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RESEARCH**

APPLICATION NUMBER:
20983

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #: N 20-983

Application Type: NDA (complete response to Approvable action)

Sponsor: GlaxoWellcome
Investigator: Multiple
Category: Bronchodilator

Proprietary Name: Ventolin HFA
USAN Name: Albuterol sulfate
Route of

Reviewer: Eugene J. Sullivan, M.D.,
FCCP

Administration: Oral Inhalation
Review Date: November 20, 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type
June 29, 2000	July 3, 2000	Complete Response
July 6, 2000	Response to request	Special Safety Update: Final

REVIEW SUMMARY: This is a Medical Officer Review of the Applicant's Complete Response to a prior "Approvable" letter issued by the Agency. The drug product is a new, non-CFC formulation of albuterol metered dose inhaler, Ventolin HFA. As discussed in the Medical Officer Review of the original NDA submission, the studies submitted with the original NDA provide adequate evidence of safety and efficacy for Ventolin HFA in the prevention and maintenance treatment of bronchospasm in adults and children, and in the prevention of exercise-induced bronchospasm. This Complete Response submission (6/29/00) sufficiently addresses the Agency's clinical comments, as listed in the "Approvable" letter. One of the Agency's comments in the "Approvable" letter pertained to evidence from the clinical trials that the HFA product consistently demonstrated a numerically smaller effect size compared to the reference CFC product. This difference was not statistically significant in most analyses. After review of the Applicant's response to this comment, we have determined that reference to this small difference should be included in the U.S. label.

Also reviewed in this document is the Final Safety Update, which was submitted on 7/6/00. This submission did not raise any new safety concerns. Finally, the 7/6/00 submission also included examples of the approved labels from other countries (Australia, United Kingdom, and Canada). Review of these documents did not suggest that any changes to the proposed US label should be made.

The application is sufficient for Approval from the clinical standpoint. Several labeling changes must be made prior to approval. These are outlined in this document (Section 3.4), and will be conveyed to the Applicant in subsequent labeling discussions.

OUTSTANDING ISSUES: Labeling discussions will be held between the Agency and the Applicant.

RECOMMENDED REGULATORY ACTION:

XX Approvable Not Approvable

SIGNATURES: Medical Reviewer:

Date: 11/20/00

Eugene J. Sullivan, MD, FCCP

Medical Team Leader:

Date: 11/20/00

Badrul Chowdhury, MD, PhD

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1. Administrative Background

On June 30, 1998, GlaxoWellcome submitted an original NDA for a non-CFC MDI formulation of albuterol sulfate, Ventolin HFA (NDA 20-983). On July 1, 1999, the Agency issued an Approvable letter for this application. The Approvable letter contained 43 comments, most of which pertained to CMC issues. The letter also included three clinical comments, a list of suggested labeling revisions, and a request for updated safety information. GlaxoWellcome has submitted a response to the Agency's comments (Letter date June 29, 2000) and a Final Safety Update (Letter date July 6, 2000). This Medical Officer Review will assess the adequacy of the Applicant's responses to the clinical comments contained in the Approvable Letter and review the Final Safety Update. The responses to the CMC comments will be reviewed by the CMC reviewer in a separate document.

2. Brief Summary of the Clinical Program

The NDA was supported by four pivotal clinical trials: two 12-week trials in adolescents and adults (SALA3002 and SALA3005); one 2-week trial in children aged 4-11 (SALA3006); and one single-dose, exercise-induced bronchospasm study in adolescents and adults (SALB2001). The program also included the following 3 studies: one single-dose, dose-ranging study in adults (SALB2003); one single-dose, methacholine challenge study in adults (SALA3009); and one 1-year, open-label safety study in adults (SALA3003).

According to the Medical Officer Review [Dr. Trontell; 6/23/99; Executive Summary of Efficacy and Safety], in all controlled trials albuterol HFA demonstrated statistically superior improvement over placebo in multiple measures of pulmonary function related to FEV₁. In those studies that also used albuterol CFC as a comparator, performance of albuterol HFA was not statistically distinguishable from albuterol CFC.* However, in the multiple-dose adolescent and adult studies, albuterol HFA showed a numerically smaller improvement in FEV₁ than was seen with albuterol CFC. This contrasts with the results of the 2-week pediatric study (SALA3006), in which the HFA formulation demonstrated slightly greater effects on PEF and FEV₁.

There was other evidence that the HFA formulation delivers a lower/less effective dose on a per actuation basis than the CFC product. In a single-dose (1200mcg) PK/PD study in healthy volunteers, the HFA formulation showed a lower C_{max} and greater T_{max} as compared with the CFC formulation. In the single-dose, dose-ranging study in adults (SALB2003) and in the single-dose methacholine challenge study in adults (SALA3009), one and two actuations of albuterol CFC were statistically indistinguishable in terms of effect, whereas significant differences were seen between one and two actuations of albuterol HFA. Finally, the combined adolescent/adult studies showed that the HFA formulation had a longer median time to onset of effect (4.2-9.6 minutes versus 3.6-4.2 minutes), had a shorter duration of effect (1.53-3.30 hours versus 2.29-3.69 hours), and was associated with more albuterol "back-up" use than the CFC formulation. This difference in albuterol "back-up" use was numerical in study SALA3005 but was statistically significant in study SALA3002.

Albuterol HFA was well tolerated and raised no safety concerns in pediatric, adolescent, and adult patients. 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.

The Medical Officer Review states: "In summary, Ventolin HFA was shown to provide statistically significant improvement over placebo in the prevention and maintenance treatment of bronchospasm in adults and children, and in the prevention of exercise-induced bronchospasm. Ventolin HFA is statistically comparable to albuterol CFC in these effects, though its effect and duration of action appear to be slightly less on average than CFC Ventolin. The clinical significance of this is unclear." [MO Review dated 6/23/99, page 6]

3. Responses to Agency's Clinical Comments

* According to the Statistical review [Dr. Gebert, 1/14/99], there were statistically significant differences between the products for onset of action and for peak effect on Day 1 in study SALA 3005 (p=0.011). The CFC product had a faster onset of action and a greater peak effect.

The action letter included three clinical comments. These were comments number 38, 39, and 40. Comment 41 related to suggested clinical labeling revisions. For ease of reference to the action letter, the discussion below will retain the comment numbers used in the letter.

3.1. COMMENT #38

This comment reads: "We note that in the two 12-week clinical trials in adolescents and adults (SALA3002 and SALA3005), Ventolin HFA Inhalation Aerosol consistently showed a smaller effect size than Ventolin CFC Inhalation Aerosol, 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 Inhalation Aerosol versus Ventolin CFC Inhalation Aerosol, particularly any studies conducted during periods of asthma exacerbation, such as in a nocturnal asthma model. These numeric differences may merit inclusion in the final product labeling."

The Applicant has no new data or analyses to provide. In response to this comment, the Applicant emphasized that comparability between the CFC and HFA formulations was established, that there was no statistical difference between the CFC and HFA formulations, and that, in the Applicant's opinion, the small numerical difference between the two formulations is not clinically meaningful.

Reviewer's Comment: The requisite evidence of safety, efficacy, and comparability have been established by the clinical program, and approval is appropriate. In the MO review of the original NDA, a small but consistent difference in effect between the HFA formulation and the CFC formulation was noted. The Applicant has not presented any data to suggest such a difference does not exist. Because it is expected that many physicians will prescribe Ventolin HFA Inhalation Aerosol for patients who have previously used the CFC formulation, it would be appropriate to include some description of the relative effectiveness of these two formulations in the product label. Specific language regarding the comparative efficacy between the HFA and CFC formulations is included in the discussion of Comment #41 below. This language has been drafted in keeping with the language that has been used in the labels for Proventil HFA Inhalation Aerosol (Schering) and Serevent Diskus (Glaxo Wellcome).

3.2. COMMENT #39

This comment reads: "In trial SALA3005 and in foreign post-marketing experience from your [] site, an increased rate of clogging relative to the Ventolin CFC Inhalation Aerosol was noted with the Ventolin HFA Inhalation Aerosol. 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 Inhalation Aerosol actuators.”

In response to this comment, the Applicant summarized the data from study SALA3005. In this study, 15 out of a total of 1,364 Ventolin HFA canisters malfunctioned, resulting in a malfunction rate of %. Of these 15 canisters, nine canisters, used by three patients, were clogged or partially clogged. Of the nine, four were to be administered QID and five were to be administered PRN. The malfunction rate in the multi-dose studies, excluding SALA3005, was %.

The Applicant addressed the potential factors that might be associated with actuator clogging which were suggested by the Agency. From the data available, the Applicant states that none of these factors seemed to contribute. Because other trials using the same material were initiated earlier and ended later and did not demonstrate a high device failure rate, product age from time of manufacture was not felt to contribute. Because none of the studies used overwrapped inhalers, the use of overwrap did not seem to contribute. There was limited information with which to assess the potential association with the number of doses delivered from the canister prior to actuator clogging. However, four inhalers that were used QID were noted to be clogged or partially clogged after 3-16 days, suggesting duration of use is not a factor. Thus, the Applicant could not identify any specific factor that might be associated with increased actuator clogging.

Reviewer’s Comment: No data are provided regarding duration of use for the PRN canisters that clogged.

Review of PEFr and diary data from the patients who experienced clogging of their canisters did not suggest decreasing effectiveness which might be attributed to the canisters becoming clogged.

Reviewer’s Note: The large difference in malfunction rates between study SALA3005 and the other clinical studies might be explained in three ways: 1) the failure rate seen in SALA3005 was a spurious finding; 2) the design of study SALA3005 in some unique way contributed to an increase in device malfunction rates within the study; or, 3) the design of study SALA3005 was uniquely sensitive in detecting device malfunctions. The low world-wide post-marketing malfunction rates discussed below are encouraging.

Ventolin HFA is manufactured at three sites.

The Applicant provides data on the total complaints and on the complaints due to actuator clogging for each site [1:190-191]. This data is summarized in the table below.

Complaint rates at the three manufacturing sites [1:190-1]			
Site	Year	Total Complaints	Complaints due to "clogging"
[redacted]	1997	0.0054%	0.0042%
	1998	0.0044%	0.0026%
	1999	0.0029%	0.0016%
[redacted]	1998	0.00012%	0%
	1999	0.00034%	0.00015%
[redacted]	1998	0.0005%	0%
	1999	0.0026%	0.0008%

The Applicant also notes that all complaints related to clogging resolved with adequate cleaning and that in January 1998 it instituted a mandatory change in worldwide labeling for Ventolin HFA to emphasize the importance of washing the actuators on a weekly basis.

Reviewer's Note: While the complaint rates (total and "clogging"-related) are higher at the [redacted] site, the actual rates are quite low. The proposed label includes information on appropriate care of the canisters.

3.3. COMMENT #40

This comment reads: "In SALA3005, unfavorable changes in physical examinations were observed in the ears, nose and throat category as follows: 8% placebo HFA; 13% albuterol HFA; and 5% albuterol CFC. In light of the increased rate of adverse events of throat irritation seen in the albuterol HFA group, and the greater rate of unfavorable ENT physical examination changes also seen in this group, provide the specific ENT findings from the CRFs that were considered unfavorable relative to baseline for all 3 treatment groups."

The Applicant submitted a table that includes the related medical history, baseline ENT physical examination findings and final ENT physical examination findings for all subjects with unfavorable changes in the ENT category on the final physical examination. The CRFs for all of these patients were also submitted. The great majority (88%) of the physical examination findings in the ENT category were nasal in origin. The findings were primarily mucosal edema and nasal discharge. Ninety-six percent of the patients with unfavorable nasal findings had a history of allergies, allergic rhinitis or sinusitis. The non-nasal findings were "mucosal edema-right TM, questionable fluid" (placebo group), thyroid nodule (Ventolin HFA group), "black tongue" (albuterol CFC group), and reddened throat (along with nasal mucosal edema and secretion and palatal ulcer in a patient in the albuterol CFC group).

The differences between groups regarding the numbers of patients with unfavorable changes in ENT physical examination were small. Although the number of such patients

in the Ventolin HFA group was slightly greater than in the placebo group (13 versus 8), such a difference is not likely meaningful. A difference nearly as great (5 patients versus 8 patients), favoring albuterol CFC over placebo was also seen, despite the fact that albuterol CFC would not be expected to be superior to placebo in this regard.

Reviewer's Comment: the information provided by the Applicant regarding ENT adverse events and physical examination changes does not suggest the changes to the label are needed.

3.4. COMMENT #41

Comment 41 provided specific revisions to the draft labeling. The Applicant has incorporated the suggested revisions.

The following changes to the label should be made [line numbers refer to the non-strike-out version of the revised package insert in the 6/29/00 submission]:

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Proposed Labeling

4. Final Safety Update

4.1. INTRODUCTION

In a document dated July 6, 2000, the Applicant submitted a Final Safety Update. This document includes additional safety data from clinical trials and spontaneous reports from July 1, 1998, the data cut-off date for the 120-day Safety Update, to February 25, 2000.

No new US trials have been performed since the 120-day Safety Update. This submission includes "interim information" on SAEs, pregnancies and withdrawals due to adverse events from the following three ongoing, non-US trials:

SERL01: A multicenter, randomized, double-blind, single-dummy, stratified parallel group study designed to determine the compliance of patients taking open-labeled fluticasone propionate (HFA) twice daily and to determine the effect that salmeterol (HFA) given twice daily has on compliance with the corticosteroid treatment. Open-labeled Ventolin HFA was given as a rescue medication to be used as need. A total of 141 patients were treated for a duration of 60 days.

SALL19: A single-center, randomized, double-blind, double-dummy, crossover study designed to investigate the efficacy and safety of cumulative doses of salbutamol delivered via the Turbohaler compared with the HFA MDI in pediatric patients with reversible airways obstruction. A total of 10 patients were treated for a duration of 5 days.

SBO40001: A prospective, non-interventional, observational study designed to determine the event rates measured after the introduction of albuterol/GR106642X compared to events measured prior to its introduction. The number of patients in this study is not given.

Case narratives are provided for the two patients that experienced SAEs in the clinical trials. Case report forms are provided for the one patient who withdrew from a study (SERL01) due to an adverse event. No deaths were reported in these trials.

Case narratives of all spontaneous reports of death, SAEs, and pregnancies that occurred during the reporting period are also included in the submission. These reports are related to commercial use of the product outside the US. As of February 25, 2000, 53 countries have approved albuterol/GR106642X Inhalation Aerosol.

The information provided in this final safety update does not suggest any previously unrecognized safety concern.

4.2. EVENTS DURING CLINICAL TRIALS

There were two serious adverse events in the SERL01 trial. In this trial Ventolin HFA was used as a rescue medication only. A 53-year old woman who was also on hormone replacement therapy developed a DVT. A 74-year old man was hospitalized with a rib fracture which was attributed to an accidental fall. There were no SAEs in the SALL19 trial. The SBO40001 trial, a post-marketing observational study, does not define or report serious adverse events.

In the clinical trials, one adverse event led to withdrawal from the study. A patient in trial SERL01 withdrew from the study due to vomiting and headaches, which were rated as mild in intensity [page 69].

No pregnancies were reported in the SERL01 or the SALL19 trials. Pregnancies occurring during the on-going observational study, trial SBO40001, are being followed. No information on these events is provided. The Applicant plans to submit narratives of all pregnancies as an Addendum to the final study report [page 4].

4.3. SPONTANEOUS REPORTS

There were 36 spontaneously reported SAEs in patients who were receiving either albuterol/GR106642X (18 patients) or albuterol of unknown formulation (18 patients). Of the 18 reports known to involve albuterol/GR106642X, ten were non-site specific (mostly lack of efficacy) and seven were associated with the lower respiratory tract (asthma/lack of efficacy). The remaining event was urticaria, generalized edema and oral irritation. Reports involving unknown formulations of albuterol included 3 exacerbations of asthma or COPD, two events of pulmonary edema, one event of bronchoconstriction, one event of ageusia and multiple organ failure, one event of tetany, one event of twitch with right sided chest pain, one event of collapse with fractured upper limb, one event of congenital disorder, and two events of possible Stevens-Johnson Syndrome. **Case narratives for all SAEs were reviewed. These cases do not suggest any previously unrecognized adverse effect of the drug.**

There were five spontaneous reports of death. These deaths were due to asthma in two cases, multiple organ failure in two cases, and cardiac failure in one case. The relationship to the drug was listed as unknown in four and unrelated in one. **Case narratives for all deaths were reviewed. The clinical significance of these deaths is not known. However, in no case was albuterol/GR106642X strongly implicated as causative.**

There were two spontaneous reports of pregnancy in patients using albuterol/GR106642X. No information about the outcomes of these two pregnancies is available. In both cases lack of efficacy was reported. In addition, there were 9 spontaneous reports of pregnancies in patients using albuterol of unknown formulation.

Outcomes of these pregnancies were: three normal pregnancies with healthy babies, two congenital abnormalities (transposition of the great vessels and cleft palate along with hip anomaly), two cases of acute pulmonary edema, one spontaneous abortion and one death. Relationship to the drug was listed as unknown for all except the two patients who developed acute pulmonary edema after being treated with albuterol for premature labor. **Case narratives for all pregnancy reports were reviewed. The clinical significance of these reports is unknown.**

4.4. APPROVED LABELING FROM OTHER COUNTRIES

Copies of the approved drug labels from Australia, United Kingdom, and Canada were submitted. Except for differences in recommended dosing, the labels differ in minor aspects. The proposed US dose is 2 puffs every 4 to 6 hours. In Canada, the recommended dose is 1-2 puffs qid. In Australia the recommended dose is 1-2 puffs every four hours, with advice to adjust the dosage in the presence of liver or renal dysfunction. In the UK the recommended dose is 1-2 puffs up to qid. Important warnings which are included in foreign labels but not the US label include: a precaution in patients with idiopathic hypertrophic subvalvular aortic stenosis and a precaution that the open-mouth administration technique has not been investigated in the Canadian label; a warning that excessive use may induce a non-responsive state in the Australian label; and a warning regarding a difference in taste compared to other inhalers in the UK label.

Cleaning of the device is recommended and described in the foreign labels, but little attention is given to the specific problem of clogging of the actuator in these labels. In the US label and "Patient's Instructions for Use" section there is a warning that the inhaler may stop spraying if not properly cleaned and a discussion of what to do if the actuator becomes blocked.

Priming instructions in the proposed US label are located in the Dosage and Administration section and in the "Patient's Instruction for Use" document. The instructions are to perform four test actuations before using for the first time and if the inhaler has not been used for more than four weeks. The product labels from Australia and the UK advise priming with *one* puff if the inhaler is new or has not been used for more than *one* week.

Reviewer's Comments: Review of these documents does not suggest that any specific changes to the proposed US label should be made.

5. Summary

As discussed in the 6/23/99 Medical Officer Review, the studies submitted with the original NDA submission provide adequate evidence of safety and efficacy for Ventolin HFA in the prevention and maintenance treatment of bronchospasm in adults and children, and in the prevention of exercise-induced bronchospasm. The Complete Response submission (6/29/00) sufficiently addresses the Agency's clinical questions, as listed in the 7/1/99 Approvable letter. As discussed above, the numeric differences

between the HFA product and the CFC product will be included in the U.S. label. The Final Safety Update (7/6/00) does not indicate any new safety concern. Therefore, no changes to the proposed label will be made based upon this submission. Also included in the 7/6/00 submission were examples of the approved labels from other countries (Australia, United Kingdom, and Canada). Review of these documents did not suggest that any changes to the proposed US label should be made.

6. Recommended Regulatory Action

The application is sufficient for Approval from the clinical standpoint. Specific changes to the proposed label should be made. These changes are listed in Section 7 below and are discussed in Section 3.4 above. They will be addressed with the sponsor in future discussions.

7. Comments to Sponsor

The following changes to the label should be made [line numbers refer to the non-strike-out version of the revised package insert in the 6/29/00 submission]:

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Proposed Labeling

Reviewed by:

ES 11/20/00
Eugene J. Sullivan, MD, FCCP
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Medical Officer Review

Division of Pulmonary Drug Products (HFD-570)

Application #:	N20983	Category of Drug:	β-adrenergic agonist
Sponsor:	Glaxo Wellcome	Route of Administration:	Inhalation
Proprietary Name:	Ventolin HFA	Medical Reviewer:	A. Trontell
USAN/Established Name:	Albuterol in HFA-134a propellant	Review Date:	June 23, 1999

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
30-Jun-1998	01-Jul-1998		Original NDA application
04-Sep-1998	08-Sep-1998	General correspondence	Proposal for submitting 120d safety update
06-Oct-1998	07-Oct-1998	Amendment	Study report for 12 mo open label safety study
29-Oct-1998	30-Oct-1998	SU	120d Safety Update
10-Nov-1998	12-Nov-1998		Additional reference missing from original submission
12-Jan-1998	13-Jan-1998	Response to request	CRFs including primary spirometry & lab reports
19-Apr-1999	20-Apr-1998	Response to request	Analyses of means of derived FEV1 values; pdf files of figures
13-May-1999	14-May-1999	Response to request	Information on clogging in clinical trials and post-marketing

Related Applications: None

Overview of Application and Review: See accompanying review

Outstanding Issues: Smaller effect size relative to CFC Ventolin, clogging, labeling

Recommended Regulatory Action

NDA/Supplements: Approval
 Approvable

Signature:

/S/

Medical Reviewer

Date: 6/23/99

Concurrence:

/S/

Team Leader

Date: 6/23/99

cc: Div File NDA 20-983

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EXECUTIVE SUMMARY OF EFFICACY AND SAFETY

Ventolin HFA uses the non ozone-damaging hydrofluorocarbon propellant HFA134a (Glaxo Wellcome designation GR106642X). Ventolin HFA is intended as a replacement for the currently marketed Ventolin Inhalation Aerosol, which uses chlorofluorocarbons 11 and 12 as propellants. The sponsor is seeking the indications of treatment and prevention of bronchospasm and prevention of exercise-induced bronchospasm in patients four years of age and older.

Ventolin HFA consists of a suspension of micronized albuterol sulfate in HFA134a in an aluminum canister that is internally coated with a fluoropolymer. No co-solvents or surfactants are included. Each actuation delivers 120mcg of albuterol sulfate, USP from the valve and 108mcg of albuterol sulfate from the actuator. The exactuator dose is equivalent to 90mcg of albuterol base. Two hundred actuations are contained in each canister.

The U.S. clinical development program for Ventolin HFA consisted of 6 placebo controlled studies of safety and efficacy. These included two 12-week trials in adolescent and adult asthmatics (SALA3002 and SALA3005), one 2-week study in children aged 4 to 11 years (SALA3006), a single dose exercise-induced bronchospasm study in adolescents and adults (SALB2001), a single dose dose-ranging study in adults (SALB2003), and a single dose methacholine challenge in adults (SALA3009). With the exception of the methacholine challenge, all studies employed CFC albuterol as an active control. In addition, an open-label one-year safety study was conducted in adolescent and adult patients (SALA3003).

In all 6 controlled studies, albuterol HFA demonstrated statistically superior improvement over placebo in multiple measures of pulmonary function related to FEV1. In those studies that also used albuterol CFC as a comparator, performance of albuterol HFA was not statistically distinguishable from albuterol CFC. In the individual and combined chronic dose adolescent/adult studies, albuterol HFA evidenced a numerically smaller improvement in FEV1 than was seen with albuterol CFC. In contrast, the single pediatric study tended to find slightly greater effects on PEF and FEV1 with albuterol HFA than albuterol CFC.

Single administrations of varying doses of albuterol HFA and CFC in the dose-ranging bronchodilation trial and the study measuring prevention of methacholine-provoked 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 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 of albuterol CFC and HFA at 100mcg and 200mcg doses.

A single dose PK/PD study (SALB1003) in healthy volunteers of 1200mcg of albuterol delivered via the HFA propellant and the CFC propellant showed a similar geometric mean AUC₀₋₁₂ with both inhalers, a lower and later C_{max} with HFA albuterol, and a significantly greater t_{max} with albuterol HFA. Pharmacodynamic comparison of 1200mcg albuterol HFA with albuterol CFC found no statistically significant treatment differences in heart rate, QTc interval, and serum potassium although the magnitude of effect on these parameters was consistently lower for the HFA formulation. Clinically, palpitations were noted less often with the HFA than with the CFC formulation.

The findings from the single dose studies suggest that Ventolin HFA 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. The greatest potential clinical concern that can be imagined would be the relative performance of Ventolin HFA in a rescue situation, such as nocturnal asthma.

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. 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.) These data are consistent with the PK findings described above for SALB1003. Mean AUC(bi) values were statistically similar for the 2 albuterol formulations, but the means in the HFA group were 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. In total, these findings reinforce the impression of slightly lower clinical effectiveness of Ventolin HFA relative to the CFC product.

With respect to exercise-induced bronchospasm, albuterol HFA and CFC provided significant and clinically comparable protection when compared to placebo HFA. 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 pulmonary functions and exacerbation rates (study SALA3005) were sufficient to discount an explicit claim of comparability of QID and PRN albuterol in terms of overall asthma control.

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, but no episodes of paradoxical bronchoconstriction.

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. 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.

In summary, Ventolin HFA was shown to provide statistically significant improvement over placebo in the prevention and maintenance treatment of bronchospasm in adults and children, and in the prevention of exercise-induced bronchospasm. Ventolin HFA is statistically comparable to albuterol CFC in these effects, though its effect and duration of action appear to be slightly less on average than CFC Ventolin. The clinical significance of this difference is unclear. Ventolin HFA was well-tolerated and raised no notable safety concerns in acute and chronic studies in pediatric, adolescent, and adult patients. Adverse events, cardiovascular effects, and neurologic effects were similar in type and magnitude to those seen with other β -adrenergic agents.

APPEARS THIS WAY
ON ORIGINAL

BACKGROUND

Regulatory History

The sponsor has worked closely with FDA clinical staff in its clinical development program. The NDA conforms with the requirements of the "Points to Consider" document for MDI and DPI products as well as FDA advice on specific protocols.

The IND was filed on September 30, 1994 and a total of 6 clinical studies (5 European, 1 US) were conducted using the original product. Subsequent CMC improvements in the product (by can internal coating and conditioning of albuterol) necessitated the submission of a new clinical plan on December 16, 1996. After discussion with FDA at a joint meeting on January 29, 1996, the clinical plan outlined 7 studies as follows:

1. Single dose comparability study of 100 and 200mcg CFC and non-CFC albuterol in 20 adult patients
2. Single dose dose-ranging study of 100, 200mcg CFC and 100, 200, and 400mcg non-CFC albuterol with 60 adult patients
3. Single dose EIB study of 200mcg CFC and non-CFC albuterol in 24 adult patients
4. 12 week study of asthma efficacy of 200mcg CFC and non-CFC albuterol in 240 patients
5. 12 week switch study of asthma efficacy of 200mcg CFC and non-CFC albuterol in 300 adult patients
6. 12 month open label safety study using 200mcg non-CFC albuterol QID and for rescue
7. 2 week safety and efficacy in asthma of 200mcg CFC and non-CFC albuterol in 90 pediatric patients

This clinical plan was acceptable to the FDA for the following indications:

- QID maintenance therapy for asthma in adult and adolescent patients
- QID maintenance therapy for asthma in pediatric patients
- Prevention of EIB in adolescent and adult patients

FDA indicated no separate pediatric EIB study would be required if data from the pediatric study (item 7 above) supported 200mcg as the safe and effective dose in the pediatric population. In addition, FDA indicated a need for a comparative PK study of 200mcg CFC and 200mcg non-CFC to address whether the change in the propellant could grossly enhance bioavailability. The sponsor submitted 1 study using the US Commercial container closure system 1200mcg (see review of SALB1003 in this document.)

In the objectives to Protocol SALA 3005, the sponsor indicated one objective was to compare QID albuterol HFA to the PRN arm (HFA placebo/albuterol HFA rescue.) FDA notified the sponsor that this comparison would not be sufficient evidence to allow a determination of an explicit PRN indication, though this indication is implied

by the current indication. FDA indicated evidence would have to come from well-controlled trials—specifically designed to examine PRBN 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.

Approach Used in this Review

The four placebo-controlled, pivotal clinical studies in support of the proposed indication were the two 12-week trials in adolescent and adult asthmatics (SALA3002 and SALA3005), the 2-week study in children aged 4 to 11 years (SALA3006), and the single dose exercise-induced bronchospasm study in adolescents and adults (SALB2001). These studies were reviewed in depth. Medical reviewer conclusions are found at the end of each study review. Also reviewed in depth was SALA3003, the open-label safety assessment of albuterol HFA. Supportive studies were generally reviewed in less detail, and included a single dose dose-ranging study in adults (SALB2003), a comparative PK/PD study of 1200mcg of albuterol HFA and albuterol CFC (SALB1003), and a single dose methacholine challenge in adults (SALA3009). Studies done using the previous container closure system were examined as part of the integrated summary of safety, and only for serious adverse events.

References to NDA submissions

In the text, references in square brackets are to volume and page numbers in the sponsor's submission. Unless otherwise indicated, data from the following studies came primarily from the volumes of the original NDA submission that are indicated below.

<u>Study</u>	<u>NDA Volumes</u>
SALA3002	56, 57
SALA3005	73, 74
SALA3006	87
SALA3009	47
SALB1003	43
SALB2003	51

SALA3003 → Clinical amendment of 10/6/98, volume 1

The 120-Day Safety Update was submitted as a single volume amendment on 10/29/98.

NON-CLINICAL REVIEW ISSUES

Chemistry

Ventolin HFA was developed as an alternative to CFC-driven pressurized metered dose Ventolin. CFC products are being phased out under the Montreal Protocol because of their contributing role in depleting the ozone layer. The hydrocarbon propellant 1,1,1,2-tetrafluoroethane (HFA134a, Norflurane, Glaxo Wellcome code GRX106642X) has been adopted as a replacement propellant for use in medical products because it is chemically inert, non-flammable, of low toxicity, and does not contribute to depletion of the ozone layer. HFA134a is the replacement propellant in Ventolin HFA. HFA134a has low solubility for conventional surfactants, poor compatibility with rubber seals presently used in many of Glaxo-Wellcome's currently marketed MDIs, and a high vapor pressure. All of these properties have complicated the development of Ventolin HFA. HFA134a is also hygroscopic and another marketed HFA product has been reported to have device clogging problems.

The currently marketed CFC Ventolin product consists of a suspension of albuterol base that is micronized and dispersed in a mixture of trichlorofluoromethane (Propellant 11) and dichlorodifluoromethane (Propellant 12) with the aid of oleic acid as a surfactant.

The active ingredient of Ventolin HFA consists of albuterol sulphate that has been "conditioned" after micronization to reduce small portions of noncrystalline drug at the surface of the microfine crystals. Ventolin HFA contains only drug substance and propellant. After performance difficulties with an initial container closure system, the to-be-marketed US commercial container closure system (USCCCS) was developed. This product has an internal blend coating to reduce deposition of the drug substance onto the can wall during use of the product

Ventolin HFA is designed to deliver 90mcg of albuterol (as 108mcg of albuterol sulfate) per actuation from the actuator, and 200 actuations per inhaler. The approximate dose of HFA per actuation is 75mg. The doses ex-valve are 120mcg albuterol sulfate or 100mcg as albuterol base.

Principal issues raised in the Chemistry review of Ventolin HFA relate to specifications for content uniformity and changing moisture/particle size distribution once the foil overwrap is removed. From beginning to end of use of the product, the mean delivered dose increases and the sponsor was requested to develop separate standards for beginning and end dose means.

Of potential clinical concern is whether the Ventolin HFA device is prone to clogging like Proventil HFA. Clogging was found in 9 returned canisters of albuterol HFA from the 12 week adolescent/adult clinical trial (SALA3005) and in 1 returned canister from the 12 month long-term open-label safety study. One CFC canister was returned in SALA3005 and the actuator found to be clogged with a foreign particle. Device

performance rates in clinical trials using the USCCCS was requested of the sponsor, and overall values are summarized in the following table.

Device Performance in Ventolin HFA Clinical Development Program

		Number Dispensed	Leaked	Clogged Actuator	Clogged valve stem	Empty (possibly leaked)
HFA	Multidose	19,748	3	9	1	4
	Single dose	433	0	0	0	0
	Total all studies	20,181	3 (0.01%)	9 (0.04%)	1 (0.005%)	4 (0.02%)
CFC	Multidose	3,344	1	1	0	0
	Single dose	150	0	0	0	0
	Total all studies	3,494	1 (0.03%)	1 (0.03%)	0	0

If device clogging of any type is considered, the overall rate for albuterol HFA in the clinical trials was 0.05% (10/20181) versus 0.03% with albuterol CFC. Of note, the solitary instance of clogging in the albuterol CFC device was due to a foreign particle, not drug product. There was no apparent explanation for why 90% of all clogging problems were associated with trial SALA3005; some study coordinators for this trial returned ALL patient canisters instead of returning only those canisters that malfunctioned. The sites were not clustered geographically (OH, GA, NJ, CA, WA), all received the same cleaning instructions, and there was no seasonal pattern since the studies spanned all seasons.

In addition to the data above, the sponsor supplied information on albuterol HFA MDI product returns from commercial batches manufactured at [redacted]. This site supplies the US commercial container closure product to nonUS markets that have received marketing approval for Ventolin HFA. During 1998, a total of 391 complaints were received on [redacted] million cans sold; 260 of these complaints were substantiated. Of the 260 substantiated complaints, 235 involved actuators that were clogged with drug when returned, but which functioned normally after washing according to patient instructions. This represents a clogging rate (by the medical reviewer's calculation) of [redacted] % or [redacted] clogged canister per [redacted] units sold, or about [redacted] fold lower than what was noted in the clinical trials experience.

In conversations with the sponsor about clogging, they indicated that they were observing more clogging with the Ventolin HFA than the Ventolin CFC device, and that they had been unable to duplicate the clogging with *in vitro* manipulations of humidity and temperature. According to the Chemistry Reviewer, cleaning studies that Glaxo performed in response to DPDP requests demonstrated that cleaning after a 7 day simulated dosing schedule (8 actuations a day) does little to affect the dosing content or the particle size distribution of the emitted dose (i.e., the controls look very similar to the canisters that were subjected to actuator cleaning). Additionally, incomplete drying of the actuator

does not appear to affect the dosing or particle size profile of the emitted dose either if the inherent variability for each of these parameters is considered.

In comparison to Ventolin HFA, Proventil HFA (which has a smaller valve orifice, 0.28mm compared to 0.51mm for Ventolin HFA) has documented a cumulative summary of complaints for the period 12/1/96 through 3/31/99 of 478 blocked or partially blocked actuators. When placed over an estimated million products sold, this results in an estimated clogging rate of % or one clogged canister per units sold. 7

Medical reviewer comment: Device clogging with Ventolin HFA has occurred in clinical trials and commercial use of the product. Approximate rates estimated from commercial sales are about 8-fold less than seen with Proventil HFA, and according to the sponsor, clogging was reversed by washing according to patient instructions. In clinical trials, the clogging rate for Ventolin HFA was 1/2000, approximately what has been estimated for Proventil HFA based on post-marketing data (1/5000).

On larger chemistry issues, approval of Ventolin HFA will be complicated by controversies over allowable specifications for dose content uniformity. This is a larger policy issue that is likely to be addressed by the CMCCC. Please consult the Chemist's review for more details.

Nonclinical Pharmacology and Toxicology

Both albuterol and HFA134a have been well characterized as to their individual toxicologic profiles. These products were shown to have an acceptable toxicity profile when combined in another formulation that included oleic acid and ethanol. Out of concern for potential irritant effects on the respiratory epithelium attributed to ethanol, the sponsor discontinued development of this formulation and reformulated Ventolin HFA as a combination comprised solely of albuterol sulfate and HFA134a without surfactants.

The to-be-marketed formulation of albuterol sulfate and HFA134a alone was evaluated in 13 week inhalation studies in the rat and dog with no unusual findings relative to what has been seen with albuterol alone. In addition, a developmental reproduction study was done in the rabbit by the inhalation route and found similar developmental effects to those previously seen with subcutaneous and oral albuterol.

Impurities noted by the chemist were all qualified by the reviewing pharmacologist. Extractables that were chemically characterized by the sponsor were also qualified. At the close of the first review cycle, 6 extractables were still uncharacterized by the sponsor and therefore not reviewed for qualification. For further information, please consult the pharmacology review.

Medical reviewer comment and conclusions: There are no preclinical safety concerns for the combination of albuterol and HFA 134a. Final approval will require

characterization and qualification of 6 extractables that remained uncharacterized at the end of the first review cycle.

Human Pharmacokinetics

A single dose PK/PD study was done in healthy volunteers to compare 1200mcg of albuterol delivered via the HFA propellant and the CFC propellant. This study showed a similar geometric mean AUC_{0-∞} with both inhalers, a lower and later C_{max} with HFA albuterol, and a significantly greater t_{max} with albuterol HFA (see table below). More HFA subjects than CFC subjects had a plasma profile of later peaks associated with the oral absorption of albuterol. HFA albuterol showed greater variability in AUC than did CFC.

	Albuterol HFA	Albuterol CFC
Geometric mean AUC _{0-∞} (ng*hr/mL) 95% CI	23.02	25.32
	15.17 – 34.92	22.42 – 28.59
Geometric mean C _{max} (ng/mL) 95% CI	2.96	4.26
	2.03 – 4.32	3.57 – 5.09
Median t _{max} (hr) Range	0.417	0.167
	0.167 – 5.017	0.083 – 0.750

Pharmacodynamic results from this protocol (SALB1003) showed a consistently smaller impact of albuterol HFA upon the medians of heart rate, QTc interval, and serum potassium when compared to CFC albuterol. Statistical comparison of the weighted means, minimum K⁺, and peak HR and QTc showed no significant differences between the two formulations. Palpitations occurred in more patients during CFC albuterol treatment (9/12 subjects) than during HFA albuterol treatment (5/12 subjects).

PK studies of GR106642X (HFA134a) showed that the propellant is a metabolically inert molecule that is eliminated essentially unchanged in the breath, with no evidence of metabolism or regional accumulation in the body. Absorption and distribution were similar in healthy patients and those with chronic obstructive pulmonary disease.

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

SALA3002

A Randomized, Double-Blind, Parallel-Group, 12-Week Study to Evaluate the Safety and Efficacy of Switching From Albuterol 200mcg (180mcg ex-actuator) in CFC Propellant 11 and 12 Administered QID to Albuterol 200mcg (180mcg ex-actuator) in GR106642X Propellant Administered QID and to Albuterol 200mcg (180mcg ex-actuator) in GR106642X Propellant Administered as Needed in Adolescent and Adult Subjects with Asthma

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 3-week single-blind run-in phase during which albuterol P11/12 (CFC) QID was administered to assess the effect of switching from the CFC to the HFA formulation. During the double-blind phase, patients were randomized to albuterol P11/12, albuterol GR106642X (HFA), or placebo GR106642X given four times daily. Back-up albuterol in the matching propellant was supplied for PRN use. Total study duration was approximately 15 weeks.

Enrollment was planned for ≥ 240 male or female patients ≥ 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 FEV₁ of 50-80% of predicted normal value, and airways reversibility ($\geq 15\%$ increase in FEV₁ 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 and spirometry was performed every 6 weeks. Visit timing was as follows:

Clinic Visit	Time of Occurrence
Screening	Initial visit
Holter Monitor Visit (selected sites)	Within 2±1 days of Screening
Visit A	14 ± 4 days from Previous Visit
Treatment Visit 1 (Day 1 – randomization)	7 ± 4 days from Visit A
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.

Subject eligibility was determined at the **Screening visit**. At this visit, all eligible subjects were dispensed PRN CFC albuterol and those not undergoing Holter monitoring were also given single blind study medication. Subjects undergoing Holter monitoring returned to the clinic for the **Holter Monitor Visit** within two days of the Screening Visit, and received single-blind study drug after the completion of the 24 hour Holter monitoring.

FLOWCHART/TIME & EVENTS TABLE

	RUN-IN PERIOD			DOUBLE-BLIND TREATMENT PERIOD					Subject Discontinuation
	Screening Visit	Holter Visit ^{f,i} 2±1 d from Screening	Treatment Visit A 14±4 d from Prev Visit	Treatment Visit 1 7±4 d from Visit A	Treatment Visit 2 21±3 d from Visit 1	Treatment Visit 3 42±3 d from Visit 1	Treatment Visit 4 63±3 d from Visit 1	Treatment Visit 5 84±3 d from Visit 1	
Informed Consent	X								
Medical History	X								
Vital Signs	X								X
Physical Examination	X							X	X ^k
Pulmonary Function Test	X ^a								X
Serial Vital Signs			X	X		X		X ^h	
Serial PFTs			X	X		X		X ^h	
12-lead ECG	X		X ^b	X ^b		X ^b		X ^b	X ^k
Holter Monitoring (at selected sites)		X ^{f,i}	X ^f	X ^f				X ^f	
Clinical Laboratory Tests	X ^l		X ^c	X ^c				X ^c	X ^k
Pregnancy Test (all females)	X ^l							X ^e	X ^k
Chest x-ray	X ^d								X ^k
Issue 3-Week Run-in Medication	X ^l	X ^f							
Issue/Exchange 12-Week Study Medication				X ^g	X	X	X		
Dispense Pm Albuterol	X	X ^f	X	X	X	X	X		
Review/Exchange Diary Cards	X ^j	X ^f	X	X	X	X	X	X	X
Adverse Event Assessment		X ^f	X	X	X	X	X	X	X
Concomitant Medications Query	X	X ^f	X	X	X	X	X	X	X
Review Proper MDI Technique (if needed)	X	X ^f	X	X	X	X	X		

- a Reversibility assessment of ≥ 15% variation of FEV₁
- 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 chest x-ray within 12 months and is > =18 years of age
- e To be done at pre-dose only
- f For Holter subjects ONLY
- g Dispensed at the BEGINNING of Visit 1

- h Dose with double-blind medication dispensed at PREVIOUS visit for serial measurements
- i 24 hour Holter to be done prior to first dose of Run-in period
- j Single-blind study drug and diary cards dispensed only to subjects NOT undergoing Holter monitoring
- k Selected tests/examinations to be repeated in follow-up if abnormality is noted or pregnancy test was positive
- l Selected tests to be repeated prior to Holter Visit or Treatment Visit 1 if abnormality is noted or pregnancy test was positive

At **Visit A** (approximately 2 weeks after dispensing single blind medication) patients were assessed for diary card compliance, clinical labs, adverse events, and asthma stability. Six hour serial spirometry was done at this visit using albuterol CFC. At **Visit 1** (~1 week after Visit A) eligible and compliant [57:33] subjects were randomized to double-blind treatment which they used prior to serial spirometry. At **Visits 2 & 4**, diary and adverse event review was done, used study medication collected, and new study medication dispensed. At **Visits 3 and 5**, serial spirometry, VS, and 12-lead ECGs were done using the double blind study medication dispensed at the previous visit. At **Visit 3**, new study medication and PRN rescue albuterol were dispensed after efficacy and safety assessments. Study-related follow-up ceased at **Visit 5** if no abnormal findings were found. At the end of the randomized treatment phase (Treatment Week 12), patients discontinued study medication without tapering.

Two months after the study was initiated, the protocol was amended so that patients recorded their asthma symptoms in the morning rather than the evening, and adverse events that occurred immediately post dose were elicited.

Study Treatments

Dosing of the single blind and double blind study medication was 2 actuations four times a day, approximately every 4 to 6 hours at the following suggested times: breakfast (6:00 AM-9: 00 AM), lunch (12:00 PM-3: 00 PM), dinner (4:00 PM-8: 00 PM), bedtime (9:00 PM-12: 00 AM). Patients were randomized to one of the following 3 double-blind study treatments:

1. Albuterol 200µg MDI in P11/12 QID
2. Albuterol 200µg MDI in GRX106642X QID
3. Placebo (GR106642X propellant alone) QID

In addition to their QID medication, each subject in the study was given a supply of PRN Albuterol/P11/12 for the single-blind run-in period and PRN albuterol in either P11/12 or GR106642X for the double-blind period as follows:

Subjects Randomized To:	Received:
Albuterol/P11/12	Albuterol/P11/12
Albuterol/GR106642X	Albuterol/GR106642X
Placebo/GR106642X	Albuterol/GR106642X

Each subject was instructed to use the PRN albuterol for the acute PRN relief of acute symptoms of asthma *only* when the study drug therapy seemed to be inadequate. When such a need occurred, subjects were instructed to inhale 2 actuations of albuterol and record this use on their diary card.

Batch numbers of study medications are displayed on page 31 of Volume 56.

Concomitant Medications

All subjects withheld beta-agonists, theophylline, ipratropium, and parenteral, oral, and inhaled steroids throughout the study and prior to the screening visit. Aqueous and powder formulations of intranasal steroids or cromolyn were allowed, but CFC or HFA formulations were not. Antihistamines, decongestants, and pm nasal decongestants were allowed with appropriate washouts before study visits.

Efficacy evaluations

The primary measure of efficacy was serial FEV₁ measurements done with appropriate medication and activity washouts. At least 8 hours had to have passed since the preceding PM dose of study drug or the last use of PRN albuterol. On each study day with serial assessments (see Flowchart), FEV₁ was determined at 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. Subjects withheld the second dose of study drug until after the 6-hour FEV₁ was completed and the Holter monitoring equipment detached. The study medication given to the subject at each of the Treatment Visits was the study medication *in use since the previous visit*.

Medical Officer Comment: *By performing serial PFTs with study medication that had been in use since the previous visit (~3 weeks), potential problems due to repeated or prolonged use of the study medication (such as device clogging) were detectable. Use of at least 8 actuations a day for 21 days translates into >82% use of the labeled number of doses per canister.*

Additional measures of efficacy consisted of subject self-ratings on diary cards of asthma, nighttime awakenings, use of back-up albuterol, the frequency of asthma exacerbations, and determinations of the best of triplicate morning and evening peak expiratory flow (PEFR) measurements. Morning and evening PEFR measurements were to be done **before** taking the morning and evening doses of study medication. Asthma self-rating was 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, annoying or affecting routine activity) [57:189].

Safety monitoring

The safety of each treatment group was assessed by medical history, physical examinations, chest radiography, vital signs, clinical laboratory tests [see 58:179], 12-lead ECG, clinic determinations of FEV₁, weekly assessment of PEFR, Subject Diary Card assessments, and clinical adverse event assessments. In addition, continuous ambulatory electrocardiography (Holter monitoring) of approximately 75 subjects was done at selected sites.

The schedule for safety assessments is displayed in the Flowchart. Diary card and adverse event assessment occurred at each treatment visit. All other safety

assessments occurred on Treatment Visits A, 1, 3, and 5. ECG and clinical laboratory tests were done both before and after dosing with the test medication. Abnormal Holter readings were defined prospectively [57:182]. Baseline safety data were the 3-week single-blind run-in phase during which the subjects received albuterol CFC.

Medical Officer Comment: *Adverse events which occurred immediately after dosing were not routinely elicited by investigators for the first 2 months of the study, so paradoxical bronchospasm or other adverse events of this type may be underreported.*

Management of Asthma Exacerbations During the Study

An exacerbation was defined as asthma requiring treatment other than with allowed concomitant medications, study medication, or back-up Albuterol[®] MDI. An exacerbation during the course of 6-hour serial spirometry was defined as asthma that required additional treatment. Subjects were treated with their PRN medications first, and given Ventolin[®] 2.5mg via nebulization if they did not respond.

Asthma exacerbations could be treated with the following medications:

- Back-up albuterol MDI
- An additional beta-adrenergic agent (oral, subcutaneous, or inhalation by nebulization) for ≤ 7 consecutive days. A requirement for more than 7 consecutive days of additional beta-adrenergic agents was considered as 2 courses.
- One course of theophylline for up to 7 consecutive days.

Use of these medications could not occur within 5 days of Treatment Visits 3 & 5.

Subjects who required > 2 courses of additional beta-adrenergic agents and/or 1 course of theophylline or who required treatment with oral or parenteral corticosteroids during the study were discontinued from the study. Subjects with an exacerbation between the Screening Visit and Treatment Visit 1 were discontinued from the study.

Power and Statistical Analysis Plan

With 80 patients per treatment group, the study had 80% power to detect a difference of 0.25 L change in FEV₁ from baseline in the repeated measures analysis of variance using two-sided tests and $p \leq 0.05$ as statistically significant. Repeated measures analyses were based upon the change in FEV₁ from the pre-dose Visit 1 baseline, as well as the pre-dose baseline from each spirometry visit. Baseline values, peak effect, onset, and offset were defined [57:42-43]. A responder was defined as a subject who achieved a 15% increase in FEV₁ from baseline within 30 minutes of dosing.

Repeated Measures Analysis of Variance was used to analyze FEV₁ for each visit where serial PFTs were performed. Repeated measures analysis included unequally weighted average of all post-dose FEV₁ measurements (WAVE) as

well as the equally weighted average of all post-dose FEV₁ measurements (referred to as repeated measures analysis in the tables and text). With WAVE, the weight for each FEV₁ (or change in FEV₁) is proportional to the time interval between this FEV₁ (or change in FEV₁) and the previous FEV₁ (or change in FEV₁); calculated according to the following formula:

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

The intent to treat population was defined as all subjects who took at least one dose of study medication. The times of onset and offset of response were calculated by linear interpolation. If serial PFTs could not be completed for clinical reasons, the last observed set of PFTs was carried forward as values for each post-intervention observation time.

Continuous electrocardiographic (Holter) monitoring was used to summarize ventricular ectopic events (VEs), supraventricular ectopic events (SVEs), and cardiac rate by treatment group for the 12-week double blind phase. Statistical tests for VEs and SVEs were based on a non-parametric rank-based test controlling for investigator. Tests of cardiac rate were based on an analysis of variance F-tests.

The sponsor combined 3 sites (#3610, #4299, and #4614) with ≤ 1 patient/treatment group to achieve a comparable number of patients to all the other sites. Modifications to the original analysis plan are discussed under the efficacy results section.

Discussion

Medical Officer Comment: *Subject blinding to treatment assignment was likely incomplete. Results about CFC versus HFA propellant perception were mixed from Protocol C94:022, "A study of the perception by asthmatic patients of differences in the inhalations from metered dose inhalers of salbutamol, salmeterol, fluticasone propionate or beclomethasone dipropionate containing either the current propellant or a non-CFC propellant, HFA 134a" [46:24]. Forty one patients were asked to determine if they could perceive and describe differences between inhalations from three MDIs, two containing CFC and one containing HFA. Of the 12 assigned to salbutamol, 5 correctly identified the odd inhaler of the three; 4 correct out of twelve would have been expected by random choice alone. Overall for all 4 products, there were 21 correct identifications out of 41 patients, more than expected by chance alone for a p value of 0.02. The distinguishing feature most commonly described was taste, followed by feel in the mouth. Smell, sound, and feel of the can on actuation were also mentioned occasionally.*

These findings indicate that differences between HFA and CFC formulations are perceptible to some users when the products are used within 5 minutes of each

other. The effect, if any, of incomplete patient blinding is likely to be greatest for subject reports, but the nature or direction of patient biases in this area cannot be predicted.

Medical Officer Check of Study Conduct

Examination of the 3 case report forms for this protocol [115:1ff] showed all 3 patients were appropriately assigned treatment [57:2ff] as designated by the randomization schedule [57:333ff]. Protocol variations were few and minor, consisting primarily of FEV1 measurements being initiated outside the allowed time window [56:137]; most of these variations were within 10 minutes of the prespecified limits. Comparison of FEV1 values from the 3 case report forms to the tables in the document was not possible initially since these data were absent from the CRFs for this protocol. A spot check of the 3 CRFs showed that the timing of the FEV1 measurements was the same as in the data listing, and that the primary record of selected BP and pulse measurements was the same as appeared in the data listings. Glaxo Wellcome provided the source data for patient #1995 (placebo HFA treatment), and comparison of predose FEV1 values from Visits A and treatment day 1 showed agreement with the line listings. Selected serum chemistry values also conformed to the line listings.

Results

Device Performance

Five patients returned 6 canisters during the course of the study because of malfunction, either variable output or too-rapid emptying of the canister. All canisters came from one of two batches, 6ZX001A (albuterol HFA) or 6ZX002A (placebo HFA). Leakage was detected in 3 canisters, and no abnormality in the remaining 3.

Conduct of the Study

As displayed in the following table below, patient randomization was well balanced across treatment arms and completion rates were comparable for the two Ventolin formulations. Withdrawals due to lack of efficacy were low and comparable across the treatment groups, and no patients receiving active treatment withdrew due to adverse events. 'Other' reasons for withdrawal were primarily due to protocol violations and non-compliance.

Patient Disposition

Disposition	Number of Patients			Total
	Placebo GR106642X	Albuterol GR106642X	Albuterol P11/12	
Randomized	104	101	108	313
Completed (% of randomized)	86 (83%)	91 (90%)	99 (92%)	276 (88%)
Withdrawn:	18	10	9	37
Other	10	7	4	21
Lack of Efficacy	4	2	5	11
Adverse Event	3	0	0	3
Failed to return	1	1	0	2

Protocol variations occurred in $\leq 10\%$ of patients and were minor. Three patients (one in each treatment group) were accidentally randomized to treatment at Visit A rather than at Treatment Day 1. Their Visit A data were used for Treatment Day 1. These three patients received 4, 1, and 11 days of double-blind treatment respectively, and were included in the Intent-to-Treat Population.

Patient Characteristics

Patient demographics, duration of asthma, and smoking history were grossly comparable across all treatment groups. The Ventolin CFC group had greater representation of older patients, correspondingly longer histories of asthma, and a greater rate of former smokers than the other two groups. The Ventolin CFC group also had fewer patients having nocturnal symptoms interfering with sleep > 3 times/week. [56:140]

No statistically significant differences were observed between screening FEV₁ values of the treatment groups. Mean FEV₁ values ranged from 2.35L (placebo GR106642X) to 2.44L (albuterol GR106642X MDI). Mean percent of predicted FEV₁ values and percent reversibility were approximately 67% and 31-33%, respectively, across the treatment groups.

The CFC group had more patients with concurrent musculoskeletal and skin conditions than the HFA and placebo patients (approximately 21 –22% versus 14-15%). The HFA and placebo patients had a higher rate of ENT conditions (11 –13%) than the CFC group (6%). Placebo patient had a slightly greater use of concomitant asthma medications maintained throughout the study and for treatment of exacerbations. All 3 treatment groups reported mean compliance with the dosing regimen of 96 – 97%; the range for the HFA group was narrower (~75% to 100%) than for the other two treatment groups.

Efficacy Findings

Three sets of analyses were done of this clinical trial. Two that were submitted with the original NDA submission analyzed the data with and without one investigator (#1415) where data problems had been noted with another study. Subsequent to the sponsor's submission, FDA raised suspicions about overall data quality with yet another investigator (#5348). The sponsor resubmitted data

sets and analyses without this second investigator who contributed a total of 14 patients to the trial. In consultation with the statistical reviewer, these subsequent analyses were restricted to functions of serial FEV₁ including: % of patients achieving effect, onset of effect, offset of effect, maximum effect, time of maximum effect, and AUC over baseline (b). These analyses were selected to see if there were any discernible differences between the CFC and HFA formulations since analyses with and without investigator #1415 showed both formulations to be significantly better than placebo HFA in improving WAVE (weighted average) 6 hour serial FEV₁ as displayed in the following table.

**Weighted Average (WAVE) of Post-Dose FEV₁ Measurements Over 6 Hours
Change from Same Day Baseline (Liters)
(Includes Sites #1415 & #5348)*****

Time	Run-In Phase ¹		
	(Placebo GR106642X)	(Albuterol GR106642X)	(Albuterol P11/12)
Visit A			
N	103	100	107
Baseline	2.48	2.56	2.45
WAVE of change	0.32	0.30	0.33
Randomized Treatment Phase			
	Placebo GR106642X	Albuterol GR106642X	Albuterol P11/12
Treatment Day 1			
N	104	101	108
Baseline	2.44	2.51	2.43
WAVE of change	0.14	0.39*	0.43*
Treatment Week 6			
N	90	97	101
Baseline	2.58	2.61	2.51
WAVE of change	0.15	0.28*	0.30*
Treatment Week 12			
N	86	91	99
Baseline	2.55	2.63	2.64
WAVE of change	0.14	0.26*	0.26*

¹All patients received albuterol P11/12 during run-in, but are displayed according to their future randomized treatment group. *p<0.021 compared with placebo GR106642X

***Values without site #1415 were within 0.02 liters of the values represented here, per ST-3 to ST-10.

As the table illustrates, run-in response to CFC albuterol was equivalent across the 3 treatment groups and comparable to the changes seen with CFC and HFA albuterol during the randomized treatment phase. The change from the same day baseline in post-dose FEV₁ over 6 hours was approximately 0.1L to 0.3L higher in the albuterol groups (0.26-0.43L) compared with the placebo GR106642X group (0.14-0.15L); these differences were statistically significant by WAVE and repeated measures analysis. The change from the same day baseline in post-dose FEV₁ over 6 hours was comparable between the albuterol groups at Treatment Day 1, Week 6, and Week 12. Pairwise comparisons showed no statistically significant differences between albuterol in GR106642X or P11/12 propellant. The apparent decline in treatment effect in the albuterol groups at weeks 6 and 12 was due to an increased baseline value in all treatment groups on those days. Changes in FEV₁ are represented graphically on the next pages.

Figure 5
 Change from Same Day Baseline Serial FEV1 (liters)
 V 91 A

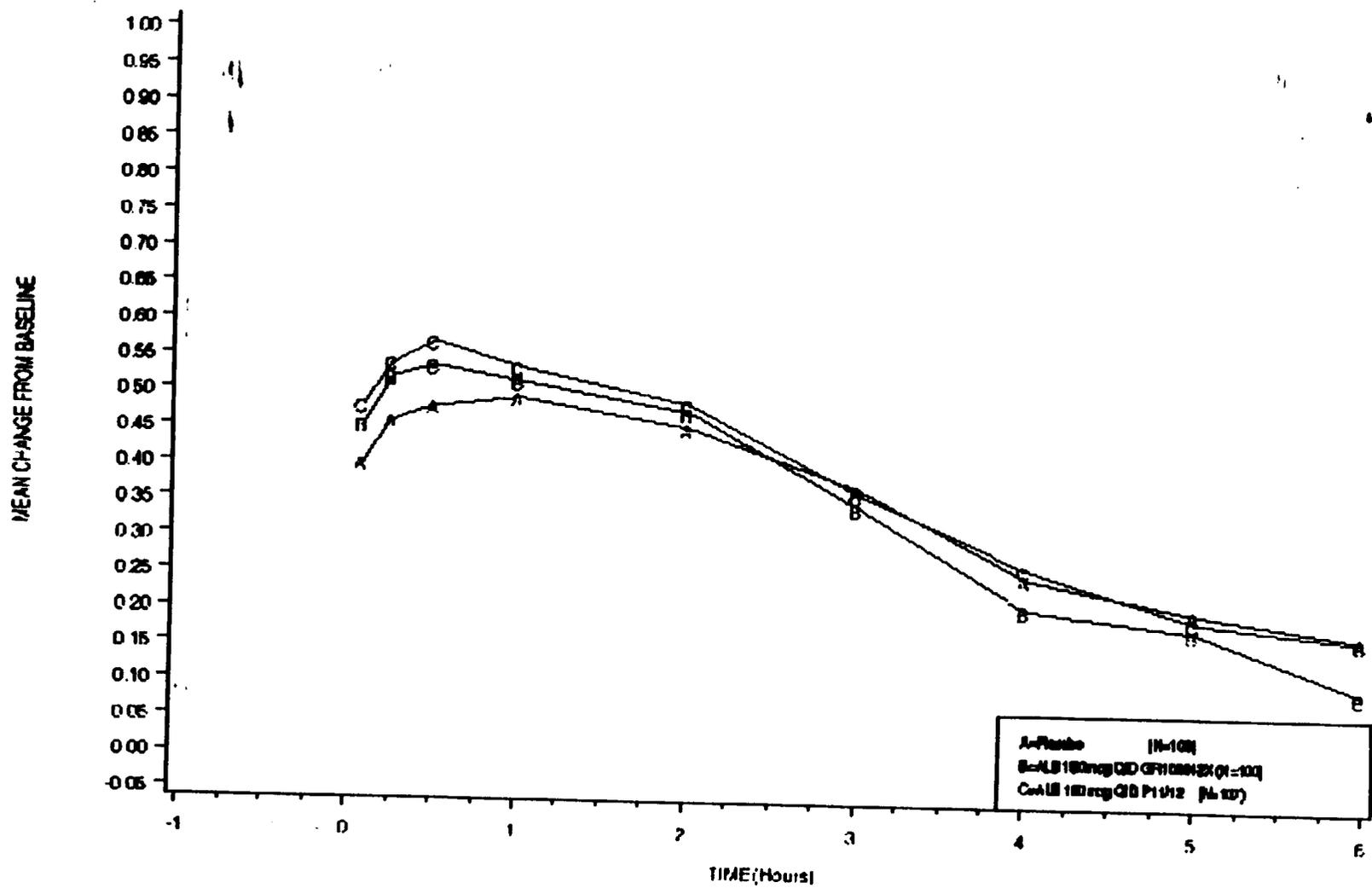


Figure 6
Change from Same Day Baseline Serial FEV1 (liters)
Treatment Day One

