval (ranging from 311 to 389 msec) prior to the start of the study drug and in two cases the prolonged QT interval resolved during the study. One subject in the Ventolin 90 mcg group

(Subject 011922-0110) with a normal QTc interval at baseline had a prolonged QTc interval post-dose at Week 4. This patient's QTc was 375 msec at baseline, 451 msec pre-dose at Week 4, and 457 msec post-dose at Week 4. This subject did not report any other symptoms and the QTc prolongation resolved with a value of 392 msec when the ECG was repeated within a week. None of the QT prolongation events were considered by the investigators to be related to the study drug. In study SB030001, a 12-lead ECG with a 30-second rhythm strip was recorded at pre and one hour post dose at visit 2 and visit 5. No subjects had unfavorable clinically significant changes in ECG during the study.

Continuous Holter monitoring was performed in the study SB030002. No significant Holter abnormalities occurred during the study. There was one adverse event of QT prolongation in the Ventolin 360 mcg group based on the ECG evaluation. The subject (009220-657) had a sinus rhythm and prolonged QT (up to 304 msec) and QTc (up to 392 msec) intermittently, which resolved after the 180 minutes post-dose assessment. The investigator did not consider this QT prolongation a SAE and a study drug related case.

7.1.11 Signs and Symptoms of Adrenergic Stimulation

Tremor, the Function Status II (R) questionnaire (Studies SB020001 and SB030001), and heart rate (Study SB030002) were used to assess the adrenergic stimulation in the studies. There was no evidence of adrenergic stimulation in the study subjects based on the assessments.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

No special studies regarding withdrawal phenomena and/or abuse potential were conduction for Ventolin HFA, as these issues were not considered to consistent with this class of drugs.

7.1.13 Human Reproduction and Pregnancy Data

These issues are not applicable to the proposed indication in pediatric subjects.

7.1.14 Overdose Experience

There is no overdose experience reported in the three clinical studies. The Applicant searched their postmarketing adverse event database for the period from 1997 to March 31, 2007. There was no apparent overdose case or pattern identified from the postmarketing adverse event searching. Current and proposed labeling for Ventolin HFA state that the expected symptoms with over dosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of these symptoms e.g., seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of Ventolin HFA. Treatment consists of discontinuation of Ventolin HFA together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm.

7.1.15 Postmarketing Experience

The Applicant searched their safety database for postmarketing and spontaneous adverse event reports for albuterol HFA. The database includes cases from clinical trials and spontaneous adverse event reports. The search covered the period from 1997 to March 31, 2007. There was no new adverse event pattern identified in subjects less than 4 years of age. The profile of adverse events in this database is consistent with those in adults and adolescents, and comparable with those reported in the clinical trials in this application.

Reviewer comment:
These data do not suggest a safety signal.

7.2 Adequacy of Patient Exposure and Safety Assessments

Adequacy of patient exposure and safety assessments is addressed below.

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

The applicant provided a summary of safety information from three clinical studies in pediatric subjects aged from birth to less than 4 years of age. Two studies (SB020001 and SB030001) were clinical efficacy and safety studies for 4 weeks in patients aged 24 to less than 48 months of age and from birth to less than 24 months of age, respectively. One study (SB030002) was a cumulative dose safety and efficacy study in patients aged from birth to less than 24 months of age. The safety information from these studies includes adverse events, laboratory data, vital signs data, and ECG data.

7.2.1.1 Study type and design/patient enumeration

There are three clinical studies in the applicant's submission of the supplemental NDA for Ventolin HFA. These studies are summarized below in Table 9.

Table 9 Summary of clinical studies providing safety information, NDA 20-983, SE013

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Subjects	Diagnosis, age of subjects
SB020001	Pivotal safety and efficacy study	Ventolin HFA 90 mcg TID for 4 weeks Ventolin HFA 180 mcg TID for 4 weeks Placebo HFA TID for 4 weeks	Three times daily for 4 weeks	Randomized, double-blind, placebo-control, parallel group, multi-center	77 male and female	subjects aged 24 to <48 months with asthma symptoms
SB030001	Pivotal safety and efficacy study	Ventolin HFA 90 mcg TID for 4 weeks Ventolin HFA 180 mcg TID for 4 weeks Placebo HFA TID for 4 weeks	Three times daily for 4 weeks	Randomized, double-blind, placebo-control, parallel group, multi-center	86 male and female	subjects aged from birth to <24 months with asthma symptoms
SB030002	Pivotal safety and efficacy study	Ventolin HFA 180 mcg every 20 minutes for the fist hour, then hourly for next 2 hours Ventolin HFA 360 mcg every 20 minutes for the fist hour, then hourly for next 2 hours	3 hours	Randomized, double-blind, cumulative dose, parallel group, multi-center	87 male and female	subjects aged from birth to <24 months with asthma symptoms

7.2.1.2 Demographics

Demographics in clinical studies in pediatric subjects are summarized in Table 10 below. The majority of subjects were of male gender (66.4%) and White race (50.4%). The age range of subjects was 1 to 47 months. There were 77 subjects (30.8%) between 2 to <4 years, 102 subjects (40.8%) between 1 to <2 years, and 71 subjects (28.4%) aged <12 months. Among the group <12 months, one subject was one month old.

Table 10 Demographics in the seven clinical pharmacology studies

Demographic characteristic	Ventolin HFA (Albuterol Sulfate Inhalation Aerosol) N = 250 n (%)
Gender	
Male	166 (66.4)
Female	84 (33.6)
Race	
White	126 (50.4)
Black	57 (22.8)
Hispanic	55 (22.0)
Others	12 (4.8)
Age, months	
Range	1 - 47
36-47	38 (15.2)
24-35	39 (15.6)
12-23	102 (40.8)
2-11	71 (28.0)
0-1	1 (0.4)

7.2.1.3 Extent of exposure (dose/duration)

A total of 250 subjects were exposed to investigational drug, Ventolin HFA (albuterol sulfate inhalation aerosol) in three pediatric clinical studies in subjects aged from birth to less than 48 months of age. The study subjects were exposed from three hours to 4 weeks. In two of the clinical studies 163 subjects were dosed three times daily for 4 weeks. One study was a cumulative dose study, in which 87 subjects were exposed to a maximum of 6 doses of the drug in 3 hours.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Other clinical data sources used to evaluate safety are reviewed below.

7.2.2.1 Postmarketing experience

The Applicant searched their safety database for postmarketing and spontaneous adverse event reports for albuterol HFA. The database includes cases from clinical trials and spontaneous adverse event reports. The search covered the period from 1997 to March 31, 2007. There was no new adverse event pattern identified in subjects <4 years old.

7.2.2.2 Summary of two supportive studies

The Applicant submitted summaries of two pediatric studies in subjects from 4 to 14 years of age to support the efficacy and safety of the test drug in pediatric population from birth to less than 4 years of age. These two studies were reviewed in the original NDA.

7.2.3 Adequacy of Overall Clinical Experience

The designs of studies in this application, as described in Section 7.2.1.1 Study type and design/patient enumeration, were adequate to allow for assessment of safety.

7.2.4 Additional Submissions, Including Safety Update

(b) (4)

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

There were no new safety signals revealed in the applicant's three pediatric clinical studies. The reported adverse events were common symptoms in pediatric population. There were no deaths in the clinical studies. A total of 4 non-fatal serious adverse events were reported across the three pediatric studies in subjects from birth to less than 4 years of age. None of the serious adverse events were considered by the investigators to be related to study medication.

The Applicant searched the company safety database for postmarketing adverse events reported for Ventolin HFA. In the albuterol HFA <4 years age group, 13 cases were identified as serious adverse events (12 spontaneous reports and one from a clinical trial). Postmarketing adverse events in children less than 4 years of age did not raise new concerns regarding a safety signal.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b) (4)

Ventolin HFA (albuterol sulfate inhalation aerosol) was approved for treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The Applicant conducted three pediatric clinical studies to evaluate the efficacy and safety of Ventolin HFA in patients from birth to less than 4 years of age with reversible airway disease.

The data from the *in vitro* and clinical studies suggest that the dose chosen for the clinical studies is not optimal. Efficacy may not be extrapolated from previously conducted clinical studies in patients 4 years of age and greater because the previously conducted studies did not use a valved holding chamber and facemask and because in vitro studies and clinical studies in children less than 4 years of age suggest that the optimal dose of Ventolin HFA has not been defined.

8.2 Drug-Drug Interactions

No formal drug interaction studies were conducted with Ventolin HFA (albuterol sulfate inhalation aerosol). In the original NDA submission, the drug-drug interaction between the use of inhaled corticosteroids (ICS) and Ventolin HFA was evaluated and no trends were identified in adverse events related to ICS use in adults, adolescents, and children 4 years of age and older. Prior studies showed the effects of albuterol on monoamine oxidase inhibitors or tricyclic antidepressants, β-adrenergic receptor blocking agents, and digoxin. The action of albuterol on the vascular system may be potentiated by co-administering monoamine oxidase inhibitors or tricyclic antidepressants. β-adrenergic receptor blocking agents may produce severe bronchospasm in patients with asthma by blocking the effect of Ventolin HFA. Although the effect of inhaled albuterol on the clearance of digoxin is unclear, a single dose intravenous and oral administration of albuterol decreases serum digoxin level by 16 to 22% in normal volunteers who had received digoxin for 10 days. The product label for Ventolin HFA appropriately addresses the potential of these drug-drug interactions.

8.3 Special Populations

The clinical studies in this supplemental NDA are conducted in pediatric population from birth to less than 4 years of age and designed to assess the efficacy of the product in this special population. Both genders and race/ethnicity groups were adequately represented in the study population. There were no significant differences in efficacy and safety assessment among gender and race/ethnicity groups. There were no other special populations studied in this NDA.

8.4 Pediatrics

The original NDA for Ventolin HFA was approved April 19, 2001 for treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The FDA issued a Written Request (WR) December 31, 2001 for the pediatric drug development for Ventolin HFA (albuterol sulfate inhalation aerosol). (b) (4)

8.6 Literature Review

The application includes a bibliography of 22 citations (15 articles and 7 abstracts) from literature searches relevant to albuterol inhalation in pediatric population. These references did not yield any new safety signals and provided efficacy data of variable reliability for asthma and other off-label indications.

8.7 Postmarketing Risk Management Plan

The Applicant stated that since the availability of Ventolin HFA through January 31, 2007, there had been approximately 41.3 million years of patient exposure to Ventolin HFA MDI worldwide. A low risk of adverse events had been observed for this product. The safety profile of Ventolin HFA MDI in the patients less than 4 years of age is comparable to that observed in older pediatric, adolescent, and adult patients. Considering the overall safety profile in this population, no specific risk management /minimization activities are proposed or required for the population less than 4 years of age.

9 OVERALL ASSESSMENT

9.1 Conclusions

(b) (4)

Albuterol HFA 180 mcg and 360 mcg MDI inhalation delivered through a facemask and valved holding chambers had no significant effect on asthma symptom scores in pediatric patients from birth to less than 4 years of age in studies SB020001 and SB030001. In study SB030002, a cumulative dose of albuterol HFA inhalation in 3-hour treatment period decreased modified Tal asthma symptom scores 49.8% and 48.4% comparing to baseline in Ventolin HFA 180 mcg and 360 mcg groups, respectively. However, there was no placebo group in study SB030002. There were no differences between albuterol HFA 180 mcg and 360 mcg groups. The safety data from the three clinical studies in pediatric patients from birth to less than 4 years of age did not identify new safety signals.

The Applicant conducted *in vitro* study to measure the particle size and to evaluate the delivered dose for Ventolin HFA through a valved holding chamber and a facemask with the MDI actuator at different air flow rates and holding times. The results showed that valved holding chambers (b) (4) of the delivered dose and (b) (4) The delivered dose for Ventolin HFA through a valved holding chamber and facemask was comparable to the delivered dose in adults without a spacer and a facemask per kilogram of body weight.

Ventolin HFA is approved for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. In clinical practice, very young pediatric patients receive off-label albuterol inhalation treatment, although more often as albuterol solution for nebulization than as an MDI formulation. (b) (4) the three clinical studies in the application identified no new safety signals. Results from *in vitro* and clinical studies should be added to the labeling for the product, as it represents important information for the practitioner.

9.2 Recommendation on Regulatory Action

(b) (4) There were no new safety signals revealed from the three pediatric clinical studies. Results from *in vitro* and clinical studies should be added to the labeling for the product, as it represents important information for the practitioner.

The original NDA for Ventolin HFA was approved April 19, 2001. The FDA issued a Written Request (WR) December 31, 2001 for the pediatric drug development for Ventolin HFA (albuterol sulfate inhalation aerosol). (b) (4)

9.3 Recommendation on Postmarketing Actions

No postmarketing actions for Ventolin HFA are recommended.

9.4 Labeling Review

(b) (4)

(b) (4)

9.5 Comments to Applicant

(b) (4)

the 3 pivotal pediatric clinical studies failed to demonstrate the efficacy of Ventolin HFA in the study patient population. *In vitro* data suggest that the dose delivered by Ventolin HFA through a valved holding chamber and facemask in children from 6 months to >5 years old was comparable on a per kilogram body weight basis to the dose delivered to adults without a spacer and a facemask. The data from the clinical and *in vitro* studies suggest that the dose chosen for the clinical studies is not optimal. Efficacy may not be extrapolated from previously conducted clinical studies in patients 4 years of age and greater because the previously conducted studies did not use a valved holding chamber and facemask and because *in vitro* studies and clinical studies in children less than 4 years of age suggest that the optimal dose of Ventolin HFA has not been defined in this population.

(b) (4)

10 APPENDICES

10.1 Review of Individual Study Reports: Study SB020001

10.1.1 Study title and administrative information

A Four-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-Center Study of **VENTOLIN™** HFA MDI delivered with facemask and two different holding chambers in subjects aged 24 to <48 months with asthma symptoms (i.e. wheeze, cough, dyspnea or chest tightness) or consistent with asthma or obstructive airway disease or bronchospasm

- Protocol approved: 12/4/2002
- Study initiated: 5/30/03
- Study completed: 12/8/03
- Date of study report: 8/20/05
- Study sites: 38 investigational sites in the U.S., 37 sites enrolled and treated subjects

10.1.2 Study objective

The primary objective of this study was to evaluate the safety and efficacy of Ventolin HFA **(**albuterol sulfate inhalation aerosol**)** 90mcg and 180mcg (TID) versus placebo in propellant 1,1,1,2-tetrafluoroethane (GlaxoSmithKline code GR106642X) when administered via two different holding chambers with facemask for 4 weeks (minimum 29 days) to study subjects that were between the ages of 24 to <48 months with asthma symptoms (i.e. wheeze, cough, dyspnea, or chest tightness). Supplemental use of rescue Ventolin HFA inhalation aerosol or albuterol by nebulizer was permitted.

10.1.3 Study design

This study was a four-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of Ventolin HFA delivered with facemask and two different holding chambers in subjects aged 24 to <48 months with asthma symptoms (i.e. wheeze, cough, dyspnea or chest tightness) or consistent with asthma or obstructive airway disease or bronchospasm. The study was conducted on an outpatient basis. Study duration was approximately 9 weeks including a 7-28 days Screening Period, 4-week Treatment Period, and a Follow-up Visit five days following the end of treatment.

10.1.4 Study population

A total of 77 male and female subjects aged 24 to <48 months were randomized into 3 study arms, 26 to Ventolin HFA 90mcg, 25 to Ventolin HFA 180mcg and 26 to placebo HFA.

Inclusion criteria:

- Age: 24 to <48 months (subjects must not be less than 2 years of age at Visit 2 and must have not reached their fourth birthday). Approximately one half of the subjects were between 36 to <48 months of age at randomization.
- Clinical Presentation: All subjects must have had a history of asthma symptoms (wheeze cough, dyspnea or chest tightness) and experienced at least 2 episodes of increased symptoms requiring medical attention and asthma pharmacotherapy within the 12 months prior to Visit 1. In addition, all subjects had to have fulfilled one of the following criteria prior to Visit 1:
  - Had required therapy with a maintenance asthma medication (other than systemic corticosteroid) on a regular basis for the 4 weeks prior to Visit 1. AND/OR
  - Had required therapy with a short acting β_2-agonist (inhaled or oral) for relief of asthma symptoms (e.g. wheeze and cough) at least 3 times per week for 4 weeks prior to Visit 1.
- MDI and Holding Chamber Use: Subjects and parents/guardians had to have demonstrated the ability to comply with the use of the MDI and the holding chamber with facemask using the demonstration kit provided to the site. Parents/guardians of the subject must have had the ability to manage study drug administration.
- Parents/guardians: Parents/guardians of subjects must have had the ability to:
  - Read, comprehend and record information collected throughout the study
  - Complete the diary record on a twice-daily basis
  - Respond to the Functional Status II Reserved questionnaire FSII(R), a measure of functional status in children with a chronic physical condition

Exclusion criteria:

- Life-threatening asthma. Life-threatening asthma was defined for this protocol as a history of significant asthma episode(s) that required admission to an intensive care unit for treatment of an acute asthma exacerbation within the six months prior to Visit 1.
- Subjects who had been treated in the emergency room (for other than routine care) or admitted to the hospital for airway obstruction on two or more occasions within the three months prior to Visit 1 were to be excluded.
- Used systemic steroid therapy as short-term or "burst therapy" completed within 14 days prior to Visit 1 or during the screening period. Treated with greater than or equal to two courses (i.e., bursts) of systemic corticosteroids during three months prior to Visit 1.
- Used systemic steroid therapy on a daily or every other day basis for greater than 4 weeks within three months prior to Visit 1 or during the study treatment period.
- Used methylphenidate, pemoline, dexedrine or Adderall within 30 days prior to Visit 1.
- Not have been exposed to an investigational drug or participated in another clinical study within 30 days prior to Visit 1 or concomitantly during the study.
- A subject was not eligible to participate if he/she had a culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear (including otitis media) that had not resolved 2 weeks prior to Visit 1. In addition, the subject was excluded if he/she experienced a culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear (including otitis media) between Visit 1 and Visit 2 (i.e., the screening period).

- A subject was not eligible to participate if he/she had taken an influenza vaccination within 3 weeks of the screening visit.
- Historical or any evidence of significant diseases. Significant disease was defined as any disease that in the opinion of the investigator would have put the subject at risk through study participation or which would have affected the safety analysis had the disease exacerbated during the study.
- Any immediate or delayed hypersensitivity to any beta-agonist or sympathomimetic drug or any corticosteroid therapy or any component of the MDI formulation.
- History of hypersensitivity to a facemask or to adhesives utilized with the ECG process.
- ECG abnormalities determined to be "clinically significant" as defined by this protocol.
- A subject was not to have had any pulmonary abnormality that was not consistent with asthma. (Note: a chest x-ray was not required for this study.)
- Clinically significant laboratory abnormalities. Clinically significant was defined as any laboratory result that, in the opinion of the investigator, placed the subject at risk through study participation.

10.1.5 Randomization

Weekly phone calls were conducted during the screening period to ascertain a subject's eligibility for continuation in the study. After meeting all inclusion criteria for the screening period, a unique treatment number and medication pack was assigned to a subject and two MDIs were dispensed at each drug dispensing visit. Subjects were assigned to study treatment in accordance with the GSK computer generated randomization schedule. The study was stratified by age group (24 - < 36 months of age and 36 - < 48 months of age) to ensure that approximately ½ of the total randomized subjects was to be 24 - < 36 months of age and the other ½ was to be 36 - < 48 months of age. A total of 77 male and female subjects aged 24 to <48 months were randomized into 3 study arms, 26 to placebo HFA, 26 to Ventolin HFA 90mcg, and 25 to Ventolin HFA 180mcg.

Table 11 Study SB020001 participation

	Placebo N=26 n (%)	**Ventolin 90 N=26** n (%)	**Ventolin 180 N=25** n (%)
Gender			
Male	16 (62%)	21 (81%)	13 (52%)
Female	10 (38%)	5 (19%)	12 (48%)
Age (months)			
Mean	35.7	36.4	35.8
Range	24 – 47	24 – 47	24 - 47
24-35 months	13 (50%)	13 (50%)	12 (48%)
36-47 months	13 (50%)	13 (50%)	13 (52%)

10.1.6 Medical devices

An AeroChamber Plus or Optichamber spacer with facemask was provided and was used exclusively for administration of the study drug. An additional chamber spacer with facemask

was provided for the administration of rescue albuterol, if needed and was used consistently throughout the study. The use of the holding chambers was not interchanged. Instructions for administration of the medication utilizing the holding chamber with facemask and the use of the peak flow meter were provided in the study reference manual and with each unit dispensed.

10.1.7 Study treatment

The double blind treatment medication was delivered via metered-dose inhalers as either Ventolin HFA 90mcg per actuation strength in propellant HFA-134a or only HFA-134a propellant (placebo) for the 29 day treatment period. The assigned double blind treatment was to be inhaled via either an AeroChamber Plus **or** Optichamber valved holding chamber with an attached facemask.

At entry to the screening period (Visit 1), all short-acting beta agonists were discontinued and replaced with GSK supplied Ventolin HFA MDI and/or albuterol nebulization for use as needed for relief of symptoms of bronchospasm throughout the study.

At entry to the double-blind treatment period (Visit 2), eligible subjects were assigned to study treatment in accordance with the randomization schedule. Subjects received one of the following treatments administered via an AeroChamber Plus **or** an Optichamber valved holding chamber with attached facemask for the duration of the treatment period:

Table 12 Treatment for Study SB020001

Treatment	Morning Dose (0600-0800 hours)	Afternoon Dose (1300-1500 hours)	Evening Dose (1900-2000 hours)
VENTOLIN HFA 90mcg TID	1 inhalation of 90mcg (Can A) 1 inhalation of placebo (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of placebo (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of placebo (Can B)
VENTOLIN HFA 180mcg TID	1 inhalation of 90mcg (Can A) 1 inhalation of 90mcg (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of 90mcg (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of 90mcg (Can B)
Placebo	1 inhalation of placebo (Can A) 1 inhalation of placebo (Can B)	1 inhalation of placebo (Can A) 1 inhalation of placebo (Can B)	1 inhalation of placebo (Can A) 1 inhalation of placebo (Can B)

Each metered dose inhaler (MDI) was "test sprayed" into the air four times before using the first time, then inserted into the holding chamber. Subjects' inhaled one puff from Can A and one puff from Can B three times daily, approximately four to six hours apart. Instructions for administration of the medication were provided with the holding chamber. In addition, treatment demonstration kits were provided for instructional purposes.

All subjects were dispensed Ventolin HFA MDI and/or albuterol by nebulizer for use, as needed for relief of acute asthma symptoms at Visit 1 and for the duration of the study. Subjects could

use either or both Ventolin HFA MDI and albuterol by nebulizer. The number of puffs and/or nebulizations of albuterol used per day were documented on the diary record by the parent/guardian. A separate valved holding chamber, other than that supplied with the study drug was used to administer rescue Ventolin HFA, if needed. One nebulization was designated as being equivalent to 2 puffs from the MDI.

10.1.8 Efficacy assessments

10.1.8.1 Primary efficacy assessment

The primary efficacy endpoint was the mean change from baseline to endpoint in 24-hour daily asthma symptom scores. Daily symptom scores were defined as the maximum value recorded for the daytime and nighttime individual symptom scores (provided the daytime and nighttime asthma symptom scores were non-missing). Baseline was the average of the non-missing values recorded on the last 7 days of the screening period. Endpoint was the average of the non-missing values during the 29-day treatment period. Asthma symptom scores were determined based upon the parent/guardian's rating of the subject's daytime and nighttime asthma symptoms (cough, wheeze and shortness of breath) recorded on the daily diary card over the treatment period.

The following scoring system was used by the parent /guardian to rate the subject's twice daily daytime and nighttime asthma related symptoms such as cough, wheeze and shortness of breath. The first (morning) recording for each day represented the assessment of the previous 12-hour nighttime period. The second (evening) recording for each day represented the assessment of that day's 12-hour daytime period.

- Nighttime symptom scores to be recorded on the diary card each morning:
  0: None; no asthma symptoms (cough, wheeze, shortness of breath)
  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

- Daytime symptom scores to be recorded on the diary card each evening:
  0: None; no asthma symptoms (cough, wheeze, shortness of breath)
  1: Mild; noticeable symptoms (cough, wheeze, shortness of breath) but not interfering with daily activities
  2: Moderate; symptoms (cough, wheeze, shortness of breath) present often, causing some interference with daily routine and activities
  3: Severe; symptoms (cough, wheeze, shortness of breath) continuous or present most of the day restricting daily routine and activities severely

10.1.8.2 Secondary efficacy assessments

Secondary endpoints included:

- Percent change from baseline in daytime asthma symptom scores at Endpoint

- Change from baseline in percentage of symptom-free 24-hour days at Endpoint
- Change from baseline in 24-hour rescue albuterol use at Endpoint

The subject's parent/guardian recorded the use of supplemental rescue albuterol on the diary record. The first or morning recording for each day represented the number of MDI puffs and/or the number of nebulizations used during the previous 12-hour nighttime period. The second or evening recording for each day represented the number of MDI puffs and/or the number of nebulizations used during that day's 12-hour daytime period. The subject's parent/guardian was reminded that if the requirement for supplemental albuterol increased markedly (50% increase) over the amount taken during the screening period, OR if the subject needed ≥ 6 puffs of rescue albuterol in a 24 hour period, OR ≥ 4 puffs in 2 consecutive 24 hour periods in addition to the TID study drug dosing, the study site was to be contacted immediately.

Other efficacy endpoints were:

- Percent change from baseline in nighttime asthma symptom scores at Endpoint
- Change from baseline in percentage of nights with no awakenings due to asthma at Endpoint
- Use of rescue systemic and/or inhaled corticosteroids (ICS) during the study
- Time to treatment failure

Treatment failure was defined as premature discontinuation from the study due to lack of efficacy. A subject who discontinued because of a clinical exacerbation that required emergency intervention, hospitalization or treatment with an asthma medication in addition to those allowed by the protocol was considered to have discontinued due to lack of efficacy. Time to treatment failure was measured from the date of treatment initiation to the date of treatment failure or the date of treatment termination.

- Change from baseline in morning (AM) peak expiratory flow (PEF) at Endpoint (for subjects who were capable of performing the maneuver)
- Change from baseline in evening (PM) PEF at Endpoint (for subjects who were capable of performing the maneuver).

AM PEF was measured each morning and PM PEF was measured each evening. Measurements were obtained prior to the AM dose of study medication and prior to the PM dose of study medication and recorded on the daily diary record. Peak flow was performed in triplicate and the highest value was recorded.

10.1.9 Safety assessments

Safety measures included the assessment of adverse events, signs and symptoms of adrenergic stimulation as assessed from the physician's assessment of tremor, the diary card and the FSII(R) questionnaire, clinical laboratory assessment, ECG results (including measurement of QTc interval, vital signs, physical examination and peak expiratory flow in subjects who were capable of performing this maneuver. A medical history, including a review of systems, was obtained

from each subject with the assistance of the subject's legally authorized representative at Visit 1 (screening). Information on the age of the onset of asthma, responses to provocative stimuli, and history of pharmacotherapy was collected.

10.1.9.1 Adverse events

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All adverse events were recorded. One week (±2 days) after the last dose of study drug was administered, the subject's parent/guardian was contacted for assessment of post-treatment adverse events.

10.1.9.2 Clinical laboratory evaluations

Routine laboratory tests for chemistry and hematology were performed at the screening and the end of the study. A central laboratory, (b) (4) was used and results were transmitted to GSK. During the study, all laboratory results that met or exceeded the laboratory reference ranges were repeated. Clinical observation of the subject was continued until the laboratory value returned to normal or in the opinion of the investigator was no longer clinically significant.

10.1.9.3 Physical examination

A healthcare provider conducted a detailed physical examination at the baseline and the end of the study. Vital signs (pulse rate, blood pressure, temperature, and respiratory rate) were determined at each study visits.

A healthcare provider evaluated tremor at each study visit. Tremor was graded using a 0-3-point scale as follows:

- 0 - no tremor present
- 1 - mild tremor (fine) present
- 2 - moderate tremor present
- 3 - severe tremor (gross motor) present- (will be recorded as Adverse Event in the CRF)

10.1.9.4 12–lead ECG and rhythm strip

A 12-lead ECG with a 30-second rhythm strip was recorded at pre and one hour post dose at visit 2 and visit 5. Rescue VENTOLIN HFA MDI or albuterol nebulization was withheld at Visit 2 and Visit 5 for at least 4 hours if possible. In addition to the initial evaluation of the ECG by the investigator, an independent electrocardiographer, blinded to treatment assignment, was responsible for providing measurements of heart rate, PR interval, QT interval, QTc interval, QRS duration, and an overall interpretation of each ECG collected in this study. If any clinically significant worsening was noted, the ECG was repeated and the investigator advised the subject of clinically appropriate follow-up.

10.1.9.5 Health outcomes assessments

The Functional Status II Reserved questionnaire (FSII(R)) assessed the health status of children aged 0 to 16 years using the proxy measure of the parent. This interviewer-administered questionnaire contained 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention during the previous two-week time period. Each item was scored on a three-point scale indicating the frequency with which a child exhibited the specified behavior or performed the specified activity. The items are summed and a total score was calculated as the percent of total possible scores. Higher scores reflected a better functional status.

10.1.9.6 Signs and symptoms of adrenergic stimulation

Adrenergic stimulation was assessed by the FSII(R) questionnaire, adverse events, and tremor.

Seven individual items were selected from the FSII(R) questionnaire to evaluate these potential signs of adrenergic stimulation as follows:

- FS2: sleep well
- FS3: seem contented and cheerful
- FS4: act moody
- FS9: seems unusually irritable or cross
- FS10: sleep through the night
- FS12: seem unusually difficult
- FS14: react to little things by crying

10.1.9.7 Worsening asthma

A clinical exacerbation was defined as worsening asthma symptoms requiring:

- An emergency room visit, intervention and/or hospitalization.
- An unscheduled doctor visit or contact requiring treatment with an asthma medication (i.e. including antibiotics for treatment of acute respiratory symptoms) not allowed by the protocol or increased use of patient's maintenance asthma medication other than rescue albuterol as defined by the physician.

Worsening asthma was treated as deemed necessary by the investigator and the exacerbation details and all treatments were recorded in the CRF.

10.1.10 Statistical plan

Analysis of variance (ANOVA) was the test method being used. GSK stated that since this is primarily a safety study and no power calculation was performed for determining sample size, statistical tests were performed for informational purposes only. A minimum of 22 completed subjects per treatment group was chosen (b) (4) The dropout rate was estimated to be 10%. Therefore, approximately 75 total subjects, or approximately 25 subjects per treatment group, were enrolled in the study.

The primary population was the Intent-to-Treat Population. The Intent-to-Treat Population was defined as all subjects who were randomized and received at least one dose of study drug. In the event a subject received a treatment other than that to which they were assigned, the subject was included in the summaries and analyses according to the treatment they actually received. Analyses based on the Intent-to-Treat Population included all available data for these subjects. This population was the basis for all summaries, analyses, listings, and figures of demographic, efficacy, safety, and health outcomes data.

In an effort to ensure treatment balance within the two age ranges (24 to <36 months, and 36 to <48 months) the randomization was stratified at a ratio of 1:1 into these two groups.

Holding chamber use was not stratified; however, approximately half of the subjects in each treatment group used the AeroChamber Plus and the other approximately half of the subjects used the Optichamber for the duration of the study. A facemask was attached to the holding chamber.

10.1.11 Results

10.1.11.1 Demographics of the study subjects

Demographic characteristics were similar across the treatment groups (Table 13).

Table 13 Demographics of the subjects in Study SB020001

		Placebo (N=26) n (%)	Ventolin 90 (N=26) n (%)	Ventolin 180 (N=25) n (%)
Gender	Male	16 (62)	21 (81)	13 (52)
	Female	10 (38)	5 (19)	12 (48)
Age (months)[a]	Mean	35.7	36.4	35.8
	Range	24 – 47	24 – 47	24 – 47
Age range	36 – 47	13 (50)	13 (50)	13 (50)
	24 - 35	13 (50)	13 (50)	12 (48)
Race/ethnicity	White	16 (62)	16 (62)	10 (40)
	Black	3 (12)	6 (23)	9 (36)
	Hispanic	6 (23)	4 (15)	4 (16)
	Asian	1 (4)	0	0
	Other	0	0	2 (8)
Concurrent Asthma Medication[b]				
	None	8 (31)	10 (38)	7 (28)
	ICS and/or leukotriene modifier	18 (69)	64 (62)	18 (72)

a. Age at randomization
b. Subjects with concurrent medication use are those taking a fixed dose of inhaled corticosteroids and/or leukotriene modifiers for asthma throughout the treatment period.

About two thirds of the study subjects used concurrent asthma medications during the study. Use of concurrent asthma medications during treatment was comparable across the three

treatment groups. Most commonly used concurrent asthma medications were montelukast sodium (38%), budesonide (36%), and fluticasone propionate (18%).

10.1.11.2 Disposition of the study subjects

Around 90% of the subjects completed the study. There was no death or withdrawal from the study due to adverse events. Table 14 listed reasons for discontinuation of the study. They were protocol violation (3), lost of follow-up (1), lack of efficacy (2), and consent withdrawn (1).

Table 14 Disposition of the subjects in Study SB020001

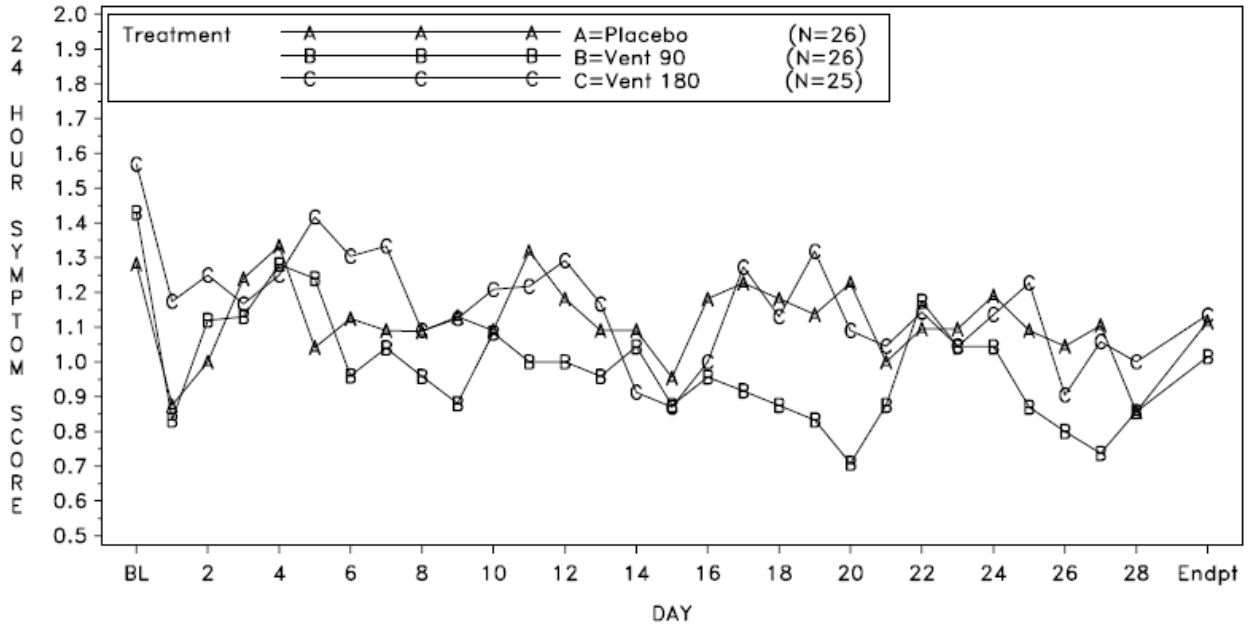
	PLACEBO N=26	VENTOLIN 90 N=26	VENTOLIN 180 N=25
Completion Status n (%)			
Completed	23(88)	24(92)	23(92)
Discontinued	(12)	2(8)	2(8)
Reason for D/C			
Adverse event	0	0	0
Protocol violation	1(4)	0	2(8)
Lost to follow-up	0	1(4)	0
Lack of efficacy	1(4)	1(4)	0
Consent withdrawn	1(4)	0	0
Other	0	0	0
Number of Deaths	0	0	0

10.1.11.3 Efficacy results

10.1.11.3.1 Primary efficacy endpoint

The primary efficacy measure was the mean change from baseline in daily 24-hour asthma symptom score at endpoint (the average of the 4-week treatment period). Daily 24-hour asthma symptom scores of treatment groups are shown in Figure 1.

Figure 1 Daily 24-hour asthma symptom scores of treatment groups, Study SB020001



Statistical analyses of changes in 24-hour asthma symptom scores from baseline to endpoint (average of the 4 week treatment period) are summarized in Table 15. Mean Baseline 24-hour asthma symptom scores were mild (noticeable symptoms, but no interference with daily activities or sleep) and similar across the treatment groups. Over 4 weeks of treatment, a slight decline in mean asthma symptom scores was noted in each of the treatment groups. No significant differences between the **VENTOLIN** HFA treatment groups and the placebo treatment group were observed and no differences in mean changes from baseline in 24-hour asthma symptom scores between the **VENTOLIN** HFA groups and the placebo group were noted at any of the four treatment weeks.

Table 15 Change from baseline in 24-hour asthma symptom scores at endpoint

	Placebo N=26	Ventolin 90 N=26	Ventolin 180 N=25
Baseline ASS[a] (SE)	1.3 (0.12)	1.4 (0.10)	1.6 (0.14)
Endpoint ASS (SE)	1.2 (0.12)	1.1 (0.12)	1.1 (0.12)
Baseline to endpoint change ASS (SE)	-0.3 (0.12)	-0.4 (0.12)	-0.4 (0.12)
Treatment comparison (to Placebo) ASS (SE) 95% CI p-value		-0.1 (0.16) -0.4 to 0.2 0.406	-0.1 (0.16) -0.4 to 0.2 0.467
Treatment comparison (to Ventolin 90) ASS (SE) 95% CI p-value			0.0 (0.16) -0.3 to 0.3 0.933

b. Asthma symptom score

The change from baseline to endpoint for daily asthma symptom scores by holding chamber in two Ventolin HFA and placebo groups are summarized in Table 4. In each holding chamber subgroup, a similar number of subjects were assigned. The mean daily asthma symptom scores were similar among all holding chamber and treatment groups except that the Ventolin 180 group had a slightly lower asthma symptom score at baseline in AeroChamber Plus group and slightly higher mean asthma symptom score in Optichamber group. The changes in 24-hour asthma symptom scores from baseline to endpoint are similar for two holding chamber groups.

Table 16 Daily asthma symptom scores at baseline and endpoint by holding chambers and treatment groups

ITT POPULATION	PLACEBO	VENTOLIN 90	VENTOLIN 180
Aerochamber Plus (N)[a]	14	14	10
Baseline (n)	13	14	10
Mean (SE)	1.4 (0.19)	1.3 (0.16)	1.8 (0.20)
Endpoint (n)[a]	14	14	9
Mean change from baseline (SE)	-0.2 (0.15)	-0.3 (0.16)	-0.6 (0.16)
Optichamber (N)[a]	12	12	15
Baseline (n)	12	12	15
Mean (SE)	1.2 (0.15)	1.6 (0.12)	1.4 (0.18)
Endpoint (n)[a]	10	12	15
Mean change from baseline (SE)	-0.3 (0.21)	-0.6 (0.14)	-0.3 (0.10)

a. Subjects numbers for each treatment group.

The change from baseline to endpoint for daily asthma symptom scores by concurrent asthma medication use in two Ventolin HFA and placebo groups are summarized in Table 5. More subjects were using concurrent asthma medications compared to the subjects not using concurrent asthma medication. The baseline mean symptoms scores for the subjects with no concurrent asthma medication use was slightly higher (1.6-1.8 symptom score) when compared with the subjects receiving concomitant medication (1.1-1.5 symptom score). The changes in asthma symptom scores from baseline to endpoint are similar for subjects using concurrent asthma medications compared to the subjects not using concurrent asthma medication in all treatment groups.

Table 17 Daily asthma symptom scores at baseline and endpoint by concurrent asthma medication use and treatment groups

	PLACEBO	VENTOLIN 90	VENTOLIN 180
Con Med Use (N)[a]	18	16	18
Baseline (n)	17	16	18
Mean (SE)	1.1 (0.14)	1.3 (0.14)	1.5 (0.17)
Endpoint (n) [a]	15	16	17
Mean change (SE)	-0.2 (0.17)	-0.4 (0.15)	-0.4 (0.11)
No Con Med Use (N)[a]	8	10	7
Baseline (n)	8	10	7
Mean (SE)	1.6 (0.20)	1.6 (0.14)	1.8 (0.19)
Endpoint (n) [a]	8	10	7
Mean change (SE)	-0.4 (0.12)	-0.4 (0.16)	-0.5 (0.15)

a. Subjects numbers for each treatment group.

10.1.11.3.2 Secondary and other efficacy results

There were nine secondary and other efficacy endpoints in this study, including changes from baseline to endpoint in daytime and nighttime asthma symptom scores, symptom-free days, rescue medication use, AM and PM peak expiratory flows, and time to treatment failure. None of these secondary and other efficacy results have shown significant difference between placebo and treatment groups (Table 6).

Table 18 Secondary and other efficacy results, Study SB020001

Efficacy endpoint		Placebo (N=26)	Ventolin 90 (N=26)	Ventolin 180 (N=180)
Percent change from baseline in daytime asthma symptom score at endpoint	Mean	-7.3	-25	-17.8
	SE	18.9	19.0	19.1
	p-value (compare to baseline)	0.703	0.191	0.356
Change from baseline in 24-hour rescue albuterol use at endpoint	Mean	-1.1	-1.6	-1.3
	SE	0.39	0.44	0.41
	p-value (compare to placebo)	----	0.366	0.798
	(compare to Ventolin 90)	----	----	0.297
Change from baseline in percentage of symptom-free 24-hour days at endpoint	Mean	10.1	19.7	19.7
	SE	6.83	6.34	6.44
Percent change from baseline in nighttime asthma symptom score at endpoint	Mean	-20.2	-22.9	-22.5
	SE	12.07	15.66	7.73
Change from baseline in percentage of nighttime with no awakenings due to asthma at endpoint	Mean	2.8	9.7	11.4
	SE	5.17	4.79	3.85
Use of rescue systemic and/or inhaled corticosteroids during the study	Subject number	1	2	0
Treatment failure	Subject number	1	1	0
	Days to treatment failure	9	18	--

Efficacy endpoint		Placebo (N=26)	Ventolin 90 (N=26)	Ventolin 180 (N=180)
Change from baseline in AM peak expiratory flow at endpoint[a] (L/min)	Mean	-6.0	7.0	8.0
	SE	3.99	2.68	4.74
Change from baseline in PM peak expiratory flow at endpoint[a] (L/min)	Mean	-2.6	6.8	10.3
	SE	3.79	4.41	4.05

a. For subjects who were capable of performing the maneuver.

Reviewer comment:
The study failed to demonstrate the efficacy of Ventolin HFA inhalation treatment at the dosage of 90 mcg and 180 mcg three times daily in this 4-week study of subjects aged 24 to <48 months with asthma symptoms. The primary efficacy endpoint, the mean change from baseline in daily 24-hour asthma symptom score at endpoint, only had a small change from baseline to endpoint. The statistical analysis showed no significant difference among placebo, Ventolin 90 mcg, and Ventolin 180 mcg groups. Nine secondary and other efficacy measurements showed no significant difference from baseline to endpoint, and among placebo and treatment groups.

The Study used two holding chambers, AeroChamber Plus and Optichamber, to deliver the testing drugs. In each holding chamber subgroup, a similar number of subjects were assigned. There were no significant differences in the change from baseline to endpoint for daily asthma symptom scores by holding chambers in placebo and Ventolin HFA groups.

10.1.11.4 Safety results

10.1.11.4.1 Extent of exposure

In this study, the median duration of exposure to study drugs was 26 days. The exposure was the same across the treatment groups (Table 19).

Table 19 Extent of exposure

	PLACEBO N=26	VENTOLIN 90 N=26	VENTOLIN 180 N=25
Exposure (days)			
Median	29.0	29.0	29.0
Range	3-36	10-38	21-43
Number of Subjects, n(%)			
N	26	26	25
<= 8 days	1 (4%)	0	0
9-15 days	1 (4%)	1 (4%)	0
16-22 days	1 (4%)	1 (4%)	1 (4%)
23-29 days	12 (46%)	14 (54%)	14 (56%)
>29 days	11 (42%)	10 (38%)	10 (40%)

10.1.11.4.2 Adverse events

A total of 33 subjects (43%) reported AE during treatment: 11 subjects (42%) in the placebo group, 9 subjects (35%) in the VENTOLIN HFA 90mcg group, and 13 subjects (52%) in the VENTOLIN HFA 180 mcg group. The reported adverse events were common symptoms in pediatric population, including upper respiratory infection, diarrhea, cough, skin disorder, and others. The adverse events occurring in more than one subject are listed in Table 20. The most frequently reported adverse event (4 cases) was ECG QT prolongation. Three of the four cases had a prolonged QT interval (ranging from 311 to 389 msec) prior to the start of the study drug and in two cases the prolonged QT interval resolved during the study. When corrected for heart rate, all four cases were found to have a normal QTc. But a subject in Ventolin 90 mcg group with normal range QT interval became a QTc prolongation after corrected for heart rate. This subject did not report any other symptoms and the QTc prolongation resolved when the ECG was repeated within a week. None of the QT prolongation events were considered by the investigators to be related to the study drug.

Table 20 Adverse events occurring in more than one subject, Study SB020001

Adverse event	Placebo (N=26) n (%)	Ventolin 90 (N=26) n (%)	Ventolin 180 (N=25) n (%)
All subjects with adverse events	11 (42)	9 (35)	13 (52)
Diarrhea	0	0	2 (8.0)
ECG QT prolonged	0	1 (4.0)	3 (12)

There was no death during the study. There was one non-fatal serious adverse event: a 33-month old subject in Ventolin 90 group experienced an asthma exacerbation during the study. This case was considered not study drug related by the investigator. There was no subject withdrawal due to adverse events during the treatment period.

10.1.11.4.3 Laboratory tests, vital signs, physical examination, and ECG

Laboratory tests included clinical chemistry and hematology panel. No meaningful or apparent differences in laboratory measurements were observed between placebo and treatment groups. There were no meaningful changes in vital signs between the measurements at baseline and the endpoint of the study. Physical examination abnormalities during the study were recorded as adverse events. The reported adverse events were common symptoms in pediatric population, including upper respiratory infection, diarrhea, cough, skin disorder, and others.

A 12-lead ECG with a 30-second rhythm strip was recorded at pre and one hour post dose at visit 2 and visit 5. No subjects had unfavorable clinically significant changes in ECG during the study. There were 4 cases of ECG QT prolongation (Table 8). After corrected for heart rate, however, the QTc of the 3 cases in the Ventolin 180 group were found within normal range. Only one subject in the Ventolin 90mcg group had an unfavorable change when compared to the pre-dose ECG for non-specific T-Wave abnormality, and prolonged corrected QT interval. This subject did not report any other symptoms and the QTc prolongation resolved when the ECG was repeated within a week.

Tremor was monitored as a symptom of adrenergic stimulation. No apparent tremor cases were observed during the study.

10.1.11.4.4 Health outcome assessment

This interviewer-administered questionnaire contained 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention. Each item was scored on a three-point scale indicating the frequency with which a child exhibited the specified behavior or performed the specified activity. Mean baseline scores indicated high pre-treatment functioning of this study population. There were no significant changes in the FSII(R) scores during the study.

Seven individual items were selected from the FSII(R) questionnaire to evaluate potential signs and symptoms of adrenergic stimulation. Mean scores were similar across the treatment groups at baseline and at endpoint. There was no evidence of adrenergic stimulation based on scores for selected items on the FSII(R) questionnaire.

Reviewer comment:
There were no new safety signals in this 4-week study of subjects aged 24 to <48 months with asthma symptoms.

10.2 Review of Individual Study Reports: Study SB030001

10.2.1 Study title and administrative information

A Four-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-Center Study of Ventolin HFA MDI delivered with facemask and valved holding chamber AeroChamber Plus in subjects from birth to <24 months with symptoms of bronchospasm (i.e. wheeze, cough, dyspnea or chest tightness) consistent with obstructive airway disease

- Protocol approved: 6/2/04
- Study initiated: 7/1/04
- Study completed: 2/23/05
- Date of study report: 7/6/07
- Study sites: 33 investigational sites in the U.S., 30 sites enrolled and treated subjects

10.2.2 Study objective

The primary objective of this study was to evaluate the safety and efficacy of Ventolin HFA **(**albuterol sulfate inhalation aerosol**)** MDI 90mcg and 180mcg (TID) delivered with facemask and a holding chamber versus HFA placebo supplemented with the use of rescue Ventolin HFA inhalation aerosol or albuterol nebulization over a 4 weeks (minimum 29 days) treatment period in subjects between the ages of birth to <24 months with symptoms of bronchospasm (i.e. wheeze, cough, dyspnea or chest tightness).

10.2.3 Study design

This study was a four-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of Ventolin HFA MDI 90 and 180 mcg TID delivered with facemask and a holding chamber versus placebo HFA in subjects between birth to < 24 months of age with asthma symptoms (i.e. wheeze, cough, dyspnea or chest tightness). The study was conducted on an outpatient basis. All subjects used the AeroChamber Plus for the duration of the study. Study duration was approximately 9 weeks including a 7-28 days Screening Period, 4-week Treatment Period, and a Follow-up Visit five days following the end of treatment.

10.2.4 Study population

A total of 86 male and female subjects aged from birth to <24 months were randomized into 3 study arms, 29 to Ventolin HFA 90mcg, 29 to Ventolin HFA 180mcg and 28 to placebo HFA. Effort was made to enroll about half of the subjects at below 12 months of age.

Inclusion criteria:

- Age: Birth to <24 months (Subjects must not be >23 months old at Visit 2)
- Clinical Presentation: All subjects must have had a history of symptoms compatible with bronchospasm (wheeze, cough, dyspnea or chest tightness) and must have had experienced at least 1 episodes of increased symptoms from obstructive airways disease requiring medical attention and asthma pharmacotherapy prior to screening. In addition, all subjects had to have fulfilled the following criteria prior to Visit 1:
  - Had required therapy with a daily maintenance[1] asthma medication (including regularly scheduled short acting β_2-agonist (oral and/or inhaled) for the preceding 3 weeks prior to Visit 1. AND/OR
  - Had required therapy with a short acting β_2-agonist (oral and/or inhaled PRN dosing) for relief of respiratory changes (e.g. wheeze, cough) prior to Visit 1.

  Maintenance medications included the following: inhaled corticosteroids (excluding systemic corticosteroid), nedocromil, cromolyn, theophylline, long-acting inhaled β_2-agonists, sustained release β_2-agonist tablets, scheduled oral short acting β_2-agonists (syrup, tablet) and leukotriene modifiers.
- MDI and Holding Chamber Use: Subjects and parents/guardians had to have demonstrated the ability to comply with the use of the MDI and the holding chamber with facemask using the demonstration kit provided to the site. Parents/guardians of the subject must have had the ability to manage study drug administration.
- Parents/guardians: Parents/guardians of subjects must have had the ability to:
  - Read, comprehend and record information collected throughout the study
  - Complete the diary record on a twice-daily basis

Respond to the Functional Status II Reserved questionnaire FSII(R), a measure of functional status in children with a chronic physical condition

Exclusion criteria:

- Life-threatening asthma/wheezing. Life-threatening asthma/wheezing was defined for this protocol as a significant asthma/wheezing episode that required admission to an intensive care unit for treatment within one month prior to Visit 1.
- Subjects who had been treated in the emergency room (for other than routine care) or admitted to the hospital for airway obstruction on two or more occasions within one month prior to Visit 1.
- Subjects with a history of intubation for respiratory distress due to airway obstruction.
- Used systemic steroid therapy as short-term or "burst therapy" completed within 14 days prior to Visit 1 or during the screening period. Treated with greater than or equal to two courses (i.e., bursts) of systemic corticosteroids during three months prior to Visit 1.
- Used systemic steroid therapy on a daily or every other day basis for greater than 4 weeks within three months prior to Visit 1.
- Used methylphenidate, pemoline, dexedrine or Adderall within 30 days prior to Visit 1 and during the study.
- Not have been exposed to an investigational drug or participated in another clinical study within 30 days prior to Visit 1 or concomitantly during the study.
- Had a culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear (including otitis media) that had not resolved 2 weeks prior to Visit 1 or during the screening period.
- Fever as defined rectal temperature >100.5^{o}F
- Born before 34 weeks gestation
- Body weight was >2 standard deviation below mean for the age
- A subject was not eligible to participate if he/she had taken an influenza vaccination within 3 weeks of the screening visit.
- Historical or any evidence of significant diseases. Significant disease was defined as any disease that in the opinion of the investigator would have put the subject at risk through study participation or which would have affected the safety analysis had the disease exacerbated during the study.
- Any immediate or delayed hypersensitivity to any beta-agonist or sympathomimetic drug or any corticosteroid therapy or any component of the MDI formulation.
- Any history of hypersensitivity to a facemask or to adhesives utilized with the ECG process.
- ECG abnormalities determined to be "clinically significant" as defined by this protocol.
- Not to have had any pulmonary abnormality that was not consistent with asthma. (Note: a chest x-ray was not required for this study.)
- Clinically significant laboratory abnormalities. Clinically significant was defined as any laboratory result that, in the opinion of the investigator, placed the subject at risk through study participation.

10.2.5 Randomization

Weekly phone calls were conducted during the screening period to ascertain a subject's eligibility for continuation in the study. After meeting all inclusion criteria for the screening period, subjects were randomized at Visit 2. A total of 86 male and female subjects aged from birth to

<24 months were randomized into 3 study arms, 28 to placebo HFA, 29 to Ventolin HFA 90mcg, and 29 to Ventolin HFA 180mcg.

10.2.6 Medical devices

An AeroChamber Plus spacer with facemask was provided and was used exclusively for administration of the study drug. An additional chamber spacer with facemask was provided for the administration of rescue albuterol, if needed and was used consistently throughout the study. The use of the holding chambers was not interchanged. Instructions for administration of the medication utilizing the holding chamber with facemask and the use of the peak flow meter were provided in the study reference manual and with each unit dispensed.

10.2.7 Study treatment

The double blind treatment medication was delivered via metered-dose inhalers as either Ventolin HFA 90mcg per actuation strength in propellant HFA-134a or only HFA-134a propellant (placebo) for the 29 day treatment period. The assigned double blind treatment was to be inhaled via either an AeroChamber Plus valved holding chamber with an attached facemask.

At entry to the screening period (Visit 1), all short-acting beta agonists were discontinued and replaced with GSK supplied Ventolin HFA MDI and/or albuterol nebulization for use as needed for relief of symptoms of bronchospasm throughout the study.

At entry to the double-blind treatment period (Visit 2), eligible subjects were assigned to study treatment in accordance with the randomization schedule. Subjects received one of the following treatments administered via an AeroChamber Plus valved holding chamber with attached facemask for the duration of the treatment period:

Table 21 Treatment for Study SB030001

Treatment	Morning Dose (0600-0800 hours)	Afternoon Dose (1300-1500 hours)	Evening Dose (1900-2000 hours)
VENTOLIN HFA 90mcg TID	1 inhalation of 90mcg (Can A) 1 inhalation of placebo (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of placebo (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of placebo (Can B)
VENTOLIN HFA 180mcg TID	1 inhalation of 90mcg (Can A) 1 inhalation of 90mcg (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of 90mcg (Can B)	1 inhalation of 90mcg (Can A) 1 inhalation of 90mcg (Can B)
Placebo	1 inhalation of placebo (Can A) 1 inhalation of placebo (Can B)	1 inhalation of placebo (Can A) 1 inhalation of placebo (Can B)	1 inhalation of placebo (Can A) 1 inhalation of placebo (Can B)

Each metered dose inhaler (MDI) was "test sprayed" into the air four times before using the first time, then inserted into the holding chamber. Subjects inhaled one puff from Can A and one puff

from Can B three times daily, approximately four to six hours apart. Instructions for administration of the medication were provided with the holding chamber. In addition, treatment demonstration kits were provided for instructional purposes.

All subjects were dispensed Ventolin HFA MDI and/or albuterol by nebulization for use, as needed for relief of acute asthma symptoms at Visit 1 and for the duration of the study. Subjects could use either or both Ventolin HFA MDI and albuterol nebulization. The number of puffs and/or nebulizations of albuterol used per day were documented on the diary record by the parent/guardian. A separate valved holding chamber, other than that supplied with the study drug was used to administer rescue Ventolin HFA, if needed. One nebulization was designated as being equivalent to 2 puffs from the MDI.

10.2.8 Efficacy assessments

10.2.8.1 Primary efficacy assessment

The primary efficacy endpoint was the mean change from baseline to endpoint in 24-hour daily asthma symptom scores. Daily symptom scores were defined as the maximum value recorded for the daytime and nighttime individual symptom scores (provided the daytime and nighttime asthma symptom scores were non-missing). Baseline was the average of the non-missing values recorded on the last 7 days of the screening period. Endpoint was the average of the non-missing values during the 29-day treatment period. Asthma symptom scores were determined based upon the parent/guardian's rating of the subject's daytime and nighttime asthma symptoms (cough, wheeze and shortness of breath) recorded on the daily diary card over the treatment period.

The following scoring system was used by the parent /guardian to rate the subject's twice daily daytime and nighttime asthma related symptoms such as cough, wheeze and shortness of breath. The first (morning) recording for each day represented the assessment of the previous 12-hour nighttime period. The second (evening) recording for each day represented the assessment of that day's 12-hour daytime period.

- Nighttime symptom scores to be recorded on the diary card each morning:
  0: None; no airway disease symptoms (cough, wheeze, shortness of breath)
  1: Mild; noticeable airway disease symptoms but not interfering with sleep
  2: Moderate; awakened once or more because of airway disease symptoms
  3: Severe; awake most of the night due to airway disease symptoms

- Daytime symptom scores to be recorded on the diary card each evening:
  0: None; no airway disease symptoms (cough, wheeze, shortness of breath)
  1: Mild; noticeable airway disease symptoms (cough, wheeze, shortness of breath) but not interfering with daily activities
  2: Moderate; airway disease symptoms (cough, wheeze, shortness of breath) present often, causing some interference with daily routine and activities
  3: Severe; airway disease symptoms (cough, wheeze, shortness of breath) continuous or present most of the day restricting daily routine and activities severely

10.2.8.2 Other efficacy assessments

Other efficacy endpoints were:

- 24-hour rescue albuterol use
- Time to treatment failure
- Daytime asthma symptom scores
- Nighttime asthma symptom scores
- Percentage of symptom-free 24-hour days
- Percentage of nights with no awakenings due to symptoms requiring albuterol treatment
- Use of rescue systemic and/or inhaled corticosteroids (ICS) during the study
- Number of subjects with asthma exacerbations

The subject's parent/guardian recorded the use of supplemental rescue albuterol on the diary record. The first or morning recording for each day represented the number of MDI puffs and/or the number of nebulizations used during the previous 12-hour nighttime period. The second or evening recording for each day represented the number of MDI puffs and/or the number of nebulizations used during that day's 12-hour daytime period. The subject's parent/guardian was reminded that if the requirement for supplemental albuterol increased markedly (50% increase) over the amount taken during the screening period, OR if the subject needed ≥ 6 puffs of rescue albuterol in a 24 hour period, OR ≥ 4 puffs in 2 consecutive 24 hour periods in addition to the TID study drug dosing, the study site was to be contacted immediately.

Treatment failure was defined as premature discontinuation from the study due to lack of efficacy. A subject who discontinued because of a clinical exacerbation that required emergency intervention, hospitalization or treatment with an asthma medication in addition to those allowed by the protocol was considered to have discontinued due to lack of efficacy. Time to treatment failure was measured from the date of treatment initiation to the date of treatment failure or the date of treatment termination.

10.2.9 Safety assessments

Safety measures included the assessment of adverse events, signs and symptoms of adrenergic stimulation as assessed from the physician's assessment of tremor, the diary card and the FSII(R) questionnaire, clinical laboratory assessment, ECG results (including measurement of QTc interval, vital signs, and physical examination. A medical history, including a review of systems, was obtained from each subject with the assistance of the subject's legally authorized representative at Visit 1 (screening). The results of these assessments were recorded in the subject's clinic notes and CRF.

10.2.9.1 Adverse events

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All adverse events were recorded. One week (±2

days) after the last dose of study drug was administered, the subject's parent/guardian was contacted for assessment of post-treatment adverse events.

10.2.9.2 Clinical laboratory evaluations

Routine clinical laboratory tests were performed at the screening and the end of the study. A central laboratory, (b) (4) was used and results were transmitted to GSK. During the study, all laboratory results that met or exceeded the laboratory reference ranges were assessed by a physician. Clinical observation of the subject was continued until the laboratory value returned to normal or in the opinion of the investigator was no longer clinically significant.

10.2.9.3 Physical examination

A healthcare provider conducted a detailed physical examination at the baseline and the end of the study. Vital signs (pulse rate, blood pressure, temperature, and respiratory rate) were determined at each study visits.

10.2.9.4 12–lead ECG and rhythm strip

A 12-lead ECG with a 30-second rhythm strip was recorded at pre and one hour post dose at visit 2 and visit 5. Rescue VENTOLIN HFA MDI or albuterol nebulization was withheld at Visit 2 and Visit 5 for at least 4 hours. In addition to the initial evaluation of the ECG by the investigator, an independent electrocardiographer, blinded to treatment assignment, was responsible for providing measurements of heart rate, PR interval, QT interval, QTc interval, QRS duration, and an overall interpretation of each ECG collected in this study. If any clinically significant worsening was noted, the ECG was repeated and the investigator advised the subject of clinically appropriate follow-up.

10.2.9.5 Health outcomes assessments

The Functional Status II(R) questionnaire (FSII(R)) assessed the health status of children aged 0 to 16 years using the proxy measure of the parent. This interviewer-administered questionnaire contained 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention during the previous two-week time period. Each item was scored on a three-point scale indicating the frequency with which a child exhibited the specified behavior or performed the specified activity. The items are summed and a total score was calculated as the percent of total possible scores. Higher scores reflected a better functional status.

10.2.9.6 Signs and symptoms of adrenergic stimulation

Adrenergic stimulation was assessed by the Functional Status II (R) questionnaire, adverse events, and tremor.

Seven individual items were selected from the FSII(R) questionnaire to evaluate these potential signs of adrenergic stimulation as follows:

- FS2: sleep well

- FS3: seem contented and cheerful
- FS4: act moody
- FS9: seems unusually irritable or cross
- FS10: sleep through the night
- FS12: seem unusually difficult
- FS14: react to little things by crying

10.2.9.7 Worsening asthma

A clinical exacerbation was defined as worsening asthma symptoms requiring:

- An emergency room visit, intervention and/or hospitalization.
- An unscheduled doctor visit or contact requiring treatment with an asthma medication (i.e. including antibiotics for treatment of acute respiratory symptoms) not allowed by the protocol or increased use of patient's maintenance asthma medication other than rescue albuterol as defined by the physician.

Worsening asthma was treated as deemed necessary by the investigator and the exacerbation details and all treatments were recorded in the CRF.

10.2.10 Statistical plan

Analysis of variance (ANOVA) was the statistical method being used. GSK stated that since this is primarily a safety study and no power calculation was performed for determining sample size, statistical tests were performed for informational purposes only. A minimum of 22 completed subjects per treatment group was chosen (b) (4) .

The primary population was the Intent-to-Treat Population. The Intent-to-Treat Population was defined as all subjects who were randomized and received at least one dose of study drug. In the event a subject received a treatment other than that to which they were assigned, the subject was included in the summaries and analyses according to the treatment they actually received. Analyses based on the Intent-to-Treat Population included all available data for these subjects. This population was the basis for all summaries, analyses, listings, and figures of demographic, efficacy, safety, and health outcomes data.

In an effort to ensure treatment balance within the two age ranges (birth to <12 months, and 12 to <24 months) the randomization was stratified at a ratio of 1:3 into these two groups.

10.2.11 Results

10.2.11.1 Demographics of the study subjects

Demographic characteristics were similar across the treatment groups (Table 22).

Table 22 Demographics of the subjects in Study SB030001

		Placebo (N=28) n (%)	Ventolin 90 (N=29) n (%)	Ventolin 180 (N=29) n (%)
Gender	Male	19 (68)	19 (66)	21 (72)
	Female	9 (32)	10 (34)	8 (28)
Age (months)[a]	Mean	13.9	14.1	16.3
	Range	3 – 23	2 – 22	6 – 23
Age range	12 – 23	18 (64)	22 (76)	24 (83)
	Birth – 11	10 (36)	7 (24)	5 (17)
	7 - 11	7	6	4
	4 - 6	2	0	1
	2 – 3	1	1	0
	0 - 1	0	0	0
Race/ethnicity	White	15 (54)	17 (59)	13 (45)
	Black	7 (25)	5 (17)	6 (21)
	Hispanic	6 (21)	7 (24)	9 (31)
	Asian	0	0	0
	Other	0	0	1 (3)
Concurrent Asthma Medication[b]				
	None	13 (46)	15 (52)	14 (48)
	ICS and/or leukotriene modifier	15 (54)	14 (48)	15 (52)

a. Age at randomization
b. Subjects with concurrent medication use are those taking a fixed dose of inhaled corticosteroids (ICS) and/or leukotriene modifiers for asthma throughout the treatment period.

About half of the study subjects used concurrent asthma medications during the study. Use of concurrent asthma medications during treatment was comparable across the three treatment groups. Most commonly used concurrent asthma medications were budesonide (79.5%) and montelukast sodium (27.3%).

10.2.11.2 Disposition of the study subjects

Around 90% of the subjects completed the study. There was no death or withdrawal from the study due to adverse events. Table 23 listed reasons for discontinuation of the study. They were lack of efficacy (6), consent withdrawn (1), and others (1).

Table 23 Disposition of the subjects in Study SB030001

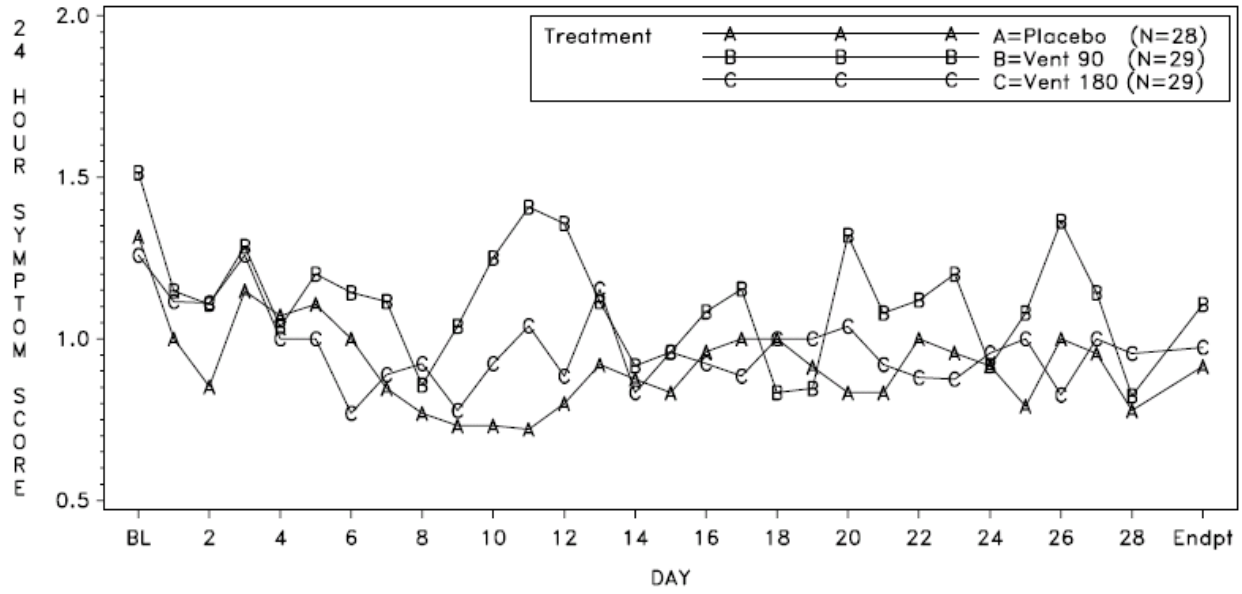
	PLACEBO N=28	VENTOLIN 90 N=29	VENTOLIN 180 N=29
Completion Status n (%)			
Completed	24(86)	28(97)	26(90)
Discontinued	4(14)	1(3)	3(10)
Reason for D/C			
Adverse event	0	0	0
Consent withdrawn	0	1(3)	0
Lack of efficacy	4(14)	0	2(7)
Lost to Follow-up	0	0	0
Protocol Violation	0	0	0
Other	0	0	1(3)

10.2.11.3 Efficacy results

10.2.11.3.1 Primary efficacy endpoint

The primary efficacy measure was the mean change from baseline in daily 24-hour asthma symptom score at endpoint (the average of the 4-week treatment period). Daily 24-hour asthma symptom scores of treatment groups are shown in Figure 2.

Figure 2 Daily 24-hour asthma symptom scores of treatment groups, Study SB020001



Statistical analyses of changes in 24-hour asthma symptom scores from baseline to endpoint (average of the 4 week treatment period) are summarized in Table 24. Mean Baseline 24-hour asthma symptom scores were mild (noticeable symptoms, but no interference with daily activities or sleep) and similar across the treatment groups. Over 4 weeks of treatment, a slight

decline in mean asthma symptom scores was noted in each of the treatment groups. No significant differences between the Ventolin HFA treatment groups and the placebo treatment group were observed and no differences in mean changes from baseline in 24-hour asthma symptom scores between the Ventolin HFA groups and the placebo group were noted at any of the four treatment weeks.

Table 24 Change from baseline in 24-hour asthma symptom scores at endpoint

	Placebo N=28	Ventolin 90 N=29	Ventolin 180 N=29
Baseline ASS[a] (SE)	1.3 (0.11)	1.5 (0.11)	1.3 (0.10)
Endpoint ASS (SE)	1.0 (0.15)	1.2 (0.14)	1.0 (0.13)
Baseline to endpoint change ASS (SE)	-0.4 (0.15)	-0.2 (0.14)	-0.3 (0.13)
Treatment comparison (to Placebo) ASS (SE) 95% CI p-value		0.2 (0.20) -0.2 to 0.6 0.334	0.0 (0.19) -0.4 to 0.4 0.978
Treatment comparison (to Ventolin 90) ASS (SE) 95% CI p-value			-0.2 (0.20) -0.6 to 0.2 0.345

a. Asthma symptom score

The change from baseline to endpoint for daily asthma symptom scores by concurrent asthma medication use in two Ventolin HFA and placebo groups are summarized in Table 25. Around half subjects in each group were using concurrent asthma medications. The mean baseline symptoms scores for the subjects with no concurrent asthma medication use was similar to the subjects receiving concomitant medication. The changes in asthma symptom scores from baseline to endpoint are similar for subjects using concurrent asthma medications compared to the subjects not using concurrent asthma medication in all treatment groups.

Table 25 Daily asthma symptom scores at baseline and endpoint by concurrent asthma medication use and treatment groups

	PLACEBO N=28	VENTOLIN 90 N=29	VENTOLIN 180 N=29
Con Med Use (N)[a]	15	14	15
Baseline (n)	15	14	15
Mean (SE)	1.3 (0.14)	1.5 (0.14)	1.3 (0.14)
Endpoint (n)	14	13	15
Mean change (SE)	-0.3 (0.13)	-0.2 (0.14)	-0.3 (0.12)
No Con Med Use (N)[a]	13	15	14
Baseline (n)	13	13	11
Mean (SE)	1.3 (0.18)	1.5 (0.17)	1.2 (0.16)
Endpoint (n)	13	13	10
Mean change (SE)	-0.5 (0.14)	-0.6 (0.18)	-0.2 (0.11)

a. Subjects numbers for each treatment group.

10.1.11.4.2 Other efficacy results

There were nine secondary and other efficacy endpoints in this study, including changes from baseline to endpoint in daytime and nighttime asthma symptom scores, symptom-free days, rescue medication use, AM and PM peak expiratory flows, and time to treatment failure. None of these secondary and other efficacy results have shown significant difference between placebo and treatment groups (Table 26).

Table 26 Other efficacy results, Study SB030001

Efficacy endpoint		Placebo (N=26)	Ventolin 90 (N=26)	Ventolin 180 (N=180)
Change from baseline in daytime asthma symptom score at endpoint	Mean	-0.2	-0.3	-0.3
	SE	0.11	0.10	0.10
Change from baseline in 24-hour rescue albuterol use at endpoint	Mean	-1.3	-1.6	-1.3
	SE	0.47	0.31	0.50
Change from baseline in percentage of symptom-free 24-hour days at endpoint	Mean	18.1	17.1	14.1
	SE	6.18	5.38	5.11
Change from baseline in nighttime asthma symptom score at endpoint	Mean	-0.3	-0.3	-0.2
	SE	0.10	0.10	0.07
Change from baseline in percentage of nighttime with no awakenings due to asthma at endpoint	Mean	12.2	16.6	11.2
	SE	4.46	5.20	4.75
Use of rescue systemic and/or inhaled corticosteroids during the study	Subject number	15	15	14
Treatment failure	Subject number	4	2	3
	Days to treatment failure: Mean	15.3	21.0	23.7
	SE	4.5	3.0	3.4

Reviewer comment:
The study did not demonstrate the efficacy of Ventolin HFA inhalation treatment at the dosage of 90 mcg and 180 mcg three times daily in this 4-week study of subjects from birth to <24 months with asthma symptoms. The primary efficacy endpoint, the mean change from baseline in daily 24-hour asthma symptom score at endpoint, only had a small change from baseline to endpoint. The statistical analysis showed no significant difference among placebo, Ventolin 90 mcg, and Ventolin 180 mcg groups. Seven secondary or other efficacy measurements showed no significant difference from baseline to endpoint, and among placebo and treatment groups.

10.2.11.4 Safety results

10.2.11.4.1 Extent of exposure

In this study, the median duration of exposure to study drugs was 29 days. The exposure was the same across the treatment groups (Table 27).

Table 27 Extent of exposure, Study SB030001

	PLACEBO N=28	VENTOLIN 90 N=29	VENTOLIN 180 N=29
Exposure (days)			
Median	29	29	30
Range	8-37	22-36	5-36
Number of Subjects, n(%)			
n	28	29	29
<= 8 days	1 (4)	0	1(3)
9-15 days	2 (7)	0	0
16-22 days	0	1 (3)	1 (3)
23-29 days	12 (43)	14 (48)	12 (41)
>29 days	13 (46)	14 (48)	15 (52)

10.2.11.4.2 Adverse events

A total of 50 subjects (58%) reported AE during treatment: 12 subjects (43%) in the placebo group, 16 subjects (55%) in the VENTOLIN HFA 90mcg group, and 22 subjects (76%) in the VENTOLIN HFA 180 mcg group. The reported adverse events were common symptoms in pediatric population, including fever, sinus tachycardia, upper respiratory infection, diarrhea, vomiting, skin disorder, and others. The adverse events occurring in more than one subject are listed in Table 28.

Table 28 Adverse events occurring in more than one subject, Study SB030001

Adverse event	Placebo(N=28) n (%)	Ventolin 90 (N=29) n (%)	Ventolin 180 (N=29) n (%)
All subjects with adverse events	12 (43)	16 (55)	22 (76)
Pyrexia	3 (11)	2 (7)	7 (24)
Sinus tachycardia	2 (7)	2 (7)	5 (17)
UR tract infection	3 (11)	0	5 (17)
Nasopharyngitis	3 (11)	2 (7)	4 (14)
Teething	3 (11)	4 (14)	1 (3)
Nasal congestion	1 (4)	3 (10)	1 (3)
Ear infection	0	1 (3)	2 (7)
Diarrhea	1 (4)	2 (7)	1 (3)
Vomiting	0	1 (3)	2 (7)
Rash	1 (4)	1 (3)	2 (7)
Dermatitis diaper	0	1 (3)	2 (7)
Eczema	0	0	2 (7)
Ventricular hypertrophy	0	2 (7)	0
Body temperature increased	0	2 (7)	0

There was no death during the study. There was one non-fatal serious adverse event reported in this study. A 9-month old male in the placebo group experienced an asthma exacerbation during the study. This case was considered not study drug related by the investigator. The subject withdrew from the study. After receiving further treatment in a hospital the subject's asthma exacerbation resolved.

10.2.11.4.3 Laboratory tests, vital signs, physical examination, and ECG

Laboratory tests included serum potassium and blood glucose measurements. Serum potassium and blood glucose values remained fairly consistent across the treatment groups over the course of the study. No adverse events of hypokalemia or hyperglycemia were reported. There were no meaningful changes in vital signs between the measurements at baseline and the endpoint of the study. Physical examination abnormalities during the study were recorded as adverse events. The reported adverse events were common symptoms in pediatric population, including fever, sinus tachycardia, upper respiratory infection, diarrhea, vomiting, skin disorder, and others.

A 12-lead ECG was recorded at pre and one hour post dose at visit 2 and visit 5. No subjects had unfavorable clinically significant changes in ECG during the study.

10.2.11.4.4 Health outcome assessment

This interviewer-administered questionnaire contained 14 items relating to the child's eating and sleeping habits, mood, behavior, energy and attention. Each item was scored on a three-point scale indicating the frequency with which a child exhibited the specified behavior or performed the specified activity. Mean baseline scores indicated high pre-treatment functioning of this study population. There were no significant changes in the FSII(R) scores during the study.

Seven individual items were selected from the FSII(R) questionnaire to evaluate potential signs and symptoms of adrenergic stimulation. Mean scores were similar across the treatment groups at baseline and at endpoint. There was no evidence of adrenergic stimulation based on scores for selected items on the FSII(R) questionnaire.

Reviewer comment:
There were no new safety signals in this 4-week study of subjects aged 24 to <48 months with asthma symptoms.

10.3 Review of Individual Study Reports: Study SB030002

10.3.1 Study title and administrative information

A Randomized, Double-Blind, Parallel-group, Multi-Center Study of Albuterol Sulfate HFA Inhalation Aerosol Delivered Cumulatively with a Valved Holding Chamber and an Attached Facemask in Subjects Between Birth to 23 Months of Age with Acute Wheezing Due to Obstructive Airways Disease

- Protocol approved: 2/23/04
- Study initiated: 9/10/04
- Study completed: 2/26/06
- Date of study report: 8/20/07

- Study sites: 16 investigational sites in the U.S. enrolled and treated subjects

10.3.2 Study objective

The primary objective of this study was to evaluate the safety and efficacy of cumulative dose administration of albuterol sulfate HFA inhalation aerosol delivered with a valved holding chamber (AeroChamber Plus) with attached facemask in an acute care clinical setting. Subjects must have been acutely wheezing due to obstructive airways disease. Two doses of albuterol sulfate HFA inhalation aerosol, 180 mcg and 360 mcg were evaluated for the treatment of bronchospasm in an acute clinical care setting.

10.3.3 Study design

This was a multi-center, randomized, double-blind, parallel-group, cumulative dose study of VENTOLIN HFA 180mcg or 360 mcg HFA inhalation aerosol in subjects between birth to <24 months of age with asthma in acute clinical care settings. The study inhalers were used in conjunction with a valved holding chamber (AeroChamber Plus) and attached facemask for the duration of the study. Subjects received VENTOLIN HFA inhalation aerosol treatments every 20 minutes in the first hour and then hourly treatments in the next two hours. Subjects were assessed at pre and post each dose for safety and efficacy. If, during the study, a subject's acute respiratory symptoms improved, and required no further dosing after any scheduled dose, he/she was excluded from any further scheduled albuterol sulfate HFA inhalation aerosol treatment. Subjects were discharged from the study sites after the final post dose evaluation. About 5-7 days after the treatment day, a follow-up phone contact was conducted to assess any post-treatment adverse events.

10.3.4 Study population

A total of 87 male and female subjects aged from birth to <24 months were randomized into 2 treatment groups, 43 to Ventolin HFA 180 mcg group and 44 to Ventolin HFA 360 mcg group. Enrollment was monitored to ensure that 30 subjects completed at least 3-treatment dosing periods in each treatment arm and a reasonable number of patients (approximately 15 subjects) were below 1 year of age including neonates.

Inclusion criteria:

- Clinical Presentation: All subjects must have had acute wheezing consistent with reversible obstructive airway disease. In addition, all subjects must have had an asthma symptoms score between 4 and 9 based on the Modified Tal Asthma Symptoms Score (a Modified Tal Asthma Symptoms Score (range, 0 to 12) was calculated by adding the scores for each of the four variables: components of respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization).

Exclusion criteria:

- History of life-threatening asthma/wheezing. Life-threatening asthma/wheezing was defined as an asthma/wheezing episode that required admission to an intensive care unit for treatment within three month prior to the study.
- Being treated in an emergency room and admitted into a hospital for airway obstruction on 2 or more occasions within three month prior to the study.
- History of intubation for respiratory distress due to airways obstruction.
- Subject's asthma symptoms as defined by the Modified Tal Asthma Symptoms Score was greater than 9, or pulse oximetry saturation was <88% while breathing room air, or if he/she exhibited signs of impending respiratory failure.
- Used systemic steroid therapy as short-term or "burst therapy" completed within 1 day prior to the screening. Used systemic steroid therapy on a daily or every other day basis for greater than 4 weeks within two months prior to the screening.
- Used methylphenidate, pemoline, dexedrine, or Adderall within 30 days prior to the screening and during the study.
- Not have been exposed to an investigational drug or participated in another clinical study within 30 days prior to the screening or concomitantly during the study.
- Had a culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear (including otitis media) that had not resolved 2 weeks prior to Visit 1 or during the screening period.
- Fever as defined rectal temperature >100.5^{o}F
- Born before 34 weeks gestation
- Bogy weight was >2 standard deviation below mean for the age
- Historical or any evidence of significant diseases. Significant disease was defined as any disease that in the opinion of the investigator would have put the subject at risk through study participation or which would have affected the safety analysis had the disease exacerbated during the study.
- Any immediate or delayed hypersensitivity to any beta-agonist or sympathomimetic drug or any corticosteroid therapy or any component of the MDI formulation.
- History of hypersensitivity to a facemask or to adhesives utilized with the ECG process.
- Not to have had any pulmonary abnormality that was not consistent with asthma. (Note: a chest x-ray was not required for this study.)
- Clinically significant laboratory abnormalities. Clinically significant was defined as any laboratory result that, in the opinion of the investigator, placed the subject at risk through study participation.

Stopping criteria

- Good response to the study treatment. A good response to the study treatment was defined as asthma symptoms having improved and the subject met all the following evaluation criteria for at least two consecutive assessments during the 3-hour treatment period.
    - The Modified Tal Asthma Symptoms Score ≤2;
    - The O_2 saturation ≥95%; and
    - No other signs and symptoms of respiratory distress

- Any clinically significant adverse event, laboratory test, physical examination, or Holter finding. Prematurely discontinuation subjects will be followed or treated until satisfactory resolution occurred.

10.3.5 Randomization

After the screening, subjects who met the randomization criteria were randomly assigned to receive one of the two double-blind treatments in a ratio of 1:1 (VENTOLIN HFA 180 mcg or 360 mcg) for cumulative dosing every 20 minutes in the first hour followed by hourly treatments in the second and third hour. Subjects had pre and post dose assessments for safety and efficacy.

10.3.6 Medical devices

An AeroChamber Plus spacer with facemask was provided and was used exclusively for administration of the study drug and the rescue albuterol. Instructions for administration of the medication utilizing the holding chamber with facemask were provided in the study reference manual and with each unit dispensed.

10.3.7 Efficacy assessments

10.3.7.1 Primary efficacy assessment

The primary efficacy measure was the percent change from baseline over the entire treatment period in the Modified Tal Asthma Symptoms Score, which included components of respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization as assessed by the investigator.

The overall Modified Tal Asthma Symptoms Score (range, 0 to 12) was calculated by adding the scores for each of the four variables: respiratory rate, wheezing, cyanosis, and accessory muscle use. Respiratory rate was determined by observation of the thoracic movement over a full minute. The degree of accessory muscle use was based on the degree of intercostals or subcostal retraction.

Table 29 Modified Tal Asthma Symptoms

Score	Resp. rate (beats/min)		Wheezing	Cyanosis	Accessory muscle use
	<6 months	≥6 months			
0	≤40	≤30	None	None	None
1	41-55	31-45	Terminal expiration with stethoscope only	Circumoral with crying only	Low
2	56-70	46-60	Entire expiration and inspiration with stethoscope only	Circumoral at rest	Medium
3	>70	>60	Expiration and inspiration without stethoscope	Generalized cyanosis at rest	High

10.3.7.2 Supportive efficacy assessment

Rescue albuterol use was recorded as a supportive efficacy endpoint. If medically indicated, subjects may have received rescue albuterol at the discretion of the investigator. The study defined rescue albuterol dose was 180 mcg (equivalent to 2 puffs), and was given with spacer and facemask. If a subject required any rescue albuterol, his/her next scheduled study drug was to be separated by at least 15minutes from rescue albuterol use.

10.3.8 Safety assessments

The safety measures included adverse events, clinical laboratory tests for blood glucose and serum potassium, continuous ECG Holter monitoring, pulse oximetry, vital signs, physical examination, and adrenergic stimulation.

10.3.8.1 Adverse events

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All adverse events were recorded.

10.3.8.2 Clinical laboratory evaluations

Routine clinical laboratory tests were performed at the screening and the end of the study. GSK provided a laboratory device to test the serum potassium and blood glucose. Laboratory results were maintained at the study site. The reference ranges of the laboratory tests for this study were defined as 3.0 to 5.8 mEq/L for serum potassium and 45-140 mg/dL for blood glucose. During the study, all laboratory results that met or exceeded the laboratory reference ranges were repeated and assessed by a physician. Clinical observation of the subject was continued until the laboratory value returned to normal or in the opinion of the investigator was no longer clinically significant.

10.3.8.3 Vital signs, physical examination, and adrenergic stimulation

A healthcare provider conducted a detailed physical examination at the screening and the end of the study. Vital signs (pulse rate, blood pressure, temperature, and respiratory rate) were determined at each study assessment.

Adrenergic stimulation was evaluated both prior to and after study drug administration, with following criteria:

- Heart rate increase by 20% when compared to baseline
- Sinus tachycardia above the limit listed below:
    - ages 1-3 weeks >185 BPM
    - ages 1-2 months >190 BPM
    - ages 3-5 months >195 BPM
    - ages 6-11 months >180 BPM
    - ages 12-23 months >160 BPM

- Investigator's clinical judgment.

10.3.8.4 Continuous Holter monitoring

Continuous Holter monitoring was performed through the study. Site personnel assessed the Holter monitor at all study assessments to ensure the ECG was properly recording. An independent electrocardiographer, blinded to treatment assignment, was responsible for providing overall interpretation of Holter readings collected in this study. Any clinically significant abnormality was to be reported as an adverse event and the investigator was to provide an assessment of the relationship, if any, to the study drug.

10.3.8.5 Pulse oximetry

Pulse oximetry, a non-invasive technique for measuring oxygen saturation was used during the study. A pediatric probe was placed on the big toe with the subject quiet, awake and in natural light. The maximum O_2 saturation was recorded after a period of at least 3 satisfactory sweeps of the pulse wave had been recorded at each assessment. If O_2 saturation fell below 88%, the subject was considered to have a poor response to study treatment and was discontinued from the study. The subject was treated as deemed necessary by the investigator.

10.3.9 Statistical plan

Analysis of variance (ANOVA) was the statistical method being used. GSK stated the primary objective of the study was to evaluate the safety of cumulative Ventolin HFA doses of 180 mcg and 360 mcg. A minimum of 30 completed subjects per treatment group was needed for this study as requested by the Agency. These subjects received a minimum of 3 doses of treatment drugs, and provided Holter monitoring data. In an effort to ensure treatment balance within the two age ranges (birth to <12 months, and 12 to <24 months) the randomization was stratified at a ratio of 1:3 into these two groups. The sample size of 30 subjects per treatment group would provide at least 90% power to detect a difference of 23% in mean percent change from baseline in Modified Tal Asthma Symptoms Score over the entire 3-hour treatment period, using a two-sample, two-sided t-test with a 0.05 significance level and assuming a standard deviation of 16%.

The primary population was the Intent-to-Treat Population. The Intent-to-Treat Population was defined as all subjects who were randomized and received at least one dose of study drug. In the event a subject received a treatment other than that to which they were assigned, the subject was included in the summaries and analyses according to the treatment they actually received. Analyses based on the Intent-to-Treat Population included all available data for these subjects. This population was the basis for all summaries, analyses, listings, and figures of demographic, efficacy, and safety data.

10.3.10 Results

10.3.10.1 Demographics of the study subjects

Demographic characteristics were similar across the treatment groups (Table 30).

Table 30 Demographics of the subjects in Study SB030001

		Ventolin 180 (N=43) n (%)	Ventolin 360 (N=44) n (%)
Gender	Male	30 (70)	27 (61)
	Female	13 (30)	17 (39)
Age (month)	Mean	10.9	10.5
	Range	1 – 23	2 – 21
Age range	12 – 23	19 (44)	19 (43)
	Birth – 11	24 (56)	25 (57)
	0 – 1	1	0
	2 – 3	3	6
	4 – 6	11	9
	7 - 11	9	10
Race/ethnicity	White	19 (44)	20 (45)
	Black	10 (23)	11 (25)
	Hispanic	9 (21)	10 (23)
	Other	5 (12)	3 (7)

10.3.10.2 Disposition of the study subjects

Less than half of the study subjects completed this 3-hour study. However, most of the pre-discontinued subjects were for the reason of good response to the study drug. There were 35 and 31 subjects received minimum of 3 doses of the test drug and the evaluation in Ventolin 180 mcg and 360 mcg groups, respectively.

Table 31 Disposition of the study subjects, Study SB030002

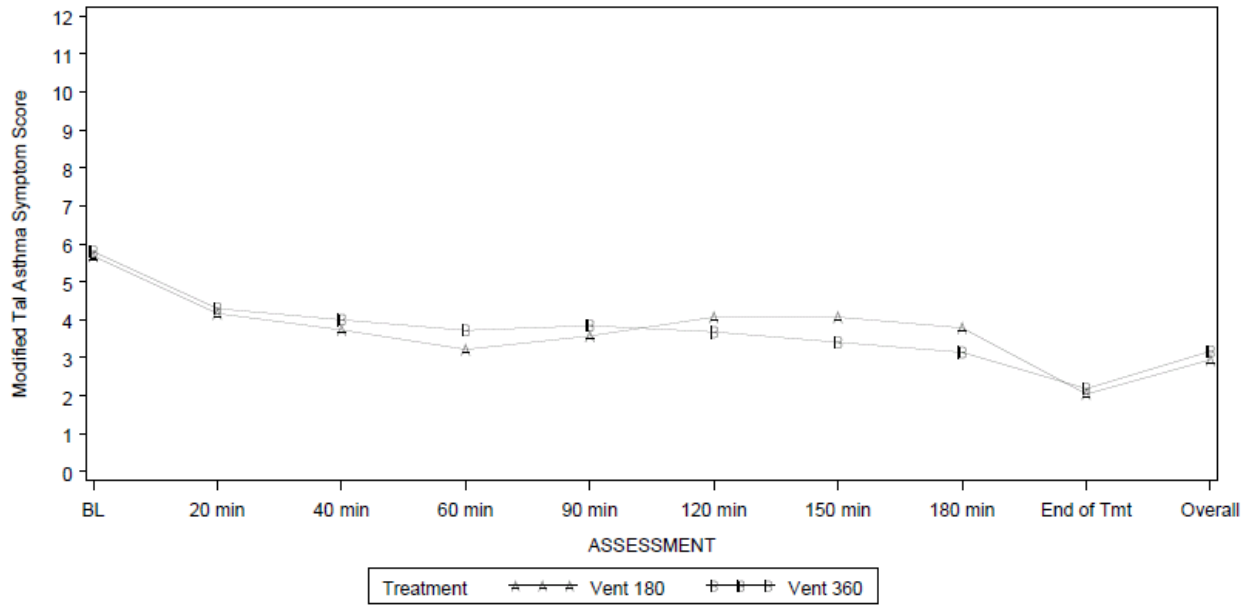
	Ventolin 180 (N=43)	Ventolin 360 (N=44)
Completion status, n (%)		
Completed minimum 3 doses	35 (81)	31 (70)
Completed the 3-hour study	14 (33)	21 (48)
Pre-discontinued	29 (67)	23 (52)
Reason for pre-discontinue, n (%)		
Consent withdrawn	0	1 (2)
Protocol violation	2 (5)	2 (5)
Due to good response	27 (63)	20 (45)

10.3.10.3 Efficacy results

10.3.10.3.1 Primary efficacy endpoint

The primary efficacy endpoint was the mean percent change from baseline over the entire treatment period in Modified Tal Asthma Symptoms Score, which includes respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilization as assessed by the investigator. Modified Tal asthma symptom scores of treatment groups are shown in Figure 3.

Figure 3 Modified Tal asthma symptom scores of treatment groups, Study SB030002



Statistical analyses of percent changes in Modified Tal asthma symptom scores from baseline to endpoint are summarized in Table 3. Mean baseline Modified Tal asthma symptom scores were 5.7 and 5.8 in Ventolin 180 mcg and 360 mcg groups, respectively. At the endpoint, mean percent changes from the baseline were -49.8 and -48.4 in Ventolin 180 mcg and 360 mcg groups, respectively. Over the 3-hour treatment, no significant differences were observed between the Ventolin 180 mcg and 360 mcg groups in Modified Tal asthma symptom scores and the percent change from the baseline.

Table 32 Percent change from baseline in Modified Tal Asthma symptom score at endpoint

	Ventolin 180 (N=43)	**Ventolin 360 (N=44)**
Baseline mean Tal score (SE)	5.7 (0.19)	5.8 (0.19)
Endpoint mean Tal score (SE)	2.9 (0.23)	3.2 (0.18)
Mean percent change (SE)	-49.8 (3.39)	-48.4 (3.68)
Treatment comparison Mean percent difference 95% CI p-value		 1.4 -7.1 10.0 0.739

10.3.10.3.3 Rescue albuterol use

There were 4 and 3 subjects used rescue albuterol during the study in Ventolin 180 mcg and 360 mcg groups, respectively. The percentage of subjects with rescue albuterol use during the study was similar across treatment groups; however the mean dose in mcg was higher in the Ventolin 360 mcg group compared to the Ventolin 180 mcg group.

10.3.10.4 Safety results

10.3.10.4.1 Extent of exposure

In this study, the median duration of exposure to study drugs was higher in Ventolin 360 mcg group. As described in 10.3.10.2, the study subjects discontinued the exposure mainly because they had a good response to the study drug.

Table 33 Extent of exposure, Study SB030002

	VENTOLIN HFA 180 N=43	VENTOLIN HFA 360 N=44
Exposure (minutes)		
Median	70.0	130.5
Range	20-205	20-250
Number of Subjects, n (%)		
n	43	44
≤20 mins	6 (14)	4 (9)
21-40 mins	4 (9)	7 (16)
41-60 mins	10 (23)	7 (16)
61-120 mins	9 (21)	4 (9)
121-180 mins	7 (16)	13 (30)
≥181 mins	7 (16)	9 (20)

10.3.10.4.2 Adverse events

A total of 7 subjects (8%) reported adverse events during the study: 4 subjects (9%) in the Ventolin 180 mcg group and 3 subjects (7%) in the Ventolin 360 mcg group. The reported adverse events were nasal congestion, rhinorrhea, ventricular extrasystoles, pyrexia, bronchial hyperactivity, tachycardia, RSV infection, and electrocardiogram QT prolongation. The adverse event of QT prolongation was in the Ventolin 360 mcg group. The subject (009220-657) had a sinus rhythm and prolonged QT (up to 304 msec) and QTc (up to 392 msec) intermittently, which resolved after the 180 minutes post-dose assessment. The investigator did not consider this QT prolongation a SAE and a study drug related case. Two subjects reported pyrexia. Other adverse events occurred in one subject. No deaths occurred during the study.

There were two serious adverse events reported in the Ventolin 360 mcg group: Subject #385 was a one-year old male who developed a fever of 102 F and worsening of wheezing after completing the study. The subject was hospitalized for 4 days with a full recovery. Subject # 403 was a 6-month old male who developed cough and wheezing after completing the study. The subject was diagnosed as an RSV bronchiolitis with a full recovery. There were no withdrawals due to adverse events.

10.3.10.4.3 Laboratory tests, vital signs, and physical examination

Laboratory tests included serum potassium and blood glucose measurements. Serum potassium values remained fairly consistent across the treatment groups over the course of the study. Blood glucose values were increased during the study in 6 and 7 subjects in Ventolin 180 mcg and 360 mcg groups, respectively. The increase in glucose values were deemed by the study site

investigators as not clinically significant and were attributed to high glucose meal consumption or concomitant corticosteroid use by the respective subjects during the study. No adverse events of hypokalemia or hyperglycemia were reported.

There were no meaningful changes in vital signs between the measurements at baseline and the endpoint of the study. Physical examination abnormalities during the study were recorded as adverse events. There were two adverse events possibly related to adrenergic stimulation: a subject with ventricular extrasystole in the Ventolin 180 mcg group and a subject with tachycardia in the Ventolin 360 mcg group. Both these subjects had within threshold values for serum potassium for both screening and end of treatment visits. The two adverse events resolved the same day and did not lead to subject withdrawal from the study.

10.3.10.4.4 Holter monitoring

There were 41 and 38 subjects had Holter evaluation in the Ventolin HFA 180 mcg and 360 mcg groups, respectively. No significant Holter abnormalities occurred.

Reviewer comment:
There were no new safety signals in this 4-week study of subjects aged 24 to <48 months with asthma symptoms.

10.4 Line-by-Line Labeling Review

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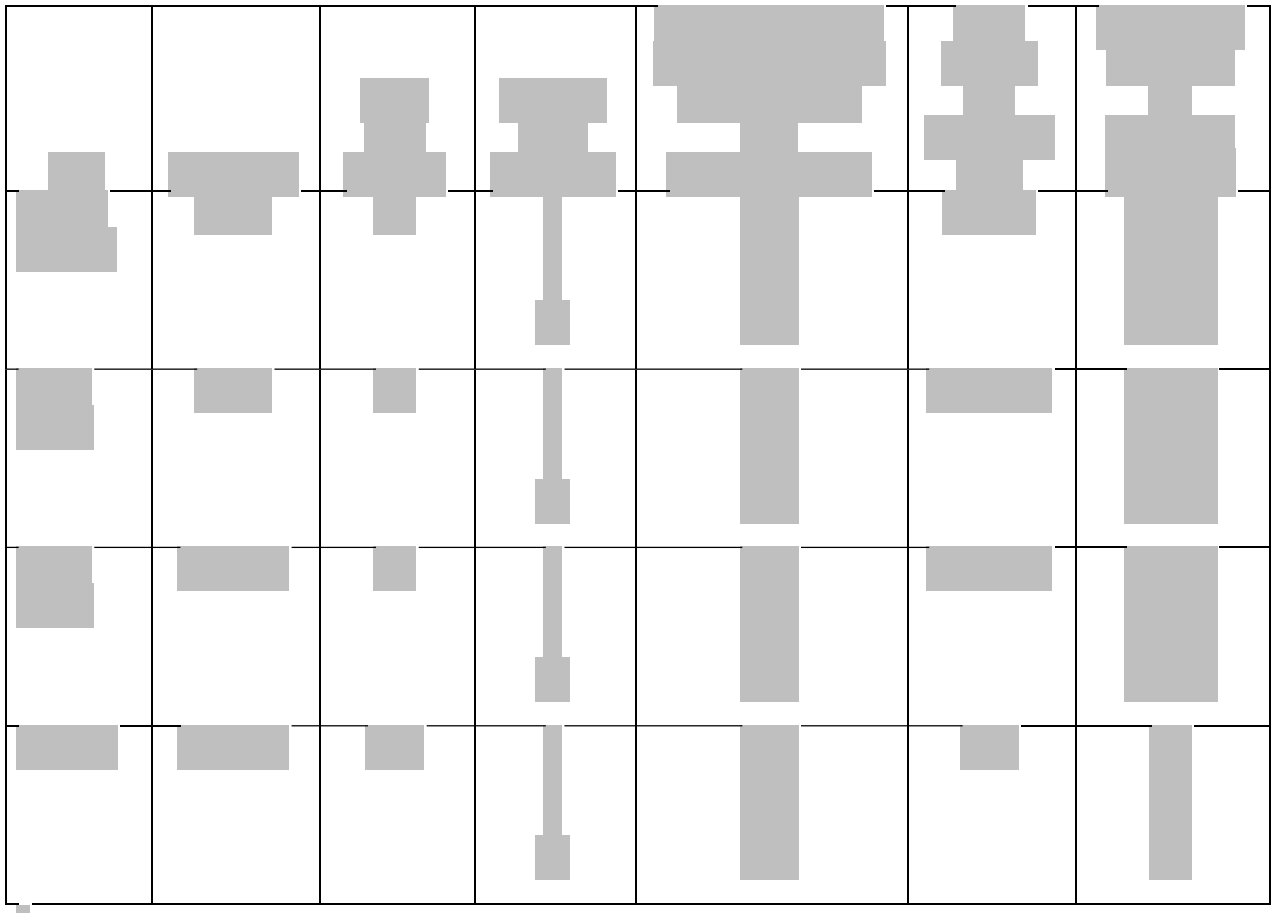

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/s/

Xu Wang
2/27/2008 05:27:14 PM
MEDICAL OFFICER

Charles Lee
2/27/2008 05:35:30 PM
MEDICAL OFFICER
I concur.