CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20,837	APPLICATION TYPE:	NDA submission
SPONSOR:	Sepracor	PRODUCT/PROPRIETARY NAME:	Xopenex
		USAN / Established Name:	Levalbuterol
CATEGORY OF DRUG:	beta agonist	ROUTE OF ADMINISTRATION:	inhalation solution
MEDICAL REVIEWER:	R. Nicklas MD	REVIEW DATE:	17 June 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
none	N/A	N/A	see below under overview

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
30 June 1997	NDA submission	see below under overview

Overview of Application/Review: As a supplement to the MOR of 25 November 1997, the following comments should be conveyed to the sponsor.

1. The wording in the INDICATIONS section of the labeling should be changed to read, "Xopenex (levalbuterol) Inhalation Solution is indicated for the relief of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease

Outstanding Issues: The above comments should be conveyed to the sponsor.

Recommended Regulatory Action: Convey comments to sponsor

N drive location:

New Clinical Studies: N/A Clinical Hold N/A Study May Proceed

NDAs:

Efficacy / Label Supp.: N/A Approvable N/A Not Approvable

Signed: Medical Reviewer: /S/ Date: 6/17/98

Medical Team Leader: /S/ Date: 6/18/98

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20,837	APPLICATION TYPE:	NDA amendment
SPONSOR:	Sepracor	PRODUCT/PROPRIETARY NAME:	Xopenex
		USAN / Established Name:	Levalbuterol
CATEGORY OF DRUG:	beta agonist	ROUTE OF ADMINISTRATION:	inhalation solution
MEDICAL REVIEWER:	R. Nicklas MD	REVIEW DATE:	24 March 1999

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
22 March 1999	N/A	amendment	see below under overview

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
30 June 1997	NDA submission	none

Overview of Application/Review: The sponsor has submitted a clinical safety update for the period from 1 July 1998 to 28 February 1999 as requested by the Division in the conference call of 16 March 1999. This safety update covers all formulations of the drug from ongoing blinded and unblinded studies involving 1131 patients. No serious AEs were reported. There was a slightly greater frequency of AEs reported after administration of 1.25 mg of levalbuterol than after administration of 0.63 mg of levalbuterol, including tachycardia and nervousness, and one patient who developed "cardiospasm" after 1.25 mg of levalbuterol. There were no AEs that were alarming and unexpected. The data reported by the sponsor at this time does not change the safety assessment made on the data submitted previously to the NDA.

Outstanding Issues: none

Recommended Regulatory Action: none

N drive location:

New Clinical Studies: N/A Clinical Hold N/A Study May Proceed

NDAs:

Efficacy / Label Supp.: N/A Approvable N/A Not Approvable

Signed: Medical Reviewer: /S/ Date: 3/24/99

Medical Team Leader: /S/ Date: 3/25/99

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20,837	APPLICATION TYPE:	NDA submission
SPONSOR:	Sepracor	PRODUCT/PROPRIETARY NAME:	Zopen
		USAN / Established Name:	Levalbuterol
CATEGORY OF DRUG:	beta agonist	ROUTE OF ADMINISTRATION:	inhalation solution
MEDICAL REVIEWER:	R. Nicklas MD	REVIEW DATE:	25 November 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
30 June 1997	1 July 1997	original NDA	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
13 October 1997	amendment	The product name originally proposed by the sponsor [redacted] was not acceptable. Subsequently, the Division accepted the name Xopenex proposed by the sponsor.
4 November 1997	IR response	Reanalysis of the data from study 024 with the exclusion of the Edwards site did not change the conclusions from the study
20 November 1997	120 day safety update	This submission contains a minimal amount of additional safety data. The revised analyses as part of this update do not change the conclusions reached previously about the safety of this drug.
1 December 1997	IR response	Reanalysis by the sponsor does not indicate that reduction in efficacy was associated with [redacted]

Overview of Application/Review: The safety and efficacy of (R)-albuterol at the dosages proposed in the labeling have been demonstrated in patients 12 years of age and older. The safety and effectiveness of (R)-albuterol have not been demonstrated in patients 3-11 years of age. The efficacy of (R)-albuterol in reversing bronchoconstriction has been demonstrated. It has not been demonstrated conclusively that (R)-albuterol prevents bronchoconstriction. No interconversion of (R)-albuterol to (S)-albuterol was demonstrated.

Outstanding Issues: Proposed labeling changes will be addressed in a separate review.

Recommended Regulatory Action: approval for 12 and older | N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: __X__ Approvable for 12 years and older _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 5/11/98

Medical Team Leader: /S/ Date: 5/26/98

CONCLUSIONS

The sponsor has demonstrated the efficacy of (R)-albuterol (levalbuterol) in reversing bronchoconstriction (bronchodilitation) acutely after a single dose and when administered as a nebulized solution tid over a period of 4 weeks (1).

The sponsor has not performed studies which are adequate to demonstrate that (R)-albuterol prevents bronchoconstriction for longer than 20 minutes after administration. After administration of, (R)-albuterol patients were protected against a fall in FEV-1 after methacholine challenge conclusively for only 20 minutes (2,3,4). The labeling will need to be changed to reflect this finding.

The dose recommended in the labeling for patients 12 years of age and older, i.e. 0.63 mg tid, is appropriate (1). The labeling also recommends a dose of 1.25 mg tid for patients 12 years of age and older who have "more severe disease". This dose is acceptable, but requires careful monitoring of patients for cardiac and other systemic effect (1).

The sponsor has not demonstrated the safety and effectiveness of (R)-albuterol directly in patients 3-12 years of age,

The sponsor has demonstrated the safety of (R)-albuterol with repetitive administration at doses of 0.625 and 1.25 mg tid over 4 weeks (1), with cumulative doses of up to 5 mg of (R)-albuterol (6,7), and based on an overall evaluation of the safety data from all studies (8).

No interconversion of (R)-albuterol to (S)-albuterol was seen.

REFERENCES

1. Study 024
2. Study 025
3. Study 007
4. Study 001
5.
6. Study 021
7. Study 008
8. ISS

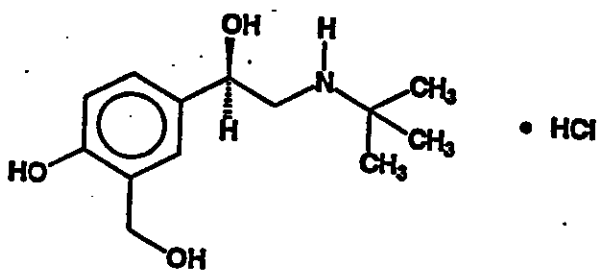
TABLE OF CONTENTS

BACKGROUND

Levalbuterol HCl ((R)-albuterol) is the (R)-isomer of albuterol and like the racemic compound is a relatively beta-2 selective agonist. The sponsor has submitted data to support the safety and effectiveness of (R)-albuterol in the treatment of acute asthma when delivered as a nebulized solution. Based on preclinical and clinical data, it is the (R)-isomer of the racemic mixture and not the (S)-isomer which is responsible for reversal of bronchoconstriction when the racemic mixture is used for the treatment of asthma. In fact, based on both preclinical and clinical data, it appears that the (S)-isomer may produce a deleterious effect, most notably in terms of bronchial hyperresponsiveness.

The sponsor initially proposed a brand name of [redacted] for this product. The Labeling and Nomenclature Committee (LNC) and the Division felt that this name was unacceptable because the name looked like and sounded like marketed drug products. The sponsor then submitted two market research studies which the sponsor felt supported the name [redacted] The Division did not feel that this data could be used to support the name [redacted] The sponsor then submitted the name [redacted] which was also felt to be unacceptable by the LNC and the Division. The sponsor subsequently submitted the name XOPENEX which has been sent to the LNC for their review. An [redacted] has been filed in [redacted] and for which the sponsor is planning to file a [redacted] in the [redacted] through the mutual recognition procedure. Levalbuterol has not been approved for marketing in any country.

Levalbuterol HCl Inhalation Solution is an isotonic, sterile, aqueous solution with no preservative, but with sodium chloride and sulfuric acid to adjust the pH. It will be packaged in a unit dose vial. The chemical structure is noted below.



The sponsor's plan for evaluation of levalbuterol was based on the 1992 FDA Policy Statement for the Development of New Stereoisomeric Drugs, focusing on the PK of the (R)-enantiomer to determine whether interconversion of (R)- to (S)-albuterol was occurring and whether there was any difference in the pharmacokinetics of the (R)-enantiomer when administered alone or as part of racemic albuterol.

The IND for this product was submitted on 28 February 1995, which was followed by a meeting with the Division on 25 July 1995, where recommendations to the sponsor were made, based on the September 1994 Points to Consider Document. At the end of the phase 2 meeting with the sponsor on 25 April 1996, it was concluded that additional studies such as special populations or drug interaction studies would only be needed if interconversion of (R)-albuterol to (S)-albuterol occurred, or if there was any difference in the pharmacokinetics when (R)-albuterol was administered alone or as the racemic mixture. Furthermore, the sponsor was told that a single 4 week repetitive dose study would be sufficient to support a claim for efficacy and safety of (R)-albuterol but that two doses of racemic albuterol should be used for comparison with (R)-albuterol in order to provide a better comparison by utilizing dose-response curves. A cumulative dose study was recommended to evaluate the systemic safety of (R)-albuterol at multiple doses.

Since racemic albuterol has been available for more than 15 years in the United States, and since the active enantiomer, (R)-albuterol, is a component of the racemic mixture, the pharmacology might be "anticipated" from prior knowledge of the racemic mixture. The non-clinical development plan, therefore, according to the sponsor, focused on comparing the (R)-isomer with

the racemic mixture, developing sensitive stereospecific bioassays for monitoring the (R)- and (S)-enantiomers in plasma and urine after inhalation, characterizing the bioavailability and elimination of each enantiomer, comparing the safety of (R)-albuterol with the racemic mixture in bridging studies and determining the relative roles of each isomer in the racemic mixture, as well as determining whether the enantiomers behave differently alone and in the racemic mixture.

From these studies, it appears that: 1) (R)-albuterol is up to twice as potent as racemic albuterol and up to 100 times more potent than the (S)-isomer at the beta-2 receptor; 2) (R)-albuterol has up to 6.5 times greater selectivity for the beta-2 receptor than for the beta-1 receptor; 3) (R)-albuterol is responsible for beta-2 agonist activity, i.e. the therapeutic efficacy of racemic albuterol; 4) while (R)-albuterol and racemic albuterol "attenuate the increase in pulmonary resistance induced by some spasmogens", (S)-albuterol not only fails to relax airway smooth muscle but under certain circumstances may augment bronchoconstriction; and 5) (S)-albuterol is not a beta-2 agonist and produced deaths in rodents, increased intracellular calcium in airway smooth muscle and bronchial hyperresponsiveness.

In vitro studies with human bronchi showed that constriction produced by histamine and LTC4 was potentiated by (S)-albuterol. (S)-albuterol also augmented eosinophil peroxidase release from human eosinophils. In vitro, (S)-albuterol activates phospholipase C and induces calcium influx into airway smooth muscle, changes that could lead to bronchial hyperresponsiveness.

The sponsor has developed an [redacted] assay for quantitation of (R)-albuterol and (S)-albuterol in human plasma and urine. In human tissue, enantiomer-selective sulfoconjugation of racemic albuterol involves higher sulfotransferase binding affinity for (R)-albuterol as compared to (S)-albuterol, contributing to an approximately 10 times greater intrinsic clearance of the (R)-isomer as compared to the (S)-isomer. The (R)-albuterol is conjugated and eliminated faster than the (S)-albuterol, resulting in a shorter half-life for (R)-albuterol which leads to a period of time when (S)-enantiomer effects are not balanced by (R)-enantiomer effects after administration of racemic albuterol.

Pharmacokinetic studies demonstrated that: 1) maximal concentrations of (R)- and (S)-albuterol are reached 15 and 50 minutes, respectively, after inhalation; 2) the Cmax of (S)-albuterol was 2-2.5 times higher than the Cmax of (R)-albuterol following administration of racemic albuterol; 3) the half-life of elimination was about 4 hours for (R)-albuterol and about 6 hours for (S)-albuterol; 4) AUC values were about 5 times higher for (S)-albuterol compared with (R)-albuterol following administration of racemic albuterol; 5) there was no interconversion of (R)-albuterol to (S)-albuterol; 6) (S)-albuterol levels were measurable in patients who had used rescue medication several hours prior to study drug administration; and at comparable dosages, the mean systemic exposure was comparable in adult males, adult females and children; 7) (R)-albuterol peak plasma levels were about 4 ng/mL after administration of both (R)-albuterol and racemic albuterol; 8) plasma concentration by time curves, AUC and half-life values were similar after administration of (R)-albuterol and racemic albuterol; and 9) 5 mg of (S)-albuterol and 10 mg of racemic albuterol by inhalation produced a Cmax for (S)-albuterol of about 10 ng/mL and the plasma concentration by time curves, AUC and half-lives after administration of (S)-albuterol and racemic albuterol were similar.

Study number	Type of study	Dosing	Patient Pop	Finding
Methacholine Challenge				
025	SD, PC, DB, CX challenge 6 and 9 hours after drug	0.625 and 1.25 mg (R)-albuterol and 2.5 mg rac albuterol	asthma, mild-moderate, adults, N = 12	no stat sig diff between (R)-albuterol or rac albut and placebo
007	SD, PC, DB, CX challenge 20 and 180 min after drug	1.25 mg (R)-albuterol, 1.25 mg (S)-albuterol, 2.5 mg rac albut	asthma, mild-moderate, adults, N = 12	both (R) alb and rac alb protected pts 20 min and 3 hrs after adm
001	SD, PC, DB, P challenge 20 and 180 min after drug	100 mcg (R)-albuterol, 100 mcg (S)-alb, 200 mcg rac albuterol	asthma, mild, adults, N = 40	(R) albuterol protected pts 20 min but not 3 hrs after admin
Clinical Pharmacol				
021	cumulative dose, ATC, DB, CX	5 mg (R) albuterol, 10 mg rac albut	asthma, mild-moderate, adults, N = 13	efficacy and safety demonstrated
006	SD, CX, open, ATC	1.25 and 5 mg of (R) and (S) albut, 2.5 and 10 mg rac albut	normal volunteers, adults, N = 27	(R)-alb more likely to produce systemic effect than 2X rac albut

008	cumulative dose, DB, CX, PC	max 3200 mg (R) and (S) albuterol, 6400 mg rac albuterol	normal volunteers, adults, N = 12	safety of cumulative high doses demonstrated
Efficacy and Safety				
005	SD, DB, CX, PC	0.31, 0.63and 1.25 mg (R)-albuterol, 2.5 mg rac albut	asthma, mild-moderate, adults, N = 20	onset and duration of effectiveness were comparable
024	RD, DB, PC, P, 4 wks Rx	0.625, 1.25 mg (R)-alb: 1.25, 2.5 mg rac albuterol	asthma, mild-moderate, adults, N = 362	comparable efficacy and safety of 0.625 mg (R)-albuterol and 2.5 mg rac albuterol; safety of (R) albuterol demonstrated

ABSTRACT FOR METHACHOLINE CHALLENGE STUDIES

METHODS: There were three studies performed to evaluate the effect of (R)-albuterol on bronchoconstriction produced by methacholine challenge, studies 025, 007, and 001. A total of 64 adult patients with mild-moderate asthma were evaluated in double-blind, placebo and active treatment-controlled, single dose studies. Two of the studies (studies 025 and 007) involving 24 patients were crossover studies and the third study (001) was a parallel study with 40 patients randomized to treatment. In one crossover study (025), 0.625 and 1.25 mg of (R)-albuterol were compared to 2.5 mg of racemic albuterol. In the other crossover study (007), 1.25 mg of (R)-albuterol was not only compared to 2.5 mg of racemic albuterol but also 1.25 mg of (S)-albuterol. In the parallel study (001), 100 mcg of (R)-albuterol was compared to 100 mcg of (S)-albuterol and 200 mcg of racemic albuterol. In one crossover study (025), methacholine challenge was done 6 and 9 hours after drug administration. In the other crossover study (007) and the parallel study (001), methacholine challenge was done 20 and 180 minutes after drug administration. The primary outcome variable in all studies was the change in PC20 or PD20 following methacholine challenge.

RESULTS: In the parallel study using a 100 mcg dose (001), (R)-albuterol protected patients against bronchoconstriction when methacholine challenge was performed 20 minutes, but not 3 hours after drug administration. In the crossover study using a 1.25 mg dose (007), protection against methacholine-induced bronchoconstriction was demonstrated for 3 hours after drug administration, although this effect was significantly greater 20 minutes after drug administration than 180 minutes after drug administration. In the crossover study which used doses of 0.625 and 1.25 mg of (R)-albuterol (025), no statistically significant protection against methacholine-induced bronchoconstriction was demonstrated at either 6 or 9 hours after drug administration, although there was a trend favoring (R)-albuterol at a dose of 1.25 mg when challenges were done 6 hours after drug administration.

DISCUSSION: Based on the data from these three studies, it can be claimed that (R)-albuterol protected patients against methacholine-induced bronchconstriction when patients were challenged 20 minutes after drug administration. (R)-albuterol did not protect patients when they were challenged 6 and 9 hours after drug administration. The ability of (R)-albuterol to protect against methacholine-induced bronchoconstriction 3 hours after drug administration is unclear. In study 007, 1.25 mg of (R)-albuterol protected patients based on PC20 for 3 hours after drug administration, whereas in study 001, where patients only received a dose of 100 mcg of (R)-albuterol, protection was not demonstrated 3 hours after drug administration. There was a suggestion from this data that (S)-albuterol might decrease protection against methacholine challenge, thereby supporting the contention that (R)-albuterol is more appropriate than racemic albuterol in the treatment of asthma because of the presence of (S)-albuterol in the racemic mixture. For example, in study 007, the mean PC20 FEV-1 when methacholine challenge was performed 180 minutes after administration of (S)-albuterol was 1.59, whereas it was 1.68 at the same time point after administration of placebo. Moreover, in study 001, the mean PD20 FEV-1 when methacholine challenge was performed 180 minutes after administration of (S)-albuterol was lower than the mean PD20 at baseline.

✦ METHACHOLINE CHALLENGE STUDIES:

● **Study 025, entitled, "Comparison among (R)-albuterol and racemic albuterol on tolerability and airway responsiveness when administered via inhalation in subjects with mild to moderate asthma" (Principal Investigator: Robert Dockhorn, Prairie View, Kansas)**

STUDY CHARACTERISTICS

❒ **number of patients: 12 enrolled; 12 completed; since all 12 patients completed the study, the efficacy population = the ITT population**

❒ **age range: 18-34 years**

❒ **patient population: mild-moderate asthma; FEV-1 70% of greater of predicted; PC20 to methacholine 4 mg/ml or less at baseline (visit 2) and 8 mg/ml or less at visits 3-5 and 3 fold or less of that obtained at visit 2**

❒ **study design: double-blind, placebo-controlled, randomized, 4-way crossover, single dose, single center, pilot study**

❒ **drug administration: 0.625 mg (lot number 00696C) and 1.25 mg (lot number 00696A) of (R)-albuterol/3 ml of unpreserved saline; 2.5 mg (lot number 02096C) of racemic albuterol/3 ml of unpreserved saline; placebo 0.9% saline/3 cc unpreserved saline; all delivered by PARI LC PLUS nebulizer with a DURA-NEB portable compressor; drug administration was followed 6 and 9 hours later by methacholine challenge; all oral or inhaled long-acting beta agonists were discontinued for the length of the study; inhaled long-acting beta agonists were withheld for 8 hours prior to each study day**

❒ periods of study: there were 6 study visits; a screening visit (visit 1); 4 treatment visits (visits 2-5); and a final visit (visit 6); the first treatment visit (visit 2) was within 2 weeks of the screening visit; visits 3-5 were separated by at least 24 hours but no more than 7 days; the final visit was within 72 hours of the last treatment visit

❒ parameters evaluated:

EFFICACY: mean % change in FEV-1 was measured 6 and 9 hours after drug administration and prior to methacholine challenge; FEV-1 was then measured every 15 minutes beginning 30 minutes after methacholine challenge; methacholine challenge was done prior to drug administration and 6 and 9 hours after drug administration, using a powder formulation obtained from [redacted] The primary efficacy endpoint was the degree of protection against bronchoconstriction following methacholine challenge based on the PC20; the degree of protection was also analyzed based on inhaled corticosteroid use.

SAFETY: adverse events; vital signs measured just prior to drug administration, 6 and 9 hours after the drug was given and prior to methacholine challenge

STUDY RESULTS

✦ No statistically significant difference was seen between any active treatment and placebo, in regard to PC20 FEV-1 either 6 or 9 hours after drug administration, although there was a trend favoring 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol (see table below, from page 32, volume 89).

Table 3. Comparison of Mean PC_{20} Across Treatments[1]

PC_{20}	(R)-albuterol 0.625 mg	(R)-albuterol 1.25 mg	Racemic albuterol 2.5 mg	Placebo (0.9% saline)	Overall p-value [2]
Post-Dose, 6 hours					
Mean (SD)[3]	0.47 (3.615)	0.53 (2.860)	0.62 (6.878)	0.49 (4.823)	0.85[4]
Post-Dose, 9 hours					
Mean (SD)[3]	0.23 (4.117)	0.36 (5.099)	0.56 (6.906)	0.26 (3.184)	0.24

[1] PC_{20} refers to the methacholine challenge dose concentration (mg/mL) at which FEV_1 is reduced by 20% relative to pre-dose.
[2] Overall treatment test was conducted using an ANOVA. The response variable is log PC_{20}. Effects included sequence, subject within sequence, period, and treatment.
[3] Means are the log PC_{20} values converted back to the original PC_{20} units (mg/mL).
[4] If the overall F-test was not significant, the pairwise tests were not performed so as to avoid multiple testing.
Reference: Section 14.2, Tables 14.2.1.1 and 14.2.2.1.

- ✦ **Since there were only 2 patients who were receiving corticosteroids, no conclusions can be reached in regard to the analysis based on whether patients were using or not using corticosteroids.**

- ✦ **No statistically significant differences were seen in mean percent change in FEV-1 between any of the active treatments and placebo at either 6 or 9 hours after drug administration.**

- ✦ **There were no severe adverse events and no adverse events which were considered to be related to study drug. Hyperkinesia and twitching seen in one patients after 0.65 mg of (R)-albuterol could, however, was consistent with possible beta agonist effect.**

- ✦ **There were no clinically significant changes in heart rate or blood pressure.**

CONCLUSION: There were no safety concerns raised by this study. The study did not, however, demonstrate the ability of (R)-albuterol to increase the provocative concentration of methacholine producing a 20% fall in FEV-1 relative to placebo and is therefore at variance with the studies described on page 5 of the labeling for this drug product. The studies described in the

labeling, however, measured protection against methacholine challenge for only 3 hours after administration of (R)-albuterol, whereas in this study, protection was assessed 6 and 9 hours after administration of (R)-albuterol. Therefore, this data does not support a general claim for "prevention of acute bronchospasm". If the sponsor wishes to use the methacholine challenge data to support this type of statement, it must be qualified to indicate that such prevention has only been demonstrated for 20, and possibly 180, minutes after administration of (R)-albuterol.

- Study 007, entitled, "Comparison among racemic albuterol, (R)-albuterol, and (S)-albuterol on tolerability and airway responsiveness when administered via inhalation in subjects with mild to moderate asthma: a double-blind, placebo-controlled, cross-over study". (Principal Investigator: Donald Cockcroft MD, Saskatchewan, Canada)

  Study Characteristics

  - ❑ number of patients: 12 entered; 12 completed; efficacy population = intent-to-treat population
  - ❑ age range: 21-29 years
  - ❑ patient population: mild-moderate asthma; FEV-1 70% or greater than predicted; responsive to ipratropium
  - ❑ study design: double-blind, placebo-controlled and active treatment controlled, 4-way crossover, single dose, randomized, single center study
  - ❑ drug administration: racemic albuterol 2.5 mg (lot # 950218); (R)-albuterol 1.25 mg (lot # 2595); (S)-albuterol 1.25 mg (lot # 5695); placebo 0.9% saline; all delivered in 3 ml of unpreserved saline via Pari-LC Jet TM nebulizer; inhaled corticosteroids allowed during study; no beta agonists during study; ipratropium for rescue
  - ❑ periods of study: baseline evaluation (visit 1); drug administration (visits 2-5 which were no farther apart than one week and at least 24 hours apart); final evaluation (visit 6 within 72 hours of the last treatment visit)
  - ❑ parameters evaluated:
    - ☛ methacholine challenge (powder from [redacted]) 20 and 180 minutes post-dosing on each study day

- pulmonary function tests: FEV-1; baseline and 20 and 180 minutes after drug administration and before methacholine challenge on each study day

- The primary efficacy variable was a comparison of the protection provided against bronchconstriction based on the PC20 measured 20 minutes and 180 minutes after drug administration

- adverse events

- vital signs: at baseline and 20 and 180 minutes after drug administration

- restlessness: based on 4 point categorical scale where 0 = absent, 1 = slight, not interfering with normal function, 2 = moderate, able to remain still with effort. 3 = severe, not controllable by patient was evaluated prior to drug administration, 20 and 180 minutes after drug administration and at discharge on each study day; difference in restlessness was assessed as much worse = absent in the first treatment to severe in the next, worse = a change of 1-2 points, same, better = improvement of 1-2 points and much better = severe to absent.

Statistical Methods

- The primary efficacy endpoint for this study was the protection against bronchoconstriction measured as the concentration of methacholine where FEV-1 was reduced by 20% from baseline (PC20) 20 and 180 minutes after drug administration. The sponsor states that, " since PC20 data do not exhibit variance homogeneity, the log10 transformation was used for the primary efficacy endpoint."

Study Results

- There were three protocol deviations that occurred in all 12 patients: 1) a methacholine challenge not specified in the protocol was conducted at visit 1; 2) the starting concentration for each methacholine challenge was determined by the site on the PC20 from the visit 1 methacholine challenge, not 0.03 mg/mL as specified in the protocol; and 3) after each visit, actual times for restlessness assessments were estimated by study personnel for visits 2, 3, 4, and 5. None of these protocol deviations would likely have influenced the study results or changed the interpretation of the data. There was no amendment submitted for such changes in the protocol.

- Both (R)-albuterol and racemic albuterol provided a statistically significant degree of protection against methacholine challenge based on mean PC20 both 20 and 180 minutes after drug administration, although the protection had diminished significantly when methacholine challenge was performed 180 minutes after drug administration (see table below)

Table 3. Comparison of Mean PC_{20} Across Treatments [1]

	(R)-albuterol 1.25 mg	racemic albuterol 2.5 mg	(S)-albuterol 1.25 mg	placebo (0.9%saline)	Overall p-value [2]
Post Dose, 20 minutes:					<0.0001
Mean (SD) [3]	12.70 (3.54)	13.17 (3.58)	2.27 (3.40)	1.26 (3.15)	
p-value [4]	<0.0001	<0.0001	0.0049	NA	
Post Dose, 180 minutes:					<0.0001
Mean (SD) [3]	3.91 (4.89)	3.30 (4.66)	1.59 (4.63)	1.68 (3.78)	
p-value [4]	<0.0001	0.0008	0.6100	NA	

[1] PC_{20} refers to the challenge dose concentration (mg/mL) at which FEV_1 is reduced by 20% relative to pre-dose.
[2] Overall treatment test was conducted using an ANOVA. The response variable is $logPC_{20}$. Effects included subject, period, treatment, and carryover.
[3] Means are the $logPC_{20}$ values converted back to the original PC_{20} units (mg/mL).
[4] If the overall test was significant ($p<0.05$), pairwise comparisons of the active treatments versus placebo (0.9% saline) were performed.
Reference: Section 14.2, Tables 14.2.1.1 and 14.2.2.1.

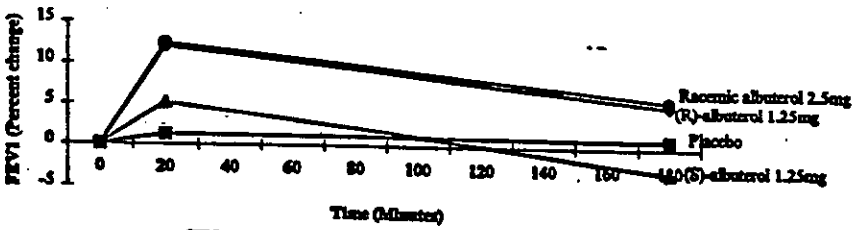
- **The change in FEV-1 after all treatments can be seen in the table below. The improvement in FEV-1 was comparable after administration of (R)-albuterol and racemic albuterol. It is interesting that patients were worse 180 minutes after administration of (S)-albuterol. Although there was a very weak bronchodilatory response after administration of both (R)-albuterol and racemic albuterol, there was a statistically significant difference from placebo, as can be seen in the figure below.**

Table 5. Comparison of Mean Percentage Change in FEV_1 Across Treatments[1]

	(R)-albuterol 1.25 mg	racemic albuterol 2.5 mg	(S)-albuterol 1.25 mg	placebo (0.9% saline)	Overall p-value [2]
Post Dose, 20 minutes:					<0.0001
Mean % change (SD)	12.0 (10.6)	12.4 (10.3)	5.2 (2.96)	1.2 (4.83)	
p-value [3]	<0.0001	<0.0001	0.1000	NA	
Post Dose, 180 minutes:					<0.0070
Mean % change (SD)	5.2 (7.65)	5.7 (10.0)	-2.9 (7.07)	0.9 (8.35)	
p-value [3]	0.1000	0.0700	0.1500	NA	

[1] Percentage change refers to the change in FEV_1 between the maximum FEV_1 achieved 20 or 180 minutes post-dose (prior to methacholine challenge) relative to the maximum FEV_1 value pre-dose.
[2] Overall treatment test was conducted using an ANOVA. The response variable was percentage change in FEV_1. Effects included subject, period, and treatment.
[3] If the overall test was significant ($p<0.05$), pairwise comparisons of the active treatments versus placebo (0.9% saline) were performed.
Reference: Section 14.2, Tables 14.2.3.1 and 14.2.4.1)

Comparison of Mean Percentage Change in FEV1 Across Treatments



- **adverse events: There was only one adverse event reported after administration of (R)-albuterol (see table below). Adverse events to treatment were based on the time period beginning on the day of that treatment and extending to the day of the next treatment.**

Table 6. Summary of All Adverse Events

	(R)-albuterol (n=12)		racemic albuterol (n=12)		(S)-albuterol (n=12)		placebo (0.9% saline) (n=12)		Total (n=12)	
	subjects n (%)	event n	subjects n (%)	event n	subjects n (%)	event n	subjects n (%)	event n	subjects n (%)	event n
All Adverse Experiences	1(8.3)	1	3(25.0)	6	3(25.0)	4	5(41.7)	9	9(75.0)	20
Body as a Whole										
headache	0	0	2(16.7)	3	2(16.7)	2	2(16.7)	2	4(33.3)	7
chest pain	0	0	1(8.3)	1	0	0	0	0	1(8.3)	1
Digestive System										
nausea	0	0	0	0	0	0	1(8.3)	1	1(8.3)	1
Nervous System										
chest tightness	0	0	1(8.3)	1	1(8.3)	1	3(25.0)	3	5(41.7)	5
dyspnea	0	0	1(8.3)	1	1(8.3)	1	0	0	2(16.7)	2
wheezing	0	0	0	0	0	0	1(8.3)	1	1(8.3)	1
Skin and Appendages										
sweating	0	0	0	0	0	0	1(8.3)	1	1(8.3)	1
Special Senses										
eye itch	1(8.3)	1	0	0	0	0	0	0	1(8.3)	1

Reference: Section 14.3.1, Tables 14.3.1.1 and 14.3.1.2)

- **vital signs: The mean heart rate increased from 72 bpm before administration of (R)-albuterol and racemic albuterol to a mean heart rate of 84 bpm 20 minutes after administration of these drugs. There was no clinically significant change in blood pressure after administration of albuterol and blood pressure remained within normal limits throughout the study.**

- **restlessness: Although there was no significant difference from baseline in restlessness scores 180 minutes after drug administration, at 20 minutes, there was a statistically significant increase in perceived restlessness after administration of (R)-albuterol and racemic albuterol. The**

amount of change from a baseline of absent restlessness 20 minutes after administration of albuterol can be seen in the table below. No restlessness was noted after administration of (S)-albuterol and only one patient noted moderate restlessness after placebo administration.

	Restlessness Assessment			
	Absent	Slight	Moderate	Severe
(R)-albuterol	1	3	6	2
	(8.3%)	(25.0%)	(50.0%)	(16.7%)
Racemic albuterol	1	5	4	2
	(8.3%)	(41.7%)	(33.3%)	(16.7%)

Reference: Section 14.5.

CONCLUSIONS: There were no safety concerns raised by the data generated in this study. Increase in heart rate and restlessness are recognized effects of albuterol. Administration of (R)-albuterol prior to methacholine challenge increased the concentration of methacholine that was needed to produce a 20% fall in FEV-1 to a degree comparable to racemic albuterol. A weak bronchodilator effect was also seen after administration of (R)-albuterol to a degree comparable to racemic albuterol in this study.

- **Study 001, entitled, "Comparison among racemic albuterol, (R)-albuterol, and (S)-albuterol on tolerability and airway reactivity when administered via inhalation in subjects with mild asthma: a double-blind, placebo-controlled, parallel group study." Principal Investigator: Pr Max Perrin-Fayolle, Dr Groscläude, France.**

  Study Characteristics:

  - **number of patients: 42 patients screened; 40 randomized to treatment; 10 patients in each of 4 study groups; 40 evaluable patients**

  - **age range: 19-46 years**

  - **patient population: asthma, mild; asthma symptoms < 3 times a week; FEV-1 > 80% predicted; PEFR at least 80% or predicted;**

  - **study design: double-blind, placebo and active treatment-controlled, parallel, randomized, single center, single dose study**

  - **drug administration: (R)-albuterol 100 mcg (batch # 022/146), (S)-albuterol 100 mcg (batch # 007/77), racemic albuterol 200 mcg (batch # S921101-C); study medication was administered using a [redacted] placebo was 0.9% saline**

  - **periods of study: screening (visit 1); 14 day run-in period; visit 2 with methacholine reactivity defined (PD20 less or equal to 1000 mcg); visit 3 - 7 days later, treatment started**

  - **parameters evaluated: The primary outcome variable was the change in PD20 from pre-dose to either the 20 minute assessment or the three hour assessment**

    - **methacholine challenge: 20 and 180 minutes after drug administration; PD20 FEV-1**

- vital signs: immediately prior to each methacholine challenge, 20 minutes after determining the PD20 and just prior to discharge on each study day

- adverse events

- peak flow data from patient's diaries

- difficulty breathing during methacholine challenge based on a visual analogue scale from 0 (absent) to 100 (intense)

Study Results:

- Smoking history and demographic data were comparable between treatment arms

- Peak flows were measured by patients throughout the study, AM and PM, and recorded in a diary. Interestingly, as can be seen in the table below, although there was no statistically significant difference between the treatment groups, peak flows were lower in patients who received (S)-albuterol.

Peak Flow Data from Diaries

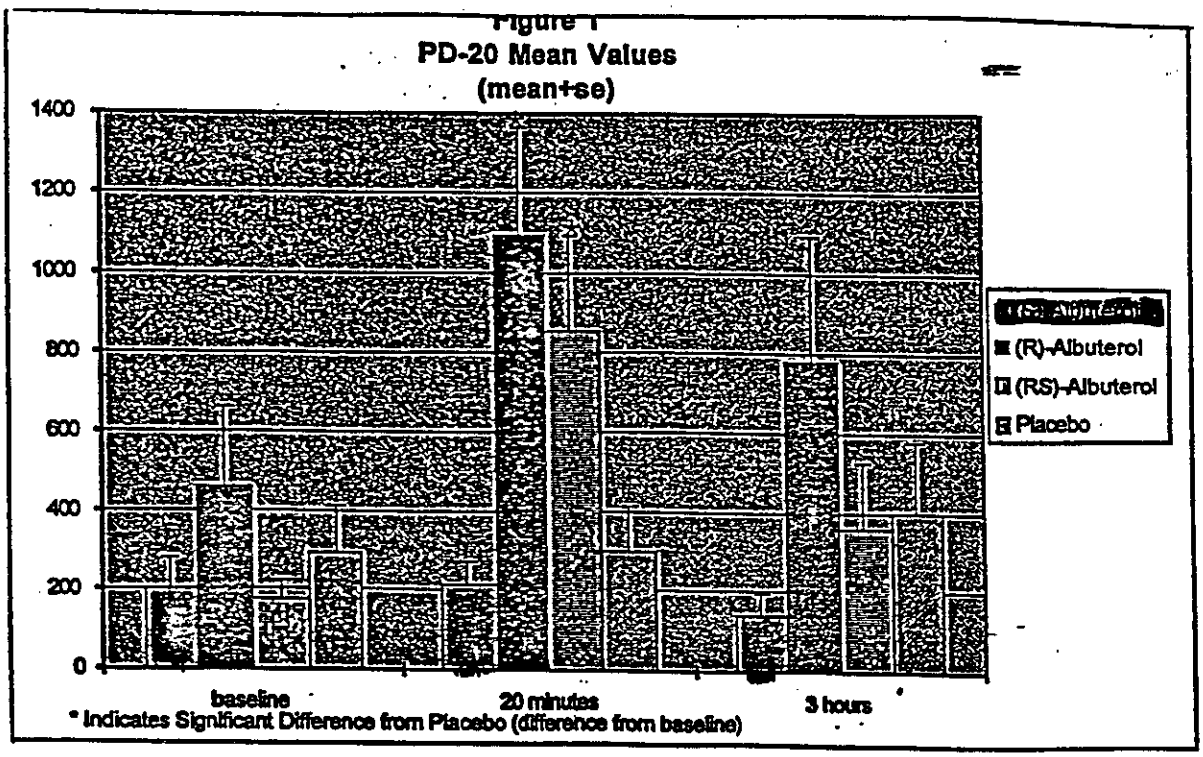
	Placebo n=10	(S)-albuterol n=10	(R)-albuterol n=10	Racemic albuterol n=10
Mean	532	487	506	509
Std Error	32	28	30	33

- Difficulty breathing during methacholine challenge: Although there was no statistically significant difference among the treatment groups, there was slightly more difficulty breathing in the group which received (S)-albuterol. This is probably not a clinically significant difference.

Difficulty of Breathing During Test
Visual Analog Scale
(0=Absent, 100=Intense)

	Placebo n=10	(S)-albuterol n=10	(R)-albuterol n=10	Racemic albuterol n=10
Mean	37.3	49.7	46.1	34.2
Std Error	6.0	8.0	8.1	5.7

- **Methacholine challenge: There was a significantly lower PD20 in the groups which received placebo and (S)-albuterol than the groups which received (R)-albuterol and racemic albuterol ($p < 0.01$) 20 minutes after drug administration (see tables below). There was a statistically significant difference 180 minutes after drug administration between (S)-albuterol and (R)-albuterol and racemic albuterol, but not between placebo and (R)-albuterol or racemic albuterol. Methacholine sensitivity was slightly increased in the (S)-albuterol group, supporting the theory that the effectiveness of racemic albuterol is diminished because of the presence of (S)-albuterol.**



Pairwise Comparisons: 20 Minute Test
Overall Comparison (p=0.00)

	Placebo	(S)-Albuterol	(R)-Albuterol
(S)-Albuterol	0.83		
(R)-Albuterol	0.00	0.00	
(R,S)-Albuterol	0.00	0.00	1.00

Pairwise Comparisons: 180 Minute Test
Overall Comparison (p=0.01)

	Placebo	(S)-Albuterol	(R)-Albuterol
(S)-Albuterol	0.08		
(R)-Albuterol	0.21	0.02	
(R,S)-Albuterol	0.40	0.00	0.40

- ❑ **vital signs: There were no clinically or statistically significant changes in heart rate or blood pressure after administration of any of the treatments.**

- ❑ **adverse events: There were no serious adverse events, nor was there any greater incidence of adverse events after active treatment than after placebo administration.**

CONCLUSIONS: There were no safety concerns raised by the data from this study. This study demonstrates that (R)-albuterol protects against bronchoconstriction from methacholine challenge performed 20 minutes, but not 3 hours after drug administration.

ABSTRACT OF CLINICAL PHARMACOLOGY STUDIES

METHODS: There were three studies (studies 021, 006, and 008) whose primary purpose was to measure plasma levels of (R)-albuterol and correlate the findings with PK and safety parameters, studies. Studies 021 and 008 were randomized, double-blind crossover studies comparing (R)-albuterol to placebo (study 008) and an active treatment control (both studies)(racemic albuterol and (S)-albuterol). In contrast, study 006 was an open-label crossover study comparing (R)-albuterol to (S)-albuterol and racemic albuterol. Studies 021 and 008 were cumulative dose studies, the former with cumulative doses of 5 mg of (R)-albuterol and 10 mg of racemic albuterol, and the latter with cumulative doses of 3.2 mg of (R)-albuterol and 6.4 mg of racemic albuterol. Study 006 compared a low dose of (R)-albuterol and (S)-albuterol (1.25 mg) with a low dose of racemic albuterol (2.5 mg) and a high dose of (R)-albuterol and (S)-albuterol (5 mg) with a high dose of racemic albuterol (10 mg). Studies 006 and 008 were in healthy volunteers and study 021 was in patients with mild-moderate asthma. There were 13, 30, and 12 patients evaluated in studies 021, 006, and 008, respectively. PK parameters were evaluated in studies 021 and 006. ECGs and serum glucose levels were performed in studies 021 and 006. Adverse events and vital signs were assessed in all three studies, as were serum potassium levels. Tremor was evaluated in study 008. FEV-1 was measured for 8 hours after drug administration in study 021.

RESULTS: Plasma levels of (R)-albuterol were higher after administration of (R)-albuterol than after administration of racemic albuterol at twice the dose of (R)-albuterol in both study 021 and study 006, except that in study 006, plasma levels of (R)-albuterol were comparable when administered as (R)-albuterol or as racemic albuterol at twice the dose of (R)-albuterol at the higher dose, i.e. 5 mg of (R)-albuterol produced plasma levels comparable to 10 mg of racemic albuterol. In study 021, the AUC for (R)-albuterol when given as the isomer was comparable to the AUC for (R)-albuterol when given as racemic albuterol, and was about 4 times less than the AUC for (S)-albuterol. The bioavailability of (R)-albuterol was greater at low doses but comparable to (R)-albuterol administered as the racemic mixture at high doses in study 006.

Mean peak increase in FEV-1 was greater after administration of racemic albuterol (61%) compared with (R)-albuterol (44%), with Tmax being quicker with racemic albuterol (219 minutes) compared with (R)-albuterol (231 minutes) and the duration of effect being longer with racemic albuterol (6.6 hours) compared to (R)-albuterol (5.7 hours).

The incidence of nervousness was slightly greater after administration of (R)-albuterol than after administration of racemic albuterol in studies 021 and 006. In fact, in study 006, the overall incidence of adverse events was greater after administration of (R)-albuterol than after administration of racemic albuterol, as was the incidence of tachycardia, headache and dizziness. By contrast, the incidence of tremor and adverse events in general were comparable after administration of (R)-albuterol and racemic albuterol in study 008.

Mean serum glucose (study 021) and potassium (studies 021 and 008) levels were comparable after administration of (R)-albuterol and racemic albuterol in certain studies but the mean change in these parameters was slightly greater after administration of (R)-albuterol than after administration of racemic albuterol in study 006. Mean changes in vital signs in studies 021 and 008 were comparable after administration of (R)-albuterol and racemic albuterol. Changes in the QTc interval were comparable after administration of (R)-albuterol and racemic albuterol in studies 021 and 006.

DISCUSSION: These studies support the safe administration of cumulative doses of (R)-albuterol up to 6.4 mg over a 90 minute period in the treatment of acute asthma. It should be recognized that these data suggest that the systemic effect produced by administration of given dose of (R)-albuterol may be slightly more than that observed when twice this dose is given as racemic albuterol, i.e. that (R)-albuterol, even at ½ the dose of racemic albuterol, may be somewhat more likely to produce systemic effects generally associated with the administration of beta agonists.

ABSTRACT OF STUDY 021

METHODS: This randomized, double-blind, two-way crossover, cumulative dose single center study of 13 adult patients with mild-moderate stable asthma compared the response to cumulative doses of 5 mg of (R)-albuterol and 10 mg of racemic albuterol administered over a period of 90 minutes by nebulizer on two separate study days separated by a washout period of 3-10 days. Parameters evaluated included change in FEV-1 over 8 hours after drug administration (AUC FEV-1 over 8 hours was the primary efficacy variable), vital signs for 8 hours after drug administration, ECGs for 3 hours after drug administration, laboratory tests, adverse events, and plasma and urine levels of (R) and (S)-albuterol for 8 hours after drug administration.

RESULTS: Since all 13 patients completed the study, the intent-to-treat and the efficacy populations were the same.

The plasma level of (R)-albuterol was slightly higher after administration of (R)-albuterol than after administration of racemic albuterol although the AUC for (R)-albuterol after administration of (R)-albuterol was comparable to the AUC for (R)-albuterol after administration of racemic albuterol. The AUC for (S)-albuterol was about 4 times higher than the AUC for (R)-albuterol after administration of racemic albuterol. There were small amounts of (S)-albuterol in (R)-albuterol. Although more variable, generally higher levels of (R)-albuterol were found in the urine after (R)-albuterol administration than after racemic albuterol administration.

There was greater bronchodilitation, as measured by the AUC for FEV-1, after cumulative dosing with the racemic albuterol than after cumulative dosing with the (R)-albuterol isomer, although these differences were not statistically significant. The mean peak percent change in FEV-1 was 44% for (R)-albuterol and 61% for racemic albuterol. The mean time to peak percent change in FEV-1 was 231 minutes after administration of (R)-albuterol and 219 minutes after administration of racemic albuterol. The average duration of effectiveness was 6.6 hours after racemic albuterol and 5.7 hours after (R)-albuterol. Patients who were not receiving corticosteroids demonstrated a greater amount of bronchodilitation than patients who were receiving corticosteroids.

The incidence of nervousness was slightly greater in patients who received (R)-albuterol, but overall there was no significant difference between the adverse events noted after administration of (R)-albuterol and racemic albuterol. There were 2 patients who had serum glucose levels above the upper limit of the normal reference range after receiving (R)-albuterol, whereas none had such an increase after receiving racemic albuterol, but there were no significant differences in mean serum glucose or potassium after administration of these two forms of albuterol. Although there was no difference between (R)-albuterol and racemic albuterol, more than 50% of the patients had a small but significant decrease in hemoglobin and hematocrit after drug administration. There were no other significant changes in laboratory tests. Mean changes in vital signs were essentially the same after administration of (R)-albuterol and racemic albuterol, although mean increase in heart rate was slightly higher after (R)-albuterol. There were no patients who had a prolongation of the QTc interval > 460 msc and the mean QTc interval was essentially the same at all time points after administration of (R)-albuterol and racemic albuterol. All ECGs were read as normal or abnormal but not clinically significant.

DISCUSSION: Cumulative dosing with (R)-albuterol produced a degree of bronchodilitation comparable to racemic albuterol. Although the mean peak effect and duration of bronchodilitation were greater, and the mean time to peak effect was shorter after administration of racemic albuterol, this difference was not likely to have been clinically significant. Therefore, the sponsor has demonstrated the efficacy of (R)-albuterol when given as cumulative doses. Although this was demonstrated in patients with mild-moderate asthma, there is no reason to believe, based on this data, that administration of (R)-albuterol to patients with more severe asthma in an acute setting would not be efficacious. It is interesting to note that both forms of albuterol were less efficacious in terms of FEV-1 if the patient had been receiving corticosteroids. The clinical significance of this finding is unclear.

Based on the data from this study, it is safe to administer cumulative doses up to 5 mg of (R)-albuterol over 90 minutes to patients with mild-moderate asthma. There is no reason to believe that it would not be safe to administer (R)-albuterol to patients with more severe asthma, as well. There was a

slightly greater number of adverse events and a slightly higher mean pulse rate noted after the administration of (R)-albuterol but these were not clinically significant differences. Based on decreases in hemoglobin and hematocrit noted after administration of both forms of albuterol, unless the sponsor can provide data to indicate that this finding was spurious, monitoring of patients for such changes should be considered after the administration of albuterol. Based on ECGs and measurement of vital signs, and compared to the response to racemic albuterol, there were no safety concerns raised by cumulative administration of (R)-albuterol.

A greater degree of efficacy and safety was seen after administration of racemic albuterol compared with (R)-albuterol, despite the fact that plasma levels of (R)-albuterol were lower when racemic albuterol was administered than after (R)-albuterol administration. The reason for this is unclear, but the pharmacokinetic and pharmacodynamic differences between racemic albuterol and (R)-albuterol demonstrated in this study, would not be expected to produce any clinically significant difference.

✦ CUMULATIVE DOSE STUDY ✦

● Study 021: A double-blind, two-way crossover study to evaluate the effects of cumulative dosing of (R)-albuterol and racemic albuterol in patients with mild-moderate asthma.

◆ STUDY CHARACTERISTICS:

❑ number of patients: 13 patients; all patients completed the study; the ITT population included all patients randomized into the study; patients who completed all 4 treatment visits made up the efficacy population; the efficacy population and the ITT population were the same.

❑ age range: 19-41 years

❑ patient population: mild-moderate asthma; stable; use of beta agonist or anti-asthma anti-inflammatory medication for at least 6 months; FEV-1 50-85% predicted; 15% or greater reversibility after 2.5 mg of racemic albuterol by nebulization

❑ study design: randomized, double-blind, two-way crossover, cumulative dose, single center study

❑ drug administration: total dose of 5 mg of (R)-albuterol (4 doses of 1.25 mg/3 ml at 30 minute intervals) compared to a total dose of 10 mg of racemic albuterol (Ventolin)(4 doses of 2.5 mg/3 ml at 30 minute intervals) administered by a PARI LC PLUS nebulizer with a DURA-NEB 2000 Portable compressor; patients were allowed to take their usual asthma medication throughout the study period except for oral or parenteral corticosteroids and long-acting beta agonists, which must have been discontinued at least 8 weeks and 48 hours, respectively, prior to visit 1

❑ periods of study: screening visit (visit 1) not more than 14 days prior to visit 2; 2 separate days of drug administration (visits 2 and 3) separated by a washout period of 3-10 days; patients were seen for

final evaluation (visit 4) between 2-7 days after visit 3; there was a washout of at least 48 hours for theophylline/antihistamines and for other asthma medications at least 8 hours prior to study visits.

❑ parameters evaluated:

EFFICACY

☛ FEV-1: AUC was the primary efficacy variable; peak percent change in FEV-1 and time to peak percent change in FEV-1 were secondary outcome variables; FEV-1 was measured immediately prior to drug administration on visits 2 and 3 and 15, 30, 60 and 90 minutes and 2, 3, 4, 5, 6, 7, and 8 hours after administration of dose 4 at visits 2 and 3; at visit 4

PHARMACOKINETICS

☛ plasma levels of (R)-albuterol and (S)-albuterol; immediately prior to drug administration at visits 2 and 3; 15 minutes after administration of doses 1-3 at visits 2 and 3; 15, 30, and 60 minutes and 3, 6, and 8 hours after dose 4 at visits 2 and 3.

☛ urine levels of (R)-albuterol and (S)-albuterol; prior to dose 1 and at 0-1, 1-2, 2-4, and 4-8 hours after administration of dose 4 at visits 2 and 3; at the conclusion of visits 2 and 3

SAFETY

☛ vital signs: immediately prior to drug administration at visits 2 and 3; 5 minutes after administration of doses 1-3 at visits 2 and 3; 15, 30, 60, and 90 minutes and 2, 3, 4, 5, 6, 7, and 8 hours after dose 4 at visits 2 and 3; at visit 4.

☛ ECGs: 12 lead ECGs immediately prior to drug administration at visits 2 and 3; 20 minutes after administration of doses 1-3 at visits 2 and 3; 15, 30, 60, and 90 minutes and 2 and 3 hours after dose 4 at visits 2 and 3; at visit 4.

- laboratory tests: at screening; on study visits 2 and 3 prior to drug administration for plasma potassium and glucose determinations; plasma glucose and potassium levels obtained 1, 2, 4, 6, and 8 hours after drug administration on study visits 2 and 3; general laboratory tests were done at the end of visits 2 and 3; at visit 4

- adverse events: the primary measure of safety was the incidence of adverse events

❑ Statistical Considerations:

- All efficacy analyses were based on the efficacy population (patients who successfully completed all 4 visits).

- Safety analyses were based on the intent-to-treat population.

- Since all 13 patients completed the study, the ITT and efficacy populations were the same.

- The primary endpoints were: 1) adverse events; 2) plasma AUC for (R)-albuterol and (S)-albuterol; and 3) AUC for FEV-1. The AUC for (R)-albuterol and (S)-albuterol were calculated were evaluated for the first hour and the entire 8 hours following the fourth and last dose using ANOVA.

- AUC for FEV-1 was also evaluated in terms of corticosteroid use.

- peak percent change in FEV-1 and time to peak percent change in FEV-1 were analyzed as secondary endpoints.

◆ STUDY RESULTS:

❑ Study Conduct: There were no protocol deviations.

❑ Safety Data:

☛ **Adverse events: There were 12 patients who experienced 27 AEs after receiving 1.25 mg of (R)-albuterol X 4 and 11 patients who experienced 29 AEs after receiving 2.5 mg of racemic albuterol X 4. Nervousness was the most frequent AE, occurring in 12 patients after receiving 1.25 mg (R)-albuterol and in 9 patients after receiving 25 mg of racemic albuterol. There were 4 patients who noted tachycardia after each treatment. No AEs were considered severe. Wheezing and increased coughing only occurred after patients received racemic albuterol. See table below for a listing of all AEs. The incidence of nervousness was slightly higher after administration of (R)-albuterol which correlates with the slightly higher plasma level of (R)-albuterol obtained after administration of this isomer.**

Summary of All Adverse Events

Body System Preferred Term[2]	Treatment Group[1]					
	(R)-albuterol 5 mg (n=13)		racemic albuterol 10 mg (n=13)		Total (n=13)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
All Adverse Events	12 (92.3%)	27	11 (84.6%)	29	13 (100.0%)	56
Body as a Whole	2 (15.4%)	2	4 (30.8%)	4	4 (30.8%)	6
Headache	2 (15.4%)	2	3 (23.1%)	3	3 (23.1%)	5
Pain chest	0	0	1 (7.7%)	1	1 (7.7%)	1
Cardiovascular System	4 (30.8%)	4	4 (30.8%)	6	6 (46.2%)	10
Hypotension	0	0	1 (7.7%)	1	1 (7.7%)	1
Tachycardia	4 (30.8%)	4	4 (30.8%)	5	6 (46.2%)	9
Digestive System	2 (15.4%)	3	1 (7.7%)	2	2 (15.4%)	5
Dyspepsia	0	0	1 (7.7%)	1	1 (7.7%)	1
Nausea	2 (15.4%)	2	1 (7.7%)	1	2 (15.4%)	3
Vomiting	1 (7.7%)	1	0	0	1 (7.7%)	1
Nervous System	12 (92.3%)	16	10 (76.9%)	11	13 (100.0%)	27
Dizziness	3 (23.1%)	3	2 (15.4%)	2	4 (30.8%)	5
Hypertension[3]	1 (7.7%)	1	0	0	1 (7.7%)	1
Nervousness	12 (92.3%)	12	9 (69.2%)	9	13 (100.0%)	21
Respiratory System	2 (15.4%)	2	5 (38.5%)	6	5 (38.5%)	8
Congestion	0	0	1 (7.7%)	1	1 (7.7%)	1
Cough Inc	0	0	1 (7.7%)	1	1 (7.7%)	1
Pharyngitis	0	0	1 (7.7%)	1	1 (7.7%)	1
Rhinitis	1 (7.7%)	1	0	0	1 (7.7%)	1
Wheezing	1 (7.7%)	1	3 (23.1%)	3	3 (23.1%)	4

Note: On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.

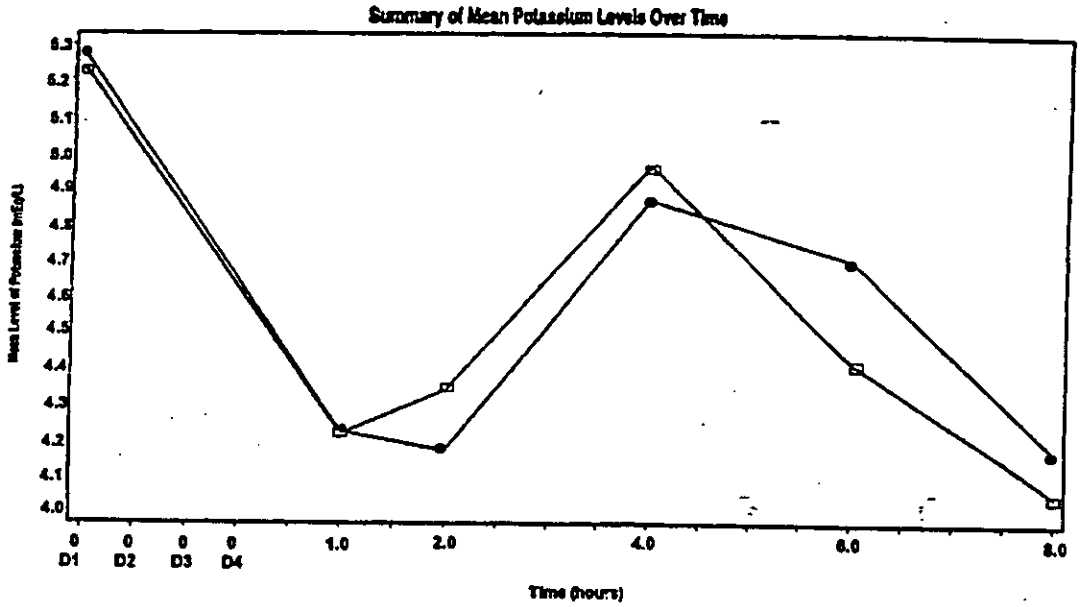
[1]Assignment of AEs to treatments was based on the period beginning on the start day of that treatment to the day prior to the start of the next treatment.

[2]Subjects may have more than one adverse event per body system and preferred term.

[3]Hypertension was incorrectly coded to the Nervous system. The correct body system is Cardiovascular.

Reference: Section 14.3.1.1.

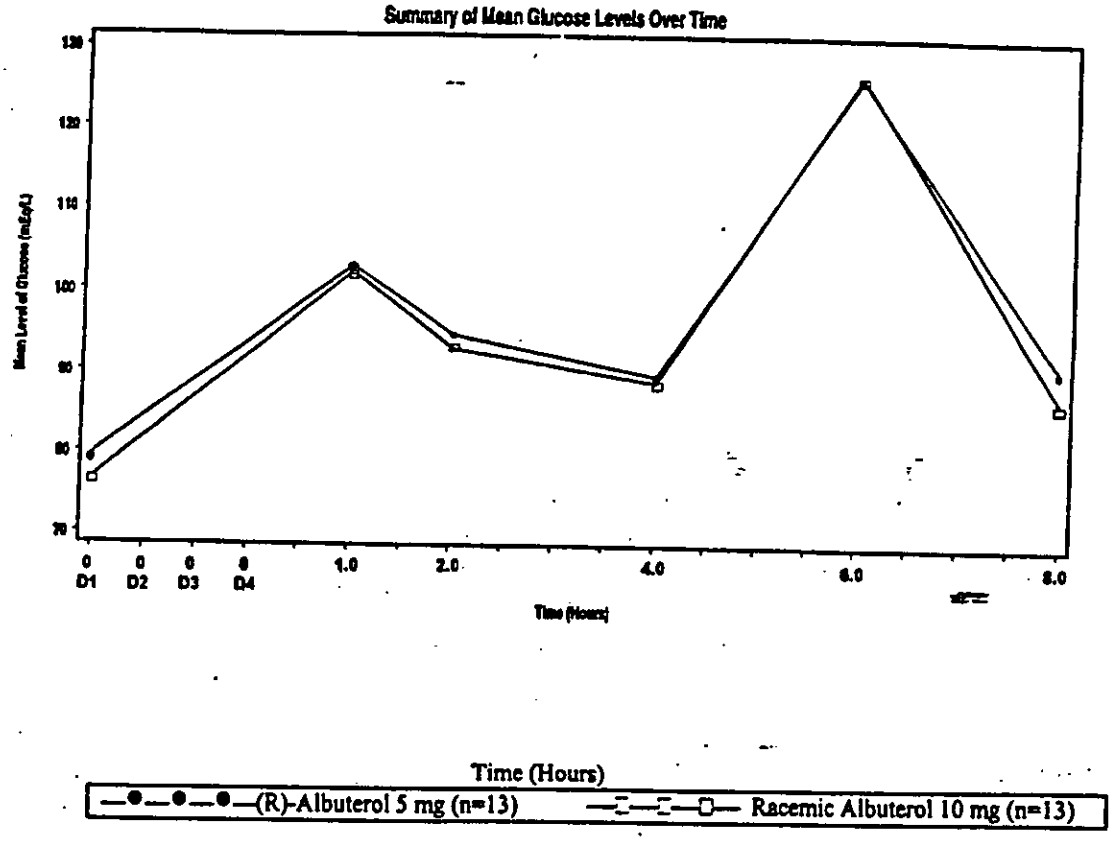
- **Laboratory Tests: The change in mean serum potassium over time can be seen in the figure below. The responses after administration of (R)-albuterol and racemic albuterol are comparable. The fall in mean serum potassium after administration of a beta agonist is not unexpected and the mean serum potassium level never went below the lower limit of the normal reference range.**



On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.
Dosing times are indicated by D1, D2, D3 and D4. Pre-dose values are shown at D1, 0 minutes.
Time of measurement is indicated by the number of minutes after a dose was given.

Reference: Section 14.5.4

The change in mean serum glucose levels after administration of (R)-albuterol and racemic albuterol can be seen in the figure below. Responses in terms of mean serum glucose levels to the two drug products was comparable. The increase in mean serum glucose after administration of a beta agonist is not unexpected and there was no clinically significant increase in mean serum glucose. There were 2 patients who had abnormally high serum glucose levels after receiving (R)-albuterol whereas there were no patients who had such a change after receiving racemic albuterol.



On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.
Dosing times are indicated by D1, D2, D3 and D4. Pre-dose values are shown at D1, 0 hours.
Measurements after dose four are indicated by the number of hours after the fourth dose.

Reference: Section 14.5.5

Mean percent change at discharge (visit 4) relative to baseline (visit 1) was compared for selected laboratory parameters (see table below)

Testing of Laboratory Changes from Baseline at Discharge

	(R)-albuterol 5 mg (n=13)		racemic albuterol 10 mg (n=13)	
	Percent Change from Baseline	p-value[1]	Percent Change from Baseline	p-value[1]
Potassium (mEq/L)				
Mean (SD)	7.8 (8.93)	0.0075	7.8 (7.17)	0.0021
Glucose (mg/dL)				
Mean (SD)	2.4 (14.80)	0.60	-3.1 (12.06)	0.34
Alkaline Phosphatase (IU/L)				
Mean (SD)	-11.2 (6.53)	<0.0001	-11.1 (7.76)	0.0005
Calcium (mg/dL)				
Mean (SD)	-3.9 (3.44)	0.0022	-3.7 (3.46)	0.0029
SGOT (IU/L)				
Mean (SD)	-11.5 (19.61)	0.10	-10.8 (16.24)	0.05
SGPT (IU/L)				
Mean (SD)	-3.2 (25.25)	0.26	-5.4 (21.32)	0.15

Note: On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.
[1] p-values were obtained from a two-sided paired t-test on the mean change from baseline.
Reference: Summarized from Sections 14.3.2.1 and 14.3.2.2.

A decrease in hemoglobin and/or hematocrit was seen in 7 of the 13 patients (5 males). The basis for this finding is unclear but the data on these 7 patients can be seen in the table below (RS= racemic albuterol; R= (R)-albuterol).

Patient	Baseline		Visit 2		Visit 3		Visit 4	
	Hgb	Hct	Hgb	Hct	Hgb	Hct	Hgb	Hct
103								
105								
202								
204								
205								
206								
207								

In 6 of the 7 patients noted in the table above, there is a pattern characterized by a fall in hemoglobin and hematocrit at the end of the first cumulative dosing (in 4 patients racemic albuterol and in 2 patients (R)-albuterol), followed by a further decrease in these parameters after the second cumulative dosing (in 4 patients (R)-albuterol and in 2 patients racemic albuterol) and an increase toward baseline 2-7 days after the second cumulative dosing period. These findings are not incompatible with an acute effect of nebulized albuterol, either racemic or (R)-albuterol, on hemoglobin and hematocrit, with a persistent chronic effect that lasts for at least 7 days after cumulative dosing with albuterol. This data suggests that patients who receive cumulative doses of albuterol to treat acute asthma should be monitored acutely and chronically for changes in hemoglobin and hematocrit.

COMMENT: ***Unless the sponsor can provide data which indicates that these findings were spurious, the labeling for (R)-albuterol (and subsequently racemic albuterol) should indicate that patients who receive cumulative doses of albuterol should have a hemoglobin and hematocrit determined before and immediately following this type of treatment, and if these lab values are decreased, further monitoring may be necessary.***

- **Vital Signs: Individual patients frequently had different responses to (R)-albuterol and racemic albuterol in terms of pulse rate, systolic blood pressure and diastolic blood pressure. For example, patient 101 had an increase in systolic blood pressure from 148 mm hg to 159 mm hg 15 minutes after dose 4 of racemic albuterol and a decrease from 145 mm hg to 127 mm hg 15 minutes after dose 4 of (R)-albuterol. These differences were not clinically significant and were extremely variable. Other changes in vital signs were atypical. For example, patient 106 had a fall in blood pressure after both (R)-albuterol and racemic albuterol and was considered to have been a hypotensive adverse event. Mean changes were, however, essentially the same after (R)-albuterol and racemic albuterol.**

- **ECGs: mean change in heart rate over 3 hours after the last dose of study drug can be seen in the table below. Patient response after administration of (R)-albuterol and racemic albuterol was comparable. Mean increase in heart rate was slightly higher after treatment with (R)-albuterol, which correlates with the slightly higher plasma levels of (R)-albuterol after (R)-albuterol was given.**

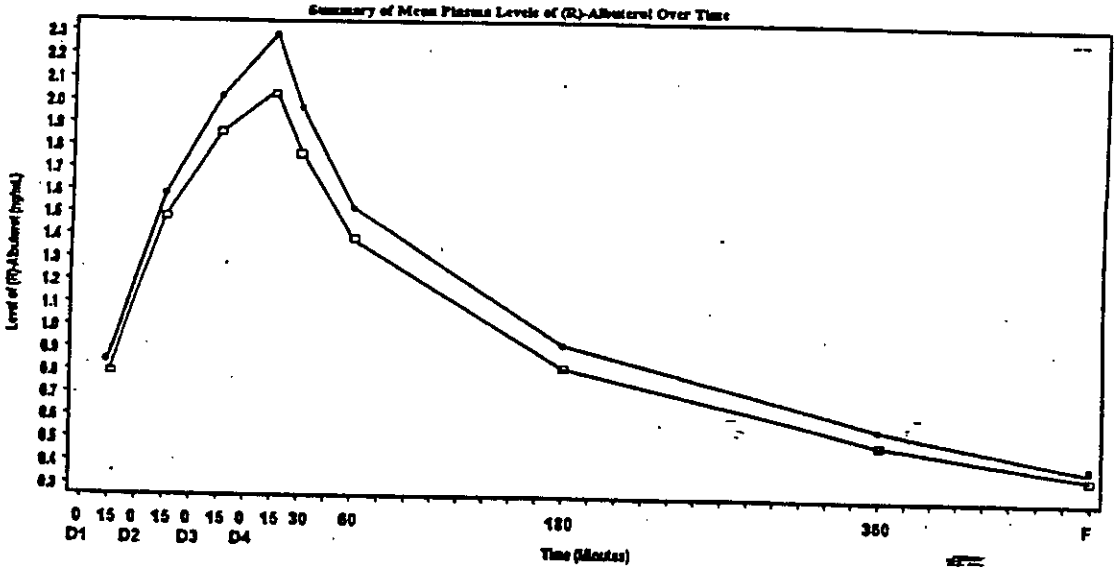
Summary of Ventricular Rate (BPM) Relative to Dosing

	Treatment Group	
	(R)-albuterol 5 mg (n=13)	racemic albuterol 10 mg (n=13)
Pre-Dose Mean (SD)	68.9 (9.84)	67.5 (10.85)
Post-Dose 1 - 20 Minutes Mean (SD)	74.9 (11.00)	69.4 (11.45)
Post-Dose 2 - 20 Minutes Mean (SD)	79.2 (12.62)	75.8 (14.76)
Post-Dose 3 - 20 Minutes Mean (SD)	82.2 (12.42)	80.4 (15.04)
Post-Dose 4 - 15 Minutes Mean (SD)	85.3 (14.44)	81.2 (19.08)
Post-Dose 4 - 30 Minutes Mean (SD)	84.3 (14.68)	78.6 (17.23)
Post-Dose 4 - 60 Minutes Mean (SD)	80.3 (13.58)	79.0 (16.47)
Post-Dose 4 - 90 Minutes Mean (SD)	77.5 (11.93)	74.3 (12.31)
Post-Dose 4 - 2 Hours Mean (SD)	77.6 (12.69)	73.5 (13.99)
Post-Dose 4 - 3 Hours Mean (SD)	73.6 (11.97)	73.5 (14.03)

Note: On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.
Reference: Summarized from Section 14.4.2.2.

In terms of QTc prolongation, there were no patients whose QTc interval was prolonged > 460 msc. In 6 patients, there was a 9-31 msc greater increase in QTc interval at some time point after administration of (R)-albuterol than after administration of racemic albuterol. There were 4 patients who had a 15-59 msc greater increase in QTc interval at some time point after administration of racemic albuterol than after administration of (R)-albuterol, and 3 patients where the maximum change in the QTc interval was approximately the same after each treatment. Mean QTc intervals were essentially the same at all time points after administration of (R)-albuterol and racemic albuterol. All ECGs were read as normal or abnormal but not clinically significant .

❑ **Pharmacokinetic Data: As can be seen in the table and figure below, the plasma level of (R)-albuterol was slightly higher after administration of (R)-albuterol than after administration of racemic albuterol. The plasma concentration of (R)-albuterol increased with each successive dose of either (R)-albuterol or racemic albuterol. The AUC for (R)-albuterol was comparable when the patient received (R)-albuterol and racemic albuterol. Mean plasma levels of (S)-albuterol after administration of (R) albuterol and racemic albuterol can be seen, as well, in the figure below.**



On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.
Dosing times are indicated by D1, D2, D3 and D4.
The final measurement, taken at 8 hours after Dose 4, is indicated by F.
Time of plasma level measurement is indicated by the number of minutes after a dose was given.
Reference: Section 14.5.1

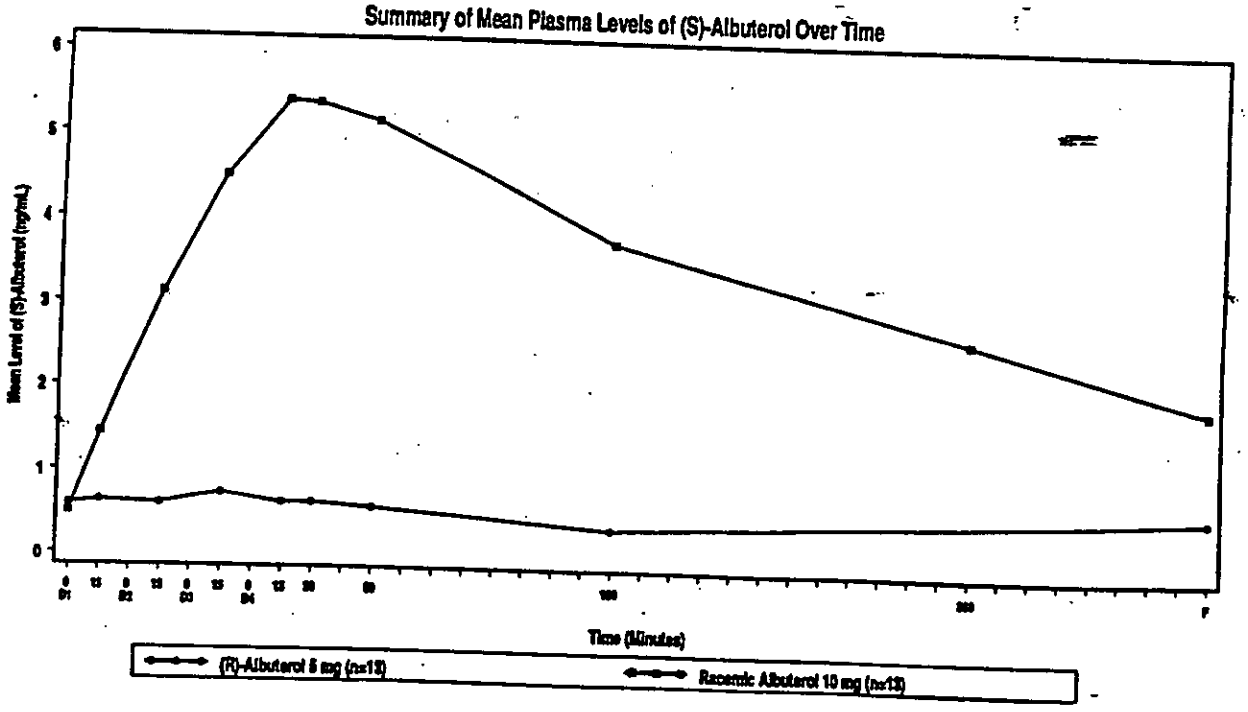
Summary of Area Under the Curve for Plasma Levels of (R)-albuterol (ng-min/mL)

	Treatment Group		
	(R)-albuterol 5 mg	racemic albuterol 10 mg	p-value[1]
AUC [0-1 Hour Post-Dose 4]			
All Subjects			
Mean (SD)	306.3 (140.18)	279.3 (85.27)	0.37
n	13	13	
Male Subjects			
Mean (SD)	280.8 (105.13)	250.6 (63.85)	0.35
n	7	7	
Female Subjects			
Mean (SD)	336.1 (178.68)	312.9 (100.23)	0.26
n	6	6	
AUC [0-8 Hours Post-Dose 4]			
All Subjects			
Mean (SD)	610.9 (262.80)	587.3 (153.36)	0.71
n	13	13	
Male Subjects			
Mean (SD)	577.3 (222.98)	526.2 (99.61)	0.46
n	7	7	
Female Subjects			
Mean (SD)	650.1 (320.41)	658.6 (182.25)	0.64
n	6	6	

Note: On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.

[1] p-values are for treatment effect on the AUC based on an ANOVA model with the following effects: sequence, subject within sequence, period, and treatment.

Reference: Sections 14.2.1.1 though 14.2.1.3; Summarized from Tables 14.2.1.1-14.2.1.3.



COMMENT: *The sponsor states that there were low levels of (S)-albuterol in the plasma of patients who received (R)-albuterol, but the levels did not increase with increased doses of (R)-albuterol, and that this was due to residual levels from previous use of the racemic albuterol as rescue medication, which was in turn due to the longer half-life of the (S)-isomer. The amount of (S)-isomer in (R)-albuterol may be important clinically and the need to address this issue was discussed with Chemistry. In addition, based on AUC for plasma levels of racemic albuterol, there is a mean level of 587 ng-min/mL of (R)-albuterol and 2117 ng-min/mL of (S)-albuterol in racemic albuterol, with slightly higher levels of (S)-albuterol consistently being demonstrated in women (this was noted as well in terms of the amount of (S)-albuterol in (R)-albuterol). The greater AUC for (S)-albuterol is primarily due to the fact that the (S)-isomer remains in the plasma for a substantially longer period of time, but the mean peak level of the (S)-isomer is also about 2 times greater than the mean peak plasma level of the (R)-isomer. If, in fact, there is substantially more of the (S)-isomer available over a longer period of time, this could be one explanation for the development of negative pulmonary effects with repetitive administration.*

Urinary (R)-albuterol levels were more variable than plasma (R)-albuterol levels (see table below), but generally higher levels of (R)-albuterol were found in the urine after (R)-albuterol administration than after administration of racemic albuterol. Also, levels of (S)-isomer were substantially greater than levels of (R)-isomer after administration of racemic albuterol, which was similar to what was found in the plasma.

Time of collection	(R)-albuterol	racemic albuterol
pre-drug	53	49
0-1 hour post-drug	769	625
1-2 hours post-drug	670	214
2-4 hours post-drug	477	510
4-8 hours post-drug	333	187

❑ **Efficacy Data: The primary efficacy endpoint was AUC for FEV-1 over the first hour after the fourth dose and over the 8 hours after the fourth dose. As can be seen in the table below, there was a greater effect on FEV-1 after cumulative dosing with racemic albuterol than after cumulative dosing with the (R)-albuterol isomer, particular in male patients. The mean peak percent change in FEV-1 (44% for (R)-albuterol and 61% for racemic albuterol) and the mean time to peak percent change in FEV-1 in minutes (231 for (R)-albuterol and 219 for racemic albuterol) were comparable between the two treatment groups. Those patients receiving corticosteroids (oral and inhaled) had a smaller AUC for FEV-1 than patients who were not receiving corticosteroids. The greatest difference in FEV-1 was seen in the racemic group between those patients taking corticosteroids and those patients who were not taking corticosteroids (see table below).**

Summary of Area Under the Curve for FEV_1 (Min-L)

	Treatment Group		
	(R)-albuterol 5 mg (n=13)	racemic albuterol 10 mg (n=13)	p-value[1]
AUC [0-1 Hour Post-Dose 4]			
All Subjects			
Mean (SD)	287.5 (46.20)	315.3 (84.12)	0.22
n	13	13	
Male Subjects			
Mean (SD)	280.2 (49.96)	330.3 (95.69)	0.20
n	7	7	
Female Subjects			
Mean (SD)	295.9 (44.36)	297.8 (72.89)	0.99
n	6	6	
AUC [0-8 Hours Post-Dose 4]			
All Subjects			
Mean (SD)	804.6 (129.71)	872.2 (209.63)	0.21
n	13	13	
Male Subjects			
Mean (SD)	799.7 (124.48)	906.3 (262.05)	0.22
N	7	7	
Female Subjects			
Mean (SD)	810.3 (147.35)	832.5 (139.79)	0.60
n	6	6	

Note: On a treatment day, subjects received four consecutive doses of (R)-albuterol 1.25 mg for a total cumulative dose of 5 mg or four consecutive doses of racemic albuterol 2.5 mg for a total cumulative dose of 10 mg.
[1] p-values are for treatment effect on the AUC based on an ANOVA model with the following effects: sequence, subject within sequence, period, and treatment.
Reference: Summarized from Sections 14.2.3.1 and 14.2.3.4, and 14.2.3.5.

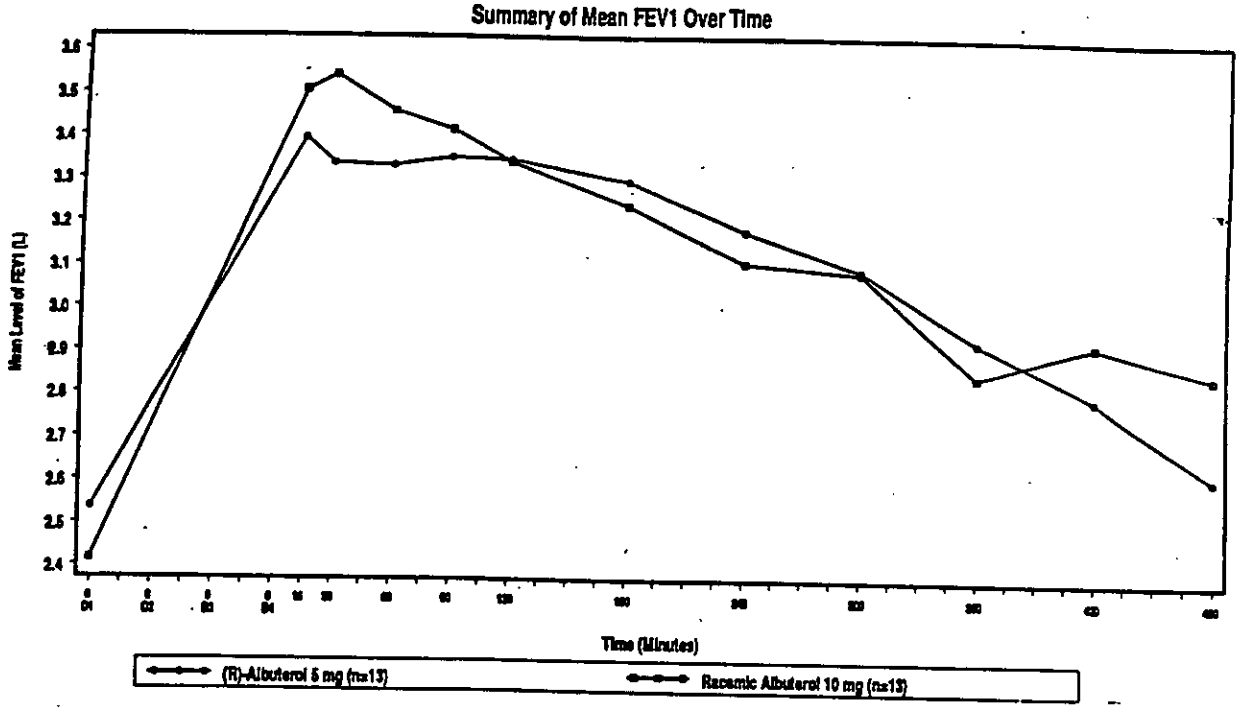
MEAN AUC FEV-1 (MIN-L)

time frame	not using corticosteroids		using corticosteroids	
	(R)-albuterol	racemic mix	(R)-albuterol	racemic mix
0-1 hour after dose 4	296	358	279	266
0-8 hours after dose 4	830	953	775	779

The average duration of effectiveness for the 13 patients studied, based on a 15% or greater increase from baseline in FEV-1, was 6.6 hours after administration of racemic albuterol and 5.7 hours after administration of (R)-albuterol. The number of patients who had a specific duration of efficacy noted after administration of racemic and (R)-albuterol can be seen in the table below. Although there was a substantially greater number of patients who had a duration of effect of at least 8 hours after administration of racemic albuterol, there were equal numbers of patients who had a duration of effect of 6-8 hours, after administration of racemic albuterol and (R)-albuterol.

Number of patients who had a 15% or greater increase in FEV-1 from baseline for a duration of 2-8 hours

hours	(R)-albuterol	racemic albuterol
2	1	1
3	1	1
4	2	0
5	0	2
6	4	0
7	2	1
8	3	8



EFFICACY CONCLUSIONS: ***Cumulative dosing with (R) albuterol produced a degree of bronchodilitation comparable to racemic albuterol. Although the mean peak effect and duration of bronchodilitation were greater, and the mean time to peak effect was shorter after administration of racemic albuterol, this difference was not likely to have been clinically significant. Therefore, the sponsor has demonstrated the efficacy of (R)-albuterol when given as cumulative doses, consistent with the way that (R)-albuterol would be administered in an acute setting. Interestingly, mean AUC FEV-1 was less after administration of (R)-albuterol and racemic albuterol if the patient was receiving corticosteroids. The clinical significance of this finding is unclear.***

SAFETY CONCLUSIONS: ***There were no safety concerns raised by the data from this study. Based on the data in this study, it is safe to give cumulative doses up to 5 mg of (R)-albuterol over 90 minutes to patients with mild-moderate asthma. There is no reason to believe that it would not be safe to administer (R)-albuterol to patients with more severe asthma, as well. There was a slightly greater number of adverse events and pulse rate after receiving (R) albuterol consistent with the slightly greater plasma levels of (R)-albuterol after administration of (R)-albuterol. Patients receiving any form of albuterol should probably be monitored for changes in hemoglobin and hematocrit.***

ABSTRACT OF STUDY 006

METHODS: This randomized, open, crossover, active treatment controlled, single dose, single center study in adult volunteers compared PK and safety parameters in 15 patients who received 1.25 mg of (R)-albuterol and (S)-albuterol as well as 2.5 mg of racemic albuterol and 15 patients who received 5 mg (1.25 mg X4) of (R)-albuterol and (S)-albuterol as well as 10 mg (2.5 mg X4) of racemic albuterol. There was a washout period of 3-7 days between treatment days. Plasma levels of (R)-albuterol and (S)-albuterol were obtained when (R)-albuterol and (S)-albuterol were given alone and when they were given as the racemic mixture. PK parameters included AUC, Cmax, T ½ CL/f, and V/f. Systemic effect was evaluated by vital signs, plasma potassium and glucose obtained 60 minutes after drug administration, adverse events, and ECGs obtained 15, 45, and 90 minutes after drug administration.

RESULTS: There were slightly higher plasma levels of (R)-albuterol measured when (R)-albuterol was administered alone at a dose of 1.25 mg, as compared with racemic albuterol administered at a dose of 2.5 mg. The relative bioavailability of (R)-albuterol was greater when administered alone at a dose of 1.25 mg compared to when it was administered as a component of racemic albuterol at a dose of 2.5 mg. Mean plasma concentrations of (R)-albuterol were almost superimposable after administration of 5 mg of (R)-albuterol and 10 mg of racemic albuterol. The relative bioavailability was comparable although greater when (R)-albuterol was administered alone at a dose of 5 mg compared with administration of 10 mg of racemic albuterol. There did not appear to be any interconversion of albuterol isomers. The clearance rate of (R)-albuterol was significantly faster than the clearance rate of (S)-albuterol. Four consecutive doses of (R)-albuterol, and (S)-albuterol and racemic albuterol as well, increased Cmax fourfold but increased the AUC more than fourfold.

After administration of 5 mg of (R)-albuterol, 12/15 patients experienced 33 adverse events, compared to 8/15 patients who experienced 23 adverse events after administration of 10 mg of racemic albuterol and 3/15 patients who experienced 5 adverse events after administration of 5 mg of (S)-albuterol.

There was a substantial increase in mean heart rate after administration of 5 mg of (R)-albuterol which was comparable to the increase seen after administration of 10 mg of racemic albuterol. There was no significant change in heart rate seen after administration of 5 mg of (S)-albuterol. A slightly greater incidence of nervousness was seen after administration of (R)-albuterol at a dose of 1.25 mg and 5 mg than was seen after administration of racemic albuterol at a dose of 2.5 mg and 10 mg. Tachycardia, headache and dizziness also occurred more frequently after administration of (R)-albuterol than after administration of racemic albuterol. The highest Cmax values were associated with the lowest mean serum potassium and highest glucose levels, with slightly greater changes in these directions being seen after administration of (R)-albuterol than after administration of racemic albuterol.

The following individual patient responses are of note: 1) a 48 year old woman developed ECG changes consistent with myocardial ischemia after administration of both (R)-albuterol and racemic albuterol, although the changes after (R)-albuterol were significantly greater; 2) a 26 year old woman experienced a syncopal episode associated with tachycardia after receiving 5 mg of (R)-albuterol that was considered probably related to drug administration, at which time her QTc interval increased to 450 msec.; and 3) a 27 year old woman had an increase in blood pressure from 109/71 to 153/116 mm Hg 15 minutes after administration of 5 mg of (R)-albuterol.

DISCUSSION: The sponsor states that the plasma (R)-albuterol levels after a dose of 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol were low (near the limit of quantitation), extremely variable and only detectable for 2-4 hours, therefore making a comparison of relative bioavailability at these doses inappropriate. This is a reasonable determination by the sponsor. The bioavailibility of (R)-albuterol when administered alone and when administered as a racemic mixture, based on the data generated by a dose of 5 mg of (R)-albuterol and 10 mg of racemic albuterol, was comparable. In general, measures of systemic effect were comparable between (R)-albuterol and twice the dose of racemic albuterol, although there is a strong impression that (R)-albuterol at a given dose is more likely to produce a systemic effect than twice the dose of racemic albuterol. This impression is based on the following: 1) after administration of 5 mg of (R)-albuterol , more patients

experienced adverse events than after administration of 10 mg of racemic albuterol; 2) One patient had more pronounced ECG changes of myocardial ischemia after administration of 1.25 mg of (R)-albuterol than after administration of 2.5 mg of racemic albuterol; 3) there was a slightly greater incidence of nervousness, tachycardia, headache and dizziness after administration of (R)-albuterol compared with racemic albuterol; 4) there was a slightly greater decrease in mean serum potassium and increase in mean serum glucose after administration of (R) albuterol compared with racemic albuterol; and 5) one patient had a syncopal episode associated with tachycardia and an increase in the QTc interval after administration of 5 mg of (R)-albuterol. While such effects are not unexpected after administration of an inhaled beta agonist, based on the results of this study, the labeling should indicate that systemic effects may be more likely to occur after administration of (R)-albuterol, despite the fact that the dose is only ½ the dose of racemic albuterol.

✦ PHARMACOKINETIC STUDIES:

● Study 006: Pharmacokinetics of (R)- and (S)- and racemic albuterol following administration by nebulization in normal volunteers to determine exposure of individuals to these products, to determine if there was any interconversion in-vivo, to determine the safety of (R)-albuterol and to determine the comparability of different doses of the R and S enantiomers of albuterol to racemic albuterol. Investigator: CL Ferguson MD, Baltimore, MD.

Study Characteristics

❑ number of patients: 30 enrolled; the evaluable population included all patients who participated in all 3 treatment periods, i.e. 14/15 patients in Group A (low dose) and 13/15 patients in Group B (high dose);

❑ age range: 18-48 years

❑ patient population: normal volunteers; FEV-1 85% or greater of predicted; no medications for 90 days

❑ study design: randomized, open, 3-way crossover, dose comparison, single dose, single center, active treatment-controlled study

❑ drug administration: 1.25 mg and 5 mg (1.25 mg X4) of both (R)-albuterol (lot number 00696A) and (S)-albuterol (lot number 00696E) by nebulization of single ampule; one group of 15 patients received the low dose of (R)-albuterol and (S)-albuterol and the other group of 15 patients received the high dose of (R)-albuterol and (S)-albuterol; all doses were administered by a Pari LC Jet nebulizer with a DuraNeb 2000 compressor; racemic albuterol (lot number 960308) (Ventolin) 2.5 mg and 10 mg (2.5 mg X4) administered by nebulizer; group A patients received 1.25 mg of (R)-albuterol, 1.25 mg of (S)-albuterol and 2.5 mg of racemic albuterol (nebulization of single ampule); group B patients received 5 mg of (R)-albuterol and (S)-albuterol and 10 mg of

racemic albuterol (consecutive administration of 4 ampules)

❑ periods of study: 5 visits; a screening visit, 3 treatment visits and a final evaluation visit; there was a washout period of 3-7 days between visits; patients remained in the clinic for 24 hours after drug administration and returned to the clinic after 48 hours.

❑ parameters evaluated:

PHARMACOKINETIC: The primary PK endpoint was AUC.

- ☛ plasma levels obtained prior to drug administration and 10, 20, 30, 45, 60, 75, and 90 minutes and 2, 3, 4, 6, 8, 12, 16, and 24 hours after drug administration

- ☛ urine samples prior to drug administration and 0-30, 30-60 minutes and 1-2, 2-4, 4-8, 8-12, 12-16, 16-24, and 24-48 hours after drug administration

- ☛ AUC(0-24), AUC, Cmax, Tmax, T ½, CL/f, V/f were calculated for (R)-albuterol and (S)-albuterol from plasma, and CLr and Ae were calculated from urine samples

SAFETY

- ☛ vital signs: prior to drug administration and 24 hours after drug administration

- ☛ plasma potassium and glucose: prior to drug administration and 60 minutes after drug administration

- ☛ adverse events

- ☛ 12 lead ECG: prior to administration and 15 and 45 minutes and 1.5 hours after drug administration on study days and 48 hours after the last dose

- ☛ laboratory tests at screening and at visit 5

- ☛ pulmonary function at screening and at visit 5, as well as 24 hours after drug administration at visits 2-4

❑ <u>statistical considerations</u>:

- ☛ All tabular summaries except primary and secondary PK endpoints were performed on the ITT population

- ☛ The null hypotheses to be tested were: 1) that the bioavailability of the single isomer within each dose group was the same when administered alone or as an equal amount of the racemate; 2) that the bioavailability of the single isomer across both dose groups was the same when administered alone or as an equal amount in the racemate; and 3) the bioavailability of four times the isomer or the racemate was equal to the higher dose.

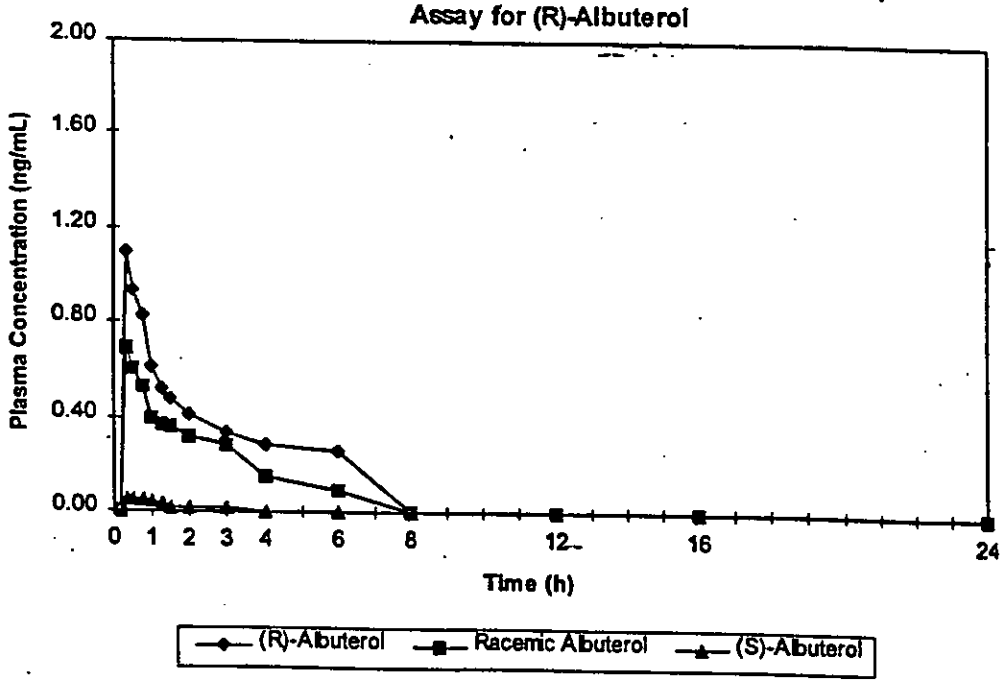
- ☛ Multivariate analyses of variance on the AUCs were used to compare treatments within each dose group.

Study Results

- ☛ Three patients prematurely discontinued the study and were excluded from the PK analysis, which included, therefore, 27 patients.

- ☛ There were comparable amounts of (R)-albuterol measured when (R)-albuterol was administered alone (single dose of 1.25 mg) or as racemic albuterol (single dose of 2.5 mg)(see figure below)

Figure 1. Mean Plasma Concentrations Over Time Group A Assay for (R)-Albuterol



☛ **The relative bioavailability of (R)-albuterol after administration of 1.25 mg of (R)-albuterol or 2.5 mg of racemic albuterol can be seen in the table below.**

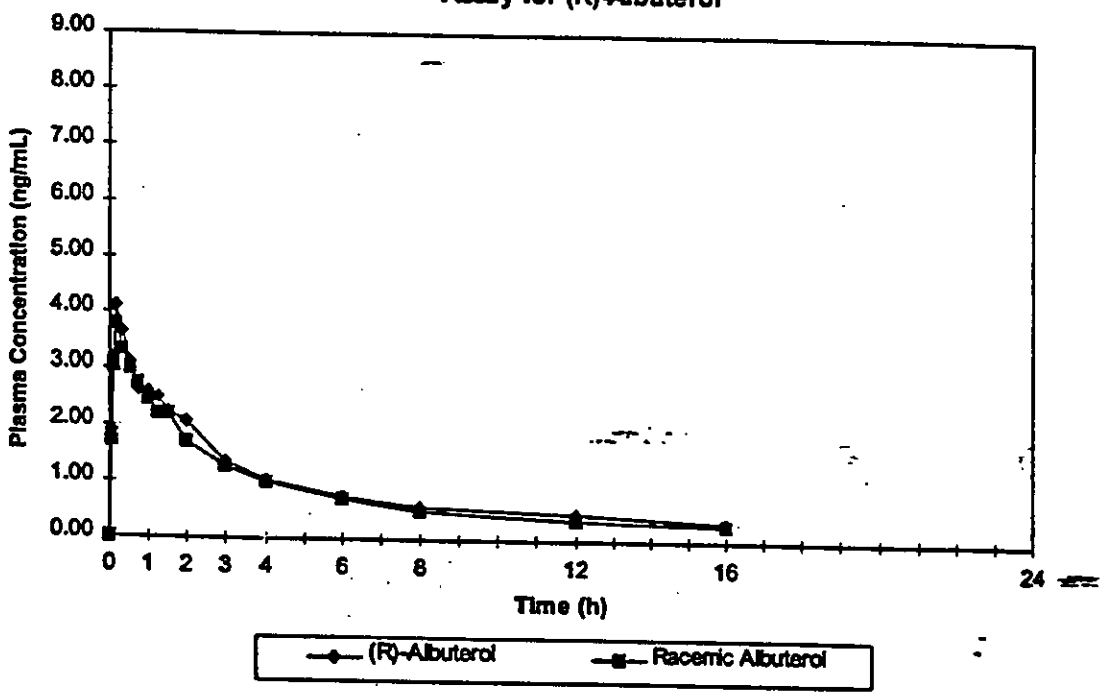
Table 3. Comparative Bioavailability Analysis of Pharmacokinetic Parameters Group A Assay for (R)-Albuterol

Treatment Summary Statistics	AUC (0→24) (ng*h/mL)	AUC (ng*h/mL)	C_{max} (ng/mL)
(R)-Albuterol			
N	14	14	14
Arithmetic Mean (SD)	2.00 (0.85)	3.26 (1.58)	1.11 (0.45)
CV (%)	42.58	48.29	40.65
Racemic Albuterol			
N	14	14	14
Arithmetic Mean (SD)	1.12 (0.78)	1.66 (0.99)	0.78 (0.41)
CV (%)	69.90	59.40	52.24
Least-Square Means (SE)			
(R)-Albuterol, 1.25 mg	2.011 (0.13)	3.256 (0.24)	1.123 (0.07)
Racemic Albuterol, 2.5 mg	1.158 (0.13)	1.710 (0.24)	0.801 (0.07)
Difference of the Least-Square Means ((R)-Albuterol - Racemic Albuterol)	0.85	1.55	0.32
95% Confidence Interval of (R)-Albuterol - Racemic Albuterol			
Lower Limit	0.46	0.84	0.12
Upper Limit	1.24	2.25	0.52
P-Value[1]	0.0001	0.0001	0.0026

Note: Subjects 011, 020, and 029 were not included in the pharmacokinetic analysis due to early withdrawal.
[1]P-value based on a t-test from a within group ANOVA model with effects for: sequence, subject (sequence), period, and treatment.
Reference: Table14.2.1.1a

- There were comparable amounts of (R)-albuterol measured when (R)-albuterol was administered alone as a single dose of 5 mg and as a single dose of 10 mg of racemic albuterol, as well (see figure below). Even more than was seen after administration of lower doses (group A), the levels of (R)-albuterol are almost superimposable. Based on this data, ½ the dose of racemic albuterol is needed to produce comparable plasma levels of (R)-albuterol after administration of (R)-albuterol.

Figure 2. Mean Plasma Concentrations Over Time Group B Assay for (R)-Albuterol



- The relative bioavailability of (R)-albuterol after administration of 5 mg of (R)-albuterol and 10 mg of racemic albuterol can be seen in the table below. This data supports the contention that (R)-albuterol at ½ the dose of racemic albuterol will produce comparable bioavailability.

Table 4. Comparative Bioavailability Analysis of Pharmacokinetic Parameters Group B Assay for (R)-Albuterol

Treatment Summary Statistics	AUC (0→24) (ng*h/mL)	AUC (ng*h/mL)	C_{max} (ng/mL)
(R)-Albuterol			
N	13	13	13
Arithmetic Mean (SD)	15.26 (8.18)	17.44 (8.56)	4.50 (2.20)
CV (%)	53.57	49.10	48.91
Racemic Albuterol			
N	13	13	13
Arithmetic Mean (SD)	14.22 (7.11)	15.98 (7.12)	4.18 (1.51)
CV (%)	49.99	44.57	36.12
Least-Square Means (SE)			
(R)-Albuterol, 5 mg	15.049 (1.28)	17.205 (1.31)	4.459 (0.34)
Racemic Albuterol, 10 mg	14.263 (1.28)	16.027 (1.31)	4.190 (0.34)
Difference of the Least-Square Means			
((R)-Albuterol - Racemic Albuterol)	0.79	1.18	0.27
95% Confidence Interval of (R)-Albuterol - Racemic Albuterol			
Lower Limit	-2.97	-2.67	-0.73
Upper Limit	4.55	5.03	1.27
P-Value[1]	0.6690	0.5322	0.5814

Note: Subjects 011, 020, and 029 were not included in the pharmacokinetic analysis due to early withdrawal.
[1]P-value based on a t-test from a within group ANOVA model with effects for: sequence, subject (sequence), period, and treatment.
Reference: Table14.2.1.1b

- **Dose proportionality was demonstrated by Cmax, i.e. mean 1.11 ng/mL after administration of 1.25 mg of (R)-albuterol and mean 4.50 ng/mL after administration of 5 mg of (R)-albuterol.**

- **Higher plasma levels were noted in MALES after the high dose of (R)-albuterol, (S)-albuterol and racemic albuterol. (S)-albuterol plasma levels were higher after the high dose of (S)-albuterol and racemic albuterol after administration to AFRICAN-AMERICAN patients than levels after administration to Caucasian patients.**

- **Secondary pharmacokinetic endpoints after low and high doses of (R)-albuterol, (S)-albuterol and racemic albuterol can be seen in the tables below.**

11.4.2 Secondary Pharmacokinetic Endpoints

The secondary pharmacokinetic parameters that were identified or calculated for (R)-albuterol and (S)-albuterol are presented by treatment administration and dose group in Tables 7 and 8, respectively. Listings of the secondary pharmacokinetic parameters by subject can be found in Appendices 16.2.14.2a through 16.2.14.2d

Table 7. Summary of Secondary Pharmacokinetic Parameters
Assay for (R)-Albuterol

	(R)-albuterol		Racemic albuterol	
Parameter / Statistics	Group A 1.25 mg dose	Group B 5 mg dose	Group A 2.5 mg dose	Group B 10 mg dose
t_{max} (h)[a]				
N	13	13	13	13
Mean (SD)	0.20 (0.07)	0.25 (0.32)	0.30 (0.37)	0.25 (0.17)
Median	0.17	0.17	0.17	0.17
Min, Max	0.17, 0.37	-0.18, 1.25	0.17, 1.50	-0.32, 1.00
CV (%)	34.44	132.50	121.68	149.40
λ_z (h^{-1})				
N	13	13	12	13
Mean (SD)	0.36 (0.27)	0.18 (0.06)	0.52 (0.19)	0.18 (0.04)
Median	0.27	0.17	0.51	0.18
Min, Max	0.08, 0.82	0.12, 0.31	0.23, 0.89	0.12, 0.25
CV (%)	76.35	29.87	36.19	23.64
$t_{1/2}$ (h)				
N	13	13	13	13
Mean (SD)	3.33 (2.45)	4.03 (1.05)	1.48 (0.61)	4.05 (0.97)
Median	2.59	3.96	1.35	3.92
Min, Max	0.84, 8.44	2.30, 5.95	0.78, 3.06	2.74, 5.73
CV (%)	74.47	26.01	41.23	24.04
CL/F (L/h)				
N	13	13	13	13
Mean (SD)	418.00 (191.74)	370.94 (217.65)	1827.30 (1239.57)	726.68 (276.30)
Median	353.19	346.94	1600.07	772.90
Min, Max	227.51, 825.21	148.04, 940.23	679.19, 5770.34	334.78, 1354.94
CV (%)	45.87	58.68	70.98	37.92
V_z/F (L)				
N	13	13	12	13
Mean (SD)	1544.94 (692.56)	1956.93 (815.28)	3007.76 (1686.41)	4211.86 (2011.49)
Median	1319.05	1893.40	2795.23	4148.16
Min, Max	747.89, 2773.41	1015.17, 3734.54	1792.23, 5923.75	1894.38, 9838.25
CV (%)	44.83	41.66	56.12	47.77

Note: Subjects 811, 820, and 829 were not included in the pharmacokinetic analysis due to early withdrawal.
[a]Negative t_{max} values indicate that maximum concentration is occurring between the first and last administration.
Reference: Appendix 14.2.1.4a

Table 8. Summary of Secondary Pharmacokinetic Parameters
Assay for (S)-Albuterol

	Racemic albuterol		(S)-albuterol	
Parameter / Statistics	Group A 2.5 mg dose	Group B 10 mg dose	Group A 1.25 mg dose	Group B 5 mg dose
t_{max} (h)[a]				
N	13	13	14	13
Mean (SD)	0.92 (1.01)	0.83 (0.91)	0.68 (0.79)	0.99 (0.93)
Median	0.50	0.37	0.36	0.50
Min, Max	0.33, 4.00	-0.32, 3.00	0.17, 3.00	0.17, 3.00
CV (%)	108.31	109.08	115.23	94.36
λ_z (h^{-1})				
N	13	13	14	13
Mean (SD)	0.15 (0.04)	0.13 (0.04)	0.15 (0.06)	0.11 (0.03)
Median	0.17	0.11	0.14	0.10
Min, Max	0.07, 0.19	0.09, 0.20	0.05, 0.29	0.06, 0.18
CV (%)	25.80	29.67	39.51	29.31
$t_{1/2}$ (h)				
N	13	13	14	13
Mean (SD)	5.12 (1.82)	5.39 (1.35)	5.22 (2.13)	6.65 (1.75)
Median	4.19	5.29	5.06	6.52
Min, Max	3.67, 9.52	3.39, 7.66	2.41, 11.50	3.93, 9.23
C.V. (%)	35.55	25.03	40.87	26.35
CL/F (L/h)				
N	13	13	14	13
Mean (SD)	236.64 (78.35)	155.92 (50.31)	171.40 (103.35)	88.93 (49.74)
Median	240.45	154.48	99.50	64.99
Min, Max	114.51, 330.78	84.83, 228.85	46.71, 383.79	35.35, 220.85
CV (%)	33.07	32.27	75.22	61.45
V_z/F (L)				
N	13	13	14	13
Mean (SD)	1662.53 (801.19)	1315.57 (341.72)	858.80 (491.32)	726.23 (400.91)
Median	1546.44	1214.29	701.61	635.75
Min, Max	989.34, 3153.53	687.75, 2295.53	281.51, 1868.76	258.79, 1749.95
CV (%)	36.15	41.18	46.77	54.43

Note: Subjects 811, 820, and 829 were not included in the pharmacokinetic analysis due to early withdrawal.
[a]Negative t_{max} values indicate that maximum concentration is occurring between the first and last administration.
Reference: Appendix 14.2.1.4b

The estimates from the Group B subjects showed a mean t_{max} of 0.83-0.99 hours with a half-life of 5-6 hours. Thus, (S)-albuterol appears to be systemically cleared more slowly than (R)-albuterol.

- There was no interconversion of albuterol isomers, with the possible exception of one patient, which was suspected of having received racemic albuterol by mistake. This is a reasonable interpretation by the sponsor.

- Change in mean heart rate can be seen in the table below. There was a substantial increase in mean heart rate after administration of the higher dose of (R)-albuterol (5 mg), which was comparable to the increase in mean heart rate seen after administration of 10 mg of racemic albuterol. There was no increase in mean heart rate seen after administration of (S)-albuterol. PK/PD modeling showed that heart rate and other ECG measures, according to the sponsor, were tightly correlated with plasma concentrations of (R)-albuterol when given either as (R)-albuterol or racemic albuterol.

Table 9. Mean Heart Rate from ECGs on Dosing Days

Albuterol Dosing	1.25 mg (R) (n=14)	2.5 mg Racemic (n=15)	1.25 mg (S) (n=14)	5 mg (R) (n=15)	10 mg Racemic (n=14)	5 mg (S) (n=13)
Pre-dose	61.9	63.8	64.4	59.7	59.2	60.7
Post - 15 minutes	72.6	71.3	65.9	88.5	89.1	59.3
Post - 45 minutes	72.6	70.4	65.3	89.1	84.9	57.2
Post - 90 minutes	68.1	67.2	62.4	77.2	76.2	56.5

- The comparison of relative bioavailability after administration of the low dose of (R)-albuterol based on AUC or secondary PK endpoints is not appropriate since most of the measurable (R)-albuterol concentration values were at or close to the limit of quantitation, there was a great deal of variability and levels were detectable for only 4 hours after drug administration.

- Consistent with in-vitro and pharmacologic data, the clearance rate of (R)-albuterol is significantly faster than the clearance rate of (S)-albuterol due to preferential sulfation. This results in significantly higher plasma levels of (S)-albuterol, a longer ½ life of (S)-albuterol and the potential for accumulation of (S)-albuterol in the plasma with repetitive dose administration of racemic albuterol.

☛ Conclusions on the PK data from this study include the following: 1) comparative bioavailability of (R)-albuterol and racemic albuterol was seen only at the high dose (5 mg of (R)-albuterol compared to 10 mg of racemic albuterol) and not with the low dose (1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol); 2) 4 consecutive doses of (R)-albuterol, (S)-albuterol or racemic albuterol did not increase drug plasma levels fourfold; Cmax did increase fourfold, but AUC increased more than fourfold; and 3) comparable bioavailability was demonstrated for each isomer when it was administered alone or as part of the racemic mixture.

☛ Adverse events:

- ✦ Group A, (R)-albuterol: 7/15 patients (12 AEs)
- ✦ Group A, racemic albuterol: 7/15 patients (10 AEs)
- ✦ Group A, (S)-albuterol: 4/15 patients (8 AEs)
- ✦ Group B, (R)-albuterol: 12/15 patients (33 AEs)
- ✦ Group B. racemic albuterol: 8/15 patients (23 AEs)
- ✦ Group B, (S)-albuterol: 3/15 patients (5 AEs)

✦ One patient, a 48 year old female had a normal ECG at baseline. Fifteen minutes after receiving 2.5 mg of racemic albuterol, she developed inverted T waves in lead III and non-specific ST-T wave changes which resolved 1.5 hours after drug administration. This patient was given (R)-albuterol 7 days later and developed extensive ST-T wave changes and inverted T waves 15 minutes after receiving (R)-albuterol which were interpreted as possibly due to myocardial ischemia or infarct, and were accompanied by first degree A-V block. The patient's ECG had returned to normal 1.5 hours after drug administration. She subsequently received (S)-albuterol without any ECG changes.

✦ There was a slightly greater incidence of nervousness after administration of both the low dose and the high dose (R)-albuterol than after administration of racemic albuterol at low and high dose. Tachycardia also occurred more frequently after administration of (R)-albuterol (47%) compared with racemic

albuterol (36%), as did headache and dizziness; (27%) after administration of (R)-albuterol as compared with racemic albuterol (7%). These differences between (R)-albuterol and racemic albuterol were primarily after high dose administration.

☛ laboratory data:

✦ serum potassium levels: The mean serum potassium level dropped below the lower limit of the normal reference range 60 minutes after administration of the high dose of (R)-albuterol, and returned to the normal reference range 6 hours after drug administration, but not to the same level as was obtained prior to drug administration. The highest Cmax values were associated with the lowest potassium levels after administration of (R)-albuterol and racemic albuterol. Serum potassium levels decreased to a level as low as 2.7 mEq/L in individual patients after administration of both (R)-albuterol and racemic albuterol. No substantive mean changes were seen after administration of (S)-albuterol.

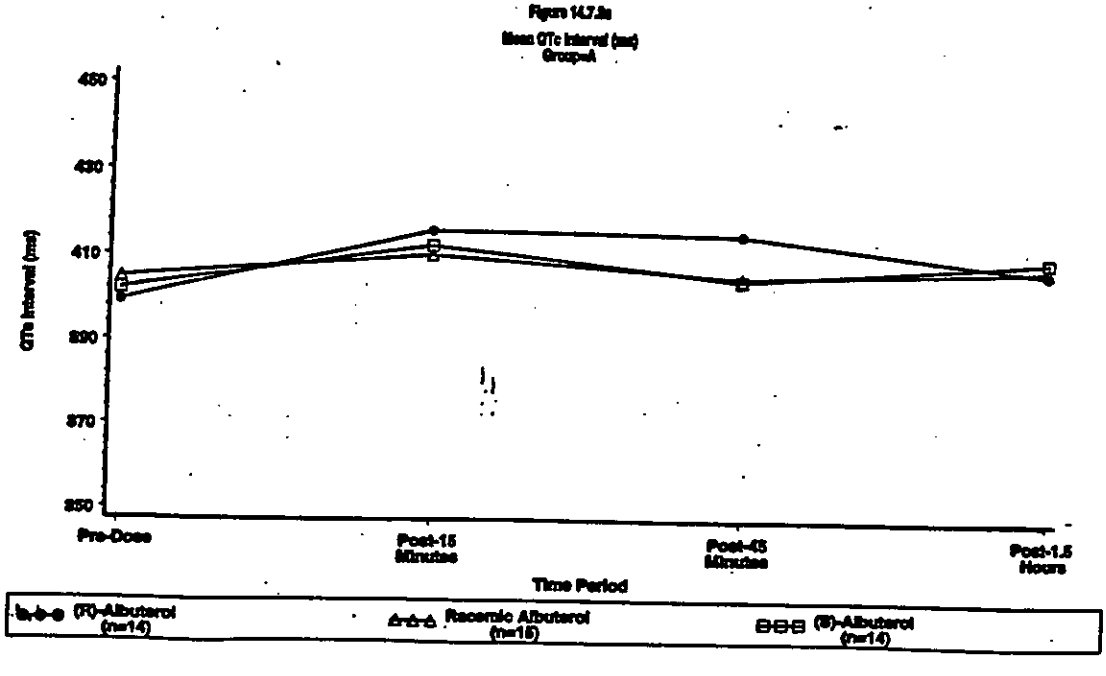
✦ serum glucose levels: The mean glucose level increased to a value above the upper limit of the normal reference range 60 minutes after administration of the high dose of (R)-albuterol and racemic albuterol. By visit 5, all patients had normal serum glucose levels. The highest serum glucose levels were associated with higher Cmax values for both (R)-albuterol and racemic albuterol. No substantive mean changes were seen after administration of (S)-albuterol.

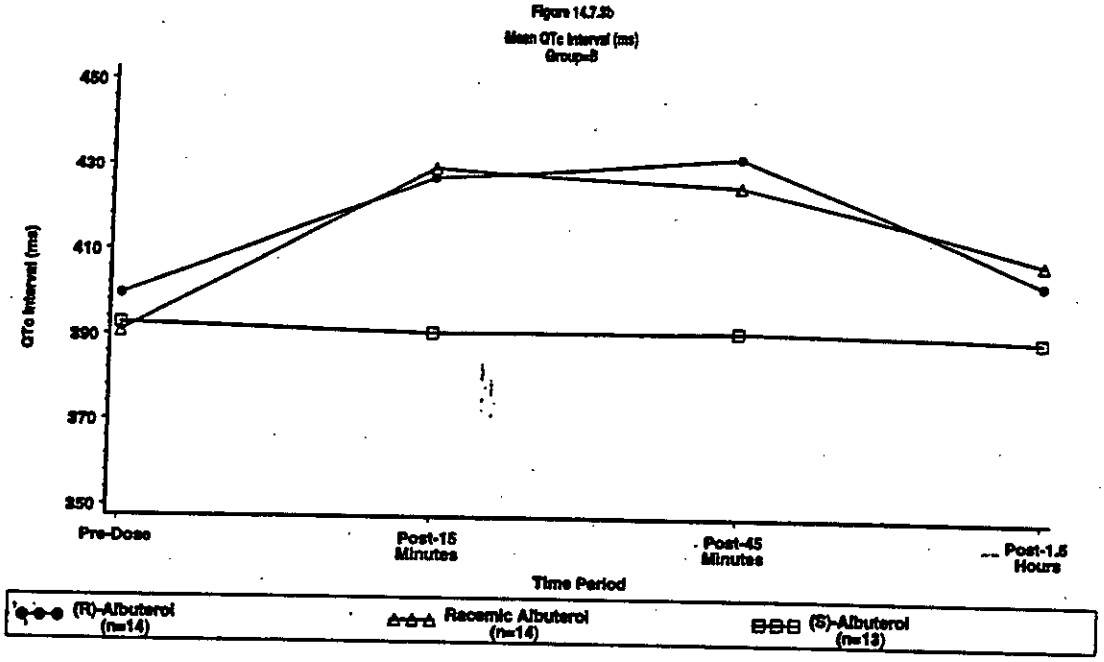
☛ ECG data: Three patients had increases in the QTc interval above 500 msc after administration of racemic albuterol (427 to 510 msc, 370 to 520 msc and 400 to 520 msc) which returned to normal by the end of the treatment day. There were no patients who had an increase in the QTc interval above 500 msc after administration of (R)-albuterol.

After administration of 1.25 mg of (R)-albuterol, the maximum mean increase in QTc interval was 17 msc 15 minutes after drug administration, and the maximum QTc interval was 470 msc at the same time. After administration of 5 mg of (R)-albuterol, the maximum mean increase in QTc interval was 32 msc 45 minutes after drug administration, and the maximum QTc interval was 490 msc 15 minutes after drug administration. Less of a mean maximum increase in QTc interval was seen after administration of 2.5 mg of racemic albuterol than after administration of 1.25 mg of (R)-albuterol and the maximum QTc interval was 440 msc. On the other hand, after administration of 10 mg of racemic albuterol, the mean maximum increase in QTc interval was 38 msc and the maximum QTc interval noted was 520 msc, which were greater than the increase seen after administration of 5 mg of (R)-albuterol.

There was a 26 year old woman who had a syncopal episode (patient 020) after receiving 5 mg of (R)-albuterol that was considered to be probably related to drug administration. This patient's QTc interval increased from 365 msec prior to drug administration to 450 msec 45 minutes after drug administration and she had tachycardia.

These results are compatible with the fact that beta agonists can increase the QTc interval and do not represent any significant or unexpected safety issue for (R)-albuterol (see figures below).





☛ vital signs: The maximum rise in mean systolic blood pressure occurred 15 minutes after administration of the high dose of (R)-albuterol, but was within the normal range. An elevation in mean systolic blood pressure was most pronounced 15 minutes after administration of the high dose of (R)-albuterol. There was no alarming increase in mean systolic blood pressure after administration of (R)-albuterol. One patient, a 27 year old female, had an increase in blood pressure from 109/71 to 153/116 mm Hg 15 minutes after administration of 5 mg of (R)-albuterol, which had decreased to 124/69 mm Hg 45 minutes after drug administration.

NOTE: The plasma (R)-albuterol levels seen after doses of 1.25 mg of (R)-albuterol and 2.5 mg of racemic albuterol were low and only detectable for 2-4 hours. The plasma levels of (R)-albuterol after administration of 5 mg of (R)-albuterol or 10 mg of racemic albuterol were detectable and allowed accurate determination of all PK parameters. Based on these findings, it appears that the PK of (R)-albuterol and (S)-albuterol administered by inhalation can be reliably determined at higher doses (5 mg of the isomer, 10 mg of racemic albuterol) when a [redacted] assay with a sensitivity of [redacted] is used.

CONCLUSIONS: The bioavailability of (R)-albuterol was greater in this study than racemic albuterol administered at 2X the dose of (R)-albuterol, especially after administration of 1.25 mg of (R)-albuterol. The sponsor attributes this to the degree of variability seen after administration of the low dose and the fact that most values of (R)-albuterol concentration were near the lower level which allowed for quantitation, based on the assay method used. After evaluation of the safety parameters measured in this study, there is a strong suggestion that (R)-albuterol at a given dose is more likely to produce a systemic effect than twice the dose of racemic albuterol. This impression is based on the following: 1) after administration of the high dose, i.e. 5 mg of (R)-albuterol, 10 mg of racemic albuterol, more patients experienced more adverse events; 2) One patient had more pronounced ECG changes of myocardial ischemia after administration of 1.25 mg of (R)-albuterol than after administration of 2.5 mg of racemic albuterol; 3) There was a slightly greater incidence of nervousness, tachycardia, headache and dizziness after administration of (R)-albuterol compared with racemic albuterol; 4) there was a slightly greater decrease in serum potassium and increase in serum glucose after administration of (R)-albuterol compared with racemic albuterol; and 5) one patient had a syncopal episode associated with an increase in the QTc interval after administration of 5 mg of (R)-albuterol.

- Study 008: entitled, "A randomized, placebo-controlled, double-blind, crossover study for the evaluation of nebulized (R)-salbutamol, (S)-salbutamol and racemic salbutamol on finger tremor in normal subjects"; Principal Investigators: DJ Clark, BJ Lipworth, UK.

  Study Characteristics

  - number of patients: 12 entered, 12 completed
  - age range: 19-22 years
  - patient population: normal volunteers
  - study design: randomized, double-blind, placebo-controlled, active treatment-controlled, 4 way crossover, single center, cumulative dose study
  - drug administration: doubling doses every 20 minutes; 200, 400, 800, 1600, and 3200 mg doses of (R)-albuterol (lot # 004-0001) and (S)-albuterol (lot # 012396A) and 400, 800, 1600, 3200, and 6400 mg doses of racemic albuterol (lot # 220912); placebo was 0.9% saline; medication delivered by [redacted] System using compressed air at a flow rate of 6 L/min
  - periods of study: washout period of at least 48 hours between treatments on 4 separate study days
  - parameters: dose-response evaluation of the following;
    - tremor; prior to initial dose and 15 minutes after each dose
    - blood pressure: prior to initial dose and 15 minutes after each dose

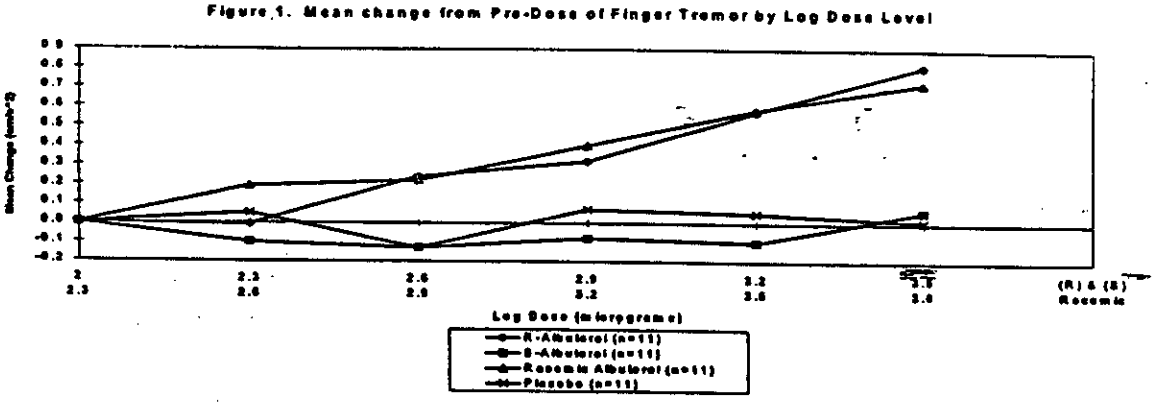
- ☛ heart rate: prior to initial dose and 15 minutes after each dose

- ☛ serum potassium: prior to initial dose and 30 minutes after each treatment

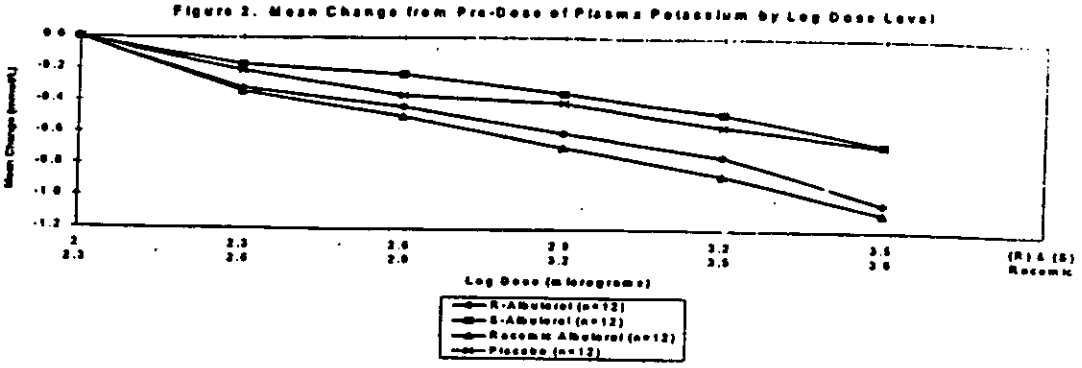
- ☛ plasma albuterol concentration: 15 minutes after administration of each dose and 30 minutes after the last dose

Study Results:

- ❑ tremor: There was a statistically significant difference between the response after administration of (R)-albuterol and racemic albuterol and after administration of (S)-albuterol and placebo ($p < 0.0001$), but not between (R)-albuterol and racemic albuterol ($p = 0.97$) (see figure below)



- ❑ serum potassium: There was a statistically significant difference between the response after (R)-albuterol and (S)-albuterol ($p = 0.006$) and (R)-albuterol and placebo ($p = 0.03$) as well as between racemic albuterol and (S)-albuterol ($p = 0.0005$) and racemic albuterol and placebo ($p = 0.003$), but not between (R)-albuterol and racemic albuterol ($p = 0.34$)(see figure below). The mean serum potassium level fell from a baseline of 4.45 to 3.42 nmol/L after (R)-albuterol with a minimum of 3.01 nmol/L after the highest dose.



- heart rate: There was a statistically significant difference between the mean response after administration of (R)-albuterol and placebo ($p = 0.005$) and administration of racemic albuterol and placebo ($p = 0.007$), but not between (R)-albuterol and racemic albuterol ($p = 0.94$), based on AUC. There was one patient who had a 35 bpm increase in heart rate after receiving (R)-albuterol, but most increases in heart rate after administration of (R)-albuterol were consistent with the expected effect from this class of drug.

- There was no significant difference after administration of any of the treatments in regard to mean systolic and diastolic blood pressure or clinically significant individual changes.

- A relative potency analysis was done using racemic albuterol as the standard, and based on the mg of racemic albuterol divided by the mg of (R)-albuterol. The relative potency of (R)-albuterol and racemic albuterol for tremor and serum potassium can be see in the table below. The sponsor's interpretation of the data is; "Since the relative potency estimates are greater than 1 unit, the (R)-albuterol treatment is considered more potent. However, on a mg to mg basis, if all response was due to the (R) isomer then the expected potency would be 2 units. Therefore, the estimates of relative potency suggest that (R)-albuterol is not responsible for all the tremorgenic or potassium changes