FEV1 Response

The following table shows the AUC(bl) as sample means and as adjusted (least squares) means based on ANCOVA. Doses of albuterol are expressed ex-valve.

AUC (bl) L*hr

		Means	Adjusted Means
Placebo		0.30	0.24
HFA	100 mcg	1.22	1.27
	200 mcg	1.66	1.69
	400 mcg	2.06	1.97
CFC	100 mcg	1.54	1.50
	200 mcg	1.70	1.77

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

The effect of study treatments on peak effect (expressed as a percentage of baseline) are displayed below.

Peak Effect (as % of Baseline)

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

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

Secondary efficacy measures are described in the following three tables. Duration and onset of action include analysis of medians since the mean data were skewed by the assumed values used in those patients who did not experience an increase of 15% over baseline. All tables indicate a dose-dependent increase in effect of albuterol HFA and albuterol CFC. The adjusted mean times for duration and onset of action were statistically superior to placebo

for all active treatment arms. Active treatments of both propellants were comparable at similar doses.

Duration of Action (hours)

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

Onset of Action (hours)

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

Responders (Percent reaching 15% improvement over baseline FEV1)

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

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

Other Special Study – Dose-Ranging Methacholine Challenge
Study SALA3009 used methacholine challenges in a 6 way crossover design to compare single doses of albuterol HFA with varying water content in the MDI. This study of 44 adult asthmatic subjects with FEV1≥70% and bronchial hyperreactivity to methacholine did not include an albuterol CFC arm for comparison. Doses of 90, 180, and 360 mcg albuterol HFA were evaluated with ~300 ppm moisture in canister (MIC), and doses of 180 and 360 mcg were evaluated with ~30 ppm MIC with comparison to placebo HFA propellant.

All albuterol treatments had an increase in the $\log_2 PD_{20}$ of more than 2 doubling doses relative to placebo, thus exceeding the difference of one doubling dose that was considered clinically and statistically significant. While there was no statistically or clinically significant difference between like doses of albuterol with differing water content, there was a clinically and statistically significant difference between the 90 mcg dose and the 180 and 360 mcg doses of albuterol HFA. There was an increase in the protective effect from 180mcg to 360mcg, but the increase was not statistically significant. The sponsor considered that the 180 mcg albuterol HFA dose was probably close to a maximum effect on the dose-response curve, so that the increase to 360mcg did not significantly influence efficacy.

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

> The methacholine challenge does demonstrate a dose response relationship between 90, 180, and 360 mcg of albuterol HFA and protection against methacholine-induced bronchial hyperresponsiveness. The study also showed that varying the moisture content of the same dose of albuterol HFA did not affect clinical comparability in the methacholine challenge model.

Analysis of Response in Subsets of the Population
Gender, age, and ethnic origin analyses were done for the combined SALA3002 and SALA3005 adolescent/adult studies and for the SALA3006 pediatric study.

Gender Analyses
Adult Trials: In studies SALA3002 and SALA3005, the weighted average (WAVE) of the change from same-day baseline FEV1 showed both males and females had a statistically superior response with HFA and CFC albuterols in comparison to placebo. Within each gender, pairwise comparisons revealed no statistically significant difference between the two albuterol formulations.

The WAVE of post-dose FEV1 showed a similar response in males and females when the change was analyzed as the percent change from baseline. This comparison normalized the observed (and physiologically expected) differences in baseline FEV1 between males and females. Although the WAVE of the change in males was 0.01 to 0.1L greater in males than females, the percentage increase in FEV1 with albuterol HFA was comparable or greater in females (11.3 –17.4%) than in males (10.7 –15.1%.)

For both genders, the WAVE of mean percent predicted FEV1 was consistently higher with albuterol HFA and CFC (72.3 – 81.6%) than with placebo (71.0 – 75.7%). The magnitude of the percentage change seen in females over the 3 treatment visits (4.5 – 12.9%) was comparable to that seen in males (6.7 – 12.2%), and by repeated measures analysis both groups showed statistical significance at nearly every time point for each albuterol formulation. When WAVE was applied, males achieved statistical significance over placebo at 6 weeks, but not females. No statistically significant differences were noted between the albuterol treatment groups within each gender group.

In both genders, the albuterol treatment groups were significantly better compared to placebo for all serial FEV1 functions: these included percentage of patients achieving effect, median onset of effect, median duration of effect, mean maximum effect, median time of maximum effect, and mean AUC(bl). Overall compared to males, females had a slightly higher percentage of patients achieving effect (by 1-7%), a faster onset of effect (by 0.6 – 6.6 minutes), a longer duration of effect (0.05 – 1.57 hr), and a greater maximum effect (0.6 – 4.4% change from base). Males receiving albuterol had mean AUC(bl) values that were 0.08 – 0.64L*hr greater than females. Males had no statistically significant differences between albuterol formulations with respect to FEV1 functions; females had statistically superior effect with CFC versus HFA albuterol in the percentage of patients achieving effect (wk 6), median onset of effect (day 1), and mean maximum effect (day 1 and week 6).

Medical reviewer comment: *Adolescent and adults dosed chronically with albuterol HFA and CFC do not evidence any notable difference in response by gender. The small observed variation in statistical significance between males and females is scattered and reveals no consistent trends of concern.*

Pediatric Trial: Analysis of treatment groups by gender in this study resulted in subgroups ranging in size from 20 –33 subjects. Analysis of post-dose mean percent predicted PEFR showed comparable responses to albuterol HFA in males (82.0 – 86.9%) and females (86.5 – 88.4%) relative to placebo (75.8 – 77.4%). The change in PEFR from same day baseline showed both males and females had superior responses with albuterol treatment relative to placebo, with variability in which albuterol formulation showed a larger effect (HFA for males by 2.2 – 6.4 L, CFC for females by 11.7 – 12.9L). Analyses of functions of serial PEFR showed both males and females had superior responses with albuterol compared to placebo, with males showing a tendency toward greater responses than females in both treatment groups.

Analysis of post-dose percent predicted FEV1 showed both males and females had higher values than placebo after HFA and CFC albuterol treatments. Females treated with HFA albuterol had a higher percentage FEV1 (4.7 –5.4%) than with CFC albuterol, whereas males showed approximately 1% higher predicted FEV1 with CFC than HFA albuterol. Mean change in baseline FEV1

was approximately 0.1 – 0.2L greater for HFA and CFC albuterol than placebo for both boys and girls. Functions of serial FEV1 showed both males and females to have improved functions relative to placebo with albuterol HFA and CFC. Overall in each treatment group, males tended to have better functions than females.

Medical Reviewer Comment: *There appears to be no clear difference in the effect of Ventolin HFA in males and females ranging in age from 4 years to adult. The slight differences occasionally seen in effect size between males and females are most probably due to chance variation.*

Age Analysis

Combined Adolescent/Adult Studies SALA3002 and SALA3005: In the combined trials SALA3002 and SALA3005, a total of 13 patients were ≥65 years old. Reanalyses of the 597 patients in the 12 to <65 year old population (98% of the total study population) were confirmatory of the findings for the entire population.

Analysis of the data for patients ≥65 years of age was complicated by the very small number of patients in each group. There were 4 patients each in the CFC and HFA albuterol groups, and 5 patients in the placebo group. With the exception of study day 1, both albuterol treatment arms exceeded placebo in the WAVE of percentage change in baseline FEV1. On study day 1, placebo had a higher mean percentage increase in FEV1 (14.2%) by WAVE versus HFA (3.9%) and CFC albuterol (9.4%). Part of the explanation may be that only ¼ HFA patients responded on treatment day 1 with an increase ≥15% in FEV1 over baseline. At treatment weeks 6 and 12, the percentage of responders in the HFA group was 67%.

Medical reviewer comment: *The small numbers of patients studied over the age of 65 years are not sufficient to make conclusions about any potential differences in effectiveness in this population relative to younger patients.*

Pediatric Chronic Dosing Study: Analyses of study SAL3006 by age groups 4 – 8 years and 9 – 11 years supported the efficacy of albuterol HFA and albuterol CFC versus placebo in both age groups. In general, albuterol HFA was similar in effect to albuterol CFC in both age subgroups in percent predicted PEFR & FEV1, mean change in baseline PEFR and FEV1, and functions of serial PEFR and FEV1. The 4 – 8 year old age group tended to have slightly greater responses on age-normalized measures of pulmonary function such as percent predicted FEV1 or PEFR. The 9 –11 year olds had greater mean changes in FEV1 and PEFR as would be expected due to their larger size. Because of small numbers of patients in each age-treatment group (range 15 – 26), comparisons of relative effectiveness of HFA versus CFC albuterol could not be done statistically.

Medical reviewer comment: *There was no pattern to suggest that efficacy of either albuterol HFA or CFC varied with patient age in this trial.*

Ethnic Origin Analyses

Combined Adolescent and Adult Studies: In studies SALA3002 and SALA3005, only 17% (106/610 patients) of the population was non-Caucasian. Because there were only 56 Black patients and 50 patients of other ethnic origins, generalizations based upon these data should be done with caution. In terms of serial FEV1 results, Caucasian and other ethnic origins groups showed data trends similar to the overall population. The Black population results were more mixed, with small effect sizes relative to Caucasians and instances where the placebo treatment effect was greater than either albuterol HFA or CFC. The same patterns held true for functions of serial FEV1. Caucasians had a clear pattern of albuterol HFA and CFC superiority to placebo, with a similar if less pronounced trend observed in patients of other ethnic origins. Blacks again had an overall lower response in functions of FEV1 in all treatment groups, with less separation in effects between the active treatment and placebo groups.

Pediatric Chronic Dosing Study: In SALA3006, there were 80 Caucasian patients, 40 Black patients, and 15 patients of other ethnic origins. In general, analyses of serial PEFR and functions of PEFR showed data trends that were similar to the overall population. In contrast to the combined adult studies where there was a small and inconsistent treatment effect seen in Black patients, Black patients in the pediatric trial had clear cut efficacy with both albuterol formulations relative to placebo. The very small number of patients of other ethnic origins showed a low and variable effect with different study treatments that is difficult to interpret. FEV1 analyses by different ethnicities showed much greater consistency of albuterol HFA and CFC effectiveness across ethnic groups.

Medical Reviewer Comment: *Analyses of small populations of non-Caucasian ethnicity provided no clear evidence of ethnic differences*

Effectiveness of Ventolin in Patients Using Concomitant Inhaled Corticosteroids (ICS)

Combined Adult Studies: The WAVE of change in FEV1 for the albuterol treatment groups in the inhaled corticosteroid (ICS) users was similar to that seen in the albuterol treatment groups that did not use ICS; all groups were superior to placebo. Within each strata of corticosteroid use, the percent predicted FEV1 for albuterol HFA was similar to that for albuterol CFC, and both groups were superior to placebo. With respect to percent predicted FEV1, patients who were not on inhaled corticosteroids had higher values (79.2 – 80.9%) with albuterol treatments than patients who were on ICS and albuterol(72.8 – 76.9%).

Analysis of functions of serial FEV1 stratified by ICS use showed all subgroups treated with albuterol to have improved functions over placebo treatment. Inhaled corticosteroid users who received albuterol had a higher percentage of patients achieving effect within 30 minutes (77-89%) compared to non-users (48 -89%); the same pattern was true for duration of effect, which was 2.49 – 3.69 hours for patients on ICS + albuterol, versus 0 - 3.74 hours for nonICS users + albuterol. Patients using albuterol HFA had a faster median onset of effect if they used ICS than if they didn't, whereas the two ICS use strata had similar median onset of effect for albuterol CFC.

Pediatric Chronic Dosing Study: Of the overall population, 36% (N=49) used ICS and the remaining 64% (N=86) did not. The changes in the percent predicted PEFR and mean change in PEFR from baseline (L/min) with albuterol HFA and CFC treatments were consistently greater than placebo regardless of whether or not ICS were also used. For the most part, the mean PEFR changes seen in the HFA and CFC albuterol groups were similar, with occasional differences likely due to small numbers of patients in each treatment-stratum (N= 13 – 33) in the opinion of the medical reviewer.

Functions of serial PEFR showed all albuterol treatment groups in both ICS strata to have better functions than placebo patients, with the exception of albuterol HFA patients not on ICS at the week 2 evaluation who had poor median onset of action, median duration of effect, and mean maximum effect. Overall, patients treated with albuterol products who also were on ICS had better functions of serial PEFR than albuterol-treated patients who were not on ICS. Responses of HFA and CFC albuterol groups within ICS strata showed no consistent differences.

The WAVE of percent predicted FEV1 by ICS use was similar between the two albuterol groups, and higher than the placebo group. The WAVE of the mean change from baseline FEV1 was greater than placebo for all albuterol-ICS combinations. For both the ICS and non-ICS subgroups, the WAVE of change was similar between both albuterol groups at treatment day 1 and treatment week 2. The WAVE of the FEV1 change was greater at day 1 than at week 2 for all active treatment groups, independent of ICS use.

Functions of FEV1 were improved over placebo in all ICS subgroups of both albuterol groups. Overall, patients on ICS had better functions of serial FEV1 than patients not using ICS. Both ICS and nonICS subgroups of albuterol HFA patients had slightly better functions than comparable groups of CFC patients.

Medical reviewer comments: *In pediatric, adolescent, and adult populations, albuterol HFA and albuterol CFC demonstrated consistent superiority to placebo in post-dose measurements of pulmonary function regardless of concomitant inhaled corticosteroid use. Although individual group sizes did not permit formal*

intercomparison of HFA and CFC albuterol groups, the two treatment groups achieved broadly similar improvements in pulmonary functions. Differences largely reflected the numeric superiority patterns seen in the overall trial, with spurious differences attributable to instability of small subgroups.

Onset of Effect

Onset of effect was examined in SALA3002, SALA3005, and SALA3006. Effect was defined as an increase in FEV1 or PEFR ≥15% above baseline. For each patient in a particular study or combination of studies, the median time to onset of effect over all assessment visits was obtained prior to calculating the summary statistics by treatment group. If a patient did not achieve effect, the onset was set to 6 hours.

Medical reviewer comment: *The use of individual patient medians over all assessment visits minimizes the contribution of large outlying data points due to non-response.*

In the combined adolescent/adult studies SALA3002 and SALA3005, the median onset of effect over all 3 assessment visits was 4.8 minutes for patients treated with albuterol HFA and 4.2 minutes for albuterol CFC. In pediatric study SALA3006 with 2 assessment visits, the median onset of effect was 4.8 minutes for PEFR and 3.6 minutes for FEV1. The respective CFC albuterol median onsets were 11.4 minutes and 96.6 minutes.

Evidence of Long-Term Effectiveness, Tolerance, and Withdrawal Effects

Although there were no trials designed to assess long-term tolerance, the peak effect in FEV1 did not decrease over the 12 week course of the adolescent/adult trials or the 2 week pediatric trial. Baseline function increased over the course of each trial, likely explaining why the change in same day baseline at the end of each of these trials was than at initiation.

Medical Reviewer Conclusions

Three chronic administration trials and two single dose evaluations compared albuterol HFA to both albuterol CFC and placebo. A sixth controlled study compared HFA albuterol with varying water content to placebo treatment in methacholine challenges. In all studies, albuterol HFA demonstrated statistically superior improvement over placebo in multiple measures of pulmonary functions. In those studies that also used albuterol CFC as a comparator, performance of albuterol HFA was not statistically distinguishable from albuterol CFC.

In numeric comparisons of effect in the individual and combined adolescent/adult studies, albuterol HFA tended to manifest slightly smaller effects than were seen with albuterol CFC. In contrast, the single pediatric study found slightly greater effects with albuterol HFA than albuterol CFC.

Single administrations of varying doses of albuterol HFA and CFC in a bronchodilation trial and one measuring prevention of methacholine bronchoconstriction showed statistically significant and dose-related improvement over placebo by each formulation. In these 2 studies, one and two actuations of albuterol CFC were statistically indistinguishable in terms of effect, whereas significant differences were seen between and one and two actuations of albuterol HFA. When albuterol HFA and CFC were directly compared in the bronchodilation trial, there were no statistically significant differences in pairwise comparisons albuterol CFC and HFA at 100 mcg and 200 mcg doses.

Comparison of albuterol HFA and CFC functions of serial FEV1 in the combined adolescent/adult studies showed both albuterol formulations to be statistically superior to placebo, though at selected time points, statistically greater effects were seen with the CFC relative to the HFA formulation. These occurred in the percent of patients achieving ≥15% improvement (week 6), the median onset of effect (day 1 and week 6), the mean maximum effect (day 1 and week 6), and the median duration of effect (day1). The median onset of effect for albuterol CFC was shorter (3.6 to 4.2 minutes versus to 4.2 to 9.6 minutes for HFA) and its duration of effect was numerically larger (2.29 - 3.69 hours versus 1.53 - 3.30 for HFA.) Mean AUC(bl) values were not statistically different for the 2 albuterol formulations, but the mean effect size in the HFA group was consistently lower than for the CFC subjects. Back-up albuterol use was significantly less in CFC than HFA patients in SALA3002, and was consistently lower in SALA3005.

The findings from the single dose studies suggest that the HFA device delivers a somewhat lower or less effective dose on a per actuation basis than the CFC product. After two puffs of either product, statistical and acceptable clinical comparability is achieved. The chronic trials in adults show a strong trend for albuterol HFA to perform slightly less well than albuterol CFC; the opposite findings in the small pediatric trial do not overcome this perception. The clinical and practical significance of the small differences in performance of the two products is unclear. It may be helpful to compare the two products in a rescue situation, such as nocturnal asthma, to clarify if this important type of use shows clinically significant differences between the two products.

Albuterol HFA and CFC provided significant and clinically comparable protection against exercise-induced bronchospasm when compared to placebo HFA.

Analyses of onset of effect in the combined trials showed a range of 4.2 - 9.6 minutes for albuterol HFA versus 3.6 - 4.2 minutes for albuterol CFC. In the combined adult chronic trials, analysis of the medians of individual patients (which discounts outliers) found a median onset of effect of 4.8 minutes for HFA albuterol and 4.2 minutes for CFC.

The sponsor conducted analyses of the adolescent/adult and pediatric chronic administration trials to support their contention that PRN use of albuterol HFA

(which occurred in the control arms) resulted in comparable clinical asthma control to QID albuterol HFA. The studies to support this comparison were not adequate in design or number, and differences in pre-dose AM PEFR (study SALA3005) pulmonary functions and exacerbation rates were sufficient to discount an explicit claim of comparability of QID and PRN albuterol in terms of overall asthma control.

Analyses of subpopulations by gender, age, ethnicity, and inhaled corticosteroid use did not reveal any distinctive differences or patterns for albuterol HFA efficacy.

In conclusion, albuterol HFA provides statistically significant improvement over placebo in the prevention and maintenance treatment of bronchospasm, and in the prevention of exercise-induced bronchospasm. Albuterol HFA is statistically comparable to albuterol CFC in these effects, though its effect and duration of action appear to be somewhat less on average than CFC albuterol.

APPEARS THIS WAY
ON ORIGINAL

INTEGRATED SUMMARY OF SAFETY

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

In addition to these 6 studies (3 acute and 3 chronic) of albuterol HFA done using the US commercial container closure system, the sponsor included safety findings from acute and chronic studies using the previous container closure system. The prior product did not have any coating on the internal surface of the can, did not use conditioned drug substance, and did not have the performance characteristics of the US commercial container closure system. For this reason, safety findings from these prior studies were examined by the medical reviewer solely for the occurrence of deaths and unusual serious adverse events.

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

Patient Disposition
Overall there were 876 patients enrolled in all clinical studies using the US commercial container closure system (USCCCS). (There were 1064 patients exposed to the previous container closure system that are not discussed here.) The percentage of patients completing the studies with the USCCCS was ≥86%, and was ≥90% in the acute studies. The only substantial difference in the numbers of patients completing the trials by demographic subgroups occurred in the pediatric chronic study, where 54.5% of Black patients completed, in contrast to 97.5% of White patients. Among Black pediatric patients, completers ranged from 54.5% for placebo treatment to 87.4% for albuterol HFA.

Of the 876 patients enrolled in studies using the USCCCS, only 10 were withdrawn due to adverse events. The most common reason for withdrawal was "other reasons", followed by lack of efficacy. "Other reasons" included non-

compliance, failure to meet entry criteria, withdrew consent, asthma exacerbation, and protocol variations.

Extent of Exposure
In chronic studies using the USCCCS, exposure to albuterol HFA was for 46 patient-years. The open label safety study SALA3003 discussed in a previous section of this document provided approximately 406 subject-treatment years of exposure to albuterol HFA. Acute exposures to albuterol HFA in SALB2001, SALB2003, and SALA3009 totaled 416.

In chronic dosing studies, 202 adolescent/adult patients were exposed to 180mcg of albuterol HFA QID and 201 were exposed to placebo HFA QID. In the pediatric chronic study, 46 patients were exposed to 180mcg of albuterol HFA QID and 43 were exposed to placebo HFA QID

The adult/adolescent chronic studies (SALA3002 & SALA3005) had roughly equal numbers of men and women exposed, with very few elderly ≥65 years (N=13, 2%) and nonCaucasians (17%) exposed to albuterol HFA. The overall daily mean of puffs of albuterol HFA ranged from 9.7/day at the start of the study to 8.8/day at its conclusion.

The pediatric chronic study (SALA3006) had a few more males (25) than females (21) exposed to albuterol HFA. Fifty-five percent of the exposed patients were in the 9-11 year old age group, with the balance aged 4 to 8 years. Overall, 41% of the exposed population was nonCaucasian. The overall daily mean number of puffs of albuterol HFA was 8.9 per day. Because of the small size of this study, some subgroups were unevenly distributed across treatment categories. Most Black boys received CFC albuterol, most Black girls received HFA albuterol, and the more of the youngest patients (ages 4 –8 years) received CFC albuterol than placebo or the other albuterol formulation.

In acute studies the percentage of men ranged from 41 – 75%, the percentage of non-Caucasians ranged from 3 – 17%, and mean ages ranged from 28 – 36 years.

Adverse Events

Adolescent and Adult Acute Exposure Studies
The incidence of adverse events in studies SALB2003, SALB2001, and SALA3009 was low and comparable across all treatment periods. The most frequently reported adverse events were upper respiratory tract infections and headaches. One cardiovascular event was reported in SALB2003, an episode of QTc prolongation with 360mcg albuterol HFA. The QTc prolongation was to 485msec from a baseline of 443 msec, and occurred in a 50 year old female who weighed 103.2 kg and continued in the study.

Adolescent and Adult Chronic Studies

Adverse events for the 12 week trials SALA3002 and SALA3005 were combined. The following table includes all adverse events that occurred in ≥3% of any treatment group. Overall, adverse events were reported by 63% of placebo patients, 64% of albuterol HFA patients, and 57% of albuterol CFC patients. The incidence of specific adverse events was generally similar across treatment groups. Organ systems where the incidence of adverse events associated with albuterol HFA or placebo HFA exceeded that of albuterol CFC by 3 percentage points were ear, nose and throat, lower respiratory, and non-site specific. Specific events where placebo or albuterol HFA exceeded the active control group by ≥3% were throat irritation, sinusitis, viral respiratory infection, and cough; of these, throat irritation and cough were considered plausibly related to drug exposure by the medical reviewer.

Adverse Events Occurring in ≥3% of Patients in Any Treatment Group
Adolescent and Adult Studies

Adverse Event	Placebo HFA	Albuterol HFA	Albuterol CFC
Ear, Nose, and Throat (any event)	75 (37%)	83 (41%)	71 (34%)
URTI	40 (20%)	39 (19%)	43 (21%)
Throat irritation	14 (7%)	21 (10%)	12 (6%)
Sinusitis	14 (7%)	10 (5%)	5 (2%)
Upper respiratory inflammation	5 (2%)	10 (5%)	11 (5%)
Nasal congestion/blockage	6 (3%)	7 (3%)	5 (2%)
Pharyngitis/throat infection	0	5 (2%)	6 (3%)
Neurology (any event)	31 (15%)	33 (16%)	30 (14%)
Headaches	29 (14%)	26 (13%)	25 (12%)
Lower Respiratory (any event)	21 (10%)	35 (17%)	18 (9%)
Viral respiratory infection	8 (4%)	14 (7%)	8 (4%)
Cough	4 (2%)	11 (5%)	4 (2%)
Bronchitis	7 (3%)	6 (3%)	4 (2%)
Gastrointestinal (any event)	22 (11%)	21 (10%)	21 (10%)
Nausea and vomiting	5 (2%)	5 (2%)	6 (3%)
Viral gastrointestinal infections	6 (3%)	2 (≤1%)	2 (≤1%)
Musculoskeletal (any event)	12 (6%)	16 (8%)	18 (9%)
Musculoskeletal Pain	8 (4%)	10 (5%)	10 (5%)
Non-site Specific (any event)	17 (8%)	16 (8%)	9 (4%)
Fever	6 (3%)	5 (2%)	5 (2%)

Specific adverse events of potential concern with beta-adrenergic agonists were rare (≤1); these included cardiovascular events (extrasystoles, tachycardia, palpitations, and hypertension), tremors, dizziness, sleep disorders, vertigo, and agitation. Headaches occurred at a similar incidence across treatment groups.

The incidence of total adverse events by week ranged from 4 – 8% and was generally similar across treatment groups. At week 3, albuterol HFA had a 12% AE rate compared to 7% in the placebo and albuterol CFC groups. This was attributable to slightly higher rates of URTIs, headaches, throat irritation, musculoskeletal pain, sinusitis, and bronchitis than other treatment groups. At week 6, throat irritation was seen more commonly in the two HFA groups (2 – 3%) than albuterol CFC (0). The medical reviewer noted no temporal trends in adverse events.

There were no reports of adverse events proximate to taking albuterol HFA. There was one report of chest tightness after use of placebo HFA in one patient after receiving placebo HFA for 23 days. This condition resolved without treatment and study medication was not interrupted. All other adverse events that occurred proximate to study drug treatment occurred in albuterol CFC patients, 4 of whom complained of chest symptoms.

Subpopulations by gender, age, and race/ethnicity mirrored the adverse event trends seen in the overall population, in the opinion of the medical reviewer. The types of adverse events were similar in males and females and there were no notable trends noted in the types or frequencies of adverse events reported. Adverse events in the very small number of patients ≥65 years showed no unusual patterns compared to patients 12 – 64 years. Analyses of adverse events by ethnic subpopulations were complicated by the small numbers of nonCaucasian patients, but overall showed no notable trends in adverse events by race/ethnicity.

Pediatric Chronic Study

In SALA3006, the number of patients who experienced at least one adverse event ranged from 14 (30%) in the albuterol HFA group, to 15 (35%) in the placebo HFA group, to 16 (35%) in the albuterol CFC group. 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. Of the 5 adverse events occurring in ≥5% of any patient group, only headache and gastrointestinal signs and symptoms occurred at a higher rate in the HFA placebo and HFA albuterol groups than the CFC albuterol group, and these elevations were minor.

There were no reports of tremors, dizziness, sleep disorders, vertigo, tachycardia, palpitations, or hypertension in this study. The sole episode of psychomotor disorders (hyperreactivity) was reported for albuterol CFC. Headaches occurred at a similar incidence across treatment groups.

Adverse events by week showed no trends of concern, with a stable incidence of headache over the 2 weeks of treatment. Five adverse events were reported proximate to dosing for either albuterol HFA or placebo HFA; none were reported for CFC albuterol. There were 3 episodes of headache (in one patient) that were

associated with placebo HFA, and one episode each of sore throat and throat spasm reported for albuterol HFA. All events resolved with minimal or no intervention, and all patients continued study treatments without interruption.

When analyzed by gender, the total incidence of adverse events was somewhat higher in girls than boys, as seen in the table below. Episodes of throat irritation were seen exclusively in girls using HFA propellant, either as placebo or albuterol. The total number of girls with throat irritation was 3.

Incidence of Adverse Events (%) by Gender

		Placebo	HFA albuterol	CFC albuterol
Overall	Males	26	24	30
	Females	45	38	46
Throat irritation	Males	0	0	0
	Females	5	10	0

Medical reviewer comment: *The exclusive occurrence of throat irritation in females exposed to HFA propellant is of doubtful clinical significance in light of the small numbers in this study. No such pattern was seen in the combined adolescent/adult studies.*

Analyses of adverse events by the age groups 4 – 8 years and 9 – 11 years showed no notable differences in the adverse event profile in younger and older patients. The 3 patients who experienced throat irritation with HFA propellant were in the 9 – 11 year old age group. One patient in the 4 – 8 year old age group 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.

Analyses of overall and specific adverse events by race/ethnicity showed no race-related trends in the adverse event profiles of pediatric patients in SALA3006.

Incidence of Adverse Events with HFA Propellant Alone
Patients assigned to placebo HFA also used albuterol HFA on a PRN basis. As previously described, adverse events in these patients were comparable to the other treatment groups in the adolescent/adult and pediatric studies. Of the adverse events occurring in ≥3% of adolescent/adult patients, only sinusitis, headaches, viral gastrointestinal infections, and fever occurred more frequently in the placebo HFA than in either of the albuterol treatment groups. In the pediatric study, this occurred only for fever.

Medical reviewer comment: *Since the placebo group used albuterol HFA on a PRN basis, there is no comparison group for the placebo HFA group to discern propellant effects from those due to the combination of albuterol with HFA.*

Spontaneous Reports of Adverse Events from the Literature
The sponsor included published reports and abstracts of 25 studies of albuterol HFA, largely done with the 3M product, Airomir. The medical reviewer scanned abstracts, graphs, and tables from these documents. These revealed no serious or unexpected adverse events in patients treated with albuterol HFA. When adverse events were noted, they were consistent with the known pharmacologic effects of albuterol and occurred at similar frequencies to CFC albuterol.

Six references on HFA-134a supplied by the sponsor were also scanned by the medical reviewer for safety data. One noted the recommended occupational exposure limit (8 hours average) for HFA-134a is 1000ppm.

One report from the US Air Force Laboratory described adverse events following inhalation of high doses (4000ppm, 0.4%v/v) of 1,1,1,2-tetrafluoroethane. In this study healthy males were exposed for 30 minutes to concentrations below the published lowest observable adverse effect level, in order to determine PK. The first person exposed to HFA-134a was exposed to 4000ppm for 4.5 minutes, at which point the person lost consciousness and "both pulse and blood pressure dropped to zero". After pulse and BP were restored, 100% oxygen was supplied but the person could not maintain consciousness while in a seated position. After 1 hour in a reclining position, vital signs returned to preexposure levels. The blood concentration for this subject was 1.29 mg/L. A second subject exposed to 4000ppm signaled a need to terminate exposure after 10.5 minutes exposure, at which time BP and pulse were increased. After exposure was aborted, BP and pulse normalized within 30 seconds; the blood concentration for this subject was 0.70 mg/L. When reexposed to 2000 ppm, the subject again experienced an increase in BP and pulse after 2.5 minutes, again with return to baseline within 30 seconds of terminating exposure. The blood concentration of HFA-134a was 0.38 mg/L at the time of termination and 0.2 mg/L 10 minutes after termination. This subject reported chest tightness, headache, and associated dizziness.

The International Pharmaceutical Aerosol Consortium for Toxicology Testing of HFA-134a (IPACT-1) and the Program for Alternative Fluorocarbon Toxicity Testing (PAFT) sponsored a study reported in April 1999 to the Division of Pulmonary Drug Products. In this study of 8 healthy human volunteers exposed to concentrations of 1000 to 8000ppm HFA-134a, there were no adverse events associated with exposure and no instability of BP and pulse was observed.

Medical reviewer comment: *In response to findings of BP and pulse instability in a study of only two patients, a repeat study in 8 patients found no toxicity concerns from HFA-134a propellant alone at concentrations of up to 8000ppm.*

Drug-Related Adverse Events

Adult Acute Dosing Studies
In SALB2003 & SALA3009, headaches were the principal drug-related adverse events noted. In SALB2003, tremors and QTc prolongation in one female patient were related to exposure to 360mcg albuterol HFA. Dizziness and mood disorder were each reported by 1 patient after 360 mcg albuterol HFA in study SALA3009. No drug related adverse events were noted in SALB2001.

Chronic Adult Studies
In combined results of SALA3002 and SALA3005, the overall incidence of drug-related adverse events was low and similar across treatment groups (6% placebo, 5% albuterol HFA, and 4% albuterol CFC). Headaches were the most common drug-related adverse event, and these occurred at similar rates (≤1%) across the 3 treatment groups. Drug-related throat irritation was seen in 1 patient in each of the three treatment groups.

Chest symptoms were attributed to drug treatment in 3 placebo HFA patients (1%), but no other groups. With albuterol HFA, one patient experienced tachycardia and another had extrasystoles on Holter monitoring. The extrasystoles occurred during the first day of treatment and were considered mild in severity (increase from 10 PVCs per hour to >10 PVCs per hour, 443 VEs over 6 hours). This patient was discontinued from the study due to the increase in PVCs.

Drug-related adverse events in other body system categories occurred at low frequencies (typically ≤1%) and showed no concerning trends or patterns in the opinion of the medical reviewer.

Overall, a higher percentage of females (5 –7%) had drug-related adverse events than did males (<1 – 5%). Women reported more headaches than males, but the incidence across treatment groups was the same (2%). No trends were noted for any other drug-related adverse events. Of the 13 patients over the age of 65 years, two had drug-related events. One patient on placebo HFA experienced chest symptoms, and one patient on albuterol HFA experienced extrasystoles; both were withdrawn from the studies. Analyses of drug-related adverse event rates by race/ethnicity were complicated by the small numbers of nonCaucasian patients, but did not suggest any notable differences in adverse event profiles by race/ethnicity.

Medical reviewer comment: *Drug-related adverse events did not show any trends or patterns of concern, either overall or by subpopulation group.*

Pediatric Chronic Dosing Study

Four patients experienced drug-related adverse events with either HFA placebo or albuterol during SALA3006. On albuterol HFA, one patient experienced epistaxis, one had throat irritation, and one had throat constriction and two occurrences of larynx swelling and edema at the same visit. The throat constriction occurred within 15 minutes of dosing, but the larynx swelling did not. All three events in this one patient occurred 2 days after randomization, were moderate in severity, and resolved without treatment on the day of onset. The patient had no further episodes during the next 5 days, at which point she was discontinued from the study at the sponsor's request due to FEV1 being outside 50-80% on treatment day 1. One placebo HFA patient experienced headaches.

Review of subpopulations of the 5 patients with drug-related adverse events (including 1 patient on albuterol CFC with psychomotor disorders) was not done by the medical reviewer because of the small numbers of affected patients.

Medical reviewer comment/conclusions on Adverse events: Acute *and chronic studies in children, adolescents, and adults using the US commercial container closure system of albuterol HFA did not reveal any concerning pattern of adverse events. Headaches were the most frequently reported events and occurred at similar frequencies across treatment groups. Throat irritation was higher in adolescent/adult albuterol HFA patients (10%) than either placebo or albuterol CFC patients (6 – 7%), but not when drug-related events were considered. Cardiovascular events were rare, as were other neurological effects associated with β-adrenergic agents. There was one event (throat constriction) reported proximate to dosing in the pediatric chronic study. There were no notable differences in subpopulations according to gender, race/ethnicity, or age group.*

Analyses of Adverse Event Rates for Use in Labeling

In the combined chronic adolescent/adult studies (SALA3002 and SALA3005), adverse events which occurred in ≥3% of patients treated with albuterol HFA and which occurred more frequently than in the placebo HFA group are represented in the following table.

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Adverse Experience Incidence in Two 12-Week Adolescent and Adult Clinical Trials

Adverse Event Type	Percent of Patients		
	Placebo (n=201)	Albuterol HFA (n=202)	Albuterol CFC (n=207)
Ear, Nose, Throat			
Throat irritation	7	10	6
Upper Respiratory Inflammation	2	5	5
Lower Respiratory			
Viral respiratory infections	4	7	4
Cough	2	5	2
Musculoskeletal			
Musculoskeletal Pain	4	5	5

Adverse events which were considered to be related to treatment but were reported by less than 3% of the adolescent and adult patients receiving albuterol HFA, but by a greater proportion of albuterol HFA patients than placebo patients include: diarrhea, laryngitis, cough, lung disorders, tachycardia, and extrasystoles.

In the pediatric chronic dosing trial (SALA3006), adverse events which occurred in ≥3% of patients treated with albuterol HFA and which occurred more frequently than in the placebo HFA group are represented in the following table.

Adverse Experience Incidence in 2-Week Pediatric Clinical Trial

Adverse Event Type	Percent of Patients		
	Placebo (n=43)	Albuterol HFA (n=46)	Albuterol CFC (n=46)
Ear, Nose, Throat			
Epistaxis	0	4	2
Throat irritation	2	4	0
Lower Respiratory			
Viral respiratory infections	0	4	2
Eye			
Allergic Eye Disorders	0	4	0

The incidence of drug-related adverse events was similar to that in the adult population. Adverse events which were considered to be related to treatment but were reported by less than 3% of the adolescent and adult patients receiving albuterol HFA and by a greater proportion of albuterol HFA patients than placebo patients include: epistaxis, throat irritation, throat constriction, and larynx swelling and edema.

The adult EIB study showed a low and comparable incidence of adverse events across all treatment periods. The adverse events seen were similar in type and frequency to those seen in the chronic adult and pediatric studies.

Deaths, Serious Adverse Events, Patients Withdrawn for Adverse Events, Other Potentially Serious Adverse Events, and Pregnancies

A total of 2392 patients received albuterol HFA via the US commercial container closure system or a previous container closure system. In addition, 3335 patients were enrolled in a post-marketing surveillance study in Germany and used albuterol HFA with the US commercial container closure system.

Deaths
The only 2 deaths that occurred in the entire clinical trial program were in SALA3003, the long-term safety study. One was due to a motor vehicle accident, the other due to diabetic ketoacidosis that occurred 5 days after completing the study. The latter patient's discharge labs showed elevated blood glucose and urine positive for glucose and ketones. This death was considered unrelated to study medication by the investigator.

One death was reported from spontaneous reports. A patient of unknown age and gender who was taking albuterol HFA experienced decreased efficacy; on follow-up, the patient had died of a cerebrovascular accident. The drug relationship was unknown. [120-day safety update: 6, 105]

Serious Adverse Events (SAEs)
In acute and chronic studies in 1328 patients using the US commercial container closure system, a total of 30 SAEs were reported by 24 patients after taking albuterol HFA. (These results include information for SALA3003, the long-term safety study.) In placebo HFA patients, there was one SAE (asthma exacerbation) reported. In acute and chronic studies in 1064 patients using the previous container closure system, a total of 10 SAEs were reported by 9 patients taking albuterol HFA; no placebo patients had a SAE. Adverse events occurring during run-in and run-out periods were not considered by the medical reviewer.

In adolescent/adult patients, no SAEs were reported in acute studies using either closure system. The only SAEs seen after randomization to albuterol HFA in the two 12-week clinical trials with the USCCCS occurred in two patients in SALA3005. One placebo patient had asthmatic bronchitis and an albuterol HFA patient had an asthma exacerbation. In the 120-day safety update report of the long-term safety study, a total of 29 SAEs were noted in 23 patients as described in the table below. All 29 SAEs were considered unrelated to study treatment and the most common was asthma exacerbation.

Serious Adverse Events SALA3003

Subject Number-	Serious Adverse Event	Days on Drug	Caused Withdrawal? (yes = +)
817	Petchia	1	+
842	Asthma exacerbation	53	+
850	Cholecystitis	79	
856	Myoma in uterus	298	
859	Asthma exacerbation Respiratory infection Asthma exacerbation	12 12 188	
868	Motor vehicle accident (MVA) death	267	+
876	Fibroids	240	
952	Anaphylactic reaction to kiwi	302	
972	Vomiting Abdominal pain Throat irritation Abdominal bleeding	209 209 209 209	
986	Asthma exacerbation	161	
1030	Asthma exacerbation	91	
1078	Cellulitis-lower leg	225	
1081	Diabetic ketoacidosis (death)	366	**
1100	Incisional hernia	100	
1108	Asthma exacerbation	61	
1187	Asthma exacerbation	173	
1195	Metrorrhagia	268	
1211	Cancer of the bladder	226	
1220	Syncope	252	
1232	Acute appendicitis	21	
1317	Myocardial infarct	295	+
1320	Hypoxemia Status asthmaticus	304 304	
1338	Rattlesnake bite	66	

** Death occurred 4 days after study discontinuation

Examination by the medical reviewer of narratives for those cases that could plausibly be attributed to study drug (#817, #972, #1220, and #1317) confirmed that the events were not related to study drug treatment.

In the pediatric study SALA3006, one patient experienced an asthma exacerbation and was withdrawn from the study.

In chronic studies using the previous container closure system, there were 10 SAEs in 9 patients randomized to albuterol HFA. Injuries and asthma exacerbations constituted the most common events; all were considered to be unrelated to drug treatment with the exception of 3 patients where the relationship was considered unlikely (events of bacterial skin infection, asthma, and anemia).

Local studies and spontaneous reports through the 120-say safety update revealed 6 SAEs in patients receiving albuterol HFA or albuterol of unknown formulation. Three of these occurred in patients on nonU.S. formulations of albuterol HFA; one was the death from CVA described in the previous section, one was of dyspnea, and the third was a report of oral/perioral numbness and feeling of throat closing in a female patient of unknown age. This patient was hospitalized and treated with cortisone with complete resolution of symptoms. For all of these events, the relationship to study drug was unknown.

The three reports with albuterol of unknown formulation were as follows: hydrops of the gallbladder in a 10 year old female, URTI and cardiac failure in a 60 year old female, and " ill defined craniofacial syndrome" in the male offspring of a woman exposed during pregnancy.

Medical reviewer comment: *Serious adverse events observed during clinical trials as well as the marketing of albuterol HFA were small in number and were either unrelated or unlikely related to drug exposure.*

Withdrawals from Clinical Trials Due to Adverse Events
In acute and chronic trials of 2392 patients using the US and previous container closure systems, 17 patients receiving albuterol HFA were withdrawn for adverse events. Among placebo patients the number was 5, and for albuterol CFC, the number was 9.

In the opinion of the medical reviewer, the only noteworthy withdrawal after randomization in USCCCS studies of albuterol HFA patients occurred in a 67 year old male who had an increase in the mean hourly frequency of PVCs on Treatment day 1. The patient was asymptomatic and untreated for this event, and was withdrawn from the study 6 days after his Holter reading. The relationship to study drug was categorized as possible by the investigator.

In the long-term safety study SALA3003 (reported through the 120-day safety update), 7 patients withdrew from the study due to an adverse event. Of the five that were considered unrelated to study treatment, 4 were SAEs discussed in under that section previously (petchia, asthma exacerbation, MVA, and MI); the fifth case was a bladder neoplasm. One subject experienced an adverse event (nervous/ irritable/ restless/ worsening migraine) that was classified as probably related to study drug, and another subject had dizziness/headache/nausea that was considered to be possibly related to study drug.

The only withdrawal from the chronic trial of the USCCCS in pediatric patients was the previously discussed SAE of an URTI. This event was considered to be unrelated to study treatment.

In studies using the previous container closure system, two withdrawals among patients treated with albuterol HFA deserve mention in the opinion of the medical

reviewer. One patient experienced tremors/palpitations that were considered probably related to study treatment. The other patient experienced chest symptoms/cardiovascular test findings/monoplegia ("heaviness and pressure in the chest") that was assessed as being possibly related to treatment.

Medical officer comment: *The significance of these isolated findings to the safety of the USCCCS is unclear. They are mentioned here for the sake of completeness.*

Pregnancies
Three pregnancies occurred during clinical trials with albuterol HFA: one in SALA3003 (USCCCS), and 2 in studies using the previous container closure system. The two pregnancies carried to term had healthy neonates; the other pregnancy was electively terminated without complications.

Two pregnancies with exposures to unknown formulations of albuterol were reported via spontaneous reports. One report from Germany reported a healthy neonate. The other report from the UK reported an ill-defined craniofacial syndrome in the male offspring of a patient who received salmeterol xinafoate (SEREVENT), albuterol sulfate (VENTOLIN), and beclomethasone (BECLOFORTE) of unknown dose and duration during the pregnancy.

Medical reviewer comment: *Overall, serious adverse events, withdrawals, and pregnancy outcomes raised no notable concerns for the safety of albuterol HFA delivered via the US commercial container closure system.*

Clinical Laboratory Evaluations
In the 6 way crossover study of varying concentrations of albuterol CFC versus albuterol HFA, the only noteworthy lab values outside threshold occurred in 2 patients in the albuterol HFA 90mcg group and 2 patients in the albuterol HFA 180mcg group who had glucose ≥1.5 times the upper limit of normal. No patients met this threshold after the 360mcg HFA albuterol exposure, or after the 90mcg or 180mcg CFC albuterol exposures. Analyses of glucose for the different treatment groups were as reported in the table below. In the opinion of the medical reviewer, the similar percentages of patients with normal values provide reassurance that there are no unusual effects of albuterol HFA upon glucose tolerance.

Glucose Values in Study SALB2003

Treatment/dose in mcg (ex-valve)	Placebo	HFA 100	HFA 200	HFA 400	CFC 100	CFC 200
Glucose transition from normal to high - # affected subjects	3	4	3	8	3	3
% patients with normal glucose	69	59	68	66	66	73

Analyses of clinical lab findings from the combined adolescent/adult studies SALA3002 and SALA3005 and from the pediatric study SALA3006 showed no treatment-related concerns in threshold changes or transitions from normal to abnormal values for any analyte. In particular, threshold analyses and transition analyses of blood glucose were similar using the two different albuterol formulations.

Medical reviewer comment: *The overall incidence of laboratory abnormalities in all studies using the US commercial container closure system was low and comparable across placebo, albuterol HFA, and albuterol CFC treatment groups.*

Cardiovascular Effects

Studies in Adults and Adolescents
In acute studies SALB2003 and SALA3009, heart rate and mean QTc intervals were normal throughout. One patient in SALB2003 had an abnormally prolonged QTc (485msec) after 360mcg of albuterol HFA. This was described as an unfavorable significant change from her "abnormal, significant" baseline ECG. Prolongation of the QTc was not seen in this patient with either 90mcg HFA albuterol or 180mcg CFC albuterol.

In the combined adolescent/adult studies SALA3002 and SALA3005, one patient with incomplete RBBB at baseline who was treated with albuterol HFA had an intermediate treatment visit (week 6) where he met QRS criteria for complete RBBB; by week 12, incomplete RBBB was again diagnosed. This was the only clinically significant ECG abnormality in albuterol HFA patients.

In SALA3002 and SALA3005, mean QTC intervals were similar across treatment groups at each evaluation and ranged from 409 – 419 msec. At each treatment visit assessment, ≤2% of patients were noted to have QTc intervals >470msec, and the percentages in this category were comparable across all treatment groups. Mean heart rates at each treatment visit were similar across treatment groups and declined between 1 – 3 bpm post dosing in all treatment groups.

Holter monitoring in the combined SALA3002 and SALA3005 studies found a low median number of VEs (range 0 –1), with 75% of patients having ≤6VEs. Four patients, all in the albuterol HFA group, had VE runs (1 patient at screening, 1 patient at treatment day 1, and 2 patients at treatment week 12). The number/frequency of patients with ≥50 VEs was comparable across treatment groups. One patient receiving albuterol HFA was dropped from the study due to an increase in VEs at treatment day 1. The median number of SVEs ranged from 0 – 4, with 75% of patients having ≤13 SVEs. The number/frequency of patients with ≥50 SVEs was comparable across treatment groups. Cardiac rates based on Holter findings were comparable in the two albuterol treatment groups, with slightly higher values in the placebo group.

Pediatric Chronic Dosing Study
In SALA3006, no notable ECG abnormalities were found. QTc intervals were ≤440msec in 83-86% of placebo patients, 87-96% of HFA albuterol patients, and 88–100% of albuterol CFC patients over the course of the study. No patient had a QTc >470msec at any time. Heart rates were comparable across treatment groups throughout the study, with the placebo group showing ~1 bpm decline post-dosing, versus 1- 4 bpm increase seen in the albuterol treatment groups.

Holter monitoring in the pediatric study found very rare instances of ectopy, with the median number of VEs equal to 0 in all treatment groups on all 3 monitored occasions (screening, day 1, week 2). Only one patient (on placebo) had a VE run, and this occurred during screening. The median number of SVEs was also low, ranging from 0-1 with 75% of patients having ≤3 SVEs. Mean heart rates by Holter were comparable across treatment groups at each visit.

Medical Reviewer Comments: *Overall there was no indication of any notable effect on cardiovascular parameters in clinical trials of pediatric, adolescent, and adult patients treated with albuterol HFA.*

Vital Signs
Acute studies: In SALB2001, the mean and mean changes in pulse, systolic and diastolic blood pressure were comparable across treatment groups. In SALB2003, categorical analyses of pulse rate, SBP, and DBP increases and decreases showed comparable distributions of changes across the six treatment groups. Analysis of mean and mean changes in DBP showed a small but consistent fall in patients treated with 360mcg HFA and 90 and 180mcg doses of CFC. In SALA3009, mean pulse, SBP, and DBP were comparable across treatment groups.

In combined adolescent and adult chronic studies (SALA3002 and SALA3005), categorical and mean analyses of pulse showed comparable findings across treatment groups. Both albuterol treatment groups had greater percentages of patients with increases in SBP>20mmHg (25-26%) versus placebo (15%). Similarly, the two albuterol treatment groups had greater percentages of patients with decreases in DBP ≥15mmHg (8-10%) than placebo (4%). WAVE of SBP and DBP were similar for all treatment groups.

In the pediatric study SALA3006, pulse was comparable across all treatment groups when examined categorically or as means. The percentage of patients with increases in pulse ≥15bpm was higher in both albuterol groups than in placebo patients. The means and weighted average of serial systolic and diastolic blood pressure readings were comparable across all treatment groups, with greater declines in both SBP and DBP ≥15mmHg in the CFC albuterol group than the other two treatment groups.

Medical reviewer comment: *Vital signs of pulse, SBP, and DBP demonstrated similar findings between placebo, albuterol HFA and albuterol CFC in pediatric, adolescent, and adult clinical trials with the US commercial container closure system. No clinically significant effects on pulse or blood pressure were seen with acute or chronic administration of albuterol HFA.*

Relevant Preclinical Data

HFA-134a
Extensive preclinical evaluations of HFA-134a found very little toxicity. Inhalation administration in rats and dogs for up to one year was well tolerated at doses ~500 fold the maximum daily clinical dose of HFA (0.02mg/kg, based on 16 metered-doses/day). Carcinogencity studies delineated a no-effect level in mice at 1200 times the maximum clinical dose in humans, and 500 times the maximum human clinical dose in rats. HFA-134a was not genotoxic and was shown to have low contact sensitizing potential. Embryolethality was noted at very high exposures (3.34 g/kg/day) in rabbits, with a NOEL that was 134 times the maximum clinical dose.

Albuterol
The toxicological profile of albuterol in animals is consistent with excessive stimulation of β1 and β2 adrenergic receptors. Reproductive effects have been noted in mice (cleft palate) and rabbits (reduced fetal body weight and minor skeletal defects). Benign leiomyomas were found in female Sprague-Dawley rats, but not in hamsters or mice.

HFA-134a and albuterol in combination
Two 3 month studies were done in rats and dogs and showed minimal changes in red cell parameters (increased in rats, decreased in dogs). Reversible increases in heart weights were seen in rats along with minimal increases in lung weights. Minor and reversible laryngeal hyperplasia was seen in 3 high dose rats (57 mcg/L of albuterol HFA) but not at lower doses, and was not seen in dogs. Reproductive studies in New Zealand rabbits found some evidence of maternal toxicity and embryotoxicity at the highest exposure concentration, with fetal anomalies typical of what had been demonstrated in the species with albuterol alone.

Dose-Response and Blood-Level Studies

Studies SALB2008 and SALA3009 found no dose-related safety concerns with single doses of albuterol HFA ranging from 90 to 360mcg ex-actuator.

Study SALB1003 compared 12 actuations (1080mcg ex-actuator) of albuterol HFA and albuterol CFC in a cross-over design in 12 healthy subjects to evaluate the PK/PD relationship of the two formulations (see Biopharmaceutics review for more details). Adverse event profiles were similar for both treatments, with 16

adverse events reported with albuterol HFA and 17 with albuterol CFC. Palpitations were associated with drug treatment in 9 albuterol CFC subjects and 5 albuterol HFA subjects. No significant treatment-related differences were observed for any of the systemic pharmacodynamic effects measured in this study (heart rate, QTc interval, and plasma potassium), but the effect from albuterol HFA was consistently less than albuterol CFC. Clinical adverse events of palpitations were also lower with albuterol HFA (5/12) compared to albuterol CFC (9/12). The rate of absorption was slower from the HFA formulation with a Cmax 30% lower and 15 minutes later than CFC albuterol. The average Cmax of this 6-fold increase in the typical dose was 3ng/mL, slightly greater than what is seen with nebulization (2ng/mL), but less than what is seen with oral administration (18ng/mL).

Drug-Demographic Interactions

Gender

In the combined adolescent/adult trials of SALA3002 and SALA3005, analyses of the most common adverse events (>3 patients) by treatment and gender subgroup showed female patients exposed to HFA propellant had more URTI (23-25%) than males (15-17%) who were comparably exposed. Males and females both had similarly elevated rates of cough and throat irritation with albuterol HFA in comparison to placebo HFA and albuterol CFC patients. No clinically significant trends by gender were seen in the pediatric study SALA3006 or the adult EIB study (SALB2001).

Age

The combined adolescent/adult trials of SALA3002 and SALA3005 had only 13 patients ≥65 years old, so meaningful comparison of age differences between elderly patients and those 12-64 years could not be done. The sponsor combined results from the previous container closure system with the US commercial container closure system so that the number of elderly patients was increased to 96. No gross differences in the overall rate of adverse events or of organ-specific adverse events were noted by the medical reviewer or reported by the sponsor. In SALA3006, analyses of adverse event by the age groups 4 – 8 years and 9 – 11 years showed no notable differences in the adverse event profile in younger and older patients.

Race/ethnic origin

Previous discussions of racial and ethnic subpopulations under adverse events noted no marked differences across racial and ethnic subgroups exposed to albuterol HFA. In the two 12-week adolescent/adult studies, 17% of the population was nonCaucasian, with 9% Blacks and 8% patients of Other ethnic origin.

In the pediatric study, 59% of patient exposures were in Caucasians, 30% (40/135) were in Blacks and 11% (15/135) were in patients of other ethnic

origins. The numbers of nonCaucasians per treatment group were too small to make meaningful comparisons of racial/ethnic differences in safety profile. As noted previously under the Disposition subsection of this section, the completion rate for Black patients in the pediatric trial was notably less (54.5%) than for White patients (97.5%). Among Black pediatric patients, completers ranged from 54.5% for placebo treatment to 87.4% for albuterol HFA.

Medical reviewer comment: *No clinically significant trends in adverse event incidence or profiles were noted for gender, age, or race/ethnicity in the trials conducted in children, adolescents, and adults using the US commercial container closure system.*

Drug-Drug Interactions

Study SALA3005 in adolescents and adults allowed the concomitant use of inhaled corticosteroids (ICS) and so permitted the analysis of potential differences in adverse events by ICS status as seen in the following table.

Most Common Adverse Events (>3 Patients) by Steroid Use Subgroup
Adolescent & Adult Studies

Adverse Events	Placebo		Albuterol HFA		Albuterol CFC	
	ICS	nonICS	ICS	nonICS	ICS	nonICS
Number of Patients	48	49	53	48	45	54
Ear, Nose, and Throat						
URTI	9 (19%)	11 (22%)	9 (17%)	9 (19%)	8 (18%)	8 (15%)
Throat irritation	3 (6%)	4 (8%)	7 (13%)	7 (15%)	5 (11%)	3 (6%)
UR Inflammation	1 (2%)	2 (4%)	4 (8%)	3 (6%)	2 (4%)	3 (6%)
Sinusitis	2 (4%)	4 (8%)	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Ear, Signs & symptoms	3 (6%)	0	0	1 (2%)	4 (9%)	1 (2%)
Neurology						
Headaches	5 (10%)	12 (24%)	6 (11%)	8 (17%)	8 (18%)	7 (13%)
Lower Respiratory						
Viral Resp Infections	0	5 (10%)	1 (2%)	4 (8%)	1 (2%)	2 (4%)
Cough	1 (2%)	0	6 (11%)	3 (6%)	2 (4%)	0
Musculoskeletal						
Musculoskeletal pain	4 (8%)	0	5 (9%)	1 (2%)	4 (9%)	3 (6%)

Overall, adverse event rates were similar for ICS patients (61%) and nonICS patients (60%). Throat irritation and cough were seen more commonly in albuterol HFA patients, in both ICS and nonICS subgroups. Cough was reported more commonly in ICS users than nonICS users within each treatment group. Headaches were more common in the placebo HFA group that was not using ICS. Drug-related adverse events occurred at a low incidence in ICS patients (7%) and nonICS patients (5%). Because of the small numbers of affected patients, no trends were discernible to the medical reviewer.

The pediatric study SALA3006 was also analyzed according to ICS use as seen in the following table. No trends in adverse events related to ICS use were apparent to the medical reviewer due to small numbers in each and

correspondingly unstable estimates. Drug-related adverse events were rare, occurring in 3 patients taking ICS and 2 patients not on ICS.

Most Common Adverse Events (>2 Patients) by Steroid Use Subgroup
Pediatric Trial

Adverse Events	Placebo		Albuterol HFA		Albuterol CFC	
	ICS	nonICS	ICS	nonICS	ICS	nonICS
Number of Patients	13	30	23	23	13	33
Ear, Nose, and Throat						
URTI	2 (15%)	0	0	1 (4%)	2 (15%)	3 (9%)
Throat irritation	0	1 (3%)	2 (9%)	0	0	0
Neurology						
Headaches	1 (8%)	3 (10%)	2 (9%)	2 (9%)	0	3 (9%)
Lower Respiratory						
Asthma	0	0	0	0	0	2 (6%)
Non-site Specific						
Fever	2 (15%)	0	0	0	0	0
Gastrointestinal						
GI Signs & symptoms	0	2 (7%)	1 (4%)	1 (4%)	0	0

Medical reviewer comment: *There were no apparent drug interactions between ICS and placebo HFA, albuterol HFA, or albuterol CFC in pediatric, adolescent, and adult patients.*

Drug-Drug Interactions between albuterol and HFA-134a propellant
Comparisons of adverse events in the placebo HFA and albuterol HFA groups showed a greater incidence of throat irritation and cough in the albuterol HFA group in the combined adolescent/adult trials. Other adverse events in this trial and in the pediatric trial (SALA3006) occurred at similar rates in placebo and albuterol HFA patients.

Drug-Disease Interactions
The clinical trial program for albuterol HFA excluded patients with significant diseases other than asthma, so interaction of albuterol HFA with these diseases cannot be assessed.

Paradoxical bronchospasm was not reported in any studies using the US commercial container closure system. Adverse events proximate to taking study medications were noted in one placebo HFA patient in SALA3005; in SALA3006, there were 2 albuterol HFA patients and 1 placebo HFA patient reporting symptoms within 15 minutes of dosing. The SALA3005 patient reported intermittent chest symptoms (chest tightness after use of placebo HFA study inhaler) that resolved without treatment or interruption of study medication. The placebo HFA patient from SALA3006 reported 3 instances of headache after using study drug. One patient using albuterol HFA in SALA3006 reported a mild sore throat, and the other reported a moderate throat spasm that resolved and did not lead to discontinuation of the study drug.

When out-of-clinic asthma exacerbations (that is, exacerbations requiring more than the use of back-up albuterol) were compared across treatment groups, there was a similar rate across treatment groups in the combined adolescent/adult studies and the pediatric study. These data suggest that albuterol HFA did not have a deleterious effect on the incidence of asthma exacerbations.

Medical reviewer comment: *The adverse event profiles for placebo HFA and albuterol HFA were similar with the exception of throat irritation and cough, where a greater incidence was seen with the albuterol HFA combination. Throat constriction proximate to dosing was noted in one patient in the chronic pediatric study using the USCCCS. Paradoxical bronchospasm was not seen and asthma exacerbation rates were not increased in these trials, suggesting no deleterious drug-disease interactions in the asthmatic population.*

Pharmacological Properties Other than the Property of Principal Interest

Beta-adrenergic agonists can affect the cardiovascular and neurological body systems and potentially modify serum chemistry values of potassium and glucose. These adverse events were examined in previous subsections which discussed effects upon vital signs, heart rate, pulse, systolic and diastolic blood pressure, QTc interval, ventricular and supraventricular ectopy, serum potassium and serum glucose. No clinically significant effects were noted in vital signs, 12-lead ECGs, Holter monitoring, or serum potassium in any of the treatment groups.

In cross-over study SALB2003, two patients in the albuterol HFA 90mcg group and 2 patients in the albuterol HFA 180mcg group had post-dose serum glucose values ≥1.5 times the upper limit of normal. No patients met this threshold after the 360mcg HFA albuterol exposure, or after the 90mcg or 180mcg CFC albuterol exposures. Elevated blood glucose (<1.5 times ULN) was seen in 8 patients receiving 360mcg of albuterol HFA in SALB2003. One patient treated with 180mcg albuterol HFA on a QID basis in SALA3003 died of DKA 5 days after completing the study. The episode of DKA was not considered to be drug-related by the investigator.

Medical reviewer comment: *The finding of slight elevations of glucose values with higher-than-normal single doses of albuterol HFA (360mcg) does not raise any significant safety concerns given the expected pharmacodynamic effects of high doses of albuterol. The two patients with glucose values beyond threshold at the two lower doses of albuterol HFA are difficult to interpret, since there was no similar elevation with the 360mcg dose of albuterol HFA, and no similar pattern seen in any of the other acute and chronic studies using HFA albuterol with the USCCCS.*

Long-Term Adverse Events
The results of the SALA3003, a one-year open label safety study of albuterol HFA and the 120-day safety update for this product were reviewed in previous sections of this document.

Withdrawal Effects
No studies were performed to assess withdrawal effects of albuterol HFA.

Drug Abuse
Addiction to fluorocarbons had been documented, although there is no clinical evidence that HFA-134a induces CNS effects or possesses other attributes which might lead to voluntary abuse. To date, there have been no reports of dependency to inhaled albuterol HFA-134a. No instances of dependency were described in the clinical trials for albuterol HFA.

Overdosage
Manifestations of overdosage with inhaled and oral albuterol formulations have been well-described in the literature. As of the 120-day safety update, no cases have been reported to Glaxo Wellcome of an overdose of albuterol HFA. The manifestations of overdose of albuterol HFA are expected to be identical to those reported with Ventolin Inhalation Aerosol: tremor, hyperactivity, headache, and increased heart rate. Possible metabolic effects of hypokalemia and hyperglycemia should also be considered and assessed.

Although no clinical studies were done to assess the effects of overdosage of HFA-134a, studies in healthy volunteers have used up to 16 actuations as a single dose and up to 10 actuations QID for 14 days. No significant effects were observed on blood pressure, pulse, ECG, and PEFR. Liver enzymes and other laboratory parameters showed no drug-related changes of significance and no serious adverse events have been reported.

Two studies were done using high exposures to HFA-134a. One observed erratic BP and pulse in 2 healthy volunteers at 2000 and 4000ppm, whereas the second study observed no instability of vital signs in 8 subjects exposed to concentrations of up to 8000ppm of HFA-134a.

Medical Reviewer Overall Comments and Conclusions

As detailed in the individual sections of this ISS, albuterol HFA was well-tolerated and raised no safety concerns in pediatric, adolescent, and adult patients. In terms of adverse events, throat irritation and cough were seen in slightly greater numbers of albuterol HFA patients than either placebo or CFC albuterol controls; drug-related rates of these events were similar across treatment groups. Cardiovascular events were rare, as were other neurological effects associated with β-adrenergic agents. There was one event (throat constriction) reported

proximate to dosing in the pediatric chronic study. There were no notable differences in subpopulations according to gender, race/ethnicity, or age group.

The overall incidence of laboratory abnormalities in all studies using the US commercial container closure system was low and comparable across placebo, albuterol HFA, and albuterol CFC treatment groups. In one acute study where 360mcg of albuterol HFA was administered, a small number of patients increased their blood glucose from normal to high values; no glucose intolerance was noted in any other study. Serious adverse events observed during clinical trials as well as the marketing of albuterol HFA were small in number and were either unrelated or unlikely related to drug exposure.

Overall there was no indication of any notable effect on cardiovascular parameters of heart rate, QTc intervals, or ectopic events in clinical trials of pediatric, adolescent, and adult patients treated with albuterol HFA. Vital signs of pulse, SBP, and DBP demonstrated similar findings between placebo, albuterol HFA and albuterol CFC in pediatric, adolescent, and adult clinical trials with the US commercial container closure system. No clinically significant effects on pulse or blood pressure were seen with acute or chronic administration of albuterol HFA.

Paradoxical bronchospasm was not seen and asthma exacerbation rates were not increased in these trials, suggesting no deleterious drug-disease interactions in the asthmatic population.

At very high and prolonged exposure levels of HFA-134a, instability of BP and pulse were observed in two healthy volunteers. The significance of these findings to the exposures likely to occur with MDI use is unclear, particularly since a second study at higher exposures did not replicate these findings.

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DATA QUALITY ASSURANCE

For the four pivotal clinical trials, the individual reviews in this document describe auditing done by the medical officer using case report forms supplied by the sponsor. These checks found no irregularities in the data reported in support of this NDA. In addition, two study sites were selected for inspection by the FDA Division of Scientific Investigations. The rationale and findings for these inspections are reported below. No substantive concerns related to data quality were raised.

Rationale and Results of Division of Scientific Investigations Inspections
The four pivotal clinical trials were reviewed jointly by the Medical and Statistical reviewers to see if there were any signals that a particular study or site needed to be audited. In the multicenter trials, no one center dominated in enrollment, nor were any suspicious patterns or types of protocol violations found. Treatment by center interactions were checked for any evidence of undue variation across study centers.

There were some irregularities in SALA 3002 which led to its selection as an audit site. One of the investigators (#5348) included in the analysis has been the subject of an FDA regulatory action and all data from this site are suspect for drug approval. The sponsor also identified a site (#1415) where audit of another study (for fluticasone) raised concerns that data integrity had been compromised; additional analyses excluding this site had been done. Finally, the statistical reviewer noted that Treatment by center interactions from SALA 3002 had the smallest p values of any of the multicenter clinical trials, although no interaction term fell below 0.05.

SALA 3006 was recommended for auditing since this was the only pivotal trial examining efficacy and safety in the pediatric population. In this study, one Massachusetts investigator contributed the greatest percentage of patients to the study (17% versus a range of 4 –14% for all other investigators).

For both sites, the Division requested a general survey of the trial conduct, IRB approval process, and conduct of internal auditing by the sponsor. In addition DSI was requested to review treatment assignment and to compare selected FEV1 values from the original data source to the values reported in the NDA.

For the investigator from SALA3002, no deviation from regulations was found and data from this study were found to be acceptable. For the investigator from pediatric trial SALA3006, minor deviations from regulations were found; 5 subjects were entered into the trial prior to obtaining IRB approval of the study. Data from this study were considered to be acceptable.

Medical reviewer comment and conclusions: *Inspections of two clinical sites found no or minor irregularities in study conduct. Data from both sites were found to be acceptable. Because of data irregularities noted in studies not contained in this NDA application, results from 2 investigators from SALA3002 (the adult 12 week "switch" trial) were considered suspect and reanalyses without data from these sites were performed by the sponsor.*

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DEFICIENCIES

Deficiencies

1. We note that in the two 12 week clinical trials in adolescents and adults (SALA3002 and SALA3005), Ventolin HFA consistently showed a smaller effect size than Ventolin CFC, albeit without statistically significant differences between the two formulations. In order to further evaluate the observed difference in effect size, provide any available additional data or analyses to further address this small apparent difference in efficacy and its clinical significance. Such data may include results of additional comparative clinical trials of Ventolin HFA versus albuterol CFC, particularly any studies conducted during periods of asthma exacerbation such as the nocturnal asthma model. These numeric differences in efficacy may merit inclusion in the final product labeling.
2. In trial SALA3005 and in foreign post-marketing experience from your site, an increased rate of clogging relative to Ventolin CFC was noted with Ventolin HFA. To evaluate this difference in actuator clogging, provide additional data or follow-up on factors that might be associated with clogging, such as product age from time of manufacture, use of overwrap, timing of removal of overwrap, the number of doses delivered from the canister, and associated clinical performance as assessed by in-clinic or home-measured pulmonary function assessments. Provide analyses from foreign marketing experience or other post-marketing surveillance to quantify and/or explain the in-use clogging of Ventolin HFA actuators..

INITIAL CLINICAL COMMENTS ON LABELING

Overall Comments

1. The labeling for Ventolin HFA should reflect current labeling standards for beta-agonists as reflected in mark-ups from the FDA regulatory project manager. These include rewordings and updates to clinical pharmacology (mechanism of action), warnings (do not exceed recommended dose), and precautions (general, information for patients, carcinogenesis etc, nursing mothers) sections.

OVERALL CONCLUSIONS

Please refer to the Executive Summary on Safety and Efficacy at the beginning of this review document, as well as the summary conclusions found at the end of the ISE and ISS.

REVIEWER RECOMMENDATION

From a clinical standpoint, Ventolin HFA is approvable for the treatment and prevention of bronchospasm in patients four years of age and older. Issues requiring further information prior to approval include the lower effect size relative to Ventolin CFC, clogging in patient use, and chemistry issues of dose content uniformity

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