CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: MAR 23 1999

NDA #:	NDA 20-949
Applicant:	Dey Laboratoires
Name of Drug:	Accuvent™ Albuterol Sulfate Inhalation Solution
Indication:	For the relief of bronchospasm in [ ]
Documents Reviewed:	Vol. 1-57. Dated May 18,1998 and SAS data sets submitted electronically on two diskettes
Statistical Reviewer:	Girish Aras Ph.D.
Medical Input:	Daniel O'Hearn MD.

1 SUMMARY OF STATISTICAL ISSUES

The clinical development program for Albuterol Sulfate Inhalation Solutions 0.042% and 0.021% was designed to support an NDA for the use of albuterol for TID administration for the relief of bronchospasm in [ ] There were three clinical trials conducted by Dey: DL-009, DL-010, and DL-019. All three studies were conducted in the pediatric asthma patient population, 6-12 years of age. Trials DL009 and DL 010 were single-dose, dose-response, and placebo controlled 4-way crossover studies to identify the dose(s) to be studied in the large safety and efficacy trial (DL-019). Trial DL-019 is the only trial reviewed here. For the review of other trials, please refer to Dr. O'Hearn's review. Trial DL-019 was a randomized, placebo-controlled, double-blind, parallel group study with a 4-week treatment period which enrolled 349 patients. Summary statistical findings are:

- Study DL-019 demonstrated that Albuterol Sulfate Inhalation Solutions of 1.5 mg albuterol sulfate (1.25 mg albuterol base) and 0.75 mg albuterol sulfate (0.623 mg albuterol base) produce statistically significant improvements in the pulmonary functions of asthmatic children between the ages of 6 and 12 years. Analyses of %Δ AUC FEV_1 showed significant improvement in FEV_1 compared to placebo at both Visits 2 and 4 in both the ITT efficacy ($p<0.001$) and evaluable ($p<0.002$) populations.
- Examining dose response, there were no statistically significant results in pairwise comparisons (Wilcoxon Rank Sum Tests) of the 1.5 mg albuterol sulfate and the 0.75 mg albuterol sulfate groups, though there was numerical difference favoring the higher dose. These observations were supported by the MAX FEV_1 analyses.
- In post hoc subset analyses the improvement with 0.75 mg albuterol sulfate did not reach statistical significance at Visit 4 for the patients with $FEV_1 \leq 60\%$ predicted, for 11 - 12 year olds, and for heavier (> 40 kg) children. Sample sizes for these subgroups were large enough to allow 80% power. This may suggest that a higher dose is needed for patients with greater disease severity, age and/or weight.

STATISTICAL REVIEW AND EVALUATION **1**

1 Summary of Statistical Issues **1**

2 STUDY DL-019 ..... **3**

2.1 INVESTIGATIONAL PLAN **3**
2.2 EFFICACY AND SAFETY VARIABLES **4**
2.2.1 Primary Efficacy Endpoint *4*
2.2.2 Secondary Efficacy Endpoints *4*
2.2.3 Safety *4*
2.3 STATISTICAL METHODS **4**
2.3.1 Statistical and Analytical Plan. *4*
2.3.2 Analysis of Baseline Data *4*
2.3.3 Analysis of Primary Efficacy Data *5*
2.3.4 Analysis of Secondary Efficacy Data *6*
2.3.4.1 Analysis of Safety Data 6
2.3.5 Changes in the Planned Analyses *7*
2.4 RESULTS **7**
2.4.1 Disposition Of Patients *7*
2.4.2 Efficacy Evaluation *8*
2.4.2.1 Demographics And Other Baseline Characteristics 8
2.4.2.2 Analysis of Efficacy 10
2.4.2.3 Proportion of Responders 16
2.4.3 Statistical/Analytical Issues *18*
2.4.3.1 Handling of Dropouts or Missing Data 18
2.4.3.2 Multicenter Studies 19
2.4.3.3 Efficacy Conclusions 19
2.4.4 SAFETY EVALUATION *19*
2.4.4.1 Brief Summary of Adverse Events 19
2.4.4.2 Display of Adverse Events 20
2.4.4.3 Analysis of Adverse Events 21
2.4.4.4 Serious Adverse Events, And Other Significant Adverse Events 22
[1] *There were no deaths in any of the treatment groups* *22*
2.4.4.5 Safety Conclusions 22

3 DISCUSSION AND OVERALL CONCLUSIONS **23**

2 STUDY DL-019

2.1 INVESTIGATIONAL PLAN

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group, 4-week treatment study of children ages 6 to 12 years with moderate asthma. Patients were randomized to treatment with 1.5 mg albuterol sulfate inhalation solution, 0.75 mg albuterol sulfate inhalation solution, or placebo (0.9% saline), administered by nebulizer TID. There were four visits including a screening visit (Visit 1), followed by a two-week placebo phase, and then three treatment visits (Visits 2-4) over a 4-week period, with a final examination at Visit 4. The first treatment visit (Visit 2) occurred within 14 ± 3 days of Visit 1. Visit 3 occurred within 14 ± 3 days of Visit 2 and Visit 4 occurred within 28 ± 3 days of Visit 2.

Prior to randomization, all patients enrolled in the study completed an initial 2-week placebo phase during which the dosages of inhaled corticosteroids, cromolyn sodium, or nedocromil were held constant and the use of $beta_2$-agonists was limited to prn (rescue) use of study-supplied albuterol [Dey MDI or Albuterol Sulfate Inhalation Solution, 3.0 mg (0.083%)]. This 2-week placebo phase was used to confirm the need for regular symptomatic $beta_2$-agonist therapy and to give patients experience with daily diaries. Patients were required to demonstrate compliance with symptom diary card records and peak flow meter measurements during the placebo phase.

On the first day of the double-blind treatment phase (Visit 2), patients were randomized to receive one of the three test drugs (1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate or placebo) three times daily for 4 weeks via the standard nebulizer. The first dose of the test drug was given in the study center. Following this treatment, spirometry measurements and safety measures were conducted at 30 minutes after the end of nebulization and on an hourly basis for 6 hours. Patients/caregivers were then provided a daily diary and instructed on how to record the following safety and efficacy data in the diaries throughout the study phase: pre-treatment peak flow readings, asthma symptoms, night awakenings, use of supplemental albuterol to control asthma exacerbations, any changes in concomitant medications and any adverse events.

Patients were to return to the study center after 14 ± 3 days of treatment for exchange of study medication and diaries and to perform spirometric evaluations before and 30 minutes after the morning administration of the study drug. The diaries were reviewed at each visit for completeness and presence of adverse events. At the completion of 28 ± 3 days of treatment, patients returned to the study center for a repeat of the 6-hour evaluation of safety and efficacy following test drug administration.

2.2 EFFICACY AND SAFETY VARIABLES

2.2.1 Primary Efficacy Endpoint

Area under the FEV_1 percent change from pre-dose versus time curve (%Δ AUC FEV_1) at Visit 4 for the ITT efficacy population (see 2.3.3 for the definition of ITT efficacy population) was the primary measure of efficacy.

2.2.2 Secondary Efficacy Endpoints

Secondary measures were %Δ AUC FEV_1 at Visit 2, the MAX FEV_1 and duration of effect (defined by $\geq$ 15% increase in FEV_1 over pre-dose measurement) at Visits 2 and 4. Other secondary efficacy parameters consisted of peak expiratory flow rates, asthma symptom scores, number of nocturnal awakenings, frequency of rescue medication use for the treatment of asthma exacerbations, global assessment of patient's response, and frequency of study discontinuation due to treatment failure.

2.2.3 Safety

Safety analysis included a review of all adverse events either reported directly to the investigator and/or all diary entries regarding safety, laboratory tests, vital signs, ECGs, and physical examinations. Electrocardiograms (12-lead ECG) were done pre-dose and at 30, 60, and 90 minutes post dose at Visits 2 and 4. During Visits 1 and 3, an ECG was done pre-dose and at 30 minutes post dose.

2.3 STATISTICAL METHODS

2.3.1 Statistical and Analytical Plan.

All statistical tests were two-sided. According to the protocol, non-parametric methods were to be used for analysis, if the primary variable exhibited non-normality. The result of a test was considered statistically significant if $p \leq 0.05$. The study was regarded as positive if tests on the primary efficacy parameters resulted in significant p-values for the overall test as well as for pairwise comparisons between active treatment arms and placebo. As per the protocol, the data were pooled across study centers for analyses. Post hoc analyses by this reviewer of treatment-by-center interaction were not statistically significant. In addition, reviewer analyses indicated that the centers did not demonstrate a statistically significant effect.

Subject compliance to the dosing regimen was calculated for the 4-week treatment phase of the study. Compliance was computed on the study requirement that three doses of study medication were to be taken each day and the treatment phase of the study was to be 28 ± 3 days. For patients discontinuing early, the last dose date was the endpoint from which the expected number of doses was calculated.

2.3.2 Analysis of Baseline Data

Demographics and baseline data for all patients were summarized and listed for the intent-to-treat (ITT) population. Baseline data include vital signs, medical history, asthma history,

tobacco assessment, physical examination, laboratory data, ECG data, and spirometry. The number and percentage of patients in each demographic, medical history, asthma history, tobacco assessment, physical examination, and ECG category was presented by treatment. Patient ages, heights, weights, vital signs, laboratory data, continuous ECG data, and spirometry was summarized using descriptive statistics. Patient age, height and weight were tested for baseline comparability between treatments using ANOVA. Patient race and gender were also tested for baseline comparability between treatments using a Fisher's Exact test.

2.3.3 Analysis of Primary Efficacy Data

As pre-specified in the protocol, three patient populations were used for analyses in the study: 1) intent-to treat (ITT); 2) ITT efficacy; and 3) evaluable. The ITT population included all patients who took at least one dose of study medication. The ITT population was used for all safety analyses. Efficacy analyses were done on the ITT efficacy and the evaluable populations.

The ITT efficacy population consisted of all patients randomized into the trial that had a minimum number of non-missed PFT data points at Visit 2 and/or Visit 4. The minimum required PFT data points were pre-dose, and post-dose 30 minutes, 1 hour, 2 hours, and 6 hours. There were only 8 patients (4 from 0.75 mg Albuterol group and 4 from placebo group) who were not included in the ITT efficacy population for the above reason. The data from one investigator, Dr. Edwards (Site 006) was discredited after the study was completed, but before the NDA was submitted to the Agency. The discreditation was based on an investigation of a study of a different product and a different sponsor, but the FDA has questioned data from that site for all studies. Therefore, the efficacy data for this study excluded Dr. Edwards' patients data (n=9: 3 per treatment group). The ITT population consists of 115, 117 and 117 patients in three treatment groups, 1.5 mg Albuterol, 0.75 mg Albuterol and placebo, respectively. The ITT efficacy population has 112, 110 and 110 patients in three treatment groups. The evaluable population was a subgroup of the ITT efficacy population consisting of patients who completed the study in compliance with the protocol. In this review, efficacy analysis based on evaluable population will not be considered.

The primary efficacy variable was the area under the FEV_1 percent change from pre-dose versus time curve (%Δ AUC FEV_1) at Visit 4. Descriptive statistics for %Δ AUC FEV_1 were summarized by treatment for the ITT efficacy and evaluable populations. Since %Δ AUC FEV_1 data were highly skewed and test for normality was statistically significant (p-value=0.0001), the planned parametric analysis was not performed. Non-parametric analyses of variance (Kruskal-Wallis Test) for the ranks of %Δ AUC FEV_1 were used to test for overall treatment effect and Wilcoxon Rank Sum Test was used to detect pairwise treatment differences. This testing procedure was pre-specified in the protocol.

The sponsor also did post hoc analyses for the %Δ AUC FEV_1, on the following subgroups:

Age:	6 - 8 yrs.; 9 - 10 yrs.; 11 - 12 yrs
Weight:	≤ 30 kg; > 30 kg and ≤ 40 kg; > 40 kg
Gender:	male; female
Race:	Caucasian, non-Caucasian
Concomitant Medication:	corticosteroid use; corticosteroid non-use
Disease Severity:	≤ 60% FEV_1 predicted normal at pre-dose; > 60% FEV_1 predicted normal at pre-dose

2.3.4 Analysis of Secondary Efficacy Data

The secondary endpoints on the primary efficacy FEV_1 parameter were the %Δ AUC FEV_1 at Visit 2, the MAX FEV_1, and the duration of response from the initial increase of 15% from pre-dose to the first time the percent change from pre-dose returned to below 15% at Visits 2 and 4. The duration of response was analyzed both by mean duration in minutes and frequency distributions for duration time groups. The %Δ AUC FEV_1 at Visit 2, MAX FEV_1, and duration in minutes were tested using a Kruskal-Wallis Test for overall treatment effect. A Wilcoxon Rank Sum Test was used for pairwise comparisons between treatments for %Δ AUC FEV_1 at Visit 2 and MAX FEV_1. The %Δ AUC FEV_1 at Visit 2 and MAX FEV_1 data were also analyzed for the same subgroups as the %Δ AUC FEV_1 at Visit 4.

$FEF_{25\%-75\%}$ and FVC measures and their percent change from pre-dose were summarized using descriptive statistics for each treatment visit. Secondary efficacy parameters were peak expiratory flow (morning and evening), asthma symptoms (daily score), number of nocturnal awakenings, frequency of rescue medication use, global assessment of how patient symptoms responded to treatment, and frequency of study discontinuation due to lack of efficacy. Weekly means of peak flow, asthma symptoms, nocturnal awakenings, and frequency of rescue medication use by patient were calculated, and descriptive statistics were calculated on the patient means. A weekly patient mean for these parameters was calculated only if the patient recorded two or more entries for a given week. These measures were summarized using descriptive statistics for each treatment group. These measures were not tested for treatment effect.

2.3.4.1 Analysis of Safety Data

Summaries of safety data are based on the ITT population which includes any subject that received study drug. Safety endpoints in this study were adverse events, laboratory tests, vital signs, physical examination, and ECG parameters.

2.3.4.1.1 Adverse Events

For analysis, all AEs were summarized by body system and preferred term based on COSTART (Version 5) coding tabular summaries are provided for all AEs. AEs potentially related to study drug, classified as having an unknown, possible, probable, or definite relationship, were summarized separately. In the case of duplicate preferred terms for a subject, the most related and most severe entry was reported for the related AE and severity

data, respectively. Treatment differences in the overall incidence of AEs for all events and potentially drug-related events, and serious AEs were tested using a chi-square test.

2.3.4.1.2 Determination of Sample Size

Sample size of 30 per treatment group would give 80% power at 5% type one error. The sponsor chose a larger sample size (100 per group) to collect a larger safety database. It was determined that 100 children were to be randomized to each treatment group, with a minimum of 80 children in each treatment group completing the testing phase.

2.3.5 Changes in the Planned Analyses

As mentioned earlier, the data from one investigator, Dr. Edwards, at Site 006 was discredited after the study was completed, but before the NDA was submitted to the Agency. The discreditation was based on an investigation of a study of a different product and a different sponsor, but the FDA has questioned data from that site for all studies. Therefore, the efficacy data for this study were reanalyzed excluding Dr. Edwards' patients data (n=9: 3 per treatment group). Those patients had been exposed to the study drug and consequently their data were included in the safety analysis.

The original planned statistical analysis called for Visit 2 observations to be carried forward to fill in for missing Visit 4 data; this was not done in the final analyses.

In the protocol, a response was defined as > 15% increase in FEV_1. For the analyses, a response was defined as ≥ 15% increase in FEV_1. This difference had no effect on the analyses.

2.4 RESULTS

2.4.1 Disposition Of Patients

A total of 349 patients were enrolled in the study: 115 patients were randomized to the 1.5 mg albuterol sulfate group; 117 patients were randomized to the 0.75 mg albuterol sulfate group; and 117 patients were randomized to the placebo (0.9% saline) group. Eighty-three percent (288/349) of the patients completed the study: 98 (85.2%) patients in the 1.5 mg albuterol sulfate group; 97 (82.9%) in the 0.75 mg albuterol sulfate group; and 93 (79.5%) patients in the placebo group. The reasons patients discontinued from the study are summarized below in Table 1.

Table 1: Patient Disposition

	1.5 mg Albuterol (N=115) N (%)	0.75 mg Albuterol (N=117) N (%)	Placebo (N=117) N (%)
Received Study Drug	115 (100)	117 (100)	117 (100)
Completed Study	98 (85.2)	97 (82.9)	93 (79.5)
Withdrawn from Study			
Reason for Withdrawal:			
Adverse event	15 (13.0)	15 (12.8)	15 (12.8)
Major protocol violation	2 (1.7)	1 (0.9)	2 (1.7)
Patient voluntarily withdrew	0 (0.0)	1 (0.9)	2 (1.7)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.9)
Lack of efficacy	0 (0.0)	1 (0.9)	0 (0.0)
Concurrent illness	0 (0.0)	0 (0.0)	1 (0.9)
Other	0 (0.0)	2 (1.7)	3 (2.6)

The number of patients discontinuing overall was similar across treatment groups, with slightly more patients in the placebo treatment group discontinuing. Of the 61 patients who withdrew from the study, 45 patients (73.8%) discontinued due to an adverse event. There were no statistical differences in the number of patients discontinuing due to adverse events across treatment groups.

2.4.2 Efficacy Evaluation

2.4.2.1 Demographics And Other Baseline Characteristics

The 349 patients were enrolled at 41 study centers across the U.S for efficacy (42 for safety). Four centers enrolled > 15 patients, 11 centers enrolled 10 - 15 patients, 17 centers enrolled 5 - 9 patients, 9 centers enrolled 1 - 4 patients, and one site did not enroll any patients. Data were pooled across study centers for analyses.

The demographic characteristics of the 349 patients who received study medication (ITT population) are summarized in Table 2.

APPEARS THIS WAY
ON ORIGINAL

Table 2: Summary of Demographics for the ITT Population

	1.5 mg Albuterol N =115	0.75 mg Albuterol N =117	Placebo N =117	P-value[1]
Age				
Mean (SD)	9.3 (1.8)	9.4 (1.8)	9.6 (1.7)	0.488
Median	9.0	10.0	10.0	
Min, Max	6.0, 12.0	6.0, 12.0	6.0, 12.0	
Gender (%)				
Female	39 (33.9)	47 (40.2)	42 (35.9)	0.596
Male	76 (66.1)	70 (59.8)	75 (64.1)	
Race (%)				
Caucasian	81 (70.4)	79 (67.5)	82 (70.1)	0.841
Black	23 (20.0)	24 (20.5)	24 (20.5)	
Asian	2 (1.7)	1 (0.9)	3 (2.6)	
Hispanic	5 (4.3)	9 (7.7)	7 (6.0)	
Other	4 (3.5)	4 (3.4)	1 (0.9)	
Height (cm)				
Mean (SD)	140.2 (11.6)	140.0 (12.1)	141.3 (11.4)	0.635
Median	140.0	140.7	141.4	
Min, Max	103.6, 178.0	115.2, 170.2	117.0, 170.0	
Weight (kg)				
Mean (SD)	39.0 (12.9)	38.1 (12.3)	40.3 (14.2)	0.431
Median	37.0	35.4	37.2	
Min, Max	16.8, 90.8	19.1, 79.4	21.8, 86.6	
% FEV_1 Predicted				
Mean (SD)	69.0 (8.0)	67.8 (8.1)	68.5 (7.9)	0.494
Range	51.1 - 89.9	50.6 - 82.6	48.9 - 81.3	
% FEV_1 Reversibility				
Mean (SD)	29.0 (14.2)	33.6 (19.3)	30.4 (16.1)	0.107
Range	12.4 - 87.4	14.6 - 141.2	14.5 - 97.7	

[1] ANOVA for H0: Treatment means are equal for Age, Height, Weight; FEV_1 % Predicted or % Reversibility; or Fisher's Exact Test for H0: No association between Gender or Race and treatment.

For the ITT population, there were no significant differences across treatment groups for any of the demographic characteristics. The mean ages of patients were 9.3, 9.4, and 9.6 years for the 1.5 mg albuterol sulfate, the 0.75 albuterol sulfate, and placebo, respectively, with each group having minimum and maximum ages of 6 and 12 years. For race, 67.5% to 70.4% of the population from each treatment group were Caucasian. The mean heights were between 140.0 cm to 141.3 cm and the mean weights were between 38.1 kg to 40.3 kg. The mean %-reversibilities was between 29.0 and 33.6 with the mean % FEV_1 predicted between 68 - 69% for all groups.

In the ITT population, over 90% of patients in each treatment group had histories of medical problems, the most prevalent involving eyes, ears, nose or throat (EENT: 83.5% in the

1.5 mg group, 90.6% in the 0.75 mg group, and 82.1% in the placebo group), respiratory system (25.2 % in the 1.5 mg group, 24.8% in the 0.75 mg group, and 19.7% in the placebo group), neurological system (33.0% in the 1.5 mg group, 24.8% in the 0.75 mg group, and 24.8% in the placebo group), and allergies (42.6% in the 1.5 mg group, 33.3% in the 0.75 mg group, and 36.8% in the placebo group). There were no notable differences in the medical history of patients assigned to the three study groups.

2.4.2.2 Analysis of Efficacy

2.4.2.2.1 Change in FEV_1 Over Time

The primary efficacy endpoint was the %Δ AUC FEV_1 at visit 4. The %Δ AUC FEV_1 data from the ITT efficacy population show that both the 1.5 mg and the 0.75 mg albuterol sulfate solutions produced significant improvement in FEV_1 (p=<0.001) over placebo following acute exposure (Visit 2) and chronic exposure (Visit 4) (Table 3). There were no significant differences between the 1.5 mg and the 0.75 mg of albuterol sulfate doses at either visit (p=0.566 Visit 2; p=0.255 Visit 4).

Table 3: Summary of %Δ AUC FEV_1 for the ITT Efficacy Population

%Δ AUC FEV_1 (%·hr)[1]	1.5 mg Albuterol N = 112	0.75 mg Albuterol N =110	Placebo N = 110
Visit 2			
N	112	109	105
Mean (SD)	99.5 (75.4)	104.5 (97.6)	43.6 (82.0)
Median	91.5	88.8	35.5
Min, Max	[redacted]		
Treatment vs Placebo P-value[2]	<0.001	<0.001	
Visit 4			
N	94	92	89
Mean (SD)	90.3 (93.6)	73.6 (76.5)	34.2 (53.1)
Median	64.7	57.2	27.3
Min, Max	[redacted]		
Treatment vs Placebo P-value[2]	< 0.001	<0.001	

[1] The %Δ AUC FEV_1 was based on the area under the FEV_1 percent change from pre-dose versus time curve. The units are '% · hrs' which is the 'cumulative percent improvement'.
[2] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for %Δ AUC FEV_1 percent change from pre-dose versus time.

The sponsor submitted post hoc subgroup analysis based on age, sex, race, weight and disease severity.

The sponsor analyzed the %Δ AUC FEV_1 data for the ITT efficacy population by the following age groups: 6 - 8 year olds, 9 - 10 year olds, and 11 - 12 year olds. Improvements due to both the active treatments were statistically significant at ≤ 0.05 p-value, except at Visit 4 for the 11 - 12 year olds exposed to the 0.75 mg albuterol sulfate dose. This dataset did not reach statistical significance (p=0.082), but the trend supported the conclusion that both 1.5 mg and 0.75 mg albuterol sulfate produce significant improvement over placebo.

No significant differences in any of the age subgroups were seen between the 1.5 mg and the 0.75 mg albuterol sulfate doses.

Expectedly, the analysis by weight showed similar results to the age analysis. Patients in the two lower weight groups, i.e., those weighing ≤ 40 kg had significant improvements following either active treatment group at both Visits 2 and 4. The heavier weight children (> 40 kg) showed significant improvement at Visit 2 regardless of the active treatment group, but at Visit 4, the improvement in the 1.5 mg albuterol group was significantly better than the 0.75 mg group (109.7 %·hr vs 58.9 %·hr, respectively, p=0.050). The improvement in the 0.75 mg group of heavier children was not significantly better than placebo at Visit 4 (58.9 %·hr vs 30.9 %·hr, p=0.101).

Both the 1.5 mg and the 0.75 mg albuterol sulfate doses were effective for both genders at Visit 2 and Visit 4 ($p \leq 0.006$).

The effect of concomitant use of nasal or oral inhaled corticosteroids on the efficacy of albuterol sulfate was examined. The percentages of patients on inhaled corticosteroids during the study were similar across the treatment groups (55.7%, 58.1% and 51.3% for 1.5 mg, 0.75 mg albuterol sulfate and placebo, respectively). Both active treatments produced significant improvements in the %Δ AUC FEV_1 whether or not the patients were taking concomitant inhaled corticosteroids. For comparison with placebo, the p-values were ≤ 0.033 for both treatment groups at both Visits 2 and 4, except with 0.75 mg albuterol sulfate without corticosteroids which had a p-value of 0.151 at Visit 4. While the active treatments were effective in both groups, the greatest improvement was measured at Visit 2 in the patients using corticosteroids (103.2 and 112.3%·hr for 1.5 mg and 0.75 mg albuterol sulfate, respectively, compared to 49.0%·hr for placebo). For patients using corticosteroids, the mean increase in %Δ AUC FEV_1 for 0.75 mg albuterol sulfate was greater at Visit 2 than at Visit 4 (112.3 vs 83.3%·hr, respectively). For the patients not using corticosteroids, the mean increase of %Δ AUC FEV_1 was less at Visit 4 than at Visit 2 for both the 1.5 mg and the 0.75 mg albuterol sulfate groups.

The impact of a bronchodilator may depend on the severity of the asthma. As a post hoc analysis, the data were examined separately for patients who had $FEV_1 \leq 60\%$ of predicted normal at the start of the treatment phase of the study (Visit 2 pre-dose). There were 56 patients in the ITT efficacy population that fell into that category. Table 4 summarizes the data for this subgroup.

Table 4: %Δ AUC FEV_1 by Disease Severity in ITT Efficacy Population

%Δ AUC FEV_1 (%·hr)[1]	1.5 mg Albuterol	0.75 mg Albuterol	Placebo
$FEV_1 \leq 60\%$ Predicted			
Visit 2			
N	19	24	13
Mean (SD)	149.7 (92.0)	162.4 (94.6)	60.6 (131.8)
Median	128.3	157.7	6.9
Min, Max	[redacted]		
Treatment vs Placebo			
P-value[2]	0.011	0.005	
Visit 4			
N	12	18	8
Mean (SD)	144.6 (108.4)	96.9 (94.6)	40.9 (51.8)
Median	145.2	104.9	32.8
Min, Max	[redacted]		
Treatment vs Placebo			
P-value[2]	0.049	0.141	
$FEV_1 > 60\%$ Predicted			
Visit 2			
N	93	85	92
Mean (SD)	89.3 (67.6)	88.2 (92.6)	41.2 (73.1)
Median	77.9	72.7	36.5
Min, Max	[redacted]		
Treatment vs Placebo			
P-value[2]	<0.001	<0.001	
Visit 4			
N	82	73	76
Mean (SD)	82.4 (89.3)	68.2 (71.5)	29.4 (42.0)
Median	63.3	53.3	26.8
Min, Max	[redacted]		
Treatment vs Placebo			
P-value[2]	<0.001	<0.001	

[1] %Δ AUC FEV_1 was calculated for the percent change in post-dose FEV_1 from the pre-dose FEV_1. The units are '% · hrs' which is the 'cumulative percent improvement'.
[2] P-value from Wilcoxon Rank Sum Test for H_0: Active arm treatment is equal to placebo for %Δ AUC FEV_1 percent change from pre-dose versus time.

For the more severe asthmatic patients, both the 1.5 mg and the 0.75 mg albuterol sulfate produced significant improvements in FEV_1 at Visit 2, but by Visit 4 the 0.75 mg albuterol sulfate, while still better than placebo, was less effective than the 1.5 mg albuterol sulfate dose for this subgroup. The same trend was detected with the less severe patients, with both active treatments producing comparable improvements at Visit 2, and the 0.75 mg albuterol sulfate producing less of an improvement at Visit 4, but even that response was still greater than double the observed placebo group response.

2.4.2.2.2 Maximum Percent Change in FEV_1

In the ITT efficacy population, the MAX FEV_1 significantly increased following 1.5 mg and 0.75 mg albuterol sulfate compared to placebo at both Visit 2 and Visit 4 (Table 5). The mean maximum percent increases across visits ranged from 26.0% to 31.8% for the active treatment groups compared to 13.4% to 15.5% for the placebo group. The mean MAX

FEV_1 were similar at Visit 2 and Visit 4 for the 1.5 mg albuterol sulfate group, but for the 0.75 mg albuterol sulfate group, the Visit 4 mean MAX FEV_1 was less than at Visit 2.

Table 5: MAX FEV_1 for the ITT Efficacy Population

Maximum Percent Change in FEV_1	1.5 mg Albuterol N =112	0.75 mg Albuterol N = 110	Placebo N = 110
Visit 2			
N	112	109	105
Mean % (SD)	29.3 (17.1)	32.0 (21.4)	15.5 (15.9)
Median	24.8	26.5	11.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	
Visit 4			
N	94	92	89
Mean % (SD)	28.6 (22.6)	26.3 (17.4)	13.4 (12.5)
Median	19.8	21.1	10.7
Min, Max	[		]
Treatment vs Placebo P-value[1]	<0.001	<0.001	

[1] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for MAX FEV_1 percent change from pre-dose.

All three age groups at both Visit 2 and Visit 4 had significant increases in MAX FEV_1 following 1.5 mg or 0.75 mg albuterol sulfate compared to placebo, as did all three weight groups. At Visit 4 for the maximum improvement, the 1.5 mg albuterol group was better than the 0.75 mg group for the heavier children.

Significant increases in MAX FEV_1 were seen also for both the female and male subgroups and regardless whether the patients were taking or not taking concomitant corticosteroids. Again, there were no significant differences between the MAX FEV_1 for two albuterol sulfate doses in those subgroups.

As with the %Δ AUC FEV_1 data, the MAX FEV_1 were examined separately for patients who had $FEV_1 \leq 60\%$ of predicted normal at the start of the treatment phase of the study (Visit 2 pre-dose). Table 6 summarizes the data for this subgroup.

APPEARS THIS WAY
ON ORIGINAL

Table 6: MAX FEV_1 by Disease Severity in ITT Efficacy Population

Maximum Percent Change in FEV_1	1.5 mg Albuterol	0.75 mg Albuterol	Placebo
$FEV_1 \leq 60\%$ Predicted			
Visit 2			
N	19	24	13
Mean % (SD)	43.7 (22.0)	47.5 (17.5)	23.5 (24.2)
Median	39.0	45.1	16.2
Min, Max	[		]
Treatment vs Placebo			
P-value[1]	0.010	0.002	
Visit 4			
N	12	18	8
Mean % (SD)	4501 (26.3)	36.6 (17.3)	18.7 (16.8)
Median	41.6	31.9	13.1
Min, Max	[		]
Treatment vs Placebo			
P-value[1]	0.034	0.024	
$FEV_1 > 60\%$ Predicted			
Visit 2			
N	93	85	92
Mean % (SD)	26.4 (14.3)	27.6 (20.5)	14.4 (14.2)
Median	23.7	23.8	11.1
Min, Max	[		]
Treatment vs Placebo			
P-value[1]	<0.001	<0.001	
Visit 4			
N	82	73	76
Mean % (SD)	26.1 (21.1)	23.9 (16.6)	11.8 (9.6)
Median	18.4	18.9	9.9
Min, Max	[		]
Treatment vs Placebo			
P-value[1]	<0.001	<0.001	

Note: MAX FEV_1 is selected as the maximum percent change in post-dose FEV_1 from the pre-dose FEV_1.
[1] P-value from Wilcoxon Rank Sum Test for H0: Active arm treatment is equal to placebo for MAX FEV_1 percent change from pre-dose.

For the more severe asthmatic ($\leq 60\%$) patients, both the 1.5 mg and the 0.75 mg albuterol sulfate produced significant improvements in FEV_1 at Visit 2 and Visit 4. The 0.75 mg albuterol sulfate produced less improvement at Visit 4 compared to Visit 2 and compared to the 1.5 mg albuterol sulfate dose at Visit 4. In the > 60% group, comparable mean maximum percent improvements were seen at both visits for both active treatment groups (23.9% to 27.6%). The mean maximum percent improvements seen with the active treatments for the $\leq 60\%$ group, were higher than seen in the > 60% group, reflecting the greater area for improvement in the more severe subject.

2.4.2.2.3 FEV_1 Percent Change

In the ITT efficacy population, significant changes in FEV_1 occurred within 30 minutes, the earliest post-treatment FEV_1 measurement, in the 1.5 mg albuterol sulfate and 0.75 mg albuterol sulfate groups compared to placebo (23.2%, 28.0%, 8.3%, respectively). (For 'descriptive' p-values associated with these results see Dr. O'Hearn's review). The improvement in FEV_1 remained elevated for both the 1.5 mg and the 0.75 mg albuterol

sulfate group compared to placebo for over 5 hours (Figure 1). However, the mean improvement dropped below 15% at the 4-hour time-point for the 1.5 mg treatment group at Visit 2. At Visit 4, similar results were obtained at 30 minutes post-dose (Figure 2). The mean improvement for the 1.5 mg albuterol sulfate group dropped below 15% at 4 hours as in Visit 2, but the 0.75 mg albuterol sulfate group dropped below 15% by 3 hours at Visit 4.

FIGURE 1

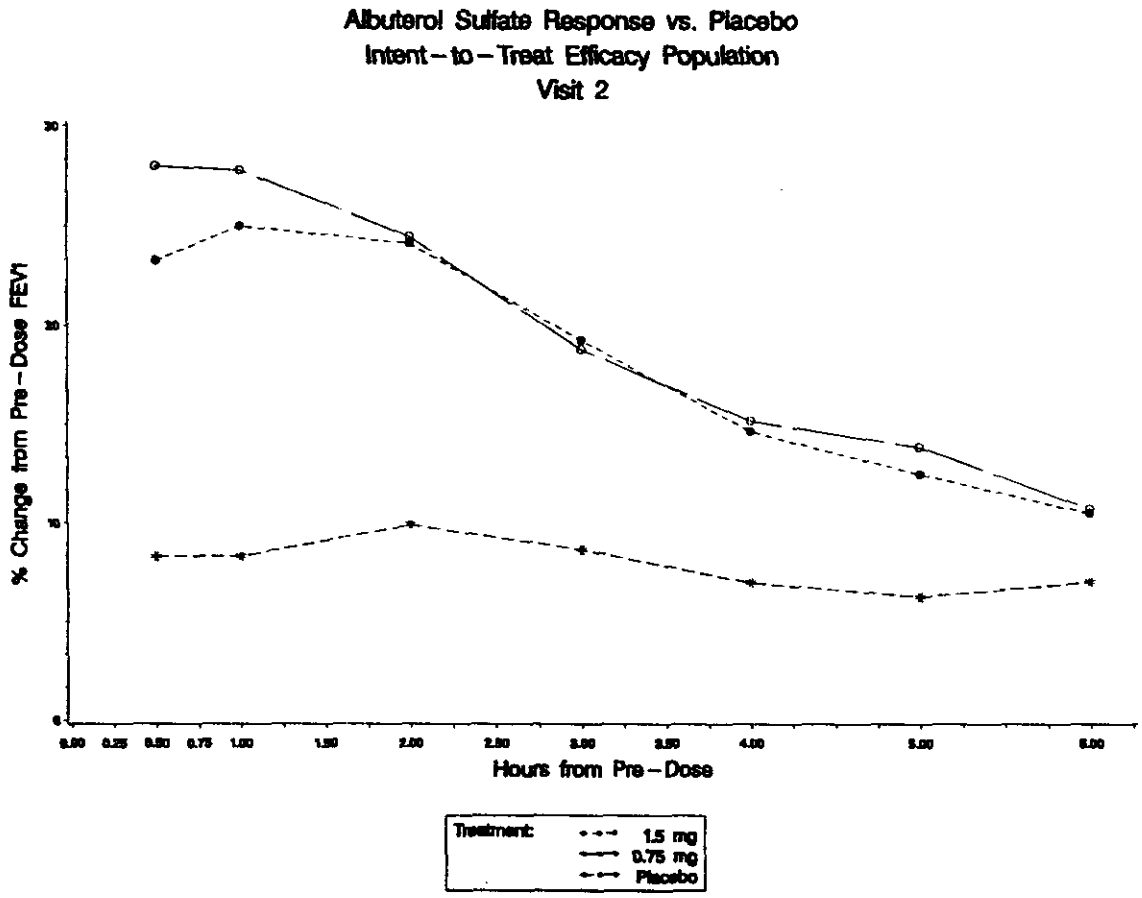
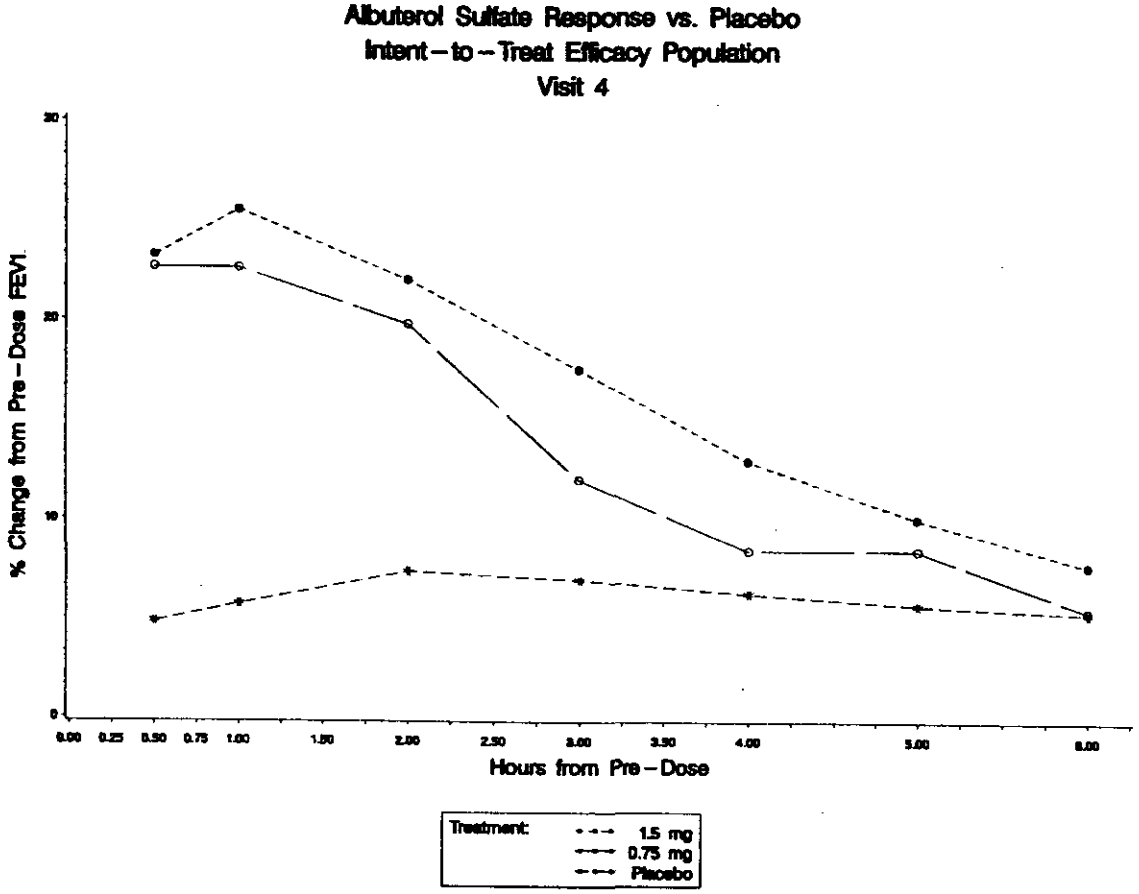


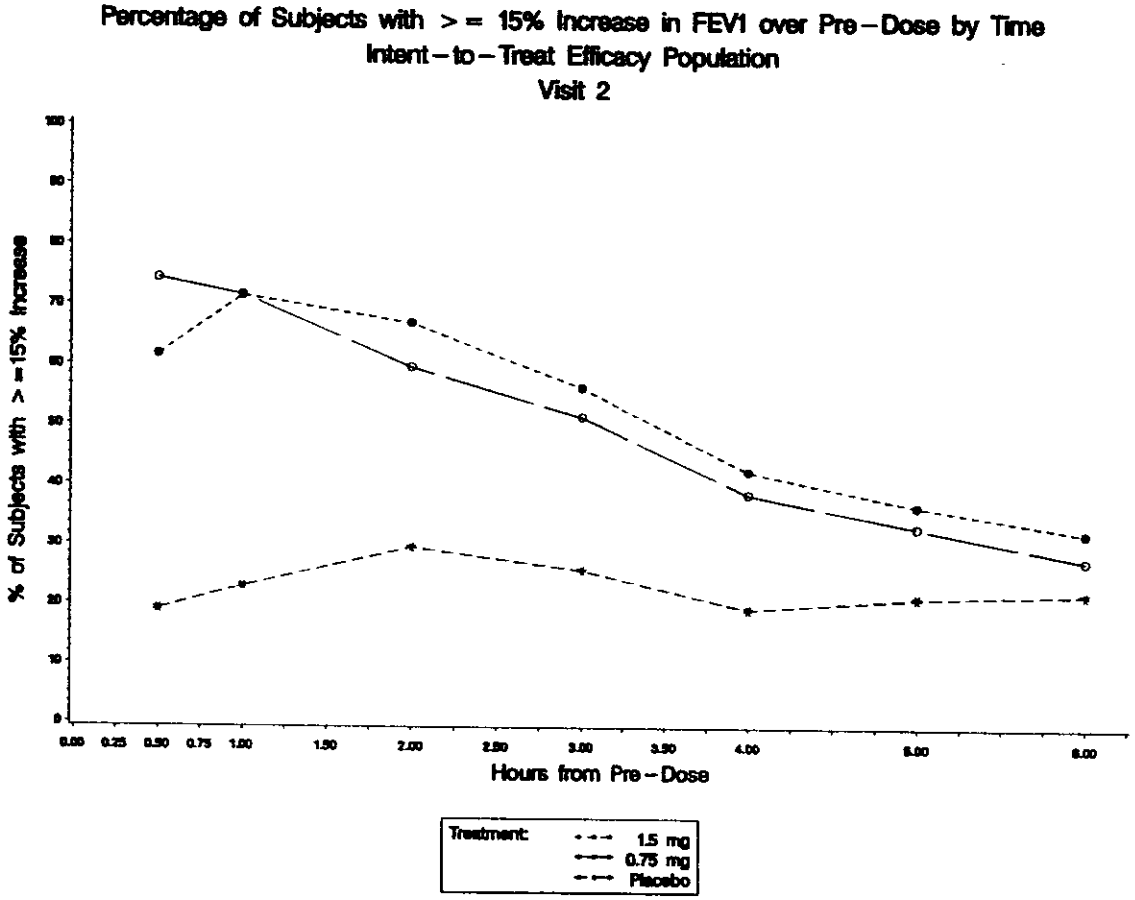
FIGURE 2



2.4.2.3 Proportion of Responders

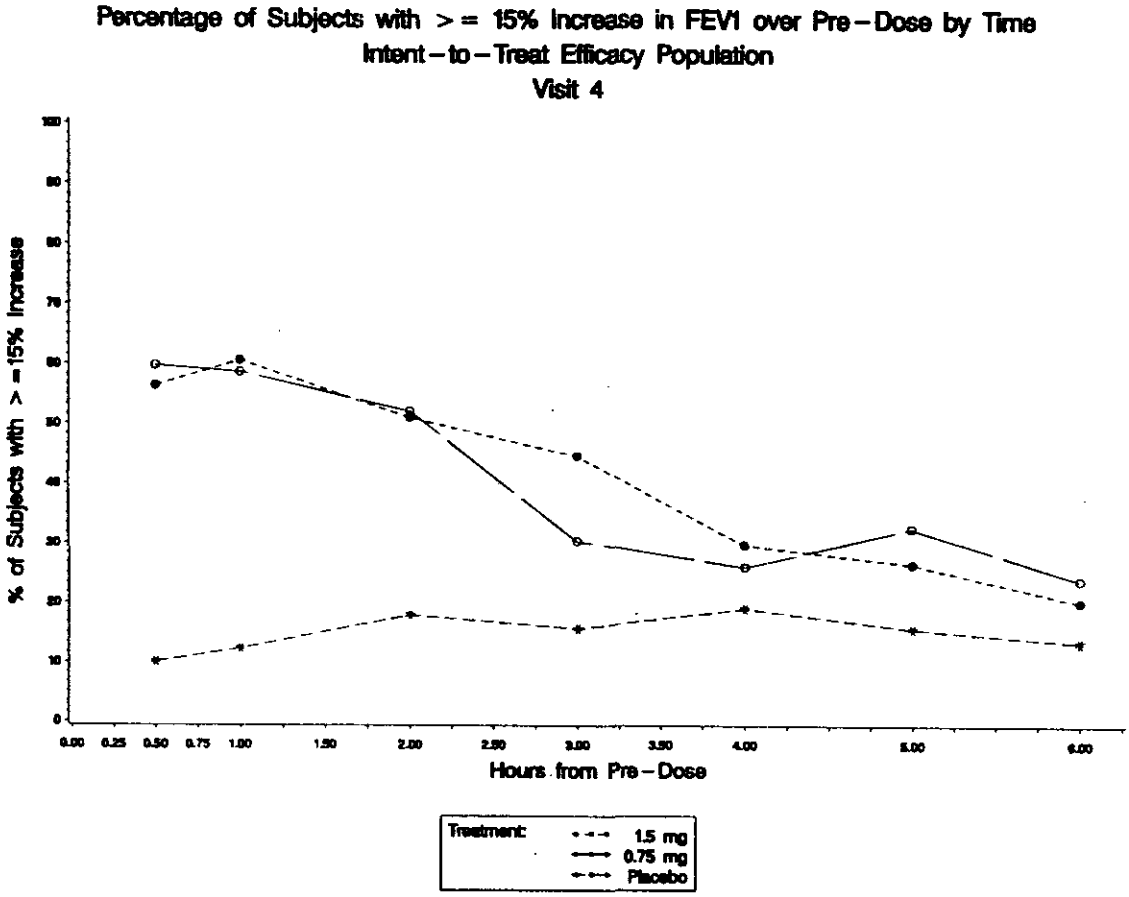
The FEV_1 data over time were further analyzed to determine the percentage of responders at each time point. A response was defined as a $\geq$ 15% increase in the FEV_1 from pre-dose. At Visit 2 in the ITT efficacy population 61.6% of the 1.5 mg albuterol sulfate group and 74.1% of the 0.75 mg albuterol sulfate group responded within 30 minutes (the earliest time point measured) compared to 19.0% of the placebo group. At Visit 2, 56.3% (63/112) of the patients receiving 1.5 mg albuterol sulfate and 51.4% (56/109) of patients receiving 0.75 mg albuterol sulfate had a response at 3 hours compared to 25.7% (27/105) receiving placebo. By 6 hours post-dose, 32.1% and 27.5% of patients receiving 1.5 mg and 0.75 mg albuterol sulfate were responding compared to 21.9% of patients receiving placebo (Figure 3).

FIGURE 3



At Visit 4, a lower percentage of patients had a response within 30 minutes (56.4%, 59.8%, and 10.1% for the 1.5 mg albuterol sulfate, 0.75 mg albuterol sulfate, and placebo, respectively). The percentage of patients receiving albuterol with a response at 3 hours was 44.7% (42/94) for 1.5 mg albuterol sulfate and 31.5% (29/92) for the 0.75 mg albuterol sulfate, but the percentage of placebo patients was 15.7% (14/89) (Figure 4).

FIGURE 4



2.4.3 Statistical/Analytical Issues

2.4.3.1 Handling of Dropouts or Missing Data

Patients were excluded from Visit 2 or Visit 4 efficacy analyses if they had missing PFT data at any of the following time points: pre-dose, 1 hour, 2 hours and 6 hours post-dose. For the few patients whose dosing time was not recorded, the scheduled time of the PFT was used in place of the calculated difference between the actual recorded time of the test and dosing time.

Dropouts (early terminations) were excluded from the evaluable population. For the ITT efficacy population, if the patients dropped during Visit 2, they were excluded from the ITT efficacy population at Visit 2 and Visit 4. If they dropped after Visit 2, the patients were dropped from the ITT efficacy population for Visit 4. The partial data for dropouts were included anywhere the ITT population was used.

2.4.3.2 Multicenter Studies

This study was conducted at 42 centers, and patients were enrolled at all centers, except one. Data were pooled across centers as stated in the protocol.

2.4.3.3 Efficacy Conclusions

Study DL-019 demonstrated that Albuterol Sulfate Inhalation Solutions of 1.5 mg albuterol sulfate (1.25 mg albuterol base) and 0.75 mg albuterol sulfate (0.623 mg albuterol base) produce statistically significant improvements in the pulmonary functions of asthmatic children between the ages of 6 and 12 years. Analyses of %Δ AUC FEV_1 showed significant improvement in FEV_1 compared to placebo in both the ITT efficacy ($p<0.001$) and evaluable ($p<0.002$) populations at both Visits 2 and 4. There were no statistically significant results in pairwise comparisons (Wilcoxon Rank Sum Tests) between the 1.5 mg albuterol sulfate and the 0.75 mg albuterol sulfate groups. These observations were supported by the MAX FEV_1 analyses.

The improvement with 0.75 mg albuterol sulfate did not reach statistical significance at Visit 4 for the patients with $FEV_1 \leq 60\%$ predicted, for 11 - 12 year olds, and for heavier (> 40 kg) children. As noted before the above subgroups were defined in a post hoc manner.

2.4.4 SAFETY EVALUATION

Following the completion of the study analyses, FDA discredited one investigator (Dr. Edward) due to an unrelated investigation of another type of asthma medication. The investigator's data (n=9: 3 per treatment group) were excluded from the efficacy data. The safety data for those 9 patients were kept in the safety section of this report.

2.4.4.1 Brief Summary of Adverse Events

A total of 350 AEs were reported by 164 of 349 (47.0%) patients. There were no significant differences in the total number of patients reporting AEs across treatment groups, however, the placebo group reported a slightly higher number of AEs and patients reporting AEs. Of the 350 AEs, 28 (8.0%) AEs were considered to be potentially related to treatment and those were similarly distributed across the treatment. The majority of AEs were considered to be moderate in severity for all treatment groups; however, in the 0.75 mg albuterol sulfate treatment group, 8.5% of patients reported AEs which were considered to be severe as compared to 0.9% in the 1.5 mg albuterol sulfate treatment group and 4.3% in the placebo treatment group. Five of the 10 patients who had severe adverse events in 0.75 mg group were classified as Asthma, while there was one severe Asthma AE for 1.5 mg and placebo groups. There were, however, only 8 moderate Asthma AEs in 0.75 group and 14 in 1.5 mg group and 11 in the placebo group. It does not appear that there is a significant signal in the increase of Asthma AEs in any particular treatment group. Furthermore, if this increase in severe Asthma AEs were important or real, then one would expect the greatest number of Asthma AEs to be in the placebo group, which is not the case. The above conclusions were discussed with Dr. O'Hearn. The largest number of AEs reported for all treatment groups was related to the respiratory system, with asthma exacerbation and rhinitis

being reported with the highest frequencies. There were few beta-agonist related AEs reported during the study.

There were no deaths in the study. Six serious adverse events (SAEs) were reported during the study. Two patients in the 1.5 mg albuterol sulfate treatment group experienced SAEs related to the respiratory system. Four patients in the 0.75 mg albuterol sulfate treatment group experienced SAEs: two related to the respiratory system, one related to the body as a whole, and one related to metabolic and nutritional disorders. Placebo patients reported no SAE. For farther details refer to Dr. O'Hearn's review.

2.4.4.2 Display of Adverse Events

Table 7 provides a summary of all AEs that occurred in at least 2% of the ITT patients in at least one of the treatment groups.

Table 7: Summary of Adverse Events that Occurred in ≥ 2% of the ITT Population

Modified COSTART Term	1.5 mg Albuterol (N=115)	0.75 mg Albuterol (N=117)	Placebo (N=117)
Total patients reporting events[1] (%)	54 (47.0)	51 (43.6)	59 (50.4%)
Total number of events	117	102	131
Body as a Whole	19 (16.5)	16 (13.7)	26 (22.2)
Allergic reaction	1 (0.9)	4 (3.4)	2 (1.7)
Fever	7 (6.1)	2 (1.7)	7 (6.0)
Flu syndrome[2]	4 (3.5)	3 (2.6)	3 (2.6)
Headache	3 (2.6)	3 (2.6)	5 (4.3)
Infection bacterial	2 (1.7)	1 (0.9)	2 (1.7)
Infection viral	0	0	1 (0.9)
Injury accident	1 (0.9)	0	3 (2.6)
Pain	1 (0.9)	0	3 (2.6)
Cardiovascular System[3]	3 (2.6)	3 (2.6)	0
Digestive System	4 (3.5)	7 (6.0)	6 (5.1)
Hemic & Lymphatic System	3 (2.6)	1 (0.9)	2 (1.7)
Lymphadenopathy	3 (2.6)	1 (0.9)	2 (1.7)
Respiratory System	36 (31.3)	36 (30.8)	45 (38.5)
Asthma[4]	8 (7.0)	5 (4.3)	12 (10.3)
Asthma exacerbation	15 (13.0)	13 (11.1)	10 (8.5)
Bronchitis	1 (0.9)	2 (1.7)	1 (0.9)
Cold symptoms	0	4 (3.4)	2 (1.7)
Cough increase	3 (2.6)	0	5 (4.3)
Pharyngitis	6 (5.2)	5 (4.3)	6 (5.1)
Rhinitis	10 (8.7)	10 (8.5)	17 (14.5)
Sinusitis	5 (4.3)	4 (3.4)	5 (4.3)
URI[5]	8 (7.0)	5 (4.3)	8 (6.8)
Skin & Appendages	9 (7.8)	2 (1.7)	7 (6.0)
Rash	3 (2.6)	1 (0.9)	5 (4.3)
Special Senses	7 (6.1)	3 (2.6)	4 (3.4)
Otitis Media	5 (4.3)	1 (0.9)	0

[1] Totals may include an adverse event with an unknown severity.

[2] Section 15, Table 21.2 summarizes "flu" as "flu synd" and "flu syndrome". For easy reading, these two categories were combined.

[3] The cardiovascular events were tachycardia 0.9% in 1.5 mg albuterol sulfate group and 0% in other groups; migraine, ST depression and hypertension occurred in < 2% of the patients per group.

[4] Asthma = worsening of asthma symptoms

[5] URI = upper respiratory infection

Note: Patients may have more than one adverse event per body system or more than one occurrence of the same adverse event. Only one occurrence of the highest severity is counted for each patient.

The proportions of patients reporting one or more potentially drug-related adverse event(s) are presented below in Table 8.

Table 8: Summary of Potentially Drug-Related Adverse Events[1]

Modified COSTART Term	1.5 mg Albuterol (N=115)	0.75 mg Albuterol (N=117)	Placebo (N=117)
Total patients reporting ≥ 1 event(s) (%)	5 (4.3%)	5 (4.3%)	8 (6.8)
Total number of events	8	9	11
Body as a Whole	2 (1.7)	2 (1.7)	1 (0.9)
Allergic reaction	0	1 (0.9)	0
Flu Syndrome	0	1 (0.9)	0
Headache	1 (0.9)	0	1 (0.9)
Infection-bacterial	0	1 (0.9)	0
Pain chest	1 (0.9)	0	0
Cardiovascular System	1 (0.9)	0	0
Tachycardia	1 (0.9)	0	0
Digestive System	1 (0.9)	1 (0.9)	0
Nausea	1 (0.9)	1 (0.9)	0
Nervous System	1 (0.9)	0	0
Hyperkinesia	1 (0.9)	0	0
Insomnia	1 (0.9)	0	0
Respiratory System	2 (1.7)	3 (2.6)	6 (5.1)
Asthma Exacerbation	1 (0.9)	1 (0.9)	3 (2.6)
Asthma, worsening	1 (0.9)	1 (0.9)	1 (0.9)
Cough increase	0	0	1 (0.9)
Rhinitis	0	1 (0.9)	1 (0.9)
Sinusitis	0	0	1 (0.9)
Skin & Appendages	0	0	2 (1.7)
Acne	0	0	1 (0.9)
Rash	0	0	1 (0.9)

[1] Potentially drug-related adverse events are those that have "possible", "probable", "definite", or missing study drug relationship.

Note: Patients may have more than one adverse event per body system or more than one occurrence of the same adverse event. Only one occurrence of the highest severity is counted for each patient.

2.4.4.3 Analysis of Adverse Events

There were no significant differences in the frequency of the AEs across treatment groups for any body system (p= ≥ 0.096). Overall, the placebo treatment group experienced slightly more adverse events than the albuterol treatment groups. The body as a whole category and the respiratory system had the greatest frequency of adverse events among patients in each treatment group. Rhinitis and asthma exacerbations were the most frequent type of events. There were no significant differences across treatment groups in the number of patients reporting AEs potentially related to study drug overall or for any body system (p= ≥ 0.136). Beta-agonist related AEs were reported by 7 (6.0%) patients receiving 1.5 mg albuterol sulfate; 5 (4.3%) patients receiving 0.75 mg albuterol sulfate; and 2 (1.7%) patients receiving placebo. The beta-agonist related AEs reported by patients during the study were dizziness, dyspnea, hyperkinesia, insomnia, nausea, tachycardia, and twitching. There was one case of hypokalemia reported during the study, in the 0.75 mg albuterol sulfate group. Most of these specific beta-agonist related AEs were reported by fewer than 3 out of the 232 (1.3%) patients receiving albuterol in this study.

2.4.4.4 Serious Adverse Events, And Other Significant Adverse Events

Table 9 below summarizes the SAEs and significant AEs by treatment group.

Table 9: Summary of Serious Adverse Events and Other Significant Adverse Events

	1.5 mg Albuterol N = 115 N (%)	0.75 Albuterol N = 117 N (%)	Placebo N = 117 N (%)
SAEs[1]	2 (1.7)	4 (3.4)	0
Significant AEs	15 (13.0)	15 (12.8)	15 (12.8)
Total	15 (13.0)	17 (14.5)	15 (12.8)

[1] There were no deaths in any of the treatment groups

2.4.4.4.1 Other Significant Adverse Events

The 45 patients who discontinued the study due to AEs were equally distributed across the three treatment groups (Table 10). Four patients who discontinued with SAEs are included in the summary. Asthma exacerbation was the most frequent AE that led to discontinuation.

Table 10: Adverse Events Associated with Study Discontinuation

Reason for Discontinuation	1.5 mg Albuterol N = 115 N (%)	0.75 Albuterol N = 117 N (%)	Placebo N = 117 N (%)
Asthma exacerbation	5 (4.3%)	8 (6.8%)	6 (5.1%)
Secondary Asthma exacerbation[1]	6 (5.2%)	3 (2.6%)	2 (1.7%)
Pneumonia/Bronchitis	1 (0.9%)	0	2 (1.7%)
Strep Throat	0	1 (0.9%)	1 (0.9%)
Upper Respiratory Infection	3 (2.6%)	5 (4.3%)	2 (1.7%)
Rhinitis/Sinusitis/Pharyngitis	0	0	2 (1.7%)
Headache/Nausea	1 (0.9%)	0	0
Ear infection	2 (1.7%)	0	1 (0.9%)
Total # of Patients Discontinuing with AEs	15 (13.0%)	15 (12.8%)	15 (12.8%)

[1] Additional asthma exacerbations were associated with the occurrence of an upper respitory or ear infections.

Most (84%) of the AEs resulting in discontinuation from the study were considered unrelated to study drug. Four asthma exacerbations were considered potentially drug related: one event in the 1.5 mg albuterol sulfate group, one event in the 0.75 mg albuterol sulfate group, and two events in the placebo group. The strep throat listed for a 0.75 mg albuterol sulfate patient was considered related to study drug, as was one of the sinusitis AEs in a placebo patient and the headache and nausea reported for a 1.5 mg albuterol patient.

2.4.4.5 Safety Conclusions

During this study, 164/349 (47%) of patients reported 350 AEs, with asthma exacerbation and rhinitis being the most commonly reported AEs. The majority (92%) of the AEs were considered unrelated to the study medication. No significant difference in the incidence of AEs were detected across the treatment groups. Beta-agonist related events were higher in the albuterol groups, showing a dose response effect, but each type of beta-agonist related

event was reported by ≤ 1.3% of the total number of patients in both albuterol group. No acute effects of albuterol on laboratory parameters were examined in this study.

3 DISCUSSION AND OVERALL CONCLUSIONS

This double-blind, randomized, four-week study demonstrated that the albuterol sulfate inhalation solution at concentrations of 1.5 mg and 0.75 mg produce significantly greater improvements in pulmonary functions than placebo in asthmatic children between the ages of 6 and 12 years. This improvement occurred whether or not the children studied were using concomitant inhaled corticosteroids. No deleterious systemic effects were seen with either the 1.5 mg or the 0.75 mg albuterol sulfate solution.

Based on the subgroup analysis presented in this review, it might be appropriate to recommend 1.5 mg albuterol solution for long term use in 11 - 12 year olds, children weighing > 40 kg and children with more severe asthma ($FEV_1 \leq 60\%$ of predicted). The 0.75 mg albuterol solution did not appear as effective as 1.5 mg dose in the subgroups discussed above. Though the grouping was post-hoc, sample sizes for the subgroups were large enough to have more than 80% statistical power to detect differences.

APPEARS THIS WAY
ON ORIGINAL

/S/ 3/23/1999

Girish Aras, PhD

Concur: Dr. Wilson /S/ 3/23/99

cc:
Orig. NDA 20-949
HFD-570 / Division File
HFD-570 / JJenkins, DO'Hearn
HFD-715 / Division File, Chron
HFD-715 / GAras
HFD-715 / ENevius, SWilson