

Figure 7  
 Change from Same Day Baseline Serial FEV<sub>1</sub> (liters)  
 Treatment Week 5

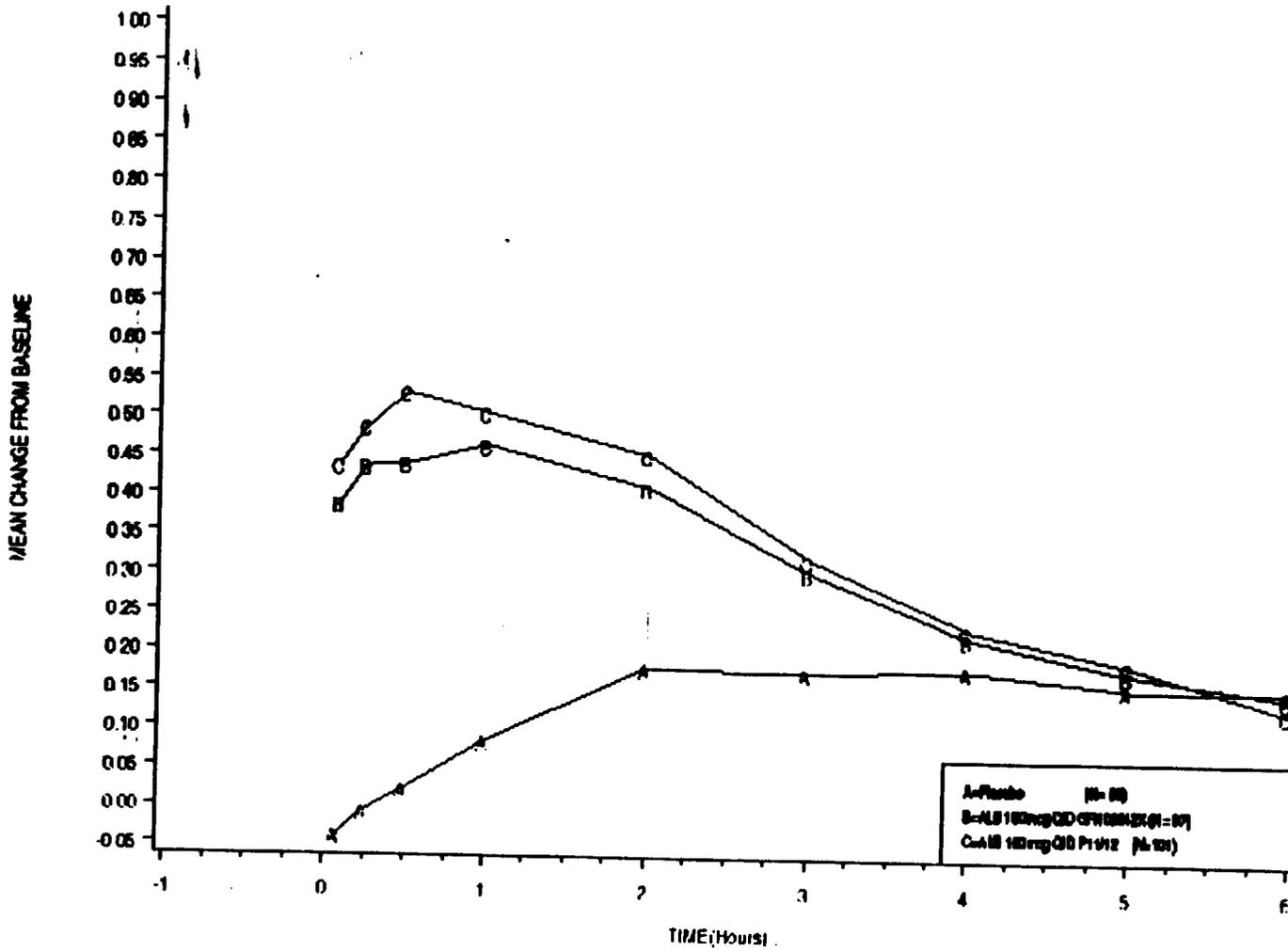
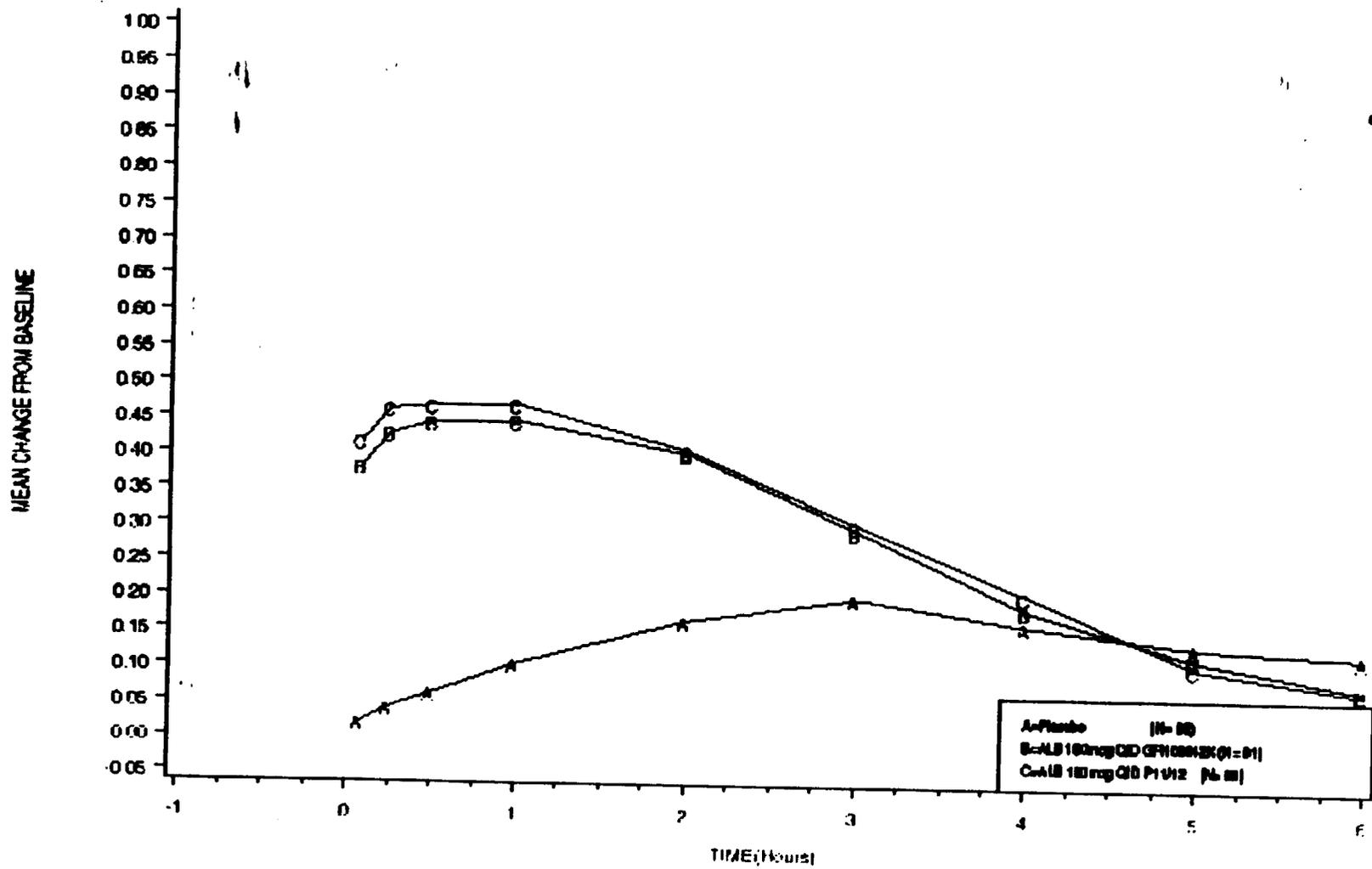


Figure 3  
 Change from Same Day Baseline Serial FEV<sub>1</sub> (liters)  
 Treatment Week 12



Related analyses of FEV1 by using treatment day 1 as the baseline or by looking at changes in percent predicted FEV showed albuterol CFC and HFA to be numerically superior to placebo. Statistically significant improvements over placebo were mostly confined to the treatment day 1 comparisons for both formulations because of the changing baseline FEV1 seen across all groups; none of the week 6 comparisons to placebo showed statistical significance. At week 12, both albuterol formulations were statistically superior to placebo in mean change from treatment day 1 baseline, but only albuterol CFC showed statistical improvement in percent predicted FEV1.

Analyses of functions of serial FEV1 confirmed albuterol CFC and HFA superiority to placebo, but revealed some performance differences between albuterol HFA and albuterol CFC as shown below.

**Analysis of Functions of 6-Hour Serial FEV<sub>1</sub>**  
(Includes sites 1415 & 5348)

Function	Week:	Placebo GR106642X				Albuterol GR106642X				Albuterol P11/12			
		A <sup>1</sup>	1	6	12	A <sup>1</sup>	1	6	12	A <sup>1</sup>	1	6	12
% Patients Achieving Effect		61	18	4	9	70	77	55	61	70	81	68	60
% Pts with WAVE ≥15% over base		44	19	16	16	42	47	30	32	42	56	42	34
Median Onset of Effect (hr)		0.09	6.00	6.00	6.00	0.08	0.07	0.38	0.20	0.07	0.06	0.07	0.16
Median Duration of Effect (hr)		1.56	0.00	0.00	0.00	2.54	2.93	0.40	1.03	2.66	3.67	1.97	1.84
Mean Max Effect (% chg from base)		27.3	14.3	13.0	13.4	27.0	28.1	23.4	22.9	30.1	30.1	27.1	23.4
Median Time of Max Effect (hr)		1.0	3.0	4.0	3.0	1.0	1.0	1.0	1.0	0.5	1.0	0.5	1.0
Mean AUC(bl) (L-hr)		2.06	0.84	0.84	0.83	2.01	2.48	1.84	1.70	2.15	2.72	1.99	1.74
Mean Change in AUC(bl) from Visit A		—	-1.2	-1.3	-1.2	—	0.4	-0.1	-0.3	—	0.6	-0.2	-0.5

All patients received albuterol P11/12 at Visit A, but are displayed according to their future randomized treatment group.

WAVE = weighted average of post-dose FEV<sub>1</sub> measurements over 6 hours. Source Data: Tables 34-41

The percent of patients with ≥ 15% increase in FEV1 within 30 minutes of treatment or by WAVE was typically lower for albuterol HFA than albuterol CFC, particularly at week 6. Median onset of effect with albuterol HFA was later, duration of effect shorter, peak effect smaller, and AUC (bl) less than seen in albuterol CFC, but these differences between the albuterol formulations were not statistically significant. Analyses of these variables without data from the two suspect investigators (see following table) also showed numerically (but not statistically) poorer response of albuterol HFA when compared to albuterol CFC,

particularly at week 6. Differences between Ventolin HFA and placebo nonetheless remained statistically significant.

**Means or medians of derived variables from Serial FEV<sub>1</sub> (l/min) and p-values**

Variable	Treatment group			P-value		
	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb CFC
<b>Treatment Day 1</b>						
Onset ( hours)	6.00	0.07	0.06	<0.001	<0.001	0.205
Duration (hours)	0.00	3.09	3.67	<0.001	<0.001	0.198
Peak ( % change)	14.0	28.1	30.2	<0.001	<0.001	0.209
Time to Peak (hours)	3.0	1.0	1.0	<0.001	<0.001	0.653
AUC (bl) (%)	0.81	2.49	2.72	<0.001	<0.001	0.249
<b>Treatment Week 6</b>						
Onset ( hours)	6.00	0.38	0.07	<0.001	<0.001	0.113
Duration (hours)	0.00	0.40	1.97	<0.001	<0.001	0.325
Peak ( % change)	13.0	23.6	27.5	<0.001	<0.001	0.081
Time to Peak (hours)	4.0	1.0	0.5	<0.001	<0.001	0.789
AUC (bl) (%)	0.83	1.86	2.00	<0.001	<0.001	0.522
<b>Treatment Week 12</b>						
Onset ( hours)	6.00	0.18	0.11	<0.001	<0.001	0.849
Duration (hours)	0.00	1.03	1.65	<0.001	<0.001	0.484
Peak ( % change)	13.4	23.2	23.5	<0.001	<0.001	0.777
Time to Peak (hours)	3.0	1.0	1.0	<0.001	<0.001	0.656
AUC (bl) (%)	0.82	1.72	1.78	0.001	<0.001	0.634

Patients who did not respond with  $\geq 15\%$  increase in FEV<sub>1</sub> were assigned an onset time of 6 hours, which introduced a skew into the calculation of means. For this reason, the sponsor used median values for comparing onset and duration of action. Mean values provided by the sponsor for comparison are displayed in the table below; these data exclude sites #1415 and #5348.

**Analysis of Timed Functions of 6-Hour Serial FEV<sub>1</sub>  
(Excludes sites 1415 & 5348)**

Function	Placebo GR106642X				Albuterol GR106642X				Albuterol P11/12			
	Week: A <sup>1</sup>	1	6	12	A <sup>1</sup>	1	6	12	A <sup>1</sup>	1	6	12
Mean Onset of Effect (hr)	2.22	4.90	5.72	5.48	1.92	1.45	2.65	2.37	1.77	1.15	1.96	2.50
Mean Offset of Effect (hr)	4.70	5.46	5.93	5.79	4.55	4.51	4.85	4.31	4.63	4.41	4.42	4.70
Mean Duration of Effect (hr)	2.48	0.57	0.21	0.31	2.63	3.07	2.20	1.94	2.86	3.26	2.46	2.20
Mean Time of Max Effect (hr)	1.5	2.9	3.4	2.9	1.4	1.5	1.1	1.4	1.0	1.3	1.2	1.2

<sup>1</sup>All patients received albuterol P11/12 at Visit A, but are displayed according to their future randomized treatment group.

WAVE = weighted average of post-dose FEV<sub>1</sub> measurements over 6 hours. Source Data: 4/19/99 response to FDA request

Analysis of responders (patients with  $\geq 15\%$  increase in FEV<sub>1</sub>) over 6 hours post dose showed both albuterol HFA and CFC groups had substantially greater percentages of responders than placebo. Compared to run in albuterol CFC at Visit A, both CFC and HFA albuterol had more responders at treatment day 1 but somewhat less at treatment weeks 6 and 12. Albuterol CFC had higher percentages of responders at all time points than albuterol HFA except for 15 minutes on treatment day 1 and 6 hours on treatment weeks 6 and 12 ( see below).

Percentage of Patients With  $>15\%$  Increase in FEV<sub>1</sub> Over Time

Timepoint	Week:	Placebo GR106642X				Albuterol GR106642X				Albuterol P11/12			
		A <sup>1</sup>	1	6	12	A <sup>1</sup>	1	6	12	A <sup>1</sup>	1	6	12
5 min		49	7	1	5	56	63	41	44	59	67	53	46
30 min		53	13	3	7	64	70	49	57	66	75	65	59
1 hr		59	13	8	13	62	71	51	54	65	74	61	61
3 hr		48	28	20	23	47	53	34	37	48	59	44	43
6 hr		28	19	21	17	22	30	24	16	28	33	19	11

<sup>1</sup>All patients received albuterol P11/12 at Visit A, but are displayed according to their future randomized treatment group. Source Data: Tables 42-45

Restricting analysis to only those patients who responded to albuterol within 30 minutes eliminated the differences in onset of effect and reduced the differences in median duration of effect. The sponsor speculated that some patients may not have achieved effect because of increases in baseline FEV<sub>1</sub> over time so that patients were at or near their ceiling of effect. In fact, the baseline of the albuterol HFA group at week 6 was about 100 cc greater than the CFC treatment group.

#### Secondary Efficacy Endpoints

Patient-recorded AM and PM PEF<sub>R</sub> changed only slightly and comparably for all treatment groups over the 12 week treatment interval. Switching propellants had no effect on AM or PM PEF<sub>R</sub>. Back up albuterol use was significantly greater in the placebo group than the HFA and CFC albuterol groups as measured by mean number of puffs and percentage of days without back-up albuterol use (see table below.)

Back-up Albuterol Use: Summary of Mean Changes from Baseline Puffs of Albuterol/ % Days with No Back-up Albuterol Use

Treatment Period	Placebo			Albuterol HFA			Albuterol CFC		
	N	# puffs	% days	N	# puffs	% days	N	# puffs	% days
Run-In Phase									
Baseline <sup>1</sup> (actual value)	104	(1.2) <sup>†</sup>	(57.0)	101	(1.1)	(61.6)	108	(1.3)	(55.3)
Randomized Treatment Phase									
Weeks 1-3	102	1.3	-16.3	101	0.2*	-4.3*	108	-0.1*#	6.0*#
Weeks 4-6	97	1.2	-14.6	100	0.1*	-3.1	105	-0.1*	7.7*#
Weeks 7-9	93	1.1	-13.9	98	0.1*	-1.1*	101	-0.2*	9.1*#
Weeks 10-12	89	1.1	-13.7	94	0.0*	1.8*	100	-0.1*	9.7*#
Weeks 1-12	103	1.2	-15.1	101	0.1*	-1.4*	108	-0.1*	7.4*#

Note: % days = percent of days with no back-up albuterol use

Source Data: Tables 50-53

<sup>1</sup>Baseline is the average of the 3-week run-in phase where all patients received albuterol P11/12.

\*p $\leq 0.015$  compared with placebo GR106642X, #p $\leq 0.030$  compared with albuterol GR106642X

Compared to the HFA albuterol group where days without backup albuterol declined during therapy, the CFC albuterol group had an increase that was significantly greater.

**Medical Officer Comment:** *Greater use of back up albuterol is consistent with the smaller median duration of effect seen with HFA albuterol in comparison with CFC albuterol.*

Patient-rated asthma symptom scores (from 1 to 4, with 4 representing the worst symptoms) varied negligibly between treatment arms, with mean changes of 0.0 or 0.1 during randomized treatment. The percentage of symptom free days (not specified but presumably the percentage of days where patients rated their symptoms as no symptoms at all; unrestricted activity) also displayed a numeric advantage of albuterol CFC over the HFA formulation. This may be explained by the higher baseline value in the albuterol HFA arm.

**Asthma Symptoms**  
**Mean Percentage Change in Symptom-Free Days**

Treatment Period	Placebo GR106642X		Albuterol GR106642X		Albuterol P11/12	
	N	% days	N	% days	N	% days
<b>Run-In Phase</b>						
Baseline <sup>1</sup> (actual value)	104	(25.3)	101	(28.9)	108	(24.9)
<b>Randomized Treatment Phase</b>						
Weeks 1-3	102	-0.3	101	0.9	108	3.5
Weeks 4-6	97	2.2	100	0.1	105	6.1
Weeks 7-9	93	2.9	98	4.1	101	7.1
Weeks 10-12	89	3.2	94	4.1	100	6.6
Weeks 1-12	103	1.4	101	2.5	108	5.3

Note: % days = percent of symptom-free days

<sup>1</sup>Baseline is the average of the 3-week run-in phase where all patients received albuterol P11/12.

Source Data: Tables 54-57

The percent of nights with no awakenings due to asthma declined slightly from baseline in all 3 treatment groups. The placebo group had a decrease of 1.9%, the albuterol HFA group 1.0%, and the albuterol CFC group a decrease of 0.1%.

Asthma exacerbations were defined to include exacerbations requiring additional medications outside of clinic visits as well as the use of PRN albuterol during clinic visits where serial spirometry was conducted. During the 12-week randomized treatment phase, total exacerbations were more common in placebo-treated patients (22 patients; 21%) compared with those in the albuterol HFA group (9 patients; 9%) or the albuterol CFC group (13 patients; 12%). Similarly, slightly more patients receiving placebo (8; 8%) had out-of-clinic exacerbations compared with those receiving albuterol HFA (4 patients; 4%) or albuterol CFC (5 patients; 5%). The incidence of asthma exacerbations was comparable between the two albuterol treatment groups.

## Safety Findings

### Extent of Exposure

Mean duration of exposure was slightly lower in the placebo GR106642X group (76.9 days) compared with the albuterol GR106642X and albuterol P11/12 groups (81.6 and 80.9 days, respectively). Patients treated with albuterol P11/12 or albuterol GR106642X on the QID regimen received 8 actuations (800mcg ex-valve) per day based on 97%+ compliance. Patients treated with placebo received 8 actuations of GR106642X propellant alone and on average 2.4 actuations/day of back-up albuterol GR106642X. The albuterol treatment arms each used an average of 1.2 actuations/day of back up albuterol in matching propellant.

### Adverse Event Data

#### Run-In Period

Adverse events were seen in 41% of the patients who discontinued during the run-in phase, and in 38% of the patients who completed the run-in phase. Among the patients who completed the run-in phase, there were some variations across the treatment groups, even though all were receiving CFC albuterol. The future placebo group had a significantly lower rate overall of AE during run-in (31%) than did the future albuterol HFA group (46%). Headaches, URTI and throat irritation were more common in the "future" albuterol HFA treatment group. Severe AE were infrequent, but again were greater in the future albuterol HFA group (6%) than either of the other two future treatment groups (2% in each). Headaches or migraine were the most commonly listed events in the severe category, occurring in 6 of the 10 patients.

The following table summarizes adverse events with an incidence of  $\geq 5\%$  in any treatment group during the run-in and treatment phases of the study.

**Most Common ( $\geq 5\%$ ) Adverse Events Occurring During Run-in and Treatment Phases (Intent-to-Treat Population)**

Adverse Event	Run-in Phase			Randomized Treatment Phase		
	(Placebo GR106642X)	(Albuterol GR106642X)	(Albuterol P11/12)	Placebo GR106642X	Albuterol GR106642X	Albuterol P11/12
Headache	8 (8%)	13 (13%)	11 (10%)	14 (13%)	14 (14%)	14 (13%)
URTI	2 (2%)	7 (7%)	3 (3%)	20 (19%)	25 (25%)	28 (26%)
Throat Irritation	1 (<1%)	7 (7%)	3 (3%)	7 (7%)	8 (8%)	4 (4%)
Sinusitis	—	—	—	8 (8%)	6 (6%)	2 (2%)
UR Inflammation	0	4 (4%)	0	2 (2%)	4 (4%)	6 (6%)
Viral Respiratory Infection	1 (<1%)	1 (<1%)	2 (2%)	3 (3%)	9 (9%)	5 (5%)
Bronchitis	1 (<1%)	0	1 (<1%)	5 (5%)	0	1 (<1%)
Musculoskeletal Pain	4 (4%)	2 (2%)	2 (2%)	6 (6%)	4 (4%)	4 (4%)

All patients received albuterol P11/12 during run-in, but are displayed according to their future randomized treatment group.

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

Source Data: Tables 64 and 66

### Randomized Treatment

Overall, the incidence of specific adverse events was similar among treatment groups (see table above). The most common adverse events during the double blind treatment phase were URTI (19-26%) and headache (13-14%). The incidence of throat irritation was low and comparable across treatment groups although slightly higher in the placebo GR106642X (7%) and albuterol GR106642X (8%) groups than in the albuterol P11/12 group (4%).

The majority of patients in each treatment group experienced at least one AE after exposure to double-blind study medication, ranging from 64 (59%) in the albuterol P11/12 group to 72 (69%) in the placebo GR106642X group (Table 66). In each treatment group, body systems with the highest incidence of adverse events were ENT (35-41%) and neurological (14-18%). No clinically notable or 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.

During randomized treatment, the HFA placebo and albuterol groups had a higher overall rate of severe AE (10 and 11% respectively) than the CFC albuterol group (3%), but when examined by overall system, there was no notable pattern to suggest an HFA-related problem. The greatest difference between HFA and CFC groups occurred in the ENT system, with 4 and 3% rates of any ENT event in the HFA groups, and 0 in the CFC group. Severe throat irritation was seen in only 2 patients, both of them in the HFA albuterol group.

When the sponsor analyzed adverse events during randomized treatment that were considered to be drug-related, 2 patients (2%) noted throat irritation with albuterol HFA, in contrast to none on placebo HFA or albuterol HFA. The rate in the albuterol HFA arm represented an increase of 1 patient (1%) over what was attributed to study drug during the run-in CFC albuterol phase.

**Medical Officer Comment:** *A slightly higher rate of throat irritation attributed to study drug was seen in the albuterol HFA arm than the albuterol CFC arm.*

### Serious adverse events

All serious adverse events occurred during the albuterol CFC run-in phase and were considered unrelated to study drug. Two patients suffered asthma exacerbations, and one each had atrial fibrillation and a fracture.

### Withdrawals due to adverse events

Of 11 withdrawals due to adverse events, 8 occurred during the run-in phase and were considered unrelated or unlikely related to study drug. The remaining three withdrawals due to AE occurred during the randomized treatment phase, all of them in the placebo GR106642X group. Of these three, one patient reported "paradoxical bronchospasm" (recoded by one of the suspect PI's as chest tightness) after receiving her first dose of placebo HFA. These symptoms

persisted for the following 2 weeks and prompted drug discontinuation. Neither this nor the other two randomized treatment period effects were considered serious.

**Medical Officer Comment:** *The patient with "paradoxical bronchospasm"/chest tightness is a soft indicator of potential hyperreactivity caused by the HFA propellant. Of note, no adverse events proximate to dosing were reported during the study.*

#### Laboratory values over time

During randomized treatment, there were limited changes in laboratory values from normal to abnormal levels, and no patterns of clinically significant treatment-related changes were noted by the medical reviewer [56: Table 74] Potassium declined from normal to low values in more CFC albuterol subjects (4%) than in either HFA albuterol (1%) or placebo (0) subjects. Eosinophils increased from normal to elevated levels in all treatment groups (10% placebo, 5% albuterol HFA, 7% albuterol CFC).

#### Laboratory Abnormalities Outside the Threshold Range

Laboratory parameters outside the threshold range during the run-in and randomized treatment phases are presented below.

#### Labs Out of Threshold Range

Abnormal Analyte	Run-in Phase <sup>1</sup>			Randomized Treatment Phase		
	(Placebo GR106642X)	(Albuterol GR106642X)	(Albuterol P11/12)	Placebo GR106642X	Albuterol GR106642X	Albuterol P11/12
Elevated WBC	0	0	0	0	0	1 (<1%)
Elevated Lymphocytes	0	0	0	0	1 (1%)	1 (<1%)
Elevated Monocytes	0	0	1 (<1%)	1 (<1%)	0	0
Elevated Eosinophils	2 (2%)	0	2 (2%)	1 (<1%)	1 (<1%)	1 (<1%)
Elevated Sodium	0	0	0	0	0	1 (<1%)
Decreased Potassium	0	0	0	1 (<1%)	0	0
Elevated Chloride	0	0	0	0	0	1 (<1%)
Decreased Bicarbonate	1 (<1%)	0	0	0	0	0
Elevated Urea Nitrogen	0	0	1 (<1%)	0	0	0
Elevated Total Bilirubin	2 (2%)	0	1 (<1%)	1 (<1%)	3 (3%)	2 (2%)
Elevated AST	0	0	0	2 (2%)	0	1 (<1%)
Elevated ALT	0	0	0	1 (<1%)	0	1 (<1%)
Decreased Glucose	0	0	0	0	0	2 (2%)

<sup>1</sup>All patients received albuterol P11/12 during run-in, but are displayed according to their future randomized treatment group.

Source Data: Tables 76 and 77

As shown in the table above, 23 patients (7 in the placebo GR106642X group, 5 in the albuterol GR106642X group and 11 in the albuterol P11/12 group) had a laboratory value outside the sponsor-defined threshold range during the randomized treatment phase.

Total bilirubin was  $\geq 2$  mg/dl for 6 patients (1 placebo GR106642X, 3 albuterol GR106642X, and 2 albuterol P11/12). For 5 of the 6 patients, the total bilirubin values fell within the threshold range at a re-test visit or the next study visit.

Patient No. 1784 (assigned to CFC albuterol) entered the study with a diagnosis of Gilbert's Syndrome and had high bilirubin levels throughout the study. The three patients who had AST levels outside the threshold range decreased to within the threshold range at a re-test or the next study visit.

**Medical Officer Comment:** *There was no concerning increase in the rate of laboratory abnormalities among patients treated with Albuterol HFA in comparison to either placebo HFA or albuterol CFC. The small number of patients with elevated bilirubin normalized on re-test with the exception of one patient (on albuterol CFC) who had Gilbert's Syndrome.*

#### Electrocardiograms

Three patients had clinically significant ECG changes during the study. In two of these patients, the abnormality occurred a single time before drug treatment (either screening or predose Visit A) and did not recur. One patient on albuterol HFA had incomplete RBBB at baseline, Visit A, and Visit 1 that bordered closely on complete. In this patient, the QRS interval increased by 4 msec at week 6 pre- and post-dose to meet criteria for complete RBBB, and then reverted to incomplete RBBB at week 12. The change at week 6 was considered insignificant by an independent cardiologist.

**Medical Officer Comment:** *The one ECG abnormality that met criteria for clinical significance while on treatment (with albuterol HFA) represented a minor change in a borderline baseline value and was unlikely related to study treatment.*

As seen in the following table, mean QTc intervals were similar among "future" treatment groups at screening and at Visit A. During randomized treatment, mean intervals were similar across groups with mean changes from Treatment Day 1 baseline that were  $\leq 6$  msec.

Mean QTc Intervals and Mean Change from Baseline for QTc Intervals

Run-In Phase			
Time	Placebo HFA	Albuterol HFA	Albuterol CFC
Screening	412	416	415
Visit A, Pre-dose	415	414	415
Visit A, Post-dose	413	414	415
Randomized Treatment Phase			
Time	Placebo HFA	Albuterol HFA	Albuterol CFC
Visit 1, Pre-dose	414	414	416
Visit 1, Post-dose	411	412	417
Mean change from baseline	-3.5	-2.0	1.1
Week 6, Pre-dose	411	415	412
Mean change from baseline	-1.8	1.7	-4.1
Week 6, Post-dose	409	414	415
Mean change from baseline	-4.1	0.6	-1.1
Week 12, Pre-dose	414	416	415
Mean change from baseline	0.3	3.3	-0.1
Week 12, Post-dose	408	413	410
Mean change from baseline	-6.0	-0.2	-5.7

In the previous table, baseline QTc is the value recorded from Treatment Day 1 pre-dose ECG.

A total of 11 patients had intervals > 470 msec during randomized treatment, 3 placebo, 6 albuterol HFA, and 2 albuterol CFC. None of these were considered to be clinically significant by the independent cardiologist, and in only 5 patients did these occur on more than one measurement. Of these five patients, two were placebo patients, two were albuterol HFA patients, and one was an albuterol HFA patient.

As seen in the following table, heart rates were similar in all treatment groups during run-in and randomized treatment, and there was no apparent effect of switching from albuterol CFC to HFA.

Heart Rate (bpm)			
	Placebo	ALB 180mcg QID GR106642X	ALB 180mcg QID P11/P12
<b>Screening Visit</b>			
n	104	101	108
Mean (SEM)	68.4 (1.09)	67.2 (1.07)	67.5 (1.09)
Min-Max	43-96	46-95	42-97
<b>Visit A, Pre-dose</b>			
n	103	100	107
Mean (SEM)	69.7 (1.18)	67.2 (1.14)	67.5 (1.07)
Min-Max	45-108	43-97	42-92
<b>Visit A, Post-dose</b>			
n	103	100	107
Mean (SEM)	67.9 (1.13)	66.0 (1.09)	65.0 (1.00)
Min-Max	42-103	40-100	40-91
<b>Day 1, Pre-dose</b>			
n	104	101	108
Mean (SEM)	67.8 (1.21)	67.2 (1.09)	67.3 (1.04)
Min-Max	40-96	43-105	41-100
<b>Day 1, Post-dose</b>			
n	104	101	108
Mean (SEM)	64.7 (1.25)	65.5 (1.03)	65.9 (0.98)
Min-Max	36-116	40-105	44-93
<b>Week 6, Pre-dose</b>			
n	90	97	101
Mean (SEM)	68.3 (1.23)	68.7 (1.20)	66.8 (1.04)
Min-Max	47-97	39-103	41-91
<b>Week 6, Post-dose</b>			
n	90	97	101
Mean (SEM)	66.3 (1.26)	67.9 (1.28)	65.6 (1.02)
Min-Max	44-96	38-105	42-96
<b>Week 12, Pre-dose</b>			
n	86	91	99
Mean (SEM)	68.5 (1.45)	68.7 (1.29)	67.3 (1.05)
Min-Max	43-105	44-102	42-90
<b>Week 12, Post-dose</b>			
n	86	91	99
Mean (SEM)	64.7 (1.36)	65.4 (1.21)	64.9 (1.08)
Min-Max	43-116	42-102	42-93
<b>Discontinuation Visit</b>			
n	14	8	7
Mean (SEM)	74.5 (3.96)	71.5 (3.33)	69.7 (4.48)
Min-Max	55-109	58-87	60-92

Holter monitoring was conducted over 24 hours at screening and over 6 hours at Visit A, Treatment Day 1; and Treatment Week 12. A total of 83 patients at 6 selected sites underwent ambulatory ECG monitoring (via Holter monitor) at Screening and at least once during the randomized treatment phase.

Ventricular ectopy occurred  $\leq 4$  times in 75% of patients throughout the study. Only 7 patients had  $\geq 50$  VEs, and this occurred in 4 patients solely during screening. Of the remaining 3 patients with  $\geq 50$  VEs, only 2 experienced them during randomized treatment. One was a placebo patient at Visit A and Week 12, and the other was an albuterol HFA patient at Screen, Visit A, and Treatment Day 1.

Supraventricular ectopy was low, with 75% of patients having  $\leq 17$  SVEs. According to MO analysis of Listing 14, 11 patients had  $\geq 50$  SVEs, and in 6 of these, SVEs occurred solely during screening or run-in testing. Of the remaining five patients, two had  $\geq 50$  SVEs at screening which were seen again during randomized treatment. The remaining 3 patients (one from each treatment group) had one occasion during randomized treatment where SVEs  $\geq 50$  were noted.

At Visit A and Treatment day 1, the mean and maximum heart rates in the placebo group were statistically greater than the active treatment arms at each hour and overall. At Treatment week 12, the maximum heart rate in the placebo group was numerically greater than either albuterol group, but the difference was statistically significant only at 5 hours.

In summary, Holter monitoring showed little effect upon cardiac rate or ectopy (either ventricular or supraventricular) of randomized treatment, other than an elevated heart rate in placebo treated patients relative to albuterol treatment arms.

**Pulse:** The following table presents a summary of increases and decreases in pulse during the run-in and randomized treatment phases of the study. During both run-in and randomized treatment phases, there were roughly comparable changes across the treatment groups with minor exceptions that did not follow any treatment-related pattern in the opinion of the medical reviewer. During run-in, decreases in pulse rate  $\geq 15$ bpm were higher in the future placebo GR106642X (10 patients) and albuterol P11/12 (11 patients) groups than in the albuterol GR106642X group (4 patients). During randomized treatment, the percentage of patients with increases in pulse  $\geq 15$ bpm was higher in the placebo GR106642X and albuterol P11/12 groups. Mean pulse rates at baseline and over 6-hours post dose were similar across the patient population during both run-in and randomized treatment. No statistically significant differences were observed among the treatment groups

**Summary of Increases and Decreases in Pulse**

<b>Run-in Phase</b>			
<b>Change</b>	<b>(Placebo GR106642X)</b>	<b>(Albuterol GR106642X)</b>	<b>(Albuterol P11/12)</b>
Increase in Pulse $\geq$ 15bpm	19 (18%)	20 (20%)	17 (16%)
Increase in Pulse $\geq$ 20bpm	10 (10%)	12 (12%)	12 (11%)
Increase in Pulse $\geq$ 30bpm	4 (4%)	4 (4%)	2 (2%)
Decrease in Pulse $\geq$ 15bpm	10 (10%)	4 (4%)	11 (10%)
Decrease in Pulse $\geq$ 20bpm	3 (3%)	3 (3%)	4 (4%)
Decrease in Pulse $\geq$ 30bpm	1 (<1%)	0	1 (<1%)
<b>Randomized Treatment Phase</b>			
<b>Change</b>	<b>Placebo GR106642X</b>	<b>Albuterol GR106642X</b>	<b>Albuterol P11/12</b>
Increase in Pulse $\geq$ 15bpm	45 (43%)	36 (36%)	45 (42%)
Increase in Pulse $\geq$ 20bpm	22 (21%)	23 (23%)	23 (21%)
Increase in Pulse $\geq$ 30bpm	8 (8%)	7 (7%)	5 (5%)
Decrease in Pulse $\geq$ 15bpm	19 (18%)	21 (21%)	19 (18%)
Decrease in Pulse $\geq$ 20bpm	6 (6%)	9 (9%)	3 (3%)
Decrease in Pulse $\geq$ 30bpm	0	1 (<1%)	0

<sup>1</sup>All patients received albuterol P11/12 during run-in, but are displayed according to their future randomized treatment group.

Source Data: Tables 90 and 92

Systolic and diastolic blood pressures were monitored during the run-in and randomized treatment phases. Categorical analyses of changes showed that during randomized treatment, the active treatment arms in comparison to placebo had greater percentages of patients with increases in SBP  $\geq$  20 mm Hg, as well as greater percentages of patients with decreases in SBP of  $\geq$  20 mm Hg. Decreases in SBP  $\geq$  15 mm Hg were more frequent in the albuterol HFA group (53% by MO calculation from summary table) than albuterol CFC patients (40%, per MO.) Yet during randomized treatment, mean SBP values at baseline and 6 hour weighted average systolic blood pressure values were comparable among treatment groups. Similarly, categorical analyses of changes in DBP showed that in comparison to placebo, active treatment arms had greater percentages of patients with increases and decreases in DBP that exceeded 20 mm Hg. Analyses of serial DBP showed the 6 hour weighted averages to be comparable across treatment groups, although at treatment day 1 and week 12 there were small but statistically significant differences among the treatment groups noted at multiple time points. The medical reviewer could see no consistent pattern across treatment groups or evaluation periods for these changes, all of which were less than 2.9 mm Hg.

Physical examination abnormalities that represented an unfavorable change relative to baseline were low in number and similar among treatment groups within each body system. The highest number of unfavorable changes was observed in the ears, nose and throat (6%, placebo GR106642X; 5%, albuterol GR106642X; and 2% albuterol P11/12). No other body systems had unfavorable changes in  $>$ 1% of patients in each treatment group.

### **Medical Officer Conclusions**

*In this study to assess the effects of switching from albuterol in CFC 11/12 to albuterol HFA, placebo HFA, or albuterol CFC, serial FEV<sub>1</sub> measurements demonstrated statistically greater bronchodilation (as assessed by repeated measures and WAVE analyses) of both albuterol HFA and albuterol CFC when compared to placebo. Maximum improvements in 6-hour WAVE FEV<sub>1</sub> from the same day baseline following both albuterol treatments ranged from 0.26-0.43L on the three assessment days; these values were comparable to albuterol P11/12 administered during the run-in phase (0.30-0.33L). Over 12 weeks of treatment, there was no significant difference between the degree of bronchodilation observed with albuterol HFA and albuterol CFC. There were no reported instances of device clogging.*

*The percent of patients with  $\geq 15\%$  increase in FEV<sub>1</sub> within 30 minutes of treatment or by WAVE was lower for albuterol HFA than albuterol CFC. Numerically the median onset of effect with albuterol HFA was later, duration of effect shorter, peak effect smaller, and AUC (bl) less than seen in albuterol CFC. These differences were not statistically significant. Backup albuterol use was statistically greater in the HFA albuterol than the CFC albuterol arm, a finding consistent with a shorter median duration of effect of HFA albuterol.*

*Albuterol HFA was generally well tolerated and showed an adverse event profile that was comparable to CFC albuterol. The data showed a slightly greater rate of throat irritation with placebo and albuterol HFA than albuterol CFC. One patient may have had paradoxical bronchospasm with placebo HFA, but no adverse events proximate to dosing were reported. Laboratory, ECG, Holter monitoring, pulse, and blood pressure monitoring did not reveal any concerning clinical changes or abnormalities with the use of albuterol HFA. Changes or abnormalities seen were small in number and percentage and did not follow any pattern suggestive of greater toxicity of albuterol HFA than the CFC formulation.*

**APPEARS THIS WAY  
ON ORIGINAL**

## **SALA3005**

A Randomized, Double-Blind, Parallel-Group, 12-Week, Study to Compare the Safety and Efficacy of Albuterol 200mcg (180mcg ex-actuator) in CFC Propellant 11 and 12 Administered QID versus Albuterol 200mcg (180mcg ex-actuator) in HFA Propellant Administered QID versus Placebo in Adolescent and Adult Subjects with Asthma.

### **PROTOCOL**

#### **Study Objectives**

To compare the safety and efficacy of albuterol 200mcg in CFC propellant, albuterol 200mcg in HFA propellant, and placebo (HFA propellant alone) administered QID for 12 weeks in adolescent and adult patients with asthma. In addition, the study compared the safety and efficacy of albuterol 200mcg PRN (placebo HFA) with albuterol 200mcg QID (albuterol HFA and albuterol CFC) in the treatment of adolescent and adult patients with asthma.

**Medical Reviewer Comment:** *In its review of Protocol SALA 3005 on 9/10/96, FDA notified the sponsor that the comparison of QID and PRN albuterol HFA in this protocol would not be sufficient evidence to allow a determination of an explicit PRN indication. FDA did note that the PRN indication is implied by the current indication of QID maintenance therapy for asthma. FDA indicated evidence would have to come from well-controlled trials specifically designed to examine PRN versus QID use, and would entail examination of asthma exacerbation rates, changes in premedication PFTs over time, as well as other markers of asthma control, such as serial methacholine challenges.*

#### **Study Design**

This was a randomized, 12-week double-blind, parallel-group, placebo-controlled, multicenter trial in adolescent and adult patients with asthma. The study included a 2-week single-blind run-in phase during which CFC (CFC) propellant alone was administered QID with Ventolin CFC MDI PRN. Patients who satisfied asthma stability, compliance, and eligibility criteria were then randomized to double blind treatment. During the double-blind phase, patients were randomized to albuterol CFC, albuterol HFA, or placebo HFA given four times daily. Back-up albuterol in the matching propellant was supplied for PRN use. Total study duration was approximately 14 weeks.

Enrollment was planned for  $\geq 240$  male or female patients  $\geq 12$  years of age, evenly apportioned to each of the 3 treatment groups. Patients were asthmatics requiring chronic pharmacotherapy for at least 6 months prior to screening, with a medication-free baseline FEV<sub>1</sub> of 50-80% of predicted normal value, and airways reversibility ( $\geq 15\%$  increase in FEV<sub>1</sub> following inhalation of VENTOLIN® Inhalation Aerosol). Typical criteria were applied to exclude patients with poorly controlled asthma, significant concurrent diseases, clinically significant abnormalities of either 12-lead ECG or 24 hour Holter, or poor compliance.

Clinic visits were scheduled every 3 weeks with serial spirometry performed at Visits 1 (day 1 of treatment), 3 (week 6 of treatment), and 5 (week 12 of treatment). Visit timing was as follows:

Clinic Visit	Time of Occurrence
Screening	initial visit
Treatment Visit 1 (Day 1 - randomization)	14 ± 3 days from Screening
Treatment Visit 2 (Week 3)	21 ± 3 days from Treatment Day 1
Treatment Visit 3 (Week 6)	42 ± 3 days from Treatment Day 1
Treatment Visit 4 (Week 9)	63 ± 3 days from Treatment Day 1
Treatment Visit 5 (Week 12)	84 ± 3 days from Treatment Day 1

Procedures and evaluations performed at each clinic visit are described in the flowchart on the following page.

The original protocol was amended about 2 weeks after the first patient was screened. Investigator questions, diary card recordings, and analyses were modified to assess symptoms occurring after each dose of the study medication. In addition, the patient assessment of asthma symptoms was changed from the evening to the morning before PEFr measurements.

#### Concomitant medications

All subjects withheld beta-agonists, theophylline, ipratropium,  $\beta$ -blockers, TCAs, and MAO inhibitors throughout the study. 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. NonCFC forms of these drugs were encouraged but not required. Antihistamines, decongestants, and PRN nasal decongestants were allowed with appropriate washouts before study visits.

**Medical Reviewer Comment:** *Note that the use of inhaled controller agents and CFC formulations is more liberal than the other adult 12 week trial, SALA 3002.*

#### Trial Medications

Glaxo Wellcome supplied the following medications for use in this trial:

Medication	Strength	Batch Number
Albuterol CFC MDI	100mcg/actuation*	6ZPA036 5Z1162P
Albuterol HFA MDI	100mcg/actuation*	6ZX001A 6ZX012B
Placebo (HFA propellant alone) MDI	---	6ZX011A 6ZX002A
Placebo (CFC propellant alone) MDI	---	4Z2276P
VENTOLIN Nebules (rescue)	0.083% - 2.5mg/3ml	960309

\*90 mcg ex-actuator; 100mcg ex-valve

# FLOWCHART/TIME & EVENTS TABLE

	Screening Visit	Treatment Visit 1 14±3 days from Screening	Treatment Visit 2 21±3 days from Visit 1	Treatment Visit 3 42±3 days from Visit 1	Treatment Visit 4 63±3 days from Visit 1	Treatment Visit 5 84±3 days from Visit 1	Subject Discontinuation
Informed Consent	X						
Medical History	X						
Vital Signs	X						
Physical Examination	X					X	X
Spirometry Test	X						X <sup>d</sup>
Reversibility Test	X <sup>a</sup>						X
Serial Vital Signs		X		X		X	
Serial PFTs		X		X		X	
Adverse Event Assessment		X	X	X	X	X	X
Concomitant Medications Query	X	X	X	X	X	X	X
12-lead ECG	X	X <sup>b</sup>				X <sup>b</sup>	X <sup>d</sup>
Holter Monitoring	X <sup>g,h</sup>	X <sup>g</sup>				X <sup>g</sup>	
Clinical Laboratory Tests	X <sup>j</sup>	X <sup>c</sup>				X <sup>c</sup>	X <sup>d</sup>
Chest x-ray	X <sup>d,e</sup>						
Pregnancy Test (all females)	X					X <sup>f</sup>	X <sup>d</sup>
Issue Placebo Run-in Medication	X						
Issue Study Medication and Review Proper MDI Technique		X	X	X	X	X <sup>i</sup>	
Dispense Pm Albuterol	X	X	X	X	X	X <sup>i</sup>	
Review Returned Diary Card		X	X	X	X	X	X
Dispense New Diary Card	X	X	X	X	X		

- a Reversibility assessment of  $\geq 15\%$  of FEV<sub>1</sub>
- b To be done pre-dose and approximately 0.75 hours post-dose
- c To be done pre-dose and approximately 1.5 hours post-dose
- d To be done only if subject has not had a normal chest x-ray within 12 months
- e Optional if subject <18 yrs of age
- f To be done as pre-dose only
- g To be done in selected subjects only
- h To be done at the Screening Visit or between the Screening Visit and Treatment Visit 1
- i Issue study medication for dosing for this Treatment Visit only
- j Selected tests/examinations to be repeated if abnormality is noted or pregnancy test was positive

### Treatment Administration

At the screening visit that marked the beginning of the 2-week single-blind placebo run-in period, each subject received one placebo MDI (CFC propellant only) and was instructed to take 2 actuations four times a day, approximately every 4-6 hours (suggested times of administration mealtimes and bedtime). Each subject also received VENTOLIN P11/P12 for PRN relief of acute symptoms of asthma.

On Treatment Day 1, patients were randomized to one of the following double-blind study treatments for 12 weeks:

Albuterol 100mcg MDI in CFC (2 puffs) QID

Albuterol 100mcg MDI in HFA (2puffs) QID

Placebo (HFA propellant alone) (2 puffs) QID

Each patient was instructed to take two actuations of study medication four times a day, approximately every 4 to 6 hours. In addition, each patient received albuterol for PRN relief of acute symptoms of asthma according to his/her randomized treatment:

Patients Randomized To QID:	Received PRN:
Albuterol CFC	Albuterol CFC
Albuterol HFA	Albuterol HFA
Placebo HFA	Albuterol HFA

### Management of Asthma Exacerbations

An exacerbation was defined as asthma requiring treatment other than with allowed concomitant medications, study medication, or back-up Albuterol MDI. Use of back-up albuterol MDI was considered an exacerbation only during 6-hour serial spirometry. Patients were treated with their PRN medication first; if they did not respond, then VENTOLIN 2.5mg via nebulization was administered. Any patient who had an exacerbation between the Screening Visit and Treatment Day 1 was discontinued from the study.

Patients who experienced an asthma exacerbation could be treated with the following medications:

- Back-up albuterol MDI.
- An additional beta-adrenergic agent up to 7 consecutive days. Only two such courses were allowed during the study.
- One course of theophylline for up to 7 consecutive days.
- One short course of inhaled corticosteroids or an increase in the dose of inhaled corticosteroids used concurrently for no longer than 7 consecutive days.

These rescue medications could not be used within 5 days of the Treatment Week 6 or 12 visits.

**Medical Reviewer Comment:** *Note that this protocol allowed rescue by inhaled corticosteroids, whereas the companion 12 week study protocol SALA 3002 did not.*

### **Efficacy Measures**

The primary measure of efficacy was 6-hour serial FEV<sub>1</sub> measurements performed at Treatment Day 1 and Weeks 6 and 12. FEV<sub>1</sub> was 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. Serial spirometry was discontinued if a patient experienced an exacerbation during a 6 hour study day.

Serial FEV<sub>1</sub> measurements were done using doses of newly dispensed QID double-blind medication.

**Medical Reviewer Comment:** *The use of newly dispensed canisters of QID medication will minimize the likelihood of detecting device performance problems associated with repeated use, such as clogging.*

Additional measures of efficacy included patient-conducted determinations of morning and evening peak expiratory flow (AM and PM PEFR), actuations of back-up albuterol, asthma-related symptom scores, number of nighttime awakenings, and asthma exacerbations. These were recorded on diary cards dispensed at each visit. Asthma symptom scores were based on the worst of four symptoms (chest tightness, shortness of breath, wheezing, and coughing) and rated on a scale of 1 (no symptoms, unrestricted activity) to 4 (symptoms at rest.)

### **Safety Monitoring**

Safety was assessed by monitoring clinical adverse events (including medical problems recorded on the diary card), clinical laboratory tests, vital signs, 12-lead electrocardiograms, continuous ambulatory Holter monitoring (at 5 sites), and physical examinations. Additionally, clinic determinations of FEV<sub>1</sub> and twice-daily assessments of PEFR were monitored for any safety concerns.

Approximately 2 weeks after study initiation, a protocol amendment was issued to all study sites in response to FDA's request to capture information about any adverse events that occurred immediately after dosing. Investigators specifically asked patients how they felt after taking each dose of study medication.

Clinical laboratory assessments done at screening, Treatment Visit Day 1, and Week 12 are described on page 36 of volume 73. Baseline Holter monitoring was for 24 hours duration at screening, and for approximately 7 hours on Treatment Day 1 and Treatment Week 12 (approximately 1 hour prior to drug administration and for 6 hours post-dose). Clinically significant findings were predefined [73:38].

#### Analysis Plan/Statistical Power

Enrollment was planned for 240 patients (80 per treatment group). Assuming the standard deviation of FEV<sub>1</sub> to be 0.55 liters and using a significance level of 0.05, 80 patients per treatment group was determined to provide at least 80% power in detecting a difference of 0.25 liters in FEV<sub>1</sub> change from baseline in the repeated measures analysis. 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 were only interpreted when the overall treatment comparison was significant.

For all analyses, investigational sites #1358 (Tarpay), #4758 (Pollard), and #7035 (Flescher) were combined due to the small number of patients enrolled, and to avoid potential bias. Each of these investigational sites had only 0-2 patients in at least one of the three treatment groups. The combined sites had a comparable number of patients to all other individual sites.

The primary population for the analysis of data from this trial (demographic, efficacy, and safety) was the Intent-to-Treat Population, defined as all patients randomized to treatment who received at least one dose of blinded study medication.

#### Efficacy Analyses

Repeated Measures Analysis of Variance was used to analyze FEV<sub>1</sub> for each visit where serial PFTs were performed. Repeated measures analysis included unequally weighted average of all post-dose FEV<sub>1</sub> measurements (WAVE) as well as the equally weighted average of all post-dose FEV<sub>1</sub> measurements (referred to as repeated measures analysis in the tables and text). With WAVE, the weight for each FEV<sub>1</sub> (or change in FEV<sub>1</sub>) is proportional to the time interval between this FEV<sub>1</sub> (or change in FEV<sub>1</sub>) and the previous FEV<sub>1</sub> (or change in FEV<sub>1</sub>); calculated according to the following formula:

$$\frac{((\text{Resp}_{5\text{min}} \times 5) + (\text{Resp}_{15\text{min}} \times 10) + (\text{Resp}_{30\text{min}} \times 15) + (\text{Resp}_{1\text{hr}} \times 30) + (\text{Resp}_{2\text{hr}} + \text{Resp}_{3\text{hr}} + \text{Resp}_{4\text{hr}} + \text{Resp}_{5\text{hr}} + \text{Resp}_{6\text{hr}}) \times 60)}{360}$$

Additional analyses of onset, offset, peak effect, duration, and AUC(bl) of serial PFTs were done according to definitions [73:41] based on when  $\geq 15\%$  elevation in baseline FEV<sub>1</sub> occurred after treatment.

Averaged values from the period prior to Treatment day one were used as the baseline for comparison of changes in PEF, back-up albuterol use, nighttime awakenings, and asthma symptom scores.

Pre-dose FEV<sub>1</sub> at Treatment Weeks 6 and 12 was the focus for the analysis of PRN albuterol use (placebo HFA) versus albuterol QID (albuterol CFC and albuterol HFA). The change from Treatment Day 1 baseline was calculated for each subject as the pre-dose FEV<sub>1</sub> at each Treatment Visit minus the pre-dose FEV<sub>1</sub> at Treatment Day 1. Secondary measurements for the analysis of PRN

compared with QID albuterol use were morning PEFr, asthma symptoms, nighttime awakenings, and asthma exacerbations during the 12-week treatment period.

**Medical Reviewer comment:** *FDA has previously informed the sponsor that more information than described will be necessary to support an explicit PRN indication. Overall, the protocol has appropriate safety and efficacy assessments.*

## **Results**

### **Device Performance**

Eight patients returned study medication during the course of the study. Investigators either returned all study medications that the patient used or simply returned the "faulty" canister. A total of 62 canisters were evaluated, 31 of HFA albuterol, 10 of HFA placebo, and 21 of CFC albuterol.

Ten canisters from four patients were partially clogged/clogged. Three patients returned nine canisters from batch 6ZX001A (albuterol HFA) which were found to be partially clogged/clogged. One canister from batch 5Z1162P (albuterol CFC) was found to be clogged due to a foreign particle embedded in the orifice. All other returned canisters were either normal or empty.

**Medical Reviewer Comment:** *These numbers, albeit small, are concerning that the device clogging seen with previously-approved HFA albuterol products may also be a risk with this product. Of the 15 of 31 returned canisters found to be defective, 60% of abnormalities (29% of all returns) were due to clogging. The balance of problems were identified as empty canisters. Of note, the problematic batch in this study (6ZX001A) was one of two batches returned by patients in Protocol SALA3002. In that trial, canisters were returned for variable output and for lasting <2 weeks, and 2/3 returned canisters were abnormal.*

### Device Performance Problems with Returned Canisters

Product/Use	Site State	# returned	Complaint	# Abnl	Abnl findings on eval
HFA Albuterol QID	WA	1	Appeared "faulty" after 16 d use. Attempted to unclog with hot water	1	Clogged
	GA	5	"would not fire well" after 3 days	3	Clogged/partially clogged
	OH	5	None	0	All normal
	Total	11		4 (36%)	
HFA Albuterol PRN	GA	5	"Felt empty"	1	Empty
	GA	5	Clogging after 10 d	5	Empty
	GA	5	None	1	Clogged/partially clogged
	OH	5	Not spraying medication that could be seen	4	Partially clogged
	Total	20		11(55%)	
HFA placebo QID	GA	5	"felt empty"	2	Empty
	GA	5	None	0	All normal
	Total	10		2 (20%)	
CFC Albuterol QID	OH	5	"No medication seemed to come out of"	0	All normal
	CA	5	None	0	All normal
	Total	10		0 (0%)	
CFC Albuterol PRN	OH	5	None	0	All normal
	NJ	1	Thought inhaler was empty	1	Empty after 102 actuations per diary - had leaked
	CA	5	Not dispensing correctly. Force dispensed by inhaler decreased	1	Clogged inhaler (foreign particle)
Total	11		2 (18%)		

Derived by Medical reviewer from Sponsor table on page 73: 28

### Study Population Results

A total of 357 patients entered the 2-week single-blind, run-in phase of the study of which 60 patients withdrew. The reasons for withdrawal included 'other' (primarily failed continuation criteria; 42 patients), lack of efficacy (8 patients), adverse events (5 patients) and failed to return (5 patients).

As seen in the following table, a total of 297 patients were enrolled and randomized to double-blind treatment: 97 to placebo HFA, 101 to albuterol HFA, and 99 to albuterol CFC.

**Patient Accountability Summary**

Disposition	Number of Patients			Total
	Placebo HFA	Albuterol HFA	Albuterol CFC	
Randomized	97	101	99	297
Completed	79	84	86	249
Withdrawn:	18	17	13	48
Lack of Efficacy	7	8	7	22
Other	10	7	4	21
Adverse Event	1	2	1	4
Failed to return	0	0	1	1

Of the 48 patients who withdrew during the study, most (90%) were either due to lack of efficacy or 'other'. The number of patients who withdrew due to lack of efficacy was similar across the treatment groups. Noncompliance and voluntarily withdrew consent were the two most frequent reasons listed for 'other' reasons for withdrawal. Four patients withdrew due to adverse events (see Safety Findings, Withdrawals due to Adverse Events.)

Protocol variations occurred in  $\leq 10\%$  of patients in each treatment group and were minor, largely consisting of timing errors in the initiation of spirometry. One patient (#2662) randomized to placebo HFA was accidentally dispensed study medication from a different study (albuterol HFA from the open-label SALA3003 study) at Week 9 (non-serial Assessment Visit). The patient received 2 doses before the site was able to re-dispense the correct study medication. The patient was allowed to continue in the study.

*Medical Reviewer Comment: Neither the number or pattern of study withdrawals is of concern. The protocol variations are minor and small in number and unlikely of clinical relevance.*

**Patient Characteristics**

No statistically significant differences were observed among the treatment groups with regard to demographic characteristics [73:117]. Most of the patients were Caucasian (87%), and slightly more than half were male (52%). Mean age was 34.2 years, with a range of 12 to 76 years. The greatest number of patients (38%) was in the 18-34 year old age strata.

Histories of asthma, smoking history, and asthma symptoms were comparable across the treatment groups. Most patients (88%) had a history of daytime symptoms that interfered with regular activities and most patients (67%) had a history of nocturnal symptoms that interfered with sleep.

At screening, mean FEV<sub>1</sub> values were comparable among treatment groups and without statistically significant differences. As seen below, mean FEV<sub>1</sub> values ranged from 2.25L (albuterol P11/P12) to 2.35L (placebo HFA). Mean percent of predicted FEV<sub>1</sub> values and percent reversibility were approximately 65% and 31-33%, respectively, across the treatment groups.

**Results Of Pulmonary Function Tests At Screening**

	Placebo	Albuterol HFA	Albuterol CFC
Number of Subjects	97	101	99
FEV1 (liters)	2.35 (0.06)	2.29 (0.06)	2.25 (0.06)
FEV1, % of Predicted	65.0 (0.84)	64.9 (0.79)	65.3 (0.96)
FEV1, % Reversibility	31.6 (1.66)	30.8 (1.45)	32.6 (1.58)

More than half (61%) of patients used concomitant asthma medications, primarily inhaled corticosteroids. Based upon the medical reviewer recalculation of Table 11 [73:122] use of inhaled corticosteroids during the trial was slightly greater in the albuterol HFA group (63%) than the placebo HFA (55%) or albuterol CFC (52%) groups. Since asthma exacerbations prompting the use of these drugs for rescue were slightly lower in the albuterol HFA patients than albuterol CFC patients (see Other Efficacy Measures, Asthma Exacerbations), the slightly greater use by albuterol HFA patients most likely reflects greater use of these products at baseline.

**Medical Reviewer Comment:** *The greater use of inhaled corticosteroids by the albuterol HFA group is relatively small, and is unlikely to significantly influence study results, though the direction of any such bias would be to minimize the difference between albuterol HFA and albuterol CFC.*

The percentage of patients who took at least one non-asthma medication was comparable across the treatment groups (85%-89%). Antihistamine use was slightly higher in the placebo HFA group (28%) compared with albuterol HFA (20%) or albuterol CFC (16%) treatment groups.

Mean compliance with as measured by patient completed diary was comparable (96.2% - 97.9%) between the three treatment groups.

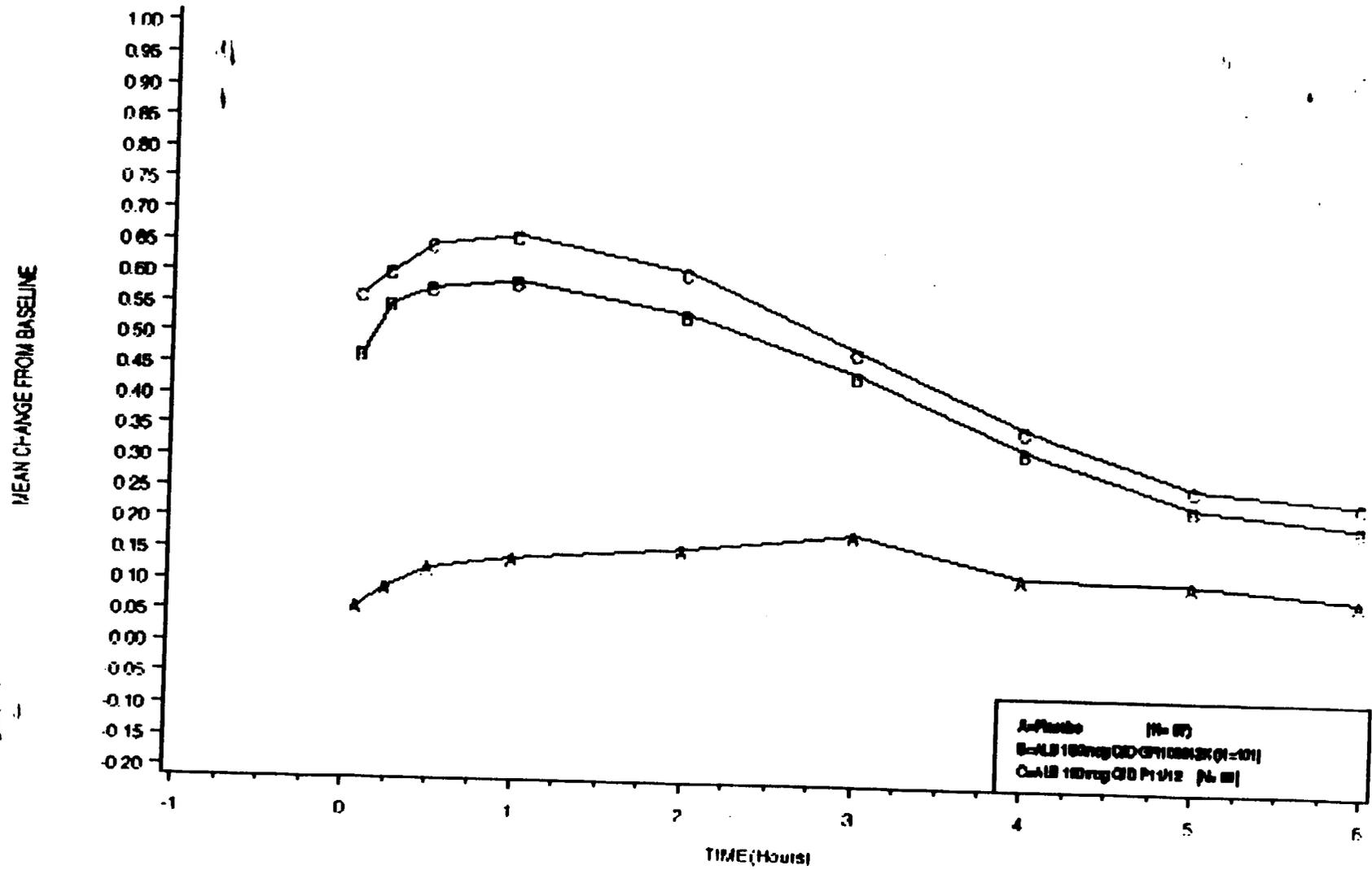
**Efficacy Findings**

**Primary Efficacy Endpoint: Serial 6 hour FEV1**

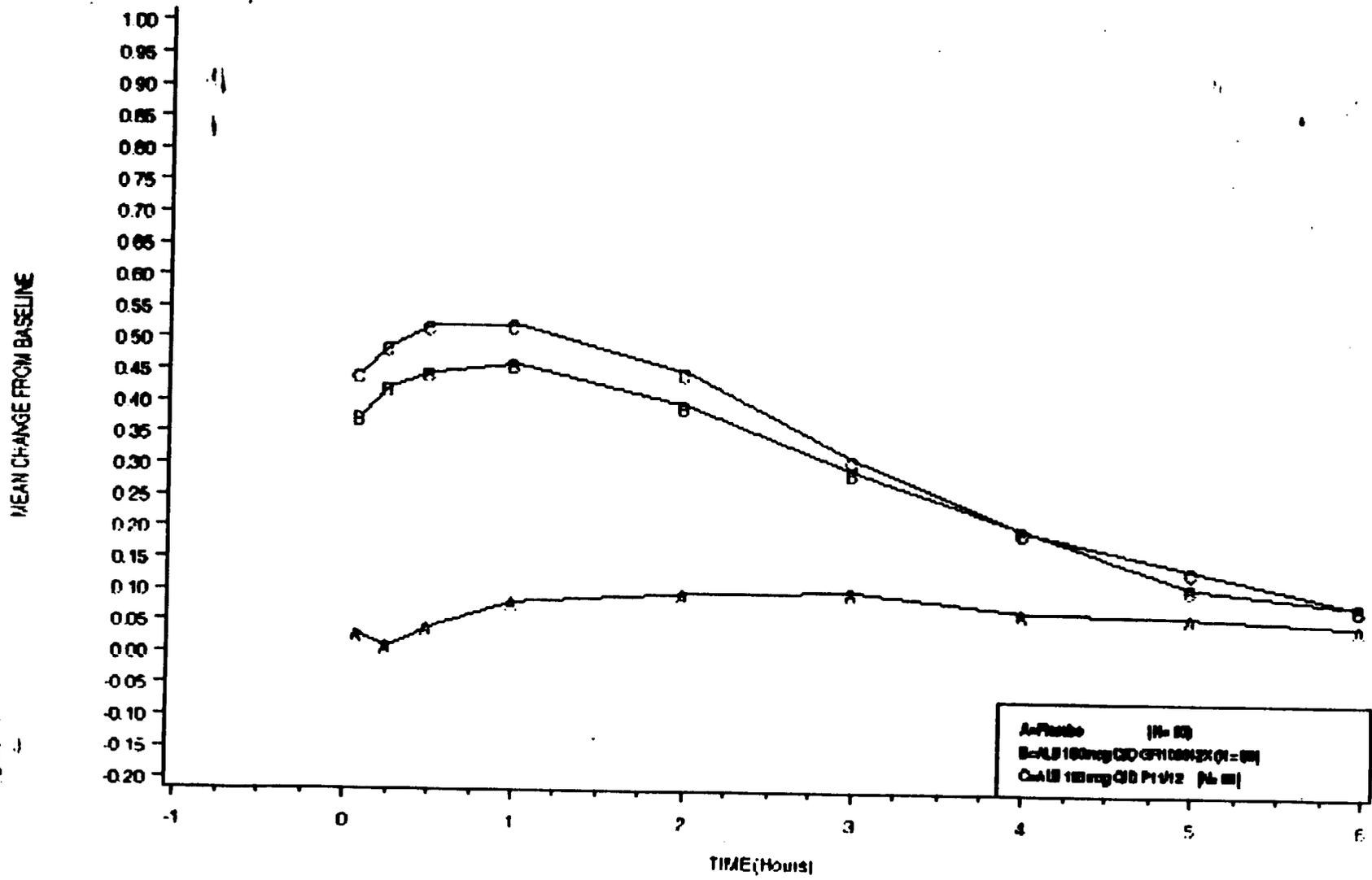
Six hour serial FEV<sub>1</sub> was analyzed by using WAVE (weighted average of post-dose FEV<sub>1</sub> of change from baseline in FEV<sub>1</sub> over 6 hours ) and repeated measures analysis (the average of post-dose FEV<sub>1</sub> of change from baseline in FEV<sub>1</sub> over 6 hours). Analyses were done relative to the same day baseline and to treatment day 1 baseline.

The figures on the following pages represent changes in serial FEV1 assessments at Treatment day 1, week 6, and week 12.

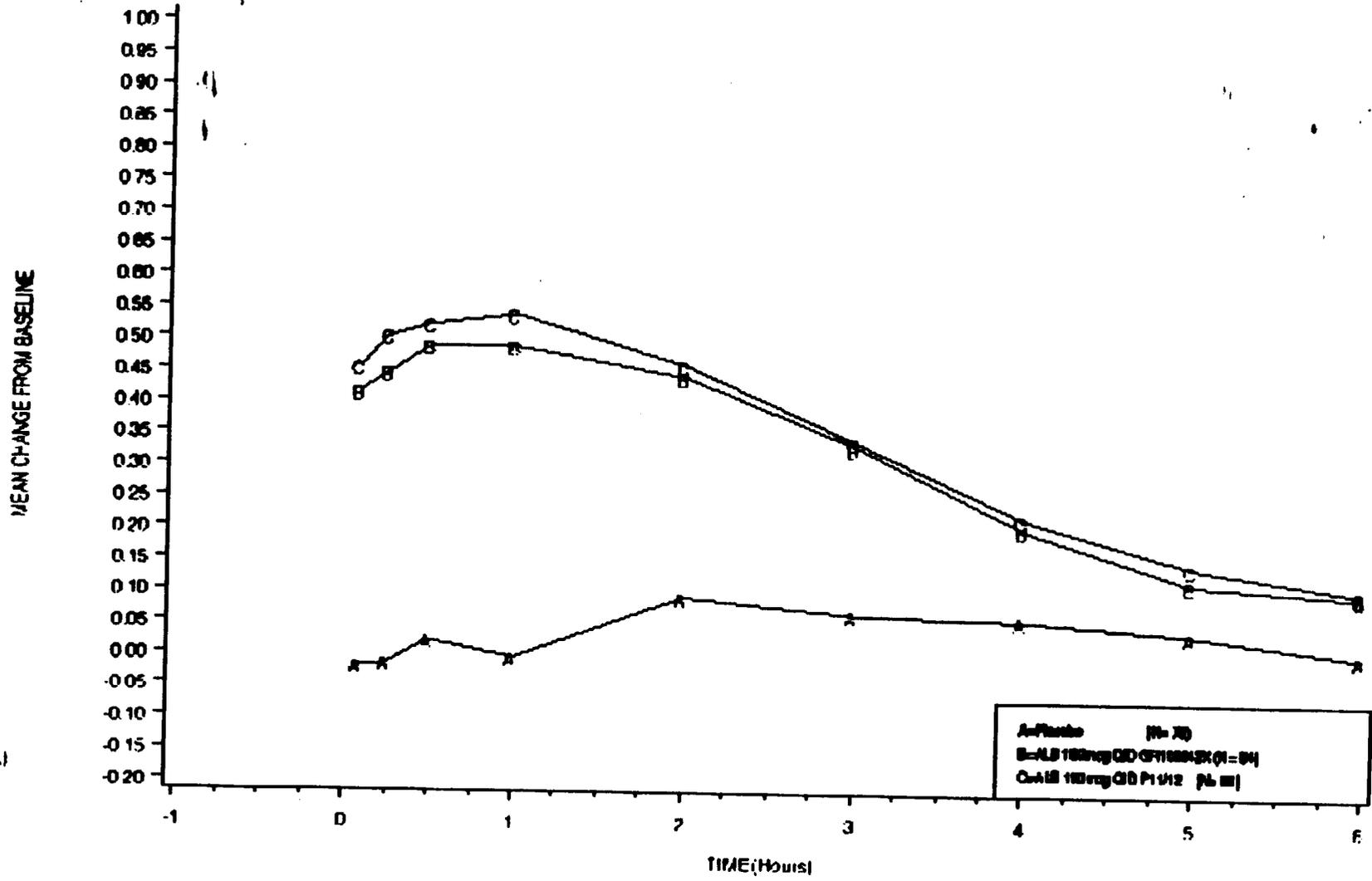
Figure 4  
 Change from Same Day Baseline Serial FEV<sub>1</sub> (liters)  
 Treatment Day One



Change from Same Day Baseline Serial FEV1 (liters)  
Treatment Week 6



Change from Same Day Baseline Serial FEV<sub>1</sub> (liters)  
 Treatment Week 12



These figures show 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 FEV<sub>1</sub>. In the figures, these differences are most marked in the first 2 – 3 hours post dose at Day 1 and Week 6 treatment assessments, suggesting a slower onset of effect in albuterol HFA relative to albuterol CFC.

#### FEV<sub>1</sub> Change from Same Day Baseline

The following table presents the weighted average (WAVE) of the change from the same day baseline in post-dose FEV<sub>1</sub> over 6 hours at Treatment Day 1, Week 6, and Week 12.

**Weighted Average (WAVE) of Post-Dose FEV<sub>1</sub> Measurements Over 6 Hours  
Change from Same Day Baseline (Liters)**

Time	Placebo HFA	Albuterol HFA	Albuterol CFC
<b>Treatment Day 1</b>			
N	97	101	99
Baseline	2.37	2.35	2.27
WAVE of the change	0.13	0.39*	0.44*
<b>Treatment Week 6</b>			
N	90	89	89
Baseline	2.53	2.45	2.42
WAVE of the change	0.07	0.26*	0.28*
<b>Treatment Week 12</b>			
N	79	84	86
Baseline	2.59	2.41	2.41
WAVE of the change	0.04	0.28*	0.30*

\*p<0.001 compared with placebo HFA

Source Data: Tables 14-19

At each visit, the WAVE of the change from the same day baseline in post-dose FEV<sub>1</sub> over 6 hours was approximately 0.2L to 0.3L higher in the albuterol groups (0.26-0.44L) compared with the placebo HFA group (0.04-0.13L); these differences were statistically significant (p<0.001). The WAVE of the FEV<sub>1</sub> change from same day baseline was comparable for the albuterol groups at Treatment Day 1, Week 6, and Week 12, and pairwise comparisons showed no statistically significant differences between albuterol in HFA or CFC propellant. Repeated measures comparisons revealed the same pattern of statistically significant improvement of each albuterol treatment group over placebo HFA (p<0.001), with no significant differences between the albuterol treatment groups.

When analyzed as the mean percent change in FEV<sub>1</sub> from same day baseline, both WAVE and repeated measures analyses showed that albuterol HFA and albuterol CFC each were statistically favored over placebo HFA at each serial assessment visit. Some statistically significant differences were noted between albuterol HFA and albuterol CFC; these were noted on treatment day 1 overall (p=0.039). Comparison of individual time points during the serial FEV<sub>1</sub> measurements revealed statistical superiority (p <0.05) of albuterol CFC over albuterol HFA for the first two hours of Treatment Visit 1 and the first hour of

treatment week 6. Analyses in which no FEV1 values were carried forward for missing data confirmed the statistical superiority of both albuterol formulations to placebo, and found no overall statistical difference between the HFA formulations. Isolated early individual timepoints (5 minutes on treatment day 1; 5, 15, and 30 minutes on treatment week 6) did show a statistically greater improvement with albuterol CFC than albuterol HFA.

**Medical Reviewer comment:** *Albuterol HFA demonstrates clear statistical superiority to placebo HFA treatment in serial FEV1. For the most part, analyses using changes relative to the same day baseline show no statistical difference in the improvements in FEV1 caused by HFA and CFC albuterol. Yet it should be noted that WAVE changes from baseline for albuterol CFC are consistently greater than albuterol HFA at all timepoints.*

. Baseline FEV1 improved in all 3 treatment groups between day 1 and week 6 of treatment, and continued to improve for the placebo HFA group between weeks 6 and 12. This likely reflects some selection pressure for "healthier" asthmatics to remain on placebo over the 12 weeks of study treatment. The increase in baseline FEV1 complicated the analyses of the mean WAVE based upon changes from the treatment day 1 baseline (data not shown). Using this approach, statistically significant improvement versus placebo was seen with albuterol HFA and albuterol CFC only at treatment day 1 and treatment week 6, even though the WAVE of the change was numerically greater ( $\geq 0.09L$ ) than placebo at all timepoints

When the WAVE of serial FEV1 was analyzed as the mean percent of predicted FEV1 (see following table), both albuterol formulations had values greater than placebo and comparable to each other and to themselves over the 3 visits. Both albuterol formulations showed statistically significant improvement over placebo at treatment days 1 and week 6. At treatment week 12, only albuterol CFC was statistically superior to placebo.

**Weighted Average (WAVE) of Post-Dose FEV<sub>1</sub> Measurements over 6 Hours  
Percent of Predicted FEV<sub>1</sub>**

Time	Placebo HFA	Albuterol HFA	Albuterol CFC
<b>Treatment Day 1</b>			
N	97	101	99
Baseline	65.5	66.5	65.6
WAVE	69.3	77.5*	78.7*
<b>Treatment Week 6</b>			
N	90	89	89
Baseline	69.9	69.4	69.5
WAVE	71.9	76.6*	78.1*
<b>Treatment Week 12</b>			
N	79	84	86
Baseline	71.8	68.7	69.3
WAVE	73.2	76.6	78.1*

\*p<0.023 compared with placebo HFA

Source Data: Tables 24-29

Repeated measures analyses of variance on percent of predicted FEV1 were statistically significant ( $p \leq 0.013$ ) in favor of the albuterol groups at all three visits, with no statistical difference noted between the two albuterol groups. The sponsor attributed the different statistical significance findings at week 12 to the differential weighting of early timepoints in repeated measures analysis versus WAVE. Repeated measures analysis favors a short-acting drug such as albuterol since the four measurements taken during the first hour (5, 15, 30, and 60 minutes) when albuterol is most active are weighted equally with those taken once every hour during the remaining 5 hours.

Other analyses of percent predicted FEV1 (using the Polgar equation for females or no values carried forward) by WAVE and repeated measures analyses found statistically significant findings to be more common using repeated measures analyses.

**Medical Reviewer comment:** *The variation seen in statistical significance using different analytic techniques is largely due to increases in the FEV1 baseline of the placebo group during the 12 week course of the study and the smaller increase in percent predicted FEV1 seen with albuterol HFA relative to albuterol CFC. The comparisons to the same day baseline are the most appropriate for a short-acting drug like albuterol, and these are convincing that albuterol HFA is more effective than placebo. The variable findings using treatment day 1 baseline and percent predicted FEV1 are largely the result of the improved placebo baseline over the course of the study. The reasons for the increased placebo baseline are not clear, and may include selection over the course of the trial for less severe asthmatics.*

#### Functions of Serial FEV1

Analyses of functions of serial FEV1 (see following table) consistently confirmed albuterols CFC and HFA were statistically superior to placebo in all seven functions of serial FEV1. When compared to albuterol HFA, CFC albuterol had greater percentages of patients achieving  $\geq 15\%$  improvement, a greater mean maximum percent change from baseline, and a larger AUC (bl) at all timepoints; of these differences; treatment day 1 mean maximum effect and median onset of effect were statistically greater for CFC albuterol. Time-related measures of effect showed no clear pattern of superiority or inferiority for either product. When analyses were confined to responders with  $\geq 15\%$  increase in FEV1 in 30 minutes [73:55], the numeric advantage of CFC in mean maximum effect and mean AUC(bl) was no longer seen.

**Analysis of Functions of 6-Hour Serial FEV<sub>1</sub>**

Function- Visit:	Placebo HFA			Albuterol HFA			Albuterol CFC		
	Day 1	WK 6	WK 12	Day 1	WK 6	WK 12	Day 1	WK 6	WK 12
% Patients Achieving Effect	25	9	9	82	63	68	89	73	79
% Pts with WAVE ≥15% over base	19	7	5	54	38	39	57	38	40
Median Onset of Effect (hr)	6.00	6.00	6.00	0.07	0.07	0.07	0.05	0.07	0.07
Median Duration of Effect (hr)	0.00	0.00	0.00	3.54	2.07	2.92	3.73	2.41	2.48
Mean Max Eff (% chg from base)	14.7	11.3	10.2	29.6	25.8	26.9	35.6	28.9	29.0
Median Time of Max Effect (hr)	3.0	3.0	3.0	1.0	1.0	0.5	1.0	1.0	1.0
Mean AUC <sub>(0-6)</sub> (L-hr)	0.81	0.44	0.25	2.49	1.69	1.84	2.79	1.89	1.98

WAVE = weighted average of post-dose FEV<sub>1</sub> measurements over 6 hours.  
Source Data: Tables 30-35

**Medical reviewer comment:** *The functions of serial FEV<sub>1</sub> are heavily influenced by the percent of patients achieving effect, so that analyses to control for the lower percent among HFA users tend to eliminate any apparent numeric advantage to the CFC product.*

Analyses of how many patients achieved a ≥15% increase in FEV<sub>1</sub> over time (see table below) showed that the percentages of patients with a ≥15% increase from baseline were substantially higher in the albuterol groups than in the placebo HFA group on all days and all timepoints. Each treatment group had declining percentages of responders from treatment day 1 to week 6 to week 12. The albuterol CFC group percentages were consistently higher than the HFA albuterol group up through the 1 hour time point at all visits, and up through the 2 hours time point on days 1 and week 6. By the hour 3 assessment, the percentages of patients achieving effect were generally similar in the two albuterol groups.

**Percentage of Patients With  $\geq 15\%$  Increase in FEV<sub>1</sub> Over Time**

Timepoint	Placebo HFA			Albuterol HFA			Albuterol CFC		
	Day	WK	WK	Day	WK	WK	Day	WK	WK
Visit:	1	6	12	1	6	12	1	6	12
5 min	11	4	3	59	54	56	76	64	63
30 min	21	9	8	74	60	64	85	67	73
1 hr	25	8	3	74	62	64	85	69	70
2 hr	24	10	14	66	52	58	81	61	59
3 hr	29	12	8	61	42	49	62	42	48
6 hr	24	11	10	27	20	19	39	20	22

Source Data: Tables 36-38

**Medical Reviewer Comment:** *These results, in combination with the functions of serial FEV<sub>1</sub>, suggest that the magnitude and onset of effect with albuterol HFA are slightly less than for albuterol CFC.*

**Other Efficacy Measures**

**PEFR:** Changes from baseline in averaged AM PEFR measurements showed numeric superiority of both albuterol groups relative to placebo, with one statistically significant elevation (seen at weeks 10-12 for albuterol CFC). Changes in PM PEFR were statistically higher than placebo for albuterol CFC at all weeks, but only for weeks 1-6 for albuterol HFA. The following table again illustrates that the magnitude of improvement for albuterol HFA is less than for albuterol CFC.

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

Treatment Period	Placebo HFA			Albuterol HFA			Albuterol CFC		
	N	AM	PM	N	AM	PM	N	AM	PM
Baseline (actual value)	97	(337)	(358)	101	(338)	(360)	99	(333)	(355)
Weeks 1-3	96	-3	-3	101	1	8*	99	1	10*
Weeks 4-6	94*	-1	-4	99	1	9*	95	6	15*
Weeks 7-9	91	-2	-1	91	2	10	92	9	16*
Weeks 10-12	87*	-7	-0	87	5	11	88	9*	16*
Weeks 1-12	96	-3	-3	101	2	9*	99	5	13*

\*Baseline is the average of the ten days immediately prior to Treatment Day 1

\*PM N value = AM N value - 1

Source Data: Tables 39 and 40

\*p<0.021 compared to placebo HFA

**Back-up albuterol use:** Both albuterol groups decreased their mean use of back up albuterol slightly, and for both groups this decrease was statistically better than the slight increase use seen with placebo treatment. The percentage of days without backup albuterol use followed the same pattern of improvement and statistical significance. The percentage increase for albuterol CFC was greater than that for albuterol HFA as seen in the following table.

**Back-up albuterol Use  
Summary of Mean Changes from Baseline**

Treatment Period	Placebo HFA			Albuterol HFA			Albuterol CFC		
	N	# puffs	% days	N	# puffs	% days	N	# puffs	% days
Baseline (actual value)	96	(3.2)	(32.2)	101	(3.1)	(31.1)	99	(3.0)	(35.0)
Weeks 1-3	96	0.3	-3.2	101	-0.8*	12.6*	99	-1.1*	16.4*
Weeks 4-6	93	0.1	2.2	99	-1.0*	14.2*	95	-1.2*	17.4*
Weeks 7-9	91	0.0	3.6	91	-1.0*	14.6	92	-1.1*	16.7
Weeks 10-12	87	0.2	1.6	87	-1.0*	16.5*	88	-1.2*	19.5*
Weeks 1-12	96	0.2	0.3	101	-0.9*	14.2*	99	-1.1*	16.7*

\*Baseline is the average of the 10 days immediately prior to Treatment Day 1.

\*p<0.039 compared with placebo HFA

% days= The percentage of days without the use of back-up albuterol

Source Data: Tables 41 and 42

**Asthma symptoms:** Asthma symptom scores changed negligibly among all treatment groups over the course of the study. The percentage of days with no asthma symptoms increased more in the albuterol groups than the placebo group, and slightly more in the HFA than the CFC albuterol group, but no treatment comparisons were statistically significant.

**Nighttime awakenings:** There was little change from baseline in any treatment group, and no statistically significant treatment comparisons.

**Asthma exacerbations:** These were defined to include out-of-clinic exacerbations (need for treatment with other than allowed concomitant medications, study medication, or back up albuterol MDI) and in-clinic exacerbations (use of back-up albuterol during serial spirometry.) The overall numbers and percentages of exacerbations were greatest for placebo, and were slightly less for albuterol HFA than for albuterol CFC.

**Frequency of Asthma Exacerbations**

	Placebo	Albuterol HFA	Albuterol CFC
Number of subjects	97	101	99
≥ 1 exacerbation of any type	22 (23%)	17 (17%)	20 (20%)
≥ 1 exacerbation in-clinic	10 (10%)	9 (9%)	8 (8%)

Derived by medical reviewer from tables 46 and 47

**Analysis of Pre-Dose FEV<sub>1</sub> (PRN versus QID):** A comparison of pre-dose FEV<sub>1</sub> values at weeks 6 and 12 showed similar improvement in all 3 treatment groups (0.13L placebo and albuterol CFC groups, 0.12 L albuterol HFA group.) At week 12, the placebo group using PRN albuterol HFA had a significantly greater increase in predose FEV<sub>1</sub> (0.22L) compared to albuterol HFA (0.07L).

**Medical Reviewer comment:** The sponsor concluded similar efficacy of QID and PRN albuterol HFA because there were no statistically significant findings in the comparison of pre-dose FEV<sub>1</sub>, morning PEF<sub>R</sub>, asthma symptoms, nighttime awakenings, and asthma exacerbations. In fact, the predose FEV<sub>1</sub> was—

significantly better with PRN than QID albuterol at the week 12 evaluation. The lack of statistically significant differences in patient-measured endpoints is not sufficient to prove similarity of efficacy. A specific PRN indication should not be granted without the kinds of studies the FDA has previously recommended to the sponsor.

**Medical Reviewer Efficacy Conclusions:** Albuterol HFA causes significant improvement in serial FEV1 when compared to placebo HFA. On derived measures of FEV1 (percentage of responders in 30 minutes, mean maximum effect, percent responders  $\geq 15\%$  over time) lower values were observed for albuterol HFA in comparison to albuterol CFC, although these rarely achieved statistical significance. Labeling may be necessary to convey the potential for diminished response relative to CFC albuterol.

## Safety Findings

### Extent of Exposure

As seen in the following table, mean exposure to double-blind study medication was similar in all 3 treatment groups. Exposures  $>84$  days were similar in the two albuterol groups, and slightly lower in the placebo HFA group.

Duration of Exposure to Study Medication

	Placebo	ALB 180mcg QID HFA	ALB 180mcg QID CFC
Number of Subjects	97	101	99
$\leq 21$ days	4 (4%)	2 (2%)	3 (3%)
22-42 days	2 (2%)	7 (7%)	3 (3%)
43-63 days	5 (5%)	5 (5%)	5 (5%)
64-84 days	25 (26%)	20 (20%)	21 (21%)
$> 84$ days	61 (63%)	67 (66%)	67 (68%)
Treatment Days			
Mean	79.4	78.3	79.6
Median	85.0	85.0	85.0

Table 48 from submission

Based on diary card reports of compliance and back up albuterol use, the two albuterol groups received 8 actuations (800 mcg ex valve) per day as QID medication, and approximately 2 actuations of PRN albuterol (200 mcg ex valve) [73:154, 73:161]. The placebo patients received 8 actuations of HFA propellant alone plus approximately 3 actuations of back up albuterol HFA.

### Adverse Events

The following table summarizes the overall occurrence of any adverse event, as well as individual occurrences which exceeded 5% in any group.

**Overall Incidence of Adverse Events and  
Those that occurred in ≥5% of patients in any group**

	Placebo HFA	Albuterol HFA	Albuterol CFC
# subjects	97	101	99
# subjects with any AE	59 (61%)	64 (63%)	56 (57%)
# events	149	177	153
URTI	20 (21%)	18 (18%)	16 (16%)
Headaches	17 (18%)	14 (14%)	15 (15%)
Throat Irritation	7 (7%)	14 (14%)	8 (8%)
Musculoskeletal pain	4 (4%)	6 (6%)	7 (7%)
UR Inflammation	3 (3%)	7 (7%)	5 (5%)
Sinusitis	6 (6%)	4 (4%)	3 (3%)
Any lower respiratory event	11 (11%)	24 (24%)*	10 (10%)
Viral Respiratory Infections	5 (5%)	5 (5%)	3 (3%)
Bronchitis	3 (3%)	6 (6%)	3 (3%)
Cough	1 (1%)	9 (9%)	2 (2%)
Nasal congestion/blockage	2 (2%)	6 (6%)	2 (2%)
Ear signs & symptoms	3 (3%)	1 (<1%)	5 (5%)

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

\*p=0.014 for comparison versus albuterol CFC (CFC)

Source Data: Table 49

The overall occurrence of any adverse event was similar in all treatment groups. When all lower respiratory tract events were considered, there was a statistically significant elevation in the albuterol HFA group relative to albuterol CFC patients. The largest number of patients in this category experienced cough; this affected 9 albuterol HFA patients (6 characterized as moderate, 2 as severe) and 2 albuterol CFC patients (2 moderate, 1 severe). This difference approached statistical significance (p=0.058) in the comparison of HFA and CFC albuterol; compared to the placebo group (1 affected patient), the elevation was statistically significant. A drug relationship with cough was suspected in more albuterol HFA patients (2%) than albuterol CFC patients (1%).

Throat irritation occurred about twice as often in the albuterol HFA group as in the other treatment groups, but this difference was not statistically significant overall or by any pairwise comparison. When investigators classified throat irritation by relationship to study drug, no throat irritation was ascribed to the albuterol HFA group, and to only 1 patient each (1%) in each of the other treatment groups.

The slight increases in selected adverse events in the albuterol HFA group relative to either placebo or albuterol HFA groups (in musculoskeletal pain, upper respiratory inflammation, bronchitis, and nasal congestion/blockage) were not considered to be clinically relevant by the medical reviewer. Headaches that were attributed to study treatment were similar in occurrence in all 3 treatment groups (2% placebo, 3% albuterol HFA, and 2% albuterol CFC.)

A total of 22 patients experienced ≥1 adverse event considered to be severe by the investigator; 7 patients (7%) were in the placebo group, 9 (9%) were in the albuterol HFA group, and 6 (6%) were in the albuterol CFC group. The

incidences of severe adverse events were comparable among treatment groups. Severe adverse events that occurred in > 1% of patients were headache (1% placebo, 3% albuterol HFA, 3% albuterol CFC) and upper respiratory tract infection (1% placebo, 2% albuterol HFA, 0% albuterol CFC).

**Serious adverse events**

There were no deaths during the study. During the placebo run-in, 2 patients experienced serious asthma exacerbations and URIs that were considered unrelated to study drug. Both patients were withdrawn from the study. During randomized treatment, 2 patients had serious adverse events, both involving asthma exacerbations occurring >78 days after initiation of study treatment. One patient was in the placebo HFA group and the other in the albuterol HFA group. Neither exacerbation was considered related to study drug.

**Withdrawals due to adverse events**

In addition to the 2 patients who had serious adverse events during the single-blind placebo run-in, 3 other patients withdrew due to adverse events prior to randomization. Four patients discontinued double-blind treatment due to an adverse event classified as non-serious (see following table).

**Patients Withdrawn due to Adverse Events**

Patient Number	Days on Treatment	Adverse Event	Relation to Study Drug
2366	84 Placebo HFA	Pneumonia	Unrelated
2398	83 Albuterol HFA	Rhinitis	Unrelated
2330	5 Albuterol CFC	Extrasystoles	Unrelated
2306	5 Albuterol HFA	Extrasystoles	Possible

Subject 2306 and 2330 were withdrawn five days after starting study drug due to increased premature ventricular contractions (PVCs) noted on Holter testing conducted on Treatment Day 1. All PVCs in both subjects were singles. Subject 2330 went from a baseline of 2 PVCs in 24 hours to 521 in 7 hours on treatment day 1; subject 2306 went from a baseline of 80 PVCs in 24 hours to 443 in 7 hours on treatment day 1.

**Adverse events Proximate to Post-Dose**

There were no reports of adverse events proximate to taking albuterol HFA, and one report of chest tightness after placebo HFA. The latter occurred on day 23 of use and resolved without treatment or interruption of study drug treatment.

**Medical Reviewer Comment:** *There are no significant safety concerns for adverse events, drug-related adverse events, serious adverse events, or withdrawals due to adverse events. Cough, throat irritation, and headache may merit mention in labeling.*

**Laboratory Abnormalities**

There was no concerning pattern of laboratory abnormalities during the trial, as illustrated in the following table.

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

<b>Abnormal Analyte</b>	<b>Placebo HFA</b>	<b>Albuterol HFA</b>	<b>Albuterol CFC</b>
<b>Below Threshold</b>			
Hematocrit	0	2 (2%)	0
Bicarbonate	0	0	2 (2%)
Glucose	1 (1%)	0	1 (1%)
Hemoglobin	1 (1%)	1 (<1%)	0
Neutrophils	1 (1%)	0	0
RBC	0	1 (<1%)	0
<b>Above Threshold</b>			
Eosinophils	3 (3%)	1 (<1%)	1 (1%)
WBC	1 (1%)	2 (2%)	0
Bilirubin (Total)	0	0	2 (2%)
Glucose	0	1 (<1%)	1 (1%)
Lymphocytes	1 (1%)	1 (<1%)	0
RBC	1 (1%)	0	0
AST (SGOT)	1 (1%)	0	0
ALT (SGPT)	1 (1%)	0	0
Urea Nitrogen	1 (1%)	0	0

The two albuterol HFA patients with a low hematocrit had this value to return to normal on retesting. The two values of elevated glucose were isolated abnormalities in these patients (1 albuterol HFA and 1 albuterol CFC) [Listing 8, 73:365].

**ECGs**

There were no clinically significant ECG abnormalities during the study. Mean QTc intervals and mean change in QTc were comparable between treatment groups as seen in the following table. No statistically significant differences were observed.

**Mean QTc Intervals and Mean Change from Baseline for QTc Intervals**

<b>Time</b>	<b>Placebo HFA</b>	<b>Albuterol HFA</b>	<b>Albuterol CFC</b>
Visit 1, Pre-dose (Baseline)	410	414	414
Visit 1, Post-dose	409	413	415
Mean change from baseline	-0.9	-1.6	0.5
Week 12, Pre-dose	414	415	418
Mean change from baseline	3.9	0.4	4.3
Week 12, Post-dose	410	412	415
Mean change from baseline	0.6	-1.9	1.4

Source Data: Tables 59 and 60

A total of 5 patients (3 albuterol HFA, 2 albuterol CFC) had QTc intervals > 470 msec after the start of randomized drug treatment. Only one patient (on albuterol HFA) had repeated episodes >470 msec, and this patient had an elevated QTc at screening (468 msec) and pre-dose day 1 (476 msec).

**Heart Rate**

Mean heart rates at screening were similar across treatment groups (range 66.6 - 70.5bpm). At each post-dose measurement, mean heart rates were

approximately 1-2 beats less than their pre-dose assessment for each treatment group. Heart rates remained comparable throughout the study.

#### Holter monitoring

A total of 59 patients at 5 selected sites underwent 24-hour ambulatory ECG monitoring (via Holter monitor) at screening and at least once (for approximately 6 hours at Day 1 and Week 12) during the randomized treatment phase.

At the 24 hour Holter screening, there was no statistically significant difference among the treatment groups in the number of patients with VEs or SVEs. The mean numbers of ventricular ectopic events (VEs) and supraventricular ectopic events (SVEs) were 1-2 orders of magnitude greater among albuterol CFC patients than either other study group, but the medians for the 3 groups were very similar. The median number of VEs was low, ranging from 0-1 at Screening, with 75% of the patients having  $\leq 7$  VEs. The median number of SVEs was also low, ranging from 1 to 5, with 75% of the patients having  $\leq 11$  SVEs.

Analysis of the number of patients with  $\geq 50$  VEs showed no concerning patterns among the treatment groups (see table below).

#### Number of Patients with $\geq 50$ VEs During Trial

	Placebo HFA	Albuterol HFA	Albuterol CFC
At screening only	0	1	2
At screening & during study	0	1	3
During study only	1	1	1
Total with $\geq 50$ VEs at any time	1	3	6

Source: Derived from Listing 10 by Medical reviewer

The 3 patients with  $\geq 50$  VEs during randomized treatment are summarized below:

- Patient No. 2332 (placebo HFA) had 3 VEs at Screen, 3 at Day 1 and 231 at Week 12.
- Patient No. 2327 (albuterol HFA) had 7 VEs at Screen, 1 at Day 1 and 57 at Week 12.
- Patient No. 2330 (albuterol CFC) had 2 VEs at Screen and 521 at Day 1.

Two patients were withdrawn from the trial because of extrasystoles noted on their treatment day 1 Holter. One was patient 2330 (albuterol CFC, see above). The investigator felt that the extrasystoles were unrelated to study treatment. In the albuterol HFA group, a 67 year old male had 80 VEs at screening, and 443 on treatment day 1. In the opinion of the investigator, his extrasystoles were possibly related to study drug treatment.

One patient in the albuterol HFA group and one in the albuterol CFC group had  $\geq 50$  SVEs only after the initiation of study treatment. Patient 2319 (albuterol CFC) had 17 SVEs at Screen and 506 at Day 1; patient 2327 (albuterol HFA) had 37 SVEs at Screen, 11 at Day 1 and 107 at Week 12.