CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: JUN 5 1998

NDA #:	NDA 20-837
Applicant:	Sepracor Inc.
Name of Drug:	Xopenex® (levalbuterol HCl) inhalation solution
Indication:	Treatment or prevention of acute bronchospasm in patients [redacted] years of age and older with reversible obstructive airway disease and attacks of bronchospasm
Document Reviewed:	Vol. 1.2, 1.97-1.139, dated July 1,1997 Additional analysis submitted on Nov 4, 1997
Data Reviewed:	4 diskettes containing SAS data-sets from Vol. 97 and 98
Statistical Reviewer:	Girish Aras Ph.D.
Medical Input:	Richard Nicklas MD.
Key words:	Bronchospasm, Albuterol

Summary of Statistical Issues

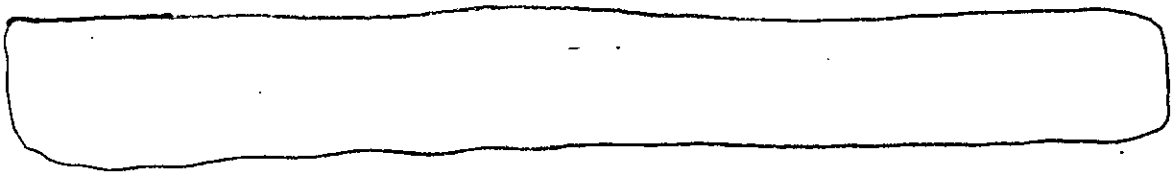
The sponsor submitted 9 clinical trials evaluating the efficacy and safety of (R)-Albuterol in 42 healthy and 502 patients with asthma: 3 methacholine challenge trials, 3 clinical pharmacology trials and 3 bronchodilator effects trials. This review evaluates the three placebo-controlled, bronchodilator effects studies which the sponsor submitted to support the claim that Xopenex® is effective in treatment or prevention of [redacted] bronchospasm in patients [redacted] years of age and older with reversible obstructive airway disease and attacks of bronchospasm. This reviewer finds, based on the above studies, that the drug is efficacious for patients 12 years or older with asthma.

- Study 051-024, a parallel, dose-ranging study of 362 patients, supports the sponsor's claim that (R)-albuterol is efficacious and safe for acute and chronic treatment of bronchospasm in asthmatic patients 12 years of age and above.

- In Study 051-024 (R)-albuterol was "comparable" to (RS)-albuterol. This comparability was not based on a statistical assessment of equivalence (i.e., established by an hypothesis testing procedure supported by appropriate sample size), but rather on a numerical comparison, combined with a finding of no statistical difference between the two treatments (i.e., a finding that the ANOVA test of a linear contrast comparing the two drugs was not significant -- p-value = 0.90).

- In this reviewer's opinion Study 051-005, a cross-over study with only 20 patients, was an exploratory trial. The results of the study provide an indication that R-albuterol (in doses of 0.31 mg, 0.63 mg, and 1.25 mg) is safe for patients with mild-

to-moderate asthma, and that the 1.25 mg dose is the most efficacious of the three test doses.



I. Introduction

This review focuses on the results of three placebo controlled, double blind, randomized, studies conducted in USA, to demonstrate the safety and efficacy of Xopenex® treatment or prevention of [redacted] bronchospasm in patients [redacted] years of age and older with reversible obstructive airway disease and attacks of bronchospasm. Characteristics of these studies are summarized in the table below. As noted above, this reviewer considers Study 051-024 the primary study in this application, while the cross-over studies, Studies 051-005 and [redacted] are viewed as supportive, exploratory trials.

Table 1 Study specification

Study	Study Design[1]	Study Period	Treatment Arm	Number of Patients	Age Range
051-024 (U.S. 33 centers)	DB P PC R 4 Weeks	07/31/96 - 01/14/97	R-albuterol 0.625 mg R-albuterol 1.25 mg Racemic albuterol 1.25 mg Racemic albuterol 2.5 mg Placebo	72 73 68 74 75	12-80
051-005 (U.S. 2 centers	DB XO PC R	05/06/95 - 07/31/95	R-albuterol 0.31 mg R-albuterol 0.63 mg R-albuterol 1.25 mg Ventolin™ 2.5 mg Placebo	20	22-51
[redacted]					

[1]Study design designated as follows: DB = Double-Blind; XO = Cross-Over; P = Parallel; R = Randomized

II. Methods and Result

A. STUDY 051-024

1. Study Objectives

The objectives of this study, as stated in the protocol, were the following:

1. Determine the comparative efficacy of two different doses of (R)-albuterol and two different doses of racemic albuterol relative to placebo in the reversal of bronchoconstriction in subjects of age greater than or equal to 12, with asthma, over the course of four weeks of TID treatment.

2. Determine the comparative efficacy of two different doses of (R)-albuterol and two different doses of racemic albuterol relative to placebo in the prevention of bronchoconstriction in subjects with asthma, as assessed by objective measurements of airflow rates and subjective evaluations by the subject.

3. Compare the safety and tolerability of two different doses of (R)-albuterol and two different doses of racemic albuterol relative to placebo.

2. Overall Study Design and Plan

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study of subjects with asthma. A seven-day period of single-blind treatment with placebo was administered before and after four weeks of double-blind treatment. During the four week parallel, treatment period, subjects were randomized to one of five treatment groups: 0.625 mg (R)-albuterol, 1.25 mg (R)-albuterol, 1.25 mg racemic albuterol, 2.5 mg racemic albuterol, or placebo. Study medication was administered by nebulization three times daily. During the entire study period, subjects were given a supply of racemic albuterol metered dose inhaler (MDI) to use as rescue medication for relief of asthma symptoms. Sixty (60) subjects in each treatment group were to complete the study, for a total of 300 completed subjects in 30 centers.

Study duration was approximately six weeks with 5 visits, including a screening visit, 3 treatment visits (Visits 2-4), and a final examination. Non-serial spirometry was performed at Visit 1 and Visit 5; serial spirometry was performed for 8 hours at Visits 2, 3, and 4. At each collection time, three forced vital capacity maneuvers were performed, and the highest actual FEV_1 was recorded on the case report form (CRF). Spirometry was not performed if the subject had used inhaled or nebulized albuterol or oral corticosteroids within eight hours of initiating the pulmonary function tests (PFTs) during clinic visits. In this case, the visit was rescheduled.

In addition to pulmonary function testing during each clinic visit, subjects were required to record diary card data daily [morning and evening peak expiratory flow rate (PEF), asthma symptoms and use of rescue medication].

The primary efficacy endpoint of interest for acute changes in lung function was the peak change in FEV_1 after four weeks of treatment relative to visit pre-dose. Other efficacy outcomes of interest included area under the FEV_1 curve, forced vital capacity (FVC) and associated $FEF_{25-75\%}$, morning and evening PEF, diary card symptoms (shortness of breath, chest tightness, cough and wheeze, nocturnal awakenings), rates of acute exacerbation, and use of rescue medication. Safety measures included physical examination, vital signs, laboratory testing, electrocardiogram (ECG) data, and adverse events (AEs).

3. Method of Assigning Subjects to Treatment Groups

Subjects were randomly assigned to one of five treatment groups in a balanced manner: 0.625 mg (R)-albuterol, 1.25 mg (R)-albuterol, 1.25 racemic albuterol, 2.5 mg racemic albuterol, or placebo. Randomization occurred separately within each site in a block size of 10 to maintain the blinding of the investigator and balance the enrollment across treatment arms. At each site, the investigator assigned the lowest randomization number to their first subject and proceeded in sequential order until the first block was completed. The next subject was assigned the lowest randomization number in the second block, and so forth.

4. Primary Efficacy Variable(s)

The primary efficacy variable was FEV_1, and the primary efficacy endpoint was the peak change in FEV_1 at Week 4 relative to visit pre-dose. Serial spirometric measurements of FEV_1 were taken over an eight hour period after dosing was performed. At each collection time, three PFT maneuvers were performed, and the highest actual FEV_1 value was recorded on the CRF. The primary analysis of efficacy examined the Visit 4 peak change in FEV_1 relative to visit pre-dose (the maximum observed Visit 4 value of FEV_1 above the pre-dose value for that day). As a secondary analysis, peak change in FEV_1 at Week 0 and Week 2 (relative to pre-dose FEV_1 on that visit) were analyzed. Additional analyses of the primary efficacy endpoint included peak changes in FEV_1 at Week 4 and Week 2 relative to study baseline (pre-dose Week 0).

5. Determination of Sample Size

In order to determine the sample size, data from previous studies were used to make assumptions about the peak change in FEV_1 parameter estimates. Data from clinical trials indicated that a reasonable assumption for FEV_1 at baseline for moderate asthmatics was 2.4 liters. From historical data the placebo effect was between 10% and 15%, so a 13% effect for placebo treatment (increase to 2.71 liters) was assumed. It was also assumed that a treatment effect of 25% (increase to 3.0 liters) would be observed, resulting in a difference in peak change FEV_1 values of 0.29. A clinically meaningful difference in FEV_1 values was 10% to 15%. Assuming a difference in peak change of 0.29, the percent increase in treatment FEV_1 over placebo would be 11%.

Assuming that the standard deviation was 0.6 at baseline and at peak FEV_1 and a conservative estimate of the correlation between time points (e.g. baseline and week 4) was 0.6, the standard deviation of peak change was approximately 0.55.

Assuming the standard deviation of the change from baseline in FEV_1 was 0.55 liters, a sample size of 60 subjects per treatment group would provide at least 80% power to detect a difference in peak change FEV_1 measures of 0.29 liters between any active treatment arm relative to placebo. This calculation was based on an analysis of variance with a significance level (alpha) equal to 0.05.

6. Demographics and Other Baseline Characteristics

The demographic characteristics of the 362 subjects who were randomly assigned to double-blind treatment are summarized descriptively by treatment group and are presented below in Table 2.

Table 2 Subject Demographics

	(R)-albuterol 0.625 mg (n=72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	placebo (n=75)	All Subjects (n=362)
Age						
Mean (SD)	36.2 (13.94)	35.0 (13.34)	37.9 (14.58)	38.3 (15.94)	35.2 (14.61)	36.5 (14.50)
Min, Max	13.0, 75.0	12.0, 72.0	13.0, 74.0	13.0, 80.0	12.0, 78.0	12.0, 80.0
Sex						
Male	26 (36.1%)	35 (47.9%)	28 (41.2%)	28 (37.8%)	29 (38.7%)	146 (40.3%)
Female	46 (63.9%)	38 (52.1%)	40 (58.8%)	46 (62.2%)	46 (61.3%)	216 (59.7%)
Race						
Caucasian	62 (86.1%)	60 (82.2%)	60 (88.2%)	65 (87.8%)	59 (78.7%)	306 (84.5%)
Black	8 (11.1%)	6 (8.2%)	6 (8.8%)	6 (8.1%)	6 (8.0%)	32 (8.8%)
Asian	0	1 (1.4%)	2 (2.7%)	2 (2.7%)	0	4 (1.1%)
Hispanic	2 (2.8%)	5 (6.8%)	1 (1.5%)	0	7 (9.3%)	15 (4.1%)
Other	0	1 (1.4%)	0	1 (1.4%)	3 (4.0%)	5 (1.4%)
Height (cm)						
Mean (SD)	168.4 (9.10)	170.4 (9.98)	168.2 (8.70)	167.7 (9.25)	166.1 (9.49)	168. 2 (9.38)
Weight (kg)						
Mean (SD)	79.8 (20.43)	79.8 (16.67)	76.8 (20.21)	76.1 (15.59)	78.2 (22.52)	78.2 (19.20%)
FEV_1 Percent of Predicted						
Mean (SD)	60.0 (8.32)	60.0 (7.29)	60.0 (6.91)	59.5 (7.29)	59.7 (7.62)	59.8 (7.47)
Min, Max						
FEV_1 Percent Reversibility						
Mean (SD)	40.9 (19.80)	41.6 (22.31)	39.9 (21.33)	39.7 (19.75)	37.1 (17.37)	39.8 (20.10)
Min, Max						

The mean age of subjects enrolled in the trial was 36.5 years (range 12-80 years), and nearly 60% were female. Approximately 85% of the patients were Caucasian. The mean percent predicted FEV_1 for all subjects was 59.8%, and the percent reversibility ranged from [redacted] The individual treatment groups were quite similar with the exception of the 1.25 mg (R)-albuterol group, which had a more even balance of male and female subjects. In addition, the peak flow measurements during the initial placebo period were higher, less rescue albuterol was used and milder symptoms were documented at baseline in this group of subjects. There were no statistically significant

differences in the FEV_1 percent of predicted (p=0.99) and FEV_1 percent reversibility (p=0.70) between the active treatment groups and the placebo group.

All subjects had asthma, and more than 50% of the subjects had a duration of > 15 years. Although the 1.25 mg racemic albuterol group had the largest percentage of subjects with a duration of asthma > 15 years (70.6%), and the 2.5 mg racemic albuterol group had the lowest number of subjects with a duration of > 15 years (43.2%). The mean number of asthma exacerbations that occurred in the 90 days prior to enrollment in the ITT population was 0.4 (range) with no significant difference between treatment groups (p=0.39). The primary causes of asthma exacerbation in all treatment groups were respiratory infections, exercise, allergens, and smoking.

The majority of the physical examination abnormalities were with the eyes, ears, nose, throat (EENT) and respiratory systems. Many subjects had baseline nasal congestion, and wheezing was osculated in approximately 25% of subjects. There were no significant physical exam (PE) abnormalities that would have resulted in exclusion from the study. Baseline vital signs were all considered to be within clinically acceptable ranges for all subjects.

7. Analysis of Primary Efficacy Data

Efficacy endpoints were summarized using the ITT population. Changes in FEV_1 were evaluated for both acute changes relative to visit pre-dose and for chronic changes by comparing peak FEV_1 at study baseline (pre-dose Week 0) to Weeks 2 and 4 post-dose. The primary efficacy analysis was conducted on the Week 4 peak change in FEV_1 relative to visit pre-dose (the maximum observed Week 4 value of FEV_1 above the pre-dose value for that day).

The null hypothesis tested was that the acute Week 4 mean peak changes in FEV_1 relative to visit pre-dose were equal across all five treatment groups. The alternative hypothesis was that at least one mean peak change in FEV_1 was not equal to the others. A similar null hypothesis testing for chronic use was that the Week 4 mean peak changes in FEV_1 relative to study baseline (pre-dose, Week 0) were equal across all five treatment groups. Treatment groups were compared for differences in peak change in FEV_1 based on an ANOVA model using SAS® PROC MIXED procedure. The model included treatments, study sites, and treatment-by-study site interactions. All of these effects were considered fixed. Assuming 30 centers and 300 subjects divided evenly across groups, the degrees of freedom for each parameter were defined as follows:

Parameter	Degrees of Freedom
Study Site	29
Treatment	4
Treatment Study Site	116
Error	150
Total	299

If the treatment-by-center interaction was not significant at 0.1, it was removed from the model. If the overall treatment F-test was significant, then four pairwise comparisons of active treatment versus placebo were performed. In addition, a one degree of freedom test comparing racemic albuterol and (R)-albuterol was performed. If the overall treatment F-test was not significant, the subsequent tests were not performed.

If the residuals from the ANOVA model were not normally distributed according a Shapiro-Wilk test at the 0.1 level, the appropriateness of the model was further examined. Outliers in the tails of the frequency distribution were removed and the model was fitted without those (six) values. Those residuals were normally distributed and randomly scattered, so the original model was considered adequate with the inclusion of the outliers as valid clinical values. In addition, rank analysis of variance was performed including these data. There were no qualitative changes to the statistical findings.

As a secondary analysis, peak change in FEV_1 at Week 2 (relative to pre-dose FEV_1 on that visit) were analyzed using an ANOVA as described in the primary efficacy analysis.

Additional analyses of the primary endpoint included peak changes in FEV_1 at Week 2 relative to study baseline (pre-dose Week 0). These were analyzed in the ANOVA as described in the primary efficacy analysis.

Efficacy analyses were conducted on the peak change in FEV_1 relative to the visit pre-dose and relative to study baseline (pre-dose Week 0). Comparisons of the mean peak change in FEV_1 at each visit relative to the visit pre-dose and relative to study baseline are shown for the ITT population in Table 3.

Table 3 Comparison of Mean Peak Change in FEV_1 [L]

	Treatment Group						
	(R)-albuterol 0.625 mg (n= 72)	(R)-albuterol 1.25 mg (n=73)	racemic albuterol 1.25 mg (n=68)	racemic albuterol 2.5 mg (n=74)	Placebo (n=75)	Overall p-value[2]	Pairwise p-value [3]
Peak Change in FEV_1 (relative to visit pre-dose)							
Week 0-							
Mean (SD)	0.86 (0.44)	0.98 (0.48)	0.82 (0.51)	0.81 (0.41)	0.36 (0.35)	<.0001	(RS) v (R)=0.0339
n	72	73	68	74	75		
Week 2							
Mean (SD)	0.73 (0.44)	0.75 (0.42)	0.70 (0.43)	0.71 (0.36)	0.30 (0.39)	<.0001	(RS) v (R)=0.58
n	69	65	63	70	70		
Week 4							
Mean (SD)	0.70 (0.38)	0.75(0.36)	0.68 (0.41)	0.76 (0.41)	0.24 (0.25)	<.0001	(RS) v (R) =0.90
n	68	62	63	69	67		
Peak Change in FEV_1 (relative to study baseline)							
Week 2							
Mean (SD)	0.75 (0.49)	0.82 (0.50)	0.68 (0.48)	0.80 (0.45)	0.38 (0.43)	<.0001	(RS) v (R)=0.55
n	69	65	63	70	70		
Week 4							
Mean (SD)	0.80 (0.50)	0.87 (0.52)	0.67 (0.50)	0.80 (0.40)	0.38 (0.52)	<.0001	(RS) v (R)=0.13
n	68	62	63	69	67		

[1] Peak change in FEV_1 refers to the peak change in forced expiratory volume in one second relative to pre-dose at Week 0 or pre-dose at each visit.

[2] Overall treatment test was conducted using an ANOVA. Effects included study site, treatment and their interaction (if significant)

[3] Pairwise tests of active treatment versus placebo and racemic albuterol versus (R)-albuterol were presented if the overall test was significant. Pairwise comparisons of active treatment vs placebo were <.0001 for all analyses

The primary efficacy analysis, the peak change in FEV_1 relative to pre-dose at Week 4, revealed that after 4 weeks of TID treatment, improvement in lung function, as measured by the peak change in FEV_1, was 'comparable' between all active treatment groups (p=0.90), and statistically different than placebo. The reader should note that the comparability of (RS) and (R) albuterol indicated is descriptive and is not in the sense of testing equivalence hypothesis. The 0.625 mg dose of (R)-albuterol produced 'comparable' efficacy as the 2.5 mg racemic albuterol. Similar findings were observed at Visit 2. The only significant difference between (R)-albuterol and racemic albuterol was observed at Week 0 (p=0.0339), where (R)-albuterol was superior to racemic albuterol.

Internal audit by the sponsor indicated that the data at Dr. Edwards' site was questionable. There were 23 patients at his site. Primary efficacy analysis without the data from Dr. Edwards' site was conducted and submitted by the sponsor (November 4, 1998 submission). The conclusions were identical to the above analysis.

8. Extent of Exposure

During the four weeks of double-blind treatment, the 362 subjects in this study received either one of the active albuterol compounds or placebo. In addition, subjects received placebo (0.9% saline) for a 7-day period before and after the double blind treatment

period, and were provided with commercially available racemic albuterol MDI for use as a rescue medication during the entire study period.

9. Adverse Events

Adverse event (AE) data for the ITT population was summarized by those events that occurred during the active treatment period and those that occurred during the second single-blind placebo period. The AEs reported before assignment to treatment were listed separately, by subject.

A total of 425 AEs were reported by 216 subjects during the four weeks of double-blind treatment. There was no statistically significant difference in the total number of AEs between treatment groups (p=.99), although the 1.25 mg (R)-albuterol, 2.5 mg racemic albuterol, and placebo treatment groups experienced a slightly higher number of AEs as compared to the two lower dose treatment groups. Of the 425 reported AEs, 133 were considered to be potentially related to treatment. The majority of the AEs (55%) were considered to be moderate, while 8% were classified severe and 37% mild. The largest number of AEs reported for all treatment groups were events relating to the respiratory system, with the AE of asthma being reported with the highest frequency followed by exacerbation of asthma. The most frequent AEs relating to beta-2 stimulation were nervousness and tremor.

A total of 48 AEs from 38 subjects were reported during the second single-blind placebo period. Of these 48 events, 6 were deemed related to treatment. Three AEs were described as severe, while the majority (54%) were considered moderate in severity.

Ten serious adverse events (SAEs) and two "alarming" AEs were reported during the entire study, including the first single-blind treatment period. One placebo-treated subject died suddenly of an asthma exacerbation, approximately 3 months after completing the study.

The AEs were coded using COSTART preferred terms and were categorized by body system. The proportion of subjects reporting one or more adverse event(s) and the total for those AEs that occurred with a frequency of ≥ 2% and greater than the frequency of placebo, or AEs associated with the use of albuterol (regardless of frequency) that occurred during the double-blind treatment period, are presented in Table 4.

Table 4 Summary of Adverse Events With Frequency ≥ 2% and > Placebo, or Associated with the Use of (R)-Albuterol or Racemic Albuterol With Onset During the Double-Blind Treatment Period

	Treatment Group									
Body System Preferred term	(R)-albuterol 0.625 mg n = 72		(R)-albuterol 1.25 mg n = 73		racemic albuterol 1.25 mg n = 68		racemic albuterol 2.5 mg n = 74		placebo n = 75	
	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n
All Adverse Events	42(58.3)	78	45(61.6)	94	40(58.8)	75	45(60.8)	92	47(62.7)	91
Body as a Whole										
allergic reaction	0		0		0		2(2.7)	2	1(1.3)	1
headache	6(8.3)	6	7(9.6)	7	9(13.2)	12	6(8.1)	6	8(10.7)	9
flu syndrome	3(4.2)	3	1(1.4)	1	2(2.9)	2	2(2.7)	2	0	
accidental injury	0		2(2.7)	2	0		0		0	
pain	2(2.8)	2	1(1.4)	1	1(1.5)	2	2(2.7)	2	1(1.3)	1
back pain	0		0		1(1.5)	1	2(2.7)	2	0	
chest pain	0		1(1.4)	1	3(4.4)	3	1(1.4)	1	0	
Cardiovascular System										
migraine	0		2(2.7)	3	0		0		0	
tachycardia	2(2.8)	3	2(2.7)	3	0		2(2.7)	2	0	
Digestive System										
dyspepsia	1(1.4)	1	2 (2.7)	2	1(1.5)	1	1(1.4)	1	1(1.3)	1
Musculoskeletal System										
leg cramps	0		2(2.7)	3	1(1.5)	1	1(1.4)	1	1(1.3)	1
Nervous System										
anxiety	0		2(2.7)	2	0		0		0	
dizziness	1(1.4)	1	2(2.7)	2	0		0		1(1.3)	1
hypertonia	0		0		1(1.5)	1	2(2.7)	2	0	
insomnia	0		1(1.4)	1	0		0		0	
nervousness	2(2.8)	3	7(9.6)	8	3(4.4)	3	6(8.1)	6	0	
tremor	0		5(6.8)	6	0		2(2.7)	2	0	
Respiratory System										
asthma	13(18.1)	13	12(16.4)	12	12(17.6)	12	15(20.3)	16	18(24.0)	18
asthma inc.[1]	6(8.3)	7	8(11.0)	9	6(8.8)	6	4(5.4)	5	9(12.0)	9
cough increased	1(1.4)	1	3(4.1)	3	1(1.5)	1	2(2.7)	2	2(2.7)	2
viral infection [2]	5(6.9)	5	9(12.3)	10	5(7.4)	5	9(12.2)	9	7(9.3)	7
pharyngitis	4(5.6)	4	0		1(1.5)	1	2(2.7)	2	6(8.0)	7
rhinitis	8(11.1)	8	2(2.7)	2	3(4.4)	3	5(6.8)	5	2(2.7)	2
sinusitis	3(4.2)	3	1(1.4)	1	3(4.4)	3	2(2.7)	2	2(2.7)	2
turbinate edema	2(2.8)	2	1(1.4)	1	0		0		0	
wheezing	1(1.4)	1	0		4(5.9)	4	1(1.4)	1	2(2.7)	2
Urogenital System										
UTI	0		0		2(2.9)	2	0		0	

Note: Subjects may have had the same adverse event more than once.

[1] Asthma inc. = asthma exacerbation. An asthma exacerbation was defined as a worsening of asthma symptoms or pulmonary function which required therapeutic intervention with oral or parenteral corticosteroids or other medications as judged necessary by the Investigator.

[2] viral infection = upper respiratory infection.

A summary of potentially related AEs with a frequency of ≥ 2% and greater than the frequency of placebo or associated with the use of (R)-albuterol or racemic albuterol are presented in Table 5.

Table 5 Summary of Potentially Related Adverse Events With Frequency ≥ 2% and > Placebo, or Associated with the Use of (R)-Albuterol or Racemic Albuterol With Onset During Double-Blind Treatment Period.

	Treatment Group									
Body System Preferred term	(R)-albuterol 0.625 mg n = 72		(R)-albuterol 1.25 mg n = 73		racemic albuterol 1.25 mg n = 68		racemic albuterol 2.5 mg n = 74		placebo n = 75	
	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n
All Adverse Events	12 (16.7)	21	23 (31.5)	41	14 (20.6)	18	20 (27.0)	32	14 (18.7)	23
Body as a Whole	4 (5.6)	4	5 (6.8)	5	3 (4.4)	5	3 (4.1)	4	4 (5.3)	6
headache	3 (4.2)	3	4 (5.5)	4	2 (2.9)	4	2 (2.7)	2	3 (4.0)	4
Cardiovascular System	2 (2.8)	3	3 (4.1)	4	0		2 (2.7)	2	0	
tachycardia	2 (2.8)	3	2 (2.7)	3	0		2 (2.7)	2	0	
Musculoskeletal System	1 (1.4)	1	2 (2.7)	3	0		0		1 (1.3)	1
leg cramps	0		2 (2.7)	3	0		0		1 (1.3)	1
Nervous System	4 (5.6)	5	13 (17.8)	20	3 (4.4)	3	8 (10.8)	9		
anxiety	0		2 (2.7)	2	0		0		0	
dizziness	1 (1.4)	1	2 (2.7)	2	0		0		0	
nervousness	2 (2.8)	3	7 (9.6)	8	3 (4.4)	3	6 (8.1)	6	0	
tremor	0		5 (6.8)	6	0		2 (2.7)	2	0	
Respiratory System	6 (8.3)	6	6 (8.2)	7	8 (11.8)	9	9 (12.2)	12	10 (13.3)	14
asthma	5 (6.9)	5	4 (5.5)	4	5 (7.4)	5	6 (8.1)	6	7 (9.3)	7
asthma inc.[1]	1 (1.4)	1	3 (4.1)	3	2 (2.9)	2	2 (2.7)	2	2 (2.7)	2
rhinitis	0		0		0		2 (2.7)	2	0	

Note: Subjects may have had the same adverse event more than once.

[1] Asthma inc. = asthma exacerbation. An asthma exacerbation was defined as a worsening of asthma symptoms or pulmonary function which required therapeutic intervention with oral or parenteral corticosteroids or other medications as judged necessary by the Investigator.

There were no significant differences in the frequency of related AEs across treatment groups for any body system other than the nervous system (p=0.0007). As noted in the table above, there were 20, 9, 5, 3 and 0 nervous system related adverse events in 1.25 mg (R)-albuterol, 2.5 mg racemic albuterol, 0.625 mg (R)-albuterol, 1.25 mg racemic albuterol treatment arms and placebo, respectively. In comparing the lower doses with the higher doses of racemic and (R)-albuterol, the anticipated beta-mediated side effects of nervousness, tremor, leg cramps, insomnia, dizziness, and tachycardia occurred at a greater frequency with the higher doses of albuterol. There was approximately a 50% - 60% increase in the incidence of nervousness with the higher dose of either racemic or (R)-albuterol. Tremors were only reported in those subjects receiving the higher doses of (R)-albuterol and racemic albuterol. Headaches occurred in subjects in all treatment groups, including the placebo group. The AE that occurred with the highest frequency in all treatment groups was asthma, with the highest percentage (20%) occurring in the placebo treatment group. Upper respiratory infections (coded as viral infection) occurred with a higher frequency in the 1.25 mg (R)-albuterol and 2.5 mg racemic albuterol treatment groups. Tremors, nervousness, dizziness, tachycardia, and leg cramps were not reported during the placebo period following the double-blind treatment period.

10. Conclusions

The study supports efficacy and safety of the drug for acute as well as chronic use for patients of age 12 or older with asthma. (R)-Albuterol is numerically comparable to (RS)-Albuterol. This comparability is not meant in the strict statistical sense of equivalence established through an equivalence hypothesis testing procedure supported by appropriate sample size, but in the sense of testing a linear contrast that compares the two treatments in the ANOVA and high p-value (such as 0.90 in this case) taken as an indication of comparability. Additional evidence to support comparability came from secondary efficacy endpoints. AUC, FVC and $FEF_{25-75\%}$ at week 0, 2 and 4 were numerically comparable for corresponding (R)-Albuterol and (RS)-Albuterol doses.

B. STUDY 051-005

1. Study Objective

The protocol stated study objectives as follows:

1. To determine the comparative efficacy of (R)-albuterol relative to racemic albuterol in the reversal of bronchoconstriction in subjects with mild-to-moderate asthma.

2. To examine the effect of increasing doses of (R)-albuterol on the magnitude and duration of bronchodilation.

3. To determine the safety of (R)-albuterol in the treatment of asthma.

2. Study Design

This was a randomized, double-blind, multi-dose, cross-over study in twenty subjects with chronic asthma. Doses of study medication evaluated in this study were as follows: R-albuterol, 0.31 mg R-albuterol, 0.63 mg R-albuterol, 1.25 mg Ventolin™ (racemic albuterol), 2.5 mg Placebo. The randomization scheme was provided by Seprocor in sets of five using a 5 x 5 Latin square design in each set.

3. Primary Efficacy Variables

The trial was a dose-response study and the efficacy analysis was exploratory. The primary efficacy variables evaluated in this study included the following:

1. Overall change in FEV_1 from pre-dose to six hours post-dose
2. Time to onset of activity
3. Duration of activity

Time to onset of activity was defined as the time at which an increase over baseline in FEV_1 of 15% or more was first observed. Duration of activity was defined as the time from onset to the time at which the FEV_1 was less than 115% of baseline.

The protocol specified that FEV_1 data were to be statistically analyzed by repeated measures (15, 30, 45 60, 75, 90, 105, 120 minutes and 3, 4, 5 and 6 hours) analysis of

variance for a Latin square design. Treatment comparisons were to be performed using tests on linear contrasts of means.

The primary comparisons of interest were between the 1.25 mg R-albuterol and placebo doses and between the 1.25 mg R-albuterol and 2.5 g racemic albuterol doses.

4. Sample size

The sample size for this study was calculated based on primary data from a previous Sepracor study (protocol 051-001). The within subject variance in FEV_1 was estimated as 0.04 so that the standard deviation of a within patient difference from baseline was estimated as $\sqrt{2} \times 0.2 = 0.28$. In order to detect a difference of 0.28L in FEV_1 and to achieve 80% power using a two-sided test at the 0.05 level, 16 patients were required. Because the study was designed using 5 x 5 Latin square, it was convenient to use a total of 20 patients.

5. Analysis of Efficacy

All of the 20 patients enrolled in the study completed the trial. The mean percent change from pre-dose FEV_1 values overall were highest for the 1.25 mg R-albuterol and 2.5 mg racemic albuterol treatments, and lowest for placebo. The comparison between 1.25 mg R-albuterol and placebo was statistically significant (p=0.0016). Comparison between 1.25 mg R-albuterol and 2.5 mg racemic albuterol was not statistically significant (0.7519). Although not statistically significant, a numerical dose-response trend for the three r-albuterol treatments with respect to overall change in FEV_1 over the six-hour observation period was observed. This trend emerged at the 60-minute post-dose observation period and was maintained through four hours post-dose. This study did not indicate statistically or clinically significant differences in time to onset of activity with any of the active treatments. Further, no dose-response with respect to time to onset of activity was apparent for the three R-albuterol treatments. However, when duration of activity was examined, the study indicated a clear dose-response relationship within the three R-albuterol treatments.

6. Adverse Events

A total of 44 adverse events were recorded in study subjects during the course of the study. The proportion of patients experiencing an adverse event, as well as total number of adverse events reported, were comparable across the five groups. All adverse events which occurred in this study were considered by the investigators to be mild or moderate in intensity, and all had resolved with no residual effects by study completion. None of the adverse events required treatment, and no patient was prematurely withdrawn from the study due to an adverse event. No unexpected serious or non-serious adverse events were observed in any treatment group.

There were no statistically significant differences among the five treatments with respect to the frequency of treatment-related adverse events.

7. Conclusions

This being a cross-over study with three primary efficacy variables without a preplanned multiple comparison procedure, the reviewer considers it to be primarily an exploratory study. It is supportive to the primary study 051-024. This study indicated that R-albuterol (in doses of 0.31 mg, 0.63 mg, and 1.25 mg) is safe in patients with mild-to-moderate asthma. All doses were well tolerated and there were no serious adverse events. With respect to efficacy, although not statistically significant, a dose-response trend for the three R-albuterol treatments with respect to overall change in FEV_1 over the six-hour observation period was observed. This trend emerged at the 60-minute post-dose observation period and was maintained through four hours post-dose. R-albuterol (1.25 mg) was statistically significantly better than placebo with respect to overall change in FEV_1 over the six-hour observation period. Comparison between 1.25 mg R-albuterol and 2.5 mg racemic albuterol was not statistically significant (0.7519). Given the size and the quality of this study, no reliable conclusion can be drawn about the comparability of the two doses.

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III. Overall conclusions

The sponsor submitted 9 clinical trials evaluating the efficacy and safety of (R)-Albuterol in 42 healthy and 502 patients with asthma of both genders. There were 3 Methacholine Challenge Trials, 3 Clinical Pharmacology Trials and 3 Bronchodilator effects trials. The reviewer reviewed three placebo-controlled (one parallel and two cross-over), broncodilator effects studies that the sponsor submitted to support the claim

that Xopenex® is effective in treatment or prevention of [redacted] bronchospasm in patients years of age and older with reversible obstructive airway disease and attacks of bronchospasm. Based on the above studies, the reviewer concludes that the drug is efficacious for patients 12 years or older with asthma. These results also suggest that (R)-albuterol is comparable to marketed drug racemic albuterol. The comparability is not meant in the strict statistical sense of equivalence established through an equivalence hypothesis testing procedure supported by appropriate sample size, but in the sense of testing a linear contrast in the ANOVA that compares the two drugs and a high p-value (such as .90 in this case) is taken as an indication of comparability.

The first (051-024) and the second (051-005) study reviewed above have patients of age 12 and older and they support the efficacy and safety of (R)-Albuterol at dose levels 0.625 and 1.25 mg. The main evidence of efficacy comes from the first study. The second study is a dose ranging study with several endpoints. In the reviewer's opinion, it is an exploratory rather than confirmatory study. The third study reviewed above [redacted]

APPEARS THIS WAY
ON ORIGINAL

/S/

Girish Aras, PhD

Concur: Dr. Wilson /S/ 6/5/98

cc:
Orig. NDA 20-837
HFD-570 / Division File
HFD-570 / JJenkins, PHonig, CKwang
HFD-715 / Division File, Chron
HFD-715 / GAras, SWilson

ga/April 15, 1998/NDA/20837/STAT/7-1-97

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