CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20950

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: MAY 28 1999

NDA #:	NDA 20-950
Applicant:	Dey Laboratoires
Name of Drug:	Duovent™ Combination Albuterol Sulfate and Ipratropium Bromide Inhalation Solution for nebulizer
Indication:	For the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator
Documents Reviewed:	Vol. 1, 36-43, 57. Dated May 27,1998 and SAS data sets submitted electronically on a CD ROM
Statistical Reviewer:	Girish Aras, Ph.D.
Medical Input:	Ray Anthracite, M.D.

1 Summary of Statistical Issues

The objective of the program for the Duovent project was to establish the safety and effectiveness of Duovent, a fixed combination of albuterol sulfate and ipratropium bromide for patients requiring more than one bronchodilator for the treatment of bronchospasm associated with COPD. The NDA contains the results of two clinical trials conducted under IND [redacted] The phase 3 trial (DL-024) enrolled 863 patients at 60 sites in the United States. The phase 1 pharmacokinetic study was conducted in healthy subjects. Only the phase 3 trial DL-024 is reviewed here.

- DL-024 was a randomized, double-blind, positive-control, crossover design trial conducted in 3 phases, with a lead-in phase, a crossover phase consisting of three 2-week double-blind crossover periods (primary analysis), followed by a 6-week, double-blind, parallel phase of extension of the final double-blind therapy, for a total of 12 weeks. The crossover phase included three treatments: Albuterol sulfate (A), ipratropium bromide (I), and the combination (AI) in all the possible (six) sequences (A→I→AI, A→AI→I, etc). The parallel phase extension was assigned the same study medication as that used in the final 2 weeks of the crossover phase. The primary effectiveness variable was the change from pre-dose (trough) baseline to peak FEV_1 measured within 8 hours after dosing (on Study Days 14, 28, and 42), following 2 weeks on each of the 3 double-blind study drugs during the crossover phase.
- A large number (289) of the patients did not complete the crossover phase of the study (33 % of the 863 randomized subjects). Though these discontinuations appear to be well distributed across treatment groups (there were no statistically significant differences), this high incidence of dropouts reduces the confidence in study results. Dropouts are a major concern in all clinical trials and are especially troublesome in crossover studies. Though the planned analysis of the data from the 3-period crossover phase of the study showed that AI was statistically significantly better than A (p-value < 0.001), and I (p-value < 0.001), due to the level of dropouts observed in this trial, it is difficult to rely on these results.
- To support the required combination claim that Duovent™ is superior to each of its components, the sponsor should describe the potential effects of this high level of dropouts on the submitted results. In exploring the potential effects of missing data,

the sponsor should perform a reanalysis based on an examination of treatment differences during the first period of the crossover phase of the trial -- analyzing this portion of the trial, *post hoc,* as a parallel group study.

- Though it appears that the results from the parallel phase of the trial were consistent with those from the crossover phase, the p-values for statistical treatment comparisons based on data from the parallel phase are not reliable due to the large number of dropouts during the crossover phase. Conditioned by study survival during the crossover phase, the patients who were included in the parallel phase treatment groups were potentially, not representative of the original randomization.
- Safety assessments demonstrated no unusal increase in the incidence of AEs associated with Dey Combination Solution compared with albuterol sulfate and ipratropium bromide.

2 Study DL-024

2.1 DESCRIPTION AND METHODOLOGY

Title of Study: A 12-week, randomized, double-blind, positive-control, crossover study of albuterol sulfate, ipratropium bromide, and the combination, as an inhalation solution in patients with chronic obstructive pulmonary disease.

Clinical Phase: Phase 3
Investigators and Study Sites: Multicenter (60 sites) trial in the United States.
Period of Trial: March 1996–January 1997
First Subject Enrolled: 20 March 1996
Last Subject Completed: 21 January 1997

Study Objectives: The trial was designed to determine the effectiveness of Dey Combination Solution compared to albuterol sulfate alone, and ipratropium bromide alone, on pulmonary function, with treatments 4 times a day for 2 weeks. This objective was addressed during the crossover phase of the trial. The secondary objectives were as follows: to evaluate the safety of Dey Combination Solution compared to the individual components, and to evaluate any subset analyses on both effectiveness and safety parameters.

Design: The study used a randomized, double-blind, positive-control, crossover design conducted in 3 phases, with a lead-in phase, a crossover phase consisting of three 2-week double-blind crossover periods (primary analysis), followed by a 6-week, double-blind, parallel phase extension of the final double-blind therapy, for a total of 12 weeks. The three crossover periods consisted of three treatments: Albuterol sulfate (A), ipratropium bromide (I), and the combination (AI). Since the parallel phase extension was assigned the same study medication as that used in the final 2 weeks of the crossover phase, the maximum duration on any of the study drugs was 8 weeks. The crossover phase incorporated all 6 possible treatment sequences.

Study Variables: The primary effectiveness variable was the change from pre-dose (trough) baseline to peak FEV_1 measured within 8 hours after dosing (on Study Days 14, 28, and 42), following 2 weeks on each of the 3 double-blind study drugs during the crossover phase. Secondary variables included the primary variable during the parallel phase, FEV_1-AUC for the time periods of 0-4, 0-6 and 0-8 hours after dosing, time to peak response, time to a 15% improvement over baseline, and duration of a 15% response over baseline during both the crossover and parallel phases. FVC was evaluated in a manner similar to FEV_1. Additional variables included the distance covered during a 6-minute walk during the crossover phase, and AEs recorded during the study.

Inclusion Criteria: Patients who were at least 40 years of age and had a diagnosis of COPD and an FEV_1 between 25% and 65% of the normal predicted values at screening were eligible to participate in this study. Patients demonstrated the ability to safely complete a 6-minute walk, had at least a 10 pack-year history of cigarette smoking, required the use of bronchodilators for at least 3 months prior to enrollment, and were judged by the investigator to be able to refrain from the use of theophylline and oral β_2-agonists for the duration of the trial.

Exclusion Criteria: Patients were ineligible to participate if they had a diagnosis of anthracosis, silicosis, any parenchymal disease not attributable to COPD, polycythemia, cor pulmonale per electrocardiogram, hypoxia, or clinically significant allergic rhinitis, atopy, or asthma. In addition, patients with clinically significant obstructive urinary disease, narrow-angle glaucoma, unstable angina pectoris or myocardial infarction in the past 6 months, known drug abuse within the past 12 months, or hospitalization for pulmonary exacerbation within the past 2 months were also excluded from participation. Patients must not have used an investigational test article within the past 30 days, and women of childbearing potential had to use adequate birth control for the duration of the study.

Sample Size: The planned sample size was 600 evaluable subjects, consisting of 100 in each of the 6 treatment-sequence groups. To achieve this goal, it was estimated that a total of 660 subjects should be enrolled. This assumed a difference in change from pre-dose baseline (trough) to peak for FEV1 of at least 0.035 L between Dey Combination Solution and each of the individual components. The power was 95%. Due to a higher dropout rate than anticipated 863 subjects were enrolled to ensure 600 subjects in the primary efficacy analysis. The sponsor should have followed the original plan of enrolling 660 subjects and minimized the dropouts, rather than continually recruiting patients during the study until the planned sample size of 600 was met.

Crossover phase: For the crossover phase, all subjects who completed at least one post-dose evaluation of pulmonary function on both the Dey Combination Solution arm (AI) and at least one of the two active control arms, either albuterol sulfate alone (A) or ipratropium bromide alone (I), were included in the corresponding portions of the primary analysis, since two separate, tests were performed (AI versus A, and AI versus I). Subjects who did not meet the above criterion were not included in the primary analysis.

Parallel phase: All subjects who completed at least the first two week assessment in the parallel phase (a minimum of four weeks of a single study drug by Study Day 56) were included in a secondary analysis for the parallel phase in which the last value recorded was carried forward.

2.2 PRIMARY ANALYSIS

The primary measure of efficacy is any subject's change in FEV1 on Treatment (AI) minus the change in FEV1 on Treatment (I) or (A) during the crossover phase of the trial. For the primary efficacy analysis, change in FEV1 is expressed as difference from the pre-dose (trough) baseline FEV1 to the peak FEV1 measured within 8 hours after dosing on the same study day (the primary variable).
The following two comparisons were tested:

H_{A0}: $\mu_{AI} = \mu_A$ Versus H_{A1}: $\mu_{AI} \neq \mu_A$

H_{I0}: $\mu_{AI} = \mu_I$ versus H_{I1}: $\mu_{AI} \neq \mu_I$

Where μ_A denotes the mean Peak FEV_1 for the Treatment A expressed as difference from the pre-dose (trough) baseline FEV_1 on the same study Day, and similarly for Treatments I and AI. These tests for H_{A0} and H_{I0} constitute a simultaneous inference problem in which both null hypotheses have to be rejected in order to show efficacy. A two sided version of the Min Test was used: each component test was carried out at a nominal $\alpha^* = 0.05$, yielding a combined $\alpha = 0.05$. (This included performing two one-sided tests and required that the smaller of the test statistics was large enough to reject the null hypothesis at a nominal $\alpha^* = 0.025$, and thus involves the one-sided Min Test at a combined $\alpha = 0.025$.)

The hypotheses were tested in the context of an Analysis of Variance that controlled for possible carryover effects due to the crossover design. Let p_A denote the peak value of the FEV_1 score on Treatment A during the crossover phase, expressed as difference from the same day's baseline, and similarly p_I and p_{AI} for Treatments I and AI. Let s_1, s_2, s_3, s_4, s_5, and s_6 denote indicator variables corresponding to the six possible treatment-sequences (I →AI→A, I→A→AI, etc.) during the crossover period. To discount the possibility of carryover, it had to be shown that the combination AI was better than the components I and A regardless of the crossover period and regardless of the preceding and intervening treatments, i.e. regardless of the treatment-sequence. For the AI versus A test, the model was

$$p_{AI} - p_A = a_1 + a_2 \times s_2 + a_3 \times s_3 + a_4 \times s_4 + a_5 \times s_5 + a_6 \times s_6.$$

The carryover coefficients $a_2 \ldots a_6$ were assessed, as a group, by the F-test.

- It was proposed in the protocol that if they were jointly found significant, H_{A0} would be rejected if the F-test for the model as a whole was significant; and AI would be presumed better than A if the estimated a_1 and the estimated $a_1 + a_i$, i=2, …, 5, were

all positive. (This would mean that AI is better than I, no matter what the sequence.)

- It was also proposed in the protocol that if the carryover coefficients were not jointly found significant, they would be removed from the model and a_1 would be tested, with AI presumed better than A if a_1 was found to be significantly positive. (This would mean that AI is better than I, and that there is no difference between sequences.) This would amount to a paired *T*-test.

The test for Treatment I proceeded similarly.

2.3 SUPPLEMENTAL ANALYSES

An ANOVA was planned and conducted that included all evaluable observations in the crossover phase. The factors in this analysis were treatment, period, treatment×period interaction, and subject. The dependent variable was the change in FEV1, baseline (pre-dose trough) to peak, for each treatment.

The following secondary analyses were planned and performed for FEV1 using the methods described:

- Treatments: Mean peak FEV_1 as a difference from baseline between Study Days 42 and 84 (parallel phase) - simultaneous T-tests;
- Treatments: Mean FEV_1-AUC up to 8 hours (crossover and parallel phases) - simultaneous T-tests (paired for crossover phase);
- Treatments: Mean time FEV_1 remains above 15% over pre-dose baseline (crossover and parallel phases) - simultaneous T-tests (paired for crossover phase);
- Treatments: Mean baseline FEV_1 across the parallel phase (Study Day 28 vs. 84 baselines) - simultaneous T-tests;
- Comparisons of mean peak FEV_1 as a difference from baseline, among 6 randomization sequences and 3 treatments (crossover phase) - three separate simultaneous one-way ANOVAs comparing treatment-sequences.

2.4 RESULTS:

Number of Patients: Planned Enrollment: 660 (to achieve 600 efficacy evaluable)
Actual Enrollment: 863
Age Range: 40-93 years (mean = 67 years)
Race (White/Black/Other): 818/35/10
Gender (Male/Female): 533/330
Randomized: 863
Evaluated for Effectiveness: 647
Evaluated for Safety: 863
Discontinued: 289

Effectiveness: In the primary efficacy analysis, the F-test did not show statistical significance indicating that the sequences (carry-over coefficients a_2, ... A_6) are not statistically significantly different. As per the protocol, they were removed from the model and a_1 was tested alone with a paired t-test. Dey Combination Solution resulted in a significantly greater increase ($p<0.001$) in FEV_1 above pre-dose (trough) measurements than both albuterol sulfate or ipratropium bromide alone, during the crossover phase of the trial (Table 1 and Figure 1).

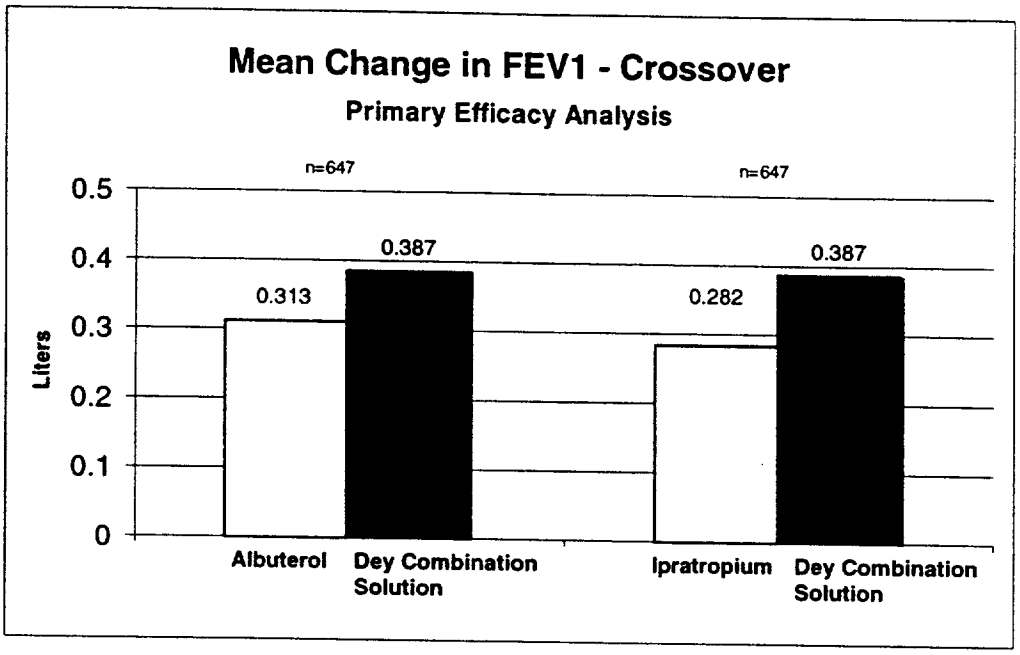
Table 1. Study DL-024—Summary of Effectiveness—Crossover phase

	AI vs. A				AI vs. I			
Parameter	n*	AI Mean	A Mean	AI vs A p-value	n*	AI Mean	I Mean	AI vs I p-value
Change in FEV_1 trough to peak (L)	647	0.387	0.313	<0.001	647	0.387	0.282	<0.001
FEV_1 AUC 0-4 Hours (L*hrs)	647	1.102	0.827	<0.001	647	1.106	0.734	<0.001
FEV_1 AUC 0-6 Hours (L*hrs)	647	1.370	1.029	<0.001	647	1.376	0.984	<0.001
FEV_1 AUC 0-8 Hours (L*hrs)	647	1.495	1.147	<0.001	647	1.503	1.137	<0.001
Time to Peak FEV_1 (hrs)	634	1.54	1.45	0.128	625	1.54	2.07	<0.001
Time to 15% Response in FEV_1 (hrs)	459	0.36	0.48	<0.001	420	0.38	0.81	<0.001
Duration 15% Response in FEV_1 (hrs)	361	4.29	3.67	<0.001	297	4.34	4.08	0.080
Change in FVC trough to peak (L)	648	0.764	0.673	<0.001	648	0.766	0.611	<0.001
FVC AUC 0-4 Hours (L*hrs)	648	1.948	1.568	<0.001	648	1.962	1.368	<0.001
FVC AUC 0-6 Hours (L*hrs)	648	2.409	1.949	<0.001	648	2.431	1.809	<0.001
FVC AUC 0-8 Hours (L*hrs)	648	2.635	2.162	<0.001	648	2.659	2.084	<0.001
Time to Peak FVC (hrs)	627	1.72	1.65	0.361	621	1.74	2.24	<0.001
Time to 15% Response in FVC (hrs)	432	0.49	0.55	0.194	393	0.49	0.85	<0.001
Duration 15% Response in FVC (hrs)	295	3.97	3.54	0.006	243	3.95	3.53	0.018
Distance for 6 Minute Walk (yds)	631	341.5	341.3	0.952	638	342.4	340.5	0.566

* n represents the number of patients with 1 pre-dose and 1 post-dose assessment for drug treatments presented.

AI, Dey Combination Solution; A, albuterol sulfate; AUC, area under the curve; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; I, ipratropium bromide

Figure 1. Study DL-024—Mean change in FEV_1—Crossover.



There was no significant effect of crossover sequence. The significance of the increase in FEV_1 was also confirmed by 6 independent analyses for each half of the primary analysis (Dey Combination Solution versus albuterol sulfate, and Dey Combination Solution versus ipratropium bromide), obtained by dividing the sample into the 6 possible treatment sequences to which the patients were randomized, and analyzing with the same method as the primary analysis ($p=0.03$ to $p<0.001$). Findings similar to the significant increases in FEV_1 were observed in the analysis of FEV_1-AUC for the time frames of 0-4, 0-6 and 0-8 hours post-dose, and for FVC. Dey Combination Solution demonstrated the rapid onset of albuterol sulfate with a mean time to peak FEV_1 1.5 hours, and the extended duration of ipratropium bromide with duration of 15% response in FEV_1 of 4.3 hours. Analyses of data from the parallel phase of the trial revealed results similar to those found during the crossover phase (Table 2).

Table 2. Dey-DL-024—Effectiveness Results—Parallel phase

Parameter	A		I		AI		AI vs A	AI vs I
	n*	Mean	n*	Mean	n*	Mean	p-value	p-value
Change in FEV_1 trough to peak (L)	206	0.275	201	0.273	203	0.353	0.001	0.001
FEV_1 AUC 0-4 Hours (L*hrs)	206	0.735	201	0.702	203	0.988	<0.001	<0.001
FEV_1 AUC 0-6 Hours (L*hrs)	206	0.896	201	0.934	203	1.213	<0.001	0.004
FEV_1 AUC 0-8 Hours (L*hrs)	206	0.986	201	1.069	203	1.323	0.003	0.026
Time to Peak FEV_1 (hrs)	206	1.4	200	1.7	203	1.5	0.509	0.105
Time to 15% Response in FEV_1 (hrs)	184	0.6	165	0.7	196	0.4	0.027	<0.001
Duration of 15% Response FEV_1 (hrs)	167	2.9	139	4.0	186	3.4	0.052	0.040
Change in FVC trough to peak (L)	206	0.562	201	0.547	203	0.686	0.017	0.009
FVC AUC 0-4 Hours (L*hrs)	206	1.236	201	1.205	203	1.798	<0.001	<0.001
FVC AUC 0-6 Hours (L*hrs)	206	1.514	201	1.608	203	2.185	<0.001	0.001
FVC AUC 0-8 Hours (L*hrs)	206	1.670	201	1.867	203	2.380	<0.001	0.017
Time to Peak FVC (hrs)	206	1.4	200	2.0	203	1.5	0.716	0.002
Time to 15% Response in FVC (hrs)	177	0.7	163	1.0	190	0.5	0.025	<0.001
Duration of 15% Response FVC (hrs)	146	2.8	137	3.5	173	3.2	0.271	0.253
Distance for 6 Minute Walk (yds)	204	361	200	362	202	354	0.541	0.503

*n represents the number of patients with 1 pre-dose and 1 post-dose assessment for drug treatments presented

AI, Dey Combination Solution; A, albuterol sulfate; I, ipratropium bromide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Overall, both the crossover and parallel phases provided very consistent results supporting the superiority of the Dey Combination Solution over both albuterol sulfate alone and ipratropium bromide alone in the treatment of COPD.

Safety: Safety analyses were undertaken on all subjects randomized. AEs were coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART). Safety assessments demonstrated no significant increase in the incidence of AEs associated with Dey Combination Solution compared with albuterol sulfate and ipratropium bromide (AEs reported in more than 2% of patients in one or more treatment groups is provided in Table 3).

Table 3. DL-024—Summary of Adverse Experiences (≥2%)

Body System and COSTART Term	Albuterol Sulfate Number (%)	Ipratropium Bromide Number (%)	Dey Combination Solution Number (%)
Number of Patients	761	754	765
N(%) of Patients with an AE*	327 (43.0)	329 (43.6)	367 (48.0)
Body as a Whole			
Headache	21 (2.8)	18 (2.4)	21 (2.7)
Infections	17 (2.2)	17 (2.3)	17 (2.2)
Pain Chest	11 (1.4)	14 (1.9)	20 (2.6)
Digestive			
Dry Mouth	27 (3.5)	55 (7.3)	43 (5.6)
Nervous			
Dizziness	12 (1.6)	15 (2.0)	15 (2.0)
Nervousness	23 (3.0)	18 (2.4)	18 (2.4)
Tremor	23 (3.0)	12 (1.6)	16 (2.1)
Respiratory			
Cough Increase	28 (3.7)	39 (5.2)	40 (5.2)
Dyspnea	63 (8.3)	52 (6.9)	49 (6.4)
Lung Disorder	36 (4.7)	34 (4.5)	49 (6.4)
Pharyngitis	27 (3.5)	27 (3.6)	34 (4.4)
Rhinitis	24(3.2)	14(1.9)	9(1.2)
Cardiovascular			
All	22 (2.9)	18 (2.4)	17 (2.2)

Note: Additional AEs reported in more than 1% of patients treated with Dey Combination Solution include constipation, diarrhea, dyspepsia, nausea, leg cramps, bronchitis, pneumonia, voice alterations, and urinary tract infections. There was a 0.3% incidence of patients with possible allergic-type reactions, including skin rash, pruritis, and urticaria.
*Regardless of relatedness to study drug.

There were 7 deaths (3 with Dey Combination Solution). There were 289 patients who discontinued (181 patients discontinued due to AEs); discontinuations were equally distributed among treatment groups. There were 76 patients with serious AEs (74 unique patients; 2 patients reported serious AEs in 2 study drug treatment groups); serious AEs were equally distributed among treatment groups and no significant patterns or findings were noted. There were 208 unique patients who discontinued due to an AE, died, or had an SAE. There were no clinically significant abnormal laboratory values.

3 Conclusions

Though the results presented (based on planned analyses) statistically demonstrate that Duovent™ is superior to each of its components (albuterol sulfate or ipratropium), supporting the sponsor's claim that the combination product is safe and effective for patients requiring more than one bronchodilator for the treatment of bronchospasm associated with COPD, the large number of dropouts observed in the study weakens this conclusion. The sponsor should further explore and discuss the sensitivity of the results and the potential impact of missing data on the analyses. It might, for example, be appropriate for the sponsor to analyze the first period of the cross-over phase of the study -- examining treatment differences for this period as if the trial had been designed as a parallel group study.

/S/

Girish Aras, PhD

Concur: Dr. Wilson /S/ 5/28/99

cc:
Orig. NDA 20-950
HFD-570 / Division File
HFD-570 / JJenkins, RAnthracite
HFD-715 / Division File, Chron
HFD-715 / GAras
HFD-715 / ENevius, SWilson