CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-570

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
10/5/99

ANDA 75-570
Drug Product: AMMONIUM LACTATE LOTION 12%
Firm: CLAY PARK LABS, INC
Reference Listed Drug: LAC-HYDRIN 12%, WESTWOOD-SQUIBB PHARMACEUTICALS, INC.

Composition

The active ingredient and proposed conditions of use are noted to be the same for the Clay Park product and the reference listed drug. Using reverse engineering, the firm believes their product is Q_1 and Q_2 similar to the innovator product, Lac-Hydrin 12%, Westwood – Squibb Pharmaceuticals, Inc.

Protocol #951317

Title: A Double Blind, Randomized, Parallel Study Comparing Two Formulations of 12% Ammonium Lactate Lotion and a Placebo for the Treatment of Ichthyosis Vulgaris

Study Period: May 2, 1997 to January 9, 1998

CRO: [redacted]

Background

The original protocol was submitted to the FDA in August, 1996 and reviewed by the Division of Dermatologic and Dental Drug Products. Several amendments were made to the protocol that was used to conduct the study based on feedback from the Agency. The firm submitted a third amendment on June 2, 1998 based upon comments made by the FDA regarding statistical analyses. They have clarified that this amendment was submitted prior to unblinding the study results for the analyses and evaluating the study results using some of the statistical methodology described in this amendment.

Objectives

The objectives of this study were to compare the clinical equivalence, efficacy, and safety of 12% Ammonium Lactate Lotion manufactured by Clay-Park Labs, Inc., Westwood-Squibb's Lac-Hydrin® 12 % Ammonium Lactate Lotion, and Clay-Park's Placebo (Vehicle Lotion without Ammonium Lactate) in the treatment of Ichthyosis Vulgaris.

Investigators

[ ]

Study Design

This was a double-blind, placebo-controlled, randomized, parallel, multi-center, comparative study with three study arms: 12% Ammonium Lactate Lotion, Clay-Park Labs, Inc.; Lac-Hydrin 12 %, Westwood-Squibb; Vehicle, Clay-Park Labs, Inc. (Placebo). Subjects with a clinical diagnosis of Ichthyosis Vulgaris were enrolled following appropriate screening. They were given treatment twice daily for 28 consecutive days. Patients were followed throughout the treatment period and for two weeks post treatment. The primary outcome was evaluated using the Ichthyosis Vulgaris symptom severity score recorded at each visit. Safety was assessed by reporting clinically observed adverse events and monitoring vital signs and physical examinations.

Inclusion/Exclusion Criteria

Inclusion Criteria

- Males and Females, aged 18 years or older
- Subjects with a minimum of two areas of affected skin with Ichthyosis Vulgaris
- Subjects must be in good general health and not have any known condition or be on any medication that will influence their Ichthyosis Vulgaris
- Subjects who have signed an informed consent
- Subjects must have a minimum score of (3) on the Ichthyosis Vulgaris Scale

Exclusion Criteria

- Subjects with previous reactions to Ammonium Lactate or other alpha-hydroxy acids
- Female subjects who are presently taking oral contraceptives must have been on the same contraceptives for a minimum of 3 months
- Female subjects must take the same oral contraceptive agent for the entire course of the trial
- Subjects with a history of psoriasis or other active skin pathology (in the region to be treated)
- Subjects who are pregnant or lactating
- Subjects taking other investigational drugs or having participated in another clinical trail within 30 days of enrollment into study
- Subjects who have received any topical medication on the affected areas within 2 weeks of the start of the study treatment

Study Visits

Visit 1 (Pre-treatment)

At the first visit patients had a complete physical examination, a medical history, and an assessment of the severity of Ichthyosis Vulgaris using the Severity of Ichthyosis Vulgaris Scale below:

Severity of Ichthyosis Vulgaris Scale
Degree of Severity

Score	Definition
0	Normal skin; No signs of dryness.
1	Barely perceptible scales.
2	Perceptible scale plus/minus reticulation present.
3	Fine scales, reticulation, and slightly rough.
4	Shallow furrows with fine scales, skin rough to touch.
5	Furrows more evident, more fine and larger scales.
6	Furrows very evident, larger adherent scales plus occasional plaques.
7	Fissures and furrows present, large scales plus plaques less than 0.5 mm in thickness.
8	Predominate fissures and deep furrows, plaques 0.5 – 1.0 mm thick.
9	Extremely deep fissures with pain, deep furrowed skin inflammation and pigmented plaques greater than 1.0 mm.

Subjects were given a Daily Personal Diary, pre-weighted bottles of study medication, and special soap, along with instructions on how to wash the affected area and apply the medication.

Visit 2 (Day 14 +/- 3 days)

Visit 3 (Day 28 +/- 3days)

The investigator questioned and examined the patients to identify any potential adverse events as well as the use of any concomitant medications. A Severity of Ichthyosis Vulgarsis assessment was repeated and the Daily Personal Diary was reviewed. An assessment was made of the subjects' study medication compliance. A Daily Personal Diary for Days 15-42, study medication, and the special soap was provided to the patient. In addition, a Global Assessment of improvement was completed.

Visit 4 (Day 42 +/- 5 days)

At the final visit, a physical examination was completed by the physician. The investigator reviewed the medical history and physical examination as necessary to identify the presence of any adverse events. The use of concomitant medications was recorded. A Severity of Ichthyosis Vulgarsis assessment was made, as well as a Global Assessment of improvement. In addition, the Daily Personal Diary for Days 28 and 42 was reviewed.

A Priori Criteria for Premature Discontinuation

At any time during the conduct of the study a subject could be discontinued upon his/her request or if the Investigator judged it was in the subject's best interest. In addition, subjects were discontinued for any of the following reasons:

-voluntary withdrawal,
-significant physical abnormality,
-significant concurrent illness or deterioration in subject's medical condition,
-significant adverse experience,
-significant non-compliance to the study protocol,
-failure to return for a study visit,
-missing more than 2 days of application of study drug in any 7 day period,
-use of any contraindicated concomitant medication.

Medication

Each subject received three 400 gram bottles of the study medication, which contained either

- Clay-Park Labs, Inc. 12% Ammonium Lactate lotion (Test)
- Westwood-Squibb, Lac-Hydrin® 12% Ammonium Lactate lotion, or
- Clay-Park Labs, Inc. Vehicle lotion (Vehicle).

Each subject was instructed to apply the study medication on all areas of the body affected by Ichthyosis Vulgaris twice daily (morning and evening). Subjects also received PURPOSE ® soap (manufactured by Johnson, Inc.) at visit 1 and visit 2. They were instructed on the appropriate procedures for cleaning affected areas before application of study medication. Subjects were assigned to receive study medications according to a randomization scheme provided by [redacted] Subjects were instructed to record the times of application of their medication in a Daily Personal Diary. They were asked not to use concomitant topical medications or medicated or abrasive cleansing products.

Randomization

A computer generated randomization list was used to assign subjects consecutively to the study. This list was provided by [redacted]. Once a subject and medication number were assigned, it was not transferred to any other subject. If additional subjects

were enrolled, they were assigned consecutive subject and medication numbers as per the randomization list. In an effort to ensure blinding of the study, the person who dispensed the medication to the subject was someone other than the Investigator who assessed the severity of the Ichthyosis Vulgaris. In addition to recording the time and date of each medication application, the Daily Personal Diaries were used to record all concomitant medications taken and all adverse events experienced. A section was also included where subjects answered questions concerning the status of his/her disease (Global Assessment).

Efficacy Variables

The evaluation and severity of the skin areas affected by Ichthyosis Vulgarsis was performed using the Severity of Ichthyosis Vulgaris Scale (see Study Visits, Visit 1 section). The overall score for each subject was calculated from the mean of all affected skin areas by adding up the individual scores and dividing by the number of affected skin areas. This score was assessed on a categorical scale (success or failure). A score of 1 or less was considered to be a treatment success and any score greater than 1 was interpreted as treatment failure. Treatment success or failure was determined at the Day 28 and Day 42 visits independently.

The evaluation of improvement of the skin area treated was performed using the Global Assessment Scale that is described below:

Global Assessment Scale

- Normal skin, or marked improvement: Skin is either normal in appearance, or is markedly less dry than at previous visit.
- Slight Improvement: A slight improvement in skin condition can be seen.
- Moderate Improvement: A reasonable improvement in skin condition can be observed.
- No change, or worse: The skin shows no sign of improvement, or is in worse condition than at previous visit.

Safety

Safety was evaluated by eliciting patients' medical histories for symptoms and adverse events, examining the subject, and reviewing changes in concomitant medications and concurrent illness.

Evaluation Criteria

Criteria for evaluability for the Intent- to-Treat analysis (ITT) were determined by a statistical plan dated June 15, 1998. Subjects who met all inclusion/exclusion criteria and who received treatment with the study medication for 28 days were evaluated for both therapeutic equivalence and efficacy. Those who missed more than 2 days application of

study drug in any 7-day period, or who failed to return for any visit were considered to have withdrawn from the study. These individuals were replaced. Subjects who were withdrawn from the study due to an adverse event were included in the Intent-to-Treat analysis. Subjects who asked to be withdrawn from the study due to lack of efficacy of the study medication were considered to be treatment failures.

Intent-to-Treat (ITT) Criteria

In order for subjects to be considered evaluable and included in the ITT analysis for efficacy parameters, at least 1 valid assessment had to have been performed both pre-treatment and post-treatment, following the first application of study medication.

Per Protocol (PP) Criteria

Subjects included in the Per Protocol analysis had complied fully with the protocol and completed all required aspects of this study. Under certain circumstances, however, the investigator was permitted to specifically approve the inclusion and analysis of a patient's data, if they deemed that it was evaluable under the Per Protocol category.

Protocol Violations

The following protocol violations were defined prior to the analysis in the statistical plan:

- Subject randomized into the study who was not eligible according to the inclusion/exclusion criteria specified in the protocol.
- Less than 70% of compliance in application of the study drug.
- Breaking the treatment code not associated with a serious adverse event.
- Treatment compliance: if subject missed more than 2 days of application of the study drug in any 7 day period. One day of missing application was defined as a day in which the 2 applications of the study medication were missed.
- Use of contraindicated concomitant medication.

Statistical Analysis

Sample Size

A sample size of 69 per group was calculated for the comparison of both active drugs based on the assumptions of a two-sided alpha of 0.05, 95% power, and a delta of 1.5 on the 10-point scale. The comparison of active versus placebo required a sample of 22 in the placebo arm based on the following assumptions: maximum variance, one-sided alpha of 0.05, 80% power, and a delta of 1.5 on the 10-point scale. A 30% dropout rate was factored into the final sample size of 230: 99 (test), 99 (reference), and 32 (placebo).

Statistical Comparisons

The efficacy variable used for therapeutic equivalence was the Ichthyosis Vulgaris Severity Score at Day 28. This was done using a categorical scale of Success or Failure and 90% Confidence Intervals on the difference between the success rate of the Test versus Reference product. The efficacy of the active treatments versus Placebo was tested at two points, the end of treatment at Day 28 and two weeks after treatment at Day 42. The latter measurement was felt to more accurately differentiate between active and Placebo treatments. The proportion of successfully treated subjects on the active treatments had to be significantly (p=0.05) greater than that for the placebo subjects.

Results

Although the study protocol specified that 230 patients were to be enrolled, only 188 subjects were randomized. However, more than 160 subjects completed the study, meeting the estimate made to achieve a meaningful sample size. Of the 188 screened and randomized, twenty-four subjects withdrew or were withdrawn from the study.

Table 1
Study Populations

	Total	**Test**	**Reference**	**Vehicle**
Total # of patients enrolled	188	85	77	26
Total # of patients withdrawn	24	10	8	6
Total # of patients completed	164	75	69	20
Subject Withdrawal				
Protocol Violation*	4	1	1	2
Adverse Event	12	6	3	3
Consent Withdrawal (personal reasons)	4	2	1	1
Lost to Follow-up	1	0	1	0
Failure to Return	3	1	2	0
Total	24	10	8	6
Analysis Data Sets				
Equivalence and Efficacy **				
Treatment Period	165	75	69	21
Treatment Period with the endpoint analysis	179	81	73	25
Post-Treatment Period	164	75	69	20
Per Protocol	159	75	65	19
Safety				
Physical Exams/Vital Signs	185	84	75	26
Adverse Events	188	85	77	26

*These protocol violations were not adequately described in the report. They were listed in accompanying tables. They are as follows:

1. Subjects #50 and # 182 were withdrawn for use of a contraindicated medication taken prior to initiation of the study. Subjects #15 and # 185 were non-compliant.
2. Subjects withdrawn due to adverse events were # 11, # 13, # 14, # 25, # 69, # 76, # 94, #108, # 110, #112, #148, and # 184.
3. Voluntary withdrawals were # 150, # 157, # 169, and # 181.
4. Subjects lost to follow-up were # 30, # 73, and # 146.

**These three subgroups and their differences were defined as follows:
Treatment Period – subjects eligible for the Intent-to-Treat efficacy analyses for the treatment period
Post-Treatment Period - subjects eligible for the Intent-to-Treat efficacy analyses for the post-treatment period
Treatment Period with the Endpoint Analysis – subjects eligible for the endpoint efficacy analyses

Protocol Adherence

The study report indicates that records of non-adherence to the protocol were verified by the monitor. The Sponsor reviewed all data listings and records of protocol violations and deviations before the blind was broken to establish the evaluability of the subjects for analysis.

Protocol Violations

The following protocol violations were defined prior to the analysis in the statistical plan:
- Subject randomized into the study who was not eligible according to the inclusion/exclusion criteria specified in the protocol.
- Less than 70% of compliance in application of the study drug.
- Breaking the treatment code not associated with a serious adverse event.
- Treatment compliance: if subject missed more than 2 days of application of the study drug in any 7-day period. One day of missing application was defined as a day in which the 2 applications of the study medication were missed.
- Use of contraindicated concomitant treatment.

Contraindicated concomitant treatment was defined in both the protocol and the study report as:
- Any topical skin treatment and/or medication during the course of the study.
- The following oral medications – Allopurinol, Reomycine, Ethionamide, Gemfibrosil, Lithium, Retinoids, Methoxsalen, Vitamin A, Vitamin B3, Vitamin B12.

The following subjects were defined as protocol violations: # 50, # 102, and # 182 were not eligible as they were on contraindicated medication at the time of the study enrollment. Subject # 50 and # 182 were withdrawn from the study. Subject # 102 completed all four study visits. Subject # 27 was treated with retinoin during the course of the study and was included in the ITT portion of the analysis. Subjects # 25, # 110, #

112, and # 15 were less than 70% compliant overall in taking study medication. Subjects #6 2, # 73, # 191, and # 192 went more than two days without application of the study drug in any 7-day period. The following subjects used contraindicated topical medication during the course of the study: # 23, # 27, # 31, # 56, # 72, # 79, # 85, # 88, # 202, # 203, # 208, # 217, # and #222. Subject # 63 was not included in the Sponsor's listing of protocol violations but was listed as taking Centrum vitamins which contain the contraindicated vitamins. In addition, patient # 141 was noted to be non-compliant.

Protocol Deviations

Protocol deviations identified in the report included only the most frequent deviation, the patient's study visit was outside the window defined in the Statistical Plan:

Visit 2 : 14 days after Visit 1 +/- 3 days
Visit 3 : 28 days after Visit 1 +/- 3 days
Visit 4 : 42 days after Visit 1 +/- 5 days

Using these criteria, the following patients had protocol deviations: # 6, # 8, # 16, # 18, # 47, # 51, # 56, # 64, # 77, # 93, # 94, # 95, # 97, # 98, # 99, and # 109. Seven subjects (# 6, # 16, # 47, # 75, # 77, # 98, and # 99) were out of the visit window for the primary endpoint visit for the bioequivalence analysis, Visit 3 (Day 28). In addition, subject # 87 missed visit 2 and Subject # 107 was noted to have failed to return.

Per Protocol Population

The subjects included in this group were carefully reviewed. The Sponsor was asked to provide a list of the patient numbers in this group and a justification for the inclusion of individual subjects who had any deviation from the protocol. The complete list was provided after a second request but no justification was given for patient inclusion and the Sponsor did not provide the documentation requested in the form of the waiver letter mentioned in the summary of subjects completing the study according to the protocol. This notation was made for three subjects who received topical medication. The Per Protocol cohort described by the sponsor includes most of the patients listed above with the protocol violation of taking contraindicated medications, topical and oral. In addition, patients with the most frequent protocol deviation of being outside a study visit window were also included.

Medical Officer Comment: *The Per Protocol group should be adjusted to exclude all the patients who, at a minimum, meet the strict criteria of the definition given by the Sponsor in the report. The group should also exclude individuals who did not complete the study according to protocol as defined in the table entitled Study Termination Summary provided with the study report. In the first scenario the following patients should be excluded: # 23, # 31, #56, # 63, # 72, # 79, # 85, # 88, # 107, # 141, # 188, # 202, # 203, # 208, # 217, and # 222. This would lead to a total sample of 143, with 65 in the Clay-Park arm, 61 in the Lac-Hydrin arm, and 17 in the Placebo arm. If all patients who did not complete the study according to protocol are excluded from this group, the following additional subjects should be taken out of this cohort: # 6, #16, # 47, # 75, # 77, # 98, and # 99. This would lead to a sample size of 127 with 59 in the Clay-Park arm, 51 in the Lac-Hydrin arm, and 17 in the Placebo arm. It is customary to exclude only those*

subjects who were out of the visit window for the bioequivalence primary endpoint from the bioequivalence analysis of the Per Protocol group, which in this case is Visit 3 (Day 28). This would lead to exclusion of the following patients: # 6, # 16, # 47, # 75, # 77, # 98, and # 99. The sample size for this group would be 136, with 62 in the Clay-Park arm, 57 in the Lac-Hydrin arm, and 17 in the Placebo arm.

Demographics

Fifty-two males and 136 females comprised the 188 enrolled subjects. The mean age was 53.6 +/- 16.3 years and subjects ranged from 18 to 94 years. Subjects in all groups were primarily Caucasian (85%). The following table demonstrates the disease characteristics in each group at baseline:

Parameter	Test	Reference	Placebo	Total
# of affected areas	6.8 +/- 3.9	7.8 +/- 5.0	8.0 +/- 5.7	7.7 +/- 4.7
Ichthyosis Vulgaris Severity Score	3.6 +/- 0.7	3.6 +/- 0.7	3.6 +/- 0.6	3.6 +/- 0.7

Therapeutic Equivalence

The endpoint defined in the protocol was the proportion of successfully treated subjects as assessed by the Ichthyosis Vulgaris Severity Score at Day 28. The Sponsor analysis showed equivalence of the following outcomes in the ITT group:

ITT Group Day 28 Treatment	Successfully treated	Total subjects	Proportion of success (%)
Test	50	75	66.7
Reference	49	69	71.0
Placebo	13	21	61.9

Per Protocol Group Day 28 Treatment	Successfully treated	Total subjects	Proportion of success (%)
Test	50	75	66.7
Reference	47	65	72.3
Placebo	11	19	57.9

They demonstrated a difference of proportions of –0.043 in the ITT group and 90% Confidence Intervals of –0.18 to 0.10. In the PP group they found a difference of proportions of –0.056 and 90% Confidence Intervals of –0.20 to 0.09.

Medical Officer Note: *The confidence interval calculations for the ITT group were repeated using a continuity correction factor. This showed a difference of -4.35% and 90% Confidence Intervals of –18.42 to 9.73.*

The Per Protocol analysis is the one that is used to determine equivalence. Using the Sponsor's sample and the continuity correction factor, the difference between the two treatment groups was –8.31% with 90% Confidence Intervals of –22.65 to 6.03. An analysis was done using the Per Protocol group adjustments recommended in the text. The adjustment that is recommended is the elimination of all protocol violations from the PP cohort. This would give a sample below:

Day 28 PP Group	*Success*	*Difference*	*90% Confidence Intervals*
Test	*43/68*	*- 7.26*	*-22.41 to 7.89*
Reference	*43/61*		

Post Treatment PP Group	*Success*	*Difference*	*90% Confidence Intervals*
Test	*24/68*	*- 8.97*	*- 24.68 to 6.74*
Reference	*27/61*		

Eliminating the out of window patients for Visit 3, the sample comparison is as follows:

Day 28 PP Group	*Success*	*Difference*	*90% Confidence Intervals*
Test	*38/62*	*- 14.15*	*-29.67 to 1.37*
Reference	*43/57*		

Neither Per Protocol Group analysis meets the bioequivalence criteria.

Efficacy

Using the overall mean score of 1 or less as the definition of success, the comparison of Test and Placebo in the ITT population at Day 28 did not demonstrate efficacy in the Sponsor's analysis (0.667 versus 0.619, p=0.345). The post-treatment ITT evaluation at Day 42 was also not found to differ between the Test group (0.333) and the Placebo group (0.250), p=0.227. The sponsor used logistic regression and repeated measures analysis of covariance and did not demonstrate any difference between the Test product and the Placebo at either Day 28 or Day 42. They did an additional analysis comparing Test and Placebo using as the success definition a score of less than 1, which they defined as a more stringent definition. Using this definition, they were still not able to demonstrate that the test treatment was better than placebo at Day 28, although they did find a difference between the two groups at Day 42. This definition was chosen after the initial analysis was unsuccessful.

Medical Officer Note: *The Sponsor did not demonstrate efficacy of the Test treatment compared to the Placebo. They also did not analyze the efficacy of the Reference drug. In response to the submission of their protocol for review, they were asked to assess the efficacy of the active treatments compared to Placebo. However, they never incorporated this latter analysis into their final protocol. The "more stringent" analysis they used to show efficacy was chosen on the basis of a failed planned analysis.*

Secondary Endpoints

The Investigator Global Assessment and the Subject Global Assessment of Improvement were compared among the three groups and no significant differences were found.

Safety

All treatment groups were assessed for safety and adverse events (ADEs) throughout the study. Thirty-eight ADEs were determined to be definitely or probably related to the treatment administered. These were distributed as follows:

	Number	Percent
Test	21/85	24.7%
Reference	13/77	16.9%
Placebo	4/26	15.4%

p = n.s.

The total number of adverse events observed was 442, of which 439 occurred in 121 subjects. These ADEs were distributed among the treatment groups as follows:

Test		Reference		Placebo	
ADEs	# patients	ADEs	# patients	ADEs	# patients
207	56	167	44	65	21

The average number of ADEs per subject was 2.4 in the test group, 2.2 in the reference group, 2.5 in the placebo group, and 2.3 in the total cohort.

The most common ADE was headache, which occurred 97 times in 48 patients during the treatment and post-treatment periods. Seventeen of these subjects were randomized to the test group and experienced 27 events, 19 were randomized to the reference group and experienced 44 headaches, and 12 subjects were randomized to the placebo group and experienced 26 events. More subjects in the test group reported paraesthesia, pruritus, and erythematous rash than did those in the other groups and more reference group subjects experienced headaches than did subjects in the other groups, although the placebo group had a much higher percentage of patients with headaches. Patients in the placebo group also reported more contact dermatitis than did those in the other groups.

ADE reports during treatment

ADE	TEST			REFERENCE			PLACEBO		
	#	# pts	%	#	# pts	%	#	# pts	%
Paresthesias	33	18	21.2	12	11	14.8	2	2	7.7
Headache	23	15	17.6	34	16	20.8	23	12	46.2
Pruritus	27	12	14.1	10	4	5.2	3	3	11.5
Rash, erythematous	14	10	11.8	8	4	5.2	--	--	--
Skin reaction, local	10	6	7.1	4	4	5.2	--	--	--
Rash	5	4	4.7	4	4	5.2	--	--	--
Dysmenorrhea	3	2	2.4	6	4	5.2	5	2	7.7
Dermatitis, contact	1	1	1.2	2	2	2.6	3	3	11.5
Dyspepsia	1	1	1.2	--	--	--	2	2	7.7

The body system most affected by ADEs was the central and peripheral nervous system, with 165 reports in 73 subjects. In the Test group, 32 subjects experienced 73 ADEs. In the Reference group, 28 subjects reported 60 events. In the Placebo group, 13 subjects experienced 32 events.

The majority of ADEs reported were of mild (197 events) or moderate (207) intensity. These were evenly distributed among the three treatment groups, although the placebo group had a greater percent incidence of severe events. Two events had an unknown severity.

	MILD	MODERATE	SEVERE
Total	197	207	36
Test - #	98	94	15
# patients	38	36	10
%	45	42	12
Reference- #	80	76	11
#patients	35	31	7
%	45	40	9
Placebo - #	19	37	10
# patients	12	13	5
%	46	50	19

The relationship of the ADEs to the study drug is presented in the table that follows. One-hundred forty-five ADEs, 92 in the Test group, 45 in the Reference group, and 8 in the Placebo group were either definitely, probably, or possibly related to the study medication. Two ADEs were definitely related to the study medication; one was contact dermatitis that occurred in a Test subject, and the other was stinging/burning that occurred in a Reference subject. The Test group had a larger proportion of possible/probable/definite ADEs than the other groups: Test – 92, Reference – 43, and Placebo – 8.

		ADE Relationship to Study Medication

Treatment	PERIOD	None *	Remote	Possible	Probable	Definite
Test N=85	Treatment	80/34/40%	4/4/5%	39/12/14%	52/20/24%	1/1/1%
	Post – Rx	28/15/18%	3/1/1%	0/0/0%	0/0/0%	0/0/0%
Reference N=77	Treatment	84/32/42%	10/6/8%	24/12/16%	18/12/16%	1/1/1%
	Post – Rx	28/14/18%	0/0/0%	0/0/0%	2/1/1%	0/0/0%
Placebo N=26	Treatment	39/16/62%	9/2/8%	9/2/8%	4/4/15%	0/0/0%
	Post - Rx	9/5/19%	0/0/0%	0/0/0%	0/0/0%	0/0/0%

* - # of events/# of patients/percent of patients

One patient experienced a serious ADE after one day of Test treatment (in situ squamous cell carcinoma of the skin, forearm) which was judged to have no relationship to the study medication.

Medical Officer Comment: *The ADEs appear to be divided proportionally among the groups. The profile does not indicate any difference between the Test and Reference products.*

Conclusion

This study fails to demonstrate the bioequivalence of Clay-Park Inc.'s, Ammonium Lactate lotion and Westwood-Squibb's Lac-Hydrin® lotion.

Specific Comments

1. The Sponsor included a number of subjects in the Per Protocol group who had protocol violations according to the definition of the protocol. They were offered the opportunity to itemize why individual subjects had been included and did not provide any additional information beyond the list of subjects in the Per Protocol group requested by the Medical Officer. When these subjects were excluded, the study failed Confidence Interval criteria. The Per Protocol sample the Sponsor analyzed also failed Confidence Interval criteria when a continuity correction was used in the analysis.
2. The Sponsor did not analyze the efficacy of the Reference drug versus Placebo.
3. The Sponsor changed the analysis criteria for the efficacy analysis of Test versus Placebo when the original analysis failed. They did not subject the equivalence analysis to the same criteria. Both analyses should use the same success criteria and a post-hoc change in endpoint is not accepted.

Recommendation

This study should be consulted to the Statistician.

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Submission Date: March 26, 1999

MEDICAL OFFICER SUMMARY REVIEW
January 10, 2000

ANDA 75-570
Drug Product: Ammonium Lactate Lotion, 12%
Firm: Clay-Park Labs, Inc.
Reference Listed Drug: Lac-Hydrin 12%, Westwood-Squibb Pharmaceuticals, Inc.

The statistician's report was reviewed and combined with the comments of the Medical Officer. This study fails to show the bioequivalence of the test and reference product for the following reasons:

1. An equivalence comparison is only valid if the reference treatment is effective against placebo in the trial. The test drug must also be effective against placebo in the trial. The sponsor did not analyze the reference drug against placebo and conducted a pooled analysis of the actives versus placebo. A separate analysis of the efficacy of test versus placebo and reference versus placebo should be conducted.
2. The Sponsor changed the efficacy criteria for the efficacy analysis of Test versus Reference when the original analysis failed and did not change the equivalence criteria. Such a post-hoc change is not desirable. The criteria for evaluating efficacy and equivalence should be the same.
3. When this analysis was done, neither the Clay-Park test product nor the Lac-Hydrin reference product was superior to the placebo treatment.
4. The efficacy test should be carried out at alpha = 0.05for a two-sided test or alpha = 0.025 for a one-sided test, not at an alpha level of 0.05 for a one-sided test.
5. The sample size calculation was not done correctly in that the previous points were not considered. In addition, the sample size was calculated for testing the difference between 2 treatments of the means of a variable with a 10-point scale while the statistical comparison was to be done on the difference in success rates of two treatments.
6. The sample size requirements were re-calculated for the efficacy testing for 15% difference using chi-square test and for equivalence testing of 15% limit using two one-sided tests (Farrington and Manning's asymptotic test procedure). The required sample size would be the maximum of the two sizes. The sample size required for the placebo group is between 100 and 170 depending on the assumed true response proportion of the placebo group. The sample size of each of the active treatment groups is between 112 and 159 depending on the true response proportion of the reference treatment group assuming that the response proportion of the reference treatment group ranges from 60% to 75%. It shows that the study was not designed with appropriate sample sizes to demonstrate the efficacy of test and reference over placebo or the equivalence of the test and reference treatments of dichotomized outcome.

7. The Per Protocol Population is used to evaluate equivalence. This population should exclude subjects who had protocol violations as well as those who were out of the visit window for the bioequivalence primary endpoint.
8. Using Wald's Test with Continuity Correction or the Farrington and Manning approach, the test and reference product do not meet bioequivalence criteria regardless of how the Per Protocol Population was defined.

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APPEARS THIS WAY
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