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Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	N20-983/
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Keywords: NDA review, clinical Studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Albuterol sulfate HFA inhalation aerosol (albuterol HFA) was approved on April 19, 2001, for the treatment or prevention of bronchospasm with reversible obstructive disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. A written request for pediatric studies, in response to a GlaxoSmithKline's proposal, was issued by the agency to evaluate the efficacy and safety of albuterol HFA in patients under 4 years of age. (b) (4)

Two of the three studies, Studies 020001 and 030001, were similarly-designed randomized, double-blind, placebo-controlled, multi-center, and parallel-group studies. The two studies had a treatment duration of 4 weeks in patients under 4 years of age with symptoms of bronchospasm associated with obstructuve airways disease. Patients were treated with albuterol HFA 90 or 180 mcg or placebo TID delivered with a holding chamber with an attached facemask. The symptom scores of wheeze, cough, dyspnea, or chest tightness were assessed daily on a scale of 0 to 3. Study 020001 enrolled 77 patients 2 to <4 years of age, of which 26, 25, and 26 were randomized to albuterol 90 and 180 mcg and placebo, respectively. Study 030001 enrolled 86 patients from birth to <2 years of age, of which 29, 29, and 28 were randomized to albuterol HFA 90 and 180 mcg and placebo, respectively. Neither of the two studies demonstrated treatment difference in asthma symptom scores among either dose of albuterol HFA and placebo. No dose response trend of albuterol HFA was seen in either study. In Study 020001, the differences of changes from baseline in the symptom scores were -0.1 with p-value 0.406 between albuterol HFA 90 mcg and placebo and -0.1 with p-value 0.467 between albuterol HFA 180 mcg and placebo. In Study 030001, the differences were 0.2 with p-value 0.334 between albuterol HFA 90 mcg and placebo and 0.0 with p-value 0.978 between albuterol HFA 180 mcg and placebo.

The third study, Study 030002, was a randomized, double-blind, multicenter, and parallel-group study without placebo control, conducted in patients from birth to <2 years of age who were experiencing acute wheezing due to obstructive airway disease. Albuterol HFA 180 or 360 mcg were given to randomized patients, with a holding chamber with an attached facemask, every 20 minutes for the first hour, and hourly for the next two hours for a maximum of 6 doses. The efficacy assessments were based on a Modified Tal Asthma Symptoms Score (MTASS). Although both albuterol treatment groups showed about 50% reduction from baseline in MTASS, no dose response was observed in the two albuterol HFA treatment groups. Without dose-response relationship, one may question if a dose level lower than albuterol HFA 180 mcg could achieve the same level of symptom reduction.

In conclusion, the three studies did not demonstrate efficacy of albuterol HFA 90 and 180 mcg TID delivered with a holding chamber with an attached facemask in asthmatic patients under 4 years of age. In addition to the concern if the tested drug had been delivered to the mouths of patients, there are issues with the study design, such as inadequate dose level, sample size, efficacy assessment, and patient population, that potentially could affect the efficacy assessment of albuterol HFA.

1.2 Statistical Issues and Findings

Although it may be conjectured that inadequate dose levels were the reason that albuterol HFA did not show efficacy in Studies 020001 and 030001, certain other issues in the study design from the perspective of this statistical reviewer could potentially affect the study results as well. These issues are discussed in this section.

The definition of daily symptom score:

The primary efficacy endpoint used in Studies 020001 and 030001 was mean percent change from baseline of daily symptom scores. The daily asthma symptom score was defined as the maximum value recorded for the daytime and nighttime individual symptom scores. The individual symptoms were wheeze, cough, dyspnea/chest tightness.

The definition of the daily asthma symptom score could potentially enroll patients with very mild disease symptoms. To understand this, consider a scenario that Patient A has only one mild symptom during the daytime, while Patient B has all the three mild symptoms during both day and night. Clearly, the asthma symptoms of the two patients are different. However, based on the definition of the daily symptom score, the two patients have the same symptom score. As the entry criterion required patients to have either or both daytime and nighttime asthma symptom scores ≥ 1 for at least 2 of 7 consecutive days of up to 28-day screening period, this reviewer's concern is that the study may have enrolled patients with very mild symptoms who might have very little room for efficacy improvement.

The definition of daily symptom score could also be indifferent to any potential treatment effect. Consider a scenario that a patient has three severe symptoms during both daytime and nighttime and after receiving treatments, only one symptom remained severe during the daytime. Such treatment effect would not be captured since by the definition of the daily symptom score, this patient has no improvement in asthma symptoms.

In both Studies 020001 and 030001, the individual symptom score was not collected. Therefore it was difficult to evaluate these concerns in the two studies.

Inadequate sample size

The sponsor mentioned in the study protocols of Studies 020001 and 030001 that the primary objective of the studies was to evaluate the safety of albuterol HFA 90 and 180 mcg TID compared with placebo. A sample size of 22 completed patients per treatment arm was chosen (b) (4)

(b) (4)

Rescue albuterol usage:

All the three studies allowed patients to use albuterol HFA and albuterol nebules as rescue medication. The use of albuterol HFA in Studies 020001 and 030001 was on as needed base. In the data set of rescue albuterol use, there were many instances where data appeared to be missing. It was not clear if the missing data was due to no records in the diary or no usage of rescue albuterol. For the available data of rescue albuterol use, no treatment differences were seen among the two dose groups of albuterol HFA and placebo. The fact that no significant difference in rescue albuterol use was observed among all treatment groups might suggest that the dose levels of albuterol HFA used in the two studies might not be adequate.

Efficacy extrapolation

(b) (4)

Studies SALT05 and SALA3006, submitted in the original NDA submission. The use of Study SALT05 was not considered appropriate as it was a single dose cross over study. The use of Study SALA3006 might not be appropriate as the extrapolation has to be made with more than one variables, i.e., different dosing regimens and different age groups. The dosing regimen in Study SALA3006 was albuterol HFA 180 mcg QID and the patient population was asthmatic patients 4-11 years of age. While the dosing regimens in Studies 020001 and 030001 were albuterol HFA 90 and 180 TID and the patients population was asthmatic patients under 4 years of age.

2. INTRODUCTION

2.1 Overview

(b) (4) three randomized, double-blind, multicenter, parallel group studies, two of the three were chronic studies (Studies SB020001 and SB030001) with placebo control and one acute study (Study SB030002) without placebo control. Both Studies SB020001 and SB030001 were 4 week duration trials and were used for the efficacy assessment of albuterol HFA 90 mcg or 180 mcg three times daily in patients with symptoms of bronchospasm. Study SB020001 was conducted in pediatric patients aged 2 to <4 years. Study SB030001 was conducted in pediatric patients from birth to <2 years. Study SB030002 was conducted in patients from birth to 23 months of age with acute wheezing to support cumulative dosing of albuterol HFA 180 mcg and 360 mcg given every 20 minutes in the first hours and hourly for the remaining 2 hours for a maximum of 6 doses.

To support the efficacy of albuterol HFA in patients under 4 years of age, two studies, SALA3006 and Studies SALT05, submitted in the previous submission were included in

this supplement. Study SALA3006 was a randomized, double-blind, placebo-controlled, and parallel group study in asthmatic patients 4-11 years age. The treatment groups included albuterol CFC 180 mcg QID, albulterol HFA 180 mcg QID, and placebo HFA. A total of 135 patients were enrolled. Study SALT05 was a randomized, double-blind, single-center, and cross-over study to in patients 6-14 years of age with histamine-induced bronchoconstriction with reversible airway obstruction. The study compared the efficacy and tolerability of a single dose of albuterol HFA 180 mcg, albuterol CFC 180 mcg, and placebo HFA administered via a pressured inhaler and spacer device. A total of 25 patients were enrolled.

2.2 Data sources

Electronic document room for NDA20-983 submitted on 9-28-2007.

3. STATISTICAL EVALUATION of individual studies

3.1 Studies SB020001 and SB030001

The primary objective of the two studies was to evaluate safety and efficacy of albuterol HFA 90 and 180 mcg TID delivered with a holding chamber with an attached facemask versus HFA placebo supplemented with the use of rescue albterol HFA or albuterol nebules.

Study design

The two studies were randomized, double-blinded, placebo-controlled, multicenter studies conducted with parallel groups in patients with symptoms of brochospasm (wheeze, cough, dyspnea, or chest tightness). Patients were randomized to albuterol 90 or 180 mcg, or placebo TID in 1:1:1 ratio. The treatments were administrated via HFA metered dose inhalers which were delivered with either an AeroChamber Plus or an Optichamber valvaed holding chamber with an attached facemask. The study included an up to 28-day screening period (Visit 1), a 29-day (4-week) double-blind treatment period (Visits 2-5), and 1-week follow-up period. The scheduled clinic visits after screening were the randomization visit at Day 1 (Visit 2), and Days 8, 15, and 29 (Visits 3-5). A telephone contact was conducted 1-week after the completion/discontinuation of the treatment. Patients enrolled had either or both daytime and nighttime asthma symptom scores >=1 for at least 2 of 7 consecutive days of the 7-28 day screening period. This reviewer had a concern that the study potentially could enroll patients with mild asthma symptoms. This concern was further discussed in the section of statistical issues.

All concomitant rescues use of short-acting beta-agonist therapy was replaced with study supplied unblinded albuterol HFA MDI 90 mcg or albuterol nebules 2.5 mg/3mL.

The main differences of the two studies were the following:

- Study SB020001 was conducted in patients 2 to <4 years of age with randomization stratified by age (2-3 and 3-4) and two holding chambers (AeroChamber Plus and Optichamber). Equal number of patients from each age group and for each kind of spacer was recruited.
- Study SB030001 was conducted in patients from birth to <2 years of age. The randomization were stratified by age groups (birth to <1 years of age and 1-<2 years of age). A quarter of the patients was recruited for the age group from birth to <1 years of age. Only AeroChamber Plus was used in this study.

Efficacy measures

Parent/guardian reported daytime and nighttime asthma symptom scores were recorded daily on diary cards, each recording reflected the symptom assessment of the previous 12-hour period. The asthma symptoms include cough, wheeze, and shortness of breath.

The nighttime symptom scores were recorded on the diary card each morning and graded as the following:

- 0=None – no asthma symptoms
- 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

The daytime symptom scores were recorded each evening and graded as the following:

- 0=None – no asthma symptoms
- 1=Mild – noticeable symptoms but not interfering with daily activities
- 2=Moderate – symptoms present often, causing some interference with daily routine and activities
- 3=Severe – symptoms continuous or present most of the day restricting daily routine and activities severely.

In addition, the following information including daytime and nighttime rescue albuterol use, nighttime awakenings, peak expiratory flow in the AM and PM which was collected in patients able to perform this maneuver in Study 20001.

Endpoints:

The primary endpoint of the two studies was the mean change from baseline in daily 24-hour asthma symptom score averaged over the 29-day treatment period (average of the non-missing values). The daily symptom scores were defined as the maximum value recorded for the daytime and nighttime individual symptom scores. The baseline symptom score was defined as the average of the last 7-day symptom scores during the screening period. Although the protocol defined primary endpoint was mean percent change from baseline in 24 hour symptom scores, the medical division preferred to use the change from baseline. Conclusions are unchanged with either endpoint.

Secondary endpoints included:

- Change from baseline in daytime asthma symptom scores

- Change from baseline in nighttime asthma symptom score
- Percentage of symptom free 24 hour days
- Change from baseline in 24 hour rescue albuterol use: Albuterol use was expressed as the number of puffs of albuterol MDI used, where one albuterol nebule equals two puffs of VENTOLIN HFA MDI. Total albuterol use was the sum of albuterol used during the past 12 hours recorded in the morning and the albuterol used during the past 12 hours recorded in the evening.
- Percentage of nights with no awakenings due to asthma requiring albuterol treatment
- Rescue systemic and inhaled corticosteroid use
- Time to treatment failure
- AM and PM peak expiratory flow in Study SB020001 in capable patients
- Rate of patients with asthma exacerbations.

Statistical methods:

The primary population for all summaries and analyses will be the Intent-to-Treat (ITT) Population. The ITT Population was defined as all randomized patients who received at least one dose of study drug. This population was used for all safety and efficacy.

The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA) with adjustments for region, baseline 24-hour asthma symptom score, age, gender, and concurrent medication use for asthma. The daytime symptom scores were also analyzed using ANCOVA, while the percentage of symptom-free 24-hour days and percentage of albuterol free 24-hour days were analyzed with the van Elteren modification of the Wilcoxon rank sum test. No multiplicity adjustment was made for multiple doses.

The sponsor mentioned in the study protocol that since the primary objective of this study was to evaluate the safety of albuterol HFA 90 and 180 mcg TID compared with placebo, a sample size of 22 completed patients per treatment arm was chosen [redacted] (b) (4)

Study results:

Seventy-seven patients enrolled in Study SB020001, 26, 26, 25 patients were randomized to placebo or albuterol HFA 90 or 180 mcg, respectively. The study was conducted in 37 centers and between the period of June 13th, 2003 and December 8th, 2003 . Only 3, 2, and 2 patients discontinued the study in placebo, albuterol HFA 90 or 180 mcg, respectively.

Eighty-six patients were enrolled in Study SB030001, 28, 29, and 29 were randomized to placebo, albuterol 90 or 180 mcg TID. This study was conducted in 30 sites between the period of July 1st, 2004 and Feburary 23rd, 2005. Eight patients discontinued the study, 4, 1, and 3 were in placebo, albuterol HFA 90 and 180 mcg, respectively.

Table 1 displays the patient account information of the two studies.

Table 1: Patient account information for Studies 020001 and 030001

	Study 020001			Study 030001		
	Albuterol 90 mcg	Albuterol 180 mcg	Placebo	Albuterol 90 mcg	Albuterol 180 mcg	Placebo
Randomized	26	25	26	29	29	28
Completed	24 (92%)	23 (92%)	23 (88%)	28 (97%)	26 (90%)	24 (88%)
Discontinued	2 (8%)	2 (8%)	3 (12%)	1(3%)	3 (10%)	4 (14%)
Adverse event	0	0	0	0	0	0
Protocol violation	0	2	1	0	0	0
Lack of efficacy	1	0	1	0	2	4
Others*	1	0	1	1	1	0

*Including lost to follow-up, consent withdrawn, and non-compliance.

The demographic and baseline information of Study SB020001 was reasonably balanced among the three treatment groups, except gender distributions. There were 62%, 81%, and 52% of male patients in placebo, albuterol HFA 90 or 180 mcg, respectively. The mean age was 3 years. About half of the patients were Caucasians (55%). The majority used ICS and/or leukotriene modifier for concurrent asthma medication (68%).

The demographic and baseline information of Study SB030001 was reasonably balanced among the three treatment groups, except the distribution in age groups. There were more patients in birth to <1 year of age group in the placebo group (36%) than that in the albuterol HFA 90 and 180 mcg groups (24% and 17%, respectively). About 68% of patients were male. The mean age was about 1.2 year. About 50% of the patients were Caucasians. About 50% of patients were ICS and/or leukotriene concurrent asthma medication users.

Efficacy results

The sponsor's primary efficacy results are displayed in Table 2. As can be seen from Table 2, all treatment groups in both studies had similar reduction in asthma symptom scores. No treatment differences were observed in neither of the albuterol HFA treatment groups in comparison to placebo in symptom score reduction in both studies.

Table 2: Primary efficacy results of Studies 020001 and 030001.

Treatment	Baseline	Chg from Baseline	Diff vs. Placebo (95% CI)	p-value
Study 020001				
Placebo (n=26)	1.3	-0.3		
Albuterol HFA 90 mcg (n=26)	1.4	-0.4	-0.1 (-0.4, 0.2)	0.406
Albuterol HFA 180mcg (n=25)	1.6	-0.4	-0.1 (-0.4, 0.2)	0.467
Study 03001				
Placebo (n=28)	1.3	-0.4		
Albuterol HFA 90 mcg (n=29)	1.5	-0.2	0.2 (-0.2, 0.6)	0.334
Albuterol HFA 180mcg (n=29)	1.3	-0.3	0.0 (-0.4, 0.4)	0.978

To understand the rescue albuterol use among treatment groups in the two studies, this reviewer analyzed the rescue albuterol use data. In this analysis, patients with missing rescue albuterol use were not included. The results are displayed in Table 3. The rescue albuterol uses during the treatment were comparable among the treatment groups.

Table 3: Rescue albuterol use analysis for Studies 020001 and 030001.

Treatment	Baseline		Chg from Baseline		2-sided p-value * compared with placebo
	N	Mean	N	lsmean*	
Study 020001					
Placebo (n=26)	24	3.11	22	-1.11	
Albuterol HFA 90 mcg (n=26)	23	3.20	23	-1.65	0.331
Albuterol HFA 180mcg (n=25)	19	4.04	17	-1.16	0.946
Study 03001					
Placebo (n=28)	27	3.56	25	-1.21	
Albuterol HFA 90 mcg (n=29)	28	3.80	28	-1.49	0.584
Albuterol HFA 180mcg (n=29)	26	3.23	25	-1.48	0.599

* ANCOVA model with baseline abuterol use and treatment as covariates.

None of the secondary endpoints has shown consistent treatment effect or consistent dose respond trend in the two studies.

3.2 Study SB030002

The primary objective was to assess the safety and efficacy of cumulative dose administration of albuterol sulfate HFA inhalation aerosol delivered via a valve holding chamber and an attached facemask in children between birth to 23 months of age who were experiencing acute wheezing due to obstructive airways disease.

Study design:

This was a randomized, double-blind, multicenter conducted with parallel groups in an acute care clinical setting where patients were seen in the emergency department (ED) or clinic. The study protocol allowed patients to receive one treatment of albuterol HFA via holding chamber with attached facemask or one treatment of nebulized albulterol inhalation solution in the ED/clinic prior to the initiation of the study. All patients must have had an asthma symptom score between 4 and 9 based on a Modified Tal Asthma Symptoms Score (MTASS). Patients from two age groups (birth to <12 months, and 12 to <24 months) were recruited. The planned recruitment was to achieve a ratio of 1:3 between the two age strata. Patients were randomized, stratified by the two age groups, to albuterol HFA 180 or 360 mcg in a 1:1 ratio. Albuterol HFA inhalation aerosol was delivered with an AeroChamber Plus and facemask every 20 minutes for the first hour, and hourly for the next two hours for a maximum of 6 doses. About 5-7 days after the treatment, a follow-up phone contact was conducted to follow-up any post-treatment adverse events.

If a patient required any rescue albuterol use, the scheduled albuterol HFA treatment must be separated by at least 15-minute from the last rescue albuterol use. In this study the rescue albuterol dose was albuterol HFA 180 mcg, given with spacer and facemask. If any patient required more than 2 rescue albuterol during the three hour treatment period, the patient was withdrawn from the study.

Efficacy evaluation:

The assessment of asthma condition was conducted at screening and every 20 minutes in the first hour and then every 30 minutes in the second and third hours. The severity of acute wheezing due to obstructive airway disease was to be expressed as the MTASS, which rates the severity of an episode according to signs and symptoms described in Table 4. The patient's treatment responses were classified to three categories during the three-hour treatment period: good response, poor response, and incomplete response. Patients who were good responders were discontinued for further scheduled treatment and were considered premature withdrawn from the study.

Table 4: Modified Tal Asthma Symptoms Score.

Score	Respiratory Rate (breaths/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	Terminal expiration and inspiration with stethoscope only	Circumoral at rest	Medium
3	>70	>60	Expiration and inspiration without stethoscope	Generalized cyanosis at rest	High

The primary endpoint was mean percent change from baseline over the entire treatment period in MTASS. The secondary endpoints included change from baseline in MTASS and rescue albuterol use.

Statistical model:

The treatment improvement from baseline was analyzed based on MTASS. The analysis was performed using ANCOVA adjusting for baseline MTASS, investigator site, age, and gender. The analysis used an intent-to-treat (ITT) population which was defined as all patients who were randomized and received at least one dose of study drug.

Study Results:

Eigthy-seven patients were enrolled to the study with 43 and 48 randomized in albuterol HFA 180 and 360 mcg, respectively. All patients were included in the ITT population. Among the 87 patients, 66 patients were included in the Fulfilled Regulatory Criteria (FRC) which was a subset of ITT population where patients received a minimum of 3 doses of study medication and had an evaluable Holter recording. The study was

conducted in the period of September 10th, 2004 –February 26th, 2006 at 16 sites. Information on patient disposition is summarized in Table 5.

Table 5: Patient disposition information.

	Albuterol 180 mcg	Albuterol 360 mcg
Randomized	43	44
ITT population	43	44
FRC population	35	31
Completed	14 (33%)	21 (48%)
Discontinued	29 (67%)	23 (52%)
Due to good response	27	20
Protocol violation	2	2
Withdrawn consent	0	1

The demographic information was balanced between the two treatment groups. About 66% was male, mean age was 0.89 year (10.6 months), 56% was in birth to <1 year of age group which was more than planned enrollment proportion (25%) for this age group, and 45% was Caucasians.

The sponsor's objective of the efficacy evaluation was to compare the treatment difference between the two albuterol HFA groups. The primary efficacy results are summarized in Table 6. As can be seen from Table 6, both treatment groups had about 50% reduction in MTASS score. However, no dose response was seen between the two albuterol HFA dose levels. This reviewer believes that it is important to demonstrate dose response relationship between the two albuterol HFA treatment groups as the study did not have placebo as control. Based on such study results, one may question if lower dose of albuterol HFA could achieve the same level of symptom reduction.

Table 6: Primary efficacy results for Study 030002.

	Albuterol HFA	Baseline	Mean % change
ITT population	180 mcg (n=43)	5.7	-49.8
	360 mcg (n=44)	5.8	-48.4
FRC population	180 mcg (n=35)	5.8	-47.2
	360 mcg (n=31)	6.0	-47.9

Results of analyses in change from baseline in MTASS were similar to the primary efficacy analyses. Only 4 and 3 patients in albuterol HFA 180 mcg and 360 mcg used rescue albuterol, respectively.

4 Findings in special/subgroup populations

The sponsor performed subgroup analyses including by holding chamber and by concurrent medication use for asthma (defined as those subjects maintaining a fixed dose of ICS and/or leukotriene modifiers throughout the treatment period). No treatment by subgroup interaction was observed based on the analyses. The reviewer's analysis results of by holding chamber are displayed in Table 7 for Study 020001. Subgroup analyses by age, gender, and race were not performed because of the small sample sizes.

Table 7: Efficacy analysis by chamber performed by the reviewer for Study 020001.

Treatment	Baseline	Chg from Baseline	Diff vs. Placebo (95% CI)	p-value
Optichamber				
Placebo (n=14)	1.2	-0.3		
Albuterol HFA 90 mcg (n=14)	1.6	-0.6	-0.3 (-0.8, 0.2)	0.289
Albuterol HFA 180mcg (n=10)	1.4	-0.3	-0.0 (-0.5, 0.5)	0.971
Aerochanber				
Placebo (n=12)	1.4	-0.2		
Albuterol HFA 90 mcg (n=12)	1.3	-0.3	0.0 (-0.5, 0.4)	0.899
Albuterol HFA 180mcg (n=15)	1.8	-0.5	0.3 (-0.9, 0.2)	0.259

5 Collective Evidence and Label Review

5.1 Collective Evidence

(b) (4)

Studies SALT05 and SALA3006, submitted in the original NDA submission. Study SALA3006 was a randomized, double-blind, placebo-controlled, and parallel group study in asthmatic patients 4-11 years age. The treatment groups included albuterol CFC 180 mcg QID, albulterol HFA 180 mcg QID, and placebo HFA. A total of 135 patients were enrolled. Study SALT05 was a randomized, double-blind, single-center, and cross-over study to in patients 6-14 years of age with histamine-induced bronchoconstriction with reversible airway obstruction. The study compared the efficacy and tolerability of a single dose of albuterol HFA 180 mcg, albuterol CFC 180 mcg, and placebo HFA administered via a pressured inhaler and spacer device. A total of 25 patients were enrolled.

The use of Study SALT05 was not considered appropriate as it was a single dose study. The use of Study SALA3006 might not be appropriate as the extrapolation has to be made with more than one variables, i.e., different dosing regimens and different age groups. The dosing regimen in Study SALA3006 was albuterol HFA 180 mcg QID and the patient population was asthmatic patients 4-11 years of age. While the dosing regimens in Studies 020001 and 030001 were albuterol HFA 90 and 180 TID and the patient population was asthmatic patients under 4 years of age.

5.2 Label review

(b) (4)

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/s/

Qian Li
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