CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

MEDICAL REVIEW

MEDICAL OFFICER CONSULTATIVE REVIEW

ANDA 73-045. Albuterol MDI

SPONSOR: A. L. Laboratories, Inc.
REVIEWER: Tunde Otulana, M.D., HFD-570
DOCs REVIEWED: Submissions of 6/12/95 & 8/1/95 (volumes 8.1, 8.2 and 9.1)

RÉSUMÉ

Twenty-five mild asthmatics completed a methacholine bronchoprovocation challenge study comparing A-L albuterol with Ventolin. The study followed OGD's Interim Guidance fairly closely except for a few infringements, one (widening of the study day baseline PD_{20} requirement) of which was agreed to by the agency before the study. Overall study conduct is acceptable, although variability within the patient data is notable. Further internal discussions are needed regarding the statistical approach for analyzing the bioequivalence in this case as well as the methodology for setting acceptable confidence intervals, in the absence of a dose-response arm within the main study. The cumulative-dose safety study showed equivalence between the two products.

1.0 BIOEQUIVALENCE STUDY (Protocol 10647).

The protocol for this study which was done in accordance with the Interim Guidance for generic albuterol was reviewed earlier in a consultative review (see MO consult review of 3/29/94). The study utilized the bronchoprovocation approach as recommended in the OGD's Interim Guidance document. The data on *in vitro* characteristics of the A-L albuterol are also included in this ANDA submission but are not discussed in this review. Below is a summary of the clinical study.

1.1 PROTOCOL SUMMARY

Study Objective: To assess bioequivalence (BE) of the generic MDI formulation of albuterol (A-L albuterol) to the reference product (Ventolin) via a bronchoprovocation model employing a methacholine challenge, in mild-moderate asthmatics..

Study Center: ✓ Only one study site was used.✓

Twenty-five (25) patients with mild asthma, aged 18 years or over were enrolled in the study. An initial screening for general health status(history, physical exam, EKG and labs) was followed by a dose-response assessment during which patients were required to have FEV1 ≥ 80% predicted, demonstrate a pre-albuterol PD_{20} to methacholine ≤ 4 mg/mL, as well as a minimum eight-fold increase in PD_{20} over baseline in response to 2 puffs (180 mcg) Ventolin. Also, a minimum 2-fold ratio of PD_{20} response to two puffs relative to one puff of Ventolin was required. Eligible patients then proceeded, within 4 weeks, to the bioequivalence study which was a single dose (90 mcg/puff), two treatment, four period, 2 sequence, double-blind, randomized, crossover design with study days separated by at least 24 hours.

Patients were randomly assigned to one of the following two sequences:

Visits→	1	2	3	4
Sequence 1	A	B	B	A
Sequence 2	B	A	A	B

(A=A-L lab albuterol, B= Ventolin, both MDIs)

On each study day, patients had a baseline methacholine challenge to determine PD_{20}, followed by administration of albuterol, and then a post-dose methacholine challenge, with at least 3 hours between the two challenges. The methacholine challenge test was carried out in a standard fashion, except that doses up to 75 and 125 mg/mL (higher than the approved 25 mg/mL dose) was used. This is acceptable since the study was done under a bio-IND.

The following other elements of the study as described in the submission met the requirements of the Interim Guidance:
- inclusion and exclusion criteria,
- training of patients,
- priming of MDIs prior to use (10 sprays were wasted each time),
- concomitant medications and wash-out periods,
- daily baseline FEV_1 and PD_{20} requirements, and
- vital signs measurement during study.

1.2 DATA ANALYSIS

A validation analysis of intra-day and inter-day variability of the bronchoprovocation challenge measurements was carried out . A subset of four asthmatic patients were included. For the intra-day analysis, two baseline methacholine challenges conducted at least 3 hours apart were compared. For inter-day analysis, data from baseline challenges over the 5 study days were used.

Primary data analysis was based on log-transformed PD_{20} comparison at the one puff dose of A-L albuterol versus Ventolin during the BE treatment phase. Secondary analysis involved calculation of Drug Activity Ratios defined as the ratio of post-dose PD_{20} divided by the pre-albuterol PD_{20} where the baseline was obtained on the same study day. The log transformed data were analyzed using a linear statistical model with factors for sequence, subjects, visit, treatment and subject by treatment interactions.

1.3 RESULTS

1.3.1 Study conduct

A total of 87 patients were recruited, of which 58 were excluded at pre-study screening and dose-response screening. The remaining 29 patients were randomized into the study, out of which 25 completed the study. Four patients who discontinued for various reasons (as described below) were excluded from the analysis, leaving 25 patients in the bioequivalence analysis. Table 1.3.1 below summarizes the patient disposition.

At the start of each study day, patients were required to meet certain criteria, some of which were additional to those recommended in the Interim Guidance:

- best $FEV_1 \geq 70\%$ predicted, and within 12% of screening FEV_1,
- $\leq 10\%$ fall in FEV_1 after buffer saline during bronchoprovocation testing, and
- baseline PD_{20} following methacholine challenge within 2 fold dilution (i.e. 50-200% of the screening PD_{20}. This requirement was later changed to 4-fold dilution (i.e. 25-400%) following discussions with the agency and a submission of a protocol amendment.

Table 1.3.1. Patient Disposition in study 10647

Total number screened for eligibility	87
Number excluded at pre-study screening on medical grounds ...overweight ...taking unallowed medications	5 4 1
Excluded at dose-response screening visits: Total ...FEV_1 less than 80% predicted ...$PD_{20} > 4$ mg/mL ...for not meeting requirement on 2:1 albuterol dose-response	53 24 10 19
Total randomized into bioequivalence phase: 87-5-53	29
Number excluded from BE analysis due to protocol violations ...failed baseline qualifying on first visit ...asthma and allergy exacerbations ...required rescue medications on 3 consecutive visits	4 1 2 1
Number of patients who completed the BE study: 29-4	25

Demographics: Of the 29 patients studied, 15 (or 52%) were males, 18 (62%) were caucasians and 6 (21%) were smokers. Mean age was 28.6, range 18 to 51, years. The patients had mild asthma. Mean screening FEV_1 was 93.9 ±12.1 % predicted; range 80 to 130 % predicted.

1.3.2 Results of screening

Three (3) of the 29 patients randomized into the study did not meet the entry PD_{20} ratio criteria. Details of these violations are shown in table 1.3.2A below. The 3 patients were among the 25 who completed the study and whose data were analyzed to support bioequivalence. The sponsor argued that their ratios were so close to the expected that it was justified to include them in the study.

Table 1.3.2A Patients who did not meet screening dose-response criteria.

	PD_{20} after 2 puffs albuterol ÷ PD_{20} pre-albuterol	PD_{20} after 2 puffs ÷ PD_{20} after 1 puff albuterol
Recommended ratio	≥ 8	≥2
Patient #103	7.4	1.8
Patient #108	6.4	1.9
Patient 119	7.7	7.7

Apart from these 3 patients, all other patients met the screening requirements. The screening dose-response PD_{20} data in the 25 study completers are summarized in table 1.3.2B below. The 'Post-dose PD_{20} ratio' is the ratio of PD_{20} on 2 puffs Ventolin versus 1 puff Ventolin. The drug activity ratio is the post-dose PD_{20}/baseline PD_{20} on 2 puffs albuterol.

Table 1.3.2B Screening visits data, n=25

Post-dose PD_{20} ratio (2:1 puffs of albuterol)	
Mean	3.73
Standard Deviation	2.13
Range	1.8 - 11.7
Drug Activity Ratio (2 puffs albuterol/pre-dose baseline)	
Mean	17.7
Standard Deviation	8.1
Range	6.4 - 32.7

There was a significant intersubject variation in both the screening post-dose PD_{20} and the Drug Activity Ratio, on review of the individual patient data . Within-subject, there was also a large interday variability in some patients. In a few instances where some patients failed to meet the study PD_{20} ratio requirement on a given day, large changes were recorded when the methacholine challenges were repeated on rescheduled visits. Examples of such changes between visits are shown in table 1.3.2C below.

Table 1.3.2C. Samples of within-subject, interday variability of Drug Activity Ratio

Patient ID. Number	First Drug Activity Ratio measurement	Repeat Drug Activity Ratio measurement	Days between measurements
109	3.8	32.1	2
114	4.2	21.4	5
117	4.8	26.3	4
125	2.9	8.0	10

1.3.3 Results of Bioequivalence testing

The sponsor provided analyses of the PD_{20} and Drug Activity Ratio as planned in the protocol. The average of one puff of Ventolin was compared to the average of one puff of A-L albuterol. Table 1.3.3A shows the 'bioequivalence ratios' in the 25 patients. On post-dose PD_{20}, A-L albuterol, based on mean data, appeared marginally less potent than Ventolin, as the 90% confidence intervals were below 1.0. However, no statistically significant difference was detected on the comparison of the 2 products on this variable and on Drug Activity Ratio.

Table 1.3.3A. Double-blind, bioequivalence phase data

Post-dose PD_{20} ratio (A-L albuterol : Ventolin); n=25	
Mean	0.81
90% Confidence Interval	0.68 - 0.98
P value	not significant
Drug Activity Ratio; n=25	
Mean	0.90
90% Confidence Interval	0.73 - 1.10
P value	not significant

The sponsor attempted to identify patients who might have showed more sensitivity to albuterol compared to the entire population by exhibiting a strong protective effect of one puff of albuterol. Thirteen (13) such patients were identified on the basis of having 1 puff albuterol/pre-albuterol $PD_{20} \geq 4$. Table 1.3.3B below shows the 'bioequivalence ratios' in that subgroup.

Table 1.3.3B. Bioequivalence analysis in 'sensitive' subgroup, n=13

Post-dose PD_{20} ratio (A-L albuterol : Ventolin); n=13	
Mean	1.02
90% Confidence Interval	0.80 - 1.30
P value	not significant
Drug Activity Ratio; n=13	
Mean	1.02
90% Confidence Interval	0.76 - 1.37
P value	not significant

1.3.4 Validation study data

Four patients from the main bioequivalence study had PD_{20} from their methacholine challenges over a 6 day period analyzed in order to validate the methacholine challenge procedure. The within-subject, intraday co-efficient of variation (CV) was 40.8% while within-subject, interday CV was 54%. The between-subject CV was not analyzed from this data.

1.4 REVIEWER'S COMMENTS

Data Interpretation: The study followed the Interim Guidance fairly closely. Therefore the issues raised by the design of this study relate to the larger issues of bioequivalence testing within the frame work of the current Interim Guidance document. Such issues include 'detector approach' versus 'population approach', ability to carry a pre-determined dose-response status from screening to the BE testing phase; appropriate data modeling (Emax, log linear etc.) and so on. All these issues (and more) present problems in interpreting the findings of this study. Re-analysis based on further internal discussions on approaches to BE testing of albuterol within the FDA is needed. Opinion on whether or not the analysis presented here meets BE requirements is deferred pending such multi-disciplinary (statisticians, clinicians, clinical pharmacologists etc.) internal discussions. Among other things, the discussions should address the following issues:

- how to handle the non-inclusion of dose-response demonstration in the BE phase of the study
- the transfer of the BE comparison from the PD_{20} axis to the dose axis
- any possibility of modeling the data from this study given that only 1 dose point exists within the BE testing itself.
- appropriateness of using the variability seen in the reference product (Ventolin) during the screening phase to set the confidence intervals for bioequivalence testing between test and reference
- statistical issues involved in setting the confidence intervals around the 1 puff (A-L albuterol : Ventolin comparison)

Study Conduct: The study complied with most of the steps outlined in the Interim Guidance. The reasons for excluding 58 patients out of the 87 screened appeared acceptable. The other four patients who dropped out of the main study for not meeting study day baseline or for having asthma exacerbation during the study also seemed to be legitimate exclusions. The sponsor provided analysis showing that despite these exclusions, the study still had adequate power to detect a difference between the two products if one existed. Agency statisticians would need to verify that this is true.

The patients included in this study were remarkably mild, with pre-study FEV_1 ranging from 80% to 130%. Since the 25 patients who completed the study met the inclusion criteria, this is not a major study conduct issue. However, it is possible that the mildness of the disease contributed to the variability seen in the data.

The sponsor relaxed the entry criterion which called for study-day PD_{20} to be within 2-fold dilution (50 to 200%) of qualifying PD_{20}. This was relaxed to a 4-fold dilution or 25 to 400%. A protocol amendment was filed and 'approved' on this change. The sponsor also argued that of the 25 patients who completed the study, 81% would have met the stricter criterion any way, and the relaxation merely helped about 5 patients not to be dropped from the study. In addition to this, the sponsor included in the bioequivalence

phase of the study 3 patients who did not strictly meet the requirement that PD_{20} ratio on 2 puffs relative to 1 puff of albuterol be ≥ 2. Two of these patients had ratios that were quite close to the target, but one had a ratio of 7.7. It is unclear to what extent these 2 'violations' made the data as variable (within-subjects and between-subjects) as it is.

Overall, the infringements in the study conduct described above are not major. If they had any effect on the study outcome, it would probably be to increase data variability and this should manifest when the data is modeled and re-analyzed for bioequivalence testing, i.e. they are likely to constitute a 'producer risk' rather than a 'consumer risk'.

2.0 CUMULATIVE-DOSE SAFETY STUDY (10667)

2.1 PROTOCOL SUMMARY

The objective of the safety study was to compare the effects of cumulative doses of A-L albuterol with Ventolin on cardiac function, serum potassium and serum glucose. The study followed closely the protocol described in the Interim Guidance. Recommendations such as canister priming, patient training, pre-study physical exam, EKG and labs were carried out as per the Guidance.

Thirteen healthy non-asthmatic subjects, 5 males and 8 females, aged 18 years and over were enrolled in the study. Ten subjects completed the study and were classified as evaluable. A double-blind, cumulative dose, two treatment, two period, two sequence, randomized, cross-over study was carried out. Each study period was separated by 72 hours.

Periods →	1	2
Sequence 1	A	B
Sequence 2	B	A

Subjects were randomly assigned to receive either A-L albuterol (A) or Ventolin (B). Each treatment consisted of a single-day cumulative dose of two (180 mcg), four (360) and six (540 mcg) puffs, administered 30 minutes apart, giving a total of 12 puffs. The doses were self-administered, after training on use of MDIs. Blood pressure, 12 lead EKG, serum potassium and glucose were measured at baseline. 15 minutes following each dose and 30, 60, 120, 180 and 240 minutes after the last dose.

2.2 DATA ANALYSIS

Baseline and post-dose safety parameters were summarized as means, SD and percent coefficient of variation. Repeated measures analysis of variance was carried to compare within and between treatment analysis of the safety measurements. Between treatment differences at each time point was analyzed using a general linear models method.

2.3 STUDY RESULTS

The ten subjects who were evaluable in the study included 4 males and 6 females, mean age 32.7 (±8.9 SD) years. All the 10 subjects completed the study. The remaining three of the 13 who were enrolled in the study were excluded due to non-compliance with dosing or timing of dosing. There were five reports of adverse events during the study: 2 on A-L albuterol (jitteriness and headache) and 3 on Ventolin (jitteriness, headache and nausea). They were said to be transient and they did not require treatment.

2.3.1 VITAL SIGNS

There was no significant difference between A-L albuterol and Ventolin with regard to the mean blood pressure measurements predose and at the 15 minutes post-dose measurements. However, a statistically significant difference was found at the 30 minutes post-6 puffs assessment. The mean systolic blood pressure at this time was 107 on A-L albuterol compared to 112 mmHg on Ventolin, $p=0.037$. This difference is unlikely to be significant clinically.

The heart rate measurements (apparently measured from R-R intervals) were not significantly different between the two arms of the study except at the 120 minutes (post-6 puffs) measurement. At that time, the mean on A-L albuterol was 65 while on Ventolin it was 69 beats/min, $p=0.038$. This difference however is unlikely to be of clinical significance.

A review of the individual patient data as provided in the data listing showed substantial variability in heart rate response within the two groups, but did not show any significant difference in pattern between the two products.

2.3.2 EKG

Lengthening of the QT and QTc intervals occurred with escalating doses of both products. However the only statistically significant differences between the two drugs occurred at 60 and 180 minutes post-dose. QT interval was longer on A-L albuterol at both time points: 401.6 versus 388.8 msec, $p=0.02$; and 401.6 versus 390.0 msec, $p=0.02$; respectively. A review of the individual patient listings of QTc showed 6 time points when the values were above normal (>440 msec) on A-L albuterol, while there were 7 such points on Ventolin. The same patient (#110) on both drugs experienced 5 of the abnormal measurements on A-L albuterol and 6 of those on Ventolin, including a predose QTc of 468 to 479 msec. Other measurements on EKG did not differ significantly between the 2 drugs at all other time points. The QT/QTc differences are unlikely to be of any clinical significance.

2.3.3 SERUM GLUCOSE AND POTASSIUM

Baseline (pre-drug) serum glucose was significantly different between the two drug groups. Mean baseline serum glucose was 63.9 mg/dL on A-L albuterol compared to 80.5 mg/dL on Ventolin., $p=0.013$. On treatment, the two drugs differed at the 15 minutes time point after each dose with the

test product appearing to produce lesser elevations of serum glucose. However, part of this may be due to the lower baseline in the test product group. Table 2.3.3 below shows the mean serum glucose measurements.

Table 2.3.3. Serum Glucose: Mean & SD. N=10 in both arms.

	A-L albuterol		Ventolin MDI		Test/Ref. Ratio
	Mean	SD	Mean	SD	
Pre-dose	63.9	19.4	80.5	13.3	0.79*
2 actuations	71.1	15.0	80.4	8.2	0.88
4 actuations	72.6	10.8	85.1	11.5	0.85#
15 min	80.0	12.2	90.5	7.6	0.88#
30 min	81.5	11.0	89.0	9.4	0.92
60 min	80.2	17.7	90.2	10.7	0.89
120 min	84.1	13.0	91.4	15.2	0.92
180 min	86.6	15.4	89.2	9.3	0.97
240 min	84.3	13.7	85.9	11.3	0.98

*p=0.01, and # p=0.04 comparing test vs reference. All other comparisons, not significant.

The mean effects of A-L albuterol and Ventolin on serum potassium were similar at all the measurement times; no statistically significant difference was demonstrated between the two drugs at all the measurement points. The measurements were generally within clinically acceptable limits, despite a slight fall in serum potassium levels with increasing albuterol dose in both groups. No significant difference in pattern was seen between the two products when the individual data were reviewed.

3.0 CONCLUSIONS ON STUDIES 10647 AND 10667

The bronchoprovocation, bioequivalence study was conducted in accordance with the Interim Guidance. Most of the recommended steps were followed. A few deviations from the protocol and from the Guidance occurred and these may account for some variability within the data but are not sufficiently significant to invalidate the study. The impact of data exclusions which lowered the 'evaluable' patient number to 25 requires attention when the data is modeled or re-analyzed. Internal discussions are needed regarding how these modeling and statistical analyses would be carried out to determine bioequivalence given the design of the study.

CONCLUSIONS cont'd.

The safety study also followed the Interim Guidance closely. The slight differences seen between A-L albuterol and Ventolin on heart rate, QT and serum glucose even though of statistical significance are of doubtful clinical significance, and would possibly fall within the natural fluctuations of those measurements. The study therefore established acceptable equivalence between the two drugs.

Tunde Otulana, M.D., Medical Reviewer, HFD-570 /S/ 5/21/96

Concurrence: Robert Meyer, M.D., Team Leader, HFD-570 /S/ 5/24/96

Concurrence: John Jenkins, M.D., Division Director, HFD-570 /S/ 5/29/96

for Rupper
HFD-102
6/6/96

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 73-045

FIRM: ALPharma, USPD

DOSAGE FORM: MDI

STRENGTH: 90 mcg/Actuation

DRUG: Albuterol MDI

CGMP STATEMENT/EIR UPDATED STATUS:
EER submitted by this reviewer and S. O'Keefe on 1-3-96 for the following facilities became acceptable on 5-29-96.

1. CCL Industries
   9 Arkwright Road
   Astmoor Industrial Estate
   Runcorn
   WA7 1NU, England
   (Manufacturing, packaging and labeling, Testing and stability testing site for the release of the drug product)
2. [redacted]
3. [redacted]
4. [redacted]

Comments: An follow-up EER need to be submitted for the above listed facilities for the present cGMP compliance status of these facilities.

BIO STUDY:
In-Vivo: Acceptable per bio review dated 4-29-97.

In-Vitro: Acceptable per bio review written by Gur J.B. Singh and signed by Director of Bioequivalence on 7-14-97.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Methods Validation completed by DDA, St. Louis, MO on 8-22-96 was found acceptable with some modification. It became acceptable after the firm submitted adequate response in their amendment dated 9-5-96.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Container used in the stability studies are identical to those listed in container section.

Expiration acceptable - 24 months based on the stability studies.

LABELING:
Satisfactory per labeling review completed on 10-8-96.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio Batch (lot # 6403). Size: [ ] canister.

BDS Source: Reference DMF [ ] for [ ] is adequate per review completed on 10-15-96 by this reviewer. No new information is submitted after this last review.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Bio/Stability batch:
Lot # 6403 and its size is [ ] units. Additional test data have been provided for batches 8671, 8834 and 8457. They were all manufactured by the same process and data are adequate.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
ALPharma's proposed production batch sizes are: [ ] units.

Manufacturing process for intended production size batches is same as used for the bio/stability batch.

cc: ANDA 73-045
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/7-17-97
HFD-625/M.Smela/7-18-97

/S/ 7/28/97

/S/
7/29/97