CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-503/S-011

JUN - 2 1999

3M Pharmaceuticals
3M Center, Building 260-6A-22
St. Paul, Minnesota 55144-1000

Attention: Marlene Peterson
Sr. Regulatory Coordinator

Dear Ms. Peterson:

Please refer to your supplemental new drug application dated May 29, 1998, received June 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proventil-HFA (albuterol sulfate) Inhalation Aerosol.

We acknowledge receipt of your submission dated December 21, 1998.

This supplemental new drug application provides for lowering the age from 12 years to 4 years and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

As agreed in your June 2, 1999, telephone conversation with Ms. Parinda Jani of this Division, the final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-503/S-011." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) "to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations." We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

/S/ 6/2/04

Robert J. Meyer, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

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FINAL PRINTED LABELING

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

77 pages
Draft labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S011

MEDICAL REVIEW(S)

MEDICAL - STATISTICAL REVIEW

Division of Pulmonary Drug Products (HFD-570)
Division of Biometrics II (HFD-715)

Application #:	NDA 20-503
Sponsor:	3M Pharmaceuticals
Category of Drug:	Short-acting β_2 Agonist
Proprietary Name:	Proventil HFA
USAN/Established Name:	Albuterol Sulfate Inhalation Aerosol
Route of Administration:	Oral Inhalation

Submissions Reviewed in This Document

Document Date	CDER Stamp Date	Submission Type
May 29, 1998	June 2, 1998	Efficacy Supplement Pediatric Asthma / EIB
September 28, 1998	October 1, 1998	4-Month Safety Update
December 21, 1998	December 28, 1998	Minor Medical Amendment

Recommended Regulatory Action: Approval

Reviewer Signature:

/S/ 6/2/99
Susan Johnson, Ph.D., Medical Reviewer **Date**

/S/ 6/2/99
Barbara Elashoff, M.S., Biometrics Reviewer **Date**

Concurrence: /S/ 6/2/99
Robert Meyer, M.D., Acting Division Director **Date**

/S/ 6/2/99
Stephen Wilson, Ph.D., Team Leader **Date**

cc: NDA 20-503
Division File
HFD 570/Jani, Johnson
HFD 715/Elashoff

TABLE OF CONTENTS

1.0 ABBREVIATIONS

The following abbreviations are used throughout this review.

3M	3M Pharmaceuticals
AUC	Area under the curve, e.g., of the response-time curve for FEV_1
bpm	Beats per minute
CFC	Chlorofluorocarbon propellant
ECG	Electrocardiogram
EIB / EIA	Exercise induced bronchospasm / asthma
FEV_1	Forced expiratory volume in one second
HFA	Hydrofluoroalkane propellant (HFA-134a)
MDI / DPI	Metered dose / dry powder inhaler
mmHg	Millimeters of mercury
PEFR	Peak expiratory flow rate
PFTs	Pulmonary function tests
Pt.#	Assigned patient number
QID	Four times a day

Note: "Salbutamol sulfate" and "albuterol sulfate" are used interchangably. The sponsor's preferred usage is salbutamol sulfate, although the recognized USAN is albuterol sulfate.

2.0 BACKGROUND

Proventil HFA was approved in August 1996 for the treatment or prevention of bronchospasm in adults and children age 12 and older. On September 23, 1998, an efficacy supplement was approved, adding the indication for prevention of exercise-induced bronchospasm in adults. The current supplement proposes the extension of these indications to children as young as four years of age.

There are two trials submitted in support of the asthma indication (Trials 1141-SILV and 1142-SILV) and one trial submitted in support of the EIB indication (Trial 1247-SILV). **Trial 1141-SILV** was a 4 week, randomized, open label, parallel group study of 63 patients between the ages of 4 and 11 comparing the safety and efficacy of 2 puffs QID of Ventolin and Proventil HFA. The primary efficacy endpoint was a comparison between treatments of the FEV_1 profile prior to and following dosing at Week 4. **Trial 1142-SILV** was a randomized, open label, crossover, cumulative dose study primarily designed to compare the safety, including pharmacodynamic endpoints, of a total of 8 puffs of Ventolin and Proventil HFA in 27 children between the ages of 6 and 11. **Trial 1247-SILV** was a randomized, single dose, crossover comparison of Proventil HFA, Proventil (CFC), Ventolin and HFA-placebo in a total of 16 pediatric patients between the ages of 6 and 11 in the prevention of EIB.

Trial 1178 was originally submitted on November 15, 1996 and a medical review was completed on June 20, 1997. The current submission of analyses from this trial was provided by the sponsor in response to the Division's request for any data regarding the use of Proventil HFA, or similar foreign formulations, in pediatric patients that were not derived from the three trials described above. These reanalyses of Trial 1178 include age stratification of the data. The trial was a three month, open label, postmarketing evaluation of the approved formulation of albuterol sulfate inhalation aerosol in the

United Kingdom. The tradename of the product used in the trial is Airomir; its formulation is not identical to that of Proventil HFA. Relevant aspects of this trial are discussed in the Integrated Summary of Safety.

This development program is based primarily on the September, 1994 Points to Consider document issued by the Division regarding "Clinical Development Programs for MDI and DPI Drug Products" and additional recommendations from the Division. The trials submitted with this application are largely designed to establish whether the selected dose of Proventil HFA is safe in the asthma pediatric population, hence Trials 1141-SILV and 1142-SILV were not required to include a placebo control. Trial 1247-SILV was required to provide adequate evidence of both safety and efficacy in support of an EIB claim and therefore the trial did include a placebo control.

There are no changes in chemistry, manufacturing and controls, and no additional pre-clinical data, associated with this supplement that impact the interpretation of the clinical data.

In prior communication with the Division, it was determined that no pediatric pharmacokinetic data were necessary to support the approval of the pediatric asthma or EIB indications. This was based primarily on results of adult pharmacokinetic data that have shown in the past only sporadic plasma albuterol levels. These data did not play an essential role in the approval of Proventil HFA for adults and were not expected to be sufficiently meaningful to substantially influence the interpretation of safety or efficacy data in the pediatric population.

3.0 CONDUCT OF THE REVIEW

The review was conducted as a joint review between Susan Johnson, Medical Reviewer and Barbara Elashoff, Biometrics Reviewer. The volumes consulted by these reviewers are noted with the title of individual study reviews. The biometrics reviewer was involved in the reviews of Trials 1141-SILV and 1142-SILV, but not in the review of 1247-SILV due to the straightforward nature of this trial's design. Where possible, the analyses and comments of the two reviewers have been blended. However, in the reviews of Trials 1141-SILV and 1142-SILV specific commentary on the biometrics perspective of the statistical outcomes has been distinguished from the clinical interpretation of the outcomes.

No request was made to the Division of Scientific Investigations to conduct inspections of the three pivotal trials. This was due to a number of factors including the previous audit experience with adult trials supporting the approval of Proventil HFA. In addition, the principal investigators involved in the pivotal trials are well known to the Division and are understood to be subject to frequent audits for clinical trials associated with other applications. No case report forms were submitted with this application as no patients were reported to have discontinued due to adverse events.

4.0 TRIAL 1142-SILV

TITLE: Cumulative Dose Response Study of HFA-134a Salbutamol Sulfate versus Ventolin in Children 6 to 11 Years of Age with Reversible Obstructive Airway Disease. (Volumes 8-9, 18-19)

INVESTIGATOR: David Tinkelman, M.D., Atlanta Georgia.

STUDY DATES: December 21, 1994 to May 9, 1995.

PROTOCOL:

This trial was a randomized, single/investigator-blind, two-period, crossover study comparing cumulative rising doses of Proventil HFA and Ventolin Inhalation Aerosol (the marketed CFC-propelled product, herein referred to as Ventolin). At a prestudy visit within two weeks prior to enrollment in the trial, patients were assessed to determine whether they adequately met eligibility criteria and to establish baseline pulmonary function.

Male and female patients between the ages of 6 and 11, inclusive, were eligible for enrollment if they met the following criteria:

- A history of at least six months of chronic stable asthma requiring short acting beta-agonist treatment.
- No hospitalization, change in asthma therapy or lower respiratory infection during the four weeks prior to enrollment.
- No upper respiratory infection during the two weeks prior to enrollment.
- Prestudy FEV_1 between 50.0 and 90.0 percent of predicted normal.
- Demonstrated reversibility of at least 15.0 percent within 30 minutes following two inhalations of Ventolin.
- No other clinically significant disease or abnormality in clinical laboratory tests, physical examination or 12-lead ECG at screening.

Washouts were required prior to entry for various medications as follows:

- Oral beta agonists, seldane or erythromycin (1 week).
- Oral or inhaled corticosteroids or salmeterol (4 weeks).
- Monoamine oxidase inhibitors, tricyclic antidepressants or beta-blockers (6 weeks).
- Astemizole (3 months).

Patients were required to withhold medications prior to pulmonary function testing as follows:

- Inhaled beta agonists and anticholinergics (8 hours).
- Cromolyn and nedocromil sodium, theophylline BID (24 hours)
- Antihistamines, theophylline QD, aspirin and NSAIDS (48 hours)

Concomitant use of inhaled corticosteroids was not allowed during the trial, although anticholinergics, cromolyn sodium, nedocromil sodium and theophylline, at fixed doses, were allowed.

There were two treatment visits following screening, separated by a minimum of 72 hours and maximum of eight days. Each treatment visit was scheduled at approximately the same time of day as the screening visit. Prior to dosing at each treatment visit, FEV_1 was assessed and required to be within ±15 percent of the

prestudy value. A predose serum potassium was determined (patients were asked to dress the antecubital fossa with two hours prior to the visit in order to anesthetize the area for venipuncture) and a 12-lead EKG and vital signs were collected.

The first dose at each visit was a single inhalation of either Proventil HFA or Ventolin, as determined by the randomization scheme. At 30 minutes following the initial dose, another single inhalation dose was administered, followed by two inhalations at 60 minutes following the initial dose and four inhalations at 90 minutes following the initial dose. A total of eight inhalations were administered within 90 minutes.

Following administration of each dose, the following assessments were made:
radial pulse (12 minutes after dosing),
sitting blood pressure (14 minutes after dosing),
serum potassium (16 minutes after 8 cumulative inhalations only),
pulmonary function testing for FEV_1 assessment (18 minutes after dosing) and
12-lead ECG (24 minutes after dosing).
Adverse events were assessed at each clinic visit for the duration of the visit and the time period between visits. At the second treatment visit, cumulative dosing procedures were followed by final physical examinations and clinical laboratory testing.

The primary efficacy response was mean percent change from predose FEV_1 at each dose level. It was specified a priori that the two treatments would be considered by the sponsor to be clinically "equivalent" if the 90 percent confidence interval on the mean difference between groups was within an interval of 15 percent. A two-sided test was used to test the hypothesis of equivalence. A sample size calculation of 24 subjects was based on a previous estimate of root mean square error as 21.7 percent, providing at least 90 percent power at an alpha = 0.05. Secondary efficacy parameter analyses included change in FEV_1 (with a clinically significant difference between treatment groups considered to be 0.34L) and change in percent of predicted FEV_1 (with a clinically significant difference of 9.8 percent).

Safety outcomes were statistically tested using the same methodology. Clinically meaningful differences between treatments were specified a priori as follows:

Serum potassium	0.55 mEq/L
Pulse rate	18 beats per minute
Systolic blood pressure	15 mmHg
Diastolic BP	10 mmHg
ECG intervals	
PR	0.03 sec
QRS	0.02 sec
QT	0.03 sec
QT_c	0.03 sec

EXPLANATION OF PLANNED ANALYSIS:

The primary analysis (as specified in the protocol) was an analysis of variance (ANOVA) with the percentage change from predose FEV1 as the dependent variable.[1] The estimates of the mean difference and standard error of this difference were calculated from the ANOVA model. A 90% confidence interval for the mean difference (at each dose level) between the treatments was generated. In addition to providing confidence intervals, the sponsor calculated p-values for the differences in mean change from predose FEV1 at each dose level.

PATIENT DISPOSITION:

A total of 42 patients were screened for this study, 27 were randomized and 24 were considered evaluable for efficacy. There were 15 patients screened who did not meet eligibility requirements. The sponsor adequately accounted for each. No patients discontinued from the study, however, three patients who completed each study period were considered non-analyzable and were replaced (Pts. # 2, # 6, and # 9). Adequate explanations were provided related to investigator error in assessing screening or predose criteria. Two additional patients, Pts. # 4 and # 24, were reported to have departures from the protocol, but data were included in the analyses.

The intent-to-treat analysis included 27 patients. The study population consisted of eight females (30 percent), 22 Caucasians (81 percent) and five African Americans (19 percent). Patient ages ranged from 6 to 11 with a mean age of 9 years. Approximately half of the patients reported having had asthma for more than five years. Treatment groups appeared comparable with respect to baseline demographic factors.

OUTCOMES:

FEV_1

Mean FEV_1 for the 24 evaluable patients at screening was 1.53 L, 72.7 percent of predicted, and there were no significant differences detected between the predose assessments for Proventil HFA and Ventolin treatments.

Although there were no statistically significant differences between Proventil HFA and Ventolin treatment means with regard to **percent change from predose FEV_1** at any dose level, there was a statistically significant linear dose response detected for Proventil HFA. A similar linear dose response was not detected for Ventolin. Summary

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[1] The fixed factors in the model were: sequence, treatment and the log (base 10) of the cumulative number of inhalations (1, 2, 4, or 8). Interactions included in the model (as fixed factors) were: sequence-by-treatment, sequence-by-$\log_{10}$ of cumulative inhalations, treatment-by-$\log_{10}$ of cumulative inhalations, and sequence-by-treatment-by-$\log_{10}$ of cumulative inhalations. Factors and interactions included as random effects were: subject within sequence, subject-by-treatment within sequence, and subject-by-$\log_{10}$ of cumulative inhalations within sequence. For each fixed effect, the sponsor used the mean square error of the appropriate random effect in the F-test.

statistics are shown below in Table 1 and a plot of these data are provided in Appendix A.

Table 1: Percentage Change from Predose FEV_1

Cumulative Inhalations (given 30 minutes apart)	Proventil HFA*	Ventolin*
1		
Mean (SD)	11.8 (13.1)	10.7 (12.6)
Range		
2		
Mean (SD)	14.5 (12.0)	14.8 (12.8)
Range		
4		
Mean (SD)	20.1 (25.2)	14.7 (12.6)
Range		
8		
Mean (SD)	22.7 (33.6)	14.2 (17.3)
Range		

* The overall p-value for the comparison of treatments was 0.217 and the p-value for the treatment by dose interaction was 0.198.

Table 2 shows the analyses of the 90 percent confidence intervals around the difference in percent change from predose FEV_1 for the two treatments. This range is the sponsor's preferred analysis. Results for both the evaluable population (as conducted by the sponsor) and the intent-to-treat population (added by the Division) are reported.

Table 2: Difference in Percent Change from Predose FEV1
Means and 90% Confidence Intervals

	Cumulative Inhalations	Estimate of difference	Standard Err of difference	90% Confidence Interval Lower Limit	Upper Limit
Sponsor's Analysis n=24 (evaluable)	1	1.17	4.01	-5.51	7.85
	2	-0.38	4.01	-7.06	6.30
	4	5.41	4.01	-1.27	12.09
	8	8.51	4.01	1.83	15.19
Reviewer's Analysis n=27 (ITT)	1	0.65	4.17	-6.29	7.59
	2	-0.45	4.17	-7.40	6.49
	4	5.18	4.17	-1.76	12.12
	8	6.12	4.17	-0.82	13.06

Table 3, on the following page, provides similar analyses, using 95 percent confidence intervals, as preferred by the Division.

Table 3: Difference in Percent Change from Predose FEV1
Means and 95% Confidence Intervals

	Means and 95% Confidence Intervals of Percentage Change in FEV1				
	Cumulative Inhalations	Estimate of difference	Standard Err of difference	90% Confidence Interval Lower Limit	Upper Limit
n=24 (evaluable)	1	1.17	4.01	-6.83	9.17
	2	-0.38	4.01	-8.38	7.62
	4	5.41	4.01	-2.59	13.41
	8	8.51	4.01	0.51	16.51
n=27 (ITT)	1	0.65	4.17	-7.65	8.95
	2	-0.45	4.17	-8.76	7.85
	4	5.18	4.17	-3.13	13.48
	8	6.12	4.17	-2.18	14.42

Both the 90 and 95 percent confidence intervals on the mean difference in percent change from predose FEV_1 between treatments fell within the accepted range of ± 15.0 percent at 1, 2, and 4 puffs, but exceeded the accepted range at 8 puffs. Therefore, at 8 puffs the two treatments did not meet the a priori definition of "equivalence" within the evaluable population, although mean the difference was within the accepted range for the intent-to-treat population.

Similarly, **absolute change from predose FEV_1** showed a statistically significant linear dose response for Proventil HFA, but not for Ventolin. No statistically significant differences were seen between treatment means at any dose level. All 90 percent confidence intervals on the differences between treatment means were within the pre-specified acceptance range of ± 0.34 L. Plots of these data are contained in Appendix B.

Change from predose percent predicted FEV_1 also provided outcomes consistent with the previous analyses. Again, a significant linear dose response was seen for Proventil HFA, but not for Ventolin. No statistically significant differences were seen between treatment means at any dose level. The 90 percent confidence interval for the difference between treatment means fell within the pre-specified range of ± 9.8 percent for 1, 2, and 4 puffs, but not at the 8 puff dose level. Appendix B contains plots of these data.

These FEV_1 analyses suggest that among this pediatric study population, there appears to have been a somewhat greater effect on FEV_1 associated with Proventil HFA than Ventolin, particularly at the highest cumulative dose (8 puffs). The clinical significance of this outcome with regard to efficacy of the products is unclear as it appears that the products were quite comparable in the range of normal clinical doses (cumulative doses of 1 and 2 puffs). Further evaluation of the safety data is necessary to determine the clinical implication of potential differences between treatments.

Serum Potassium

Mean serum potassium at screening for the 27 patients included in the intent-to-treat analysis was 4.21 mEq/L, with no significant difference between sequence groups. Only 26 patients were included in the predose analysis and Proventil HFA analysis due to hemolysis of the sample from Pt. #15 on the Proventil HFA day, but there was no significant difference between treatment groups. Mean values were 4.39 and 4.27 mEq/L for Proventil HFA and Ventolin, respectively.

After 8 cumulative inhalations, there was a mean change of - 0.49 mEq/L for the Proventil HFA treatment and - 0.23 mEq/L for the Ventolin treatment. These changes were significantly different (p=0.025). Among individual patients, a maximum fall of 1.4 mEq/L was observed with Proventil HFA treatment and 1.0 mEq/L was observed with Ventolin treatment. Nineteen percent (5 of 26) of the Proventil HFA patients and 11 percent (3 of 27) of the Ventolin patients fell below 3.4 mEq/L, the lower limit of the pre-specified serum potassium reference range. The 90 percent confidence interval on the difference between mean change in serum potassium fell within the pre-specified limits of ± 0.55 mEq/L.

These findings appear consistent with the FEV_1 outcomes in that Proventil HFA was associated with a greater effect in this study population. While FEV_1 outcomes may be primarily reflective of local delivery of albuterol to the lungs, serum potassium provides additional evidence that systemic exposure from Proventil HFA may also have been greater than with Ventolin. However, the overall difference between the two treatments does not appear to have substantial clinical safety implications.

Pulse Rate

Mean pulse rate at screening was 79 bpm, with no significant difference between sequence groups. Predose means were 78 and 80 bpm for the Proventil HFA and Ventolin treatments, respectively, with no significant difference between treatments.

The mean maximum change from predose pulse rate was an increase of 5 bpm for both Proventil HFA and Ventolin following 8 cumulative inhalations. The mean Proventil HFA pulse rate was increased over predose at each dose level, while the Ventolin means fell from predose after one and two cumulative inhalations. Minimum and maximum changes for individual patients did not appear to show a clinically meaningful trend to differentiate the treatments. Confidence intervals around the difference in treatment means were within the pre-specified limit of ± 18 bpm at each dose level.

Although there was a minor discrepancy in response between treatments at lower doses, pulse rate outcomes do not suggest clinically meaningful differences between the two treatments or safety concerns regarding either product in the pediatric population.

Systolic Blood Pressure

Mean systolic blood pressure at screening was 99 mmHg, with no significant difference between sequence groups. Predose measurements were not significantly different at 97 and 94 mmHg for Proventil HFA and Ventolin treatments, respectively.

Mean changes were negligible, less than 2 mmHg for both treatments at each dose level. Minimum and maximum changes among individual patients did not appear to suggest a difference between treatments. The confidence intervals around the difference between treatment means were well within the pre-specified limit of ± 15 mmHg at each dose level.

Systolic blood pressure outcomes do not suggest clinically meaningful differences between treatments or safety concerns in the pediatric population.

Diastolic Blood Pressure

Mean diastolic blood pressure at screening was 67.5 mmHg, with no significant difference between sequence groups. The predose mean for Proventil HFA was 67 mmHg, while the predose mean for Ventolin was 63 mmHg.

Mean changes were less than 2 mmHg for each treatment and confidence intervals on the differences between means were within the pre-specified limit of ± 10 mmHg. Minimum and maximum changes among individual patients did not appear to suggest a clinically meaningful trend. There were no apparent safety concerns suggested by this endpoint.

Electrocardiogram

Mean ECG data at **screening** were as follows: ventricular rate (79 bpm), PR interval (0.125 sec), QRS interval (0.091 sec), QT interval (0.369 sec) and QT_c (0.418). There was a statistically significant difference between the two sequence groups with regard to ventricular rate, but no significant difference was observed between sequence groups at the predose assessments. There was 0.009 sec difference between mean QT intervals at **predose** (Proventil HFA having the higher rate of 0.375 sec), which was found to be statistically significant. The difference between treatments with respect to QT_c (0.002 sec), PR (0.000 sec) and QRS (0.002) were not significant at predose.

Change from predose **ventricular rate** was significantly different overall between the two treatment groups, but the interaction between treatment and dose was not significant. The increase in rate was consistently higher for the Proventil HFA treatment, with mean increases ranging from 2.3 bpm following one puff to 10.0 bpm following 8 cumulative puffs. Despite a higher mean ventricular rate at baseline (2 bpm), the Ventolin treatment mean decreased by 1.7 bpm following one puff and was increased by only 2.7 bpm following 8 cumulative puffs. This endpoint may be reflective of a greater systemic effect of Proventil HFA relative to Ventolin, however, none of the

confidence intervals around the differences in treatment means were outside of the pre-specified clinically significant difference of ± 18 bpm.

Changes from the predose **PR interval** were minimal for both treatments, with mean declines of 0.006 sec or less. Changes in **QRS interval** were also minimal, with mean increases of 0.006 or less. Confidence intervals for PR and QRS differences were within pre-specified ranges of ± 0.03 and 0.02 sec, respectively.

Changes from predose **QT interval** suggest differences between responses to Proventil HFA and Ventolin. There was a statistically significant difference between mean QT interval responses to the two treatments in that the Proventil HFA group showed a decline from predose ranging between 0.013 and 0.016 sec at each dose level, with no apparent dose response trend. Ventolin did show a dose response trend with mean declines in QT interval from predose ranging between 0.001, after a single puff, to 0.005 sec, following 8 puffs. Confidence intervals for the differences in QT intervals were within pre-specified ranges of ± 0.03 sec at any dose level.

Changes from predose **QTc** do not appear to reflect the same disparity between treatments as QT intervals. Mean QTc for both treatments declined from predose after one and two puffs, then increase following four and eight puffs. The confidence intervals for mean QTc differences did not exceed the pre-specified ranges of ± 0.03 sec at any dose level.

Adverse Events

Seven (26 percent) of the 27 patients included in the intent-to-treat analysis reported at least one adverse event (Pt. #s 3, 6, 9, 13, 18, 19 and 23), including six patients in each treatment group. Most events were reported at clinic visits for both treatments and included dermatitis (prestudy), injured thumb, otitis media, coughing and rhinitis. Pt. # 13 reported nasal congestion/rhinitis only at the Ventolin treatment visit.

A single event appeared to be directly related to treatment as it occurred during dosing on a study day. One patient (# 19) reported a bad taste in association with four puffs of Proventil HFA. The taste lasted approximately one hour and, hence, was also reported in association with the eight puff dose. No patients reported an adverse event during dosing with Ventolin.

The adverse event profiles of the two treatments did not appear to differ in a clinically significant fashion, with the exception of taste perversion. Taste perversion has been observed with Proventil HFA in a variety of clinical settings and is currently included in the labeling as "inhalation taste sensation."

DISCUSSION AND CONCLUSION:

FEV_1 and serum potassium, unlike the vital sign, ECG and adverse events, do suggest a potential difference between Proventil HFA and Ventolin. Both of these assessments imply a more pronounced effect for Proventil HFA. The FEV_1 outcomes seen in this trial could have implications for the relative efficacy of this product, while the serum potassium is suggestive of potential safety concerns from more extensive systemic exposure. These potential differences need to be further evaluated in the setting of extended clinical use. Trial 1141, a four week safety and efficacy trial, will be evaluated to determine the whether these findings have clinically significant implications for longer term treatment with regular dosing.

APPEARS THIS WAY
ON ORIGINAL

5.0 TRIAL 1141-SILV

TITLE: 4-Week Safety and Efficacy Study of HFA-134a Salbutamol Sulfate Versus Ventolin in Children with Reversible Obstructive Airway Disease. (Volumes 2-7, 12-17)

INVESTIGATORS: Richard Wyatt, M.D., Minneapolis MN
David Tinkelman, M.D. and Robert Berkowitz, M.D., Atlanta GA (single site)
Edwin Bronsky, M.D., Salt Lake City UT
James Kemp, M.D., San Diego CA
Gail Shapiro, M.D., Seattle WA

STUDY DATES: June 29, 1995 to January 9, 1996
There were two protocol amendments, both incorporated prior to enrollment of the first patient.

PROTOCOL:

This trial was a randomized, four-week, open-label, age stratified, parallel group study to compare Proventil HFA and Ventolin Inhalation Aerosol. This was not a blinded or placebo-controlled trial. Patients who met enrollment criteria at the Prestudy Visit participated in a seven day run-in period, during which they received their currently prescribed medication. Following the run-in period, each patient was randomized to receive an assigned medication during the four-week treatment period. The 63 patients enrolled in the trial were stratified by age into two groups; age 4 to 7 years (15 patients) or age 8 to 11 years (48 patients).

Male and female patients between the ages of 4 and 11, inclusive, were eligible for enrollment if they met the following criteria:

- A history of asthma, as determined by the investigator, extending back at least 6 months prior to screening.
- Current use of a short acting inhaled β_2 agonist.
- FEV_1 of at least 50 percent of predicted normal following a six hour period without β_2 agonist use.
- Stable asthma as defined by no changes in asthma therapy, no more than eight puffs per day of β_2 agonist, and no hospitalizations or emergency room visits during the four weeks prior to screening.
- Demonstrated reversibility of at least 12 percent within 30 minutes following two puffs of Ventolin.
- No history of upper respiratory infection within 2 weeks prior to screening or lower respiratory infection within 4 weeks prior to screening.
- No other clinically significant disease or abnormality in clinical laboratory tests, physical examination or 12-lead ECG at screening.
- Demonstration of adequate inhalation dosing and spirometry technique.

Washouts were required prior to entry, and throughout the trial, for various medications as follows:

- Theophylline (3 days).
- Salmeterol or oral beta-agonist (1 week).
- Oral corticosteroids, inhaled anticholinergics or other investigational agent (4 weeks).
- Monoamine oxidase inhibitors, tricyclic antidepressants or beta-blockers (6 weeks).
- Astemizole (80 days).

Patients were required to withhold medications prior to pulmonary function testing as follows:

- Cromolyn and nedocromil sodium (1 hour).
- Inhaled beta agonists (6 hours).
- Methylxanthine containing food and beverages (8 hours).
- Inhaled corticosteroids or short-acting antihistamines (12 hours).
- Long-acting antihistamines or antibiotics (24 hours).
- Aspirin and NSAIDS (48 hours).

Concomitant use of these medications, including regular use of inhaled corticosteroids and bursts of oral corticosteroids, were allowed during the trial.

During the run-in period, patients were required to use at least two inhalations of their currently prescribed therapy four times per day. Patients were allowed two attempts to complete the run-in phase. During the four week treatment phase, patients were required to use at least two inhalations of their assigned treatment four times per day.

Efficacy assessments included PFTs that were conducted at Day 1 and Week 4 clinic visits, prior to dosing of two puffs of study medication and at 10, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes after dosing. ECG and vital signs were recorded prior to dosing and prior to the 60 minute PFTs. Patients were rescued with one or two inhalations of study medication or nebulized albuterol in the event that their FEV_1 fell below 40 percent of predicted normal during PFTs. Evaluations of adverse events and medication use were conducted at the Week 2 clinic visit.

Primary efficacy assessments included change from predose in percent predicted FEV_1, FEV_1 AUC, peak percent change in FEV_1, duration of effect and proportion of responders. The sponsor did not select a single primary endpoint. Secondary efficacy assessments included FEV_1 time-to-onset and peak effect, and change from predose at each time interval of the six hour assessment period. These primary and secondary assessments were analyzed using a pre-specified ANOVA model with pooled center, age group, treatment, treatment by center, and treatment by age group as interactions in the model.

Additional secondary efficacy assessments included daily diaries that were used by patients or their parents to record PEFR (immediately before the morning and bedtime doses of study medication, using best of three efforts), medication use (morning and

evening), asthma disability symptoms (immediately before bedtime dose) and sleep disturbance scores (immediately before morning dose). Investigators provided a global assessment score of asthma control. Sleep disturbance was rated on a 0 to 4 scale:
0 = No significant asthma symptoms during the night.
1 = Asthma symptoms causing waking once, or early waking.
2 = Asthma symptoms causing waking twice, or more (including waking early).
3 = Asthma symptoms causing you to be awake for most of the night.
4 = Asthma symptoms so severe that you did not fall asleep at all.

Four asthma symptoms were rated daily, wheeze, cough, shortness of breath and chest tightness. Each was rated on a 0 to 5 scale:
0 = Not present.
1 = Symptoms present, but caused little or no discomfort.
2 = Mild symptoms that became annoying but caused little or no discomfort.
3 = Moderate symptom that caused discomfort, but did not affect your normal daily activities.
4 = Severe symptom that interfered at least once today with normal daily activities.
5 = Symptom so severe that you could not go to work/school, or carry out other normal daily activities.

Investigator global assessments of how well the treatment controlled the patients' asthma during the study were made on a 1 to 5 scale:
1 = Very good
2 = Good
3 = Fair
4 = Poor
5 = Very Poor

Safety was assessed with vital signs, 12-lead ECGs, adverse events, clinical laboratory tests and physical examinations. Adverse events were recorded at clinic visits and were not recorded in the daily diaries. Clinical laboratory tests (hematology, serum and urine chemistry) and physical examinations were performed pre-study and at study completion.

PATIENT DISPOSITION:

There were 103 patients **screened** for this study. Forty of these patients were not enrolled for the following reasons:
4 patients had a screening FEV_1 of less than 50 percent of predicted normal.
24 patients failed to meet reversibility criteria.
1 had an intercurrent illness.
4 withdrew consent.
7 failed for other reasons (failure to meet other eligibility criteria or unable to tolerate procedures).

All 63 patients **enrolled** in the trial completed the run-in phase and the treatment phase of the trial; 33 in the Proventil HFA group and 30 in the Ventolin group. Patient ages ranged from 4 to 11 in the Ventolin group and 5 to 11 in the Proventil HFA group. Twelve patients (36 percent) of the Proventil HFA group were female, while 10 (33 percent) of Ventolin group were female. Approximately 90 percent of each group was Caucasian. One patient in each group was "Black" and the remaining four patients were "Asian/Pacific Islander" (1 patient) or "American Indian" (3 patients). Mean and range for weight, height, duration of asthma were comparable between groups.

Approximately 90 percent of each group reported having allergies. Other aspects of patients' medical histories, e.g., occurrence of otitis media or bronchitis, appeared comparable between groups.

Use of **concomitant medication** during the trial appeared comparable between treatment groups. All patients used inhaled albuterol prior to entry in the trial. Nine (27 percent) of the Proventil HFA group and nine (30 percent) of the Ventolin group used orally inhaled corticosteroids during the trial. In addition, seven (21 percent) of Proventil HFA patients and six (20 percent) of Ventolin patients used a nasal corticosteroid. Cromolyn sodium was used by four patients (12 percent) and five patients (15 percent) from these treatment groups, respectively. Three patients in each group reported using albuterol nebulizer treatments during the study.

Compliance and **medication use** were assessed based on mean number of inhalations per day, as assessed by the weight of returned canisters. Per protocol, this figure should ideally be 8 puffs per day, but was 7.5 for the Proventil HFA group and 7.2 for Ventolin. Six patients, approximately 20 percent, of each treatment group were less than 60 percent compliant. Four Proventil HFA and one Ventolin patient used more than 140 percent of the expected amount of medication. These figures suggest that while compliance to protocol was not optimal, differences between treatment groups were minimal and unlikely to have altered the validity of the treatment comparisons. These compliance deviations may be attributable in part to the pediatric population involved and the protocol-specified QID regimen. The protocol-specified QID regimen differs from the PRN regimen that is likely the typical the pattern of use for these patients.

Diary data regarding medication use were analyzed by two week segments (Weeks 1-2 and Weeks 3-4) and by treatment group. Each analysis found mean use of 8.2 to 8.5 inhalations daily, suggesting some discrepancy between diary data and canister weight compliance determinations, but no overall difference between treatment groups.

There were eight patients reported to have had **protocol violations**, including six Proventil HFA patients and two Ventolin patients. Of these, two appear to have had the potential to significantly affect these patients' outcomes in the trial. Pts #505 had a final assessment six weeks, rather than four weeks, after initiation of the treatment phase. In the final two weeks of this period, the patient used two inhalations of Proventil HFA on an as needed basis instead of four times a day. Pt #514 in the Ventolin group did not receive drug on a total of five study days during Weeks 3 and 4. While these two protocol violations may have changed outcomes for these two patients, it is unlikely that they significantly altered the overall outcome of the trial.

The **intent-to-treat** population was used consistently for the analyses. The intent-to-treat population was the same as the study population in this trial, although diary data were missing for patients at various times.

EFFICACY OUTCOMES:

FEV_1

Mean **prestudy** predicted FEV_1 was 79.7 percent of predicted for the Proventil HFA group and 79.6 percent of predicted, for the Ventolin group. Absolute mean predose FEV_1 at the prestudy visit was 1.45 L for both groups and percent reversibility was comparable for the two groups.

Appendices D and E show plots of the **percent change from predose** FEV_1 on Day 1 and at Week 4, respectively. No statistically significant differences were seen between treatment groups at any timepoint. However, Day 1 data suggested a slightly better response to the Ventolin product and Week 4 suggested a slightly better response to Proventil HFA. The mean data from Week 4 appear to be consistent with the outcomes of Trial 1142, the cumulative dose study, which appear to support enhanced activity/delivery of the Proventil HFA formulation.

The results of the reviewer's analyses for other primary and secondary efficacy variables (intent-to-treat population at Week 4) are provided in Table 4. The sponsor's results of the same endpoints are provided in Appendix C.

Table 4: Statistical Reviewer Results from ANOVA*

	Proventil HFA Mean (SE)	Ventolin Mean (SE)	Difference	95% CI	P-Value
AUC (as percent improvement over predose FEV_1)	49.6 (11.2)	37.8 (12.9)	11.75	(-22.5, 46.0)	0.4943
AUC (as absolute improvement over predose FEV_1)	0.66 (0.15)	0.53 (0.17)	0.13	(-0.33, 0.59)	0.5813
Time-to-Onset of effect (minutes)	7.3 (1.2)	6.2 (1.5)	1.08	(-2.7,4.9)	0.5640
Duration of effect (hours)	2.3 (0.4)	1.7 (0.5)	0.5	(-0.8,1.8)	0.4233
Peak FEV1 (% change from predose)	21.2 (2.4)	17.9 (2.8)	3.3	(-4.0,10.7)	0.3718
Peak FEV1 (% of predicted normal FEV1)	98.6 (2.4)	97.1 (2.7)	1.5	(-6.7,8.8)	0.6773
Time-to-Peak (minutes)	52.6 (6.5)	55.4 (7.5)	-2.8	(-22.8,17.2)	0.7808

*The means, 95% confidence intervals and p-values in this table were obtained from an ANOVA with pooled center, age group (4-7 and 8-11 years), and treatment group as factors, and treatment-by-center and treatment-by-age group as interactions. The data at week 4 were used for each dependent variable.

Mean **AUC** (expressed as percent improvement over predose and absolute FEV_1 value in liters) was greater for the Proventil HFA treatment group. No statistically significant difference between treatments was seen for AUC.

Onset of effect, the time to 12 percent improvement over predose using linear interpolation, was calculated for patients who were "responders," i.e., those who achieved a 12 percent improvement. In the statistical analyses of the responder subgroup, no significant difference was observed between treatments.

Duration of effect was defined as the time between time-to-onset and time to termination. Time to termination was the time after which FEV_1 fell below 12 percent over predose for two consecutive measurements, as determined by linear interpolation. No statistically significant differences were seen between means. Duration of effect, as defined for these analyses, was shorter than the labeled 4 to 6 hour dosing interval for

both Proventil HFA and Ventolin. However, both drugs demonstrated some effect, i.e., improvement over predose, throughout the 6 hour evaluation period and these patients had near "normal" mean FEV_1's at baseline (i.e., approximately 80 percent).

Peak FEV_1, expressed as either percent change from predose or as percent of predicted normal FEV_1, showed no statistically significant differences between treatments, but numerically favored Proventil HFA.

Time to peak response also showed no statistically significant differences between treatments. Mean data numerically favored Ventolin.

The number and proportion of **responders** in the Proventil HFA group was greater than that in the Ventolin group, although no statistically significant differences were observed. Less than 60 percent of the patients achieved a 12 percent response and this is attributable to the mild to moderate nature of these patients' asthma and the often observed lack of reproducible responses in such testing.

Statistical Reviewer Comment: This reviewer tested the interaction effects at the alpha=0.25 level. There was a statistically significant treatment-by-age group interaction in two of the models (Peak FEV1 as percent of predicted: p=0.0291 and Duration of Effect: p=0.1229). The source of the Peak FEV1 interaction was a difference in the Week 4 responses of the older children on Proventil HFA (105.69) as compared to the younger children (90.14), see Table 5. The younger and older children on Ventolin responded similarly (older: 96.13, younger: 96.97). The difference in response for the younger and older children on Proventil HFA was present at baseline as well (older: 105.71, younger: 90.99), therefore this interaction is probably not due to differences in treatment effects between younger and older children. The source of the Duration of Effect interaction was a difference in response between younger and older children in both treatment groups. The older children appeared to respond better to Proventil HFA, whereas the younger children responded better to Ventolin. Since the number of older children is small and these interactions were seen in only two of the seven efficacy variables (one of which had a baseline difference), the statistically significant interaction effects are likely due to chance.

Table 5: Results of Variables With Differences in Treatment Effects by Age Group

		Older Children (8-11 years)			Younger Children (4-7 years)			
		Ventolin n=6	Salbutamol n=9	Difference		Ventolin n=24	Salbutamol n=24	Difference
Peak FEV1 (% of predicted normal FEV1)	Day 1	94.72	105.71	10.99	Day 1	95.91	90.99	-4.92
	Week 4	96.13	105.69	9.56	Week 4	96.97	90.14	-6.83
	Change	1.41	-0.18	-1.59	Change	1.06	-0.85	-1.91
Duration of Effect	Day 1	1.99	1.88	-0.11	Day 1	2.2	1.9	-0.30
	Week 4	1.24	2.46	1.22	Week 4	2.19	1.63	-0.56
	Change	-0.75	0.58	1.33	Change	-0.001	-0.27	-0.27

Statistical Reviewer Conclusions: The FEV_1 results of this study do not demonstrate a statistically significant difference between treatment groups. However, the study was open-label, had five primary efficacy endpoints, and was powered to detect only very large differences between treatment groups. The study had small numbers of patients per treatment group (n=30 and 33) and would have resulted in a p-value less than 0.05 only if differences between treatment groups had been very large (i.e., the study had about 80 percent power to detect differences of 1.5 hours for Duration of Effect, 40 units for AUC as a percent improvement, and about 22 minutes for Time to Peak). Therefore the lack of statistical significance is not very informative. The mean differences between treatment groups and the 95% confidence intervals around the differences characterize the study results in a more interpretable manner. The confidence intervals provide a range of likely values for the true differences in mean responses between treatment groups. To achieve comparability, the confidence intervals should be within what the medical reviewer considers to be a "clinically relevant value" for each endpoint.

Overall, FEV_1 outcomes appear to demonstrate clinical comparability between the Proventil HFA and Ventolin treatments. While Proventil HFA may have demonstrated superiority on some mean values, these differences were not statistically significant and do not appear to be large enough to have important clinical implications.

PEFR

Morning and evening PEFR values from diary data were summarized and analyzed by two week intervals, i.e., Weeks 1-2 and Weeks 3-4. No statistically significant differences were found between treatment groups in either morning or evening scores for either interval. Morning mean values were 210.7 and 222.7 L per minute for Proventil HFA at Weeks 1-2 and Weeks 3-4, respectively, while Ventolin means were 223.3 and 229.4 during the same intervals. Evening means were 222.0 and 235.2 for Proventil HFA at Weeks 1-2 and Weeks 3-4, respectively, while Ventolin means were 245.0 and 249.6 during the same intervals. At each assessment, Ventolin group means exceeded those of Proventil HFA. Since a somewhat less disparate trend was also observed prior to use of assigned treatment (during run-in) the implications of this difference in terms of true differences in effects between these products is unclear.

Asthma Disability Symptom Scores

Mean disability scores were also analyzed by two week intervals, Weeks 1-2 and Weeks 3-4. For both intervals, mean scores for each of the four symptoms (shortness of breath, chest tightness, wheezing, and cough) ranged on a five point (0 to 4) scale, indicating that the overall severity of symptoms was minimal and there was little fluctuation. No statistically significant differences between treatment groups was found. In contrast to the FEV_1 data that suggested some trends toward greater efficacy with Proventil HFA, maximum individual values were highest among the Proventil HFA patients in seven of the eight analyses. There appeared to be no significant trend toward improvement or worsening during the study for either treatment group.

Sleep Disturbance Scores

Mean sleep disturbance scores were 0.2 and 0.4 on a six point scale (0 to 5) for Proventil HFA at Weeks 1-2 and Weeks 3-4, respectively. Scores for these same intervals were 0.2 and 0.1, respectively, for Ventolin HFA. No significant differences were noted between groups. It is unclear that the trend shift toward a more severe score in the Proventil HFA group, or an improved score among Ventolin patients, can be considered clinically relevant given the small increments of change and the minimal overall severity.

Use of Rescue Medication During PFTs

Three patients required rescue medication during clinic visits, including two patients in the Proventil HFA treatment group (# 319 on Day 1 and # 513 at Week 4) and one Ventolin patient, # 414. Each of these patients was in the 8 - 11 year old age range. Patients # 319 and # 414 required two puffs of study medication, while Patient # 513 also required an albuterol nebulization treatment.

Investigator Global Assessment

Investigators did not provide ratings of "very poor" or "poor" for either treatment in their Week 4 global assessments. For Proventil HFA, 24 percent of patients were rated as "very good," 61 percent were rated as "good," and 15 percent were rated as "fair." For Ventolin, 40 percent of patients' responses to therapy were rated as "very good" and 60 percent of patients were rated as "good." In interpreting this metric, as well as the other subjective assessments, it is important to note that this was an open label trial. In addition, the Proventil HFA product had not been approved in the U.S. at the time this trial was conducted and, unlike Ventolin, practitioner familiarity with the product was not widely established.

Efficacy Conclusion

FEV_1 parameters did suggest that, like Trial 1142, there was a slightly enhanced response in association with Proventil HFA relative to Ventolin. This relationship was not shown to occur in all patients, nor did the difference appear to have significant clinical implications. PEFR, asthma disability symptom scores, sleep disturbance scores, investigator scores and use of rescue medication did not tend to favor Proventil HFA and did not demonstrate a clinically relevant difference between treatments.

Age stratification was included as a factor in statistical models used for analyses and did not appear to be a clinically significant determinant of any response differences between treatments. Overall, it appears that Proventil HFA and Ventolin performed comparably in this study population. Further evaluation of the safety outcomes is necessary to confirm this conclusion.

SAFETY OUTCOMES:

Adverse Events

There were no deaths and no discontinuations due to adverse events during this trial. One patient experienced a serious adverse event. Patient # 117, an 11 year old male, was hospitalized with an acute appendicitis attack and subsequently had an appendectomy. The patient was reported to have missed one day of dosing during his hospitalization.

Nineteen (58 percent) of Proventil HFA and 13 (43 percent) of Ventolin patients experienced at least one adverse event. Table 6 lists the adverse events reported by more than five percent of either treatment group and is the table proposed for inclusion in product labeling. The five percent level represents two or more patients in each treatment group and, by comparison to the "universe" of adverse events reported, has been determined to have captured the majority of events that occurred in the trial. Additional events that occurred within the Proventil HFA group (one patient reported each event) included: allergic reaction, chest pain, epistaxis, constipation, diarrhea, dyspepsia, insomnia, cyanosis and skin disorder. Gastroenteritis and arthropathy were each reported by one patient in the Ventolin group.

Table 6: Adverse Events Reported by More than 5 Percent of Either Treatment Group, N (%)

	Proventil HFA (N = 33)	Ventolin (N = 30)	P-Value*
Body as a Whole			
Fever	1 (3%)	3 (10%)	0.340
Central/Peripheral Nervous System			
Dizziness	0	2 (7%)	0.223
Headache	5 (15%)	4 (13%)	1.000
Gastro-Intestinal			
Abdominal pain	2 (6%)	0	0.493
Nausea	1 (3%)	4 (13%)	0.183
Resistance Mechanism			
Infection - Bacterial	2 (6%)	1 (3%)	1.000
Otitis Media	2 (6%)	0	0.493
Respiratory System			
Acute asthma episode	3 (9%)	2 (7%)	1.000
Coughing	3 (9%)	2 (7%)	1.000
Increased asthma symptoms	1 (3%)	2 (7%)	0.601
Pharyngitis	2 (6%)	4 (13%)	0.412
Rhinitis	4 (12%)	6 (20%)	0.498
Sinusitis	1 (3%)	2 (7%)	0.601
Skin and Appendages			
Urticaria	2 (6%)	0	0.493

* The p-value for the overall treatment comparison is based on a two-sided Fischer's Exact Test.

Given the relatively low incidence of adverse events, it is difficult to use incidence rates to assess which events may potentially be treatment-related. It appears that most events are expected in this population. Urticaria and abdominal pain may have had a somewhat stronger association with Proventil HFA, while fever, dizziness, nausea and rhinitis appear more likely to have occurred in Ventolin patients. The incidences of

acute asthma episodes and increased asthma symptoms were low and do not appear to have differed in a clinically meaningful way between treatments.

Vital Signs

Proventil HFA and Ventolin treatment groups had very comparable predose mean pulse rates and systolic and diastolic blood pressures at both Day 1 and Week 4 assessments. Mean changes in **pulse rate** during the six hour interval on each day were less than three beats per minute at any timepoint for either treatment. There were no statistically significant differences between treatments and no clinically significant trends were observed.

Systolic blood pressure tended to increase from predose during treatment on Day 1, but decline at Week 4, for both treatments. Maximum mean change was 3.2 mmHg. **Diastolic blood pressure** appeared to show no trends and minimal changes during each dosing interval. Maximum mean change was 2.5 mm Hg. No statistically significant differences were observed between the groups and mean changes did not appear to have clinical significance.

ECG

Change from predose in **ventricular rate** and **PR, QRS, QT and QTc intervals** were compared between treatment groups on Day 1 and Week 4 at 60 minutes postdose. The maximum increase in ventricular rate was 44 bpm (a Ventolin patient) and in QTc was 56 msec (a Ventolin patient). No significant differences were observed between groups and no mean or individual changes appeared to be clinically significant.

Clinical Laboratory Assessments

Two statistically significant differences were observed between treatment groups. Urinalysis results revealed a statistically significant difference primarily because more Ventolin patients (N = 4) were reported to have transitioned from normal to low specific gravity between prestudy and Week 4 than did Proventil HFA patients (N = 1). In hematology findings, mean cell volume among Proventil HFA patients exhibited a mean decline of 2.56, while Ventolin patients exhibited a mean decline of 0.54. Neither of these differences appear to have clinical significance.

All patients had normal serum potassium at Week 4, although one patient in each treatment group had transitioned from low to normal during the trial. Among Proventil HFA patients prestudy potassium (in mEq/L) was 3.967 and at Week 4 was 3.952. In comparison, the Ventolin group mean was 3.953 at prestudy and 3.989 at Week 4.

Nonfasting glucose declined among Proventil HFA patients from 89.45 at prestudy to 88.06 at Week 4 and among Ventolin patients from 89.80 at prestudy to 86.36 at Week 4.

Several patients had elevated eosinophil levels, thought to be due to concomitant allergic disease.

Overall, no clinically significant changes appeared to have occurred and clinically significant differences between groups did not appear evident.

Physical Examinations

Physical examinations findings were consistent with those expected in this pediatric population of asthmatics and were not dissimilar for the two treatment groups. Clinically meaningful changes were not reported for any patients between prestudy and study completion.

Device Performance

The study flow algorithms, instructions to patients regarding "press-and-breathe MDI Technique" and the "Patient Information and Consent Form" fail to describe having informed patients of the need to maintain the device by washing it on a weekly basis. However, this study was conducted prior to the approval of this product in adults and the Division's awareness of the device performance issues, i.e., the potential for the device to become clogged and inoperable if improperly maintained, and it is likely that the washing instructions were not provided to patients. In a February, 1997 meeting with the sponsor, the Division was told that there were 6 canisters returned to the clinic due to blockages. This issue will be discussed further in the Integrated Summary of Safety.

Safety Conclusion

Adverse events, vital signs, ECG, clinical laboratory evaluations and physical evaluations do not show significant safety concerns for either treatment and do not appear to indicate clinically significant differences between treatments.

DISCUSSION AND CONCLUSION:

While Trial 1142 suggested potential differences in the effects of Proventil HFA and Ventolin, Trial 1141 failed to confirm that any such differences resulted in clinically significant differences in patient outcomes after four weeks of treatment in patients age 4 to 11 years. Trial 1141 was not blinded or placebo controlled, design elements which were agreed to by the division primarily due to the ethical constraints in this pediatric population. The trial did, however, appear to adequately establish that in the subject population, the safety and efficacy of Proventil HFA and Ventolin can be considered clinically comparable. Additional clinical data are available from Trial 1247, a placebo controlled comparison of these treatments in pediatric patients with exercise-induced asthma.

6.0 TRIAL 1247-SILV

TITLE: Single-Dose Safety and Efficacy Study of HFA-134a Albuterol (Proventil HFA), Proventil (CFC), Ventolin (CFC) and HFA-134a Placebo in Children with Exercise-Induced Asthma. (Volumes 10-11)

INVESTIGATOR: Robert Dockhorn, M.D., Prairie Village KS

STUDY DATES: April 18, 1997 to October 20, 1998
There were no amendments made to the protocol.

PROTOCOL:

This trial was a randomized, single-blind, placebo-controlled, four-period crossover comparison of Proventil HFA with CFC formulations of Proventil and Ventolin and HFA-134a Placebo (placebo) in children age 6 to 11 years with exercise-induced asthma (EIA). During each treatment period, patients received a dose of two inhalations from one of the four inhalers. An exercise challenge was conducted at 30 minutes postdose. Each treatment period was scheduled for approximately the same time of day and treatment periods were separated by a period of 3 to 10 days.

Male and female patients between the ages of 6 and 11, inclusive, were eligible for enrollment if they met the following criteria:

- A history of mild-to-moderate asthma, as determined by the investigator (no demonstration of FEV_1 reversibility required), extending back at least 6 months prior to screening.
- Asthma with an exercise-induced component defined as a demonstrated decrease in FEV_1 of at least 20 percent, but not more than 50 percent within 30 minutes following two prestudy exercise challenge tests.
- Stable asthma as defined by no changes in asthma therapy and no hospitalizations or emergency room visits during the four weeks prior to screening.
- Current use of a short acting inhaled β_2 agonist.
- No contraindications for exercising maximally.
- FEV_1 of at least 70 percent of predicted normal following an eight hour period without β_2 agonist use.
- No history of upper respiratory infection within 2 weeks prior to screening or lower respiratory infection within 4 weeks prior to screening.
- No other clinically significant disease, obesity (> 95 percentile of weight table for age and height) or abnormality in clinical laboratory tests (hematology and blood chemistry, no urine chemistry), physical examination or 12-lead ECG at screening.
- Demonstration of adequate inhalation dosing and spirometry technique.

Washouts were required prior to entry, and throughout the trial, for various medications as follows:

- Theophylline or salmeterol (48 hours).
- Oral beta-agonist, cromolyn sodium or nedocromil sodium (1 week).
- Other investigational agent (4 weeks).
- Monoamine oxidase inhibitors, tricyclic antidepressants or beta-blockers (6 weeks).
- Oral or injectable corticosteroids (8 weeks).
- Astemizole (3 months).

Patients were required to withhold medications prior to pulmonary function testing as follows:

- Inhaled β_2 agonists (8 hours).
- Methylxanthine or alcohol containing food and beverages (8 hours).
- Anticholinergics, inhaled corticosteroids, aspirin and NSAIDs (12 hours).
- Antihistamines (48 hours).

Concomitant use of these medications, including regular use of inhaled corticosteroids and stable immunotherapy regimen, were allowed during the trial.

A prestudy visit was conducted to assess eligibility. Procedures included exercise challenge testing to define the appropriate treadmill settings for speed and elevation. Exercise challenge testing was performed until a target heart rate in the range of 160 to 180 bpm was achieved for not less than six minutes. During testing, heart rate and rhythm were monitored continuously and blood pressure was monitored every two minutes. Exercise testing was terminated in the event of adverse changes in blood pressure, chest pain, dizziness, threatening arrhythmia or depression of the ST segment using Lead II. If needed, albuterol was administered as rescue medication via inhaler or nebulizer.

PFTs commenced following the conclusion of exercise challenge. PFTs were assessed at 5, 10, 15, 30 , 45, 60, 75 and 90 minutes after completion of exercise testing, immediately preceded by an assessment of heart rate, rhythm and blood pressure. Patients who experienced a decline in FEV_1 of at least 20 percent, but not more than 50 percent, within 30 minutes following exercise challenge (patients had two opportunities at least 24 hours apart to meet this criteria) had a confirming exercise challenge at least 24 hours after the previous test.

At each of the four treatment visits, dosing was preceded by assessment of vital signs, ECG and PFTs. FEV_1 was required to be within 10 percent of the prestudy value, but not less than 70 percent of predicted normal. Patients dosed themselves, under supervision of the study coordinator, using two inhalations of the assigned treatment, per the randomization scheme for the particular visit. The study coordinator who supervised dosing was required to be a different person than the PFT and exercise challenge test technician. The protocol did not expressly state any additional provisions for blinding.

Exercise challenge commenced 30 minutes postdose; procedures were the same as in the prestudy visits. In addition to collection of vital signs every 2 minutes and continuous rhythm assessment, a final 12-lead ECG was conducted 15 minutes after the last PFT. Adverse events were collected throughout each of the four treatment visits. Following the fourth visit, final evaluation of clinical laboratory tests, physical examinations and a 12-lead ECG were conducted.

The primary efficacy variable was the smallest percent change from predose FEV_1 following exercise challenge (i.e., the smallest positive or largest negative percent change over the 90 minute post-exercise period). Secondary efficacy variables included the smallest absolute change from predose FEV_1, the smallest change from

predose FEV_1 as a percent of predicted, percent change and absolute change from predose FEV_1 at each data collection timepoint, change from predose FEV_1 as a percent of predicted at each data collection timepoint and the proportion of protected/unprotected patients. Patients were considered unprotected if their FEV_1 was found to be at least 20 percent below predose at any of the post-exercise data collection timepoints.

Analyses of all variables, except protected vs. unprotected patients, were conducted by comparing the active treatments to placebo using an ANOVA model with treatment, period, sequence and patient-within-sequence factors. The analyses of protected vs. unprotected patients compared each active treatment to placebo using McNemar's Test.

The primary safety variables were adverse events, the presence/absence of ECG changes consistent with ischemia and ventricular arrhythmias, and abnormal blood pressure. Secondary safety measures included vital signs, ECG results, physical examinations and clinical laboratory assessments.

A sample size of 16 patients was determined to be necessary to show a 10 percent difference between any two treatments, assuming a common within-patient standard deviation of 8 percent, a statistical power of at least 90 percent and a Bonferroni-adjusted (for the three active comparisons to placebo) significance level of $\alpha = 0.017$.

PATIENT DISPOSITION:

There were 51 patients screened for the study, of which 16 were randomized. The 35 patients not randomized were adequately accounted for and included 20 patients who did not have a 20 percent drop in FEV_1 post-exercise challenge, eight patients who withdrew consent, four patients who did not meet the baseline 70 percent FEV_1 criteria, one patient who was unable to complete the exercise challenge, one patient with a URI and one patient who developed an asthma exacerbation between the two prestudy visits.

Of the 16 randomized patients, 15 patients completed the study. Patient 009 did not return after completing the second treatment period, because the patient's mother expressed concern about the patient missing school.

There were seven patients with a total of 16 departures from the protocol, regarding scheduling (three patients did not come to clinic precisely at appointed times) or predose FEV_1 (four patients had predose values less than 70 percent of predicted, with a minimum of 66 percent). All patients were allowed to continue in the study.

Patient ages ranged from 6 to 11 years with a mean of 9.4 years. Distribution of ages at the initial study visit were:

11 year olds - 4 patients
10 year olds - 4 patients
9 year olds - 4 patients
8 year olds - 2 patients
7 year olds - 1 patient
6 year olds - 1 patient.

Five patients (31 percent) were female and 75 percent were Caucasian.

EFFICACY OUTCOMES (FEV_1):

The efficacy analyses conducted by the sponsor included the 15 patients who completed the trial. Mean FEV_1 values prior to predose were very comparable among the four treatments, ranging . FEV_1 as a percent of predicted was also comparable among groups and ranged No statistically significant differences were found.

The **mean smallest (smallest positive or largest negative) percent change from predose FEV_1** observed during the post-exercise period is presented in Table 7.

Table 7: Smallest Percent Change from Predose FEV_1

	Proventil HFA	Proventil	Ventolin	Placebo
Mean	1.9*	-0.3*	-0.7*	-25.5
SD	16.4	11.4	13.5	16.0
Range				

* Statistically significant difference from placebo, $p < 0.001$.

All active treatments were statistically superior to placebo. The mean value for Proventil HFA was numerically higher than that of either active treatments, but the difference did not appear to have clinical significance.

The analyses of **mean smallest (absolute) change from predose FEV_1** were consistent with the smallest percent change outcomes. Means were 0.05, 0.0, -0.01 and –0.44 for the Proventil HFA, Proventil, Ventolin and placebo treatments, respectively. Each active treatment was statistically superior to placebo.

Smallest mean percent change from predose FEV_1 as a percent of predicted were also consistent with smallest percent change outcomes. Means were 2.1, -0.3, -0.5 and –19.7 for the Proventil HFA, Proventil, Ventolin and placebo treatments, respectively. Each active treatment was statistically superior to placebo.

Mean percent change from predose FEV_1 is shown in Appendix F. Each active treatment group was statistically superior to placebo at each timepoint up to and including the 60 minute post-exercise evaluation. At 75 and 90 minutes post-exercise, only Proventil HFA and Proventil were statistically superior to placebo. The magnitude of the difference among the three active treatments is small and does not appear to have clinical significance.

The analyses of **mean absolute change from predose FEV_1** over the post- exercise study period showed a similar profile as the percent change analyses. The three active treatments were statistically superior to placebo at each evaluation up to and including the 45 minute post-exercise evaluation. At 60, 75 and 90 minutes post-exercise, only Proventil HFA and Proventil were significantly superior to placebo. At 90 minutes post-exercise, mean values were 0.22, 0.19, 0.12 and –0.01 L for the Proventil HFA, Proventil, Ventolin and placebo treatments, respectively.

Analyses of **mean percent change from predose FEV_1 as a percent of predicted** resulted in identical statistical outcomes as the analyses of mean percent change from predose. At 90 minutes post-exercise, mean values were 9.6, 8.8, 5.6 and –0.8 percent for the Proventil HFA, Proventil, Ventolin and placebo treatments, respectively.

Patients whose FEV_1 decreased from predose by 20 percent ("unprotected patients") comprised 7 percent (1 patient), 7 percent (1 patient), 0 percent (0 patients) and 67 percent (10 patients) of the Proventil HFA, Proventil, Ventolin and placebo treatments, respectively. There were statistically fewer unprotected patients in each of the active treatment groups than in the placebo group.

There were no significant interactions between treatment and any of the demographic subgroups tested (age, gender, ethnic origin), however, the test for interaction between treatment and age was marginally significant ($p = 0.059$). Data from Pt # 006, the youngest patient and only six year old randomized to the trial, highly influenced this outcome because she did not respond to any treatment. Her smallest percent changes in FEV_1 were: - 44.2 (Proventil HFA), -23.7 (Proventil), -18.1 (Ventolin) and -19.1 (placebo). With the exception of the placebo treatment, these values were the smallest observed for the entire treatment data set. These data indicate that this patient was not responsive to treatment any of the active treatments, which may be reflective of an ineffective inhalation technique.

Efficacy Conclusion: Each efficacy analysis established the statistical superiority of all three active treatments relative to placebo. The analyses of the entire post-exercise interval suggested a somewhat prolonged effect of Proventil HFA and Proventil relative to Ventolin. Numerical trends among the smallest change outcomes support this observation, however proportion of responders analyses numerically favored Ventolin. However, differences among the treatments were small and, overall, there appears to be evidence that each of the active treatments performed in a clinically comparable fashion relative to each other.

SAFETY OUTCOMES:

Safety analyses included the 16 patients randomized to the trial.

There were no deaths or serious adverse events during this trial. There were no **adverse events** reported during treatment periods. Two adverse events were reported

during washout periods; Pt. # 002 experienced abrasions and contusions related to a motor vehicle accident and Pt. # 013 experienced an outer ear infection.

Predose vital signs were very similar for the four treatment periods. No statistically significant differences were observed among treatments for heart rate (approximate mean, 80 bpm), systolic blood pressure (approximate mean, 105 mmHg) or diastolic blood pressure (approximate mean, 67 mmHg). Post-exercise **heart rate** showed mean increases from predose of up to18 bpm at 5 minutes after exercise and similar changes among the treatment groups. Mean heart rate fell steadily during the 90 minute post-exercise period to a mean increase of approximately 2 bpm above predose for each group at final measurement. There were no statistically significant or clinically meaningful differences between active treatments and placebo, nor did there appear to be clinically important differences among the active treatments.

Mean change from predose **systolic blood pressure** ranged from approximately 8 to 11 mmHg for the four treatment groups at 5 minutes post-exercise. Means values fell steadily to within 1 to 2 mmHg of predose at 90 minutes post-exercise. Mean change from predose **diastolic blood pressure** ranged from approximately 3 to 5 mmHg at 5 minutes post-exercise and were within -2 to 0 mmHg of predose for each treatment at 90 minutes post-exercise. No clinically or statistically significant changes were seen in the comparison of active treatments to placebo and no apparent clinically important differences among the active treatments.

The **12-lead ECG** data were collected at predose and within 15 minutes following the 90 minute PFT. There were **no clinically meaningful cardiac abnormalities** at either timepoint in any of the four treatments. Mean **ventricular rate** was approximately 77 bpm for each treatment at predose and approximately 80 bpm for each treatment at postdose. No clinically or statistically significant differences were seen among treatments. Mean **PR interval** changes between predose and postdose among the four treatment groups ranged from 0 to 0.004 seconds. Mean **QRS interval** changes ranged among the four treatment groups, mean **QT interval (uncorrected)** changes ranged and mean **QTc interval** changes ranged No statistically or clinically significant differences were observed in comparison of the active treatments to placebo, nor were clinically significant differences apparent among the active treatments. The maximum QTc observed at any time in during predose or postdose assessment was 0.445 seconds, essentially within normal limits.

Prestudy and poststudy **clinical laboratory** test results showed a minimal number of abnormalities. None appear to be clinically significant. The predominant abnormality was eosinophilia, an expected finding for this population, over 80 percent of whom were reported to be atopic.

Physical examinations were largely unremarkable. Two patients had bilateral inspiratory wheeze at the prestudy visit, but neither were reported to have had the same finding upon completion of the study.

Safety Conclusion: There were no adverse events which suggested differences among the treatments in this trial. The vital sign and ECG data were remarkable in that the outcomes of the placebo and active treatments were virtually indistinguishable, with no clinically meaningful cardiac abnormalities in any treatment group. There appeared to be no trends among the active treatments with regard to vital sign or ECG data.

DISCUSSION AND CONCLUSION:

Proventil HFA appears to have been well tolerated and effective for EIA in the patient population studied and does not appear to be clinically distinguishable from the active comparators in this trial. This trial did not include patients age 4 and 5 years of age, as proposed for inclusion in the labeling, and only one patient each at ages 6 and 7 years. Age was not determined to be a statistically significant factor in the efficacy outcomes, although the 6 year old patient in this trial was unresponsive to any treatment. While these data do not provide empirical evidence of efficacy in the youngest proposed population, the trial also does not appear to provide reason to suspect that Proventil HFA would be ineffective all patients age 6 or younger. Safety concerns appeared to have been minimal in this trial and it may be reasonable to generalize the outcomes of this trial to patients age 6 or younger based on safety data from other trials.

7.0 INTEGRATED SUMMARY OF EFFECTIVENESS

As previously agreed with the sponsor, the disparate trial designs in this application do not afford the opportunity to integrate findings. The sponsor did provide a summary (Volume 11) which reiterated the data that have been previously reviewed for each of the individual trial summaries. Trials 1141-SILV and 1142-SILV were not required to establish efficacy in pediatric asthma based on placebo-controlled designs, given the prior experience with adult trials.

Both of these trials did, however, establish that, in general, there was a lack of statistically significant differences between Proventil HFA and the active control, Ventolin (CFC). In addition, the observed numerical differences between treatment outcomes for these products were not found to generate concerns regarding a potential difference in clinical effectiveness. The two products did perform in a clinically comparable fashion in pediatric patients at a dose of two inhalations QID. There are minimal data on which to draw conclusions for children age 4, 5 and 6, given the low numbers of such patients enrolled in these trials. However, this factor primarily influences generalization of safety findings and will be further addressed in the Integrated Summary of Safety.

8.0 INTEGRATED SUMMARY OF SAFETY

As with the Integrated Summary of Efficacy, the disparate designs of the three pivotal trials, 1141-SILV, 1142-SILV and 1247-SILV do not allow substantial integration of safety outcomes. Each trial showed a low incidence of adverse events, with the four week evaluation in 1141-SILV showing comparable outcomes to those seen in adult patients and in marketed CFC-propelled albuterol metered dose inhalers. Safety evaluations of vital signs, heart rate and rhythm, from 12-lead ECGs at doses up to 8 cumulative puffs, clinical laboratory evaluations and physical examinations showed expected outcomes, with no evidence of clinically important distinctions between Proventil HFA and marketed CFC products in patients ages 5 to 11.

The four month safety update submitted October 1, 1998 specifies that no additional safety data relevant to the supplement have become available since its original submission on May 29, 1998. No data were submitted.

The clinical trials submitted in support of this application provided data on a small number of patients in age range 4 to 6 (no patients who were age 4, 3 patients age 5 and 4 patients age 6) who were exposed to Proventil HFA. To supplement this database, the Division requested of the sponsor at the time of filing that they submit any additional data from their global development plan regarding use of Proventil HFA or similar formulations in the pediatric population. The sponsor provided reanalyses of Trial 1178-SILV, a three month, open label, postmarketing comparison of Airomir, the U.K. formulation of HFA-134a albuterol sulfate, and a marketed CFC albuterol. The formulation of Airomir is known to differ somewhat from that of Proventil HFA, but neither the in vitro or in vivo performance of the two products have been compared.

This trial was previously reviewed, without regard to age stratification, in a review dated June 20, 1997 and found to be suggestive of clinical comparability between the products involved with regard to reported adverse events.

In Trial 1178-SILV, clinical investigators were asked to retrieve patient medical records monthly for three months to note hospitalizations or other acute care events, any adverse events and any changes in prescribed medication. There were 43 patients age 0 to less than 4 years, 53 patients age 4 to less than 7 years, and 231 patients age 7 to less than 12 years enrolled in this trial who received Airomir. There were a total of 88 patients who received the CFC comparator. Adverse events were provided by age group. Each group was found to have a low incidence of adverse events and the "universe" of adverse events for each group was similar to that seen in the adult trials and in Trial 1141-SILV. These analyses provide supportive evidence of a favorable safety profile in a sizable number of patients whose age range, particularly 4, 5 and 6 year olds, were underrepresented in the U.S. trials. While the Airomir product is not identical to Proventil HFA, these data suffice to support the safety of HFA 134a albuterol sulfate in the lower age range of the proposed population.

Of additional concern for use in the pediatric population, as it has been in the adult population since early 1997, is the propensity of the Proventil HFA actuator to become clogged with drug particulate and to cease functioning. Extensive instructions were added to the labeling in 1997 to instruct patients regarding appropriate maintenance of their inhaler device, including proper washing and drying. In a February,1997 meeting, the sponsor indicated that six inhalers had been returned by patients to clinic sites during Trial 1141-SILV and were reported to have been clogged. Similar experience was not reported for Trials 1142-SILV or 1247-SILV, presumably because Proventil HFA inhalers were not provided to patients for home use. The Division continues to monitor monthly reports regarding clogging experience from the sponsor and will continue to do so. In addition, there is active review underway of

It does not appear that there is reason to anticipate that the introduction of inhalers to a broad pediatric population would alter the observed device clogging rate. As with all pediatric medication, caregivers must be expected to adequately supervise the use and maintenance of medications and it is the Division's expectation that the current labeling regarding actuator/device maintenance will provide adequate information to support caregivers in doing so.

9.0 LABELING

The proposed labeling changes appear to be intended to parallel the currently approved labeling for adults. The following changes should be conveyed to the sponsor.

In the Clinical Trials subsection of CLINICAL PHARMACOLOGY, change the third paragraph pertaining to pediatric data to read, "The mean time-to-onset of a 12% increase in FEV_1 was 7 minutes and the mean time to peak effect was approximately 50 minutes. The mean duration of effect as measured by a 12 percent increase in FEV_1 was 2.3 hours. In some pediatric patients, duration of effect was as long as 6 hours."

In the Information for Patients subsection of PRECAUTIONS, add the following statement. "In general, the technique for administering Proventil HFA to children is similar to that for adults. Children should use Proventil HFA under adult supervision, as instructed by the patient's physician."

The ADVERSE REACTIONS section should be modified to eliminate the [redacted] The sentence which is proposed to precede the table should be modified to read, "Adverse events reported in a 4-week pediatric clinical trial comparing Proventil HFA and a CFC 11/12 propelled albuterol inhaler occurred at low incidence rates and were similar to those seen in the adult trials.

In the DOSAGE AND ADMINISTRATION section, modify the proposed statement regarding prevention of exercise induced bronchospasm from [redacted] to "2 inhalations 15 to 30 minutes before exercise."

In the opening of the PATIENT'S INSTRUCTIONS FOR USE, add the statement, "Children should use Proventil HFA under adult supervision, as instructed by the patient's doctor."

10.0 CONCLUSION

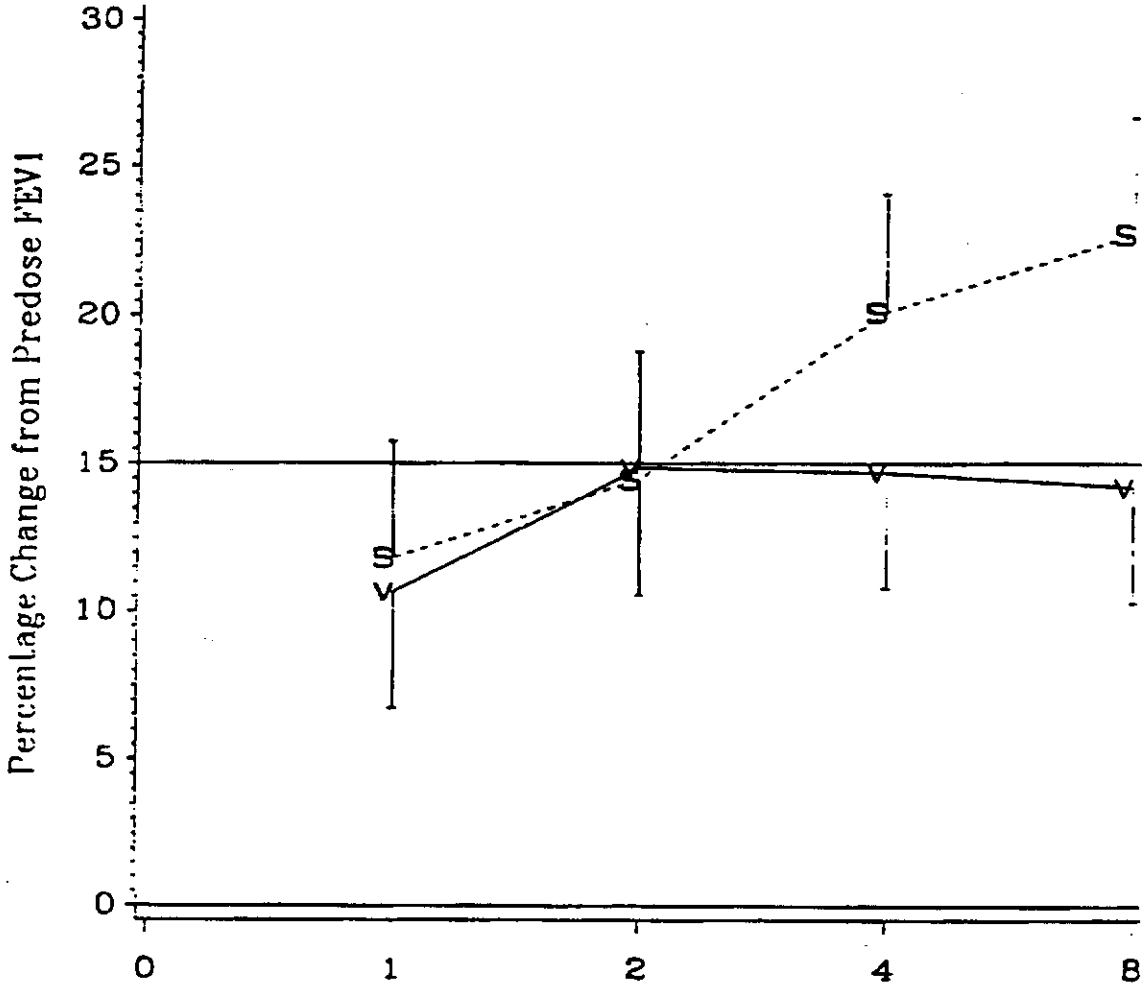
This supplemental application provides adequate evidence of the safety and effectiveness of Proventil HFA in the treatment of asthma in pediatric patients ages 4 to 11 years. In addition, clinical comparability has been adequately demonstrated between Proventil HFA and marketed CFC-propelled albuterol products. Safety and effectiveness of Proventil HFA in the prevention of exercise-induced bronchospasm in pediatric patients age 4 to 11 year has also been adequately established. This application is approvable pending labeling changes noted above.

11.0 APPENDICES A - F

Appendix A

Trial 1142

Mean (SE) Percentage Change from Predose FEV1
(24 Patients Completing the Study)

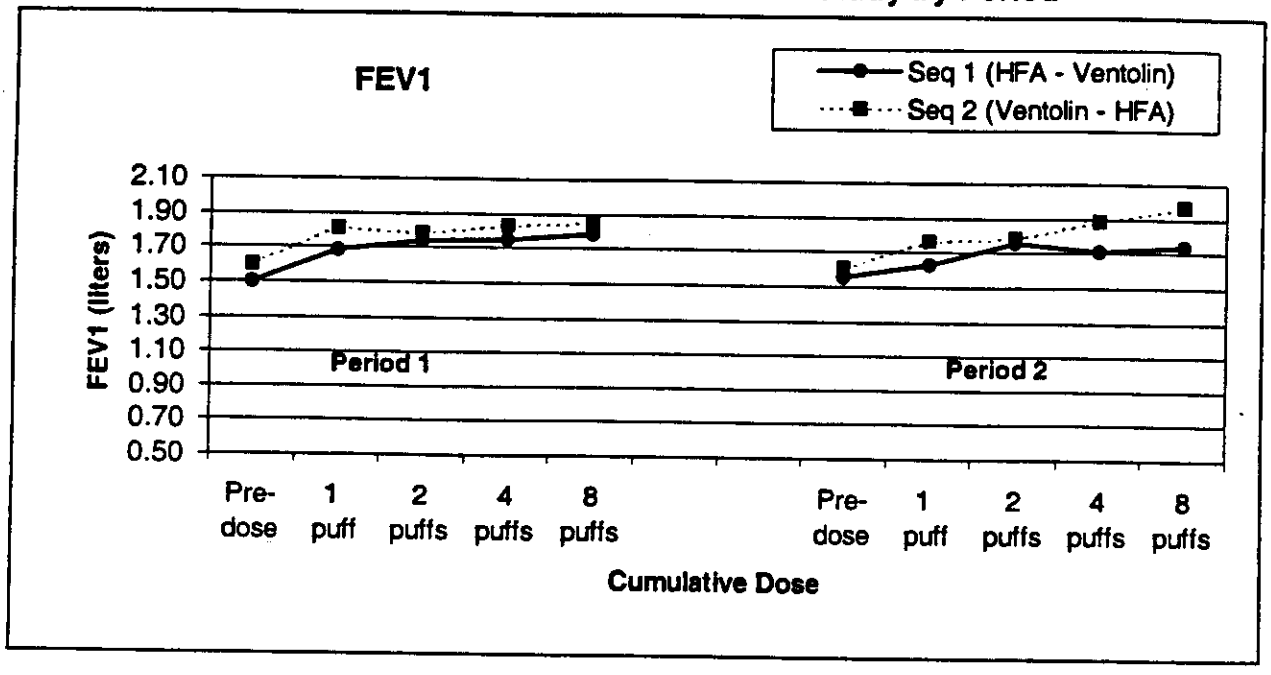


Line at 15% Represents a Clinically Meaningful Effect

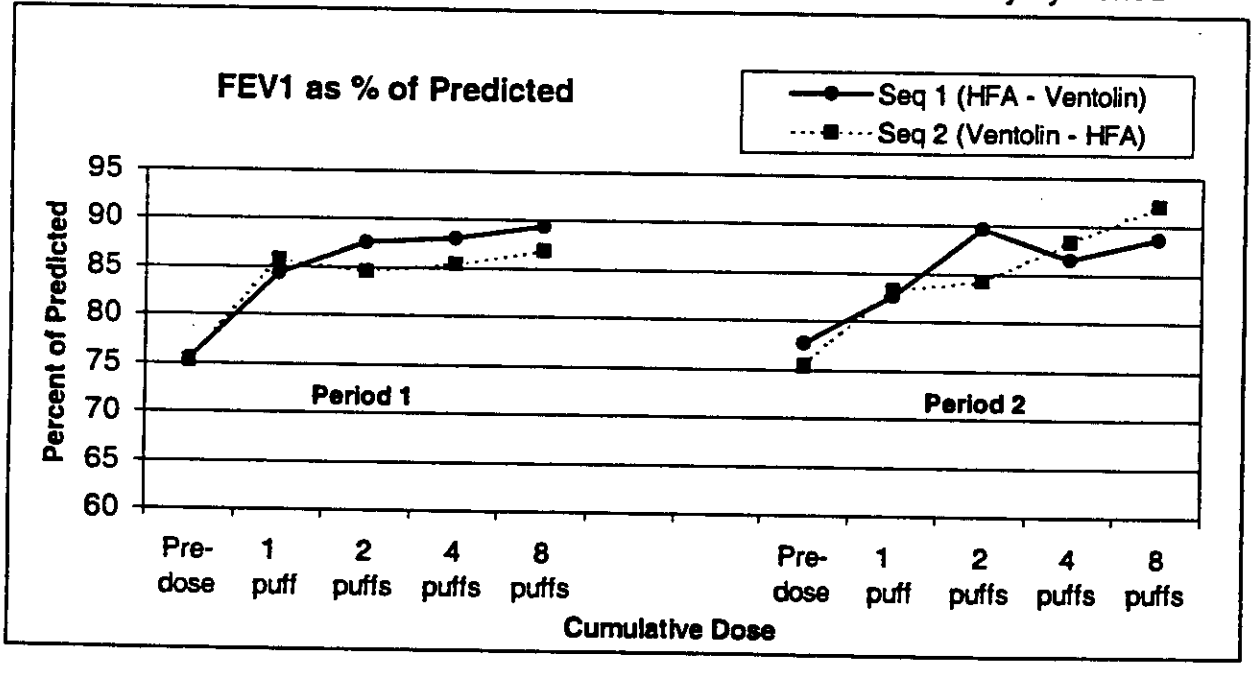
S = HFA-134a Salbutamol Sulfate
V = Ventolin (CFC 11/12 Salbutamol)

Appendix B

Trial 1142: FEV1 Results of Cross-Over Study by Period



Trial 1142: FEV1 as % of Predicted Results of Cross-Over Study by Period



Appendix C

Trial 1141

Summary of FEV_1 Results
Intent-to-Treat Analysis

Variable	HFA-134a Salbutamol Sulfate N = 33	Ventolin N = 30	P-Value[d]
Duration of Effect[a]			
Mean (hr.)	2.28	1.76	0.442
SD	2.13	2.36	
Range			
AUC			
Mean (% x hr.)	50.52	38.00	0.487
SD	52.94	61.41	
Range			
AUC			
Mean (L x hr.)	0.64	0.53	0.649
SD	0.73	0.83	
Range			
Peak % Change[b]			
Mean	21.37	18.01	0.386
SD	13.58	10.75	
Range			
Peak as % Predicted			
Mean	97.68	97.27	0.911
SD	13.89	11.37	
Range			
Time to Peak			
Mean (min.)	50.0	56.9	0.480
SD	30.7	33.1	
Range			
Responders[c]			
No. of Responders	20	16	0.486
% Responders	60.6	53.3	
Time to Onset for Responders			
Mean (min.)	7.4	6.2	0.507
SD	5.2	3.0	
Range			

[a] Duration of effect was defined as the time that the FEV_1 first increased 12.0% over the predose FEV_1 within 30 minutes after two inhalations of study drug administration until two consecutive measurements had a decrease in FEV_1 to less than 12.0% of predose FEV_1.

[b] Mean percent change from predose to peak FEV_1 (within 2 hours of administration of two inhalations of study medication)

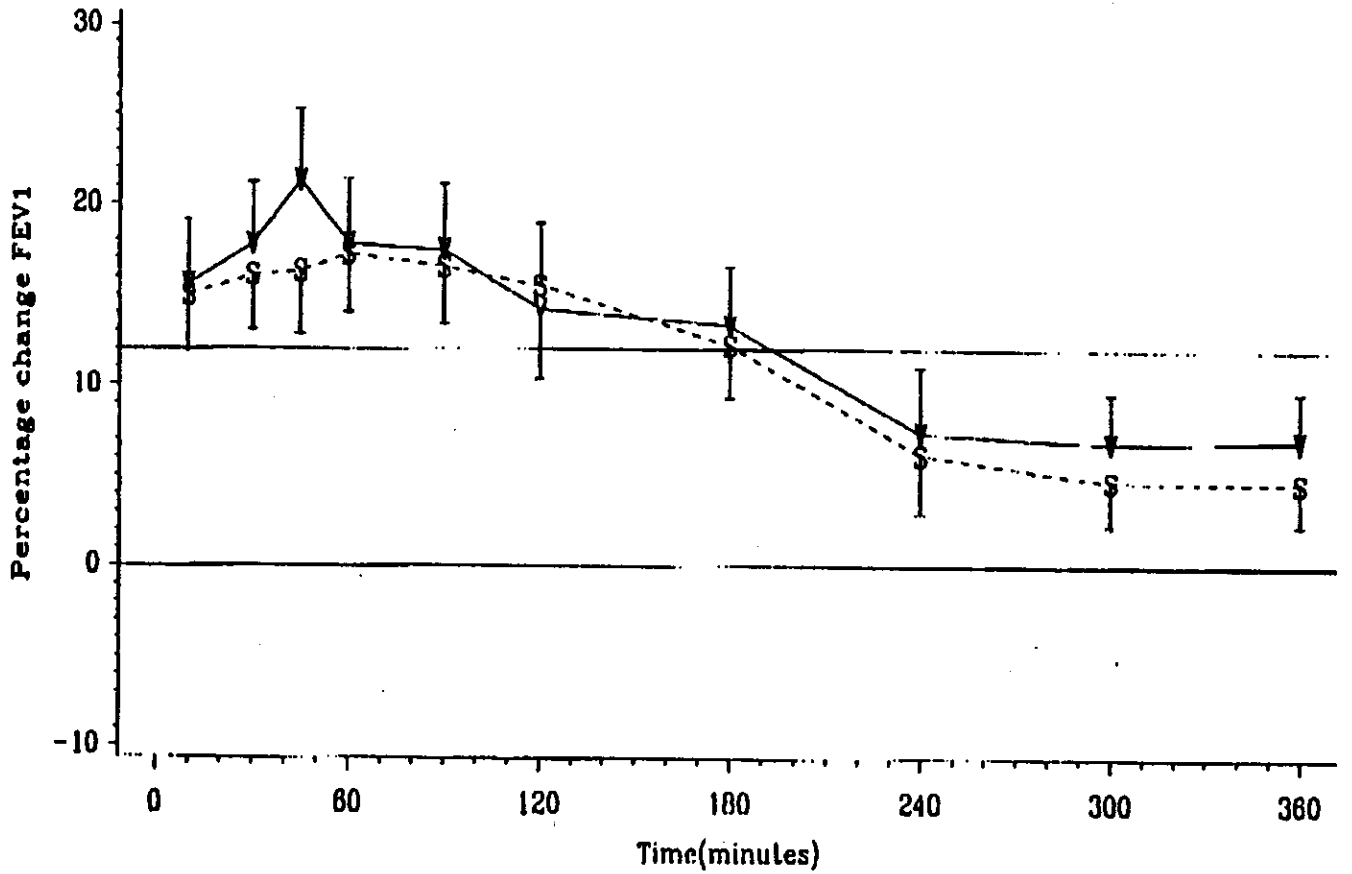
[c] Responders are defined as patients whose FEV_1 increased at least 12.0% over predose FEV_1 within 30 minutes of two inhalations of study medication

[d] The p-value is from the test of the null hypothesis that the two treatment group means were equal using an ANOVA with pooled center, age group, treatment and interactions as factors in the model.

Appendix D

Trial 1141

Mean (SE) Percentage Change from Predose FEV1 at Study Day 1



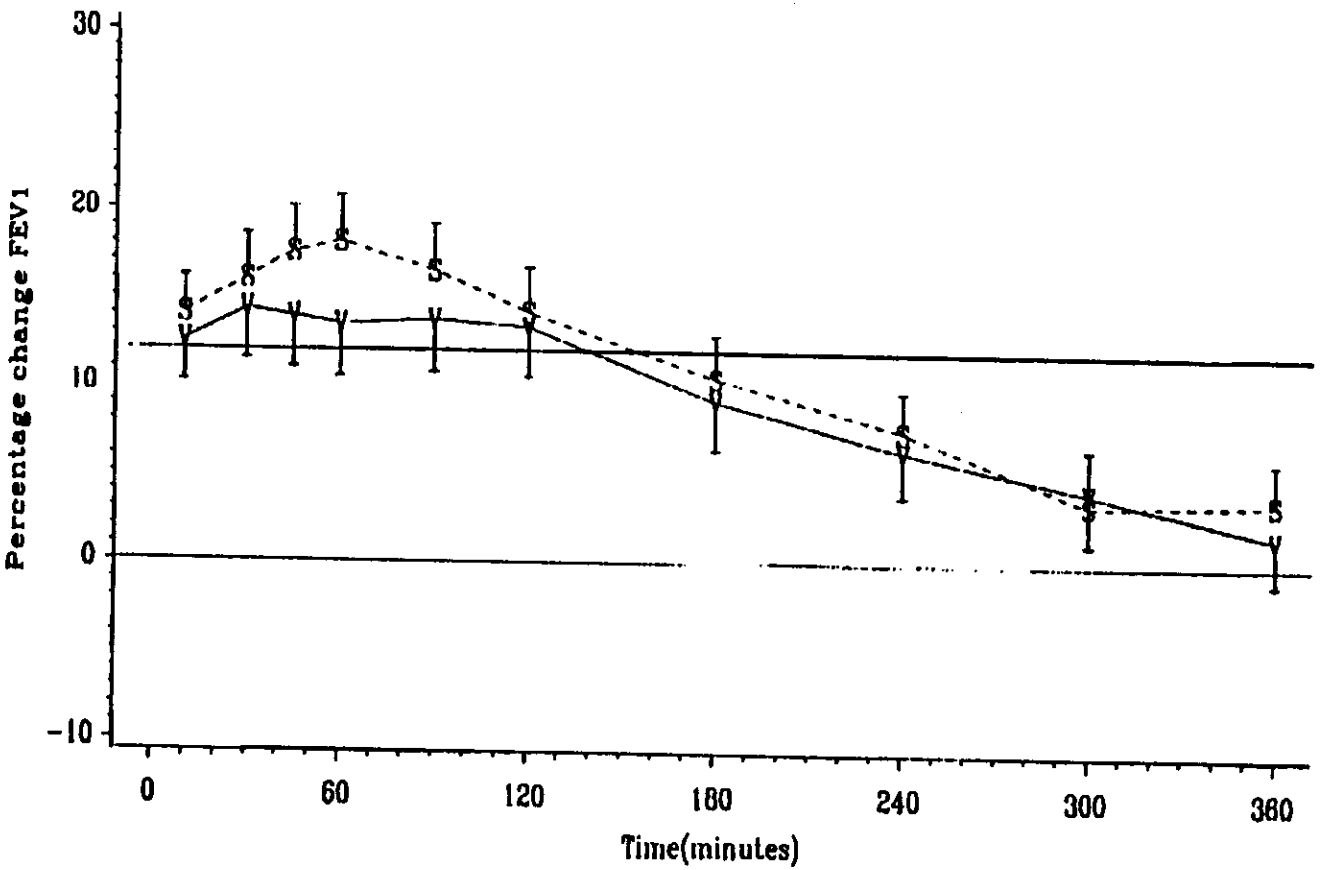
S=HFA-134a Salbutamol Sulfate (N= 33)
V=Ventolin (CFC-11/12 Salbutamol) (N= 30)
The line at 12% represents a clinically meaningful effect

01MAR96

Appendix E

Trial 1141

Mean (SE) Percentage Change from Predose FEV1 at Study Week 4



S=HFA-134a Salbutamol Sulfate (N= 33)
V=Ventolin (CFC-11/12 Salbutamol) (N= 30)
The line at 12% represents a clinically meaningful effect

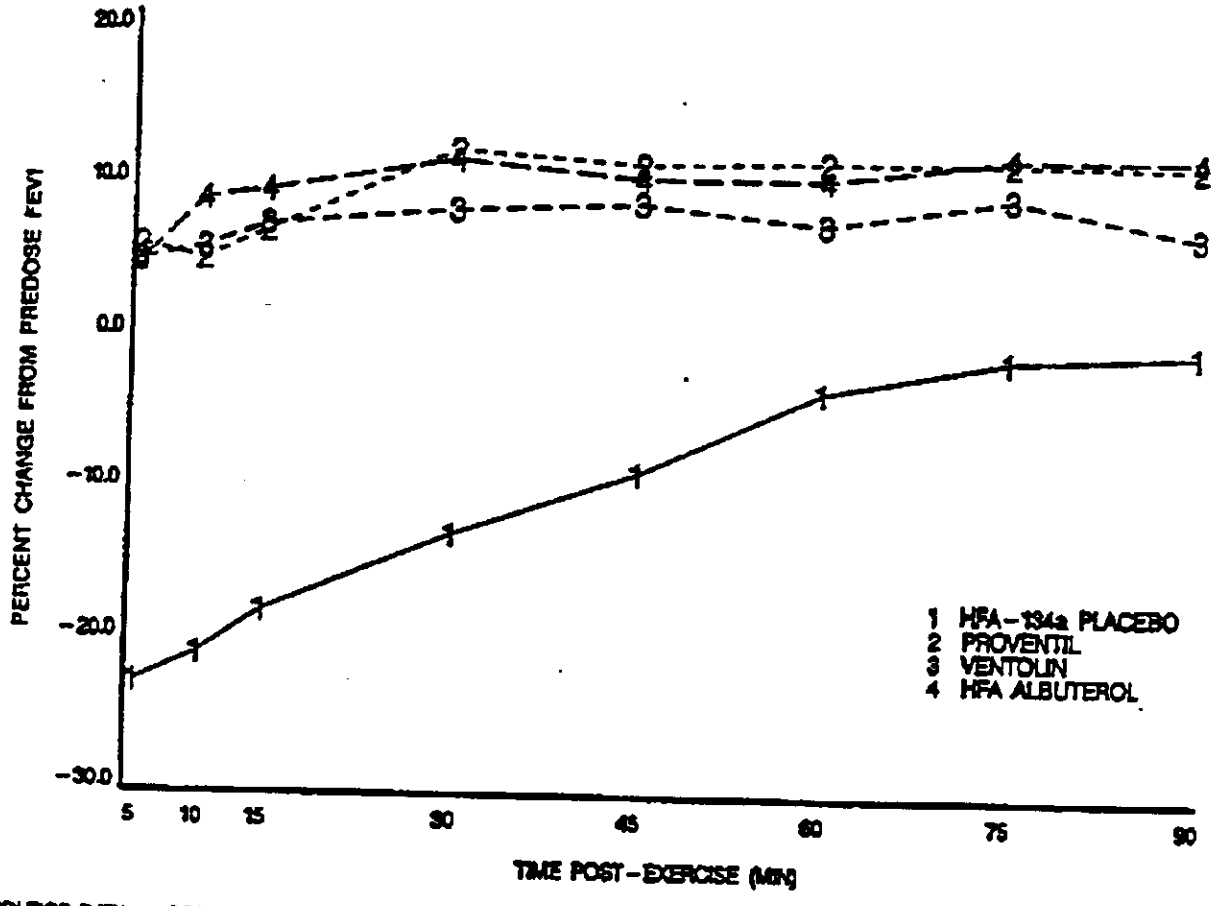
07MAR96

Appendix F

Trial 1247

Post-Exercise Mean Percent Change from Predose FEV_1[@]

(15 Patients Completing the Study)



SOURCE DATA: APPENDIX VIII SECTION 3.3
DATE: 12/09/97

PROGRAM NAME: EFFICACYSAS
DATA SET READ: STATANALYSIS

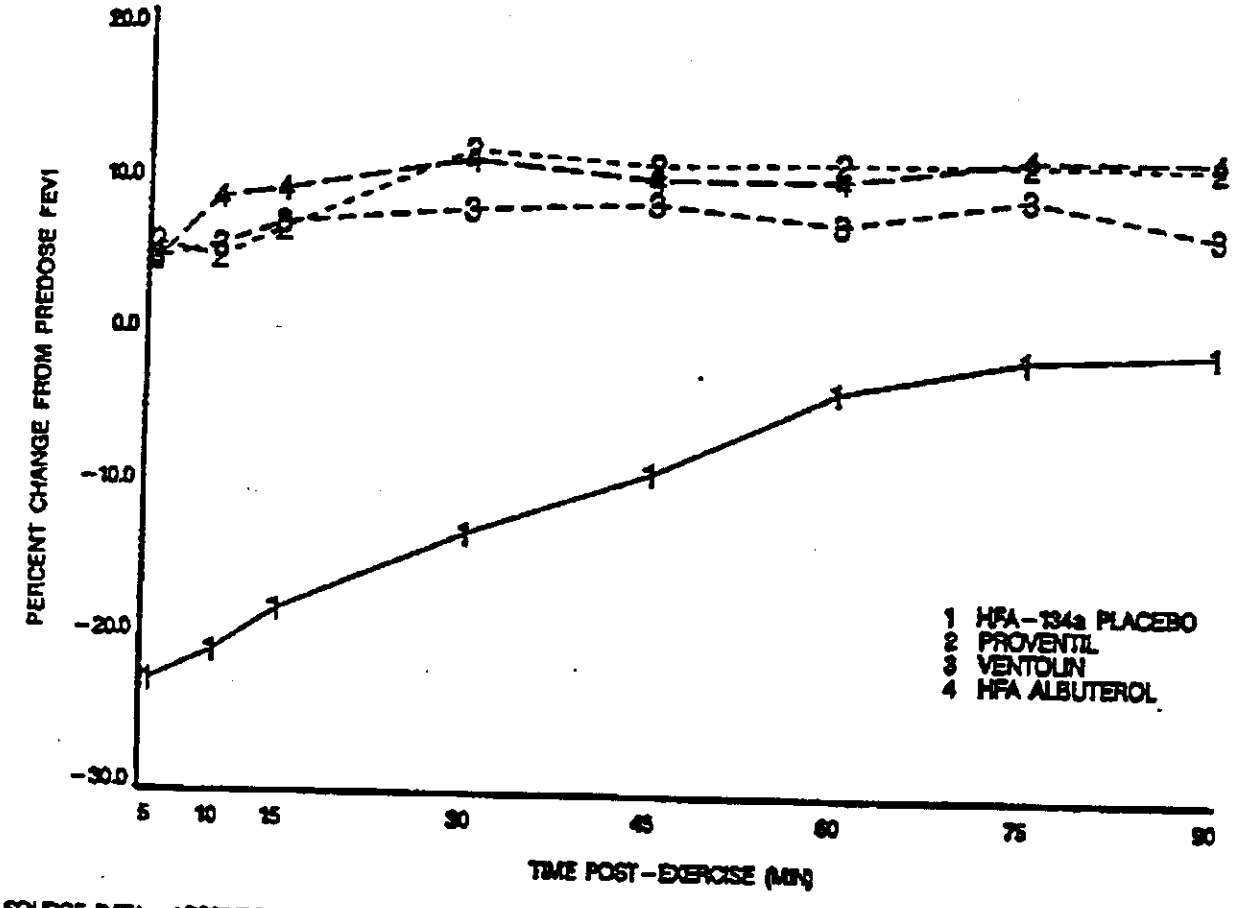
@ Means are adjusted for treatment, period, treatment sequence and patient.

Appendix F

Trial 1247

Post-Exercise Mean Percent Change from Predose FEV_1@

(15 Patients Completing the Study)



SOURCE DATA: APPENDIX VIII SECTION 3.3
DATE: 12/09/97

PROGRAM NAME: EFFICACYSAS
DATA SET READ: STATANALYSIS

@ Means are adjusted for treatment, period, treatment sequence and patient.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S011

PHARMACOLOGY REVIEW(S)

Review of Pharmacology and Toxicology Data

Reviewer: V Whitehurst

Division: Division of Pulmonary Drug Products.

HFD: HFD 570

Review Completion Date: June 1, 1999.

NDA: NDA 20-503

Information to be conveyed to the sponsor: Yes- see revised labeling.

Supplement Number: SE1 - 004

Sponsor: 3 M Pharmaceuticals

Drug: Proventil- HFA (Albuterol Sulfate Inhalation Solution)

Drug Class: Beta – Adrenergic Agonist

Indication: Treatment of asthma

Route of Administration: Inhalation

Dose: 2 inhalations (120 mcg from the valve per each inhalation), 4-6 times a day.

Introduction and History :
The attached request is revision of the labeling for Proventil HFA for children 4 years of age and older. In the pharmacology review, dated August 10, 1998, the labeling for adults was revised. This review will include the labeling for adults and children 4 years of age and older. In our previous labeling, we have used the youngest child having the least weight to calculate the potential risk. In this label a 4 year old weighting 16 kg was used in the calculation.

Label for Proventil HFA for adults and children 4 years of age and older:
Labeling for Proventil HFA should be revised as following

Preclinical Section- Page 40:
Lines 5-7 beginning with _ _ should be removed, revised and placed in the Teratogenic Effect-Pregnancy section as shown below.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 10 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 5 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1400 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 670 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 190 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 90 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH_1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 280 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Teratogenic Effects-Pregnancy: Category C
Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 7 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses

from females treated subcutaneously with 2.5 mg/kg isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at 50 mg/kg (approximately 560 times the maximum recommended daily inhalation dose for adults on mg/m^2 basis).

In an inhalation reproduction study in Sprague-Dawley rats, albuterol sulfate/HFA 134 formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 60 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of PROVENTIL HFA or albuterol sulfate in pregnant women. PROVENTIL HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiples medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Overdosage:
The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 5600 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 2700 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol is approximately 450 mg/kg (approximately 2500 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis and approximately 1200 times the maximum recommended inhalation daily dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 11000 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis and approximately 5300 times the maximum recommended inhalation

daily dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined.

Calculations for children 4 years and adults listed are below.

	age	mg/dose	doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	4	0.24	6	1.44	16	0.09	25	2.25
Adult	>12	0.24	6	1.44	50	0.03	37	1.07

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	diet	500	3	1500	1408	666.7	1400	670
rat	diet	2	6	12	11.3	5.3	10	5
hamster	diet	50	4	200	188	88.9	190	90
Reproduction and Fertility:								
rat	inhalation	10.5	6	63	59.1	N/A	60	N/A
rat	oral	50	6	300	281.5	N/A	280	N/A
Teratogenicity:								
mouse	sc	0.025	3	0.075	0.07	N/A	< 1	N/A
mouse	sc	0.25	3	0.75	0.70	N/A	< 1	N/A
mouse	sc	2.5	3	7.5	7.0	N/A	7	N/A
rabbit	po	50	12	600	563.1	N/A	560	N/A
extra			—	—	—	N/A	—	N/A
Overdosage:								
mouse	oral	2000	3	6000	5631	2666.7	5600	2700
rat	oral	450	6	2700	2534	1200	2500	1200
rat	sc	2000	6	12000	11261	5333.3	11000	5300

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
			rat	6		

Recommendations:
Revised labeling should be conveyed to the sponsor.

/S/

Virgil Whitehurst 6-2-99
Pharmacologist

/S/
2-Jun-99

CC: Division file
HFD-570/VWhitehurst
HFD-570/MVogel
HFD-570/PJani

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S011

ADMINISTRATIVE DOCUMENTS

GENERIC DRUG ENFORCEMENT ACT OF 1992

CERTIFICATION

This information is submitted in accordance with Section 306(k) (1) of the ACT (21 U.S.C. 335a (k)(1)).

I certify that 3M Pharmaceuticals did not and will not use the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connections with this pediatric supplement for Proventil, HFA, NDA 20,503.

Marie D. Kuker, RPh, RAC
Manager, Regulatory Affairs North America

5/26/98
Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20503	**Trade Name:**	PROVENTIL-HFA INHALATION AEROSOL
Supplement Number:	11	**Generic Name:**	ALBUTEROL SULFATE
Supplement Type:	SE1	**Dosage Form:**	Aerosol, Metered; Inhalation
Regulatory Action:	AP	**Proposed Indication:**	The supplemental new drug application provides for lowering the age from 12 years to 4 years and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

6/7/99 The supplement was approved on 6/2/99.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PARINDA JANI

/S/

Signature

6.7.99

Date

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ON ORIGINAL

3M Pharmaceuticals

3M Center Building 260-6A-22
St. Paul, MN 55144-1000

CLAIMED EXCLUSIVITY FOR NDA 20,503, SUPPLEMENT 011 FOR A PEDIATRIC INDICATION

3M claims exclusivity, in accordance with 21 CFR 314.50(j)(4) and with reference to 21 CFR 314.108(b)(5). 3M Pharmaceuticals certifies that this application contains new clinical investigations as set forth in 21 CFR 314.108, that are essential to approval of the application and were conducted or sponsored by 3M.

In addition, 3M Pharmaceuticals certifies that the studies conducted were essential to approval. To support this statement, a list of all published studies or publicly available reports of clinical investigations that support the use of HFA albuterol sulfate in the pediatric population (ages 4-12) is attached.

3M certifies that the attached list is complete and accurate and in the opinion of 3M, these published studies and reports do not provide a sufficient basis for the approval of a pediatric indication for Proventil HFA without reference to the new clinical investigations included in this application. The literature does not support the indication since no studies relevant to the use of Proventil HFA in the pediatric population (ages 4-12) were found.

Marie De Gayner Kuker RPh, RAC
Manager, Regulatory Affairs
North America

5-25-99
Date

APPEARS THIS WAY
ON ORIGINAL

Relevant References to Use of HFA Albuterol Sulfate in Children (ages 4-12)

Item #1:

TITLE: Effect of electrostatic charge in plastic spacers on the lung delivery of ***HFA*** - ***salbutamol*** in ***children*** .

AUTHOR: Anhoj J.; Bisgaard H.; Lipworth B.J.
CORPORATE SOURCE: Prof. B.J. Lipworth, Dept. Clin. Pharmacol. Therapeutics, Ninewells Hospital Medical School, Dundee DD1 9SY, United Kingdom

SOURCE: British Journal of Clinical Pharmacology, (1999) 47/3 (333-336).
Refs: 15
ISSN: 0306-5251 CODEN: BCPHBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Aims. The effect of the electrostatic charge in plastic spacers in vivo on drug delivery to the lung of hydrofluoroalkane (***HFA***) ***salbutamol*** spray was studied in ***children*** . Methods. Five ***children*** , aged 7-12 years, were included in a 3-way crossover randomised single-blind trial. Salbutamol HFA spray was delivered on 3 different study days from plastic spacers with mouthpiece. Pre-treatment of the spacers differed between study days: (a) Non-eletrostatic 350 ml Babyhaler (coated with benzalkonium chloride) (b) New 350 ml Babyhaler (rinsed in water), and (c) New 145 ml AeroChamber (rinsed in water). Plasma salbutamol was measured before and 5, 10, 15 and 20 min after inhalation of four single puffs of 100 .mu.g salbutamol. C(max) and C(av) (5-20 min) were calculated as a reflection of lung dose. Results. For C(max): (A) Non-electrostatic Babyhaler 4.3 ng ml-1 (B) New Babyhaler 1.9 ng ml-1 (C) New AeroChamber 1.6 ng ml-1: AvsB (95% CI for difference 0.5-4.5 ng ml-1, A vs C (95% CI for difference of 0.7-4.8 ng ml-1). The geometric mean ration for A:B was 2.4 fold, and for A:C was 2.9 fold. The value for C(av) were similar with ratios for A:B of 2.4 fold, and A:C of 4.1 fold. The nonelectrostatic Babyhaler delivered a significantly ($P < 0.05$) higher lung dose (for both C(max) and C(av)) than either of the other two spacers. Conclusions. The electrostatic charge in plastic spacers reduced lung dose in ***children*** by more than two-fold. This is clinically significant and the use of potentially electrostatically charged should be avoided.

Item #2:

TITLE: Effect of electrostatic charge in plastic spacers on the lung delivery of ***HFA*** - ***salbutamol*** in ***children*** .

AUTHOR(S): Anhoj, J. (1); Bisgaard, H. (1); Lipworth, B. J.
CORPORATE SOURCE: (1) Dep. Paediatr., Natl. Univ. Hosp., Copenhagen Denmark

SOURCE: European Respiratory Journal, (Sept., 1998) Vol. 12, No. SUPPL. 28, pp. 378S.
Meeting Info.: European Respiratory Society Annual Congress Geneva, Switzerland September 19-23, 1998 The European Respiratory Society
. ISSN: 0903-1936.
DOCUMENT TYPE: Conference
LANGUAGE: English

TI Effect of electrostatic charge in plastic spacers on the lung delivery of ***HFA*** - ***salbutamol*** in ***children*** .

Animals; Chordates; Humans; Mammals; Primates; Vertebrates

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-503 SUPPL # 011

Trade Name Proventil HFA Inhalation Aerosol
Generic Name albuterol sulfate inhalation aerosol
Applicant Name 3M Pharmaceuticals HFD- 570

Approval Date: June 2, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /_ _/ NO /_ X _/

   b) Is it an effectiveness supplement?

   YES /_ X _/ NO /__/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Applicant has not specified the number of years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than

deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #_____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES /_X__/ NO /__/

   (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

   YES /___/ NO /_X_/

   If yes, explain:_____

   (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

   YES /___/ NO /_X_/

If yes, explain:_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 1141-SILV

Investigation #2, Study # 1142-SILV

Investigation #3, Study # 1247-SILV

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 1141-SILV

Investigation #2, Study # 1142-SILV

Investigation #3, Study # 1247-SILV

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
/X_/ NO /___/ _____

Investigation #2
/X_/ NO /___/ _____

Investigation #3
/X_/ NO /___/ _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

/S/ 6/2/99

Parinda Jani Date
Project Manager

/S/ 6/7/99

Robert J. Meyer, M.D. Date
Acting Division Director

cc:
Original NDA 20-503
Division File HFD-570
HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PATENT STATEMENT

In accordance with FDCA 505(b) and 21 CFR §314.53, the following information is provided:

U.S. Patent No. 5,766,573 is owned by 3M Pharmaceuticals and expires on November 28, 2009. This patent claims the method of use for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

U.S. Patent No. 5,225,183 is owned by 3M Pharmaceuticals and expires on July 6, 2010. This patent claims the drug product for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

U.S. Patent No. 5,695,743 is owned by 3M Pharmaceuticals and expires on November 4, 2014. This patent claims the drug product and method of use for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

U.S. Patent No. 5,439,670 is owned by 3M Pharmaceuticals and expires on July 6, 2010. This patent claims the drug product for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

U.S. Patent No. 5,605,674 is owned by 3M Pharmaceuticals and expires on February 25, 2009. This patent claims the drug product for which approval is sought. A claim of patent infringement could reasonably be asserted under this patent if a person not licensed by 3M engaged in the manufacture, use or sale of the drug product for which approval is sought.

Ted Ringsred May 20, 1999

Ted K. Ringsred Date
Office of Intellectual Property Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S011

CORRESPONDENCE

Division Director's Memorandum

Date:	Tuesday, June 01, 1999
NDA:	20-503
Sponsor:	3M Pharmaceuticals
Proprietary Name:	Proventil HFA (albuterol sulfate) Inhalation Aerosol

Introduction: This is a supplemental NDA for the Proventil HFA MDI to seek approval for asthmatic children between the ages of 4 – 11 (currently Proventil HFA is approved down to age 12) and to add the pediatric exercise-induced bronchospasm indication.

CMC: The CMC review was not critical to this efficacy supplement. It should be mentioned that some of the data supporting cleaning instructions that the division had requested when the clogging issue was uncovered were reviewed by the CMC reviewer (Dr. Schroeder) prior to this action. Although these data did not answer all pertinent cleaning/clogging issues, they do not raise any significant concerns that would necessitate a change in the cleaning instructions prior to this action.

Pharmacology/toxicology: No new issues, given the lower age range is 4 and above. Labeling multiples of human dosage will need to be revised.

Clinical / Stastical: Drs. Johnson and Elashoff generated a joint review document for this sNDA, for which Dr. Meyer performed the secondary clinical review. As such, I am in agreement with Dr. Johnsons's and Elashoff's review document and refer the reader to that review for details. Essentially, the data from trials SILV-1141, 1142, and 1247 support the safety and efficacy of this product for the treatment of bronchospasm and prevention of EIB in the 4 – 11 year old age group. This conclusion is based in part on the previous finding of safety and efficacy of the Ventolin MDI for these same indications (based on the 505(b)(2) paradigm), to which the Proventil HFA was compared.

Auditing / Data Checking: The Division elected not to request routine DSI audits of these studies due to the known efficacy of these agents and the combination. No circumstances that would have elicited a "for cause" audit were discovered in the review. The medical officer and statisticians performed their own auditing/checking of the data and did not identify any crucial problems that would invalidate the study conclusions.

Labeling: The labeling as proposed is largely acceptable, a few modifications are suggested per the medical/statistical reviews and the pharm/tox reviews.

Conclusions: This sNDA should be approved once labeling is agreed upon. There are no resultant phase 4 commitments at this time that arise from this specific review.

/S/

Robert J. Meyer, MD 6/1/99
Acting Director,
Division of Pulmonary Drug Products.

APPEARS THIS WAY
ON ORIGINAL

3M Pharmaceuticals

3M Center Building 260-6A-22
St. Paul, MN 55144-1000

Snc-011

SUPPL NEW CORRESP

DUPLICATE

3M

May 25, 1999

John Jenkins, MD, Director
Division of Pulmonary Drug Products (HFD-570)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 10B-03
5600 Fisher Lane
Rockville, MD 20857

Attention: **Parinda Jani, Project Manager**

Subject: **NDA 20,503**
Proventil® HFA (albuterol sulfate) Inhalation Aerosol
Information to Supplement #011

Dear Dr. Jenkins:

As requested, by Parinda Jani, Project Manager, attached is the updated Patent and Exclusivity information for supplement #011 submitted May 29, 1998. Supplement #011 supports a pediatric indication for Proventil HFA (albuterol sulfate) Inhalation Aerosol.

Sincerely,

Marlene V. Peterson
Sr. Regulatory Associate

Ted K. Ringsred
Intellectual Property Counsel

Office of Intellectual
Property Counsel

May 20, 1999

3M

Food and Drug Administration
Center for Drug Evaluation and Research
Park Bldg., rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re: Time Sensitive Patent Information – Orange Book Listing
NDA 20-503

Dear Sir or Madam:

This information is submitted in compliance with FDCA §505(b) and 21 CFR §314.53(c)(2)(ii) in order to amend and supplement the previous submission of patent information in connection with the application for approval of 3M's Proventil HFA™ albuterol sulfate metered dose inhaler product (NDA 20-503).

The undersigned declares that U.S. Patent No. 5,225,183 covers the formulation, composition, and/or method of use of 3M's Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under section 505(b)(1) of the FDC Act.

The undersigned declares that U.S. Patent No 5,695,743 covers the formulation, composition, and/or method of use of 3M's Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under section 505(b)(1) of the FDC Act.

The undersigned declares that U.S. Patent No. 5,439,670, covers the formulation, composition, and/or method of use of 3M's Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under section 505(b)(1) of the FDC Act.

The undersigned declares that U.S. Patent No. 5,605,674 covers the formulation, composition, and/or method of use of 3M's Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under section 505(b)(1) of the FDC Act.

Minnesota Mining and
Manufacturing Company

PO Box 33427
St. Paul, MN 55133-3427 USA
612 736 5839
612 736 3833 Facsimile
29 7023 Telex
tkringsred@mmm.com

The undersigned declares that U.S. Patent Nos. 5,766,573 covers the formulation, composition, and/or method of use of 3M's Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under section 505(b)(1) of the FDC Act and is currently the subject of a Supplemental application for approval.

Sincerely,

Ted Ringsred

Ted K. Ringsred
Office of Intellectual Counsel

APPEARS THIS WAY
ON ORIGINAL