

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-769**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION.

MAR 20 1997

**NDA#/Drug class:** 20-769/1S

**Applicant:** Yamanouchi Europe B.V.  
The Netherlands

**Name of Drug:** Locoid lipocream (hydrocortisone butyrate 0.1%)

**Documents Reviewed:** Volumes 15, 16, 17, 18, 19, and 19a, dated September 03, 1996, and data on disks provided by the sponsor

**Type of Report:** Statistical/Clinical.

**Indications:** Psoriasis vulgaris

**Medical Officer:** Phyllis Huene, M.D., HFD-540

### INTRODUCTION

The sponsor of this NDA, Yamanouchi Europe B.V., is the holder of three approved NDAs for other topical formulations of Locoid (hydrocortisone butyrate) 0.1%. The approved NDAs are:

- NDA 18-514, Locoid Cream formulation, approved March 3, 1982
- NDA 18-652, Locoid Ointment formulation, approved October 29, 1982
- NDA 19-116, Locoid Lotion formulation, approved February 25, 1987

The strength of hydrocortisone butyrate in all of these formulations is 0.1%, the same strength as in the Locoid Lipocream formulation.

The purpose of this submission was to demonstrate that Locoid Lipocream 0.1% is safe and effective in treatment of patients with psoriasis vulgaris. The FDA granted line extension status to this NDA. This means that one pivotal trial is enough for the NDA to be approved.

The sponsor has provided a report on the pivotal study (Protocol 92-LOC-04/BRO 3800-03) to support the claim that Locoid Lipocream is safe and effective in the treatment of psoriasis vulgaris.

### STUDY INFORMATION

#### A. Objective of Study

The objective of this study was to compare the efficacy and safety of up to four weeks twice daily treatment of 0.1% hydrocortisone butyrate fatty cream (Locoid

Lipocream) to its cream vehicle and to detect any clearing.

## **B. Overall Study Design**

### **Type of Study**

The design was a two center, double-blind, randomized, parallel-group study of the use of 0.1% Locoid Lipocream twice daily compared to Lipocream Vehicle twice daily. The course of treatments was up to four weeks with evaluation at the end of two weeks and four weeks.

### **Patient Selection**

Two centers were planned for participation in the study, each enrolling 20-30 patients in order to yield a total of 60 evaluable patients (30 per group). Patients were included in the study if they were generally healthy outpatients aged 12 years and older, were males or non-pregnant, non-lactating females and they presented signs of moderate plaque-type psoriasis vulgaris defined as the sum of scores of scaling, erythema, induration and pruritus for a total minimum score of 6.

Patients were excluded from the study if they had used any topical treatments which had a known beneficial effect on psoriasis vulgaris within two weeks prior to the start of the study. For other exclusion criteria see the reviewing medical officer's report.

### **Dose Selection and Blinding Procedure**

Tubes with the study medications were sequentially numbered according to a computer-generated random code. Both the patient and the investigator were blind relative to which medication had been assigned. Thus, the study was double-blinded with respect to the two drugs.

### **Duration of Treatment and Follow-Up**

The study medication was applied twice daily for up to four weeks with evaluations at the end of Week 2 (Day 15) and Week 4 (Day 29). If the target lesion cleared at Week 2, treatment ended.

### **Criteria for Drug Effectiveness**

#### **a. Total signs and symptoms**

With respect to the target lesion, reduction in signs and symptoms (scaling,

erythema, induration, pruritus), or clearing was taken as the primary response variable to compare efficacy of the test drug to its vehicle. All signs and symptoms were scored on a 5-point rating scale (from 0 - 4). Total signs and symptoms equals the sum of scores for the 4 individual signs and symptoms and, therefore, ranges from 0 to 16. For a patient to be included in the study, the total signs and symptoms of the target lesion must be at least 6.

- b. Assessment of response to therapy by physician. Definition of effective treatment.

At follow-up visits Day 15 and 29, the investigator rated the global clinical response to treatment of all treated lesions as follows:

Clinical Cure:	Complete improvement from Baseline
Marked Improvement:	Approximately 75% or more improvement, but less than complete improvement
Moderate Improvement:	Approximately 50% or more improvement but less than 75% improvement
Slight improvement:	Less than 50% improvement
No Change:	No detectable improvement
Exacerbation:	Increase in overall severity of the condition

The original protocol defined "effective treatment as a complete cure (no residual signs and symptoms)". Over a four week period, this did not appear to be a realistic assumption. For the purposes of this study, the physicians' rating of global clinical response to treatment of either cleared or marked improvement was taken as effective treatment. The reviewing medical officer is in agreement with this reviewer's suggestion.

- c. Assessment of response to therapy by patient.

The study assistant asked the patient at Day 15 and Day 29 to rate both the overall response to treatment and how well the medication was tolerated. The following scale was used for both assessments:

0 = poor, 1 = fair, 2 = good, 3 = very good, or 4 = excellent.

### Primary efficacy variables and primary timepoint.

The primary efficacy variables were target lesion total score of signs/symptoms and physician's assessment of global clinical response. The primary efficacy timepoint was Day 29. Since the objective of the study was to demonstrate the superiority of Locoid Lipocream relative to both primary efficacy variables, no P-value adjustment due to multiple comparisons was necessary.

### C. Analysis Plan

#### 1. Data Sets Analyzed

The efficacy analysis is based on all efficacy evaluable patients admitted to the study. A patient was considered efficacy evaluable if they had at least one follow-up visit after baseline.

#### 2. Statistical Analysis

All tests performed in this analysis were two-sided. Between treatment, demographic characteristics, psoriasis history, other history, location of lesions, baseline signs and symptoms (scaling, erythema, induration, pruritus), and overall severity of all lesions were compared to assess baseline comparability. For background characteristics, mean age and height were compared using a two-tailed t-test. Sex and race (Caucasian vs. non-Caucasian) distributions were compared using Fisher's Exact Test.

For psoriasis history, between treatment duration of the current episode was compared using the Wilcoxon Rank Sum Test. To compare the proportions of patients who had their current episode treated, the Fisher's Exact Test was used. Similarly, for the proportions of patients with other medical conditions, other medications taken in the past four weeks, and allergies to medications, group comparisons were made using Fisher's Exact Test.

The proportions of patients in each group with site location affected, site location treated, and site location evaluated were each compared using Fisher's Exact Test.

For signs and symptoms, the group total signs and symptoms scores were compared using a two-sample t-test, and the distributions of the specific signs and symptoms were compared across treatments using the van Elteren test adjusted for investigators. Similarly, the overall severity of all lesions was compared between groups using van Elteren test adjusted for baseline measures of signs and symptoms. Additionally, changes from baseline in the numeric scores were

compared using a t-test. Physician's rating of global response as well as patient's assessment of response to therapy were compared across treatment groups using the van Elteren test adjusted for investigators.

Compliance in the study was assessed by comparing proportions of patients with first application according to protocol, proportions of patients who had visit days within three days of the target visit day, and those who changed concomitant medications during the course of the study. The comparisons were made using Fisher's Exact Test.

## **RESULTS**

### ***Patient Enrollment and Disposition***

Sixty-seven patients were admitted to the study, 35 (52.2%) randomly assigned to Locoid Lipocream and 32 (47.8%) randomly assigned to Lipocream vehicle. All patients were evaluable for efficacy and safety since all had at least one follow-up visit. One Lipocream Vehicle patient terminated early from the study because of an adverse event. The distributions of patient admissions, follow-up, and disposition are shown in Tables 1 and 2.

TABLE 1  
NUMBER OF PATIENTS COMPLETING EACH VISIT

CHARACTERISTICS	LOCOID LIPOCREAM	LIPOCREAM VEHICLE	TOTAL
NUMBER ADMITTED	35	32	67
Beutner	18 (51%)	16 (50%)	34 (51%)
Piacquadio	17 (49%)	16 (50%)	33 (49%)
DAY 15	35	32	67
Beutner	18 (51%)	16 (50%)	34 (51%)
Piacquadio	17 (49%)	16 (50%)	33 (49%)
DAY 29	35	31	66
Beutner	18 (51%)	15 (48%)	33 (50%)
Piacquadio	17 (49%)	16 (52%)	33 (50%)

Day 15 corresponds to the first follow-up visit, and Day 29 corresponds to the second follow-up visit.

Note: Patient 26 of the Lipocream Vehicle group withdrew from the study at Day 3. Data from this visit was analyzed with all other patient's Day 15 data, and is thus included in the total for patients with a Day 15 visit.

TABLE 2  
DISPOSITION OF PATIENTS

	TREATMENT GROUPS		
	LIPOCREAM	VEHICLE	TOTAL
NUMBER ADMITTED	35	32	67
Completed Study	35(100%)	31 (97%)	66 (99%)
Early Withdrawal			
Non-compliance	0	0	0
Adverse event	0	1 (3%)	1 (1%)
Lost to follow-up	0	0	0
Personal reasons	0	0	0
Treatment failure	0	0	0
Target lesion cleared by Week 2	0 0	0 0	0 0
Other			
Total Efficacy Patients	35	32	67
Total Safety Patients	35	32	67

Completed study = total patients seen on Day 29 visit or classified as early cures.

Total efficacy patients = total patients enrolled (including patients whose lesion cleared at Week 2) less patients with no follow-up after baseline.

Total safety patients = total patients enrolled less patients with no follow-up visit after baseline.

Note: Lost to follow-up means that the patient did not return for a visit with no other explanation. Patients with no follow-up were excluded from the efficacy and safety analysis.

### **Background**

There were no significant differences ( $P > 0.62$ ) in age, sex, race or height between the two groups. The mean age was 46 years, 66% were male, 87% were Caucasian, and the mean height was 69 inches (174 cm). There were no differences ( $P > 0.63$ ) between the treatment groups, relative to psoriasis history in terms of duration of the current episode as well as whether or not the current episode had been treated.

Patient groups were also similar ( $P > 0.27$ ) with respect to the other significant history parameters of "other medical condition, other medications taken in past four weeks, and allergies to medication."

No differences were found ( $P > 0.1$ ) in the distributions of sites affected, treated, and evaluated. One-third of all patients had elbows evaluated, 25% had either the front or back of their trunk evaluated, and 19% had either their upper or lower legs evaluated.

The groups were also similar ( $P > 0.29$ ) with respect to baseline signs and symptoms. All patients presented with signs of scaling, erythema, and induration. Sixty-nine percent of all patients had signs of pruritus.

Overall disease severity was minimal for 1 (3%) patient, and 72% presented with moderate or severe. No baseline differences between the two groups were noted ( $P = 0.73$ ).

### **Compliance**

Compliance was assessed by ensuring that the first application was made at the first visit under the supervision of the investigator or a qualified assistant, by adherence to a regular schedule of follow-up at Days 15 and 29, and by a review of changes in concomitant medications. All patients had their first treatment application performed under supervision. Ninety-six percent of all patients had a visit within three days of the target day visit at Day 15. Similarly 94% of all patients had a follow-up visit within three days of Day 29. This "window" of three days was not a protocol requirement, but is presented here to provide a generalized view of how promptly patients returned for their follow-up visit. The groups were similar ( $P > 0.1$ ) in terms of compliance to adhering to follow-up visits.

Twenty-five percent of all patients changed concomitant medication during the course of the study, 9 in the *Locoid Lipocream* group and 8 in the Vehicle group. No differences ( $P = 1.0$ ) in changes in concomitant medications were found between the two groups.

### **Efficacy**

For each efficacy variable, the last value recorded for the patient was assessed and reported in each table as the "End Point" results. Only one patient assigned to Lipocream Vehicle terminated the study early, so Day 29 and End Point results will be the same, and thus are not referenced later on. The ITT and Efficacy evaluable populations in this study were the same, and therefore, the ITT analysis will not be referenced later on.

Total Target Lesion Signs and Symptoms

Patients assigned to Locoid Lipocream had a greater reduction in the total signs and symptoms at Day 15 and at Day 29 than those assigned to Lipocream Vehicle. Of a possible total of 16, the Locoid Lipocream group decreased from 9.4 at Baseline to 5.2 at Day 15, and 4.1 at Day 29. The corresponding baseline, Day 15, and Day 29 results for the Vehicle group were 9.4, 7.2, and 6.2, respectively. The decreases were significantly greater for the Locoid Lipocream group than for the Vehicle group at Day 15 (t-test:  $p=0.002$ ) and at Day 29 (t-test:  $p=0.002$ ). Table 3 shows the results for total target lesion signs and symptoms in efficacy evaluable patients.

TABLE 3  
TARGET LESION TOTAL SCORE OF SIGNS AND SYMPTOMS  
EFFICACY EVALUABLE PATIENTS

FOLLOW-UP WEEKS	TREATMENT GROUPS		p-value
	LIPOCREAM	VEHICLE	
<b>BASELINE</b>			
mean (se)	9.4 (0.4)	9.4 (0.3)	0.936
n	35	32	
<b>Day 15</b>			
mean (se)	5.2 (0.4)	7.2 (0.3)	0.000
mean change (se)	-4.2 (0.5)	-2.3 (0.3)	0.002
n	35	32	
<b>Day 29</b>			
mean (se)	4.1 (0.5)	6.2 (0.4)	0.001
mean change (se)	-5.3 (0.6)	-3.1 (0.4)	0.002
n	35	31	
<b>End Point</b>			
mean (se)	4.1 (0.5)	6.3 (0.4)	0.000
mean change (se)	-5.3 (0.6)	-3.2 (0.4)	0.002
n	35	32	

Total score= Scaling+Erythema+Induration+Pruritus

Two-sided p-value is based on two-sample t-test

### Individual Target Lesion Signs and Symptoms

Decreases in all individual signs and symptoms for the Locoid Lipocream group were significantly greater than for the Lipocream Vehicle group at Day 15. At Day 29, decreases in all individual signs and symptoms with the exception of pruritus were significantly greater for the Locoid Lipocream group than for the Lipocream Vehicle group. (Significance was based on the van Elteren test adjusted for investigators.)

#### **Scaling**

Patients were evaluated on a five point scale of no scales, minute scales, thin scales, scales adherent, or scales thick. At baseline no patients had scaling classified as either none or minute. Significantly greater decreases in scaling were noted for the Locoid Lipocream group than for the Vehicle group at Day 15 (van Elteren:  $p=0.002$ ) and at Day 29 (van Elteren:  $p=0.004$ ). At Day 15 the severity of scaling was either minute or none for 77% of the Lipocream group as compared to 50% of the Vehicle group. At Day 29, the corresponding percentages were 83% and 68%, respectively.

#### **Erythema**

Patients were evaluated on a five point scale of normal color, mild, pronounced redness, marked redness, and typical erythema. At baseline no patients had either normal color skin or mild erythema. Significantly greater decreases in erythema were noted for the Locoid Lipocream group than for the Lipocream Vehicle group at Day 15 (van Elteren:  $p=0.006$ ) and at Day 29 (van Elteren:  $p=0.004$ ). At Day 15 the severity of erythema was either normal color or mild for 26% of the Locoid Lipocream group as compared to 16% of the Vehicle group. At Day 29, the corresponding percentages were 51% and 23%, respectively.

#### **Induration**

Patients were evaluated on a five point scale of not palpable, very minor, easily palpable, elevated lesions, and severe lesions. At baseline no patients had either non-palpable or very minor induration. Significantly greater decreases in induration were noted for the Locoid Lipocream group than for the Lipocream Vehicle group at Day 15 (van Elteren:  $p=0.028$ ) and at Day 29 (van Elteren:  $p=0.001$ ). At Day 15 the severity of induration was either not palpable or very minor for 43% of the Locoid Lipocream group as compared to 16% of the Lipocream Vehicle group. At Day 29, the corresponding percentages were 57% and 23%, respectively.

## **Pruritus**

Patients were evaluated on a five-point scale of no complaint, little discomfort, itching complaints, troublesome, and severe. At baseline 34% of all Locoid Lipocream patients and 28% of all Lipocream Vehicle patients had either no complaint or little discomfort. Borderline significantly greater decreases in pruritus were noted for the Locoid Lipocream group than for the Lipocream Vehicle group at Day 15 (van Elteren:  $p=0.050$ ), but not at Day 29 (van Elteren:  $p=0.164$ ). At Day 15 the severity of pruritus was either no complaint or little discomfort for 77% of the Locoid Lipocream group as compared to 56% of the Lipocream Vehicle group. At Day 29, the corresponding percentages were 83% and 74%, respectively.

## **Physician Assessments**

Physicians evaluated patients on a six-point scale of clinical cure, marked improvement, moderate improvement, slight improvement, no change, and exacerbation. No patient in the study had an exacerbation of their condition. Patients assigned to Locoid Lipocream had statistically significantly better evaluations at Day 15 (van Elteren:  $p=0.009$ ) and at Day 29 (van Elteren:  $p=0.001$ ) than those assigned to Lipocream Vehicle. As a measure of effectiveness, at Day 15, 17% of the Locoid Lipocream group and 0% of the Lipocream Vehicle group had either a clinical cure or marked improvement. The corresponding percentages for Day 29 were 37% and 0%, respectively (Table 4).

## **Patient's Assessment**

Patients evaluated their response to treatment using a five-point scale of excellent, very good, good, fair, and poor. Patients assigned to Locoid Lipocream had statistically significantly better evaluations at Day 15 (van Elteren:  $p=0.013$ ) and at Day 29 (van Elteren:  $p=0.006$ ) than those assigned to Vehicle. At Day 15, 43% of the Lipocream group and 6% of the Vehicle group had evaluated their response to treatment as either excellent or very good. The corresponding percentages for Day 29 were 46% and 16%, respectively (Table 5).

TABLE 4  
 PHYSICIANS' ASSESSMENT OF GLOBAL CLINICAL RESPONSE TO TREATMENT  
 EFFICACY EVALUABLE PATIENTS

FOLLOW-UP WEEKS	TREATMENT GROUPS		p-value
	LIPOCREAM	VEHICLE	
<b>DAY 15</b>			
Clinical Cure	0	0	0.009
Marked Improvement	6 (17%)	0	
Moderate Improvement	6 (17%)	3 (9%)	
Slight Improvement	13 (37%)	14 (44%)	
No change	10 (29%)	15 (47%)	
Exacerbation	0	0	
n	35	32	
<b>DAY 29</b>			
Clinical Cure	2 (6%)	0	0.001
Marked Improvement	11 (31%)	0	
Moderate Improvement	4 (11%)	6 (19%)	
Slight Improvement	14 (40%)	13 (42%)	
No change	4 (11%)	12 (39%)	
Exacerbation	0	0	
n	35	31	
<b>END POINT</b>			
Clinical Cure	2 (6%)	0	0.001
Marked Improvement	11 (31%)	0	
Moderate Improvement	4 (11%)	6 (19%)	
Slight Improvement	14 (40%)	14 (44%)	
No change	4 (11%)	12 (38%)	
Exacerbation	0	0	
n	35	32	

End Point is the last visit for patients with at least one follow-up.

Two-sided p-value is based on van Elteren test adjusted for investigators

TABLE 5  
 PATIENT'S ASSESSMENT OF RESPONSE TO TREATMENT  
 EFFICACY EVALUABLE PATIENTS

FOLLOW-UP WEEKS	TREATMENT GROUPS		p-value
	LIPOCREAM	VEHICLE	
<b>DAY 15</b>			
Excellent	5 (14%)	1 (3%)	0.013
Very Good	10 (29%)	1 (3%)	
Good	7 (20%)	13 (41%)	
Fair	8 (23%)	8 (25%)	
Poor	5 (14%)	9 (28%)	
n	35	32	
<b>DAY 29</b>			
Excellent	5 (14%)	1 (3%)	0.006
Very Good	11 (31%)	4 (13%)	
Good	8 (23%)	8 (26%)	
Fair	6 (17%)	8 (26%)	
Poor	5 (14%)	10 (32%)	
n	35	31	
<b>END POINT</b>			
Excellent	5 (14%)	1 (3%)	0.007
Very Good	11 (31%)	4 (13%)	
Good	8 (23%)	9 (28%)	
Fair	6 (17%)	8 (25%)	
Poor	5 (14%)	10 (31%)	
n	35	32	

End Point is the last visit for patients with at least one follow-up.  
 Two-sided p-value is based on van Elteren test adjusted for investigators

### ***Subset efficacy analysis***

This analysis was conducted to assess any differences in efficacy between males and females and between patients aged less than 50 years and those over 50 years. No significant differences in efficacy of Locoid Lipocream were found

between gender and age groups ( $P > 0.5$ ).

### **Safety**

A total of 27 (40%) of all patients reported an adverse event during the course of the study. No difference was found between the treatment groups relative to the number of patients with adverse events ( $P \geq 0.37$ ). The most common types of events were Body as a Whole (Locoid Lipocream: 8, Lipocream Vehicle: 8;  $P = 0.8$ ), Respiratory System (Locoid Lipocream: 3, Lipocream Vehicle: 5;  $P = 0.37$ ), and Skin and Appendages (Locoid Lipocream: 3, Lipocream Vehicle: 2;  $P = 0.7$ ).

Four patients (Locoid Lipocream: 3, Vehicle: 1) had a drug related adverse event and stopped or interrupted use of study medication. The difference between the two treatment groups was not significant:  $P = 0.35$ . All other Lipocream Vehicle patients with drug-related events continued use of their assigned treatment without interruption. One Lipocream Vehicle patient dropped out of the study because of an adverse event, malaise/drowsiness. This event was not considered to be drug related.

### **REVIEWER'S CONCLUSIONS (which may be conveyed to the sponsor)**

*The results of the pivotal study (Protocol BRO 3800-3) support the sponsor's claim that Locoid Lipocream is statistically significantly more effective than its vehicle ( $P < 0.009$ ).* ✓

*The sample sizes in the Locoid Lipocream and Vehicle groups were 35 and 31, respectively, with the observed difference in total signs/symptoms score being 2.10. These sample sizes were sufficient because at the 2-sided alpha level of 0.05, the observed difference must be 1.28 or greater in order to be significant. The power of the study was 90%.*

*Relative to the first primary efficacy variable, total target signs and symptoms, Locoid Lipocream produced significantly ( $P \leq 0.002$ ) greater reductions from baseline at both Day 15 and Day 29. Relative to the second primary efficacy variable, physician's global assessment, Locoid Lipocream was statistically significantly superior to vehicle at both follow-up visits with  $P \leq 0.009$ . Since the objective of the study was to demonstrate the superiority of Locoid Lipocream relative to both primary efficacy variables, no P-value adjustment due to multiple comparisons was necessary.*

**Results for the secondary efficacy variables supported the results for the primary efficacy variables. The results for the ITT and Efficacy evaluable populations in the study were similar. The results of subset analysis demonstrated no significant differences in efficacy between males and females or between age groups of under and over 50 years.**

**There was no difference between the two treatment groups relative to the number of patients with adverse events ( $P \geq 0.37$ ). One patient (vehicle group) dropped out of the study because of an adverse event (which was not considered drug related).**

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Chron.

This review contains 15 pages including 5 tables.

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