Mean cardiac rates from Holter monitoring were comparable among treatment groups at screening and treatment day 1, with no statistically significant differences observed. At treatment week 12, the mean cardiac rate in the albuterol CFC group (78.3 bpm) was lower than in the placebo and albuterol HFA groups (80.5 and 83.7 bpm, respectively); the minimum heart rate for the albuterol CFC group was statistically lower (p=0.027) than the other treatment groups. Overall maximum cardiac rates were comparable across all treatment groups.

Medical Reviewer Comment: *The isolated occurrences of increased VEs, SVEs, and heart rate changes do not suggest any cardiotoxicity of albuterol HFA.*

Pulse
Categorical analyses of increases and decreases in pulse with therapy are found in the following table.

Summary of Increases and Decreases in Pulse

Change	Placebo HFA	Albuterol HFA	Albuterol CFC
Increase in Pulse ≥15bpm	38 (39%)	41 (41%)	45 (45%)
Increase in Pulse ≥20bpm	16 (16%)	18 (18%)	25 (25%)
Increase in Pulse ≥30bpm	5 (5%)	8 (8%)	3 (3%)
Decrease in Pulse ≥15bpm	10 (10%)	15 (15%)	19 (19%)
Decrease in Pulse ≥20bpm	4 (4%)	6 (6%)	10 (10%)
Decrease in Pulse ≥30bpm	0	1 (<1%)	0

Source Data: Table 68

In 73% of albuterol CFC patients, pulse increased ≥ 15 bpm, in comparison to 67% of albuterol HFA and 60% of placebo patients. Similarly, albuterol CFC patients had the highest percentage (29%) of patients with a decline in pulse ≥15 bpm, compared to 22% in the albuterol HFA group and 14% in the placebo group.

Most of the increases in pulse rate ≥30bpm were single occurrences. Four patients (2 placebo, 2 albuterol HFA) had increases in pulse rate ≥30 for multiple timepoints on one serial day, with the maximum heart rate in all cases ≤104. In 2 patients (1 placebo, 1 albuterol HFA) pulse increases were accompanied by increases in SBP and DBP; the albuterol HFA patient showed an increase ≥30 bpm at the 3, 4, 5, and 6 hour measurements. In the opinion of the medical reviewer, the low rate of these occurrences raises no safety concerns.

Blood Pressure
The following table shows that changes in systolic blood pressure among the 3 treatment groups were comparable during the trial.

Summary of Increases and Decreases in Systolic Blood Pressure

Change	Placebo HFA	Albuterol HFA	Albuterol CFC
Increase in Systolic BP ≥15mmHg	39 (40%)	35 (35%)	39 (39%)
Increase in Systolic BP ≥20mmHg	17 (18%)	21 (21%)	24 (24%)
Increase in Systolic BP ≥30mmHg	3 (3%)	4 (4%)	2 (2%)
Decrease in Systolic BP ≥15mmHg	34 (35%)	40 (40%)	37 (37%)
Decrease in Systolic BP ≥20mmHg	16 (16%)	20 (20%)	16 (16%)
Decrease in Systolic BP ≥30mmHg	4 (4%)	1 (<1%)	3 (3%)

Source Data: Table 72

The majority of changes in SBP ≥30 mm Hg occurred at only one time point. Where they occurred at multiple time points, their occurrence was confined to either the placebo or the albuterol CFC groups.

Diastolic blood pressure changes were also comparable across the 3 treatment groups, as seen in the table below. Declines in DBP ≥20mm Hg were more common in the two albuterol treatment groups than placebo.

Summary of Increases and Decreases in Diastolic Blood Pressure

Change	Placebo HFA	Albuterol HFA	Albuterol CFC
Increase in Diastolic BP ≥15mmHg	20 (21%)	19 (19%)	21 (21%)
Increase in Diastolic BP ≥20mmHg	9 (9%)	3 (3%)	8 (8%)
Increase in Diastolic BP ≥30mmHg	2 (2%)	0	3 (3%)
Decrease in Diastolic BP ≥15mmHg	23 (24%)	25 (25%)	23 (23%)
Decrease in Diastolic BP ≥20mmHg	2 (2%)	10 (10%)	9 (9%)
Decrease in Diastolic BP ≥30mmHg	0	1 (<1%)	0

Source Data: Table 76

One patient in the albuterol HFA group had decreases in DBP ≥30mm Hg one time at both treatment weeks 6 and 12, with a minimum DBP of 52mm Hg. Overall there were no statistically significant differences observed among treatment groups, although 3 times points post dose on day 1 showed statistically significant but clinically insignificant differences ≤3.2mm Hg.

Physical Examinations

At screening, the percentage of patients who had a physical examination abnormality was comparable among treatment groups within each body system. Across treatment groups, the most common physical examination abnormalities were observed in the ears, nose and throat (27% to 30%) and hair and skin (3% to 7%) body systems. The number of patients who had an unfavorable change in a physical examination abnormality relative to screening was low and similar among treatment groups within each body system. The greatest incidence of unfavorable changes were observed in the ears, nose and throat group (8%, placebo HFA; 13%, albuterol HFA; and 5% albuterol CFC) and the hair and skin group (3% placebo HFA; 1% albuterol HFA, and 2% albuterol CFC). No other body systems had unfavorable changes in >2% of patients in any treatment group.

Medical reviewer comment: *In light of the increased rate of adverse events of throat irritation seen in the albuterol HFA group, and the greater rate of unfavorable ENT physical examination changes also seen in this group, it would be valuable to ask the sponsor to provide the specific ENT findings from the CRFs that were considered unfavorable relative to baseline for all 3 treatment groups.*

Medical Reviewer Conclusions

Efficacy
Both albuterol HFA and albuterol CFC demonstrated clear superiority to placebo HFA in serial FEV1 measurements. This superiority was statistically significant for both albuterol formulations with few exceptions; these occurred in selected week 12 comparisons of HFA albuterol to the placebo group, which had experienced an increase in predose FEV1 compared to pre-trial baseline. Analyses of seven functions of serial FEV1 (ie. onset, duration, maximum effect) consistently confirmed albuterols CFC and HFA were statistically superior to placebo.

Figures of changes in serial FEV1 measurements illustrate that the magnitude of the increase seen with albuterol HFA was less than with albuterol CFC when examined as the change or mean percent change from same day baseline, or as the percent of predicted FEV1. In the figures, these differences are most marked in the first 2 – 3 hours post dose at Day 1 and Week 6 treatment assessments. At week 12, the difference between albuterols CFC and HFA did not vary in magnitude over the 6 hour assessment period.

When albuterol HFA and CFC groups were compared statistically, no significant differences were seen between these two groups in analyses of FEV1 changes relative to same-day baseline. Analyses of the mean percent increase in same-day baseline FEV1 found albuterol CFC to be statistically greater than albuterol HFA on treatment day 1 overall, for the first two hours of treatment on day 1, and for the first hour of treatment at week 6. When functions of FEV1 were analyzed, CFC albuterol had greater percentages of patients achieving ≥15% improvement, a greater mean maximum percent change from baseline, and a larger AUC (bl) at all timepoints than albuterol HFA. Of these differences, treatment day 1 mean maximum effect and median onset of effect were statistically significant. When the percentage of patients with ≥15% increase in FEV1 during serial measurements was compared for albuterols CFC and HFA, the CFC formulation consistently had higher percentages during the first hour's measurements.

In secondary efficacy measures based upon patient reported data, both albuterol formulations caused statistically significant improvement relative to placebo in puffs of back-up albuterol use and days without back up albuterol. The

improvements were consistently larger with albuterol CFC than albuterol HFA but without statistical significance. AM and PM PEFR were improved relative to placebo in both albuterol groups, but statistically significant only for selected PM PEFR measurements. Other endpoints (asthma symptoms, nighttime awakenings, and asthma exacerbations) showed little change or difference among the treatment groups.

Device Performance
Clogging was noted in 9 canisters of albuterol HFA returned for poor performance, and raises the concern that clogging seen with currently approved HFA preparations may occur in this product as well. Only 1 canister of CFC albuterol was clogged, and that was by a foreign particle.

Safety
Albuterol in CFC and HFA propellant was well-tolerated and did not raise any significant safety concerns. Serious adverse events occurring during randomized treatment were within expectations for an asthmatic study population (one patient in each albuterol group had an asthma exacerbation near the end of trial.) Withdrawals due to adverse events were small in number and evenly distributed among the placebo and two active treatment groups. No adverse events were reported proximate to dosing for albuterol HFA.

Throat irritation and cough were elevated in albuterol HFA patients relative to the other treatment groups, and for cough, this elevation was statistically significant. Drug-related cough was similar in incidence in the 3 treatment groups, however. Severe adverse events occurred infrequently, and were seen in >1% of patients only in the case of headache (1% placebo, 3% albuterol HFA, and 3% albuterol CFC) and upper respiratory tract infection (1% placebo, 2% albuterol HFA, 0% albuterol CFC).

Laboratory findings, ECGs, vital signs, Holter monitoring, and physical examination results did not raise any safety concerns.

Conclusions
Albuterol HFA and CFC used QID cause significant bronchodilation when compared to placebo. The absolute magnitude of bronchodilation with albuterol HFA is comparable, but slightly less than with albuterol CFC. Some measurements suggest that this difference is greatest during the first few hours after use.

The data provided in this study alone do not support an explicit or separate PRN indication for albuterol HFA.

One batch of albuterol HFA demonstrated clogging problems in 9 canisters returned for being 'faulty'. The rate of this occurrence within the clinical trial program should be determined.

SALA3006

A Randomized, Double-Blind, Parallel-Group, Clinical Trial Assessing the Safety and Efficacy of Albuterol 200mcg (180mcg ex-actuator) QID in CFC Propellant 11/12 Versus Albuterol 200mcg (180mcg ex-actuator) QID in HFA Propellant Versus Placebo (HFA) in Pediatric Subjects Aged 4-11 Years with Asthma

Study Design

This was a randomized, double-blind, parallel-group multi-center clinical trial, with a 2-week treatment period, assessing the safety and efficacy of albuterol CFC QID, albuterol HFA QID and placebo HFA QID in pediatric patients with asthma. The study included a 1 to 2-week run-in period during which patients were allowed to use only the permitted anti-asthma medications stated in the protocol, and trade label **VENTOLIN**† (albuterol CFC) for PRN relief of acute symptoms of asthma. Upon demonstration of satisfactory asthma stability, compliance, and study eligibility at the end of the run-in period, patients were randomized to albuterol CFC, albuterol HFA or placebo HFA (albuterol HFA PRN) given four times daily during the 2-week double-blind treatment period. Total study duration was approximately 3 to 4 weeks.

Enrollment was planned for 90 males and premenarchal females 4 to 11 years of age (30 per treatment group) who demonstrated a baseline FEV_1 (medication-free) of 50-80 percent of predicted normal value (Polgar) and airways reversibility (≥15% increase in FEV_1 or PEFR following inhalation of 2 puffs of **VENTOLIN**).

Clinic visits were scheduled as follows:

Clinic Visit	Time of Occurrence
Screening	Initial visit
Treatment Day 1	7 to 14 days from Screening
Treatment Week 2	14 days ± 2 days after Day 1

The procedures and evaluations performed at each visit are described in the flowchart on the following page. Holter monitoring was performed at screening and at Treatment Day 1 and Treatment Week 2 at selected sites.

The original protocol was amended once on 11/5/96 before any study sites were initiated. It clarified that that the primary measure of efficacy would be serial measurements of FEV_1 (for 6-11-year-old subjects and 4 and 5-year-old subjects who could perform the spirometry maneuver) and PEFR measurements (performed by all patients using the Mini-Wright Peak Flow Meter). Spirometry would be performed for patients 6-11 years of age and 4 and 5 year olds who

Flowchart/Time & Events Table

	Visit:	Screening		Treatment Visit 1	Treatment Visit 2	Discontinuation Visit (if applicable)
		-7 to -14 Days From Visit 1		Day 1	Week 2 14 days ± 2 Days After Visit 1	
Informed Consent		X				
Medical History		X				
Physical Examination		X			X	X
Vital Signs		X		X	X	X
24-Hour Holter Monitoring		X[e]				
12-Lead ECG and Rhythm Strip		X		X[a]	X[a]	X
6-Hour Holter Monitoring[b] (at selected sites)				X[b]	X[b]	
Clinical Laboratory Tests		X			X[c]	X
Review MDI Inhalation Technique		X		X	X	
Pulmonary Function Testing		X				X
Reversibility Assessment		X				
6-Hour Serial Vital Signs and PFTs[d]				X	X	
Issue Peak Flow Meter		X				
Diary Card Dispensed		X		X		
Dispense PRN Ventolin		X				
Double-Blind Meds Dispensed				X		
Adverse Event and Concurrent Medication Review				X	X	X
Collect PRN Ventolin				X		
Collect All Study Medication					X	X
Discharge from Study					X	X

a Pre-dose and 0.75 hours post-dose

b To be performed at selected sites

c. Pre-dose

d Serial vital signs and assessments of pulmonary function: ***Both*** PEF and spirometry for all subjects will be performed 30 minutes pre-dose, immediately pre-dose (time 0), and the following times post-dose: 5 minutes, 15 minutes, 30 minutes, 1, 2, 3, 4, 5, and 6 hours

were able to perform the maneuver, and PEFR would be performed by all patients. In addition, if a 4 or 5 year old qualified based upon PEFR instead of FEV_1, then *only* serial PEFR values would be collected during Treatment Day 1 and Treatment Week 2.

Study Population

The study population was stratified in a 1:1 ratio into 2 age ranges: 4-8 years and 9-11 years. Children had to demonstrate a baseline FEV1 or PEFR of 50-80% of Polgar predicted normal, and reversibility of ≥15% after 2 actuations of Ventolin MDI with CFC propellant. A spacer was allowed for the determination of reversibility, but at no other time during the trial. Four to five year olds who could not produce reliable FEV1 values (repeat values ± 10%) were assessed for eligibility using a Mini-Wright Peak Flow Meter to assess PEFR.

Standard inclusion and exclusion criteria were applied to exclude patients with unstable asthma, significant medical conditions, poor compliance, and recent respiratory tract infection.

Concurrent medications that were withheld throughout the study included beta-agonists, theophylline, ipratropium, β-blockers, TCAs, Ritalin, and MAO inhibitors. Parenteral and oral steroids were withheld throughout the study and 1 month prior to the screening visit. Stable regimens of inhaled steroids, cromolyn, and nedocromil were allowed during the study as long as the AM dose was withheld on clinic visit days. Intranasal steroids or cromolyn were also allowed. Antihistamines, decongestants, and PRN nasal decongestants were allowed with appropriate washouts before study visits. Stable regimens of immunotherapy were allowed if no doses had occurred the day before or the day of a Treatment visit.

Patients who exacerbated out-of-clinic, or who required more than their PRN medication and Ventolin 2.5 mg by nebulization during 6-hour study days, were discontinued from the trial

Study Treatments

The following medications were used during the trial.

Medication	Strength	Batch Number	Review Date
Albuterol CFC MDI	100mcg/ actuation*	5Z1162P 6ZP0118	30 Jun 98 31 Mar 99
Albuterol HFA MDI	100mcg/ actuation*	6ZX001A 6ZX012B	31 Mar 98 30 Sept 98
Placebo (HFA propellant alone) MDI	—	6ZX011A	31 Jan 98
VENTOLIN Nebules (rescue)	0.083% - 2.5mg/3ml	960309	28 Feb 98

Each subject received **VENTOLIN** at the Screening Visit and was instructed to take 2 actuations for PRN relief of acute symptoms of asthma until Treatment Day 1 (one to two weeks.)

Patients were randomized at Treatment Day 1 to one of the following double-blind study treatments:

- Albuterol 100mcg MDI in CFC (2 puffs) QID
- Albuterol 100mcg MDI in HFA (2 puffs) QID
- Placebo (HFA propellant alone) (2 puffs) QID

Each subject was instructed to take two actuations of study medication four times a day, approximately every 4 to 6 hours.

Each subject received albuterol for PRN relief of acute symptoms of asthma, in matching propellant, according to his/her randomized treatment:

Patients Randomized To:	Received:
Albuterol/CFC	Albuterol/CFC
Albuterol/HFA	Albuterol/HFA
Placebo/HFA	Albuterol/HFA

Efficacy Measures

The primary measure of efficacy was serial measurements of FEV_1 (for 6-11 year olds and those 4-5 year old patients capable of performing spirometry) and PEFR, using the Mini Wright Peak Flow Meter (for all patients). On each study day with serial assessments, FEV_1 and PEFR were determined 30 minutes prior to dosing, immediately pre-dose (time 0 hour), and at the following times post-dose: 5, 15, 30 minutes, and 1, 2, 3, 4, 5, and 6 hours. At each of these time points, duplicate determinations were performed.

Additional measures of efficacy were recorded by the subject/parent on daily diary cards. These included subject-conducted determinations of morning and evening peak expiratory flow (AM and PM PEFR), asthma symptoms scores, frequency of nighttime awakenings, use of back-up albuterol, and the frequency of asthma exacerbations. AM and PM PEFR were the best of duplicate efforts. Symptom scoring was done daily before the AM PEFR and rated from 1 (no symptoms) to 4 (symptoms at rest). Exacerbations were defined as asthma requiring treatment other than allowed concomitant medications, study medications, or back-up albuterol MDI. Exacerbations during 6 hour study visits were recorded on the patient's CRF.

Safety Measures

Safety was assessed by monitoring physical examinations, clinical laboratory tests (including serum pregnancy tests for all females), 12-lead electrocardiograms, and clinical adverse events, including those which occurred after each dose of study medication. Vital signs were obtained at screening, discontinuation, and during spirometry.

Continuous ambulatory Holter monitoring was conducted at 6 study centers on approximately 45 patients (15 each treatment arm.) A baseline 24 hour recording was done at or near the screening visit. Seven-hour recordings (from 1 hour prior to dosing through 6 hours after dosing) were done at each Treatment Visit (day 1 and week 2.) Clinically significant findings were defined [87:41].

Data Analysis Plan
A remote data capture system (AVANTEC) was used to capture visit report forms which were then subject to a variety of quality assurance methods including validation against a random sample of original records.

Enrollment was planned for 90 evaluable patients (30 completed patients per treatment group). Using previous pediatric asthma trials, the sponsor assumed that 12.23% was a reasonable assumption for the standard deviation of FEV_1 percent of predicted (Analysis of Covariance with baseline FEV_1 as the covariate). Using a significant level of 0.05, 30 patients per treatment group provided at least 80% power in detecting a difference of 10% in percent of predicted FEV_1 between any two treatment groups. Two-sided tests were used throughout the analysis and, unless otherwise specified, p-values of 0.05 or less were considered statistically significant. P-values were not adjusted for the number of comparisons made, but pairwise p-values were only interpreted when the overall treatment comparison was significant.

The primary population for analysis was the Intent to Treat population, defined as all patients randomized to treatment who received at least one dose of blinded study medication. Subgroup analyses by the stratification age groups (4-8 years, 9-11 years) were <u>not</u> performed.

The primary measure for efficacy analyses for all patients was serial PEFR measurements. For patients aged 6-11 and those 4 and 5 year old patients who were able to perform spirometry, the primary measure of efficacy was serial FEV_1 measurements, with particular attention focused on percent of predicted FEV_1. Analysis of serial PEFR and FEV1 for responders, onset, offset, duration, peak effect, AUC(bl), and by WAVE (weighted average of postdose values over 6 hours) was defined in the same manner as the 12 week adult trials [87:47.] Repeated measures analysis (involving equal weighting of postdose measurements) was also done.

Treatment groups were compared at each treatment visit using an Analysis of Covariance F-test controlling for investigator and using baseline percent of predicted PEFR/FEV1 as the covariate. Sources of variation due to interaction between treatment and investigator were analyzed in a separate model (which included sources of variation due to treatment, investigator, treatment by investigator interaction, and using baseline percent of predicted PEFR as the covariate.) A test for homogeneity was also performed. Onset, offset, duration

of effect and time to maximum effect were analyzed using a van Elteren test (an extension to the Wilcoxon-Mann-Whitney test) controlling for investigator.

Medical Reviewer Comments: *The protocol is well-designed to assess short and intermediate efficacy and safety of albuterol formulations in pediatric patients. Although the sponsor notes the primary endpoint (percent change in predicted PEFR and/or FEV1) was not explicitly stated in the protocol, it was implied in their statistical power analyses and its use is appropriate metric for the pediatric population.*

Medical Reviewer Check of Study Conduct
Examination of the single case report form for this protocol [115:313] showed that the allocation number/treatment assignment from the randomization schedule agreed with the designated treatment [87:270]. Line listings of FEV1 from screening and Treatment Day 1 FEV1 agreed with the CRF, as did selected line listings of laboratory values from the screening and discontinuation visits.

Protocol variations occurred in a total of 8 patients (6%), were evenly distributed across the 3 treatment groups, and consisted primarily of FEV1 measurements being initiated outside the allowed time window [87:127]. There were trivial errors (1 to 2 each) in randomization and in patient continuation in the trial based on the basis of FEV1; these were considered by the medical Reviewer not to be of significance to the overall study results.

Results
Device Performance
There were no malfunctioning canisters of medication returned to Glaxo Wellcome during the study.

Study Population Results
Randomization was stratified into two groups in an effort to ensure treatment balance in the two age ranges: 4-8 years old and 9-11 years old. In the opinion of the medical reviewer, a reasonable balance of patient ages was achieved. A total of 61 subjects ages 4-8 years and a total of 74 subjects ages 9-11 years were entered into the study. In the 4-8 year old group, 18, 20, and 23 subjects were randomized to placebo HFA, albuterol HFA, and albuterol CFC, respectively. In the 9-11 year old age group 25, 26, and 23 subjects were randomized to placebo HFA, albuterol HFA, and albuterol CFC, respectively.

Medical Reviewer tallies of the number of 4 to 5 year old patients [89:16ff] indicated 5 such patients in the placebo group, 6 in the albuterol HFA group, and 7 in the albuterol CFC group.

Medical Reviewer comment: *The numbers of patients at the lower end of the age spectrum was small but reasonable for the overall size of the trial. Given the*

small numbers of patients overall, by the two age strata, analyses by age would likely be misleading and not worthwhile.

A total of 41 patients withdrew during the run-in period of the study. The number of patients randomized to the 3 treatment groups and that were withdrawn during the study are described in the following table.

Patient Accountability Summary

Disposition	Number of Patients Placebo HFA	Albuterol HFA	Albuterol CFC	Total
Randomized	43	46	46	135
Completed	36	41	41	118
Withdrawn:	7	5	5	17
Other	4	5	2	11
Lack of Efficacy	2	0	2	4
Adverse Event	0	0	1	1
Failed to return	1	0	0	1

Source Data: Table 3

Of the 17 patients who withdrew, most (11) withdrawals were due to 'other' reasons, primarily protocol variations and non-compliance. The number of patients who withdrew due to lack of efficacy was low (4 patients). One patient receiving albuterol CFC withdrew due to an adverse event (exacerbation of asthma).

Other than had a greater percentage of males in the CFC albuterol group (72%) than the other two treatment groups (53-54%), the patients in the three treatment groups had comparable demographics. Overall, 59% of the patients were Caucasian, 30% were Black, 8% were Hispanic and 2% were of Other origins. Sixty percent were male. The mean age was 8.3 years and 55% of the patients were in the 9 to 11 year old age stratum.

Duration and severity of asthma were similar among the treatment groups, with 2 to 3 more CFC albuterol patients distributed into categories representing longer histories of asthma and greater numbers of emergency visits for asthma. Current medical conditions other than asthma were present in 87% of patients overall [Medical Reviewer calculation based on table 9, Vol 79:130]. The most of common of these were classified as non-site specific, which included allergies (67-85%). The CFC albuterol group had the highest rate of any current medical condition (96%) as well as the highest rate of non-site specific problems (85%.)

As seen in the table below, baseline pulmonary function was similar in the three treatment groups.

Results Of Pulmonary Function Tests At Screening

Pulmonary Function Test value[1]	Placebo n	Placebo mean (se)	ALB 180mcg HFA n	ALB 180mcg HFA mean (se)	ALB 180mcg CFC n	ALB 180mcg CFC mean (se)	p-
Number of Subjects	43		46		46		
FEV1 (Liters)	40	1.31 (0.06)	45	1.30 (0.06)	42	1.37 (0.07)	0.703
FEV1, % of Predicted	40	64.2 (1.44)	45	69.9 (1.52)	42	65.7 (2.00)	0.073
FEV1, % Reversibility	39	32.1 (2.57)	42	32.3 (2.99)	38	27.2 (2.00)	0.223
PEFR (L/Min)	4	94 (12.8)	5	111 (13.3)	6	120 (10.8)	0.478
PEFR, % of Predicted	4	68.8 (6.25)	5	82.8 (9.94)	6	70.6 (5.55)	0.534

[1] P-values are based on an Analysis of Variance F-test.

Concomitant medication use was similar among the treatment groups, with a slightly greater rate of any corticosteroid use for asthma among HFA albuterol patients (50%) than CFC albuterol patients (33%). Use of corticosteroids for conditions other than asthma was also less in the CFC albuterol group (7%) than in either the placebo or HFA albuterol groups (19% and 17% respectively.) Treatment compliance was very similar (range 88.2 to 90.0%) across treatment groups.

Medical Reviewer Comment: *The albuterol CFC group appears to have had 4 –5 more patients (~10%) with complicated pulmonary disease as represented by longer duration of asthma, number of emergency visits in the preceding year, and the existence of atopy. This is a small difference whose impact is likely to be minor and more likely to affect parameters such as exacerbations and nighttime awakenings, rather than in-clinic assessments of pulmonary function in response to albuterol.*

Efficacy Findings

Analytical issues

Serial PFTS were analyzed by WAVE (a weighted average of postdose PFTs over 6 hours) and repeated measures analysis. WAVE was defined as follows:

$$[(Resp_{5min} \times 5) + (Resp_{15min} \times 10) + (Resp_{30min} \times 15) + (Resp_{1hr} \times 30) + (Resp_{2hr} + Resp_{3hr} + Resp_{4hr} + Resp_{5hr} + Resp_{6hr}) \times 60]/360$$

Repeated measures analysis gives equal weights to results from all time points, so that the four measurements taken during the first hour when the albuterol is most active are weighted equally with those taken hourly during the remaining 5 hours.

WAVE analyses examined sources of variation by ANCOVA due to interaction between treatment and investigator and none were found to be statistically significant. Repeated measures analyses also examined this interaction, and

found statistically significant findings only at some time points on treatment day 1. Since the inclusion of treatment by investigator interaction term in the model did not affect the overall treatment inference, it was not included in the main effects model.

Graphic Overview of Efficacy Findings

At both Treatment Day 1 and Week 2, albuterol HFA performed as well or better than albuterol CFC in serial assessments of pulmonary function when assessed as a percentage of predicted; figures 3 illustrates these findings with respect to FEV1 (pdf versions of figures were provided only for FEV1 analyses). These analyses and those which examined mean change (as seen in figures 13 and 14) showed that albuterol HFA frequently outperformed albuterol CFC in the first several hours, with comparable performance thereafter. Only in the comparisons of absolute PEFR and FEV1 values (illustrated in Figure C28 for FEV1) did albuterol HFA show a lesser response than CFC albuterol; this may be attributable to the larger same day baseline value found in the albuterol CFC treatment group.

Primary Efficacy Measures: 6-Hour Serial PFTs

Serial PEFR was evaluated for all patients, and serial FEV1 for 6-11 year olds and those 4-5 year olds who could perform the maneuver. Both endpoints were analyzed principally as the mean percent of their predicted values.

WAVE analysis of percent of predicted PEFR in children 4 –11 years of age was as follows:

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*

*$p \leq 0.023$ compared with placebo HFA

By this method of analysis, both albuterol groups showed statistically significant greater percent predicted PEFR (80.3 – 81.8%) over placebo (~71%) at day 1 and week 2 of treatment, and no statistically significant difference between each other in pairwise comparisons. The same pattern of statistical superiority was seen when serial PEFR data were analyzed by repeated measures analysis, as the percent change in percent predicted PEFR, as the percent predicted PEFR with no values carried forward, or as the percent predicted PEFR at week 2 using treatment day 1 as a baseline.

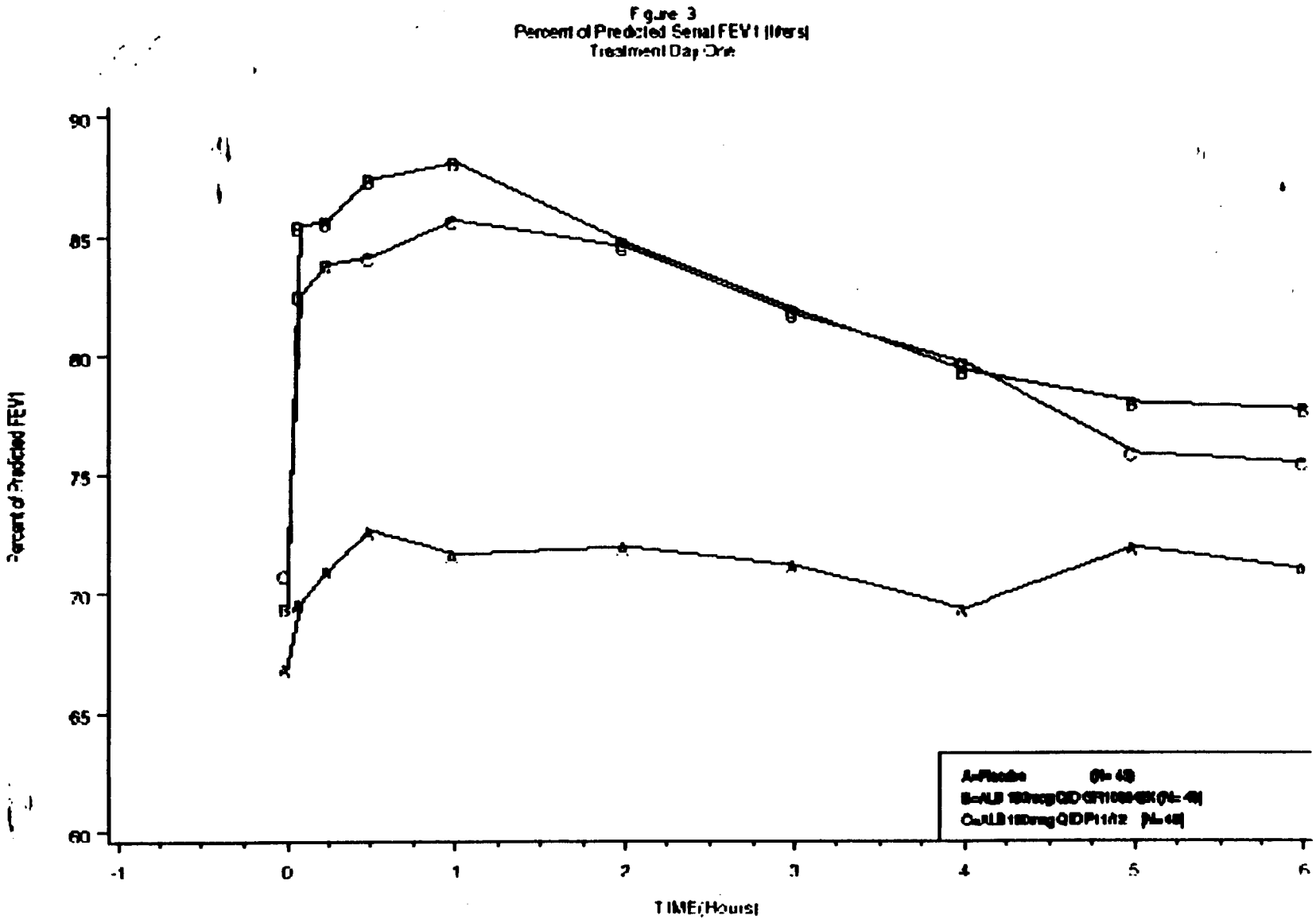


Figure 3
Percent of Predicted Serial FEV1 (liters)
Treatment Day One
Percent of Predicted FEV1
90
85
80
75
70
65
60
-1
0
1
2
3
4
5
6
TIME(Hours)

Figure 13
Change from Same Day Baseline Serial FEV1 (liters)
Treatment Day One

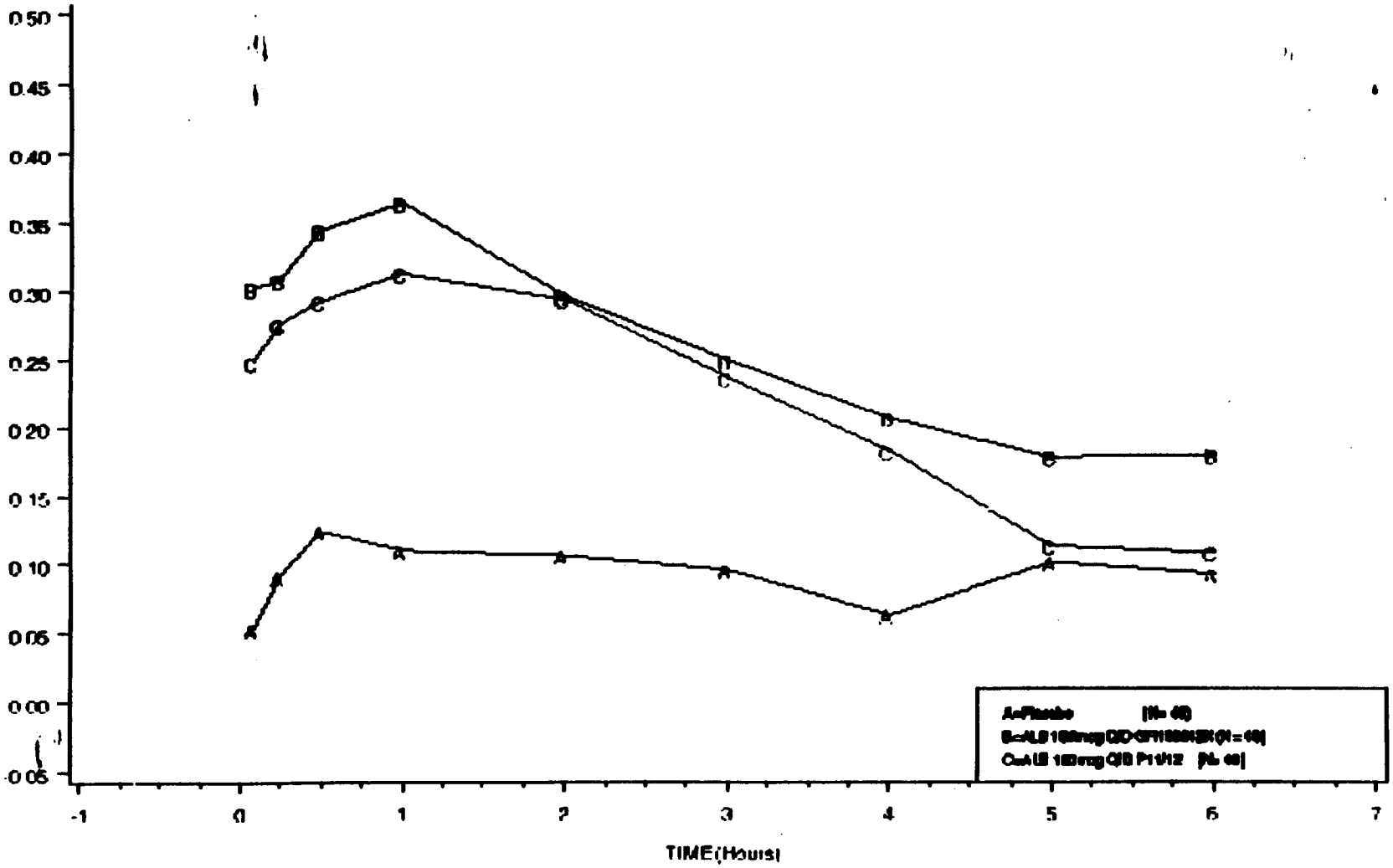


Figure 14
Change from Same Day Baseline Serial FEV1 (Hers)
Treatment Week 2

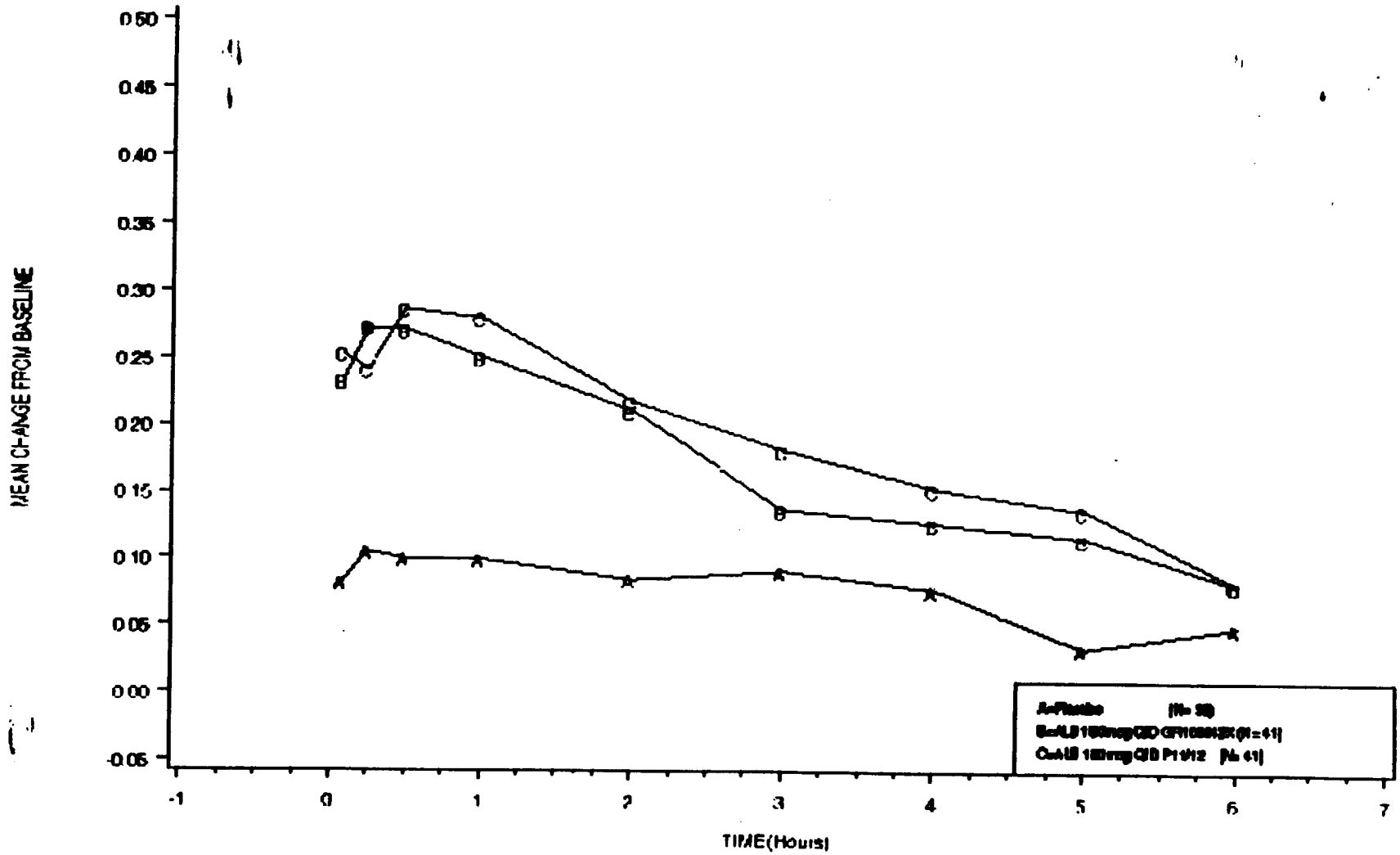
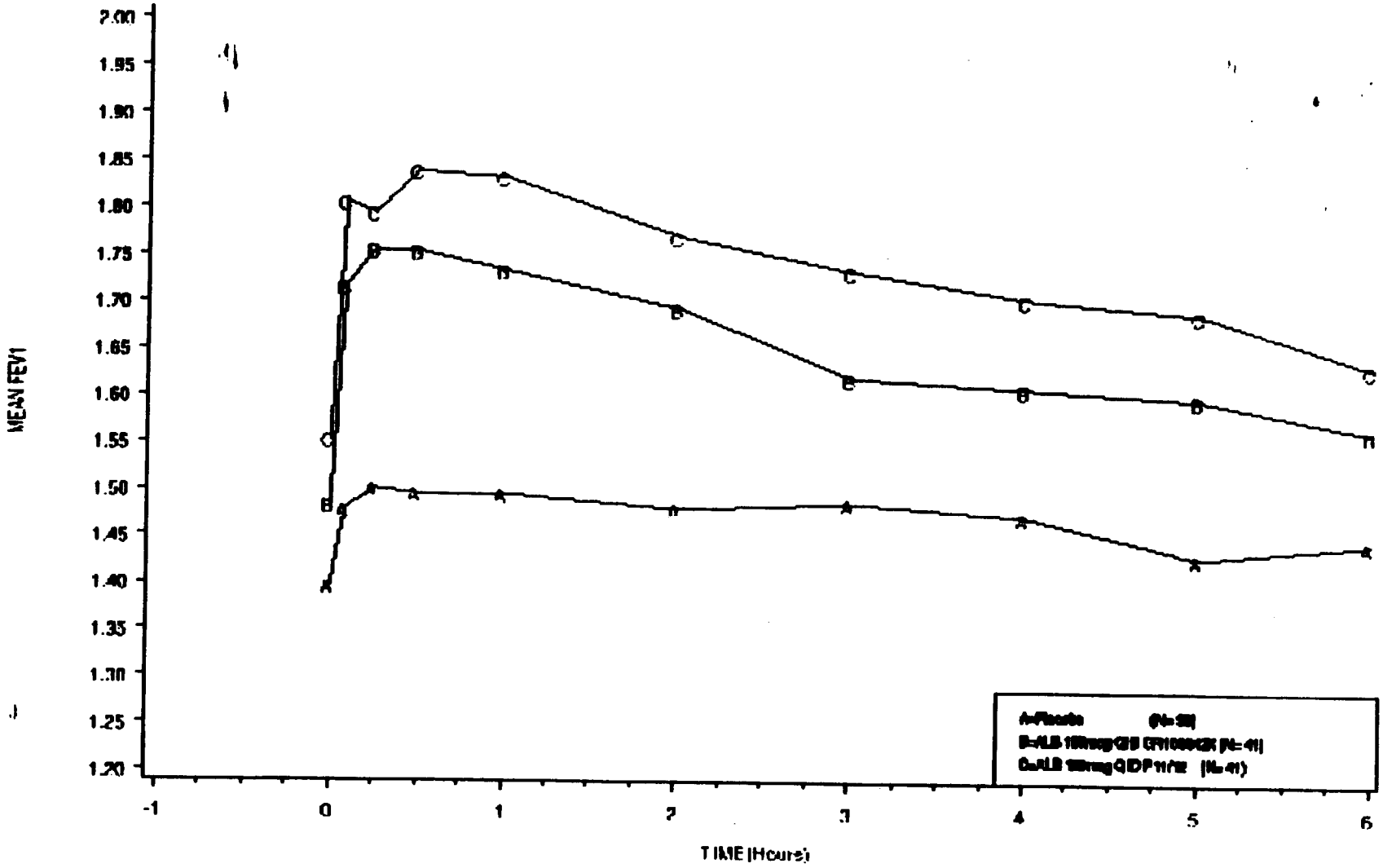


Figure C28
Serial FEV1 (litres)
Treatment Week 2



Analysis of percent predicted FEV1 for 6 – 11 year olds by WAVE also showed both albuterol groups caused statistically significant improvement over placebo at day 1 and week 2 of treatment, with no statistically significant difference between the two formulations, as seen in the following table:

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

Repeated measures analysis confirmed these findings, as did analyses of the percent change in percent predicted FEV1 and the percent of predicted FEV1 without values carried forward. Using the day 1 of treatment as the baseline for week 2 analyses, both albuterol formulations were numerically superior to placebo, but only albuterol HFA achieved statistical significance.

Medical Reviewer Comment: *Albuterol HFA and CFC both caused significant improvement in serial PEFR and FEV1 measurements of percent predicted values over 6 hours when compared to placebo. The improvement seen with albuterol HFA was slightly greater numerically (1-2 percentage points) than that seen with albuterol CFC. For both albuterol formulations, the effect size for PEFR and FEV1 decreased at week 2 of treatment relative to treatment day 1; this appears due to an increase in the same day baseline between day 1 and week 2.*

Secondary Efficacy Measures
Secondary efficacy measures included analyses of PEFR and FEV1 in terms of absolute and percent change from baseline (either same day or treatment day 1.) Derived functions of PEFR and FEV1 such as onset and duration of action were analyzed overall and among those patients who had a ≥15% response within 30 minutes.

Secondary Efficacy Measures of PEFR
Analyses of change in PEFR by WAVE (see table below) and repeated measures analysis show the same pattern of statistical superiority seen using percent predicted PEFR; both albuterol HFA and CFC were statistically superior to placebo at both treatment day 1 and week 2, and without statistically significant differences in pairwise comparison of the two formulations.

Weighted Average (WAVE) of Change from Same Day Baseline Post-Dose PEFR Measurements Over 6 Hours (Liters/min)

Visit	Placebo HFA	Albuterol HFA	Albuterol CFC
Treatment Day 1			
N	43	46	46
Baseline	191	187	201
WAVE of Change	15.1	30.0*	30.8*
Treatment Week 2			
N	36	41	41
Baseline	201	203	214
WAVE of Change	13.6	23.5*	26.4*

Analyses of the percent change from same day baseline PEFR were similar to the above. In analyses using the treatment day 1 PEFR baseline , statistically significant differences from placebo were infrequent at the treatment week 2 visit. Although the increases in PEFR seen with HFA and CFC albuterol were at least 50% greater than with placebo (see table below), overall statistical significance by WAVE analysis was not seen at the week 2 time point. Repeated measures analysis did show a statistically significant improvement with albuterol HFA over placebo at week 2, and no statistically significant difference between the HFA and CFC formulations.

Weighted Average (WAVE) of Post-Dose PEFR Measurements Over 6 Hours Change from Treatment Day 1 Baseline (Liters/min)

Visit	Placebo HFA	Albuterol HFA	Albuterol CFC
Treatment Week 2			
N	43	46	46
Baseline	191	187	201
WAVE of Change	20.7	37.9	33.7

Derived from 87:61

Analyses of derived values from serial PEFR data (see following table) showed that both albuterol HFA and albuterol CFC were significantly superior to placebo at treatment day 1 and week 2 evaluations for onset of effect, duration of effect, mean maximum effect, and mean AUC(bl). The percentage of patients achieving ≥15% increase over baseline PEFR was significantly larger at day 1 and week 2 for albuterol HFA than for placebo. CFC albuterol showed improvement over placebo at both time points, but this improvement was statistically significant only at week 2. Numerically, both albuterol formulations had larger percentages of patients achieving WAVE ≥15% over baseline, but these differences were statistically significant only for albuterol CFC at week 2 of treatment.

Analysis of Functions of 6-Hour Serial PEFR

Function / Visit:	Placebo HFA Day 1	Placebo HFA Week 2	Albuterol HFA Day 1	Albuterol HFA Week 2	Albuterol CFC Day 1	Albuterol CFC 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

Since the derived functions of serial PEFR set onset and offset of effect to 6 hours for those patients who did not experience an increase in PEFR ≥15% within 30 minutes of dosing, the comparisons of duration of effect of albuterol HFA and albuterol CFC are potentially skewed. To overcome this, the sponsor conducted analyses using only those patients whose PEFR increased ≥15% within 30 minutes of dosing. By these analyses, median duration of effect was greater in the albuterol CFC group at Treatment Day 1 and Treatment Week 2 (5.11 and 4.97 hours, respectively) compared with albuterol HFA (3.52 and 3.39 hours, respectively). A similar trend was also noted for mean AUC(bl) at Treatment Day 1 and Week 2 (241- and 228L-hr, respectively) for albuterol CFC, and for albuterol HFA (208 to 207L-hr, respectively). Analyses of the percentage of patients at serial time points with ≥15% increase in PEFR from same day baseline showed both albuterol formulations had greater percentages than placebo, with the exception of albuterol HFA where there was a steeper drop-off in percentage achieving effect at the 5 and 6 hour time points.

Secondary Efficacy Measures of FEV1

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

In analyses of change from treatment day 1 baseline FEV1 by WAVE, both HFA and CFC albuterol had larger increases than placebo (see following table), but none of the overall treatment comparisons was statistically significant. By repeated measures analysis, only albuterol HFA was statistically greater than placebo.

Weighted Average (WAVE) of Post-Dose FEV_1 Measurements Over 6 Hours Change from Treatment Day 1 Baseline

Visit	Placebo HFA	Albuterol HFA	Albuterol CFC
Treatment Week 2			
N	39	41	40
Baseline	1.38	1.37	1.51
WAVE of Change	0.09	0.25	0.18

Functions of serial FEV1 (see table below) showed that both albuterol HFA and albuterol CFC were statistically better than placebo on treatment day 1 and week 2 in the percentage of patients achieving effect, the median onset of effect, median duration of effect, the mean maximum effect, and the mean AUC(bl). In general, derived functions for albuterol HFA (such as % of patients achieving effect, duration of effect, and mean maximum effect) were numerically greater than for albuterol CFC. The median time of maximum effect was shorter and the percentage of patients with WAVE ≥15% over baseline was greater for the two albuterol formulations than for placebo, but statistically significant findings were noted only on treatment day 1 comparisons.

Analysis of Functions of 6-Hour Serial FEV_1

Function / Visit:	Placebo HFA Day 1	Placebo HFA Week 2	Albuterol HFA Day 1	Albuterol HFA Week 2	Albuterol CFC Day 1	Albuterol CFC 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

Responder analyses (see table below) showed the median onset of effect in both albuterol treatment groups to be rapid, about 3 – 3.6 minutes. Median duration of effect among responders was of roughly comparable duration for the two albuterol treatment groups, with an overall decline in duration of effect in both groups from treatment day 1 to treatment week 2. Albuterol CFC was actually worse than placebo in median duration of effect and mean maximum effect at treatment week 2.

Analysis of Functions of 6-Hour Serial FEV_1 (30-min Responders)

Function / Visit:	Placebo HFA Day 1	Placebo HFA Week 2	Albuterol HFA Day 1	Albuterol HFA Week 2	Albuterol CFC Day 1	Albuterol CFC Week 2
% Patients Achieving Effect†	32	24	88*	69*	70*	63*
Median Onset of Effect (hr)	0.19	0.10	0.05	0.06	0.06	0.06
Median Duration of Effect (hr)	1.65	4.46	4.07	3.17	4.21	2.50
Mean Max Effect (% chg from baseline)	29.9	34.2	36.3	32.9	32.5	31.5
Median Time of Max Effect (hr)	2.0	0.5	0.5	0.5	0.5	0.5
Mean AUC(bl) (L-hr)	1.38	1.15	1.68	1.27	1.71	1.45

†Effect = an increase in FEV_1 of ≥15% above baseline (average of -30 minute and 0 minute FEV_1 measurements at Treatment Day 1).

Analyses of the percentage of patients with ≥15% increase in FEV1 over time showed both albuterol groups to be have higher percentages than placebo at all time points at day 1 and week 2 of treatment. The percentage of responders diminished in both albuterol groups between day 1 and week 2 of treatment.

Other Efficacy Measures

AM and PM PEFR: As seen in the following table, mean change from baseline in AM and PM PEFR was higher in the two albuterol treatment groups than in the placebo group. The change for albuterol HFA was greater than for albuterol CFC, but only albuterol HFA was significantly greater than placebo for the 2-week trial period.

AM and PM PEFR (L/min) Values
Summary of Mean Changes from Baseline

Treatment Period	Placebo HFA N	Placebo HFA AM	Placebo HFA PM	Albuterol HFA N	Albuterol HFA AM	Albuterol HFA PM	Albuterol CFC N	Albuterol CFC AM	Albuterol CFC PM
Baseline[1] (actual value)	43	(194)	(200)	46	(189)	(204)	46	(199)	(214)
Week 1	41	2	4	46	17	13	46	9	12
Week 2	40	2	-0	45	17	17	46	8	10
Weeks 1-2	41	2	3	46	17*	15*	46	9	11

[1]Baseline is the average of the seven days immediately prior to Treatment Day 2
*p≤0.014 compared to placebo HFA

Back-up Albuterol Use: Back up albuterol use declined in all treatment groups during the trial, with the decline in mean number of puffs approximately twice as great in the albuterol treatment groups as in the placebo group. These changes were statistically significant in comparison with the placebo, as were the changes in the percentage of days with no back-up albuterol use. There were no significant differences between the HFA and CFC albuterol formulations. treatment period.

Back-Up Albuterol Use
Summary of Mean Changes from Baseline

Treatment Period	Placebo HFA N	Placebo HFA # puffs	Placebo HFA % days	Albuterol HFA N	Albuterol HFA # puffs	Albuterol HFA % days	Albuterol CFC N	Albuterol CFC # puffs	Albuterol CFC % days
Baseline[1] (actual value)	42	(2.6)	(42.6)	46	(3.1)	(28.1)	45	(3.0)	(30.5)
Week 1	41	-1.0	13.6	46	-1.9	38.0	46	-1.9	38.7
Week 2	39	-0.4	6.5	45	-1.8	36.2	46	-2.0	40.0
Weeks 1-2	41	-0.8	11.5	46	-1.8*	36.4*	46	-2.0*	39.5*

[1]Baseline is the average of the seven days immediately prior to Treatment Day 1
% Days = Days with no back-up albuterol
*p≤0.033 compared with placebo HFA

Asthma symptoms: Across the weekly treatment intervals and entire 2-week treatment period, there was a slight increase from baseline (0.1) in the daily mean asthma symptoms scores in the placebo HFA group and a slight decrease

(-0.1 and-0.3) in the two albuterol groups. The albuterol HFA group was significantly (p=0.014) better than the placebo HFA group for the entire 2-week treatment period, and there were no significant differences between the albuterol treatments. Mean changes from baseline in the percentage of days with no symptoms were higher in both albuterol treatment (7.1 to 15.6) groups than the placebo HFA group (0.9.) However, none of the overall treatment comparisons were statistically significant.

Nighttime awakenings: The mean percent of nights with no awakenings showed little change from baseline and was generally comparable across the treatment groups over the entire treatment period, ranging from -0.1 to 5.7%. None of the overall treatment comparisons were significant.

Asthma exacerbations: Overall, few patients (10) had an asthma exacerbation (13 episodes) during the 2-week randomized phase. Most of the 8 incidences of in-clinic exacerbations on 6 hour visit days were judged to be due to withholding anti-asthma medication. The albuterol CFC-treated group had fewer patients experiencing in-clinic exacerbations (1 patient) than those receiving albuterol HFA (2 patients) or placebo HFA (5 patients). The albuterol HFA-treated group had fewer patients experiencing out-of-clinic exacerbations (0%) compared with those receiving placebo HFA (2 patients; 5%) or albuterol CFC (3 patients; 7%).

Medical reviewer comment: *Counts of exacerbations by the medical reviewer disagreed with the sponsor's by one patient for selected values. These differences are not of any clinical significance.*

Safety Results

Extent of exposure

Mean duration of exposure was slightly lower in the placebo HFA group (14.0 days) compared to the albuterol HFA and albuterol CFC groups (15.1 and 15.3 days, respectively). This could be explained by the slightly higher dropout rate for the placebo HFA group (16%) than seen in the albuterol groups (11% each). In the albuterol CFC group 85% of the patients were exposed to study drug for >14 days, compared to 76% for placebo HFA patients and 78% for albuterol HFA patients.

Adverse Events

The number of patients who experienced at least one adverse event ranged from 14 (30%) in the albuterol HFA group, to 15 (35%) in the placebo HFA group, to 16 (35%) in the albuterol CFC group. No statistically significant differences among treatment groups were observed for the overall incidence of adverse events or for the incidence of adverse events by body system. Adverse events occurring in ≥5% of any patient group are described in the table below and demonstrate no statistically significant differences among the treatment groups. None is suggestive of a safety problem with albuterol HFA, in the opinion of the medical reviewer.

Most Common (≥5%) Adverse Events Occurring During Treatment Periods (Intent-to-Treat Population)

	Placebo HFA n=43	Albuterol HFA n=46	Albuterol CFC n=46
URTI	2 (5%)	1 (2%)	5 (11%)
Headache	4 (9%)	4 (9%)	3 (7%)
Gastrointestinal discomfort and pain	2 (5%)	1 (2%)	2 (4%)
Gastrointestinal signs & symptoms	2 (5%)	2 (4%)	0
Fever	2 (5%)	0	0

Note: Frequencies represent the number of patients having a particular adverse event.

Since adult 12 week protocols were suggestive of slightly greater rates of throat irritation and cough with albuterol HFA, related events were summarized by the medical Reviewer from tables 51 and 52 and follow below. Mild throat irritation was seen in 2 albuterol HFA patients, in 1 placebo HFA patient, and no albuterol CFC patients. One patient on albuterol HFA experienced throat constriction within 5 minutes of study drug administration, and 2 episodes of moderate larynx swelling and edema for which the timing in relation to dose was not specified. No action or comment was noted by the investigator about these events. All three events were resolved on the same day of onset, did not prompt study withdrawal, and were considered possibly related to study drug. Adverse events of cough were mild and similar in occurrence in the two albuterol treatment groups.

Adverse Events Occurring During Treatment Periods (Intent-to-Treat Population)

	Placebo HFA n=43	Albuterol HFA n=46	Albuterol CFC n=46
Throat irritation – mild	1 (2%)	2 (4%)	0
Throat constriction/larynx swelling & edema - moderate	0	1 (2%)	0
Cough – mild	0	1 (2%)	1 (2%)

Note: Frequencies represent the number of patients having a particular adverse event.

Two other adverse events were considered to be drug-related and were increased in the albuterol HFA group relative to the two other groups, but the number of patients was small. One patient (2%) experienced mild epistaxis and another (2%) experienced mild throat irritation within 15 minutes after taking study medication. These subjects had been on albuterol HFA for 1 day and 6 days, respectively. The events resolved and both patients completed the study.

Deaths, Serious Adverse Events, and Other Significant Adverse Events
There were no deaths during the study, and no serious adverse events associated with albuterol HFA treatment. The only patient withdrawal occurred in the albuterol CFC group, and was secondary to an asthma exacerbation. Five adverse events in 3 patients were noted to occur within 15 minutes of taking study medications (see following table). None of these patients withdrew because of adverse events.

Adverse Events Proximate to Post-Dose for Randomized Medications

Subject #	Adverse Event	# Days on Treatment	Severity	Study Drug Relationship	Treatment
3803	Sore Throat (throat irritation)	6	Mild	Possible	Albuterol HFA
3804	Throat Spasm (throat constriction)	3	Moderate	Possible	Albuterol HFA
3810	Headache Headache Headache	9 13 14	Mild Mild Mild	Unlikely Unlikely Unlikely	Placebo HFA

Medical Reviewer Comment: *Local reactions in the throat and larynx occurred in a few patients on albuterol HFA and none of the albuterol CFC patients. Despite the small numbers of patients affected, the timing of these events is suggestive of a causal relationship and they should be mentioned in the product labeling.*

Clinical Laboratory
Overall, the frequency of analyte changes was low and comparable between treatment groups and no trends were observed. Laboratory parameters with ≥1 patient in any treatment group outside the threshold range during the 2-week treatment phase are presented in the table below.

Labs Out-of-Threshold Range after Exposure to Study Drug

Abnormal Analyte	Placebo HFA	Albuterol HFA	Albuterol CFC
Decreased Neutrophils	1 (2%)	0	0
Elevated Lymphocytes	2 (5%)	0	0
Elevated Eosinophils	0	3 (7%)	3 (7%)
Elevated Total Bilirubin	0	0	1 (2%)
Elevated Glucose	1 (2%)	0	0

Source: Table 58

Medical Reviewer comment: *There are no clinical laboratory concerns for albuterol HFA.*

Electrocardiograms
No clinically significant ECG abnormalities were noted in either the albuterol HFA or the placebo HFA groups. Mean QTC intervals were similar among the treatment groups at Screen, Treatment day 1, and week 2 (see below). Mean changes in QTc interval were ≤4.8msec for each treatment group, with the exception of the discontinuation visit values based upon small numbers of

patients. Mean heart rates were consistent with the known pharmacodynamics of albuterol, with an increase in mean heart rate of 1–4 beats after dosing with either albuterol HFA or albuterol CFC, and a decline of about 1 beat in the placebo HFA group.

Mean QTc Intervals and Mean Change (msec) from Baseline for QTc intervals

Time	Placebo HFA	Albuterol HFA	Albuterol CFC
Run-In Phase			
Screening	418	417	418
Randomized Treatment Phase			
Visit 1, Pre-dose	422	415	416
Visit 1, Post-dose	420	418	419
Mean change from baseline	-2.2	3.1	3.0
Week 2, Pre-dose	420	417	419
Mean change from baseline	-2.2	1.7	1.4
Week 2, Post-dose	418	420	418
Mean change from baseline	-4.4	4.8	-0.1
Discontinuation Visit			
Discontinuation	427	415	422
# patients	6	4	4
Mean change from baseline	14.5	2.5	15.3

Source: Tables 60 & 61

Holter Monitoring

Analyses of Holter readings for VEs and SVEs showed no statistically significant differences among treatment groups at screening, treatment day 1, and treatment week 2. The median number of VEs was 0 in all groups at all three measurements, with a maximum mean value of 3.1 VEs in 6 hours (seen on treatment day 1 in the albuterol CFC group.) The median number of SVEs was ≤1 in all groups at all three measurements. One patient (on albuterol CFC) had a high maximum value at screening (1313 SVEs) and Treatment Day 1 (943 SVEs); these decreased to 1 SVE at treatment week 2.

Analysis of cardiac rates from the 3 treatment groups found no statistically significant treatment differences overall. Mean, minimum, and maximum cardiac rates in all 3 groups were within 2 beats of each other. On treatment day 1, mean heart rate in the albuterol HFA group was consistently 1 – 2 beats greater than the other 2 treatment groups throughout the 8 hour monitoring period. This difference was not statistically significant, nor was it seen at treatment week 2.

Pulse

The percentage of patients with increases in pulse ≥15, ≥20 and ≥30bpm was comparable between the albuterol treatment groups though higher than the placebo HFA group during the double-blind treatment period. Comparable numbers of patients (4 – 5 per treatment group) had increases in pulse ≥30bpm during the randomized treatment phase. The percentage of patients with decreases in pulse ≥15, ≥20, and ≥30bpm was comparable between treatment

groups. At each evaluation during the randomized treatment phase, mean pulse rates at baseline and 6-hour weighted average pulse rates were comparable among treatment groups and without statistically significant differences.

Blood pressure
The means and weighted average of serial systolic blood pressure readings were comparable across all treatment groups. Decreases in SBP ≥15mmHg were more common in the CFC albuterol group (50% of patients) than either the placebo or HFA albuterol groups (32 – 35% of patients). For diastolic blood pressure measurements, means of the three groups were comparable, although the CFC albuterol group had greater percentages of patients with increases in DBP ≥15mmHg (47%) and decreases ≥15mm Hg (37%) than seen in the placebo or HFA albuterol groups (range 15 – 26%). No statistically significant differences in treatment group means were seen for either SBP or DBP.

Physical Examination
Physical exam abnormalities were comparable among the treatment groups at baseline. Detrimental changes in exam occurred in a small number of subjects, and at similar rates among the group; in particular, unfavorable changes in ear, nose, and throat exam were comparable in all groups (10% in placebo patients, 15% in albuterol HFA patients, and 13% in albuterol CFC patients.)

Medical Reviewer Conclusions
When serial PEFR and FEV1 were assessed as the percentage of predicted values, albuterol HFA and albuterol CFC were both statistically superior to placebo. There were no statistically significant differences between the two albuterol groups, although the albuterol HFA group averaged 1 – 2 percentage points greater mean values than the albuterol CFC group. Secondary efficacy analyses which examined change and percentage change of PEFR and FEV1 were confirmatory of the primary efficacy analyses. Analyses of derived functions of serial PEFR and FEV1 showed albuterol HFA to be statistically superior to placebo in the percentage of patients achieving effect (≥15% increase over baseline), mean onset of effect, duration of effect, mean maximum effect, and mean AUC (bl). Albuterol CFC had a similar pattern of superiority to placebo, with the exception of the percent of patients achieving effect on treatment day 1, where statistical significance over placebo was not achieved. Duration of effect as measured by FEV1 and PEFR declined from treatment day 1 to treatment week 2 for both albuterol formulations.

Both albuterol formulations showed clear numeric superiority to placebo patients in AM and PM PEFR, back up albuterol use, and asthma symptom scores; for albuterol HFA, all these differences were statistically significant. Nighttime awakenings were comparable among the 3 treatment groups during the course of the trial.

Headache was the only common (≥5%) adverse event that occurred in more albuterol HFA than albuterol CFC patients (7%), and the rate of this was the same as in placebo HFA patients (9%). Throat irritation and larynx constriction/swelling/edema occurred in a total of 2 patients proximate to albuterol HFA dosing, and was not seen in either the CFC albuterol or placebo groups. Laboratory exams and cardiac evaluations revealed no concerning abnormalities. Vital signs and physical exams were likewise unremarkable.

The results of this study indicate that:

- *Compared with placebo HFA, both albuterol 200mcg in propellant HFA QID and albuterol 200mcg in CFC propellant CFC QID produced clinically and statistically significant improvements in pulmonary function.*
- *Treatment with albuterol 200mcg in HFA propellant QID is safe and well tolerated.*
- *Both albuterol 200mcg in propellant HFA QID and albuterol 200mcg in CFC propellant CFC QID produced clinically comparable improvements in pulmonary function in pediatric patients aged 4-11 years, with asthma.*

APPEARS THIS WAY
ON ORIGINAL

SALB2001

A Single-Centre, Randomised, Double-Blind, Placebo Controlled, Cross-Over Study to Compare the Protective Effect of Single Doses of Salbutamol Administered by Pressurised Inhaler Propelled by a Mixture of Propellants 11 and 12 or by an Alternative Propellant GR106642X Against Exercise-Induced Bronchospasm in Patients with Reversible Airways Obstruction.

Study Objective

The primary objective of the study was to compare the bronchoprotective effect of single doses of albuterol HFA with albuterol CFC against exercise-induced bronchospasm.

PROTOCOL

Study Design

This study used a single-center, randomized, double-blind, placebo controlled and three-way crossover design. A screening (run-in) period of 1 – 14 days was followed by three treatment visits, each separated by 1- 14 days. Seven to 14 days after the last treatment visit was a follow-up visit. The 5 scheduled clinic visits were as follows: a screening visit (Clinic Visit 1) at the start of the screening period, three treatment visits (Clinic Visits 2-4), and a follow-up visit (Clinic Visit 5).

Repeat treatment visits were allowed up to two times if the predose FEV1 at that visit varied by >15% in comparison to the screening visit. Approximately 30 adult and adolescent asthmatics were targeted for enrollment. Patients withheld all short-acting β-agonists throughout the trial with the exception of Ventolin MDI on a PRN basis. Subjects were randomized at treatment visit 1 (clinic visit 2) to receive single doses (2 puffs) of the following at clinic Visits 2-4 :

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

Study Population

Patients were male and female asthmatics aged 12 – 45 years with baseline FEV1≥65% and demonstrated exercise-induced bronchospasm (EIB)≥20% on screening evaluation. Typical inclusion and exclusion criteria were applied to exclude unstable asthmatics, those with other serious or complicating medical illnesses, and those with a recent URTI or sinusitis. Patients were withdrawn form the study if their highest pre-dose FEV1 was >15% of the highest 5-minute pre-exercise FEV1 established at screening.

Intranasal forms of steroids and cromolyn were allowed throughout the study without any washouts. Inhaled corticosteroids, cromolyn, long-acting β-agonists, inhaled anticholinergics, methylxanthines, and leukotriene antagonists were all

allowed as long as appropriate washout periods had passed prior to clinic visits. If the inhaled steroid dose was increased for an exacerbation, only courses ≤7 days were allowed and the dose had to be reduced to that prior to the exacerbation, otherwise the patient was withdrawn from the study.

Inhaled short-acting β-agonists of any kind were NOT allowed at any time during the study. Neither were oral/parenteral corticosteroids, nor could they have been used within 1 month of the screening visit.

Study Treatments

A treatment pack containing one inhaler was supplied to each subject at each treatment visit. Study medications came from the following batches:

Trial medication details					
Product	**Strength (per dose)**	**Packaging**	**Inhaler**	**Batch no.**	**Expiry date**
Albuterol HFA	100mcg*	200 dose	Pressurised metered-dose inhaler	6ZX012B	31 March 1998
Albuterol CFC	100mcg*	200 dose	Pressurised metered-dose inhaler	5Z1162P	30 June 1998
Placebo HFA	-	200 dose	Pressurised metered-dose inhaler	6ZX011A	31 July 1998**

*The dose of medication quoted is ex-valve. The corresponding ex-actuator dose is 90mcg.

At each treatment visit where exercise challenge was done, subjects took 2 actuations (each one minute apart) from the inhaler. Dosing was done 30 minutes prior to exercise challenge, so that the 5-minute pre-exercise FEV1 was determined at 25 minutes post-dose.

Definition/Management of Acute Asthma Exacerbations

For the purpose of the study, an acute exacerbation of reversible airways obstruction was considered to be a worsening of symptoms which required an increase in use, or change in the subject's regular medication for reversible airways obstruction. The need for VENTOLIN alone during a clinic visit was considered as a worsening of symptoms only and not an acute exacerbation.

The following actions were recommended if an exacerbation occurred:

Exacerbation Timing	**Action**
During screening period	Discontinue patient from study
Between treatment clinic visits	Continue only if ≤7d use of an additional β-agonist; assess EIB ≥5d after last dose of additional med
	If increased steroid or antibiotics given, dose ≤7d and assess EIB ≥5d after last antibiotic or ≥14d after last increased steroid dose
During clinic visit	If required more than Ventolin MDI or nebulization, any drug could be used and event considered to be an acute exacerbation

Efficacy Measures
The primary efficacy endpoint for the study was the maximum percentage fall in FEV_1 post-exercise when compared to the pre-exercise FEV1 determined at 25 minutes dosing and 5 minutes before exercise. At each exercise challenge conducted with a study treatment, patients had to have a pre-dose FEV1 that was within 15% of the pre-exercise FEV1 established at screening. Patients who did not meet these criteria were allowed 2 additional opportunities per clinic visit before being discontinued from the study.

Patients were administered study drug 25 minutes before pre-exercise FEV1 was determined (which was 5 minutes before exercise.) A standardized treadmill challenge was used so that patients exercised at least 6 minutes at ≥80% of their maximum predicted heart rate [49:31]. The temperature and humidity of the inspired air were controlled during exercise.

After the exercise challenge test, triplicate FEV_1 and FVC maneuvers were measured at 5, 10, 15, 20, 25, 30 and 60 minutes post-exercise. At each time point, the highest of the triplicate FEV_1 maneuvers was recorded in the CRF. The maximum percentage fall in FEV_1 from baseline was calculated using the following equation:

$$\frac{\text{5 minute pre-exercise } FEV_1 - \text{Lowest post-exercise } FEV_1}{\text{5 minute pre-exercise } FEV_1} \times 100$$

In this equation, pre-exercise FEV1 is the value obtained 25 minutes post-dosing (that is, 5 minutes before exercise). The secondary efficacy endpoint was the FEV_1 value recorded 5 minutes pre-exercise (that is, 25 minutes post-dosing) with study medication.

Safety Assessments
Safety was assessed via adverse events monitoring and serial vital signs during clinic visits. Clinical labs, ECGs, and physical examinations were performed at the screening visit to assess whether patients should participate in the trial. During the exercise challenge test, subjects were connected to an ECG monitor so that the heart rate could be monitored and recorded at specified time points.

Sample Size and Data Analysis
The sample size of 24 subjects had ≥80% power to detect a significant difference of 12% in the maximum percentage fall in FEV1; this was based upon a standard deviation of 14% in the maximum percentage fall. Missing data due to rescue VENTOLIN use was replaced with the last value of FEV1 recorded prior to VENTOLIN use.

Medical officer comment: *The LVCF approach is an appropriate technique for handling missing data. Such an approach may underestimate the maximum fall*

in FEV1, but if rescue VENTOLIN use occurred more likely during the placebo period, the direction of the bias would be towards the null hypothesis of no effect.

The primary analysis was an analysis of variance (ANOVA) appropriate for a crossover model with terms for subject, period and treatment. The treatment by period interaction term and first-order carryover effects were both investigated. Three pairwise comparisons were tested:

- Placebo versus (vs) 200mcg albuterol HFA
- Placebo versus (vs) 200mcg albuterol CFC
- 200mcg albuterol CFC vs 200mcg albuterol HFA

As a secondary analysis, paired comparisons of percentage fall in FEV_1 were conducted using a non-parametric crossover analysis based on the Wilcoxon Rank Sum (also known as the Wilcoxon-Mann-Whitney test), stratified by the period of the treatment not in the comparison. The same 3 sets of pairwise comparisons as the primary analysis were performed. No adjustments were made for multiplicity.

Medical Officer Check of Study Conduct

No patients were discontinued from the trial, so no case report forms were available to check the randomization or primary data values against the line listings. A total of 7 subjects deviated from the protocol, three of them on more than one occasion. The most common violation (9 times in 6 subjects) was initiation of FEV1 measurements more than 2 hours outside the allowed time frame in relation to the screening visit. In one patient, the time deviation occurred consistently at all treatment visits and ranged from 41 to 91 minutes. The only other violation of note was the accidental continuation of a subject whose predose FEV1 was >15% (32.3%) of the preexercise screening FEV1. All subjects were included in the efficacy analysis.

Medical Officer Comment: *The protocol violations are minor and should not materially affect the results of the study.*

Results

Study Population

Of 53 subjects recruited to the study, 24 were randomized. Of these, 23 patients received all three treatments. One patient was withdrawn after two treatment arms (CFC albuterol and placebo), when predosing FEV1 values at the third treatment visit were not within 15% of the preexercise FEV1 from screening visit.

Demographics

Of the 24 subjects, 18 (75%) were male and 20 (83%) were Caucasian/white. Four subjects were Asian. Mean age was 27 years (range 19 to 45 years). The majority (54%) reported a history of asthma >15 years. Current medical conditions were largely allergies and ENT conditions. On physical exam, 6

subjects had either mild wheezing or decreased air entry described. Two subjects (8%) and eight subjects (33%) continued using their long-acting β2-agonist and inhaled corticosteroids into the treatment period respectively. Five (21%) subjects were considered to have changed their asthma medication during a treatment period by taking their rescue VENTOLIN at a treatment visit for worsening of asthma symptoms following exercise challenge (see "Exacerbations/Worsening Of Asthma Symptoms".)

Efficacy Findings

Maximum Percentage Fall in FEV1 Post-Exercise

Adjusted means of the maximum percentage fall in FEV1 post-exercise were based on estimates of the population means after adjusting sample means for subject and period via the ANOVA model, and were as follows:

Placebo HFA	33.7%
Albuterol HFA	15.4%
Albuterol CFC	14.9%

The percentage fall in the placebo group was significantly greater ($p<0.001$) than both albuterol formulations. Albuterol CFC and HFA performed similarly, and there was no statistically significant difference between them.

Medical officer inspection of individual subjects' unadjusted FEV1 values [Listing 10, 49:107ff] confirmed the overall conclusions of the ANOVA analyses. There was only one instance where a subject (#874) had a clear response to CFC albuterol but did respond to HFA albuterol. In this subject, the maximum fall in FEV1 was 25% at baseline, 28% with placebo, 23% with albuterol HFA, and 5% with albuterol CFC. Analysis of the crude FEV1 values according to whether or not the FEV1 fell ≥20% yielded the results displayed in the following table.

Number/Percent of Patients with a Maximum Post-Exercise Fall in FEV1 ≥20%

Baseline	Placebo	Albuterol HFA	Albuterol CFC
24/24 (100%)	19/24 (79%)	9/23 (39%)	9/24 (38%)

Secondary analyses of maximum percentage fall in FEV1 based on non-parametric analyses were confirmatory of the parametric ANOVA analyses. The following table these analyses based upon medians for the 3 treatment groups.

Non-Parametric Analyses of Maximum Post-Exercise Fall in FEV1

	Placebo	Albuterol HFA	Albuterol CFC
Raw medians	30.2	6.8	6.5
Frequency Distribution			
Max % Fall ≤10	1 (4%)	13 (57%)	13 (54%)
10<Max % fall ≤20	4(17%)	1 (4%)	3 (13%)
Max % fall >20	19 (79%)	9 (39%)	8 (33%)
Median difference vs. control	N/A	-17.0% (p<0.001)	-19.8 (p<0.001)
Median difference vs. HFA alb	N/A	N/A	-0.6% (p=0.638)

Secondary Efficacy Measure (Pre-Exercise FEV1)
The secondary efficacy measure was the FEV1 value recorded 25 minutes post dosing/5 minutes pre-exercise. The adjusted estimates of population FEV1 means using ANOVA to adjust for subject and period were as follows:

Placebo	3.70 L
Albuterol HFA	4.07 L
Albuterol CFC	4.13 L

The adjusted mean for the subjects receiving placebo HFA was 3.70 L, which was significantly lower than both active treatments (p<0.001 for both pairwise comparisons between placebo and active treatments). Albuterol HFA was comparable in effect to albuterol CFC, and there was no statistically significant difference between them.

Safety Findings

Extent of exposure
24 subjects each were exposed to placebo and albuterol CFC. 23 subjects were exposed to albuterol HFA since one patient was withdrawn when her pre-dosing FEV1 at the third treatment visit was repeatedly >15% of the screening value.

Adverse Events
Adverse events were categorized according to whether they occurred pre-treatment, during treatment, or post-treatment. During treatment events occurred after dosing with study medication up until midnight (inclusive) of the day of treatment visit; post-treatment events occurred any time after midnight of and until the time of administration of the next study treatment.

Prior to the first study medication administration, 6 subjects reported adverse events. The adverse events were URTI (3 subjects), throat irritation (2 subjects), cough (1 subject), vomiting (1 subject) and musculoskeletal pain (1 subject). During treatment, 1 patient (after exposure to albuterol HFA) reported epistaxis which occurred more than 4 hours after dosing and was not considered to be drug related. No adverse events occurred within 15 minutes of dosing of any study medication. Post-treatment adverse events occurred in 1 placebo patient (URTI), one albuterol HFA patient (headache), and 4 albuterol CFC patients (1

each URTI, headache, tonsillitis, and contusions/hematomas.) The following table describes the adverse events which occurred during and/or after study medication. No drug-related adverse events were reported during this combined period.

Number (%) Of Patients Experiencing A Particular Adverse Event During/Post Treatment

	Placebo	Albuterol HFA	Albuterol CFC
Number of patients (n)	24	23	24
Number of patients with adverse events	1 (4%)	2 (9%)	4 (17%)
EAR NOSE & THROAT Any event	1 (4%)	1 (4%)	2 (8%)
Upper respiratory tract infection (URTI)	1 (4%)	0	1 (4%)
Epistaxis	0	1 (4%)	0
Tonsillitis	0	0	1 (4%)
Headaches	0	1 (4%)	1 (4%)
Contusions & hematomas	0	0	1 (4%)

No deaths, serious adverse events, pregnancies, or withdrawals due to adverse events occurred during the trial.

Vital Signs

A small number (1 –2 patients in each treatment group) exceeded predefined threshold values of SBP, DBP, and pulse. The pattern and duration of these excesses raised no safety concerns in the opinion of the medical reviewer. When each of these parameters was analyzed according to changes ≥10% pre-exercise values, the 3 treatment groups yielded comparable numbers of affected patients as seen in the following tables. The majority of these values were above the pre-exercise values.

Subjects with Values ≥10% More or Less than Pre-Exercise Values

	Placebo	Albuterol HFA	Albuterol CFC
Number of patient (ITT)	24	23	24
Pulse	14	15	12
Systolic Blood Pressure	5	6	4
Diastolic Blood Pressure	8	11	8

Exacerbations/Worsening of Asthma Symptoms

No subject experienced an exacerbation of his or her asthma during the study. Five subjects in the Intent-to-Treat Population experienced a worsening of symptoms following the exercise test. Three subjects experienced a worsening of symptoms following treatment with placebo, and one subject each experienced a worsening of symptoms following treatment with 200mcg albuterol HFA and 200mcg albuterol CFC.

Medical Officer Conclusions

This study compared the bronchoprotective effect of single doses of albuterol HFA and CFC in 24 adolescent and adult patients with exercise-induced bronchoconstriction. Analysis of the primary efficacy variable of the maximum

percentage fall in FEV_1 post-exercise demonstrated that 200mcg albuterol HFA and 200mcg albuterol CFC produced statistically significant greater protection against exercise-induced bronchoconstriction when compared to placebo HFA ($p<0.001$). Comparison of the 200mcg dose of both albuterol formulations showed comparable protection ($p=0.848$; 95% CI-5.3 to 4.4 %). These results were further supported by the statistical results of the non-parametric analysis.

The results of the statistical analysis for the secondary efficacy variable showed that both formulations of albuterol had a significantly greater effect on the pre-exercise FEV_1 when compared to placebo HFA ($p<0.001$), and at a dose of 200mcg showed comparable clinical effect ($p= 0.360$; 95% CI –0.06 to 0.17L). Overall, the incidence of adverse events on the day of treatment with study medication was very low with only one subject reporting an adverse event after receiving 200mcg albuterol HFA. Similarly the incidence of post-treatment adverse events was very low. There were no deaths, unexpected, serious, proximate or drug related adverse events reported, no pregnancies and no reports of paradoxical bronchospasm.

Only one subject was withdrawn from the study following randomization, due to the 15 minute pre-dosing FEV_1 being >15% of the 5 minute pre-exercise FEV_1 at the screening or repeat screening visit. There were no notable differences between treatments for the vital sign parameters measured. Although there were a number of the vital sign parameters which at 60 minutes post-exercise, had not returned to the pre-exercise value, there were no differences between treatment groups.

No subject experienced an exacerbation of their asthma during the study or post exercise, but five subjects experienced a worsening of their asthma symptoms post-exercise at the clinic visit. Three of these subjects had received placebo HFA.

The results of the study demonstrate that single doses of 200mcg albuterol formulated with GR106642X and albuterol formulated with propellants 11 and 12, showed a comparable bronchoprotective effect against exercise-induced bronchoconstriction at the same dose in adult asthmatics.
No notable difference in the safety was seen in this population of subjects between albuterol HFA and albuterol CFC, and both were comparable to placebo HFA.

SALA 3003

A 12-Month, Open-Label Trial To Assess The Long-Term Safety Of Albuterol 200 Mcg QID In GR106642X Propellant Via The MDI In Adolescent And Adult Subjects With Asthma

OBJECTIVES
To assess the long-term safety of albuterol 200 mcg in HFA propellant (GR106642X) administered QID via MDI for 12 months in an open-label trial

Study Design
This 12-month, open-label multicenter trial enrolled >400 asthmatics patients ≥12 years of age with FEV1 ≥60% predicted and documented reversibility ≥15% to Ventolin in CFC propellant. After a 5 –14 day run-in period between the screening visit and visit 1, patients demonstrating appropriate asthma stability and compliance were assigned to open label albuterol HFA for QID and PRN use. Clinic visit 2 occurred 2 weeks after visit 1; subsequent visits (3 – 15) occurred every 4 weeks through week 52 (Visit 15). No efficacy measurements were performed. After 21 sites began enrollment (approximately 2.5 months after study initiation), the protocol was amended to include specific worksheet and investigator queries about how the subject felt after each dose of study medication.

Concomitant Medications
The following medications were withheld prior to screening and for the duration of study participation:

- Any form of inhaled or oral beta-agonists, including long-acting formulations.
- Oral or parenteral atropine
- Inhaled ipratropium
- Oral or parenteral steroids (short courses of oral steroid bursts were allowed for asthma exacerbations)
- β-antagonists, TCAs, and MAOIs

The following drugs were allowed during the course of the study provided each was withheld for appropriate intervals prior to each clinic visit.

- Inhaled, intranasal, or topical corticosteroids
- Cromolyn and nedocromil (all forms)
- Antihistamines and decongestants, short and long-acting
- Theophylline, all forms

Asthma exacerbations were allowed to be handled by the investigator with therapy that was "deemed appropriate". If multiple exacerbations occurred that required oral steroids, the sponsor reviewed whether the subject should continue participation in the study.