Study Treatments
Albuterol HFA used in this trial was from batch 6ZX001A, and the Ventolin CFC used during run-in was from 6ZPA036. Two actuations of study medication were administered at approximately 4 – 6 hour intervals, with a separate back up albuterol HFA canister to relieve acute symptoms. On study visit days, the AM dose of open label study medication was administered in the clinic at the end of the visit.

Safety Evaluations
These consisted of adverse event and asthma exacerbation monitoring, clinical laboratory tests, vital signs, ECGs, physical exams, CXR, and subject diary card assessments. FEV1 was monitored at clinic visits prior to the first AM dose of study medication. The schedule of those events that occurred intermittently is described in the following table.

Evaluations	Visits
Predose spirometry	Screening, 1 – 15
ECGs, vital signs	Screening, 1, 5, 8, 12, 15
Clinical Labs	Screening, 8, 15
PE	Screening, 8, 15

Diary card data were summarized for each patient by transcribing data from the Subject Worksheets for the 7 days immediately prior to a treatment visit. The data transcribed included morning PEFR, nighttime awakenings, back-up albuterol use, and whether asthma interfered with activities. Baseline was defined as the 7 days immediately prior to treatment visit 1 when albuterol HFA was dispensed.

Medical reviewer comment: *Because of its open-label, uncontrolled design, results from this study will be most useful in determining if safety findings occurring after 12 weeks exposure to albuterol HFA are materially different in number or type from those occurring during the first 12 weeks of exposure. Otherwise, this study has limited ability to discriminate treatment-associated safety findings from the spontaneous background rate.*

Results

Device Performance
One subject from Dr. Padua's site (#4500, in Mayasguez, PR) returned one PRN albuterol HFA canister and reported that only a small amount of medication appeared to be coming out. Glaxo evaluation found that the suspension was coming out slowly because of clogging of the drug in the valve stem. No other device malfunctions were noted in the study report.

Study Population Results

A small number of patients failed to complete the trial because of adverse events (7 subjects, 2%) or lack of efficacy (7 subjects, 2%). [Table 2, Clinical Amendment Vol 1:109]. Forty-five patients (10%) withdrew for "other" reasons; these were chiefly due to withdrawal of consent or non-compliance. The bulk of protocol variations occurred in patients who were seen outside the specified time windows for Clinic visits. Eight patients each (2%) fell outside of the inclusion and exclusion criteria. In the opinion of the medical reviewer, these variations did not raise concerns about the interpretability of findings from this trial.

Demographic analyses of the 452 intent-to-treat subjects showed the following:

- 50% male
- 64% Caucasian, 29% Hispanic, 5% African American
- Mean age 36.3 years, range 12-77 with 16% ≤17 years and 5% ≥65 years

Overall, 43% of subjects had a history of asthma ≥ 15 years, 16% had ≥1 episode of asthma requiring emergency care within 12 months of starting the study, and 3% had been hospitalized at least once for asthma. The majority (70%) did not smoke. During the study, 70% of patients used inhaled corticosteroids and 23% used oral corticosteroids. Xanthines and βagonists were used by 15% and 12% of patients respectively to treat asthma and asthmatic exacerbations. There was extensive use (44 - 57% of patients) of antihistamines, nasal decongestants/cold cures, and corticosteroids for treatment of rhinitis. Socioeconomic data were collected but were not considered to be relevant for review by the FDA medical reviewer.

Exposure

86% of patients had >300 days exposure to albuterol HFA. Mean exposure was 328 days for 452 subjects, or approximately 406 subject-treatment years.

Safety Findings

Adverse events

Ninety-two percent of patients experienced at least one adverse event after exposure to study drug. Body systems with the highest incidence of adverse events were the ear, nose, and throat (75%), lower respiratory (40%) and gastrointestinal (34%) systems. Overall the most common adverse events were URTI (44%), headaches (22%), and bronchitis. Seventeen specific adverse events with an incidence ≥ 5% were reported by the sponsor [Clinical Amendment Vol 1:45]. Of these, 4 events were examined by the medical reviewer based upon potential associations seen during study treatment in the adult 12 week placebo controlled trials.

Adverse Events During 12 Months Exposure
That Were Also Seen During 12 Week Controlled Pivotal Trials

Adverse Event	Total N (%)	Number Classified as			
		Mild	Moderate	Severe	Drug-Related
Headaches	101 (22%)	47	49	15	13 (3%)
Throat irritation*	51 (11%)	40	13	2	4 (<1%)
Cough	39 (9%)	25	15	0	2 (<1%)
Hoarseness/ dysphonia	12 (3%)	6	8	0	1 (<1%)

* Distinct from pharyngitis/throat infection

Twenty percent (n=89) of subjects experienced at least one adverse event considered to be severe. Viral respiratory infections (3%) and headaches (3%) were the only adverse events rated as severe which occurred in >1% of subjects.

Adverse events that occurred in ≥3% of subjects in any month were summarized by month of their occurrence [Clinical Amendment Vol 1: 46]. These included URTI, headaches, bronchitis, upper respiratory inflammation, musculoskeletal pain, and sinusitis/sinus infection. Headaches occurred at a slightly higher incidence in the first month (7%) than in all subsequent months (range 2 –4%). None of these adverse events showed an increased incidence with increasing duration of exposure. In addition to these events, the medical reviewer examined 8 additional adverse events for their monthly incidence over the course of the trial. These included throat irritation, hoarseness/dysphonia, dizziness, nausea/vomiting, diarrhea, cough, fever, and chest symptoms. Again, no increase in incidence over time was noted; most declined in incidence after the first month of the study. Throat irritation occurred at a relatively stable monthly incidence over time, with 3 – 9 patients affected (<1 to 2%) per month.

Overall, 10% of subjects experienced at least one adverse event that was considered to be possibly, probably, or almost certainly related to the study drug. The body system with the highest incidence of drug-related adverse events was the neurological body system (5%) of which most were headaches. Throat irritation attributed to study drug was described in 4 patients (<1%). Overall, the incidence of specific drug-related adverse events was low. Headache was the only drug-related adverse event that occurred in >1% of subjects.

Deaths

There were 2 patient deaths during the study. A 66 year old female died in a motor vehicle accident after 9 months on study, and a 41 year male died of diabetic ketoacidosis 4 days after completing the study. The patient with DKA had discontinuation labs showing a nonfasting blood glucose of 456 mg/dL and urine positive for glucose and ketones. His nonfasting blood glucose was normal at screening, and 233 mg/dL at treatment visit 8 (week 24). Both deaths were considered unrelated to study drug by the investigator, and the medical reviewer concurs with this assessment.

Serious Adverse Events
A total of 23 subjects (5%) reported 29 serious adverse events [Clinical Amendment Vol 1:48]. All 29 serious adverse events were assessed by the investigator as being unrelated to treatment. The following table eliminates those events where a potential drug relationship was considered to be highly implausible by the medical reviewer (ie. rattlesnake bite, MVA).

Selected Serious Adverse Events

Adverse Event	#	Age (yr)	Gender	Withdrawn from study
Asthma exacerbation	6	12 – 66	50% female	1 yes, 5 no
Status asthmaticus with hypoxia	1	53	Male	No
Vomiting, abd pain & bleeding, throat irritation	1	40	Female	No (h/o PUD)
MI	1	52	Male	Yes
DKA	1	41	Male	No (died after d/c)

Medical reviewer comment: *The numbers and type of "plausibly" associated adverse events do not suggest any association of albuterol HFA.*

Withdrawals due to Adverse Events
Seven patients were withdrawn during the study due to adverse events. Of these, 2 withdrawals were clearly unrelated to study drug (hematuria secondary to bladder cancer, MVA) in the opinion of the medical reviewer. Of the remaining 5 withdrawals, 2 cases were due to headache complicated by other symptoms; these occurred on the first day of treatment and were considered by dechallenge responses to be possibly or probably related to study drug treatment. One was a 31 year old woman who complained of nervousness, irritability, restlessness, and migraines on the first day of treatment. The second case was a 46 year old female who complained of dizziness, headache, and nausea. Other adverse events causing study withdrawal included one case of facial petechia that did not recur on rechallenge, 1 subject with an asthma exacerbation, and one patient with an MI. All were considered by the investigator (and the medical reviewer) to be unrelated to study treatment.

Pregnancies/Other significant adverse events
No adverse events proximate to drug dosing were reported during the study. One pregnancy occurred after 6 months of exposure and was electively terminated without complications.

Laboratory Abnormalities
The number of patients with a shift in laboratory values from normal to Screening to abnormal at treatment Visit 15 was generally low (n≤17, ≤4%). Blood glucose, eosinophils, and ALT exceeded these values. Their numbers and other associated lab values of interest were as follows:

Selected Laboratory Shifts from Normal to Abnormal

	Number (%) Changing in Described Direction	
	Normal to high	Normal to low
Eosinophils	19 (4)	0
ALT	25 (6)	0
AST	16 (4)	0
Bilirubin	9 (2)	0
Glucose	33 (8)	19 (4)

Patients with lab values beyond threshold range were limited in number, and ≤2% for any one abnormality. Analytes listed above or with ≥1% of patients outside threshold values included the following:

Eosinophils	8 subjects (2%) above threshold of 15%
ALT	3 subjects (<1%) above threshold of >120
AST	1 subject (<1%) above threshold of >100
Bilirubin	5 subjects (1%) above threshold of ≥2
Glucose	7 subjects (2%) above threshold of >175
	4 subjects (<1%) below threshold of <55
Hemoglobin	7 subjects below threshold of 11.4 (males) or 10.4 (females)

Most of the patients with labs exceeding threshold values had abnormalities of these parameters at baseline, including all 5 patients with elevated bilirubin. Of the 7 subjects with elevated glucose, only one (the patient who died from DKA) moved from a normal to a high level over the course of the trial. In the opinion of the medical reviewer, the pattern of laboratory abnormalities did not raise any concerns for the safety of albuterol HFA.

Vital Signs & ECGs

The ranges and means of pulse rate, systolic blood pressure, and diastolic blood pressure were similar between all visits. Clinically significant ECG abnormalities were noted in 4 patients a total of 8 times; one patient had 5 findings of RBBB after a finding of bifascicular block at screening. Of the remaining patients, two had borderline abnormalities that met criteria on one occasion and then reverted to borderline status. The remaining patient had a finding of hyperacute T wave abnormality with normal potassium, calcium, and magnesium levels.

Mean heart rates based upon ECGs were similar across treatment visits. Mean QTc intervals ranged from 411-416 msec at each treatment visit, with 86% to 94% of subjects having QTc ≤440 msec. Eight patients had one QTc interval >470 msec while on study, and 3 additional patients had this occur on multiple measurements. None of the occurrences was considered clinically signficant by the central cardiologist. Eight of the 11 patients with QTc >470 msec were females (mean age ~46 years by medical reviewer calculation); the 3 male patients were either 14 or 15 years old [Clinical Amendment Vol 4:28ff]. One 14 year old male had QTc intervals of 563 and 610 msec at treatment visits 12 and

15 respectively. Other than low normal potassium and magnesium levels, he had no metabolic or drug-related explanation for his prolonged intervals.

Medical Reviewer Comment: *The overall number of ECG abnormalities was low. Prolonged QTc findings occurred in <3% of patients and were seen most commonly in reproductive age females where QTc variability is known to be high. Without a placebo group for comparison, none of the ECG findings is compelling in number or pattern to suggest a cardiac safety risk of albuterol HFA.*

Physical examination data did not reveal any concerning pattern of detrimental changes in patients over the course of the study.

Asthma Stability (FEV1 and Exacerbations)
An asthma exacerbation was defined as asthma requiring treatment other than with allowed concomitant medications, study medication, or back-up albuterol MDI. Exacerbations were not reported as adverse events unless they resulted in a hospital admission or met the criteria of a serious adverse event.

Thirty percent of patients experienced ≥1 asthma exacerbation during the course of the study, with twelve percent of patients having 2 or more exacerbations during the study. The monthly incidence of exacerbations ranged from 3 –7% with slightly higher values observed at the beginning of trial. Baseline FEV1 values (predose) remained stable at 80 – 82 % of predicted during the 52 weeks of treatment.

Diary Card Assessments
The mean of patient-measured AM PEFR improved by 13.4 L/min over the course of the trial and ranged from 3.9 to 19.4 L/min during study treatment. The mean percent of nights with no awakenings due to asthma also increased slightly from a baseline of 83% to 93% at treatment week 52. Mean daily back-up albuterol use declined slightly (from 2.84 puffs at baseline to 0.56 at treatment week 52) and the percentage of days without back-up albuterol use went from 42% at baseline to 79% at treatment week 52. The percent of days with no asthma interference increased during the study from a baseline of 77% to 875 by week 52.

Medical Reviewer Comments: *FEV1 and subject diary cards measurements of AM PEFR showed no deterioration in pulmonary function during the course of the study. Likewise there was no increase in nighttime awakenings, back-up albuterol use, or asthma interference. The salutary changes in diary card measures may represent enrichment of the patient population for the healthiest asthmatics, who were most likely to continue on trial over its entire 12 month duration.*

Medical Reviewer Conclusions

During approximately 400 patient years of exposure, 200 mcg of albuterol HFA administered QID was well tolerated and demonstrated no change in the profile of adverse events that were seen during controlled clinical trials. There was no increase or change in the pattern of adverse events seen in first 3 months versus the last 9 months of the study. Serious adverse events occurred in a low percentage of patients (5%), and none of these events were considered to be drug-related. The two deaths seen during the trial (from a motor vehicle accident and DKA) were not likely related to albuterol HFA exposure. Headache was the one drug-related adverse event that occurred in >1% of subjects, with throat irritation attributed to drug in 4 patients (<1%). Headache and throat irritation occurred at relatively constant incidences over the 12 month course of the trial.

None of the laboratory, vital signs, ECG, or physical examination results indicated a safety concern in this population. FEV1 measurements were stable or slightly improved during the trial, and subject-completed diary card evaluations showed no deterioration in PEFR, nighttime awakenings, back-up albuterol use, or asthma interference with normal activities.

Overall, albuterol HFA demonstrated no long-term safety concerns over 12 months of QID administration to adolescent and adult asthmatics.

120-DAY SAFETY UPDATE

Scope

The 120-day safety update included complete results from the long-term open-label safety study of albuterol HFA in adolescents and adults (SALA3003). These results were unchanged from what was discussed in the section of this document where SALA3003 is discussed. The 120-day safety update did compare results from the first 12 weeks of SALA3003 with the combined adolescent and adult 12-week studies (SALA3002 and SALA3005), and these data are reviewed below.

The 120-day safety included spontaneous reports of deaths, serious adverse events and pregnancies that occurred during the current reporting period from commercial use of the product outside the U.S. A literature review was also provided. Only those data not already incorporated into the Integrated Summary of Safety are discussed in this portion of the review.

Status of Approvals and On-going Studies

Fifteen countries have approved albuterol HFA from December 31, 1997 to October 27, 1998. No new clinical trials of albuterol HFA were started during this reporting period. One study was completed of patients receiving open-label fluticasone propionate in HFA propellant and randomized to rescue albuterol as either HFA or CFC propellant. In this study (FLTB4008), there were no reports of serious adverse events, deaths, pregnancies, or withdrawals due to adverse events. A post-marketing surveillance study is currently being conducted in the UK with approximately 12,000 patients and will conclude in January 2000.

Updates to SALA3003

No new or additional information was provided on deaths, serious adverse events, withdrawals, pregnancies, clinical laboratory evaluations, vital signs, ECGs, QTc intervals, or heart rate changes occurring in SALA3003. This information is analyzed in the review of SALA3003 as well as the ISS. The only new information provided in the 120-day SUR was a comparison of weekly adverse event incidence rates.

The weekly incidence rates of the most common adverse events were compared for SALA3003 and the combined trials of SALA3002 and SALA3005. Headaches and upper respiratory tract infections (URTIs) were the most commonly reported conditions, and occurred at similar rates throughout the 12-week period in all studies. The ranges seen over the 12 weeks for these adverse events and the occurrence of any adverse event are described in the following table.

Range of Weekly Percentages for Weeks 1 –12
Combined SALA3002 and SALA3005 versus SALA3003

	SALA3002 & SALA3005 combined			SALA3003
	Placebo	HFA albuterol	CFC albuterol	HFA albuterol
Patients with ≥1 event	4 – 8	5 – 12	3 – 10	4 – 11
URTI	<1 – 3	<1 – 4	<1 – 4	2 – 3
Headaches	0 – 3	<1 – 3	0 – 4	<1 - 3

Prepared by medical reviewer from table 9, 120-day safety update

Medical reviewer comment: *The adverse events seen in the long-term safety study were similar in type and number to those seen in the 12 week controlled trials, and raised no significant safety concerns for albuterol HFA.*

Serious Adverse Events Reported from Spontaneous Sources

Serious adverse events concerning deaths, serious adverse events, and pregnancies from Glaxo Wellcome's Product Surveillance Database were incorporated into the corresponding sections of the Integrated Summary of Safety and are not repeated here.

Reports from the Literature not otherwise reported

A total of 12 articles on albuterol HFA and HFA alone that were published between January 1 1998 and June 30 1998 were provided. Their relevance to the safety evaluation of Glaxo's product is unclear, since they dealt with either Proventil HFA or Airomir. One article did mention a potential safety-related matter and is summarized below.

Tinkelman et al. (1998) reported on the safety profiles of Proventil HFA and Ventolin with regular use for 12 weeks. They noted a significantly greater rate of adverse events of tachycardia in albuterol HFA patients (n=13, 7%) than either HFA placebo (N=1, 1%) or CFC Ventolin (N=4, 2%). In the discussion, the authors indicated that grouping of the terms tachycardia and palpitations resulted in no significant differences across the treatment groups, and mean heart rates after dosing were similar for Proventil HFA and Ventolin.

Medical officer comment: *These findings cannot be extrapolated to Glaxo's HFA albuterol.*

Medical Reviewer Conclusions

The 120-day safety update presented no new data of concern about the safety of albuterol HFA.

SALB2003

A Single Center, Randomized, Double-Blind, Six-Way Crossover Study To Compare The Efficacy And Safety Of Single Doses Of Salbutamol 100 And 200mcg In Propellant 11 And 12, Salbutamol (As Salbutamol Sulfate) 100, 200 And 400mcg In GR106642X Propellant, And Placebo (GR106642X Propellant Alone) In Adolescent And Adult Patients With Reversible Airways Obstruction

Objectives

The primary objectives were to demonstrate comparability in terms of efficacy and tolerability between albuterol HFA and albuterol CFC, and to demonstrate a dose-response between the different doses of both albuterol HFA and albuterol CFC.

PROTOCOL

Study Design

The study was a single center, randomized, double-blind, six-way crossover design with a 4-14 day screening (run-in) period to assess eligibility. Six treatment visits (Visits 2 –7) were separated by 1 – 14 days, with a final follow-up visit (Visit 8) occurring 7-14 days after the cessation of the treatment period. Clinic Visit 1 was the screening visit.

At each treatment visit, the predose FEV1 had to vary <15% from the pre-VENTOLIN screening visit FEV1. If variation was ≥15%, the patient was rescheduled up to two times, with each visit falling between 1 and 14 days of the previous visit.

During run-in, patients stopped using their usual short-acting β-agonists and used only study-supplied VENTOLIN on a PRN basis. Other asthma medications were continued. At Visit 2, patients were randomized to a treatment sequence so that at each treatment visit they received varying doses of the two formulations by inhaling from 4 different canisters.

- Placebo HFA (4 inhalations of HFA propellant alone)
- 100mcg Albuterol HFA (1 inhalation albuterol HFA, 3 inhalations HFA propellant alone)
- 200mcg Albuterol HFA (2 inhalations albuterol HFA, 2 inhalations HFA propellant alone)
- 400mcg Albuterol HFA (4 inhalations albuterol HFA)
- 100mcg Albuterol CFC (1 inhalation albuterol CFC, 3 inhalations CFC propellant alone)
- 200mcg Albuterol CFC (2 inhalations albuterol CFC, 2 inhalations CFC propellant alone)

Subjects were males and females ≥12 years with mild to moderate asthma (FEV1 50-85% predicted) with demonstrated reversibility of ≥15% using VENTOLIN MDI with CFC propellant. Typical inclusion and exclusion criteria were applied to exclude patients with unstable asthma, serious medical conditions, or inability to tolerate drug washouts before FEV1 testing. Withdrawals occurred if

- the subject required more than two 7 day courses of additional βagonists and/or one 7 day course of prednisolone
- abnormal and clinically significant findings in ECG or clinical labs
- variability of predose FEV1 at a 3 treatment visits was ≥15% of the predose FEV1 at screening

Trial Medications
Batch numbers for the study medications were as follows:

Albuterol HFA	6ZX001A
Albuterol CFC	5Z1162P
Placebo HFA	6ZX002A
Placebo HFA	4Z2276P

Concurrent Medications
Patients were allowed to continue throughout the study on stable doses of inhaled corticosteroids (including intranasal), cromolyn, and nedocromil. Long-acting oral and inhaled β agonists, antihistamines, and decongestants were permitted with appropriate washout periods before treatment visits. Inhaled short-acting β agonists were NOT allowed in any form or combination, nor were methylxanthines or systemic corticosteroids.

Exacerbations
Exacerbations during the screening period led to study withdrawal. Between clinic visits, patients were allowed limited courses of additional β-agonist or oral prednisolone, which if exceeded, resulted in study withdrawal. During a clinic visit, the patient was first treated with VENTOLIN by MDI or nebulization. If a patient exacerbated and required additional therapy with β-agonist, oral antibiotics, oral prednisolone, or an increased dose of inhaled steroids, clinic assessments were rescheduled to allow an appropriate washout period (ranging from 5 days for β agonists to 21 days after oral prednisolone.)

Efficacy & Safety Endpoints
Serial FEV1 measurements were performed at treatment visits 2 –7, and were timed to occur immediately before dosing, and then 15 minutes, 30 minutes, 1, 2, 3, 4, 5, and 6 hours post-dose. The primary efficacy endpoints were the AUC under the FEV1 curve adjusted for baseline and the peak effect. Secondary endpoints were duration, onset, weighted mean FEV1, percent of responders, and time to offset.

Safety was assessed by adverse events, ECGs pre and post dosing with study medication, and serial vital signs during treatment visits.

Data Analysis and Sample Size
Assuming a standard deviation in FEV1 of 0.3L and a significant difference of 0.16L, a sample of 60 evaluable subjects had 80% power to detect such a difference.

AUC (bl) was calculated using the trapezoidal rule [51:43]. Weighted mean FEV1 adjusted for baseline was defined as the AUC divided by the length of spirometric testing (usually 6 hours). Responders, onset, offset and duration were defined in terms of an increase of 15% in same day predosing FEV1.

ANCOVA appropriate to a crossover design was used with baseline as a covariate. Missing data points were interpolated or the last value carried forward was used. Onset and offset were set to 6 hours if the subject did not respectively increase or decrease their FEV1 during testing by 15% from baseline. Because these assumed values led to some skew in the data, non parametric analyses were also done in addition to ANCOVA. Because of some nonhomogeneous variances for peak effect for different treatments, additional statistical analyses including nonparametric analyses were done. These analyses, as well as their lack of statistical adjustments for multiple comparisons, were not considered to be problematic for evaluation according to the Statistical reviewer.

Medical Reviewer Comment: *The only potential concern raised by the study protocol and analysis plan is the use of LVCF, in particular for peak effect, this may bias results to reject the null hypothesis. However, analysis of the limited number of patients who exacerbated during clinic testing showed that rescue VENTOLIN was not administered to any until after serial spirometry had been completed.*

Study Conduct
No Medical reviewer check of study conduct was made for this protocol. Protocol violations occurred in 22 (35%) of the intent-to-treat population, and of these, 12 violated more than one criteria or the same criteria on more than one occasion. Most protocol variations were in the timing of FEV1 assessments, and in the use of non-permitted asthma medications; the latter were patients who continued using their VENTOLIN MDI into the study, instead of using the VENTOLIN MDI provided at study initiation.

Results

Study Population
Of 85 subjects recruited, 63 were randomized. Of these, 6 withdrew; 3 were for excessive predose FEV1 variability from baseline, and the remaining 3 were for

reasons unrelated to study drug treatment. 57 subjects received study medication at all 6 treatment visits.

Study subjects were evenly apportioned by sex (49% were male) and almost exclusively (97%) Caucasian/white with 3% Asian. The mean age was 36 years (range 13 to 63 years), with 4 subjects below the age of 18. Seven subjects (11%) continued using their long acting βagonist and 47 subjects (75%) continued using inhaled corticosteroids into the treatment period.

Efficacy Results

AUC(baseline)
The following table shows the AUC baseline results as sample means and as adjusted (least squares) means based on ANCOVA

AUC (baseline) L*hr

		Means	Adjusted Means
Placebo		0.30	0.24
HFA	100mcg	1.22	1.27
	200mcg	1.66	1:69
	400mcg	2.06	1.97
CFC	100mcg	1.54	1.50
	200mcg	1.70	1.77

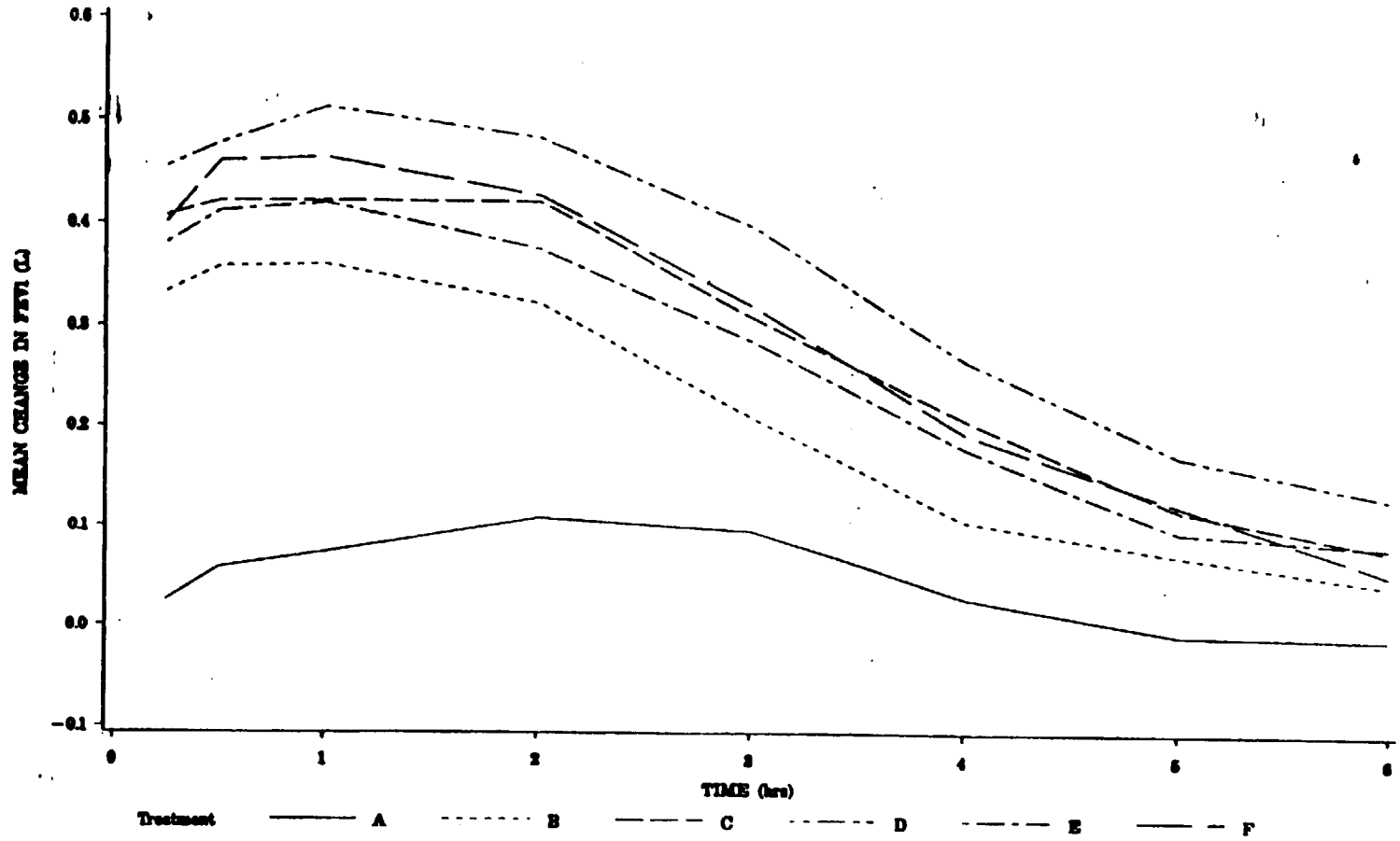
Each active treatment was statistically superior to placebo. Pairwise comparison of results from 100mcg HFA and 100mcg CFC formulations showed no statistically significant difference. Similarly, the 200mcg strengths of the two formulations were not statistically distinct in effectiveness. While statistically significant differences were found between 100 and 200mcg of albuterol HFA, the difference between these two dosage strengths of the CFC formulation was not statistically significant. The difference between 200 and 400mcg of albuterol HFA were marginally significant (p=0.055). Overall, the findings were considered to be supportive of a dose-response relationship by the sponsor.

Peak Effect
The effect of study treatments on peak effect (expressed as a percentage of baseline) are displayed below. Figure 5 on the following page displays these results graphically.

Peak Effect (as % of Baseline)

		Means	Adjusted Means
Placebo		109	108.8
HFA	100mcg	119	119.9
	200mcg	123	123.2
	400mcg	126	125.5
CFC	100mcg	121	121.2
	200mcg	122	123.0

FIGURE 5 - CHANGE IN SERIAL FEV1(L) FROM BASELINE: INTENT-TO-TREAT POPULATION



A = Placebo
B = Salbutamol 100mcg GR100643X
C = Salbutamol 200mcg GR100643X
D = Salbutamol 400mcg GR100643X
E = Salbutamol 100mcg P11/P12
F = Salbutamol 200mcg P11/P12

Each active treatment was statistically superior to placebo. Pairwise comparison of results using the same labeled dosage strengths (100mcg and 200mcg) of HFA and CFC formulations showed no statistically significant differences. The 100mcg HFA strength was statistically different from 200mcg, but this was not the case for the two doses of the CFC formulation. The increase from 200 to 400mcg HFA albuterol was also not statistically significant.

Medical Reviewer comments: *Although statistical significance was not achieved between each subsequent dose of the two formulations, numerically there was evidence for a dose response relationship.*

The ANCOVA model showed evidence of a significant treatment by baseline interaction such that the effect of active treatment compared to placebo was more marked for subjects with very low baseline FEV1. When the placebo data were removed from the model, the interaction term ceased to be significant. The sponsor indicated that the effect of active treatment was still well summarized by the adjusted means from the model without the treatment by interaction term, and that nonparametric analyses were similar to the parametric model results.

Secondary Efficacy Measures
Duration of action by means, adjusted means, and medians was as described in the following table. Analysis of medians was done since the mean data were skewed by the assumed values used in those patients who did not experience an increase of 15% increase over baseline.

Duration of Action (hours)

		Means	Adjusted Means	Median
Placebo		0.46	0.36	0.00
HFA	100mcg	1.66	1.77	0.59
	200mcg	2.26	2.33	2.02
	400mcg	2.76	2.66	2.95
CFC	100mcg	2.12	2.10	1.96
	200mcg	2.17	2.34	2.06

All active treatments were statistically superior to placebo. The only pairwise comparison of active treatments that was statistically significant was the difference in duration between the 100 and 200mcg strengths of albuterol HFA

Medical Reviewer comment: *The mean, adjusted mean, and median values all indicate a much greater difference between 100 and 200mcg albuterol HFA than between 100 and 200mcg albuterol CFC.*

Onset of Action

Onset of action (time to reach a post dose FEV1 15% above baseline) was analyzed in terms of means, adjusted means, and medians due to the assumed values for the patients who did not achieve a 15% increase.

Onset of Action (hours)

		Means	Adjusted Means	Median
Placebo		4.96	5.08	6.0
HFA	100mcg	2.49	2.47	0.37
	200mcg	2.03	2.01	0.28
	400mcg	1.77	1.88	0.21
CFC	100mcg	2.12	2.15	0.23
	200mcg	1.74	1.53	0.25

All active treatments were statistically superior to placebo, and without significant differences on pairwise comparisons. In all analyses, onset in the 100mcg HFA group was notably later than the other active treatment doses.

Number of responders

As seen in the table below, the percentage of responders with active treatment was much greater than placebo and increased with increasing dose.

Responders (Percent reaching 15% improvement over baseline FEV1)

		%
Placebo		25.4
HFA	100mcg	61.0
	200mcg	71.7
	400mcg	74.1
CFC	100mcg	67.8
	200mcg	75.0

Secondary Efficacy Analyses

Figures 5 and 6 illustrate the mean and percentage change in FEV1 for the 6 treatment groups over 6 hour serial testing. Both illustrate the comparability of the 200mcg HFA albuterol dose with the 200mcg CFC formulation. In each figure, it is apparent that there is less similarity between the 100mcg strengths of the two formulations.

The following data derived from ST-6 & 7 show the changes in FEV1 from baseline and percent change in FEV1 at 1 hour after dosing with study medication:

Placebo 0.07L (3%)
HFA 100mcg 0.36L (16%)
HFA 200mcg 0.42L (19%)
HFA 400mcg 0.51L (24%)
CFC 100mcg 0.42L (19%)
CFC 200mcg 0.46L (20%)

Medical Reviewer Comment: *There was a statistical difference in effectiveness (seen in AUC, peak effect, and duration between 100 and 200mcg of albuterol HFA, but not between the same doses of albuterol CFC. The relative similarity in response of one and two puffs of albuterol CFC implies that these two doses are near the plateau of the dose-response curve. The statistical and/or numeric difference consistently seen between one and two puffs of HFA albuterol implies that the per puff dose and/or effectiveness is less than albuterol CFC, but that at two puffs, this formulation is comparable to 200mcg of albuterol CFC.*

Safety Results

Adverse Events

These were analyzed according to whether they occurred before, during, or post-treatment. Only during and post-treatment events were considered to be of relevance by the Medical reviewer. Events occurring during treatment were defined to include events post-dosing up to midnight of the day of the treatment visit; after midnight but before the next treatment visit were considered to be post-treatment. The following table derived from table 24 reports the numbers and percentages of patients experiencing any adverse event during or post-treatment.

Number (%) Experiencing Any Adverse Event

Treatment Group		N	During	Post
Placebo		59	7 (12%)	7 (12%)
HFA	100mcg	59	2 (3%)	7 (12%)
	200mcg	60	4 (7%)	4 (7%)
	400mcg	58	5 (9%)	6 (10%)
CFC	100mcg	59	2 (3%)	10 (17%)
	200mcg	60	4 (7%)	10 (17%)

In general, the numbers of affected patients in any one category of adverse event was low and comparable among the treatment groups. The most common adverse events during and post treatment are summarized in the following table.

Most common Adverse Events

	Placebo	HFA 100	HFA 200	HFA400	CFC100	CFC200
No. subjects (%) Experiencing Event During Treatment						
Asthma	3 (5%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (3%)
Headaches	2 (3%)	1 (2%)	1 (2%)	2 (3%)	0	1 (2%)
No. subjects (%) Experiencing Event Post- Treatment						
URTI	2 (3%)	4 (7%)	2 (3%)	0	4 (7%)	2 (3%)
Cough	0	2 (3%)	0	1 (2%)	0	0
Chest symptoms	0	0	0	2 (3%)	0	0

The 2 subjects with chest symptoms after taking 400mcg Albuterol HFA were both young women (ages 21 and 26 years), and both episodes occurred ≥5 days after the treatment visit. One was a 1 minute episode of sharp chest pain, the

other was "left-side and across-the-back pain" which lasted for 6 days before it resolved. Neither of these episodes raised any safety or causality concerns in the opinion of the medical reviewer.

Adverse events that were considered to be drug-related are summarized in the following table. These all occurred during treatment; no drug-related adverse events were reported post-treatment.

Drug-Related Adverse Events

	Placebo	HFA 100	HFA 200	HFA400	CFC100	CFC200
No. subjects (%) Experiencing Event During Treatment						
Headaches	1 (2%)	1 (2%)	1 (2%)	2 (3%)	0	0
Tremors	0	0	0	1 (2%)	0	
QTc prolongation	0	0	0	1 (2%)	0	0

The QTc prolongation was to 485 msec from a baseline of 443 msec, and occurred in a 50 year old female who weighed 103.2 kg and continued in the study. This event is best examined in the context of the total QTc data for the study, discussed under the ECG subsection.

There were no deaths, serious adverse events, or pregnancies during the study. Two patients withdrew during the study due to unrelated adverse events (perforated eardrum and worsening of asthma.)

Laboratory Abnormalities

The small numbers of patients (1 – 5 per treatment group) who experienced laboratory values at or above threshold values typically had raised values of these parameters at baseline. None were reported as an adverse event. In the opinion of the medical reviewer, none of the elevations raised a significant safety concern; they included 1 or 2 patients each with abnormalities of blood glucose, bicarbonate, GGT, MCV, and lymphocyte count.

When shifts in laboratory data from normal to abnormal values were analyzed, there was a suggestion of a dose-related increase in glucose among the patients receiving 400mcg of albuterol HFA, as seen in the following table. According to the medical reviewer, the solitary occurrence of a normal potassium falling to a below normal value in this same treatment group hints at a clinical picture consistent with excessive β-agonist activity.

Shifts from Normal to Abnormal Values with Study Treatment – Number of Affected Subjects

	Placebo	HFA 100	HFA 200	HFA 400	CFC 100	CFC 200
Glucose NH	3	4	3	8	3	3
Potassium NL	0	0	0	1	0	0

Source: ST-18

Glycosuria was noted in 6 subjects during active treatment, but in 3 of these subjects, glycosuria was noted at baseline. Of the 3 patients with a normal baseline urinalysis, two had glycosuria solely with 100mcg albuterol HFA, and the third had glycosuria with 100mcg albuterol HFA as well as with placebo, 200mcg HFA albuterol, and 100mcg CFC albuterol [51:Listing 15]. In the opinion of the medical reviewer, the absence of a dose-response relationship and the small numbers of affected patients suggest that these are spurious abnormalities that are not treatment-related.

ECG

Of the 3 patients with one or more QTc intervals ≥440msec, all had this abnormality noted at baseline or a predose assessment. The one patient with a QTc >470msec after 400mcg HFA albuterol had a predose QTc interval of 443 at that visit, as well as two other predose QTc intervals measured at 448 and 454msec. No subject had a QTc interval above 440 msec for either the 100 or 200mcg HFA albuterol groups. Overall, these findings raise no repolarization concerns for any of the active treatments in the opinion of the medical reviewer [51:Listing 16].

Vital Signs

Threshold changes in vital signs occurred in a small number of patients (0 –3 per treatment group). Categorical analyses of pulse rate increases and decreases [51:ST-19] were comparable in distribution across the six treatment groups. Analyses of changes in systolic and diastolic blood pressure showed comparable changes among the treatment groups, with a slightly higher rate of DBP falls greater than 15mmHg observed in the 400mcg HFA group (31%) than in the 200mcg HFA group (16%), CFC 100mcg group (24%), or the CFC 200mcg group (24%).

Exacerbations

Six patients experienced an exacerbation during the study, and of these, 4 subjects had a single exacerbation only. The remaining two subjects reported multiple exacerbations during the course of the study. By treatment group, the following numbers of patients experienced an exacerbation on or after treatment:

Placebo	3
HFA 100	1
HFA 200	2
HFA 400	1
CFC 100	2
CFC 200	3

All patients who exacerbated during a treatment visit were treated with VENTOLIN MDA after the 6 hour serial FEV1 measurement.

Medical Reviewer Comment: *The overall rate and pattern of adverse events, laboratory, ECG, and vital sign changes raise no safety concerns for the two formulations of albuterol tested. There was some suggestion that 400mcg HFA albuterol manifested some of the pharmacodynamic consequences of excessive βagonist activity, with higher rates of hyperglycemia and the sole instance of lowered potassium in the trial. The one instance of QTc prolongation occurred in a patient with some prolongation at baseline and at other predose assessments, and is offset by the lack of any other observations of QTc elevation in the study population.*

Medical Reviewer Conclusions

All doses of albuterol as CFC (100 and 200mcg) and HFA formulations (100, 200, and 400mcg) were statistically superior to placebo in their effect on serial FEV1. A dose-response relationship was evident with both the HFA and CFC formulations. Doses of the HFA and CFC formulations were clinically comparable, with greater similarity between the 200mcg doses than between the 100mcg doses. Numerically, the 100mcg HFA dose was slightly less effective than the 100mcg CFC formulation. Also, the differences in effect between the 100 and 200mcg dosage strengths of the CFC formulation were substantially less than those seen between the same strengths of the HFA propellant product. These findings are suggestive that the HFA device delivers a lower /less effective dose on a per actuation basis than the CFC product, but that after two puffs, the clinical comparability is acceptable.

No safety concerns were raised in this study, other than the suggestion that a 400mcg dose of albuterol HFA may be associated with known side-effects of excessive β-agonist activity (hyperglycemia and hypokalemia).

SALB1003

A Randomized, Two-Way, Crossover Study To Compare The Pharmacokinetics And Pharmacodynamic Effects Of Albuterol After Single Inhaled Doses Of 1200mcg From Albuterol HFA And Albuterol CFC Inhalers In Healthy Subjects.

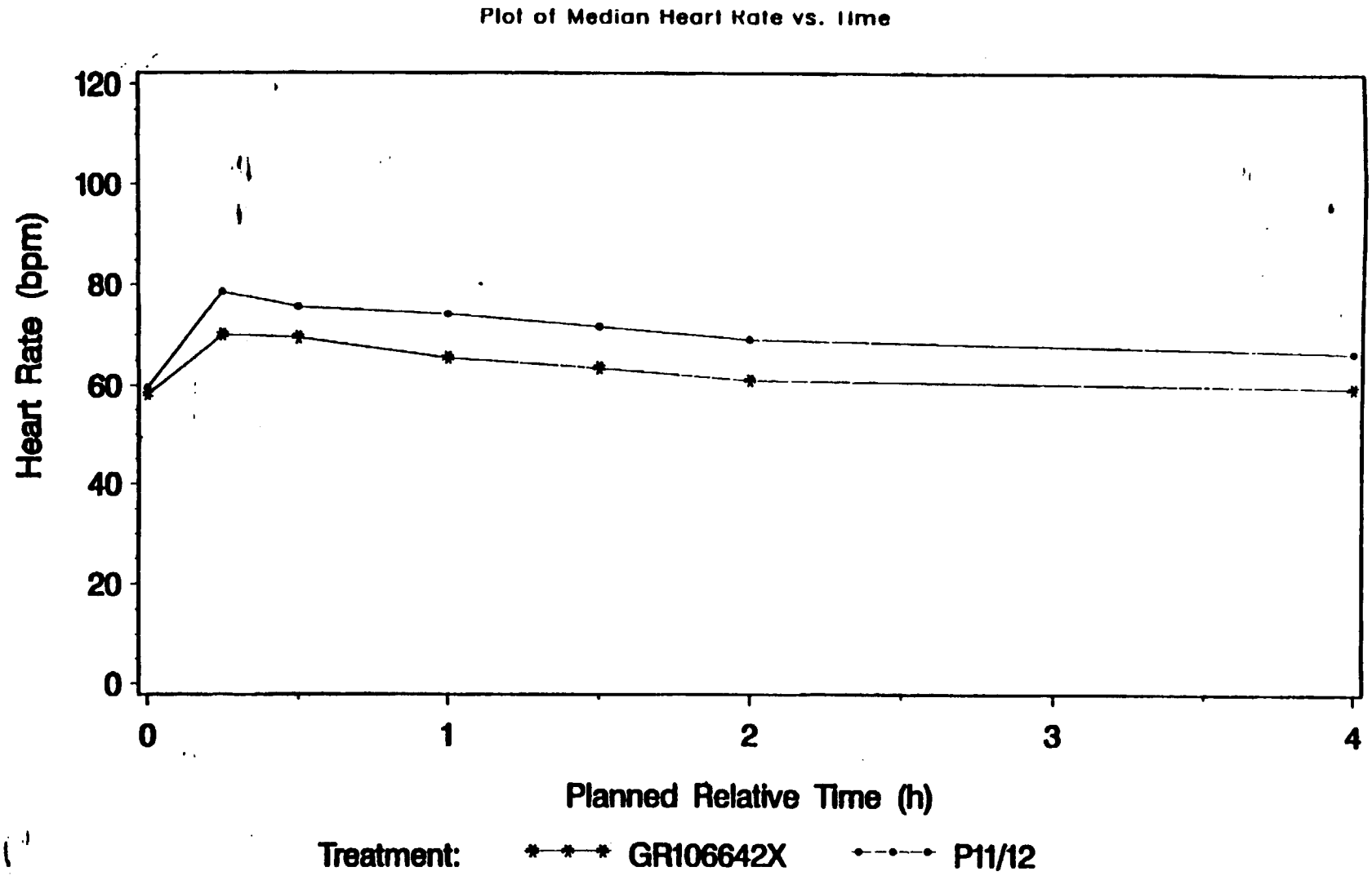
SALB1003 was a randomized, two-way, crossover study to compare the pharmacokinetics and pharmacodynamic effects of albuterol after single inhaled doses of 1200mcg from albuterol HFA and albuterol CFC inhalers in healthy subjects. Pharmacodynamic results from this protocol showed a consistently smaller impact of albuterol HFA upon the medians of heart rate, QTc interval, and serum potassium when compared to CFC albuterol. The following figure for heart rate is illustrative of the type of difference seen. Statistical comparison of the weighted means, minimum K^+, and peak HR and QTc showed no significant differences between the two formulations. Palpitations occurred in more patients during CFC albuterol treatment (9/12 subjects) than during HFA albuterol treatment (5/12 subjects).

Medical Officer Comment: *At single doses of 1200mcg, albuterol HFA had a consistently smaller impact on pharmacodynamic endpoints of heart rate, QTC interval, and serum potassium than did albuterol CFC. Although the means and extremes of these endpoints were not statistically significant in their differences, the consistently lower values with albuterol HFA suggest that this product has marginally lower drug delivery than the CFC formulation. The finding of a lower rate of palpitations in HFA patients versus CFC patients supports this conclusion as well.*

Plasma albuterol levels appeared to be directly related to changes in HR and decreases in QTc intervals, but there was no clear relationship of plasma albuterol to serum K.

The pharmacokinetic findings showed a similar geometric mean AUC_∞ with both inhalers, a lower and later Cmax with HFA albuterol, and a significantly greater tmax with albuterol HFA. More HFA subjects than CFC subjects had a plasma profile of later peaks associated with the oral absorption of albuterol. HFA albuterol showed greater variability in AUC than did CFC.

	Albuterol HFA	Albuterol CFC
Geometric mean AUC_∞ (ng*hr/mL)	23.02	25.32
95% CI	15.17 – 34.92	22.42 – 28.59
Geometric mean Cmax (ng/mL)	2.96	4.26
95% CI	2.03 – 4.32	3.57 – 5.09
Median tmax (hr)	0.417	0.167
Range	0.167 – 5.017	0.083 – 0.750


Plot of Median Heart Rate vs. Time
Heart Rate (bpm)
120
100
80
60
40
20
0
0
1
2
3
4
Planned Relative Time (h)
Treatment:
GR106642X
P11/12

SALA3009

A Randomized, Double-Blind, Double-Dummy, Six-Way Crossover Comparative Trial of Single Doses of Albuterol in HFA Propellant with Different Water Content via the MDA versus Placebo (HFA) in Adult Subjects with Asthma

This study used methacholine challenges in a 6 way crossover design to compare single doses of albuterol HFA with varying water content in the MDI. This study of 44 adult asthmatic subjects with FEV1≥70% and bronchial hyperreactivity to methacholine did not include an albuterol CFC arm for comparison. Doses of 90, 180, and 360 mcg albuterol HFA were evaluated with ~300 ppm moisture in canister (MIC), and doses of 180 and 360 mcg were evaluated with ~30 ppm MIC with comparison to placebo HFA propellant.

The study was designed to see if the increase in moisture content that occurs because HFA is hygroscopic would have any impact on clinical performance. Samples of the "wet" and "dry" inhalers were analyzed for moisture and particle size at the start and finish of the study. The "wet" MDIs were over-wrapped and did not contain a desiccant, and the "dry" MDIs were over-wrapped and contained a 2g silica gel desiccant. Fine particle mass was tested by cascade impaction. The "wet" MDIs had 285ppm at the start and 299ppm at the end, while the corresponding "dry" values were 28ppm and 33 ppm.

All albuterol treatments had an increase in the $\log_2 PD_{20}$ of more than 2 doubling doses relative to placebo, thus exceeding the difference of one doubling dose that was considered clinically significant. While there was no statistically or clinically significant difference between like doses of albuterol with differing water content, there was a clinically and statistically significant difference between the 90 mcg dose and the 180 and 360 mcg doses of 'wet" (~300ppm) albuterol HFA. There was an increase in the protective effect from 180mcg to 360mcg, but the increase was not statistically significant. The sponsor considered that the 180 mcg albuterol HFA dose was probably close to a maximum effect on the dose-response curve, so that the increase to 360mcg did not significantly influence efficacy. Safety evaluations done in this trial showed no notable adverse events or laboratory abnormalities.

Medical reviewer comment: *Since albuterol CFC was not evaluated in this trial, the reviewer cannot conclude whether the statistically significant separation in effect between 90 and 180 mcg of albuterol HFA is comparable to what would have been seen with the same doses of abluterol CFC. It does confirm that 90 mcg of albuterol HFA is not near the maximum effect on the dose-response curve, as was seen in protocol SALB2001.*

The sponsor offered the results of this study to support an in-use shelf life of 6 months, claiming that the clinical comparability seen in this trial outweighs

specification deviations due to differing moisture content and fine particle mass distribution. The following limitations of this study limit its ability to override product quality specifications:

- *Clinical endpoints may be insensitive to important differences in product quality*
- *The more clinically relevant bronchodilation endpoint was not assessed*
- *The study was not designed as an equivalence trial*
- *The study size is small*
- *The study cannot address the impact of a low particle size distribution of an individual puff since the puffs that were actually used by patients were not assessed*

INTEGRATED SUMMARY OF EFFICACY

Studies Forming the Basis of the ISE
A total of 6 double-blind, placebo-controlled studies were done using the US commercial container closure system and form the basis for the integrated summary of efficacy. Each study has been reviewed individually elsewhere in this NDA (see table of contents). Five of these studies involved CFC albuterol as an active control: SALA3002, SALA3005, SALA3006, SALB2001, and SALB2003. The sixth study (SALA3009) tested albuterol HFA with differing moisture levels in the canister versus placebo in methacholine challenges.

In terms of new efficacy analyses in the ISE, the principal new analysis is of the combined 12 week trials in adolescents and adults (SALA3002 and SALA3005). Analyses of subgroups in these and the other trials are also provided. There was one two–week pediatric trial (SALA3006), one EIB trial (SALB2001), a single dose dose-response trial in adolescents and adults (SALB2003), and single dose dose-response trial using methacholine challenge to assess efficacy in adults (SALA3009). For these trials, the ISE is largely a recapitulation of the individual study reports discussed elsewhere in this review, so their presentation is abbreviated.

Studies In Support Of The Claim For The Treatment And Prevention Of Asthma In Pediatric, Adolescent, And Adult Patients

The two 12 week adolescent and adult studies (SALA3002 and SALA3005) and the two-week study in children 4 – 11 years are the pivotal studies to support this claim. The 12-week studies had sufficiently similar designs that their primary efficacy data (change from same day treatment baseline FEV1) were combined. Secondary efficacy data based upon the run-in baseline period were not combined, since these two studies had different medication use during the run-in period. SALA3002 patients used albuterol CFC on a QID and PRN basis during run-in, whereas SALA3005 patients used PRN only.

SALA3002 and SALA3005 randomized and treated a combined total of 610 patients. All patients were asthmatics ≥12 years of age, with baseline FEV1 between 50 and 80% of predicted and documented reversibility ≥15% with Ventolin MDI. The studies allowed the same concomitant medications with the exception of inhaled corticosteroids; SALA3002 did not allow the use of these products whereas SALA3005 did as long as the patients remained on stable doses established at least 1 month before screening. The pediatric study (SALA3006) allowed inhaled corticosteroids according to the same criteria.

Primary efficacy assessments in all chronic dosing studies were based upon 6 hour serial FEV1 and PEFR changes analyzed by repeated measures analysis

and weighted average (WAVE). Serial PFTs were performed at treatment day 1 in the adult and pediatric studies, at weeks 6 and 12 of treatment in the adolescent/ adult studies, and at week 2 in the pediatric study. Repeated measures analysis equally weights all post-dose PFT measurements, while WAVE weighs each measurement in proportion to the time it contributed to the total observation period of 360 minutes. For example, the first measurement at 5 minutes is weighted by 5/360 whereas the 2, 3, 4, 5, and 6 hour measurements are each weighted by 60/360.

The run-in period for SALA3002 was 3 weeks long, during which subjects used CFC albuterol QID and PRN. The two-week long run-in period for SALA3005 used placebo QID and PRN albuterol CFC. The SALA3002 run-in was intended to assess the effects of "switching" to the HFA from the CFC formulation. SALA3002, SALA3005, and SALA3006 all shared the objective of assessing the relative efficacy of the two albuterol formulations versus placebo.

Studies SALA3002, SALA3005, and SALA3006 were also evaluated by the sponsor to compare albuterol PRN versus QID, although this comparison did not follow FDA recommendations.

Comparison of Indicators of Effectiveness in Adequate and Well-Controlled Adolescent and Adult Chronic Dosing Studies

Serial FEV1 data from treatment day 1and weeks 6 and 12 were combined for SALA3002 and SALA3005. Diary data (of AM and PM PEFR, back-up albuterol use, asthma symptom scores, and nighttime awakenings) were NOT combined. Two suspect investigators from SALA3002 (#5348 and #1415) were included in the overall tally; they contributed a total of 27 patients, 9 placebo, 10 HFA, and 8 CFC. Their removal from the analyses of trial SALA3002 did not affect the conclusions of that trial either qualitatively or quantitatively.

Medical reviewer comment: *Since the two suspect investigators represent <5% of the combined trials, their impact upon the study findings is likely to be extremely small and should not affect the conclusions of this overall efficacy assessment. However, the inclusion of potentially corrupted data in the package labeling should not be allowed, and the sponsor should be asked to reanalyze those portions of these combined studies that they plan to include in product labeling.*

Demographics

A total of 610 patients were treated in the combined trials SALA3002 and SALA3005. Of these, 202 were treated with albuterol HFA, 207 were treated with albuterol CFC, and 201 were treated with placebo HFA. The PRN medication for each treatment arm was identical to the QID medication with the exception of the placebo group, which used albuterol HFA on a PRN basis.

The 3 treatment groups had similar age, gender, and ethnic distributions. Across treatment groups, male enrollment was 52-54%, Caucasian race was 81-84%, Black race was 9%, and other ethnic origins ranged from 7 to 10%. The mean age ranged from 31.2 to 33.1 years, with the range from 12 to 77 years.

FEV1 Response

Serial FEV1 response was assessed as the change from same-day baseline FEV1 and as percent of predicted. The following two tables describe the WAVE of these two measurements.

Weighted Average (WAVE) of Post-Dose Serial FEV1 Measurements over 6 hours Change from Same-Day Baseline (Liters) SALA3002 and SALA3005

	Placebo GR106642X	Albuterol GR106642X	Albuterol P11/12
Treatment Day 1			
N	201	202	207
Baseline	2.41	2.43	2.35
WAVE of change	0.14	0.39*	0.43*
Treatment Week 6			
N	180	186	190
Baseline	2.55	2.53	2.46
WAVE of change	0.11	0.27*	0.29*
Treatment Week 12			
N	165	175	185
Baseline	2.57	2.53	2.53
WAVE of change	0.09	0.27*	0.28*

*p<0.001 compared with placebo HFA

Weighted Average (WAVE) of Post-Dose Serial FEV1 Measurements over 6 hours Percent of Predicted SALA3002 and SALA3005

	Placebo GR106642X	Albuterol GR106642X	Albuterol P11/12
Treatment Day 1			
N	201	202	207
Baseline	67.7	67.4	67.0
WAVE	71.6	78.1*	79.5*
Treatment Week 6			
N	180	186	190
Baseline	71.6	70.5	70.2
WAVE	74.5	77.9*	78.9*
Treatment Week 12			
N	165	175	185
Baseline	72.4	70.2	72.0
WAVE	75.0	77.7	79.9*

*p<0.020 compared with placebo HFA

Both analyses show clear superiority of both albuterol treatments compared to placebo. Statistically significant improvement was seen with both CFC and HFA products at all time points, with the exception of week 12 percent predicted FEV1 for HFA. With both endpoints, no overall statistically significant differences were seen between the two albuterol groups by WAVE. By repeated measures analysis, the percent predicted FEV1 for albuterol CFC was significantly greater than for albuterol HFA at week 12.

Although HFA and CFC albuterol each beat placebo statistically, and on the whole showed no statistically significant differences between each other, the effect size seen with the HFA formulation was somewhat less than with CFC albuterol. These numeric differences are described in the table below for FEV1 and percent predicted FEV1.

Range of Differences in Effect Size
CFC – HFA albuterol
Combined SALA3002 & SALA3005

Treatment Visit	Change in Serial FEV1 (L)	Percent Predicted (%)
Day 1	0.03 – 0.06	0.8 – 2.2
Week 6	0.01 – 0.09	-0.1 – 2.7
Week 12	0 – 0.4	1.8 – 3.3
Overall WAVE	0.01 – 0.04	1.0 – 2.2

Prepared by Medical reviewer using Tables C2-C13

The WAVE of the changes in serial FEV1 with CFC albuterol were larger than HFA albuterol by 0.01L (week 12) to 0.04L (day 1). Since the WAVE is not an intuitive measure, differences in the FEV1 changes of serial timepoints for each week were computed as well. These showed that CFC albuterol improved FEV1 from 0 to 0.09L more than HFA albuterol. In all instances, the maximal differences seen between HFA and CFC albuterol were less than the changes seen within the placebo group at each assessment.

By WAVE, the difference in percent predicted FEV1 ranged from 1.0 to 2.2 percentage points, at 6 and 12 weeks respectively. The maximum difference between CFC and HFA albuterol that was seen at any individual time point was 3.3 percentage points.

In analyses of all functions of serial FEV1 (see following table), both albuterol formulations were found to be statistically superior to placebo. At selected time points, statistically greater effects were seen with the CFC relative to the HFA formulation. These occurred in the percent of patients achieving ≥15% improvement (week 6) , the median onset of effect (day 1 and week 6), the mean maximum effect (day 1 and week 6), and the median duration of effect (day1). The median onset of effect for albuterol CFC ranged from 3.6 to 4.2 minutes, compared to 4.2 to 9.6 minutes for HFA albuterol. Duration of effect ranged from 1.53 - 3.30 hours for albuterol HFA, and from 2.29 - 3.69 hours for CFC albuterol. Mean AUC(bl) values were not statistically different for the 2 albuterol formulations, but the mean effect size in the HFA group was consistently lower than for the CFC subjects.

Analysis of Functions of 6-Hour Serial FEV_1
SALA 3002 and SALA3005

Function	Placebo HFA			Albuterol HFA			Albuterol CFC		
Visit:	Day 1	WK 6	WK 12	Day 1	WK 6	WK 12	Day 1	WK 6	WK 12
% Patients Achieving Effect	21	7	9	80*	59*	64*	85*	71*#	69*
% Pts with WAVE ≥15% over base	19	11	11	50*	34*	36*	56*	40*	37*
Median Onset of Effect (hr)	6.00	6.00	6.00	0.07*	0.16*	0.08*	0.06* #	0.07* #	0.07*
Median Duration of Effect (hr)	0.00	0.00	0.00	3.30*	1.53*	2.06*	3.69* #	2.29*	2.40*
Mean Max Eff (% chg from base)	14.5	12.1	11.9	28.8*	24.5*	24.9*	32.7* #	28.0* #	26.0*
Median Time of Max Effect (hr)	3.0	3.0	3.0	1.0*	1.0*	0.8*	1.0*	0.8*	1.0*
Mean $AUC_{(0)}$ (L-hr)	0.83	0.64	0.55	2.48*	1.77*	1.76*	2.75*	1.94*	1.85*

WAVE = weighted average of post-dose FEV_1 measurements over 6 hours.
*p<0.001 compared to placebo HFA
p≤0.032 when compared to albuterol HFA

The percentage of patients achieving ≥15% increase from baseline in FEV1 values over time (see following table) was highest at treatment day 1 in all 3 treatment groups. Over the first three hours post-treatment, albuterol CFC had between 2 and 12% more patients responding than did albuterol HFA. The largest differences between the 2 albuterol formulations were seen at the earliest timepoints (≤1 hour) and ≤6 weeks of treatment

Percentage of Patients With ≥15% Increase in FEV_1 Over Time
SALA3002 and SALA3005

Timepoint	Placebo HFA			Albuterol HFA			Albuterol CFC		
Visit:	Day 1	WK 6	WK 12	Day 1	WK 6	WK 12	Day 1	WK 6	WK 12
5 min	9	3	4	61	47	50	71	58	54
30 min	16	6	7	72	54	61	80	66	65
1 hr	19	8	8	73	56	59	79	65	65
3 hr	21	16	16	57	38	43	60	43	45
6 hr	21	16	14	28	22	18	36	19	16

Other Efficacy Measures
Efficacy measures based upon subject diaries were analyzed separately for SALA3002 and SALA3005 since the baseline comparison period differed for the two studies. SALA3002 subjects used QID albuterol CFC during run-in, whereas SALA3005 subjects used PRN albuterol CFC. Complete discussion of these efficacy endpoints can be found under the individual study reviews.

Asthma symptom scores and nighttime awakenings showed little change across placebo and active treatment groups in both SALA3002 and SALA3005. The percentage of symptom-free days was greater with each active treatment than with placebo in both studies, but no statistically significant differences were found. AM and PM PEFR showed no differences across treatment groups in SALA3002. In SALA3005, the overall PM PEFR was significantly improved with both CFC and HFA albuterol therapy relative to placebo, and the AM PEFR showed improvement with active treatments over placebo but without statistical significance. Numerically the CFC group had greater improvements in AM and PM PEFR than the HFA group in SALA3005, but none of these differences were statistically significant.

Daily use of back-up albuterol was significantly greater in placebo subjects than either CFC or HFA albuterol patients in both SALA3002 and SALA3005. There were no statistically significant differences between HFA and CFC albuterol with the exception of weeks 1 –3 in SALA3002 where the CFC group had less use of PRN albuterol than the HFA group. The percentage of days with no back-up albuterol use was significantly greater than placebo for both HFA and CFC albuterol in both SALA3002 and SALA3005. In SALA3002, the percentage days without back-up albuterol use increased significantly more for albuterol CFC than for albuterol HFA.

Medical Reviewer comment: *Less use of back-up albuterol with QID CFC versus HFA albuterol is consistent with shorter duration of effect of HFA that was suggested by previous analyses of functions of serial FEV1.*

The frequency of all asthma exacerbations was higher in the placebo group (22%) compared with the albuterol treatment groups (13% HFA, 16% CFC). Out-of-clinic exacerbations were similar for the two albuterol groups (6% HFA, 8% CFC) and less than were seen with placebo (10%).

Switching Propellants
SALA3002 was designed to evaluate the efficacy of the new propellant in patients who switched from three weeks treatment with QID + PRN albuterol CFC to albuterol HFA. In those patients switched to QID albuterol HFA, the WAVE of change in FEV1 was comparable (0.26 - 39L) to that seen during run-in (0.30L). There was no evidence of any efficacy problems proximate to the time the switch occurred; the mean percent predicted FEV1 achieved was stable at

the time of the switch (day 1) and at the week 6 and 12 evaluations. There was no evidence of a lag in effectiveness in switching.

PRN indication

The Division is on record (comments of Dr. Robert Meyer, 8/27/96 in his medical review of protocol SALA3005) that specific determination of PRN dosing as being a preferred and explicitly stated mode of dosing would have to come from well-controlled trials specifically designed to examine this issue. In example, the Division suggested a need for study designs that included examination of asthma exacerbation rates, changes in pre-medication PFTs over time, as well as other markers of asthma control, such as serial methacholine challenges.

Notwithstanding the Division's comments, Glaxo pursued analyses of their two 12 week adolescent/adult clinical trials to support a conclusion that PRN albuterol provides comparable clinical benefits to QID dosing with less total daily exposure to albuterol. These analyses did not provide compelling evidence of comparability in the opinion of the medical reviewer. In these protocols (SALA3002 and SALA3005) the placebo group was exposed solely to PRN albuterol HFA during randomized treatment, in contrast to the active treatment arms which received QID albuterol. Glaxo examined the relative effects of PRN and QID dosing on AM (predose) PEFR, asthma symptoms, nighttime awakenings, and asthma exacerbations in the placebo (PRN) and active treatment arms to determine if "comparable clinical benefits" existed. All of these parameters were based upon patient daily diary recordings.

Medical Reviewer comment: *Comparison of QID and PRN albuterol based upon patient-reported parameters should have included objective assessments of compliance, such as metered dose inhalers that record the amount and timing of use. Poor compliance with the QID treatment regime would bias any determination of difference with PRN to the null. Reliance upon self-reported compliance undermines the ability to make comparability claims.*

Glaxo's conclusions of comparability were based upon the absence of statistically significant differences between PRN and QID albuterol HFA when averaged over the 12 week period for endpoints of AM PEFR, asthma symptoms, nighttime awakenings, and exacerbations. While the average 12 week comparisons for these endpoints did not show statistical differences, the QID HFA group did outperform the PRN group numerically in AM PEFR (SALA3005), percentage of symptom free days (SALA3002 and SALA3005), nighttime awakenings (SALA3002 and SALA3005), and exacerbations (SALA3002 and SALA3005 combined). In addition, QID albuterol CFC showed statistical superiority to PRN treatment in AM PEFR for weeks 10-12 (SALA3005) and nighttime awakenings for weeks 1-3 (SALA3002). In the opinion of the medical reviewer, these results alone do not support the comparable effectiveness of PRN and QID albuterol HFA.

Medical reviewer comment: *The absence of statistically significant differences between PRN and QID albuterol HFA does not provide sufficient evidence for the conclusion that PRN albuterol provides comparable clinical benefits to QID dosing with less total daily exposure to albuterol. The study design is limited by the absence of meaningful compliance data to determine if QID and PRN dosing really occurred. In addition, the finding of comparability does not necessarily imply equal effectiveness; it could also imply equal ineffectiveness, as was suggested when statistically significant differences were noted in comparison to QID albuterol CFC. The weight of clinical evidence from the patient-reported measures of symptoms, nighttime awakenings, and AM PEFR suggest that placebo/PRN albuterol HFA does not provide the same level of asthma control as does QID administration of either CFC or HFA albuterol. If the sponsor wishes to pursue a distinct claim for PRN use above what is implied in the current albuterol labeling, additional studies will have to be done.*

Comparison of Indicators of Effectiveness in an Adequate and Well-Controlled Pediatric Chronic Dosing Trial

The data in this section come from SALA3006, which is reviewed in depth in a separate section of this document. As such, only selected material of relevance will be included here.

SALA3006 examined a total of 135 patients between the ages of 4 and 11 years; 46 received albuterol HFA, 43 received placebo HFA, and 46 albuterol CFC. Across treatment groups the majority of patients were male (53-72%) and Caucasian (54-63%). Mean age ranged from 8.3 –8.4 years. The run-in for this study consisted of PRN albuterol CFC, similar to what was done in the run-in period for SALA3005 with adolescent and adult patients. Since the 4- 5 year olds who were unable to perform spirometry had only PEFR assessments, fewer patients are included in the analysis of FEV1 than of PEFR.

Analysis of mean percent predicted PEFR and FEV1 (see tables following) showed both HFA and CFC albuterol treatment groups to be statistically superior to placebo by WAVE and repeated measures analysis on treatment day 1 and at week 2. There were no significant differences between albuterol HFA and CFC response.

Weighted Average (WAVE) of Post-Dose PEFR Measurements over 6 Hours
Percent of Predicted PEFR

Visit	Placebo HFA	Albuterol HFA	Albuterol CFC
Treatment Day 1			
N	43	46	46
Baseline	69.7	71.5	71.0
WAVE	76.1	84.1*	82.9*
Treatment Week 2			
N	36	41	41
Baseline	72.3	78.5	76.7
WAVE	77.4	87.5*	86.7*

*p≤0.023 compared with placebo HFA

Weighted Average (WAVE) of Post-Dose FEV_1 Measurements over 6 Hours
Percent of Predicted FEV_1

Visit	Placebo HFA	Albuterol HFA	Albuterol CFC
Treatment Day 1			
N	39	41	40
Baseline	66.9	69.4	70.8
WAVE	71.3	81.5*	80.3*
Treatment Week 2			
N	34	36	35
Baseline	67.4	73.4	72.6
WAVE	71.0	81.8*	80.6*

*p≤0.040 compared with placebo HFA

Medical reviewer comment: *In contrast to the adolescent and adult chronic trials, SALA3006 saw a slightly greater effect with albuterol HFA than with albuterol CFC. In addition, the improvement in percent predicted FEV1 associated with albuterol HFA was greater in children (9.0 – 12.6L) than was seen in the combined adult studies (7.4 – 10.7L) or in SALA3005 alone (7.2 – 11.0L) through the 6 week evaluation.*

Functions of serial FEV1 showed both albuterol formulations to be statistically superior in performance to placebo HFA at day 1 and week 2 in the median onset of effect, mean maximum effect, and in mean AUC(bl). Additional parameters with significant findings are indicated with an asterisk in the following table. No statistically significant differences were noted between the two albuterol formulations. The median onset of effect was 4.8 – 9.6 min in the albuterol HFA group and 11.4-12 minutes in the albuterol CFC group.

Analysis of Functions of 6-Hour Serial PEFR

Function / Visit:	Placebo HFA		Albuterol HFA		Albuterol CFC	
	Day 1	Week 2	Day 1	Week 2	Day 1	Week 2
% Patients Achieving Effect†	40	33	80*	68*	61	61*
Median Onset of Effect (hr)	6.00	6.00	0.08*	0.16*	0.20*	0.19*
Median Duration of Effect (hr)	0.00	0.00	2.58*	1.61*	1.09	1.86*
Mean Max Effect (%change from base)	21.9	19.7	35.8*	28.0*	31.5*	26.6*
Median Time of Max Effect (hr)	3	3	1	1*	2	2*
Mean AUC(bl) (L-hr)	93	79	189*	153*	192*	166*
% Pts with WAVE ≥15% over baseline	31	17	44	37	52	41*

† Effect = an increase in PEFR of ≥15% above baseline (average of -30 minute and 0 minute PEFR measurements at Same Day Baseline).
WAVE = weighted average of post-dose PEFR measurements over 6 hours.
*p≤0.025 compared with placebo HFA

The percentage of patients achieving ≥15% increase in serial PEFR over time (see data in individual study review) was greater for both albuterol formulations than for placebo. The HFA percentages were greater than or equal to the corresponding CFC percentages, with the exception of the 5 hour time point at day 1 and the 6 hour time point at week 2 (data not shown - see individual study review).

Analyses of change in FEV1 by WAVE (see table below) showed both albuterol HFA and albuterol CFC were numerically superior to placebo at treatment day 1 and week 2. Statistically significant improvement over placebo was seen at all time points with albuterol CFC. Albuterol HFA was statistically superior to placebo at week 2, with marginally significant findings (p=0.051) at treatment day 1. Pairwise comparisons of the two albuterol formulations were without statistically significant findings. Analyses using repeated measures analysis showed both formulations to be significantly superior to placebo in FEV1 change at all time points, with no significant difference between the two formulations.

Weighted Average (WAVE) of Change from Same Day Baseline Post-Dose FEV_1 Measurements over 6 Hours (Liters)

Visit	Placebo HFA	Albuterol HFA	Albuterol CFC
Treatment Day 1			
N	39	41	40
Baseline	1.38	1.37	1.51
WAVE of Change	0.10	0.24*	0.20*
Treatment Week 2			
N	34	36	35
Baseline	1.40	1.48	1.55
WAVE of Change	0.07	0.16†	0.17*

*p≤0.019 compared with placebo HFA
†p=0.051 compared with placebo HFA

Analysis of functions of serial FEV1 (see table below) were generally consistent with the functions of serial PEFR. In these older patients, 22 of 28 placebo-albuterol treatment comparisons were statistically significant, compared to 21 of 28 comparisons made using PEFR data. In median onset of effect and mean maximum effect, albuterol HFA showed statistical superiority to CFC albuterol as well as to placebo. The median onset of effect was 3 – 4.2 minutes for HFA albuterol, and 4.2 – 9 minutes for CFC albuterol. Albuterol HFA showed numeric superiority to CFC albuterol in all function areas.

Analysis of Functions of 6-Hour Serial FEV_1

Function	Placebo HFA		Albuterol HFA		Albuterol CFC	
Visit:	Day 1	Week 2	Day 1	Week 2	Day 1	Week 2
% Patients Achieving Effect†	32	24	88*	69*	70*	63*
Median Onset of Effect (hr)	6.00	6.00	0.05*#	0.07*	0.07*	0.15*
Median Duration of Effect (hr)	0.00	0.00	3.75*	2.41*	3.10*	0.32*
Mean Max Effect (% change from base)	18.2	16.0	33.3*#	26.3*	26.2*	24.1*
Median Time of Max Effect (hr)	3.0	2.0	0.5*	1.0	1.0*	1.0
Mean AUC(bl) (L-hr)	0.60	0.45	1.52*	1.01*	1.31*	1.13*
% Pts with WAVE ≥15% over base	21	15	61*	31	43	29

†Effect = an increase in FEV_1 of ≥15% above baseline (average of -30 minute and 0 minute FEV1 measurements at Treatment Day 1).
WAVE = weighted average of post-dose FEV_1 measurements over 6 hours.
*p≤0.023 compared with placebo HFA
#p Significantly different relative to CFC albuterol

With the exception of the 2 week measurement done at 6 hours post-dose, the percentage of patients with ≥15% increase in FEV1 was greater in HFA albuterol than CFC albuterol at all time points.

Other Efficacy Measures
Mean changes in AM and PM PEFR, asthma symptom scores, and back-up albuterol use showed albuterol HFA to be statistically superior to placebo when evaluated over the combined 2 weeks of treatment. For these parameters, there were no statistically significant differences between the HFA and CFC albuterol products. Nighttime awakenings showed little change from baseline across treatment groups. Asthma exacerbations of all types were lowest in the albuterol HFA group (2%) in comparison to the placebo group (14%) and the CFC albuterol group (7%).

PRN versus QID
The QID dosing group used a total daily dose of approximately 9 actuations/day and the PRN group approximately 2 actuations/day. In this study, AM PEFR, asthma symptom scores, and total asthma exacerbations showed superior effectiveness of QID treatment versus PRN administration.

Medical Reviewer comment: *HFA albuterol is clearly superior to placebo treatment in the prevention and chronic treatment of bronchospasm in pediatric, adolescent and adult subjects. In general, the clinical response to HFA albuterol was statistically comparable to that seen with CFC albuterol.*

Grouped efficacy findings in adolescents and adults indicate a clear trend for HFA albuterol to perform numerically (but not statistically) more poorly than CFC albuterol. The observed differences in FEV1 improvement between HFA and CFC albuterol were small and of minimal clinical significance (0.01 – 0. 04L by WAVE) in the moderate asthmatic patient population studied. Of somewhat greater clinical concern are the differences seen in the percentage of responders, onset of effect, and mean maximal effect. Overall they suggest slightly less efficacy/effective dose with albuterol HFA than CFC upon chronic administration to adolescents and adults.

HFA and CFC albuterol were statistically comparable in the 2 week pediatric study. In contrast to the adolescent/adult studies, pediatric study data showed a trend for numerically greater efficacy of HFA albuterol over CFC albuterol. This was seen in terms of PEFR, FEV1, and functions of these serial measurements.

Studies in Support of the Claim of Prevention of Exercise-Induced Bronchospasm (EIB)

One randomized, double-blind, placebo controlled, 3-way crossover study (SALB2001) was conducted with the US commercial container closure system to assess the efficacy of single doses of 180 mcg albuterol HFA in preventing the symptoms of EIB. This study's findings were reviewed in depth in a previous section of this document, and so only the most salient features are described here.

The study enrolled a total of 24 male and female asthmatic subjects aged 12 – 45 years with baseline FEV1≥65% and demonstrated exercise-induced bronchospasm (EIB)≥20% on screening evaluation. The only restricted asthma/allergy medications were short-acting β-agonists, oral, and depot corticosteroids. All other medications, including intranasal and inhaled corticosteroids, were allowed with appropriate washouts before EIB testing.

Subjects were randomized to receive single doses (2 puffs) of the following medications at clinic Visits 2-4 :

- Placebo HFA
- 200mcg albuterol HFA (180 mcg ex-actuator)
- 200mcg albuterol CFC (180 mcg ex-actuator)

The primary efficacy measure was the maximal percent fall in FEV1 following exercise; the percentage fall used the FEV1 value from 5 minutes before exercising (approximately 25 minutes after dosing) as the baseline.

Demographics
Of the 24 subjects, 18 (75%) were male and 20 (83%) were Caucasian/white. Mean age was 27 years (range 19 to 45 years). All 24 patients were treated with albuterol CFC and placebo, and 23 received albuterol HFA.

FEV1 Response

The following table shows the adjusted means (for subject and period via ANOVA) and raw medians for maximum percentage fall in FEV1(%).

Maximum Percentage Fall (%) in FEV1 Post-Exercise

	Placebo	Albuterol HFA	Albuterol CFC
Adjusted means	33.7	15.4	14.9
Raw medians	30.2	6.8	6.5

Each albuterol group was statistically superior to placebo. No statistically significant differences were noted between the two albuterol control groups.

The secondary efficacy measure was the mean FEV1 value recorded 25 minutes post dosing/5 minutes pre-exercise with adjustments via ANOVA for subject and period. The adjusted means were as follows:

Placebo 3.70 L
Albuterol HFA 4.07 L
Albuterol CFC 4.13 L

The adjusted mean for placebo subjects was significantly lower($p<0.001$) than both active treatments. Albuterol HFA was comparable in effect to albuterol CFC, and there was no statistically significant difference between them.

Medical Reviewer comment: *Albuterol HFA and CFC provided significant and clinically comparable protection against exercise-induced bronchospasm when compared to placebo HFA.*

Analysis of Dose-Response and Other Special Studies
One study, SALB2003, was conducted to evaluate dose response to albuterol HFA compared to CFC or placebo. SALB2003 was reviewed in a previous section of this document and so is presented here in brief. Study SALA3009 was done to evaluate the protective effect in methacholine challenges of varying doses of albuterol HFA with two different levels of moisture in the canister.

Adolescent and Adult Dose-Ranging Study
SALB2003 used a randomized, double-blind, placebo-controlled, 6-way crossover design to assess the efficacy of the following treatments in 63 adult and adolescent subjects with baseline FEV1 50-85% predicted and with reversibility of ≥15%:

- Placebo HFA
- 90 mcg Albuterol HFA (ex-actuator)
- 180 mcg Albuterol HFA (ex-actuator
- 360 mcg Albuterol HFA (ex-actuator)
- 90 mcg Albuterol CFC (ex-actuator)
- 180 mcg Albuterol CFC (ex-actuator)

Measurements of FEV1 were obtained at predose baseline, 15 and 30 minutes, and 1, 2, 3, 4, 5, and 6 hours post-dose. The primary efficacy measures were AUC(bl) and peak effect.

Demographics
The 63 randomized study subjects were evenly apportioned by sex (49% were male) and were almost exclusively (97%) Caucasian/white. The mean age was 36 years (range 13 to 63 years), with 4 subjects below the age of 18. Between 58 and 60 subjects received each of the six study treatments.