CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20950

MEDICAL REVIEW

Hilfiker

FEB 22 2000

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-950	APPLICATION TYPE:	NDA amendment
SPONSOR:	Dey	TRADE NAME:	DuoNeb™
CATEGORY:	bronchodilator	GENERIC NAME:	albuterol-ipratropium solution
		ROUTE:	inhalation
MEDICAL OFFICER:	Raymond F. Anthracite	REVIEW DATE:	2/18/2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

DOCUMENT DATE	CDER DATE	SUBMISSION TYPE	COMMENTS
11/29/99	12/2/99	amendment	approvable response

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS

REVIEW SUMMARY:

The sponsor has offered complete and compelling answers to both clinical questions. Labeling has been reviewed and revised.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

NEW CLINICAL STUDIES:	____	HOLD	____	MAY PROCEED
NDA/SUPPLEMENTS:	XX	APPROVABLE	____	NOT APPROVABLE
OTHER SUBMISSIONS:	____	(ACTION)		

SIGNATURES

Reviewer: /S/ _____. Date: 2/18/2000

Team Leader: /S/ _____. Date: 2/22/2000

I. SUMMARY

The sponsor has offered complete and compelling answers to both clinical questions. Labeling has been reviewed and revised.

II. RESPONSE TO CLINICAL QUESTIONS

II.A. POSSIBLE INTERACTION BETWEEN AE'S AND DISEASE SEVERITY

We requested that the sponsor analyze baseline disease severity by the presence or absence of cotherapy with albuterol and ipratropium. Those patients with baseline cotherapy were assumed to be more severe than those receiving a less intensive regimen. The following table addresses this request.

PERCENTAGES OF PATIENTS WITH AE's BY BODY SYSTEM BASED ON DISEASE SEVERITY AS DETERMINED BY PRIOR COTHERAPY WITH BOTH ALBUTEROL AND IPRATROPIUM

	Severity	Albuterol	Ipratropium	DuoNeb
Body System	More / Less	n = 332 / n = 429	n = 329 / n = 425	n = 332 / n = 433
Any AE	More	42.8	44.1	50.9
	Less	43.1	43.3	45.7
Body As Whole	More	11.4	10.3	12.7
	Less	11.0	14.1	10.9
Cardiovascular	More	3.0	2.1	2.1
	Less	2.8	2.6	2.3
Digestive	More	7.8	13.1	14.2
	Less	7.9	13.9	14.1
Metabolic & Nutrition	More	1.5	1.8	1.2
	Less	1.9	1.4	2.1
Musculoskeletal	More	2.7	1.2	5.4
	Less	2.1	2.8	1.4
Nervous	More	8.1	6.1	8.4
	Less	10.3	9.4	8.8
Respiratory	More	25.0	25.2	25.0
	Less	22.4	22.1	25.2
Skin & Appendages	More	1.8	1.5	0.9
	Less	2.1	2.4	1.2
Special Senses	More	3.0	2.7	2.1
	Less	2.3	1.9	1.6
Urogenital	More	1.8	1.5	4.5
	Less	1.9	4.2	3.2
Body Systems = 10	% Less > % More	5	7	5
	% More > % Less	5	3 -	5

Body systems in which a greater percent of patients reporting AE's were from more severe patients than less severe were counted and displayed in the last line of the table above. By this criterion, there was no interaction between patients reporting AE's, disease severity and DuoNeb. Five-point-two percent (5.2%) more than less severe patients reported AE's with DuoNeb. This degree of difference was not seen with ipratropium (0.8%) and albuterol showed fewer more severe than less severe patients

reporting AE's (-0.3%). This is the only evidence of AE and disease severity interaction and it is weak.

An additional and unrequested analysis was performed by the sponsor. Disease severity was defined by baseline $FEV_{1.0}$, which broke the cases into approximately equal numbers among the three categories. In the table below, "N" refers to the number of patients in the severity/drug category, "n" is the number of patients reporting any AE and the "(%)" is 100 x (n/N).

PERCENTAGES OF PATIENTS WITH AE's BY BODY SYSTEM BASED ON DISEASE SEVERITY AS DETERMINED BY BASELINE FEV1.0				
Severity By FEV1.0	N n (%)	Albuterol	Ipratropium	DuoNeb
≤ 30% pred.	Total Patients in Category	237	234	239
	Patients With Any AE (%)	92 (38.8)	114 (48.7)	118 (49.4)
31 - 45% pred.	Total Patients in Category	267	266	264
	Patients With Any AE (%)	123 (46.7)	111 (41.7)	116 (43.9)
≥ 45% pred.	Total Patients in Category	257	254	262
	Patients With Any AE (%)	112 (43.6)	104 (40.8)	133 (50.8)

Only ipratropium shows dose ordering of increased percent patients reporting any AE's with increasing disease severity, as defined by baseline $FEV_{1.0}$.

II.B. POSSIBLE ADDITIONAL INFORMATION NOT SUBMITTED

Narrative summaries of deaths, discontinuations due to AE's and serious AE's seemed to include details that were not found in the case report forms. The sponsor replied that additional information was submitted on MedWatch forms and that all of these were submitted and in our possession. I had neglected to scrutinize the MedWatch forms in the original NDA review.

III. LABELING REVISIONS

III.A. FIRST YELLOW TAB

Make corrections as indicated.

III.B. SECOND YELLOW TAB

Delete the graph depicting the parallel phase of the study. The remaining graph of the crossover phase was the primary efficacy endpoint. The parallel phase graph adds nothing of clinical relevance, unless one wants to infer minimal evidence of tachyphylaxis by comparing the two, which I think is unwarranted.

III.C. THIRD YELLOW TAB

Delete all Geriatric Use verbiage and add the highlighted portion of the attached text fro 21 CFR 201.57(f)(10). The median age in the only pivotal trial submitted was 67 years of age, so the 863 patients were about evenly divided between those 65 years of age and over and those under age 65 years. With these numbers of randomized patients we didn't see much of an age-related safety signal that was unique to the combination solution. I looked in the original submission for the numbers required by the "boilerplate" recommendation but couldn't find them. The sponsor can find the number of patients over age 64 and over age 74 and can add these numbers, as required by the regulation.

The table has been deleted in favor of one showing adverse events where the combination solution showed the highest frequency of patients reporting the AE. The premise is that we are identifying safety concerns that are possibly relevant to the product that we are approving. The table that I taped in is reproduced below for cutting and pasting. In a slightly different form, this table is in my review on page 25.

PATIENTS (%) REPORTING ADVERSE EVENTS BY TREATMENT GROUP WHERE THE COMBINATION SOLUTION SHOWED THE HIGHEST PERCENTAGE			
Body System **COSTART Term**	**Albuterol** **n (%)**	**Ipratropium** **n (%)**	**Combination Solution** **n (%)**
NUMBER OF PATIENTS	761	754	765
N (%) Patients with AE	327 (43.0)	329 (43.6)	367 (48.0)
BODY AS A WHOLE			
pain	8 (1.1)	4 (0.5)	10 (1.3)
pain chest	11 (1.4)	14 (1.9)	20 (2.6)
Digestive			
diarrhea	5 (0.7)	9 (1.2)	14 (1.8)
dyspepsia	7 (0.9)	8 (1.1)	10 (1.3)
nausea	7 (0.9)	6 (0.8)	11 (1.4)
Musculo-skeletal			
cramps leg	8 (1.1)	6 (0.8)	11 (1.4)
Respiratory			
bronchitis	11 (1.4)	13 (1.7)	13 (1.7)
lung disease	36 (4.7)	34 (4.5)	49 (6.4)
pharyngitis	27 (3.5)	27 (3.6)	34 (4.4)
pneumonia	7 (0.9)	8 (1.1)	10 (1.3)
Urogenital			
infection urinary tract	3 (0.4)	9 (1.2)	12 (1.6)

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-950
HFD-570/Medical Team Leader/Chowdhury
HFD-570/Medical Reviewer/Anthracite
HFD-570/Pharmacology Reviewer/Whitehurst
HFD-570/Chemistry Reviewer/Kim
HFD-570/Project Manager/Hilfiker

Hilfiker

MEDICAL OFFICER REVIEW
Division Of Pulmonary Drug Products (HFD-570) MAY 24 1999

APPLICATION #:	20-950	**APPLICATION TYPE:**	NDA
SPONSOR:	Dey Laboratories	**PROPRIETARY NAME:**	Duovent
CATEGORY:	combination of two bronchodilators	**USAN NAME:**	albuterol & ipratropium
		ROUTE:	inhaled
MEDICAL OFFICER:	R. F. Anthracite, M.D.	**REVIEW DATE:**	

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
28 May 1998	29 May 1998	new NDA	505(b)2 submission

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a 505(b)(2) submission for Duovent™, a nebulizer solution of albuterol sulfate and ipratropium bromide (6:1 by weight), for the treatment of bronchospasm in patients with Chronic Obstructive Pulmonary Disease who require more than one bronchodilator drug. The single pivotal trial was a 3-period, 6-week, crossover phase followed by a 6-week, parallel-group phase comparing four-times-daily self-administration of three aerosolized bronchodilators, albuterol, ipratropium and a combination of the two. The study enrolled 863 patients with mild-to-severe COPD. Efficacy was shown by statistically significant improvement in trough to peak $FEV_{1.0}$ of the combination solution over both active controls during the eight hours after dosing in the crossover phase. The primary efficacy variable and most of the secondary variables in both the crossover and parallel phases showed that the combination solution had a faster onset, greater peak effect and longer duration of action than either of its components. Patients with lower baseline spirographic flows more frequently reported adverse events when treated with the combination solution than did patients with less severe flow obstruction suggesting a disease-severity-treatment interaction of the combination solution for adverse events. Evidence of paradoxical bronchoconstriction was sought in adverse event reports and by examining $FEV_{1.0}$ declines from baseline after treatments that did and did not contain ethylenediaminetetracetic acid and none was found. Industry-sponsored and literature-based trials generally supported efficacy and safety of the combination solution.

OUTSTANDING ISSUES:

1. Edit labeling.
2. Non-critical comments to be sent to the sponsor.

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	_____	**HOLD**	_____	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	XXX	**APPROVABLE**	_____	**NOT APPROVABLE**

SIGNATURES

Reviewer: /S/ — **Date:** 14 May 1999

Team Leader: /S/ — **Date:** 5/24/99

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This is a 505(b)(2) submission for Duovent™, a nebulizer solution of albuterol sulfate and ipratropium bromide (6:1 by weight), for the treatment of bronchospasm in patients with Chronic Obstructive Pulmonary Disease who require more than one bronchodilator drug. The active drug components have been marketed for inhaled use as both innovators and as generic products and have long historic precedents as safe and effective drugs for this indication. An innovator combination product, Combivent, is available as a metered dose inhaler and has a similarly known safety and efficacy record.

The sponsor conducted a single, large pivotal trial for efficacy and safety, referencing industry-sponsored and literature-based data for support. The design of this trial was a 3-period, 6-week, crossover phase followed by a 6-week, parallel-group phase comparing four-times-daily self-administration of three aerosolized bronchodilators, albuterol, ipratropium and a combination of the two. The study enrolled 863 patients with mild-to-severe COPD. Efficacy was shown by statistically significant improvement in trough to peak $FEV_{1.0}$ of the combination solution over both active controls during the eight hours after dosing in the crossover phase. The primary efficacy variable and most of the secondary variables in both the crossover and parallel phases showed that the combination solution had a faster onset, greater peak effect and longer duration of action than either of its components. Most of the secondary spirometric efficacy variables also demonstrated statistical superiority of the combination over both comparators. The six-minute walking distance test did not discriminate among the three treatments in either phase. Review of industry-sponsored and literature-based studies supported the efficacy of the combination solution.

Safety was assessed by weekly adverse event reports during the twelve-week study. Respiratory and digestive system adverse events were slightly more common with the combination solution than either component and more frequently considered to be 'related' to the drug. Patients with lower baseline spirographic flows more frequently reported adverse events when treated with the combination solution than did patients with less severe flow obstruction suggesting a disease-severity-treatment interaction of the combination solution for adverse events. Deaths and serious adverse events were fairly evenly distributed among the three treatments. Early terminations due to adverse events were most common with the combination solution. Laboratories and electrocardiograms done at the start and finish of the study were reported as adverse events and none were attributed to the combination solution. About one third of the randomized patients dropped out before the end of the study, most terminating in the first four weeks. Analysis of dropouts by last-treatment-taken and by treatment sequence within visits and phases did not reveal any disproportion among the three treatments. Industry-sponsored and literature-based studies also supported the safety of the combination solution.

Evidence of paradoxical bronchoconstriction was sought in adverse event reports and by examining $FEV_{1.0}$ declines from baseline after treatments that did and did not contain ethylenediaminetetracetic acid (EDTA). Neither analysis yielded evidence

implicating the combination solution with this event. Secondarily, EDTA was not linked to evidence of paradoxical bronchoconstriction.

This would rate an 'approval' action were it not for unresolved chemistry concerns. Also unresolved is the approvability of this formulation given the extant exclusivity of Combivent, which should terminate in October 1999. A few non-critical clinical queries will be addressed to the sponsor, and are included in the appropriate section of this review. The only outstanding clinical issue that remains is the label, which is unedited, at this time.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-950
HFD-570/Division Files
HFD-570/Office Director-Division Director/Jenkins
HFD-570/Medical Reviewer/Anthracite
HFD-570/Statistical Reviewer/Aras
HFD-570/Chemistry Reviewer/Kim
HFD-570/BioPharm Reviewer/Chen
HFD-570/PharmTox Reviewer/Whitehurst
HFD-570/Project Manager/Hilfiker

COMMENTS TO THE SPONSOR

1. There appears to be an interaction of adverse event reporting with disease severity. Using the same baseline indices of severity as before (using albuterol and ipratropium prescription cotherapy), analyze the distribution of adverse event types by two-category severity [23:147-8].

2. The narrative summaries of deaths, discontinuations and serious adverse events included more detailed information than was to be found in the case report forms. This may have been achieved by immediate local follow-up of these events but also raises the possibility of additional information sources that we failed to identify or to which we did not have access. How were these detailed narratives constructed?

GENERAL INFORMATION

NOTE TO READERS

Square brackets are used throughout this review to include references to the original NDA volumes, items and pages. When a volume contains more than one 'item' and has duplicate page numbers, the 'item' number is enclosed in parentheses after the volume number and is separated from the page by a colon. The words, 'FAX' or 'Telecon' preceding a date and optional volume, item and page reference distinguishes FAX communications and teleconferences. A leading date indicates a separate submission and is followed by an optional volume, item and page reference. Several volumes/items/pages, submissions and events may all be referenced in one set of brackets; e.g., **[VOL(ITEM):PAGE, PAGE-Page, VOL:PAGE-Page, DATE VOL(ITEM):PAGE, FAX DATE]**.

FOREIGN MARKETING

This formulation has not been approved, submitted for approval or withdrawn from marketing in any foreign country [1(3):38].

CHEMISTRY

Albuterol sulfate, the racemic form of albuterol, is a relatively selective beta-2 adrenergic bronchodilator that is manufactured by[ ]
Dey Labs was granted approval for an aerosol solution of albuterol on 2/21/92 (ANDA #72-652). Ipratropium bromide is an anticholinergic bronchodilator and a monohydrated quaternary ammonium compound that is chemically related to atropine. It is manufactured by[ ] Dey Labs was given approval for an aerosol solution of ipratropium on 1/10/97 (ANDA #74-755) [1(3):41].

PRECLINICAL TOXICOLOGY

Acute and subchronic toxicity studies were carried out in rats and dogs to determine the potential for interaction or synergy between ipratropium bromide and albuterol sulfate using a ratio of albuterol to ipratropium of 6:1 by weight. The results of these studies indicated that the concomitant administration of ipratropium bromide and albuterol sulfate did not produce enhanced toxic effects relative to those caused by the drugs individually [1(3):85-6].

Albuterol Sulfate

Subchronic and chronic toxicity studies were performed in rats, dogs and monkeys dosed orally or by inhalation. In some animals, albuterol sulfate caused mild edema, myocardial necrosis and hypertrophy of left ventricular muscle fibers. These changes resolved after cessation of treatment. Albuterol produced dose-dependent increase in the incidence of mesovarial leiomyomas of the mesovarium in rats, which may have been strain-dependent. The effects of albuterol on fetal development were determined in mice, rats and rabbits. The frequency of albuterol induced malformations

was 10% in the mouse. Albuterol sulfate was not found to be mutagenic by standard tests [1(3):50-1].

Ipratropium Bromide

The acute, subchronic and chronic toxicity was studied in mice, rats, guinea pigs, rabbits, dogs and monkeys after intravenous, subcutaneous, inhalation and oral administration. The deaths that occurred were due to curariform muscular paralysis, but the lethal dose in rats and monkeys could not be determined. No evidence of toxic effects other than transient changes associated with the pharmacological action of the drug was seen in rats, dogs or monkeys given the drug chronically by inhalation. The anticholinergic toxicities seen in rats and dogs were dryness of the oral and nasal mucosa, mydriasis, inhibition of lacrimation, conjunctivitis sicca, coprostasis and tachycardia. Some impairment of liver function was seen at high doses including hepatocellular fatty changes and increases in serum transaminases and bilirubin. Standard tests for carcinogenicity, fertility and reproductive impairment, teratogenicity and mutagenicity were negative [1(3):64-5].

CLINICAL PHARMACOKINETICS (PK)

Albuterol Sulfate

The PK profile for albuterol after inhalation is similar to the profile following an oral dose since up to 90% of an inhaled dose may be swallowed. After an oral or inhaled dose, peak concentrations are achieved in 1-3 hours. The absolute bioavailability is in the range of[ ]%. The rate of absorption of an oral dose is decreased by food, but the extent of absorption is not effected. Albuterol is extensively distributed to tissues (V_d = 156 L) but penetrates the central nervous system minimally. It has a plasma elimination $t_{1/2}$ in the range of 4-7 hours. The pharmacologically active (-)R-enantiomer of albuterol is rapidly metabolized to the inactive sulfate and has a lower bioavailability than the inactive (+)S-enantiomer. Most of the absorbed dose is excreted in the urine [1(3):96].

Ipratropium Bromide

PK work on ipratropium after therapeutically effective doses has not been reported because the plasma concentrations are extremely low. Inhaled ipratropium appears in plasma within 2 minutes and peaks in 1-3 hours. Less than % of the dose reaches the systemic circulation and the absolute bioavailability is about %. Data on tissue distribution is from animals and showed the highest concentrations in the gastrointestinal tract, liver and kidneys, with much lower concentrations found in brain, lung and muscle. The plasma $t_{1/2}$ ranges from 1.5-4.0 hours. Following oral or inhaled doses, about 90% of the dose is excreted in the feces. The kidneys excrete only about 3% on the inhaled dose, although renal clearance is almost six times the glomerular filtration rate suggesting substantial active secretion. Absorbed ipratropium is metabolized to about eight inactive compounds and the major ones result from ester hydrolysis to yield the metabolite and [1(3):100].

Combination Solution

The PK profile of albuterol sulfate and urine recovery of ipratropium bromide, when simultaneously administered, was reported for the Dey combination solution (Study DL-031) and for the Boehringer Ingelheim metered dose inhaler (MDI), Combivent. The PK of ipratropium was not investigated for the Dey combination solution because the dose used would have provided plasma concentrations below the limits of detection.

Albuterol PK was determined in 15 healthy subjects in a two-period, double-blind, crossover design that compared one double-dose of the combination solution (6.0 mg albuterol sulfate, 1.0 mg ipratropium bromide) with one double-dose of the Dey albuterol sulfate inhalation solution (6.0 mg albuterol sulfate). Three of the subjects did not show measurable plasma levels of albuterol and excreted little or no albuterol and ipratropium in their urine. These findings suggest that these three subjects did not inhale either of the nebulized treatments [1(3):102-5]. Data from all 15 subjects were used in the following PK table.

N20-950 DL-031: MEAN ± SD PHARMACOKINETIC PARAMETERS FOR 15 SUBJECTS (13M/2F) [1(3):105]

Formulation	Active Drug	Dose (mg)	C_{Max} (ng/mL)	t_{Max} (hours)	$AUC_{0\text{-}24\ hrs}$ (ng*hr/mL)	Urine Excretion (% dose)
Combination Solution	albuterol sulfate	6.0	4.6 ± 2.9	0.78 ± 0.38	24.2 ± 14.5	8.4 ± 8.9
	ipratropium bromide	1.0				3.9 ± 5.1
Albuterol Solution	albuterol sulfate	6.0	4.9 ± 2.6	0.82 ± 0.33	26.6 ± 15.2	8.8 ± 7.3

Albuterol, in the combination solution, showed very slightly smaller mean PK parameters than it did delivered in the albuterol-only solution.

Combivent

A double-blind, three-period, crossover trial was used to study MDI's of ipratropium as Atrovent (42 mcg), albuterol (240 mcg) and both as Combivent (ipratropium 42 mcg, albuterol 240 mcg) in 12 male subjects. Plasma ipratropium bromide levels were below the limits of detection in 94% of the blood samples obtained. Following Combivent, a mean of 4.0 (± 3.6)% of the dose was excreted in the urine. Following Atrovent, a mean of 11.9 (± 7.9)% was recovered from the urine. This was interpreted as a significant decrease in the ipratropium availability of Combivent, hence, of coadministration with albuterol. The mean percent of the ipratropium dose excreted in the urine was similar with Combivent and with the Dey combination solution aerosol. The mean AUC's for albuterol from the inhalation solution aerosol and from Combivent were significantly different (Combivent = 140.1 ± 30; albuterol inhalation solution = 178.3 ± 7). The range of t_{Max} and the amounts of albuterol sulfate excreted in the urine were variable but were similar for Combivent and the albuterol inhalation solution [1(3):105-6]. The simultaneous coadministration of albuterol sulfate and ipratropium bromide decreased the systemic bioavailability of both compounds and the ipratropium component showed the greatest decrease.

DL-024 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 (COPD)

SUMMARY

The novel design of this trial was a 3-period, 6-week, crossover phase followed by a 6-week, parallel-group phase comparing four-times-daily self-administration of three aerosolized bronchodilators, albuterol, ipratropium and a combination of the two. The study enrolled 863 patients with mild-to-severe COPD who tended to be at the more severe end of the spectrum, mostly males and overwhelmingly of Caucasian ethnicity. Efficacy was shown by statistically significant improvement in trough to peak $FEV_{1.0}$ of the combination solution over both active controls during the eight hours after dosing in the crossover phase. The combination solution provided about a 30% greater change in this measure than both active controls in the crossover and in the parallel phases of the trial. The primary efficacy variable and most of the secondary variables in both the crossover and parallel phases showed that the combination solution had a faster onset, greater peak effect and longer duration of action than either of its components. Most of the secondary spirometric efficacy variables also demonstrated statistical superiority of the combination over both comparators. The six-minute walking distance test did not discriminate among the three treatments in either phase.

Safety was assessed by weekly adverse event reports during the twelve-week study. Respiratory and digestive system adverse events were slightly more common with the combination solution than either component and more frequently considered to be 'related' to the drug. Patients with lower baseline spirographic flows more frequently reported adverse events when treated with the combination solution than did patients with less severe flow obstruction. This was not as apparent with the other treatments suggesting a disease-severity-treatment interaction of the combination solution for adverse events. Deaths and serious adverse events were fairly evenly distributed among the three treatments. Early terminations due to adverse events were most common with the combination solution and least frequent with ipratropium. Laboratories and electrocardiograms done at the start and finish of the study were reported as adverse events and none were attributed to the combination solution. About one third of the randomized patients dropped out before the end of the study, most terminating in the first four weeks. Analysis of dropouts by last-treatment-taken and by treatment sequence within visits and phases did not reveal any disproportion among the three treatments.

Evidence of paradoxical bronchoconstriction was sought in adverse event reports, including those that might have misclassified this finding. Paradoxical bronchoconstriction was also assessed by examining $FEV_{1.0}$ declines from baseline after treatments that did and did not contain edetate disodium (ethylenediaminetetracetic acid = EDTA). Neither analysis yielded evidence implicating the combination solution with

this event. Secondarily, EDTA was not linked to evidence of paradoxical bronchoconstriction.

OBJECTIVES

The trial was designed to determine the efficacy of an inhalation solution combining albuterol and ipratropium, compared to solutions of albuterol sulfate alone, and ipratropium bromide alone. All treatments were administered 4 times a day to patients with COPD. Comparative efficacy was addressed during the 6-week, three-way crossover phase of the trial. Secondary objectives were to evaluate the safety of the combination solution compared to the individual components, and to evaluate various subsets for both efficacy and safety. These were addressed in the 6-week parallel-group phase of the study [23:175].

PROTOCOL

The trial was a randomized, double-blind, positive-control, crossover study conducted in 3 phases, with a lead-in phase; a crossover Phase 2 consisting of three, 2-week double-blind crossover periods (primary analysis); followed by a 6 week, double-blind, parallel-group Phase 3. The three active treatments (albuterol sulfate, ipratropium bromide, and the combination of the two) in the crossover design incorporated all six possible treatment sequences. Albuterol and ipratropium were used at the recommended dose of each, four times daily, in these respective active control arms. The combination-treatment arm used the same doses of each individual component and same QID dosing interval used in the active control groups. The study medication was supplied in double-blind packaging with a separate randomization for each group (block) of six subjects to ensure a relatively equal distribution of treatment sequences within sites.

A lead-in period (first phase) was used to assure compliance with concomitant medication restrictions. Immediately prior to baseline measurements on the first day of dosing, treatment-sequence assignments were randomly made. Subjects self-administered blinded study medication by inhalation four times each day by nebulizer, for two weeks each, for three treatment sequences. Up to two additional doses of blinded study medication were permitted each day, as necessary, to treat symptoms. Patients without access to their nebulizer, who required rescue medication, were allowed to self-administer albuterol by a metered dose inhaler supplied by the sponsor. At the end of each two-week treatment period, subjects returned to the study sites early in the morning for measurement of pre- and post-dose pulmonary function, and for overall assessment. Subjects who experienced an exacerbation during the crossover phase were temporarily withdrawn and allowed to re-enter at the start of the two-week period from which they withdrew after recovering. After the three double-blind, two-week treatment periods in the crossover phase, all subjects were assigned to a 6-week, double-blind extension corresponding to the final treatment to which they had been randomly assigned. At the end of 12 weeks the trial terminated [23:78-9, 175-6, 24:448, 455-6, 462]. The double-blind, crossover and parallel phases are shown in the table below.

N20-950 DL-024: STUDY MEDICATION ASSIGNMENT DURING EACH TWO-WEEK PERIOD [24:436]						
Sequence	Crossover (6 Weeks)			Parallel Extension (6 Weeks)		
	Days 1 to 14	Days 15 to 28	Days 29 to 42	Days 43 to 56	Days 57 to 70	Days 71 to 84
1	A	I	AI	AI	AI	AI
2	I	AI	A	A	A	A
3	AI	A	I	I	I	I
4	A	AI	I	I	I	I
5	I	A	AI	AI	AI	AI
6	AI	I	A	A	A	A
Key: A = albuterol I = ipratropium AI = albuterol & ipratropium			Sustained Single Treatment (8 Weeks)			

TREATMENT

The study medications were supplied in low-density polyethylene unit-dose vials containing a solution for inhalation from a standard nebulizer. Dosing was one vial four times each day, before meals and at bedtime, with the provision for up to two additional doses per day, if necessary [23:79]. Dey combination solution, Batch F451, was used in this clinical trial, in the human pharmacokinetic (PK) study, DL-031, and as a supportive stability batch. This formulation was the same as the to-be-marketed batch except that the former was not overwrapped. The batch history is provided in the table below [2:133, 3/8/99 EMail from Dr. Chong-Ho Kim].

N20-950 DL-024: BATCH HISTORY [2:133]						
Batch Code	Size (L)	Vial Size (mL)	Fill Volume (mL)	Mfr Date (mo/yr)	Overwrap	Purpose
IRN1		5	3	4/95	No	EDTA effect on albuterol degradation
IRN2		5	3	4/95	No	
IRN3		5	3	4/95	No	
C595		5	3	3/95	No	stability with and without EDTA
C596		5	3	3/95	No	
F451		3	3	1/96	No	clinical & support stability
E055		3	3	4/97	Yes	NDA stability batches
E056		3	3	4/97	Yes	
E057		3	3	4/97	Yes	

Each 3 mL vial from batch F451 contained 3.0 mg albuterol sulfate (2.5 mg albuterol base) and 0.5 mg ipratropium bromide monohydrate, as well as additional ingredients shown below [2:70].

N20-950 DL-024: COMPOSITION OF DEY COMBINATION SOLUTION, DUOVENT™ [2:70]		
Component	Amount/Vial	% of Solution
albuterol sulfate USP**	3 mg (2.5 mg of base)	0.083 (base)
ipratropium bromide monohydrate EP	mg	
sodium chloride USP	mg	
hydrochloric acid 1N	mL	
edetate disodium USP	mg	
purified water USP, q.s.	mL	
**3 mg albuterol sulfate = 2.5 mg albuterol base		

This inhalation solution was to be administered by nebulizer as a fixed combination of two bronchodilators and is indicated for the treatment of bronchospasm in COPD patients who required more than one bronchodilator [23:13, 24:448-50]. The reference products that were used as active controls contained albuterol sulfate (Lot 453) at 3.0 mg in 3 mL volume and ipratropium bromide monohydrate (Lot 452) at 0.5 mg in 3 mL volume [23:79, 176].

Rescue medication was allowed as up to two doses of the nebulizer solution or albuterol metered dose inhaler (MDI) provided by the sponsor for use when the nebulizer was not available [24:455-6, 462]. Theophylline preparations were allowed during the lead-in phase and restricted during crossover and parallel group phases. Oral and inhaled steroid use was permitted throughout the trial, if it remained constant. The topical use of cromolyn was permitted to treat rhinitis and conjunctivitis. Patients taking non-bronchodilator medication on a chronic basis were allowed to continue that medication unless otherwise directed by the investigator and this included beta-blocking agents [24:472].

PATIENTS

The total planned enrollment was 660, 110 for each of the six treatment sequences in the first crossover phase of the study [24:450]. Generally, mild to moderately severe COPD patients with at least some past history of smoking who required inhaled bronchodilators, but could be maintained on them alone were the subjects of this study.

Inclusion Criteria

All of the following conditions must have been met [24:449].

1. at least 40 years of age
2. diagnosis of chronic obstructive pulmonary disease according to the criteria of the American Thoracic Society, with an $FEV_{1.0}$ of 25-65% of predicted normal value at the screening visit
3. $FEV_{1.0}$ at baseline visit must be within 15% (absolute) of $FEV_{1.0}$ at the lead-in visit
4. ability to safely complete a 6-minute walk; at the investigator's discretion, pulse oximetry may be used to assure that O_2 saturation does not fall below 88% in subjects who may be at risk
5. cigarette smoking history of at least ten pack-years

6. require the regular use of one or more bronchodilators for the prior 3 months
7. ability to refrain from theophylline beginning up to two days prior to the lead-in and baseline visits, and refrain completely after randomization
8. ability to refrain from salmeterol and oral β-agonists beginning up to 24 hours prior to the lead-in and baseline visits, and refrain completely after randomization
9. ability to conform to the requirements of this protocol, and willingness to grant written informed consent to participate in this study

Exclusion Criteria

Subjects were to be excluded from the trial if any of the following conditions were met [24:449-50].

1. anthracosis or silicosis as a primary diagnosis
2. other pulmonary parenchymal diseases not attributable to COPD (a prior chest radiograph compatible with this diagnosis is sufficient)
3. history of asthma, allergic rhinitis, or atopy (the intention is to exclude these as clinically significant components of the subject's airway disease)
4. clinically significant, obstructive urinary disease
5. history of narrow angle glaucoma
6. unstable angina pectoris or myocardial infarction within the past 6 months
7. known hypersensitivity to any of the component products of the study medications
8. pregnancy, lactation or females of child-bearing potential who are not maintaining adequate contraception during the trial; (Female patients must be post-menopausal, surgically sterile, or use an acceptable form of contraception throughout their participation in the study. Acceptable forms of birth control include hormonal agents (i.e., oral contraceptives, Depo-Provera®, or Norplant®), barrier contraception used in conjunction with spermicidal jellies, or abstinence.)
9. hospitalization for pulmonary exacerbation during the two months immediately preceding the trial
10. previous (within 1 year) or current drug abuse, including alcohol abuse
11. require theophylline use during the trial (after randomization)
12. polycythemia, requirement for home O_2 use; cor pulmonale by ECG criteria; or other complication of hypoxia
13. administration of any investigational test article within 30 days preceding the first dose of study medication; a "test article" is defined as any material (placebo, drug or biologic) dispensed under the provisions of a clinical protocol
14. any condition which, in the opinion of the investigator or sponsor, would place the individual at undue risk, or potentially compromise the results or interpretation of the study results

PARAMETERS

The primary efficacy variable was the change from pre-dose (trough) baseline to peak $FEV_{1.0}$ measured within eight hours after dosing on study days 14, 28 and 42 following two weeks on each of the three study drugs during the crossover phase. Analysis was performed on all subjects who completed at least one post-dose evaluation

of pulmonary function on both the combination solution and at least one of the active controls. The model was ANOVA applied to a simultaneous inference problem in which two null hypotheses had to be rejected in order to show efficacy; i.e., that the combination formulation was better than both of the active controls. Secondary analyses included the primary variable during the parallel phase, $FEV_{1.0}AUC$ for the time periods of 0-4, 0-6 and 0-8 hours after dosing, time to peak response, time to 15% improvement over baseline and duration of a 15% response over baseline during both crossover and parallel phases. Additional variables included the distance covered during the 6-minute walk and other spirogram-derived variables [23:175, 215-7].

Safety variables included history, physical examination, AE's, clinical laboratory testing and 12-lead ECG's. AE's were determined weekly, at each every-two-week clinic visit and by telephone contact approximately one week after each visit [23:208-9]. Laboratory studies included hematology, chemistry, urinalysis, serum theophylline levels and serum pregnancy testing in women of child-bearing potential. The various hematology, chemistry and urinalysis parameters were not completely specified in the protocol but were discernible from the tabular listings:

N20-950 DL-024: CLINICAL TEST COMPONENT IDENTIFICATION [23:131, 24:417-34, 465, 468-71]	
Laboratory Test	**Components**
Chemistry	albumin, alkaline phosphatase, ALT, AST, BUN, Ca, CO_2, Cl, cholesterol, creatinine, GTT, globulin, glucose, PO_4, K, Na, total bilirubin, total protein, triglycerides, uric acid
Hematology	hematocrit, hemoglobin, red cell count and indices (MCV, MCH, MCHC), white cell count, differential, platelets
Urinalysis	pH, specific gravity
Other	serum theophylline, serum HCG (pregnancy)

Collection frequency and timing of these various safety and efficacy variables are shown in the flow chart below.

N20-950 DL-024: STUDY TIME AND EVENTS FLOW CHART [23:196, 24:436]									
Description >>	**Screen**	**Run-In**	**Crossover**				**Parallel Extension**		
Study Day >>	**-28**	**-7 (±2)**	**1**	**14**	**28**	**42**	**56**	**70**	**84**
Medical History & Informed Consent	X								
Physical Examination	X								X
Interview & Pulmonary Examination		X*	X*	X	X	X	X	X	X
Spirometry	X	X	X	X	X	X	X	X	X
Clinical Laboratories & ECG	X								X
Serum Pregnancy Test	X**								X**
6-Minute Walk		X		X	X	X	X	X	X
Serum Theophylline Level			X	X	X	X			X

* used to update baseline medical history
** women of child-bearing potential, only

Like the components of the various laboratory tests, the analytic plan for ECG's was not completely specified in the protocol. ECG's were sampled during screening and at the last visit, were not recorded on the case report forms and clinically significant changes were reported as AE's [1(3):194].

DEMOGRAPHICS

This was largely a study of Caucasians (94%), most of who were males (62%). The shaded cells in the table below facilitate comparisons of gender and race between different patient groups in the trial. The further break down of these two demographic categories by treatment sequence for 'all randomized', 'crossover', and 'parallel' categories of the study failed to show any systematic disproportion [24:260-2]

N20-950 DL-024: GENDER AND RACIAL DEMOGRAPHICS [24:260-2]							
		All Randomized (N = 863)		Crossover (N = 663)		Parallel (N = 610)	
Category	Sub-Category	n	%	n	%	n	%
GENDER	Female	330	38.2	248	37.4	229	37.5
	Male	533	61.8	415	62.6	381	62.5
RACE	Native American	2	0.2	1	0.2	1	0.2
	Asian	2	0.2	2	0.3	2	0.3
	Black	35	4.1	29	4.4	28	4.6
	Hispanic	5	0.6	4	0.6	4	0.7
	White	818	94.8	626	94.4	574	94.1
	Egyptian	1	0.1	1	0.2	1	0.2

The average participant in this study was 66 years of age, was 5 feet 7 inches tall and weighed 170 pounds. Cells containing mean values for these demographic parameters are shaded in the table below to aid in comparison among patient groups. Further break down of these three demographic categories by treatment sequence showed similar values for all sequences [24:260-2].

N20-950 DL-024: AGE, HEIGHT AND WEIGHT DEMOGRAPHICS [24:260-2]				
Category	Sub-Category	All Randomized	Crossover	Parallel
AGE (years)	mean	66.3	66.3	66.0
	median	67.0	67.0	67.0
	SD	9.3	9.0	9.1
	range	40-93	40-93	40-91
	n (count)	863	663	610
HEIGHT (cm)	mean	170.1	170.4	170.4
	median	170.0	170.0	170.0
	SD	10.0	9.9	10.0
	range	135–207	135-198	135-198
	n (count)	863	663	610
WEIGHT (kg)	mean	76.4	77.0	76.8
	median	74.9	74.9	74.5
	SD	18.9	18.8	18.9

N20-950 DL-024: AGE, HEIGHT AND WEIGHT DEMOGRAPHICS [24:260-2]				
Category	Sub-Category	All Randomized	Crossover	Parallel
	range	22.2–154	22.2-152	22.2-152
	n (count)	863	663	610

Baseline spirographic variables are shown in the table below with shaded cells containing mean values. The average individual suffered moderate-to-severe COPD and had actual $FEV_{1.0}$ values of about 1.16 Liters and ratios of $FEV_{1.0}$/FVC of less than 50%. Further break down by treatment sequence showed similar values of spirographic variables for each [24:263-5].

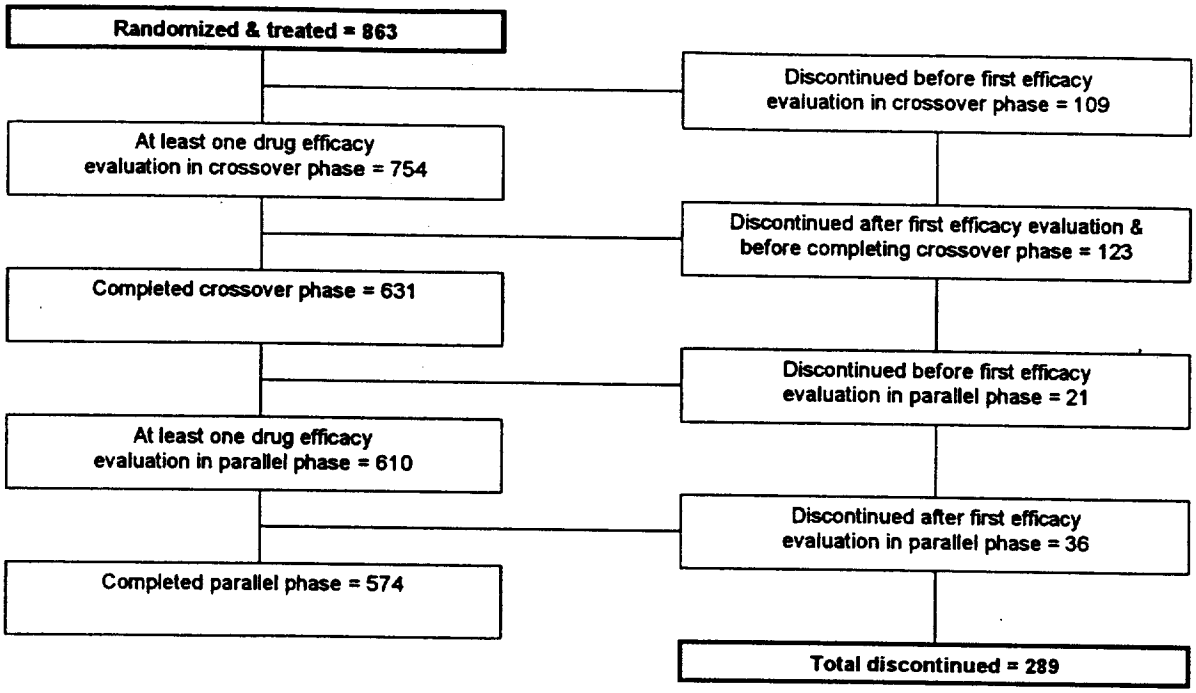
N20-950 DL-024: BASELINE PULMONARY FUNCTION [24:263-5]				
Category	Sub-Category	All Randomized	Crossover	Parallel
Baseline (day 1) $FEV_{1.0}$ (Liters)	mean	1.145	1.166	1.176
	median	1.030	1.050	1.070
	SD	0.473	0.474	0.480
	range	0.40-3.33	0.40-3.33	0.40-3.33
	n (count)	863	663	610
Baseline (day 1) FVC (Liters)	mean	2.412	2.440	2.448
	median	2.310	2.330	2.330
	SD	0.828	0.831	0.834
	range	0.66-5.77	0.66-5.77	0.66-5.77
	n (count)	863	663	610
Baseline (day 1) $FEV_{1.0}$/FVC (%)	mean	48.1	48.6	48.8
	median	47.0	47.0	47.0
	SD	12.7	13.0	13.1
	range	19-90	19-90	19-90
	n (count)	863	663	610

The three treatments were compared over a variety of baseline demographic and spirographic variables by randomized treatment sequence and by different phases of the study. These all failed to indicate disproportion of these variables among treatments that might have occurred had randomization failed or had dropouts biased the distribution of patients. The only possible criticism is the overwhelming number of Caucasian patients in the trial, which might limit extrapolation of the results. This ethnic bias has been a feature of many other clinical studies submitted to this division.

EFFICACY

Disposition of Subjects

After the lead-in period, a total of 863 patients at 60 sites were randomized and began treatment. For a variety of reasons, 289 patients withdrew prematurely and the remaining 574 completed the entire 12-week study [23:224]. A chronology and enumeration of the withdrawals is shown below [24:437].



Patients dropping out and remaining at each visit were presented by treatment sequence in the table below. The majority of the dropouts occurred within the first four weeks of the study and there was an even distribution among all six sequences at virtually all visits [27:1425].

N20-950 DL-024: PATIENT COMPLETION SUMMARY [27:1425]							
Treatment Sequence*	Lead-In	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84
1	144	129	116	112	108	105	102
2	145	128	118	109	106	101	98
3	144	119	107	102	102	99	96
4	147	131	115	104	100	93	90
5	139	122	104	99	95	93	92
6	144	125	113	106	100	99	98
Completed	863	754	673	632	611	590	576
Dropouts/Visit	0	109	81	41	21	21	14
Total Dropouts	0	109	190	231	252	273	287

*TREATMENT SEQUENCES

1 =	A	I	AI	AI	AI	AI
2 =	I	AI	A	A	A	A
3 =	AI	A	I	I	I	I
4 =	A	AI	I	I	I	I
5 =	I	A	AI	AI	AI	AI
6 =	AI	I	A	A	A	A

This table differs very slightly from the 'organization chart' display presented immediately above it. The 'chart' lists 631 patients having completed the crossover phase and the table indicates that the number was 632. Similarly, the chart totals 574

patients completing the entire 12-week trial and the table gives the number as 576. These are categorical counting discrepancies probably based on differing boundary conditions and are not of sufficient magnitude to effect this analysis [24:437, 27:1425].

The following table summarizes the completion status of all randomized patients, listed by last treatment taken prior to termination. Only about two thirds of the patients completed the entire study, but they seem to have been evenly distributed over last-treatment-taken by several 'reasons for termination.' Though six deaths are reported here, seven are referenced elsewhere [24:259, 335].

N20-950 DL-024: PATIENT STATUS BY LAST TREATMENT TAKEN BEFORE TERMINATION AS COUNT (% RANDOMIZED) [24:259]				
	Last Treatment Taken Before Termination			All Treatment Groups
Patient Status	Albuterol	Ipratropium	Combination	
patients randomized	291 (100)	277 (100)	295 (100)	863 (100)
patients completing normally	195 (67.0)	184 (66.4)	195 (66.1)	574 (66.5)
patients discontinued prematurely	96 (33.0)	93 (33.6)	100 (33.9)	289 (33.5)
adverse event	62 (21.3)	53 (19.1)	66 (22.3)	181 (20.9)
lost to follow-up	1 (0.3)	2 (0.7)	0 (0.0)	3 (0.3)
terminated by sponsor	2 (0.6)	1 (0.3)	2 (0.6)	5 (0.5)
death	1 (0.3)	2 (0.7)	3 (1.0)	6 (0.6)
patient withdrew consent	19 (6.5)	18 (6.4)	13 (4.4)	50 (5.7)
other	11 (3.7)	17 (6.1)	16 (5.4)	44 (5.0)

In summary, patient dropouts throughout the trial appear to be most frequent early in the trial, diminishing with successive visits. The dropouts appear to be fairly evenly divided among the six treatment sequences and among the three treatments last taken before termination. From these observations, there is no reason to believe that randomization was compromised by bias resulting from prematurely discontinuing patients. Dropouts due to AE's will be reported in the 'SAFETY' portion of this review.

Efficacy in the crossover phase was analyzed for all subjects and visits that met the prospective inclusion criteria of at least one post-dose assessment of $FEV_{1.0}$ after 14 days on both the combination solution and at least one other active control drug. Therefore, a patient who completed the albuterol arm and the ipratropium arm, but not the combination arm, would have been excluded from both portions of the efficacy analysis. Moreover, the 216 patients excluded from one of the portions of the efficacy analysis were not necessarily the 216 patients excluded from the other portion. A total of 663 patients contributed to the 647 comparisons in each portion of the primary efficacy analysis (AI vs., A and AI vs. I). There were 753 patients included in the secondary efficacy analyses of $FEV_{1.0}$ in the crossover phase. This greater number than was included in the primary analysis was due to the less stringent inclusion requirements for secondary analyses; i.e., patients must have had only one of three post-dose evaluations. Subject exclusions from efficacy analyses are shown in the following table [Telecon 4/30/99, 23:225-6, 24:266].

N20-950 DL-024: PATIENTS EXCLUDED FROM EFFICACY ANALYSES [24:266]										
Treatment Sequence*	At Each Visit (by Day)						From Primary		From Secondary	
	14	28	42	56	70	84	Al vs. A	Al vs. I	XOver	Parallel
1	16	28	32	36	40	42	32	32	16	36
2	17	27	36	41	44	48	36	27	17	39
3	25	37	42	42	45	49	37	42	25	42
4	16	32	43	48	54	57	32	43	16	48
5	17	35	41	44	46	47	41	41	17	44
6	19	31	38	44	45	46	38	31	19	44
Total	110	190	232	255	274	289	216	216	110	253

*TREATMENT SEQUENCES

1 =	A	I	Al	Al	Al	Al
2 =	I	Al	A	A	A	A
3 =	Al	A	I	I	I	I
4 =	A	Al	I	I	I	I
5 =	I	A	Al	Al	Al	Al
6 =	Al	I	A	A	A	A

No obvious pattern emerged from this tabular display of patients excluded from analysis by visit and treatment sequence to suggest any systematic bias.

Crossover Phase

The table below is a summary of the results of all statistically significant measures of efficacy during the crossover phase of the trial that showed the combination solution was superior to both of its individual components (active controls). This was the case for the primary variable, 'change in $FEV_{1.0}$ trough to peak', as well as for most of the secondary measures [23:98].

N20-950 DL-024: EFFICACY MEASURES IN THE CROSSOVER PHASE SHOWING STATISTICALLY SIGNIFICANT SUPERIORITY OF THE COMBINATION SOLUTION OVER BOTH ALBUTEROL AND IPRATROPIUM [23:98]						
Parameter	Al vs. A			Al vs. I		
	n	Al Mean	A Mean	n	Al Mean	I Mean
PRIMARY VARIABLE						
change in $FEV_{1.0}$ trough to peak (Liters)	647	0.387	0.313	647	0.387	0.282
SECONDARY VARIABLES						
$FEV_{1.0}$ AUC 0-4 hours (Liter-hours)	647	1.102	0.827	647	1.106	0.734
$FEV_{1.0}$ AUC 0-6 hours (Liter-hours)	647	1.370	1.029	647	1.376	0.984
$FEV_{1.0}$ AUC 0-8 hours (Liter-hours)	647	1.495	1.147	647	1.503	1.137
time to 15% response in $FEV_{1.0}$ (hours)	459	0.36	0.48	420	0.38	0.81
change in FVC trough to peak (Liters)	648	0.764	0.673	648	0.766	0.611
FVC AUC 0-4 hours (Liter-hours)	648	1.948	1.568	648	1.962	1.368
FVC AUC 0-6 hours (Liter-hours)	648	2.409	1.949	648	2.431	1.809
FVC AUC 0-8 hours (Liter-hours)	648	2.635	2.162	648	2.659	2.084
duration of 15% response in FVC (hours)	295	3.97	3.54	243	3.95	3.53

The combination solution provided a 24% increase in the primary efficacy measure compared with albuterol alone and a 37% increase compared with ipratropium alone [23:99]. The 'time to 15% response in $FEV_{1.0}$' showed that bronchodilation occurred more rapidly with the combination solution than with either component and that ipratropium demonstrated the slowest onset of action. The conceptual interpretation of the $FEV_{1.0}$ AUC measures added no new information to these other measures. The various FVC outcomes were largely redundant except for the 'duration of 15% response in FVC' which showed a 12% greater duration of action of the combination solution compared with both active controls.

A graphical representation of the mean change in $FEV_{1.0}$ at various times up to eight hours after dosing (not included) shows similar rising rates (onsets of action) and duration of action for all three. Peak effects on this measure of the three treatments were ordered as follows: combination > albuterol > ipratropium [23:100].

The secondary efficacy variables that failed to achieve statistical significance showing superiority of the combination solution to either or both components are shown in the table below.

N20-950 DL-024: SECONDARY EFFICACY MEASURES IN THE CROSSOVER PHASE WHICH FAILED TO SHOW STATISTICALLY SIGNIFICANT SUPERIORITY OF THE COMBINATION SOLUTION TO EITHER OR BOTH ALBUTEROL AND IPRATROPIUM [23:98]

Parameter	Al vs. A			Al vs. I		
	n	Al Mean	A Mean	n	Al Mean	I Mean
time to peak $FEV_{1.0}$ (hours)	634	1.54	1.45	625	1.54	2.07
duration of 15% response in $FEV_{1.0}$ (hours)	361	4.29	3.67	297	4.34	4.08
time to peak FVC (hours)	627	1.72	1.65	621	1.74	2.24
time to 15% response in FVC (hours)	432	0.49	0.55	393	0.49	0.85
distance for 6-minute walk (yards)	631	341.5	341.3	638	342.4	340.5

A longer duration of action of the combination solution is suggested by the mean values for 'duration of 15% response in $FEV_{1.0}$'. The 6-minute walk failed to show any distance/speed difference between any of the active treatments and all mean velocities were less than 2 miles/hour.

Parallel Phase

By definition, all efficacy measures for the parallel phase were secondary. Those that showed statistically significant differences on Day 84, after an additional six weeks of treatment, between the combination solution and both of its components (active controls) are shown in the table below [23:102, 24:468].

N20-950 DL-024: EFFICACY MEASURES IN THE PARALLEL PHASE SHOWING STATISTICALLY SIGNIFICANT SUPERIORITY OF THE COMBINATION SOLUTION OVER BOTH ALBUTEROL AND IPRATROPIUM [23:102]

Parameter	Albuterol (A)		Ipratropium (I)		Combination (AI)	
	n	Mean	n	Mean	n	Mean
change in $FEV_{1.0}$ trough to peak (Liters)	206	0.275	201	0.273	203	0.353

N20-950 DL-024: EFFICACY MEASURES IN THE PARALLEL PHASE SHOWING STATISTICALLY SIGNIFICANT SUPERIORITY OF THE COMBINATION SOLUTION OVER BOTH ALBUTEROL AND IPRATROPIUM [23:102]						
Parameter	Albuterol (A)		Ipratropium (I)		Combination (AI)	
	n	Mean	n	Mean	n	Mean
$FEV_{1.0}$ AUC 0-4 hours (Liter-hours)	206	0.735	201	0.702	203	0.988
$FEV_{1.0}$ AUC 0-6 hours (Liter-hours)	206	0.896	201	0.934	203	1.213
$FEV_{1.0}$ AUC 0-8 hours (Liter-hours)	206	0.986	201	1.069	203	1.323
time to 15% response in $FEV_{1.0}$ (hours)	184	0.60	165	0.70	196	0.40
change in FVC trough to peak (Liters)	206	0.562	201	0.547	203	0.686
FVC AUC 0-4 hours (Liter-hours)	206	1.236	201	1.205	203	1.798
FVC AUC 0-6 hours (Liter-hours)	206	1.514	201	1.608	203	2.185
FVC AUC 0-8 hours (Liter-hours)	206	1.670	201	1.867	203	2.380
time to 15% response in FVC (hours)	177	0.70	163	1.00	190	0.50

These data are a recapitulation of the findings of the crossover phase. The combination solution provided a 29% greater 'change in $FEV_{1.0}$ trough to peak' compared with ipratropium and a 28% improvement compared with albuterol. The more rapid onset of action was shown by the 'time to 15% response in $FEV_{1.0}$' and in 'time to 15% response in FVC'. The 6-minute walk again did not discriminate between treatments and actually showed a slightly slower mean distance and speed for the combination solution (354 yards) than for either component (albuterol = 361 yards, ipratropium = 362 yards). All mean walking velocities were about 2 miles/hour and were slightly improved for all treatments in the parallel phase, compared with the crossover phase [23:102].

Changes in baseline pulmonary function and responsiveness to active treatments over time were both presented in tabular form. The trough $FEV_{1.0}$, over the eight weeks of the same and final treatment (visits on days 28 to 84), showed mean changes of less than 40 mL for all treatments. A further breakdown by sequence did not suggest any large systematic effect associated with any treatment [24:297-8]. The mean peak to trough change in $FEV_{1.0}$ at each visit after the first showed a slight decline in response for each of the three treatments, but the magnitude of this declining mean change was, in most cases, less than 50 mL [24:271-2]. If even a small degree of tachyphylaxis was present, it was similar for all treatments.

By the primary efficacy variable and by most of the secondary variables, the crossover and parallel phases both showed that the combination solution had a faster onset, greater peak effect and longer duration of action than either of its components. Whether these findings for the combination solution could have been approximated by doubling the dose of either active component is an unanswered but provocative question.

SAFETY

Deaths

Seven patient deaths occurred during the course of this trial and are shown in the table below. Except for patient #104003, whose demise was considered as 'possibly related' by the clinical investigator, the remaining six were considered to be 'unrelated'

to treatment [24:335]. Examination of the case report forms (CRF's) and tabular summary of patient narratives were not as informative as the table below [29:2297-301, 46:829-53, 51:2373-97, 52:2750-74, 2899-923, 53:3426-50, 56:4462-86, 4512-36].

N20-950 DL-024: DEATHS [24:335]

Site	Patient	Treatment Group	AE Terms		Dates		
			Preferred	Verbatim	1st Rx	Last Rx	Death
02	082003	I	sudden death	sudden death	7/16/96	8/27/96	9/17/96
11	076003	AI	apnea, coma	respiratory arrest, coma	6/10/96	7/17/96	7/29/96
20	139005	I	apnea	respiratory arrest	9/25/96	9/25/96	9/25/96
34	104003	AI	heart arrest	possible CP* arrest	9/16/96	9/16/96	9/22/96
35	026004	A	CVA*	CVA*	4/10/96	4/21/96	4/26/96
35	062004	AI	heart arrest	cardiac/respiratory arrest	6/1/96	6/11/96	6/13/96
61	140005	I	death	killed in MVA*	10/25/96	11/22/96	11/23/96

* CP = cardiopulmonary CVA = cerebral vascular accident MVA = motor vehicle accident

Full patient narratives were presented for all deaths, early terminations due to AE's and SAE's, whether or not they resulted in premature discontinuation. The deaths were extracted and further summarized below [29:2312, 2329-30, 2334, 2336, 2342, 2355].

082003 This 78 year old Caucasian male died suddenly 12 days after normal and uneventful termination of the study immediately after an altercation with a neighbor. The last medication taken had been ipratropium. His past medical history included mitral regurgitation, aortic stenosis, supraventricular tachycardia, coronary artery disease, hypertension, Kaposi's sarcoma, and two bullectomies.

076003 The patient was a 71 year old Caucasian male who suffered a respiratory arrest with coma 81 days after study randomization. The last medication taken was the combination solution after 52 days of treatment with it. He became dyspneic, diaphoretic and unresponsive at home. He was transported to the hospital with full ventilatory support and arrived in shock, acidemia, with disseminated intravascular coagulation and non-oliguric renal failure from acute tubular necrosis. He succumbed while on 'Do Not Resuscitate' status.

139005 This 71 year old Caucasian male died after a respiratory arrest the day of study randomization, the first day on ipratropium. He was found apneic by his spouse, was transported to a local hospital where he arrived pulseless, in cardiac asystole and apneic. Death was pronounced one hour after arrival in the emergency room. COPD had been diagnosed for 21 years and he had no other significant medical history.

104003 This 74 year old Caucasian male died suddenly 52 days after randomization and after 20 days on the combination solution. He initially reported difficulty breathing and his pre-dose $FEV_{1.0}$ was found to be 66% of the pre-dose baseline value. On the day of his demise, he awakened with chest pain and dyspnea. He lost consciousness and was transported to a local hospital where resuscitative efforts were unsuccessful. Exactly why this was deemed to be 'possibly related' to the study drug is not apparent.

026004 The patient was a 76 year old Caucasian female who died suddenly of a cerebrovascular accident (CVA) 17 days after randomization and after taking albuterol. On the second day of treatment she reported tremors, dry mouth and heart pounding. Eleven days later she suffered an extensive bilateral CVA confirmed by computerized tomographic scan. The Doppler showed total occlusion of the right internal carotid artery and moderate disease of the left. Her past history included coronary artery disease, atrial fibrillation, hypertension and borderline diabetes mellitus.

062004 The patient was a 64 year old Caucasian female who had a cardiopulmonary arrest and died 41 days after randomization and after taking the combination solution. After announcing to her family that she was having breathing difficulty, she began a nebulizer treatment and lost consciousness. She was resuscitated but later found to have anoxic encephalopathy and life support was discontinued.

140005 A 50 year old Caucasian male died as a result of injuries sustained in a motor vehicle accident. His status as a possible vehicle operator was not reported. His past history included ischemic heart disease.

These death narratives included more detailed information than was to be found in the CRF's or anywhere else in this submission. This may have arisen from immediate local follow-up of these events but also raises the possibility of additional information sources that we failed to identify or to which we did not have access.

Adverse Events (AE's)

The following table lists AE's by treatment group and COSTART term where the combination solution was associated with the highest percentage of AE's and where the AE frequency was $\geq$ 1% of the total patients in one or more treatment groups [23:121, 24:382-3].

N20-950 DL-024: ADVERSE EXPERIENCES OCCURRING IN $\geq$ 1% OF $\geq$ 1 TREATMENT GROUP(S) AND WHERE THE COMBINATION TREATMENT SHOWED THE HIGHEST PERCENTAGE [23:121, 24:378-80, 382-3]			
Body System COSTART Term	Albuterol n (%)	Ipratropium n (%)	Combination Solution n (%)
Number of Patients	761	754	765

N20-950 DL-024: ADVERSE EXPERIENCES OCCURRING IN ≥ 1% OF ≥ 1 TREATMENT GROUP(S) AND WHERE THE COMBINATION TREATMENT SHOWED THE HIGHEST PERCENTAGE [23:121, 24:378-80, 382-3]			
Body System COSTART Term	Albuterol n (%)	Ipratropium n (%)	Combination Solution n (%)
N (%) Patients with AE	327 (43.0)	329 (43.6)	367 (48.0)
Body As A Whole			
pain	8 (1.1)	4 (0.5)	10 (1.3)
pain chest	11 (1.4)	14 (1.9)	20 (2.6)
Digestive			
diarrhea	5 (0.7)	9 (1.2)	14 (1.8)
dyspepsia	7 (0.9)	8 (1.1)	10 (1.3)
nausea	7 (0.9)	6 (0.8)	11 (1.4)
Musculo-skeletal			
cramps leg	8 (1.1)	6 (0.8)	11 (1.4)
Nervous			
dizziness	12 (1.6)	15 (2.0)	15 (2.0)
Respiratory			
bronchitis	11 (1.4)	13 (1.7)	13 (1.7)
cough increased	28 (3.7)	39 (5.2)	40 (5.2)
lung disease	36 (4.7)	34 (4.5)	49 (6.4)
pharyngitis	27 (3.5)	27 (3.6)	34 (4.4)
pneumonia	7 (0.9)	8 (1.1)	10 (1.3)
voice alteration	12 (1.6)	12 (1.6)	12 (1.6)
Urogenital			
infection urinary tract	3 (0.4)	9 (1.2)	12 (1.6)
Shaded cells are COSTART terms also considered to be 'related' and most frequently so for the combination solution.			

The total numbers of patients with any AE's were similar for the two component treatments and somewhat higher (~5%) for the combination solution treatment group. Respiratory and Digestive AE's were the most common in the table above. A plausible mechanism to explain the more frequent AE's for the combination solution among these two body systems is not immediately apparent.

A review of the tabular summary of 'Related Treatment Emergent Adverse Events By Study Drug' suggested that raters considered 'pain chest,' 'diarrhea,' 'dyspepsia,' 'nausea,' 'cramps leg,' 'dizziness,' 'bronchitis,' 'pharyngitis' and 'pneumonia' to be more frequently related to the combination solution than to either component, but the margins were small [24:378-80, 469-70, 480]. The COSTART terms considered to be more frequently 'related' are shaded in the table above. According to the protocol, AE raters consisted of sponsor's clinical monitors or the Drug Safety Committee, but did not include the clinical investigators [23:209]. Verification of this was sought from the sponsor and this revealed that the practice of relatedness attribution did not follow the protocol. In practice, the clinical investigator judged causality and severity and recorded these on the CRF. SAE's were a special case where the monitor reviewed the

investigator's assessment of severity and causality was assigned by the Data Safety Committee. Dr. Lindberg of Dey Laboratories provided assurance that in no case was the severity assigned by the clinical investigator rendered less related by the monitor or the committee [Telecon 4/30/99, Memo 4/30/99].

SPECIAL POPULATIONS

Gender

Females reported a greater number of AE's compared with males but did so for each of the three treatments. This effect was postulated to be a consequence of the relatively greater dose for body size in females [23:143].

Age

There was no overall pattern of treatment-emergent AE's with age and treatment, but there are a few caveats. There was a slight trend toward a greater number of AE's overall and for the 'Cardiovascular' body system for albuterol and for the combination solution. A greater number of patients over age 65 years reported AE's in the 'Digestive' body system with ipratropium and the combination solution. These associations were not particularly strong [23:144-5].

Disease Severity

There were 384 of 863 patients who received both albuterol sulfate and ipratropium bromide by prescription prior to starting this study. These patients had a baseline $FEV_{1.0}$ of 1.07 L compared with 1.20 L for the remaining patients. This subset of patients with more severe COPD reported AE frequencies that were similar to the overall AE frequencies by treatment [23:147-8].

N20-950 DL-024: PERCENT OF PATIENTS REPORTING ONE OR MORE ADVERSE EVENTS, BY DISEASE SEVERITY [23:121, 147-8]

	Albuterol Sulfate (n = 761)	Ipratropium Bromide (n = 754)	Combination Solution (n = 765)
All Patients	43.0	43.6	48.0
More Severe COPD	42.8	44.1	50.9
Less Severe COPD (estimated)	43.2	43.2	45.7

The AE frequency of the 'more severe COPD' group is a subset of the overall AE frequency, by treatment. This fact allows the estimation of the AE frequency for the 'less severe COPD' group, also by treatment, and shows a discrepancy toward a greater number of 'more severe COPD' patients than 'less severe COPD' patients reporting AE's with the combination solution than with the other two treatments. From these data, there appears to be a disease-severity-treatment interaction. However, the data displays submitted do not show the nature of the AE's reported by patients with more or less severe COPD.

Hepatic or Renal Insufficiency

The combination solution has not been studied in patients with hepatic or with renal insufficiency [23:149].

Serious Adverse Events (SAE's)

A total of 76 patients experienced 82 SAE's by tabular summary, though these numbers are slightly inconsistent between the narrative and tabular presentations. There were approximately the same number in each treatment group and the majority were considered to be 'unrelated' to the study medication [23:128, 24:356-60, 381].

N20-950 DL-024: SERIOUS ADVERSE EVENTS [23:128]			
Study Drug	Patients With SAE's		
	Related	Unrelated	Total
Combination Solution	4	23	27
Albuterol	5	21	26
Ipratropium	2	21	23
TOTALS	11	65	76

The majority of these were attributed to the respiratory system, but eight were sudden and considered, at least in part, to have a cardiac etiology. These included the following categories: 'myocardial infarction,' 'sudden death,' 'blockage of coronary artery' and 'cardiopulmonary arrest.' The treatment groups were equally represented among these eight, three occurring with the combination treatment solution, three with albuterol and two with ipratropium [23:128, 24:356-60].

Discontinuations Due To Adverse Events

There were 187 patients who discontinued due to an AE in this study six (*sic*) of whom were deaths. Among the total number of patients discontinuing prematurely, the three treatments were represented in the following order: combination solution (74), albuterol (65) and ipratropium (48). 'Related' AE's were slightly more frequent in the combination solution group (34) than in the albuterol (26) or ipratropium (25) arms [23:129]. The patient narratives did not reveal any commonality within treatments for this outcome and spot checks of the CRF's showed so little relevant clinical information that they were not exhaustively reviewed [29:2297-2367]. The need for further clarification of the information sources used to construct patient narratives was addressed earlier.

Clinical Laboratory & ECG Evaluations

The study design did not permit attribution of hematology, chemistry or urinalysis laboratory changes to treatment groups because the labs were collected at baseline and on Day 84, the last day of the parallel phase. However, no laboratory abnormalities were reported as AE's. The sponsor cited no early discontinuations due to laboratory abnormalities, but early discontinuations would be impossible given the two collection times, one before the study started and one after it terminated [23:131, 24:436].

Electrocardiograms were similarly performed only at the start and end of the study and none were reported as AE's associated with the combination solution [1(3):194, 23:141].

Vital Signs & Weight

These were not recorded on the CRF's and I can find no specification in the protocol for if, or when, they were to be determined. However, the sponsor reports that clinically significant changes in these safety parameters were to be recorded as AE's, that 'this activity was verified with monitoring' and that no AE's due to changes in weight or vital signs were found in the combination solution group [23:142].

Rescue Medication Use

Up to two extra doses of the blinded nebulization aerosol could be administered daily for symptomatic relief, if required. In the event that the symptomatic patient did not have access to the nebulizer, an albuterol MDI was distributed for use as needed [23:79, 176, 24:455, 462]. Neither of these occasions of extra medication use were captured in this trial [Telecon 5/3/99].

EDTA and Paradoxical Bronchoconstriction

The albuterol sulfate and Dey combination solution used in this study both contained 0.1 g/L of EDTA. The ipratropium bromide inhalation solution contained no EDTA and none of the solutions contained benzalkonium chloride (BAC). Safety information was obtained on all patients following nebulization at each study visit specifically to assess paradoxical bronchoconstriction. The sponsor implies that this was not found but doesn't state it directly and goes on to add that there were very few reports of bronchoconstriction in the entire study. Additionally, post hoc analysis of all respiratory AE's that could have been misclassified paradoxical bronchoconstriction was carried out for the COSTART terms: 'apnea,' 'asthma,' 'cough increase,' 'dyspnea' and 'lung disorder.' For example, the verbatim terms 'bronchospasm' or 'wheezing' would have been assigned to the COSTART term 'asthma' and the verbatim, 'exacerbation of COPD' would have translated to 'lung disorder.' A comparison of these AE rates or the total respiratory AE's between study drugs showed no trend towards increased AE rates associated with EDTA-containing solutions of albuterol sulfate and the combination solution [23:138-9].

N20-950 DL-024: RESPIRATORY AE's THAT COULD BE BRONCHOSPASM [23:139]			
Patient Category or COSTART Term	Albuterol Sulfate Number (%)	Ipratropium Bromide Number (%)	Combination Solution Number (%)
Total Patients	761 (100)	754 (100)	765 (100)
Patients with Resp. AE's	179 (23.5)	177 (23.5)	192 (25.1)
apnea	0 (0)	2 (0.3)	1 (0.1)
asthma	5 (0.7)	4 (0.5)	5 (0.7)
cough increased	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)

N20-950 DL-024: RESPIRATORY AE's THAT COULD BE BRONCHOSPASM [23:139]			
Patient Category or COSTART Term	Albuterol Sulfate Number (%)	Ipratropium Bromide Number (%)	Combination Solution Number (%)
ipratropium bromide solution (shaded cells) has no EDTA, the other two solutions have 0.1 g/L concentration of EDTA			

These data suggest that misclassification of respiratory AE's was not a likely source of occult or paradoxical bronchoconstriction.

Paradoxical bronchoconstriction could be described as a decrease in $FEV_{1.0}$ from baseline at various time points following administration of a study drug. The following two tables address the conditions of 'any decrease from baseline' and 'decrease of > 15%.'

N20-950 DL-024: NUMBER (%) OF PATIENTS WITH ANY DECREASE IN $FEV_{1.0}$ [23:140]						
Time Post-Dose (min)	Albuterol Sulfate		Ipratropium Bromide		Combination Solution	
	Total	Decreased	Total	Decreased	Total	Decreased
15	682	49 (7.2)	684	93 (13.6)	687	34 (5.0)
30	679	39 (5.7)	680	55 (8.1)	683	25 (3.7)
ipratropium bromide solution (shaded cells) has no EDTA, the other two solutions have 0.1 g/L concentration of EDTA						

N20-950 DL-024: NUMBER (%) OF PATIENTS WITH > 15% DECREASE IN $FEV_{1.0}$ [23:140]						
Time Post-Dose (min)	Albuterol Sulfate		Ipratropium Bromide		Combination Solution	
	Total	Decreased	Total	Decreased	Total	Decreased
15	682	3 (0.44)	684	12 (1.75)	687	1 (0.15)
30	679	4 (0.59)	680	4 (0.59)	683	2 (0.29)
ipratropium bromide solution (shaded cells) has no EDTA, the other two solutions have 0.1 g/L concentration of EDTA						

These data support the observation that the ipratropium solution without EDTA was associated with more numerous patients showing both any $FEV_{1.0}$ decrease and an $FEV_{1.0}$ decreased > 15% than were the other two solutions which did contain EDTA. Therefore, EDTA was not implicated in producing paradoxical bronchoconstriction within 15-30 minutes of drug administration. A comparison of the two EDTA-containing solutions showed that the combination solution, which contained ipratropium, was associated with less frequent $FEV_{1.0}$ decreases and less frequent > 15% $FEV_{1.0}$ decreases [23:140].

ADDITIONAL DATA

SAFETY

Demographics

In addition to the large Dey sponsored study, safety data have been summarized from published information, industry-sponsored studies and medical literature, utilizing the combination or simultaneous use of albuterol sulfate and ipratropium bromide. The numbers of subjects/patients involved in all relevant studies and the extent of exposure are summarized in the table below [23:114-5].

NDA #20-950: EXTENT OF EXPOSURE IN SAFETY STUDIES [23:116]			
Study Type	Number of Studies (Nebulizer/MDI)	Number of Patients (Combination/Total)	Treatment Duration (Days)
CLINICAL PHARMACOLOGY	1/1	27/27	1-2
Dey DL-031	1/0	15/15	2
Industry-Sponsored	0/1	12/12	1
CONTROLLED STUDIES - COPD	10/15	2936/5285	1-85
Dey DL-024	1/0	765/863	56
Industry-Sponsored	2/4	1338/3500	4-85
Literature-Based	7/11	832/922	1-12
CONTROLLED STUDIES - Literature	16/5*	964/1727	1-12
Asthma	14/4	907/1634	1-12
Cystic Fibrosis	1/1	21/21	1
Bronchiolitis	1/0	36/72	1
TOTAL	24/18	3926/7039	1-85
* 6 studies are counted twice because they contain both Asthma and COPD patients			

There were 24 literature and industry studies that exposed 2170 COPD patients to the combination of albuterol and ipratropium. About 40% of the trials employed nebulizers and 60% used MDI's. The dosage for albuterol ranged from 0.15 to 0.80 mg in the MDI studies and from 0.60 mg to 10 mg in the nebulizer studies. The ipratropium dosage was 0.03 mg to 0.16 mg for the MDI trials and from 0.25 mg to 0.50 mg for the nebulizer studies. The weight ratio of albuterol sulfate to ipratropium bromide ranged from 2.5 to 5 in the MDI studies and from 5 to 20 in the studies using nebulizers. Considering both delivery methods together, the duration of treatment was from 1 to 85 days [23:115-7].

The demographic characteristics of age, gender and race of all patients treated with albuterol and ipratropium combination therapy and evaluated for efficacy or safety are shown in the following table [23:116].

NDA #20-950: DEMOGRAPHIC CHARACTERISTICS OF SAFETY & EFFICACY STUDIES [23:116]				
Type	Number of Studies	Age Range in Years (mean)	Male/Female/Unk (sum)	White/Black/Other
Clinical Pharmacology	2	18-58 (32.9)	25/2/0 (27)	4/11/0

NDA #20-950: DEMOGRAPHIC CHARACTERISTICS OF SAFETY & EFFICACY STUDIES [23:116]				
Type	Number of Studies	Age Range in Years (mean)	Male/Female/Unk (sum)	White/Black/Other
Dey (DL-031)	1	18-58 (33.1)	13/2/0 (15)	4/11/0
Industry-Sponsored	1	21-47 (32.7)	12/0/0 (12)	unknown
Controlled Studies - COPD	26	16-93 (65.4)	881/616/1438 (2935)	1030/67/12
Dey (DL-024)	1	40-93 (66.3)	475/290/0 (765)	723/34/8
Industry-Sponsored	6	40-88 (64.7)	324/180/834 (1338)	367/33/4
Literature-Based	18	16-84 (64.8)	182/46/604 (832)	unknown
Controlled Studies - Literature	24*	0.125-85 (29.4)	231/315/454 (1000)	27/96/3
Asthma	18	5-85 (29.0)	201/288/418 (907)	27/96/3
Cystic Fibrosis	2	6-22 (13.2)	10/11/0 (21)	unknown
Bronchiolitis	1	0.125-1 (0.78)	0/0/36 (36)	unknown
TOTAL	42	0.125-93 (56.3)	1237/833/1892 (3962)	1121/174/15
* six studies were counted twice because they included both asthma and COPD patients				

The 2170 COPD patients drawn from industry-sponsored and literature-based studies ranged in age from 16 to 88 years. The ages were skewed to older patients and the mean age was over 64 years. When gender was documented, the majority of patients were male, but in most of the studies gender was not reported. Race was also largely undocumented, but was listed as 'White' when documentation was available.

In literature-based studies of other indications and clinical pharmacology studies, 1012 subjects have been exposed to the combination of albuterol sulfate and ipratropium bromide. The reported patient ages ranged from 1.5 months to 85 years. Many of the studies did not report gender or race. Gender was reported in 55% of the subjects and 56% of these were female. Race was reported in only 12% of the subjects, the majority of whom were black (76%) [23:117].

Deaths

There were no deaths in the Dey pharmacokinetic study (DL-031) in healthy subjects. In the industry-sponsored or literature-based studies, 6 deaths were patients exposed to the combination of albuterol sulfate and ipratropium bromide, but in none of these was the death considered to be causally related to the drug used [23:131].

Serious Adverse Events (SAE's)

There were no SAE's in the Dey study (DL-031) of pharmacokinetics in healthy subjects. In the seven industry-sponsored or literature-based studies in which these data were reported, 81 patients out of a total of 2791 experienced 99 SAE's which were evenly distributed among the treatment arms. Thirty-three of 1148 patients treated with the combination reported 38 SAE's and no increased frequency of SAE's with combination therapy was found [23:128].

Discontinuations Due To Adverse Events

There were no discontinuations due to AE's in the Dey pharmacokinetic study (DL-031). In the industry-sponsored or literature-based studies of COPD patients treated with the combination of albuterol sulfate and ipratropium bromide there were 91 patients who quit prematurely because of AE's. These were evenly distributed among the three treatment arms [23:129-30].

EDTA and Paradoxical Bronchoconstriction

Edetate disodium (ethylenediaminetetracetic acid = EDTA) has been used as preservative in pharmaceutical products including inhalation solutions. The characteristics of the two approved non-Dey inhalation solutions are shown in the table below [23:134].

NDA #20-950: MARKETED INHALATION SOLUTIONS CONTAINING EDTA [23:134]

Trade Name	Drug Name	Manufacturer	EDTA Concentration	NDA Numbers
Alupent	metaproterenol SO_4	Boehringer Ingelheim	0.5 g/L	18-761 002 18-761 001 17-659 001

Both inhalation solutions of metaproterenol sulfate contain five times the EDTA found in the Dey Combination solution. No reports in the literature or in publicly available sources associate paradoxical bronchoconstriction with beta-agonist inhalation solutions that contained EDTA up to 0.5 g/L.

The original formulation of Atrovent was reported to cause paradoxical bronchoconstriction in about one quarter of the asthmatic patients exposed to it. This formulation contained both 0.25 g/L of benzalkonium chloride (BAC) and 0.5 g/L of EDTA. A number of clinical studies demonstrated that preservative-free ipratropium bromide did not cause paradoxical bronchoconstriction in asthmatic patients. In one study 6 of 22 patient showed a fall in $FEV_{1.0}$ after inhaling Atrovent. When these same 6 patients inhaled a solution of ipratropium without BAC and EDTA, all showed bronchodilation by an increase in $FEV_{1.0}$. Inhalation of the preservatives administered separately produced dose-related bronchoconstriction, which persisted for longer than 60 minutes. The concentrations of the two preservatives producing bronchoconstriction in asthmatic patients were:

BAC	mean = 0.30 g/L	(range =
EDTA	mean = 2.60 g/L	(range

The BAC range included the dose in the Atrovent formulation, but the EDTA range did not. Therefore, in the absence of mutual potentiation, BAC may have been the

bronchoconstricting agent. In support of this hypothesis, nonclinical studies have suggested that BAC may potentiate bronchoconstriction in asthmatic patients [23:134-7].

EFFICACY

Demographics

The extent of patient exposure in efficacy studies to the inhaled combination of albuterol sulfate and ipratropium bromide is shown in the table below. These include one less industry-sponsored MDI trial than was included in the safety database [23:94, 115].

NDA #20-950: EXTENT OF EXPOSURE IN CONTROLLED COPD EFFICACY STUDIES [23:94]			
Study Type	Number of Studies (Nebulizer/MDI)	Number of Patients (Combination/Total)	Treatment Duration (Days)
Dey DL-024	1/0	765/863	56
Industry-Sponsored	2/3	972/2766	4-85
Literature-Based	7/11	832/922	1-12
TOTAL	10/14	2569/4551	1-85

The descriptive demographic breakdown of gender, age and race are so similar to statistics for the safety review in this section that they will not be represented [23:95, 116].

Positive Trials

The efficacy of the combination of albuterol and ipratropium in COPD patients was assessed in 23 industry-sponsored and literature-based controlled clinical trials. In 15 of the studies (6 nebulizer, 9 MDI), combination therapy resulted in significant improvements in the majority of spirographic endpoints, compared with either drug alone.

Equivocal or Negative Trials

There were 7 studies (2 nebulizer, 5 MDI) that reported combination therapy as not significantly different from either component alone. Three (3 MDI) of these 7 trials demonstrated a trend towards superiority of the combination solution as measured by onset and duration of action that did not reach statistical significance. Two (2 MDI) of the 7 administered albuterol and ipratropium in sequence, giving the first drug until maximum bronchodilation had occurred and then adding the second drug. These showed no advantage of adding the second drug. The results suggested that maximizing the first dose of two sequentially administered bronchodilators might not be the same as simultaneous administration of lower doses of both drugs. The last 2 (2 nebulizer) were simply negative studies showing no benefit of the combination over the two component drugs administered separately. The results of the twenty-third study were not revealed [23:103-4].

Long-Term Trials

Four (1 nebulizer, 3 MDI) industry-sponsored and literature-based studies have evaluated the efficacy of albuterol sulfate and ipratropium bromide in patients with COPD for up to 85 days. All studies demonstrated significant improvements in spirographic variables of the combination over single drugs. No studies have extended efficacy demonstration past 85 days [23:111].

4 of 14

JUL 15 1998

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-950	**APPLICATION TYPE:**	NDA
SPONSOR:	Dey Laboratories	**PROPRIETARY NAME:**	Duovent
CATEGORY:	combination of two bronchodilators	**USAN NAME:**	albuterol & ipratropium
		ROUTE:	inhaled
MEDICAL OFFICER:	R. F. Anthracite, M.D.	**REVIEW DATE:**	15 July 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
28 May 1998	29 May 1998	new NDA	45-Day Filing Meeting

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a 505(b)2 NDA that relies on a single trial in COPD patients to show the efficacy of an aqueous nebulizer solution of albuterol sulfate and ipratropium bromide (6:1 by weight). This trial has only the components of the combined solution as positive controls without a placebo arm and relies on the published literature for a large safety data base. An additional pharmacokinetic study of the effect of ipratropium on albuterol blood levels completes the original studies submitted by this sponsor. The most recent information we have is that approval of this NDA cannot occur until expiration of Boehringer-Ingelheim's exclusivity for Combivent in October 1999.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	_____	**HOLD**	_____	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	_____	**APPROVABLE**	_____	**NOT APPROVABLE**

SIGNATURES

Reviewer: /S/ **Date:** 15 July 1998

Team Leader: /S/ **Date:** 7/21/98

SUMMARY

This is a 505(b)2 NDA that relies on a single trial in COPD patients to show the efficacy of an aqueous nebulizer solution of albuterol sulfate and ipratropium bromide (6:1 by weight). This trial has only the components of the combined solution as positive controls without a placebo arm and relies on the published literature for a large safety data base. An additional pharmacokinetic study of the effect of ipratropium on albuterol blood levels completes the original studies submitted by this sponsor. The most recent information we have is that approval of this NDA cannot occur until expiration of Boehringer-Ingelheim's exclusivity for Combivent in October 1999.

The application appears well-indexed, complete, and to have addressed the concerns and conditions expressed at the pre-NDA Meeting in June 1997. The anticipated completion date for the medical review will likely be earlier than the PDUFA deadline, owing to the small number of studies to review.

TIME LINE

Submitted:	05/28/98
CDER Date:	05/29/98
MO Received:	06/09/98
21-Day Filing Meeting:	06/29/98
45-Day Planning Meeting:	07/15/98
Division Signing Date:	05/14/99
PDUFA Date:	05/28/99

PRE-NDA MEETING (17 JUNE 1997) EXCERPTS

PHARMACOLOGY

There are three preclinical issues which must be addressed regarding Duovent®.

1. Dey must show that the combination of albuterol and ipratropium does not increase the toxicity seen with either agent separately. We are especially interested in the combination product's effect on the cardiovascular system. This information may be provided through:

   a. an extensive literature search (assuming adequate data are available in the published literature); or
   b. a 30 day study using two animal species (one rodent and one nonrodent) comparing each individual agent and the combination product.

2. The proposed formulation contains EDTA as a chelating agent. EDTA is known to be a bronchoconstrictor. Dey must provide data that shows inhalation of this agent is safe. This information may be provided through:

   a. an extensive literature search (assuming adequate data are available in the published literature); or
   b. a six month inhalation study in one species (the most appropriate animal species).

3. The labeling should include the most current information available regarding the toxicity of the combination product.

When Dey submitted the original ANDA for albuterol they believed that EDTA was a qualified excipient. They will have to look at their original data to determine how they came to that conclusion. Dey wanted to know if the Division's toxicity concerns are diminished by the numerous years that albuterol and Atrovent have been marketed. Dr. Jenkins explained that these data only come from the adverse reporting system and it reports data on the individual products which may or may not be administered together. This system does not provide long term toxicity (carcinogenicity, etc.) data for the combination product.

If the data cannot be determined through a literature search, the Division will work with Dey laboratories to develop an adequate toxicology protocol.

BIOPHARMACEUTICS

Dey should conduct a literature search to determine if one agent has any affect on the other agent when given as a combination product in humans. If this information is not found in the literature search, a study needs to be conducted. We are aware that it would be difficult to obtain ipratropium serum levels and note that the dose might have to be increased to 3 or 4 times the normal dose to get a discernible concentration. Our main pharmacokinetic concerns are for albuterol. The assays currently available are more specific and it should not be difficult to obtain good results.

CLINICAL

The FDA has approved NDA's based on a single adequate and well-controlled study, but the Division encourages sponsors to conduct two adequate and well-controlled clinical studies. If Dey plans to submit the NDA with only one study, the Division would like Dey to conduct an adequate literature search to obtain additional data to support the combination use of albuterol and ipratropium in the treatment of COPD. There is no placebo arm in Dey's trial. However, if the combination product proves superior to each one of the components, and each component is an approved product, the current design is acceptable. This will be a review issue, however.

BIOMETRICS

Please clarify the following two concerns. Address the possibility of side effects carried over into the parallel portion of the study affecting the comparison of side effect profiles during the parallel phase. When the NDA is submitted please explain and provide references for the analyses. Upon preliminary review, the SAS data files appear adequate.

REGULATORY

Currently this application does not qualify as a 505(b)1 application. The sponsor of a 505(b)1 application must conduct or have right of reference to all of the required studies needed for submission and approval. To qualify for 505(b)2 application, Dey must list the reference product(s) that the application is based on. Additionally, the applicant must certify that: 1) no patents have been filed for the reference product; 2) the patent on the reference product has expired or will expire including the dates; or 3) the patent is invalid or will not be infringed upon by the marketing of the proposed NDA. This certification must be filed with the original application.

1. Obtain right of reference to the Combivent NDA from Boehringer. This would enable Dey to use any data submitted in the Combivent NDA. Dey needs to receive authorization from Boehringer for right of reference.

2. Submit data via literature search for preclinical, biopharmaceutics and clinical in addition to data from the actual study conducted.

3. Dey may reference Combivent but can only receive tentative approval (TA). Once the exclusivity has expired then Dey's NDA could receive final approval.

Currently Dey plans to use Atrovent and albuterol as the reference products for this NDA. They have not decided if they will reference Combivent. Combivent has exclusivity until October 1999.

POST MEETING FOLLOW-UP
Donald Hare, from the Office of Generic Drugs, expressed his opinion that Dey's 505(b)2 new drug application could not be approved pending expiration of Boehringer Ingelheim's exclusivity for Combivent even if Dey does not reference the Combivent NDA and even if Dey provides data in support of the combination product from the literature and/or their own studies. The sponsor was informed of this possibility on July 16, 1997 by Ms. Denise P. Toyer, Project Manager.

SUMMARY OF EXCERPTS

1. A literature search must be conducted to show the safety of the combination product and EDTA when administered by inhalation as part of the preclinical section. If acceptable literature cannot be found to support safety, Dey will contact the Division with proposed study protocols for review.

2. Dey will conduct a literature search to show the pharmacokinetics (PK) of the combination product in humans. If data unavailable, Dey will consider doing PK study.

3. Dey will conduct a literature search to provide additional clinical support for the combination use of albuterol and ipratropium in the treatment of COPD. These data will be reviewed by the Division and may be the basis to obviate the need for a second adequate and well-controlled clinical trial.

FOREIGN MARKETING

none

LABELING CLAIMS

- ✓ indicated for treatment of bronchospasm in COPD patients requiring more than one bronchodilator
- ✓ action may last up to 4-5 hours
- ✓ patient age ≥ 18 years
- ✓ recommended QID with up to two additional doses allowed per day
- ✓ supplied as a 3 mL sterile solution in low-density, polyethylene, unit-dose vials containing 2.5 mg of albuterol (0.083%) and 3.0 mg of albuterol sulfate and 0.5 mg (0.017%) of ipratropium bromide in a clear, colorless, isotonic, sterile, aqueous solution with pH adjusted to 3-5
- ✓ safety and efficacy are the same for patients with ages < 65 years and patients aged > 65 years

NEW STUDIES SUBMITTED BY DEY

CLINICAL PHARMACOLOGY TRIAL (DL-031)

This was a double-blind, single-dose, two-treatment, two-period, two-sequence, randomized, crossover design carried out in healthy, non-asthmatic, adult subjects. Two vials of the Dey test solution or two doses of albuterol were administered by nebulizer fifteen minutes apart. Treatment was given on two days, which were six days apart and consisted of a single dosing period of thirty-minutes. Pharmacokinetic parameters were determined in plasma (albuterol) and urine (albuterol and ipratropium) samples. No differences in plasma albuterol pharmacokinetic parameters were found between albuterol given alone or in combination with ipratropium.

CONTROLLED COPD TRIAL (DL-024)

This was a twelve-week, randomized, double-blind, positive-control, crossover study of albuterol sulfate, ipratropium bromide and the combination, as inhalation solutions in patients with COPD. The three study phases were: 1)a Run-In Phase; 2)a Crossover Phase consisting of three, two-week crossover periods which incorporated all six possible treatment sequences; and, 3)a six-week, three-arm Parallel Phase in which the patient received the same medication that was given in the last Crossover Phase sequence. Dosing was four times each day, before meals and at bedtime, with the provision for up to two additional doses each day, if necessary. The combination was found to be statistically superior to each component by a number of different spirographic endpoints.

EXPOSURE SAFETY DATA BASES

The safety data base was derived from three study types, clinical pharmacology studies, controlled clinical trials of COPD patients and controlled clinical trials of patients with other indications. Each of these three trial types contained contributing information from this sponsor (Dey) and published literature derived from either industry-sponsored studies or other non-industry-sponsored investigations [23:(8)114-6].

DEMOGRAPHIC CHARACTERISTICS OF SAFETY STUDIES [23:(8)116]				
Type	**Number of Studies**	**Age Range (mean)**	**Male/Female/Unk (sum)**	**White/Black/Other**
Clinical Pharm.	2	18-58 (32.9)	25/2/0 (27)	4/11/0
Dey (DL-031)	1	18-58 (33.1)	13/2/0 (15)	4/11/0
Industry	1	21-47 (32.7)	12/0/0 (12)	unknown
COPD Controlled	25	16-93 (65.4)	981/516/1438 (2935)	1090/67/12
Dey (DL-024)	1	40-93 (66.3)	475/290/0 (765)	723/34/8
Industry	6	40-88 (64.7)	324/180/834 (1338)	367/33/4
Literature	18	16-84 (64.8)	182/46/604 (832)	unknown
Other Controlled	24*	0.125-85 (29.4)	231/315/454 (1000)	27/96/3
Asthma	18	5-85 (29.0)	201/288/418 (907)	27/96/3
Cystic Fibrosis	2	6-22 (13.2)	10/11/0 (21)	unknown
Bronchiolitis	1	0.125-1 (0.78)	0/0/36 (36)	unknown

DEMOGRAPHIC CHARACTERISTICS OF SAFETY STUDIES [23:(8)116]				
Type	**Number of Studies**	**Age Range (mean)**	**Male/Female/Unk (sum)**	**White/Black/Other**
TOTAL	42	0.125-93 (56.3)	1237/833/1892 (3962)	1121/174/15
* six studies were counted twice because they included both asthma and COPD patients				

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-950
HFD-570/Division Files
HFD-570/Team Leader/Honig
HFD-570/Medical Reviewer/Anthracite
HFD-570/Pharmacologist/Whitehurst
HFD-570/Chemist/Kim
HFD-570/Statistician/Aras
HFD-570/Biopharmaceutics/Chen
HFD-570/PM/Hilfiker

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-950	**APPLICATION TYPE:**	NDA
SPONSOR:	Dey	**TRADE NAME:**	DuoNeb™
CATEGORY:	nebulizer solution	**GENERIC NAME:**	albuterol/ipratropium
		ROUTE:	oral inhaled
MEDICAL OFFICER:	Raymond F. Anthracite	**REVIEW DATE:**	6 March, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

DOCUMENT DATE	CDER DATE	SUBMISSION TYPE	COMMENTS
02/23/2001	02/26/2001	safety update	literature review

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS
11/29/99	amendment (approvable response)	approvable
03/28/98	new NDA (505b2)	approvable

REVIEW SUMMARY:

This submission contains all new information related to albuterol sulfate and ipratropium bromide published since May 1999. It includes 6 journal articles and 3 foreign abstracts. The safety information reported here is consistent with known effects of both components administered by nebulization via the oral inhaled route.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION

NEW CLINICAL STUDIES:	____	PROCEED	____ HOLD	____	(HOLD TYPE)
NDA/SUPPLEMENTS:	____	APPROVAL	____ APPROVABLE	____	NOT APPROVABLE
OTHER ACTION:	FILE TO NDA.				

SIGNATURES

Reviewer: _____ **Date:** 03/06/2001

Team Leader: _____ **Date:** _____

/s/

Raymond Anthracite
3/6/01 04:18:08 PM
MEDICAL OFFICER