CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 23 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-837	**Type of Submission:**
XOPENEX™ (levalbuterol)	Response to AE Letter
Inhalation Solution	**Submission Date:**
	8/6/98
Sepracor, Inc.	
111 Locke Drive	**Reviewer:**
Marlborough, MA 01752	Brad Gillespie, PharmD

Backgound The original XOPENEX NDA was submitted on June 30, 1997. The Human Pharmacokinetics section was reviewed by Brad Gillespie (see 6/16/98 Clinical Pharmacology & Biopharmaceutics Review). Two comments were generated and communicated to the sponsor in a July 1, 1998 Approvable Letter. The sponsor's responses to those comments are the subject of this review.

Original FDA comments are **bolded**
The sponsor's responses are *italicized*
FDA evaluation of the response is <u>underlined</u>

B.3 Based on the data presented for Protocol 051-006, it appears that study medication in the low-dose treatment group may have been mislabeled at some point prior to administration. Provide a thorough accounting for all subjects and the treatment that they received in this study. Additionally, provide a satisfactory explanation for the following unexpected data observed from Subjects 004 and 014; (1) quantifiable levels of R-albuterol present in the plasma and urine after administration of the pure S-albuterol treatment; and (2) neither S- nor R-albuterol were detected in plasma or urine after administration of the levalbuterol and racemic albuterol treatments.

The sponsor argues that the lack of quantifiable R- and S- isomers in Subject 014 are most likely due to inexperience with the inhalation equipment, since the study was conducted with healthy volunteers who would not have experience with such equipment. This hypothesis is supported by Subject 014's observed plasma levels after administration of S-albuterol- among the lowest enrolled in the trial.

With regard to Subject 004, the sponsor has ruled out the possibility of a manufacturing, labeling or test product accounting error. After the last treatment, Sepracor analyzed the solution remaining in the nebulization bowls ([redacted] assay). They determined that in bowls of subjects who received a single isomer in the final period, a concentration of approximately 0.45 ng/mL was detected. In subjects who received the racemate, 0.85 ng/mL was observed. Subject 004's bowl had a concentration of 0.59 ng/mL. Examination of the observed clinical data, shows that the ratio of R to S isomer is markedly different in Subject 004 than that in subjects receiving the racemate. Lastly, the sponsor concluded that racemization appears unlikely since no interconversion from R-

to S- was observed and that if S- was converting to R-, a decrease in S- would be expected. This change was not observed. Based on these findings, the sponsor has concluded that the most reasonable cause for R-albuterol to be present after administration of S-albuterol is contamination. They believe that the nebulization bowl was not cleaned between Treatments 2 (R-albuterol) and 3 (S-albuterol). The remaining solution evaporated, leaving an R-albuterol residue. When S-albuterol was added, the R-residue was re-dissolved and administered with the S-albuterol treatment.

The sponsor's explanations for these unusual study results are plausible. Nevertheless, both explanations suggest that the study facility lacks properly controlled operating procedures, shedding doubt on the overall validity of the study. These shortcomings should be considered in light of the available clinical data. If this study is critical to the approvability of this product, the Office of Clinical Pharmacology & Biopharmaceutics recommends that the Division of Scientific Investigation audit its conduct.

B4. As also indicated in the marked up draft labeling, Table 1, under the Pharmacokinetics section, should be modified to include results obtained in the low dose group of protocol 051-006 (1.25 mg levalbuterol and 2.5 mg racemic albuterol). Time to maximum plasma concentration (T_{max}) should be described as the median (range). References to (S)-albuterol data, to include that presented in Figure 3, should be omitted. Additionally, the labeling narrative should be modified to indicate that the exposure of (R)-albuterol is higher when administered at the recommended dose of pure enantiomer than at a corresponding dose of the racemate.

Changes to Table 1 have been made, as requested. (A copy of the revised package insert is enclosed in Appendix B3)

The pharmacokinetics section of the proposed package insert is evaluated below.

The proposed pharmacokinetics section of the label with FDA comments in redline/strikeout is presented below.

Pharmacokinetics

The inhalation pharmacokinetics of **Xopenex** Inhalation Solution were investigated in a randomized cross-over study in 30 [redacted] nebulization using a PARI LC Jet+™ nebulizer with a DuraNeb 2000 compressor.

[redacted]

Table 1: Mean (SD) Values for Pharmacokinetic Parameters in Normal Volunteers

	Xopenex 1.25 mg	Ventolin® 2.5 mg	Xopenex 5 mg	Ventolin® 10 mg
C_{max} (ng/mL)				
(R)-albuterol		0.8 (0.41)	4.5 (2.20)	4.2 (1.51)
~~(S)-albuterol~~	~~None Detected~~	~~1.6 (0.74)~~	~~None Detected~~	~~1.9 (1.80)~~
t_{max} (h)[γ]				
(R)-albuterol	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (-0.18*, 1.25)	0.2 (-0.28*, 1.00)
~~(S)-albuterol~~[2]	~~None Detected~~	~~(0.5 (0.33, 1.00))~~	~~None Detected~~	~~(0.28*, 2.00)~~
AUC (ng•h/mL)				
(R)-albuterol	3.3 (1.58)	1.7 (0.99)	17.4 (8.56)	16.0 (7.12)
~~(S)-albuterol~~	~~None Detected~~	~~11.1 (5.71)~~	~~None Detected~~	~~27.03~~
$t_{½}$ (h)				
(R)-albuterol	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)
~~(S)-albuterol~~	~~None Detected~~	~~5.1 (1.8(1)~~	~~None Detected~~	~~5.9 (1.35)~~

[γ] Median (Min, Max) reported for t_{max}

*A negative t_{max} indicates C_{max} occurred between first and last nebulizations.

Recommendation The Office of Clinical Pharmacology & Biopharmaceutics has reviewed the sponsor's response to the Human Pharmacokinetics comments outlined in the July 1, 1998 Approvable Letter. While their response to Comment 3 satisfactorily explains Subject 004 and 014's unusual results, it raises doubt about the overall credibility of the study. This should be considered in light of the available clinical data. If the results of this study are critical to the approvability of this product, the Office of Clinical Pharmacology & Biopharmaceutics recommends that it be audited by the Division of Scientific Investigation. With regard to Comment 4 and the proposed package labeling, it is acceptable, provided that the sponsor modify it as shown in the marked up version, above.

/S/ 12/4/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

/S/ 12/23/98

FT Ramana Uppoor, PhD, Team Leader

cc:
HFD-570 (NDA 20-837, Divisional File, Jani, Nicklas, Honig)
HFD-870 (ChenME, Hunt, Uppoor)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

JUN 16 1998

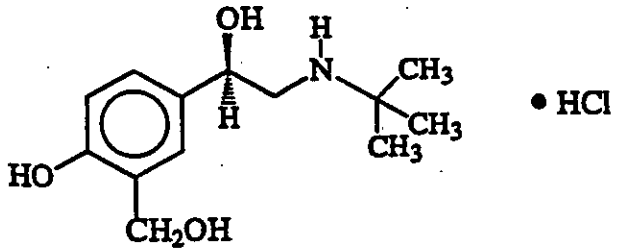
Clinical Pharmacology & Biopharmaceutics Review

NDA 20-837
XOPENEX™ (levalbuterol)
Inhalation Solution

Sepracor, Inc.
111 Locke Drive
Marlborough, MA 01752

Type of Submission:
New NDA, NME, 1S
Submission Date:
6/30/97

Reviewer:
Brad Gillespie, PharmD



Synopsis XOPENEX™ is levalbuterol ((R)-albuterol), a relatively short acting, chiral, β-adrenergic agonist. It is formulated as a sterile, clear, colorless and preservative-free solution. The proposed indication is for the treatment or prevention of [redacted] bronchospasm in adults and [redacted] with reversible obstructive airway disease [redacted] The sponsor proposes marketing XOPENEX as a solution for inhalation [redacted] 0.63 and 1.25 mg levalbuterol [redacted] /3 mL vial). The proposed dose will be 0.63 mg - 1.25 mg three times daily in adults and [redacted] With regard to chirality, XOPENEX is [redacted] (R)-albuterol. While interconversion of (R)-albuterol to (S)-albuterol was not observed in a trial where subjects received (R)-, (S)- and racemic albuterol, (R)-albuterol plasma concentrations were observed in one subject after inhalation of (S)-albuterol. While this finding is possibly due to mis-labeling of study medication, the possibility of interconversion cannot be ruled out. After inhalation of a single-dose of 1.25 mg levalbuterol, a peak plasma concentration of 2.00 (CV-43%) ng/mL was observed approximately 10 (range: [redacted] minutes after inhalation. Total exposure, as measured by $AUC_{0-\infty}$ was 3.26 (CV-48%) ng•hr/mL. The elimination half-life was approximately 3.33 (CV-74%) hours. In the same study, subjects also received 2.5 mg racemic albuterol. (R)-albuterol exposure was demonstrated to be markedly higher after administration of levalbuterol than after administration of racemic albuterol (1.5 to 2 times greater, as measured by C_{max} and AUC). The Medical Officer assigned to this product should be mindful of its increased (R)-albuterol exposure relative to that of racemic albuterol.

APPEARS THIS WAY
ON ORIGINAL

Background Levalbuterol HCl ((R)-albuterol), a selective β-agonist, is the (R)-isomer of albuterol. Racemic albuterol is currently marketed as a variety of oral and inhaled preparations. XOPENEX is levalbuterol formulated in three strengths as an inhalation solution for nebulization ( )0.63 and 1.25 mg levalbuterol base/3mL vial). The sponsor has proposed that (R)-albuterol is responsible for the efficacy observed after administration of albuterol, while the (S)-isomer contributes to adverse events. Therefore, the sponsor has proposed the marketing of ( ) levalbuterol, indicated for the treatment or prevention of bronchospasm in adults ( ) with reversible obstructive airway disease and attacks of bronchospasm. In addition to the pivotal clinical safety and efficacy trial, the sponsor has submitted 4 studies in the Human Pharmacokinetics section of the NDA. Only one of these was considered pivotal and is reviewed in this document. The other three pharmacokinetic studies were not selected for a thorough review, but were instead summarized and discussed in the summary section of this Review. As discussed at the 4/25/96 End-of-Phase 2 meeting, the pharmacokinetic evaluation of levalbuterol is based on: [1] determining whether interconversion of (R)- to (S)-albuterol occurs and [2] whether there are any differences in the pharmacokinetics of (R)-albuterol when administered as a single enantiomer or the racemate.

Formulations Levalbuterol hydrochloride has a molecular weight of 275.8 and is a white to off-white crystalline solid, soluble in water at approximately 180 mg/mL. XOPENEX is formulated as a sterile, clear, colorless and preservative-free solution of levalbuterol. It is available in three strengths as an inhalation solution for nebulization ( )0.63 and 1.25 mg levalbuterol base/3mL vial). The batch (00696A) from the pivotal pharmacokinetic study reviewed for this submission (Protocol 51-006) was the same formulation as that proposed for marketing.

Summary of Bioavailability

In protocol 051-006, healthy adult subjects received single doses of (R)-, (S)- and racemic albuterol. This was a three-way crossover within a parallel group design, i.e., after subjects were assigned to either the high (5 mg dose of enantiomers and 10 mg dose of the racemate) or the low (1.25 mg dose of enantiomers and 2.5 mg dose of the racemate) dose group, they were crossed over in a randomized fashion to each of three treatments. It is evident that in the low dose group, (R)-albuterol exposure was markedly higher after administration of a 1.25 mg dose of levalbuterol than after administration of a 2.5 mg dose of racemic albuterol (1.5 to 2 times greater, as measured by C_{max} and AUC). In the high dose group, levalbuterol was bioequivalent to the racemate with regard to (R)-albuterol. Since the maximum proposed dose of levalbuterol is 1.25 mg three times daily, the lower dose group is probably most relevant. In addition, the sponsor collected limited plasma samples in three of its clinical safety and efficacy trials. While not adequate to support a formal pharmacokinetic analysis, relative exposures ((R)-albuterol concentrations after administration of levalbuterol relative to after administration of racemic albuterol) observed support the results obtained in Protocol 051-006. The higher exposure of (R)-

albuterol observed after levalbuterol dosing compared to racemic albuterol should be kept in mind when evaluating the clinical safety and efficacy database for this product.

Summary of Pharmacokinetics

After a single 1.25 mg dose of levalbuterol in Protocol 051-006, a peak plasma concentration of 2.00 ng/mL (CV-43%) was observed approximately 10 (range: [redacted] minutes after inhalation. Total exposure, as measured by $AUC_{0-\infty}$ was 3.26 (CV-48%) ng•hr/mL. The elimination half-life was approximately 3.33 hours (CV-74%). After a single 5 mg dose of levalbuterol, a peak plasma concentration of 4.50 ng/mL (CV-49%) was observed approximately 10 (range: [redacted] minutes after inhalation. Total exposure, as measured by $AUC_{0-\infty}$ was 17.44 (CV-49%) ng•hr/mL. The elimination half-life was approximately 4.03 hours (CV-26%). While interconversion of (R)-albuterol to (S)-albuterol was not observed in a trial where subjects received (R)-, (S)- and racemic albuterol, (R)-albuterol plasma concentrations were observed in one subject after inhalation of a single 1.25 mg dose of (S)-albuterol. While this finding is possibly due to mis-labeling of study medication, the possibility of interconversion cannot be ruled out.

Assay Validated [redacted] methods were used for plasma and urine (R)- and (S)-albuterol determinations.

Comments

Comment 1 specifically refers to Protocol 051-006

1. Based on the data presented, it appears that study medication in the low dose treatment group may have been mislabeled at some point prior to administration. The sponsor is requested to provide a thorough accounting for all subjects and the treatments that they received. Additionally they should provide a satisfactory explanation for the unexpected data observed from Subjects 004 (quantifiable levels of (R)-albuterol present in the plasma and urine after administration of the pure (S)-albuterol treatment) and 014 (neither (S)- nor (R)-albuterol were detected in plasma or urine after administration of the levalbuterol and racemic albuterol treatments).

Comment 2 is a preliminary comment referring to the proposed package insert

2. Table 1, under the Pharmacokinetics section, should be modified to include results obtained in the low dose group of Protocol 051-006 (1.25 mg levalbuterol and 2.5 mg racemic albuterol). Time to maximum plasma concentration (T_{max}) should be described as the *median (range)*. References to (S)-albuterol data, to include that presented in Figure 3, should be omitted. Additionally, the labeling narrative should be modified to indicate that the exposure of (R)-albuterol is higher when administered at the recommended dose of pure enantiomer than at a corresponding dose of the racemate.

After these modifications are complete, The Office of Clinical Pharmacology will provide more detailed labeling comments.

Recommendation The Human Pharmacokinetics section of this NDA and the respective section of the product labeling has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, and has been found satisfactory to support approval of the application provided that the sponsor satisfactorily addresses Comments 1 - 2.

Please forward the above comments and recommendation to the sponsor.

/S/ 6/16/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

/S/ 06/11/98

RD: Ramana Uppoor, PhD., Team Leader

/S/ 06/16/98

FT: Ramana Uppoor, PhD., Team Leader

cc:
HFD-570 (NDA 20-837, Divisional File, Jani, Nicklas, Honig)
HFD-705 (Karen Higgins)
HFD-870 (ChenME, Hunt, Uppoor)
HFD-850 (Lesko, Huang)
CDR (Barbara Murphy)

APPEARS THIS WAY ON ORIGINAL

Pharmacokinetics of (R)-, (S)- and Racemic Albuterol Following Administration by Nebulization in Normal Volunteers

Protocol No. 051-006 **Volumes** 1.29-1.40
Investigator

Study Dates 7/15/96 - 8/10/96
Analytical Facility
Analysis Dates 9/5/96 - 10/15/96 (plasma), 12/16/96 - 1/29/97 (urine)

Objectives (1) To determine if the exposure of a subject to (R)-albuterol nebulized as a single isomer is the same as the exposure achieved after administration of racemic albuterol. (2) To determine if there is *in vivo* interconversion of (R)- and (S)-albuterol. (3) To determine if exposure to a 1.25 mg dose of (R)-albuterol is proportional to a 5.0 mg dose of (R)-albuterol.

In this study, healthy subjects were assigned to either Group A (low dose) or Group B (high dose). Once assigned to a group, subjects were randomized to one of three treatments, (R)-albuterol, (S)-albuterol or racemic albuterol. All six treatments are summarized below:

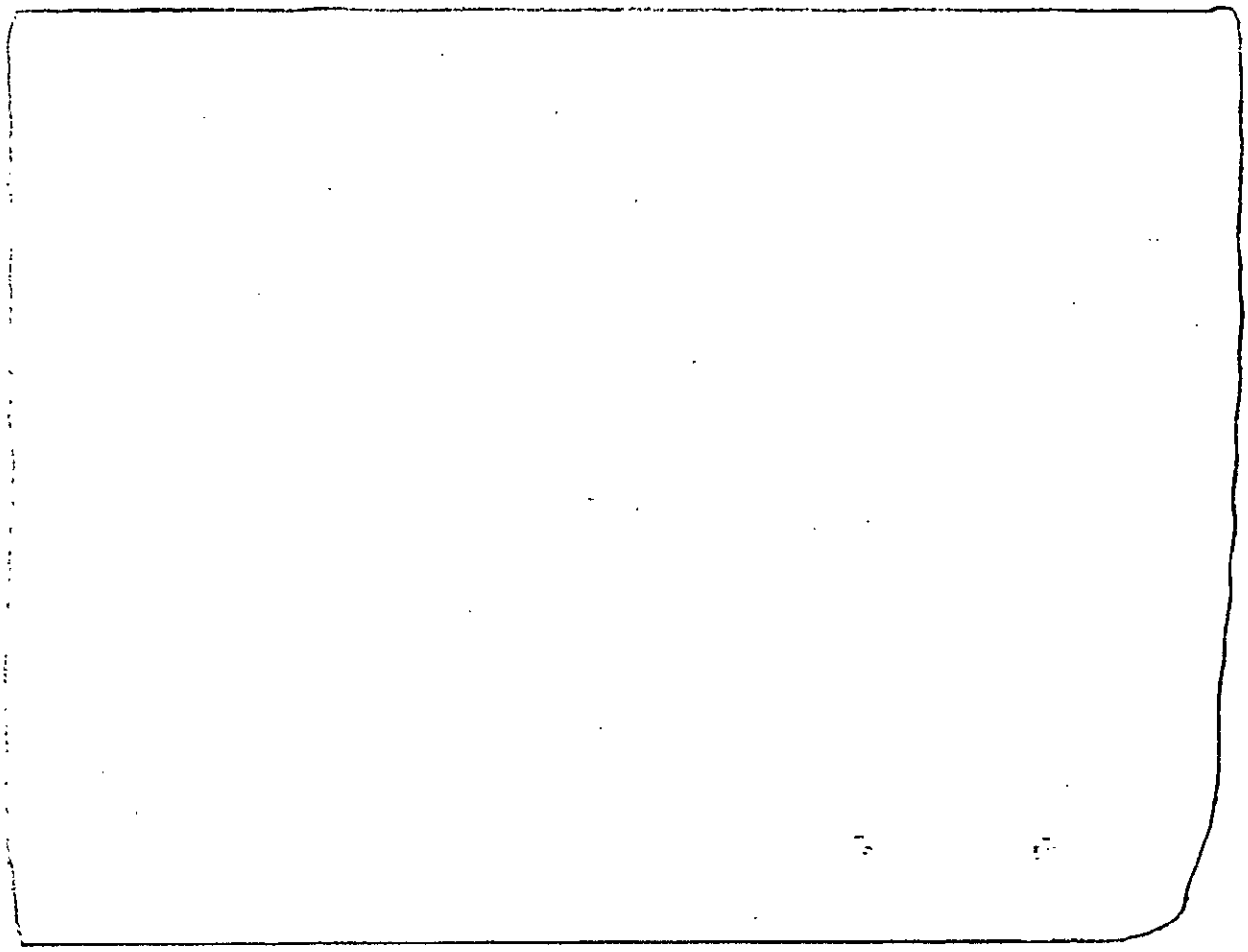
Group A:
1.25 mg (R)-albuterol
1.25 mg (S)-albuterol
2.50 mg racemic albuterol (Ventolin)

Group B:
5.0 mg (R)-albuterol
5.0 mg (S)-albuterol
10 mg racemic albuterol (Ventolin)

Formulations
(R)-albuterol 1.25 mg/3mL - Lot No. 00696A
(S)-albuterol 1.25 mg/3mL - Lot No. 00696E
Racemic albuterol (Ventolin) 2.5mg/3mL - Lot No. 960308

Study Design A total of 30 healthy, non-smoking adult male and female (at least 25% of the subjects were of each gender in both Groups) volunteers were included in this open-label, randomized, single-dose, 2 parallel group, 3-treatment, 3-period crossover study. After an overnight fast, subjects received a single dose of study medication. Volunteers continued fasting and remained ambulatory for 4 hours after study drug administration. At this time, regular meals were served. A washout interval of at least 3 but no more than 7 days separated the dosing periods. Subjects were confined for the first 24 hours after dosing and abstained from the consumption of xanthine containing

foods and beverages. Blood samples were obtained for plasma (R)- and (S)-albuterol determinations just prior to (zero hour), 10, 20, 30, 45, 60, 75, 90 minutes and 2, 3, 4, 6, 8, 12, 16 and 24 hours post dose (end of nebulization). Urine was collected prior to and at 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-12, 12-16, 16-24 and 24-48 hour intervals after dosing.



Data Analysis

Pharmacokinetic (both enantiomers): Plasma- $C_{max,}$, T_{max}, AUC_{0-24}, $t_{1/2}$, CL/f and V/f. Urine- CL_R, Ae

Statistical: Details for the statistical analysis of the primary endpoints AUC and C_{max} are described in detail in Dr. Karen Higgins' Statistical Review of this study (see attachment). Summary statistics were generated to describe the remaining secondary endpoints.

Results A total of 14 of the subjects enrolled in Group A completed all phases of the study. Subject 011 withdrew consent and was discontinued. Of the 15 subjects in Group B, 13 completed the trial. Subject 020 withdrew consent and Subject 29 was discontinued due to chest pain. The pharmacokinetic analysis presented by the sponsor was based on the remaining 27 volunteers. Mean plasma (R)- and (S)-albuterol versus

time profiles are presented in Figures 1 - 4. Descriptive statistics of the secondary endpoints are provided in Tables 1 and 2.

Figure 1. Mean (R)-Albuterol Plasma Concentrations After a Single-1.25 mg Dose of (R)-Albuterol, After a Single 2.5 mg Dose of Racemic Albuterol and in Subject 004 After a Single 1.25 mg Dose of (S)-Albuterol

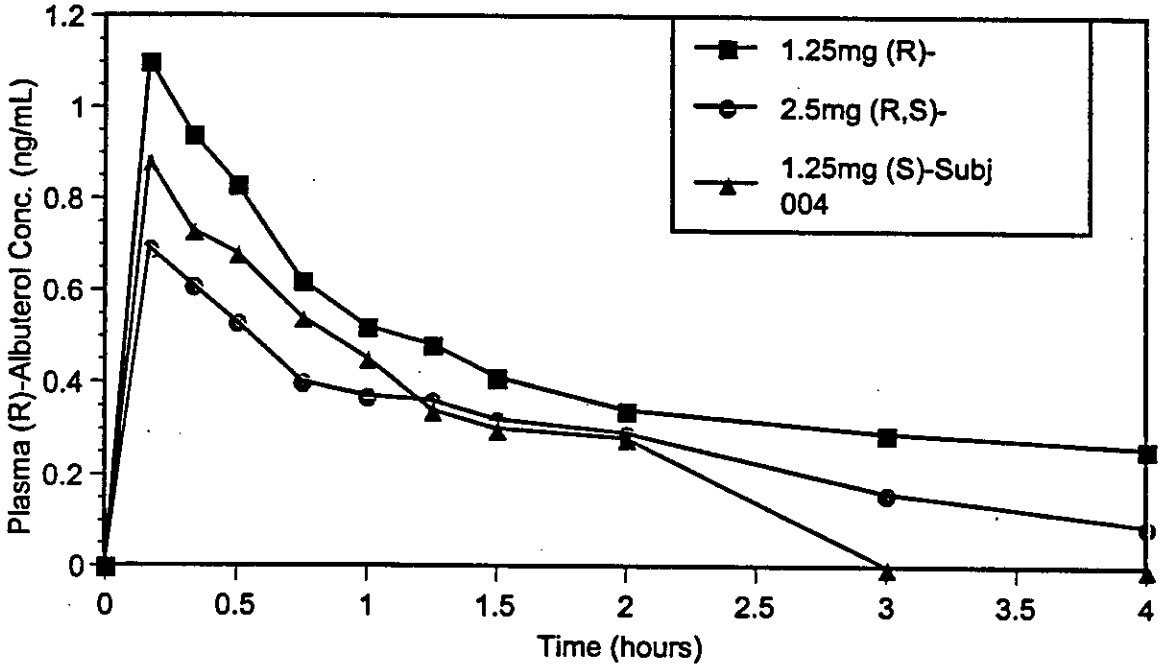


Figure 2. Mean (R)-Albuterol Plasma Concentrations After a Single-5 mg Dose of (R)-Albuterol and After a Single 10 mg Dose of Racemic Albuterol

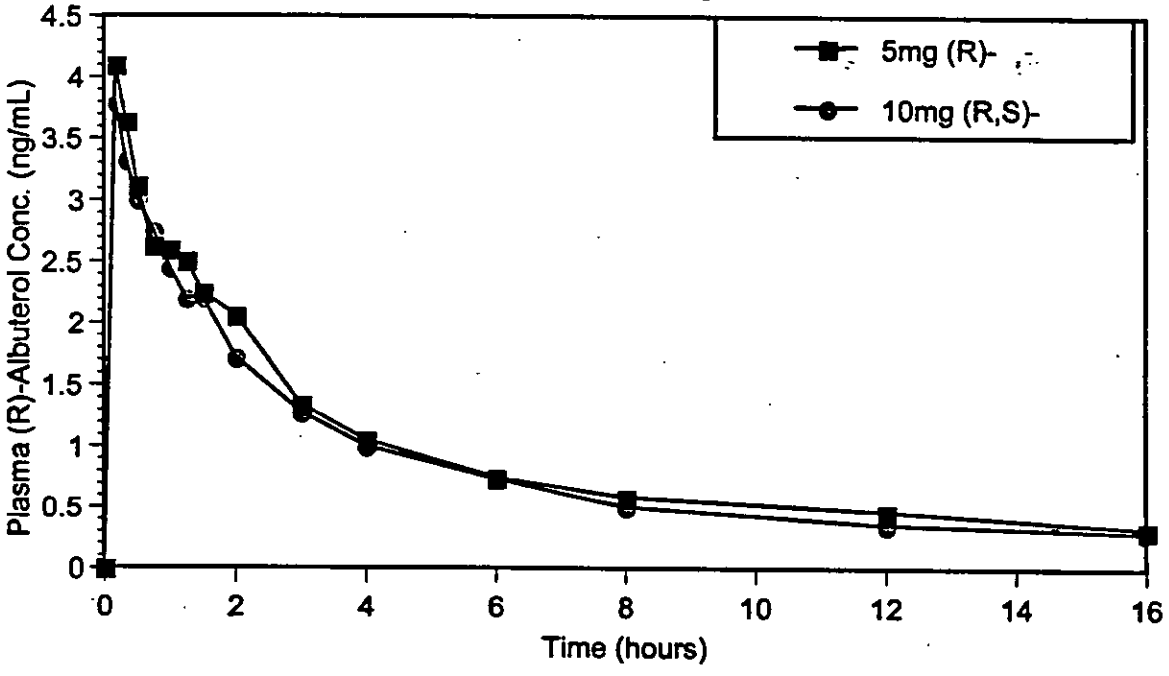


Figure 3. Mean (S)-Albuterol Plasma Concentrations After a Single-1.25 mg Dose of (S)-Albuterol, After a Single 2.5 mg Dose of Racemic Albuterol and in Subject 004 After a Single 1.25 mg Dose of (S)-Albuterol

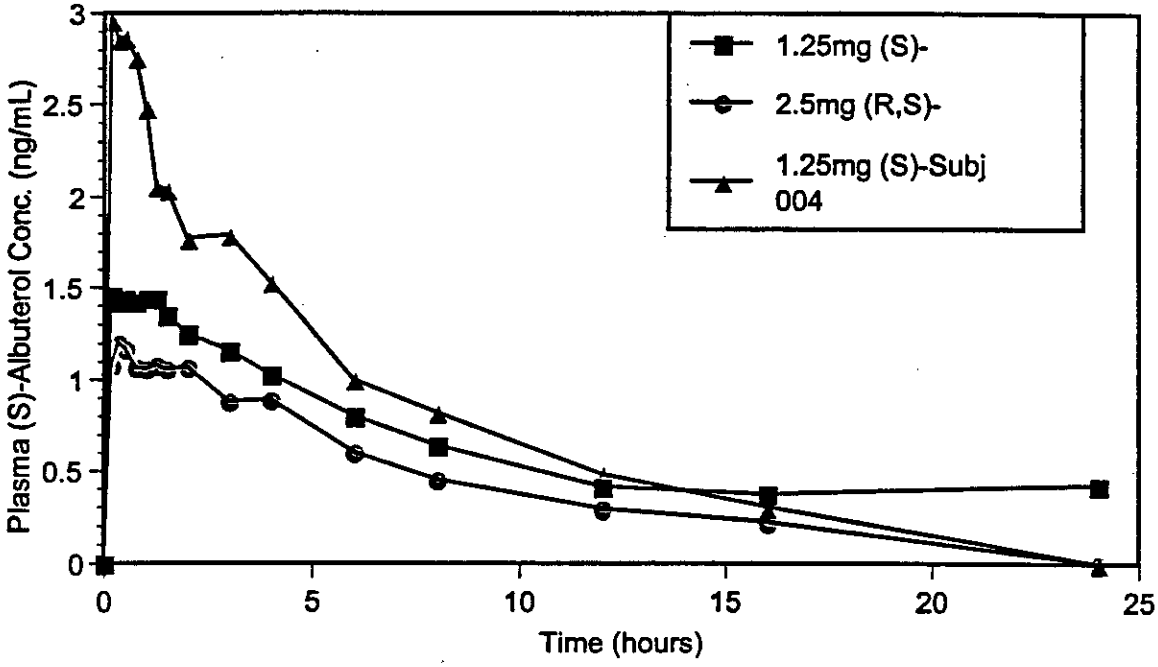


Figure 4. Mean (S)-Albuterol Plasma Concentrations After a Single-5 mg Dose of (S)-Albuterol and after a Single 10 mg Dose of Racemic Albuterol

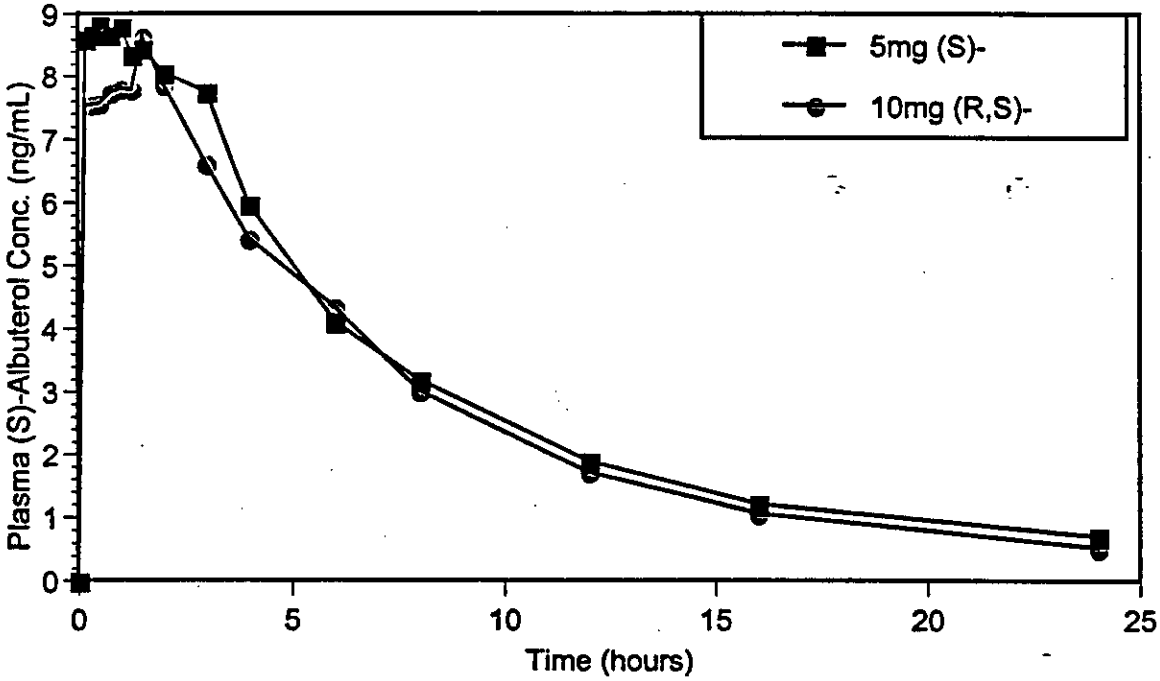


Table 1. Descriptive Statistics of Pharmacokinetic Endpoints (%CV) from Subjects in the Low Dose Group (Group A) and Estimates for Subject 004 After Inhalation of (S)-Albuterol

Dose (treat.)	t_{max}[1] *(hours)*	C_{max} *(ng/mL)*	$AUC_{0-\infty}$ *(ng•hr/mL)*	$t_{1/2}$ *(hours)*	*CL/f (L/hour)*	*V/f (L)*	*Ae (μg)*	CL_R *(L/hour)*
(R)-albuterol								
1.25 mg (R)	0.17	2.00	3.26	3.33	418	1545	51.6	17.3
		(43)	(48)	(74)	(46)	(45)	(43)	(35)
Subject 004	**0.17**	**0.88**	**1.69**	**1.02**	**739**	**1090**	**37**	**22.0**
1.25 mg (S)								
2.5mg (RS)[2]	0.17	0.78	1.71	1.48	1887	3008	32.5	24.7
		(53)	(55)	(41)	(71)	(36)	(54)	(91)
(S)-albuterol								
1.25 mg (S)	0.36	1.81	13.27	5.22	137.4	858	107.4	8.8
		(43)	(54)	(41)	(75)	(47)	(53)	(35)
Subject 004	**0.17**	**2.96**	**20.11**	**5.51**	**62.15**	**494**	**188.7**	**9.4**
1.25 mg (S)								
2.5 mg (RS)	0.50	1.64	11.14	5.12	236.6	1663	95.6	8.7
		(45)	(51)	(35)	(33)	(36)	(56)	(28)

Table 2. Descriptive Statistics of Pharmacokinetic Endpoints (%CV) from Subjects in the High Dose Group (Group B)

Dose (treat.)	t_{max} *(hours)*	C_{max} *(ng/mL)*	$AUC_{0-\infty}$ *(ng•hr/mL)*	$t_{1/2}$ *(hours)*	*CL/f (L/hour)*	*V/f (L)*	*Ae (μg)*	CL_R *(L/hour)*
(R)-albuterol								
5 mg (R)	0.17	4.50	17.44	4.03	370.9	1957	312.7	18.2
		(49)	(49)	(26)	(59)	(42)	(56)	(21)
10mg (RS)	0.17	4.18	15.98	4.05	728.7	4211	305.2	19.2
		(36)	(45)	(24)	(38)	(48)	(47)	(37)
(S)-albuterol								
5 mg (S)	0.50	11.31	81.56	6.65	80.9	736	747.5	9.48
		(52)	(58)	(27)	(61)	(54)	(55)	(19)
10 mg (RS)	0.37	9.99	74.08	5.89	155.9	1315	801.3	10.9
		(48)	50)	(23)	(33)	(41)	(51)	(29)

A description of the statistical comparison of pharmacokinetic parameters across treatments and groups is provided in Dr. Karen Higgins' attached Review.

Discussion

From the data submitted in this study report, it is evident that in the low dose group (Group A: 1.25 mg (R)-albuterol, 1.25 mg (S)-albuterol and 2.5 mg racemic albuterol), the individual isomers were not bioequivalent to racemic albuterol when administered as a nebulized solution. In the high dose group (Group B: 5 mg (R)-albuterol, 5 mg (S)-albuterol and 10 mg racemic albuterol), levalbuterol was bioequivalent to racemic albuterol with regard to the (R)-isomer.

As stated in the sponsor's study report, there is no apparent interconversion of the (R)-isomer to the (S)-isomer. It is clear, though, that quantifiable levels of (R)-albuterol

[1] Median (range)
[2] (RS)= racemic albuterol

were present in the plasma and urine of Subject 004 after inhalation of the pure (S)-albuterol treatment. Additionally, both plasma and urine levels of (S)-albuterol were also detected. Further, results obtained for Subject 014 in the low dose group are also not consistent with the treatments supposedly administered. In this case, neither (S)- nor (R)-albuterol were detected in plasma or urine after administration of the levalbuterol and racemic albuterol treatments. In this subject, the only drug observed was (S)-albuterol after inhalation of the pure (S)-isomer. While it is possible that some interconversion of the (S)- to the (R)-isomer is occurring, these findings suggest that study medication may have been somehow mislabeled prior to administration.

Comment

Based on the data presented, it appears that study medication in the low dose treatment group may have been mislabeled at some point prior to administration. The sponsor is requested to provide a thorough accounting for all subjects and the treatments that they received. Additionally they should provide a satisfactory explanation for the unexpected data observed from Subjects 004 (quantifiable levels of (R)-albuterol present in the plasma and urine after administration of the pure (S)-albuterol treatment) and 014 (neither (S)- nor (R)-albuterol were detected in plasma or urine after administration of the levalbuterol and racemic albuterol treatments).

Conclusion

It is evident that in the low dose group, (R)-albuterol exposure is markedly higher after administration of a 1.25 mg dose of levalbuterol than after administration of a 2.5 mg dose of racemic albuterol (1.5 to 2 times greater, as measured by C_{max} and AUC). In the high dose group, levalbuterol was bioequivalent to the racemate with regard to (R)-albuterol. Since the maximum proposed dose of levalbuterol is 1.25 mg three times daily, the lower dose group is probably most relevant. This higher exposure of (R)-albuterol observed after levalbuterol dosing compared to racemic albuterol should be kept in mind when evaluating the clinical safety and efficacy database for this product.

While there is no evidence of levalbuterol interconverting to (S)-albuterol, data was presented suggesting that (S)- to (R)-albuterol interconversion is possible. More likely, study drug was mislabeled so that one subject inadvertently received racemic albuterol instead of (S)-albuterol. Nevertheless, until proven otherwise, the Medical Officer assigned to this product should be cognizant of the possibility of interconversion.

Statistical Report on Pharmacokinetics of [redacted] (levalbuterol HCl) Inhalation Solution, Sepracor Inc., NDA 20-837

OCPB reviewer: Bradley Gillespie

Study No. 051-006: Pharmacokinetics of (R)-, (S)- and Racemic Albuterol Following Administration by Nebulization in Normal Volunteers.

This study was a 3-way crossover study in two parallel groups. The objective was to determine the pharmacokinetics of (R)- and (S)- albuterol (Test products) when given by nebulization as a single dose (low dose) or as four consecutive doses (high dose) and to compare their exposure to comparable doses of racemic albuterol (Reference, Ventolin®).

Study Objectives (page 4 of study report)

A. To determine whether the exposure of a subject to (R)-albuterol administered as a single isomer was the same as exposure when racemic albuterol was administered. Similarly, to determine whether exposure of a subject to (S)-albuterol administered as a single isomer was the same as exposure when racemic albuterol was administered.

B. To determine whether there was any interconversion of (R)- and (S)- albuterol *in vivo*.

C. To determine the safety of (R)-albuterol.

D. To determine whether exposure of subjects to a 1.25 mg dose of (R)-albuterol was proportional to exposure to a 5.0 mg dose of (R)-albuterol. Similarly to determine if exposure to a 1.25 mg dose of (S)-albuterol or a 2.5 mg dose of racemic albuterol was proportional to exposure to a 5.0 mg or 10.0 mg dose, respectively.

Note that objective D was not stated in the protocol dated June 3, 1996 or in the amendment to the protocol dated July 8, 1996.

Study design

This study was a 3-way crossover dose comparison open label study done in parallel in two groups of subjects. Fifteen subjects were assigned to a low dose group, Group A, and fifteen subjects were assigned to a high dose group, Group B. Subjects were randomized to the sequence of 3 treatments using a [redacted] within each group. The treatment groups are as follows:

Group A:

T_{RA} = 1 x 1.25 mg (R)-albuterol

T_{SA} = 1 x 1.25 mg (S)-albuterol

R_{RA}, R_{SA}= 1 x 2.25 mg racemic albuterol, reference (Ventolin®)

Group B:

T_{RB} = 4 x 1.25 mg (R)-albuterol

T_{SB} = 4 x 1.25 mg (S)-albuterol

R_{RB}, R_{SB} = 4 x 2.25 mg racemic albuterol, reference (Ventolin®).

Note that it does not state in the study report that the subjects were randomized to one of the two groups. In the protocol dated June 3, 1996 there was no mention of the group randomization. In the amendment dated July 8, 1996, it was stated in the study design section that "upon entry into the study, subjects will first be randomized with equal allocation to Group A or Group B." In the statistics section of the same amendment it states that "The first 15 subjects will be assigned to Group A and the remaining subjects will be assigned to Group B." This is not considered random assignment.

Dropouts

As stated in the protocol, an evaluable subject is one who completed all three treatments. There were 14 evaluable subjects in Group A and 13 evaluable subjects in Group B. Subject 011 from Group A voluntarily withdrew consent after receiving the racemic albuterol in the first period and obtaining zero concentration values of (R)- and (S)-albuterol. Subject 020 from Group B voluntarily withdrew consent after receiving (R)-albuterol in period one and obtaining normal blood levels for (R)-albuterol. Subject 029 from Group B was discontinued due to chest pain in period 2 while receiving (R)-albuterol.

Data Analysis

Pharmacokinetic endpoints:

As stated by the company, the primary endpoints of (R)-albuterol or (S)-albuterol were area under the concentration-time curve from pre-dose through 24 hours post-dosing, AUC(0-24) and area under the concentration-time curve extrapolated to infinity, AUC. A secondary endpoint was the maximum observed concentration, Cmax. Though typically these endpoints are log-transformed in the analyses, the company analyzed them on the natural scale due to an absence of measurable interconversion which resulted in zero levels.

Hypotheses tested:

As stated in the study report, the following null hypotheses would be tested:

1) bioavailability of the single isomer of interest within each dose group was the same when it was administered singly or as an equal amount in the racemate,
$H_0 1: T_{RA} = R_{RA}$, $H_0 4: T_{SA} = R_{SA}$, $H_0 2: T_{RB} = R_{RB}$, $H_0 5: T_{SB} = R_{SB}$;

2) bioavailability of the single isomer of interest across both dose groups was the same when it was administered singly or as an equal amount in the racemate,
$H_0 3: T_{RA} = R_{RA}$ and $T_{RB} = R_{RB}$, $H_0 6: T_{SA} = R_{SA}$ and $T_{SB} = R_{SB}$;

3) the bioavailability of four times the lower dose of (R)-albuterol, (S)-albuterol, or racemic albuterol was equal to the higher dose,
$H_0 7: 4*T_{RA} = T_{RB}$, $H_0 8: 4*T_{SA} = T_{SB}$, $H_0 9: 4*R_{RA} = R_{RB}$ and $4*R_{SA} = R_{SB}$.

Note that, as stated above, there was no mention of hypotheses 7, 8, or 9 in the protocol. This set of hypotheses tests across groups. Due to this non-random assignment into Groups A and B, comparison across groups should not be made.

Hypotheses 1-6 are correct if interest is in determining a difference between (R)-albuterol or (S)-albuterol given alone or as racemic albuterol. If the main interest is in determining that similar blood levels are obtained, then these hypotheses should be changed in order to reject a null hypothesis that the two are different. Not rejecting a null hypothesis that two treatments are the same is not the same as concluding that they are the same. One of the conclusions made in the study report is that "the comparative bioavailability of (S)-albuterol administered as a single isomer is equivalent when it is administered as an equal amount in the racemate for both the 1.25 and 5.0 mg doses," which implies that a test of equivalence should be performed rather than a traditional hypothesis test to a show difference.

Company's analysis:
Analysis was performed using ANOVA in SAS GLM. The ANOVA models to test for a significant difference between (R)- and (S)-albuterol versus the racemic albuterol (hypotheses $H_0$1, $H_0$2, $H_0$4, and $H_0$5) were performed on the original scale and included factors, sequence, period, treatment, and subject within sequence. The hypothesis testing for a difference between (R)-albuterol and racemic albuterol in Group A ($H_0$1) found very significant differences for AUC(0-24), AUC, and Cmax (p=.0001, .0001, .0026) with the (R)-albuterol group showing higher concentrations than the racemic albuterol group. These same tests in the high dose group ($H_0$2), Group B, did not show significant differences between (R)-albuterol and racemic albuterol (p=.6690, .5322, .5814).

The results for (S)-albuterol did not show significance in Group A ($H_0$4) for AUC(0-24), AUC, and Cmax (p-values =.0862, .0948, .2766) or Group B ($H_0$5) (p=.5013, .4038, .3096) between (S)-albuterol and racemic albuterol.

Comments $H_0$1, $H_0$2, $H_0$4, and $H_0$5: The sponsor's analysis that tests for a difference between (R)-albuterol when it was administered alone or as a racemic included the value for the subject's period when (S)-albuterol was administered. The value for this period will always be zero since no interconversion was detected (except subject 04, see below section on interconversion). Since this response is fixed at zero, it contains no error and cannot be assumed to be normally distributed. It is my opinion that this period for each subject should be removed in the analysis of (R)-albuterol. Analyses without the period containing the (S)-albuterol administration were conducted. The results were similar to those of the sponsors. The corresponding p-values for Group A for AUC(0-24), AUC, and Cmax were p=.0007, .0014, .0024 and for Group B were p=.4212, .2882, .4003. This same argument holds for tests on (S)-albuterol and those tests were also rerun without data from the subjects' periods where (R)-albuterol was administered. The

results for Group A for AUC(0-24), AUC, and Cmax were p=.0425, .0444, .2104 and for Group B were p=.2230, .1251, .1436.

The results for $H_0$3 and $H_0$6 were discussed in the conclusion and were given in section 14.2.1.3. Factors in the model included across-group pooled sequence, group, across-group pooled period, and treatment. The sponsor did not find any significant differences between (R)-albuterol and racemic albuterol (p-values=.6279, .3133, .4449 for AUC0-24, AUC, and Cmax). For (S)-albuterol, the p-values were .6313, .4963, and .3378.

Comments $H_0$3 and $H_0$6: Since there are different treatments in the two groups, the sequences in Group A do not correspond to the sequences in Group B. Therefore, six sequences should be included in the model rather than the 3 used by the company. Pooling period across groups should only be done if the periods for Group A are the same as the periods for Group B (i.e., same day, same location) and if subjects were randomized to group. We repeated this analysis using separate sequences and periods for each group, treating the different groups as different studies. Note that this analysis does not combine the two groups' data. Also, the comments listed above for $H_0$1, $H_0$2, $H_0$4, and $H_0$5 also hold here. Our analyses for (R)-albuterol do not contain the data (zero values) obtained from (S)-albuterol administrations and the (S)-albuterol analyses do not contain the data from the (R)-albuterol administrations. Our results are qualitatively similar, we do not reject the null hypotheses, though the p-values are reduced. The p-values for AUC(0-24), AUC, and Cmax for (R)-albuterol were .3024, .0857, .1775 and for (S)-albuterol, they were .1725,.0697, .0970.

The hypotheses for the tests for proportionality ($H_0$7) were rejected (found not to be proportional) for AUC(0-24) and AUC, though was not rejected for Cmax (p=.5375) for (R)-albuterol. The hypotheses for (R)-albuterol levels after racemic administration ($H_0$9-first part) rejected proportionality for AUC(0-24), AUC, and Cmax. The tests for proportionality were also rejected for all 3 endpoints for (S)-albuterol ($H_0$8) and racemic ($H_0$9-second part).

Comments $H_0$7, $H_0$8 and $H_0$9: As stated in the hypotheses section, since subjects were not randomized to group, comparison across group should not be conducted.

The company stated that the results in Group A are unreliable since most of the measurable (R)-albuterol concentration from Group A subjects were at or close to the limit of quantitation. Two dosage levels were given because there was concern that the usual clinical dose would not produce appreciable serum levels.

Equivalence analysis

As stated above, with the conclusions that the sponsor is making, tests for equivalence rather than tests for differences seem more appropriate. Typically, equivalence of two compounds is

concluded if all of the 90% confidence intervals for the ratios (T/R) of each of the endpoints of interest lie entirely in the interval (0.8, 1.25).

A bioequivalence analysis was performed for (R)-albuterol administered alone (test) and (R)-albuterol in a racemic (reference) for Groups A and B, separately, and without including the subject's value when (S)-albuterol was administered. The pharmacokinetic endpoints (AUC(0-24), AUC and Cmax) were log-transformed in the analysis. The model, run in SAS proc mixed, included terms for period, sequence, and treatment, with a random term for subject. The results are given in Table 1. The first column states the pharmacokinetic endpoint. Column 2 gives the estimated difference between test and reference in log scale (Mdiff) with its corresponding 90% confidence interval. Columns 3 and 4 give the estimated ratio and 90% confidence interval back-transformed. Column 5 states whether it passed or failed the BE criterion. Column 6 gives p-value obtained from the test for a difference (hypotheses $H_0$1 and $H_0$2). A similar table, Table 2, is given for (S)-albuterol. These analyses show that for Group B, the two formulations are bioequivalent for (R)-albuterol and (S)-albuterol, except that Cmax for (S)-albuterol fails the test of bioequivalence in Group B. For Group A, they are not bioequivalent for (R)- or (S)-albuterol.

Interconversion

The second objective, B, was to look for an interconversion of (R)-albuterol to (S)-albuterol or (S)-albuterol to (R)-albuterol. It was stated in the study report that there was no interconversion. By inspection of the blood level graphs of (R)-albuterol, it suggests that there may have been interconversion of (S)-albuterol to (R)-albuterol in Subject 4.

Conclusions

Our analysis showed bioequivalence of (R)-albuterol administered as a single isomer and administered as racemic albuterol for the high dose group, Group B, but not for the low dose group, Group A. This is similar to the conclusions stated in the study report, though their conclusions were based on not rejecting the null hypothesis. For (S)-albuterol, administered as a single isomer and as racemic albuterol, the high dose did not show bioequivalence for Cmax, but did for both AUC(0-24) and AUC. The low dose, Group A, did not show bioequivalence for any of the 3 endpoints.

From the hypothesis testing of (R)-albuterol in Group A, we can conclude that there is evidence of significant differences between (R)-albuterol administered alone and as racemic albuterol for all three pharmacokinetic endpoints tested. The conclusions from the equivalence analysis are similar to the conclusions made by the sponsor on the hypotheses tests conducted within group. A summary of the analysis is given in Table 3.

Comments

1. Since this study was to determine if exposure was equal between two groups, a bioequivalence analysis is more appropriate than typical hypothesis testing.
2. Though their analyses testing that the administration of the single isomers equaled that of the racemic in both groups ($H_0$3 and $H_0$6) did not reject the null hypotheses, this does not conclude that the two are equivalent or even comparable as stated in their conclusions.
3. Since the tests for proportionality ($H_0$7, $H_0$8 and $H_0$9) tests between groups and since the patients were not randomized to group, these tests may not be valid.

[redacted]

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April 14, 1998

Concur: [redacted]

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cc:
Original NDA 20-837

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Table 1: Equivalence analysis for (R)-albuterol

Endpoint	Mdiff (90%CI)	Estimated Ratio	90% Confidence Interval	Pass or Fail (.80, 1.25)	p-value on difference (T-R)
GROUP A RCmax	0.4027 (0.2176, 0.5879)	1.4959	(1.2431, 1.8002)	Fail	p=0.0024
RAUC(0-24)	0.6879 (0.4326, 0.9432)	1.9895	(1.5413, 2.5682)	Fail	p=0.0007
RAUCinf	0.7194 (0.4778, 0.9610)	2.0532	(1.6125, 2.6143)	Fail	p=0.0014
GROUP B RCmax	0.0146 (-0.1717 , 0.2009)	1.0147	(0.8422, 1.2225)	Pass	p=0.4003
RAUC(0-24)	0.0221 (-0.1647, 0.2088)	1.0223	(0.8481, 1.2322)	Pass	p=0.4212
RAUCinf	0.0371 (-0.1420, 0.2161)	1.0378	(0.8676, 1.2412)	Pass	p=0.2882

Table 2: Equivalence analysis for (S)-albuterol

Endpoint	Mdiff (90%CI)	Estimated Ratio (T/R)	90% Confidence Interval	Pass or Fail (.80, 1.25)	p-value on difference (T-R)
GROUP A SCmax	0.0244 (-0.1860, 0.2348)	1.0247	(0.8303, 1.2647)	Fail	p=0.2104
SAUC(0-24)	0.0695 (-0.2525, 0.3915)	1.0720	(0.7769, 1.4792)	Fail	p=0.0425
SAUCinf	0.0637 (-0.2192, 0.3467)	1.0658	(0.8032, 1.4144)	Fail	p=0.0444
GROUP B SCmax	0.0604 (-0.1329, 0.2536)	1.0623	(0.8756, 1.2887)	Fail	p=0.1436
SAUC(0-24)	0.0135 (-0.1682, 0.1952)	1.0136	(0.8452, 1.2156)	Pass	p=0.2230
SAUCinf	0.0385 (-0.1366, 0.2135)	1.0393	(0.8723, 1.2380)	Pass	p=0.1251

Table 3: Summary results of hypothesis tests

(R)-Albuterol Assay	P-values: Our analysis	Sponsor's analysis	(S)-Albuterol Assay	P-values: Our analysis	Sponsor's analysis
$H_0$1: $T_{RA}=R_{RA}$			$H_0$4: $T_{SA}=R_{SA}$		
AUC(0-24)	0.0007	0.0001	AUC(0-24)	0.0425	0.0862
AUC	0.0014	0.0001	AUC	0.0444	0.0948
Cmax	0.0024	0.0026	Cmax	0.2104	0.2766
$H_0$2: $T_{RB}=R_{RB}$			$H_0$5: $T_{SB}=R_{SB}$		
AUC(0-24)	0.4212	0.6690	AUC(0-24)	0.2230	0.5013
AUC	0.2882	0.5322	AUC	0.1251	0.4038
Cmax	0.4003	0.5814	Cmax	0.1436	0.3096
$H_0$3: $T_{RA}=R_{RA}$ and $T_{RB}=R_{RB}$			$H_0$6: $T_{SA}=R_{SA}$ and $T_{SB}=R_{SB}$		
AUC(0-24)	0.3024	0.6279	AUC(0-24)	0.1725	0.6313
AUC	0.0857	0.3133	AUC	0.0697	0.4963
Cmax	0.1775	0.4449	Cmax	0.0970	0.3378

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Comments

1. The physical and chemical properties of the drug substance/product were adequately described.

2. The proposed package insert was annotated, allowing identification of source studies for data verification.

3. The sponsor proposes marketing three separate strengths: [redacted] 0.63 mg and 1.25 mg/ampule. It appears that the to-be-marketed formulation was used for all of the pivotal clinical studies. This will be verified by the CMC reviewer assigned to this NDA (Dr. V. Shah).

4. Adequate assay validation data has been provided by the sponsor.

Recommendation The Office of Clinical Pharmacology & Biopharmaceutics' (OCPB) has reviewed the human pharmacokinetics section of this submission in a cursory fashion, and has found it acceptable for filing.

/S/ 7/15/97

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cc:
HFD-570 (NDA 20-837, Divisional File, Jani, Pina)
HFD-870 (ChenME, Conner, Hunt)
HFD-850 (Lesko, Huang)
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