

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-076**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

---

---

PRODUCT (Generic Name):	Hydrocortisone butyrate 0.1% lotion
Proposed PRODUCT Brand Name:	Locoid® Lotion
DOSAGE FORM:	Topical Lotion
NDA:	22- 076
PROPOSED INDICATIONS:	<hr/>
DOSING REGIMEN:	Twice Daily
INTENDED POPULATION:	3 months and older
NDA TYPE:	505 (b) (1)
SUBMISSION DATE:	July 20, 2006
SPONSOR:	Ferndale Laboratories, Inc.
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Sue Chih Lee, Ph. D.
OCPB DIVISION:	DCP III
OND DIVISION:	HFD 540

---

---

b(4)

### EXECUTIVE SUMMARY

Hydrocortisone butyrate is currently marketed in the USA in other Locoid® formulations, all by Ferndale and all in 0.1% concentrations. Locoid® cream (NDA 18-514, approved 3/31/82), Locoid® ointment (NDA 18-652, approved 10/29/82), and Locoid® Lipocream (NDA 20-769, approved 9/8/97) are each indicated for "relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses." Locoid® solution (NDA 19-116, approved 2/25/87) is indicated for "relief of the inflammatory and pruritic manifestations of seborrheic dermatoses." According to the sponsor and the medical reviewer, Dr. Kenneth A. Katz, there have been no major safety concerns or labeling changes with other Locoid® formulations and no discontinuations for safety (as opposed to marketing) reasons.

The clinical pharmacology program consists of the following three studies. These studies were also considered as part of the clinical development program.

- *Vasoconstrictor study to rank the relative potency of hydrocortisone butyrate lotion 0.1% with respect to approved topical corticosteroid preparations in human volunteers (Study 01-036)*
- *A randomized, blinded, single-center evaluation of the vasoconstrictive properties of 0.1% hydrocortisone butyrate lotion in normal healthy volunteers (Study 03-097)*
- *An open label adrenal suppression study of hydrocortisone butyrate lotion 0.1% used 3x daily in pediatric subjects aged 3 months to less than 18 years with moderate to severe atopic dermatitis (Study 04-101)*

The clinical development program for Locoid® lotion included two phase 3 studies, one of which (04-103, in pediatrics) was considered pivotal and one of which (03-074 in adults) was considered supportive from a clinical perspective. Phase 1 studies included dermal safety studies (repeated insult patch test, cumulative irritation, primary irritation, photoallergenicity) and two vasoconstrictor assay studies. One Phase 2 study assessed HPA axis suppression.

**Efficacy and Safety:** According to medical reviewer Dr. Kenneth A. Katz, Locoid® lotion was clinically and statistically significantly more effective compared to vehicle lotion in both phase 3 studies. The duration of the pivotal study (04-103) was four weeks, with success for the primary endpoint defined as a Physician's Global Assessment (PGA) score of 0 ("clear") or 1 ("almost clear"), with at least a 2-point reduction from baseline. Also, in these two phase 3 studies, AEs observed did not raise significant safety concerns with four weeks of twice daily use.

Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man. The sponsor conducted two vasoconstrictor studies with Locoid® lotion. However, none of these 2 studies was conclusive enough to assign potency ranking for Locoid® lotion.

The sponsor conducted a HPA axis suppression study, in lieu of the conventional PK study, as part of the safety assessment. Locoid® lotion was evaluated in an HPA axis suppression study in 83 evaluable subjects, ages 3 months to 18 years, with at least 25% body surface area (BSA) involvement with atopic dermatitis. The subjects applied Locoid® lotion three times daily for four weeks. Seven subjects (8.4%) showed laboratory (but not clinical) findings of adrenal suppression (as measured by Cortrosyn® stimulation tests [CST]), of whom six recovered normal responses within one month and one within six months.

The proposed dosing regimen is twice daily topical use for no longer than four weeks in

patients three months of age or older.

**Recommendation:**

The Clinical Pharmacology and Biopharmaceutics section of NDA 22-076 is acceptable with suggestion for labeling changes.

Primary Reviewer:

Tapash K. Ghosh, Ph.D.  
Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation III

Team Leader: Sue Chih Lee, Ph.D. \_\_\_\_\_

**Table of Contents**

Executive Summary	1
Table of Contents	3
Review	4
Individual Study Report	6
Sponsor's proposed labeling text	23

## **BACKGROUND:**

Hydrocortisone butyrate is a synthetic, non-fluorinated, corticosteroid. Four topical dosage forms of hydrocortisone butyrate, 0.1% are currently being marketed under the trade name Locoid. The four topical preparations of hydrocortisone butyrate are a cream, lipocream, ointment and solution. The current 505(b)(1) NDA application provides information for a lotion dosage form of hydrocortisone butyrate, a line extension application. The sponsor for the new hydrocortisone butyrate topical formulation developed the four other hydrocortisone butyrate topical formulations that are currently on the market.

Like other topical corticosteroids, hydrocortisone butyrate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings or widespread application may increase the possibility of hypothalamic-pituitary-adrenal (HPA) axis suppression.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids.

Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man. The sponsor conducted two vasoconstrictor studies with Locoid® lotion. However, none of these 2 studies was conclusive enough to assign potency ranking for Locoid® lotion.

The sponsor conducted a HPA axis suppression study, in lieu of the conventional PK study, as part of the safety assessment. Locoid® lotion was evaluated in an HPA axis suppression study in 83 evaluable subjects, ages 3 months to 18 years, with at least 25% body surface area (BSA) involvement with atopic dermatitis. The subjects applied Locoid® lotion three times daily for four weeks. Seven subjects (8.4%) showed laboratory (but not clinical) findings of adrenal suppression (as measured by Cortrosyn® stimulation tests [CST]), of whom six recovered normal responses within one month and one within six months.

**GENERAL ATTRIBUTES**

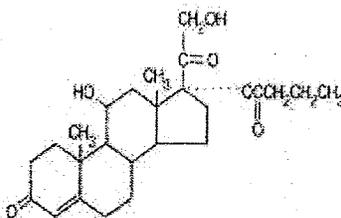
**Trade name:** Locoid® Lotion (0.1%)

**Generic name:** Hydrocortisone butyrate

**Chemical name:** [Pregn-4-ene-3, 20-dione, 11, 21-dihydroxy-17- [(1-oxobutyl) oxy (11β)-]

**Molecular formula/molecular weight:** C<sub>25</sub>H<sub>36</sub>O<sub>6</sub>/432.56

**Chemical Structure:**



**Description and Composition of the Drug Product:**

Four formulations were originally developed by the Sponsor for this product. Two of these four formulations, R6539 and R6546, had acceptable bulk chemical uniformity and visual appearance results and were chosen to scale up to develop the manufacturing process. Ultimately, based on the results of 24 month room temperature and six month accelerated stability data, formulation R6546 presented less total impurities content than R6539. Therefore, R6546 was selected as the final formulation for this product. The composition of the R6546 Locoid lotion, 0.1% is provided below.

Ingredient	% w/w
Hydrocortisone butyrate, USP	0.10
Butylated hydroxytoluene, NF	
Butylparaben, NF	
Ceteth-20	
Cetostearyl alcohol, NF	
Citric acid, USP, —	
Light mineral oil, NF	
White petrolatum, USP	
Propylparaben, NF	

b(4)

Safflower oil, USP	
Sodium citrate dihydrate, USP	
Purified water, USP	


b(4)

Hydrocortisone butyrate is a white to practically white powder with a molecular weight of 432.56. It is practically insoluble in water, slightly soluble in ether, soluble in methanol, in alcohol, and in acetone, and freely soluble in chloroform.

**Reviewer's suggested Labeling Changes:**

---

**INDIVIDUAL STUDY REPORTS**

**NDA: 22-076/Study 01-036**

**Study Dates: Jul, 05 – Aug, 05**

**A Vasoconstrictor Study to Rank the Relative Potency of Hydrocortisone Butyrate 0.1% Lotion with Respect to Approved Topical Corticosteroid Preparations**

**Objectives:**

To determine the clinical potency of two test products containing hydrocortisone butyrate 0.1% in relation to currently-used low-, mid-, and high-potency topical corticosteroid formulations, all of which have been approved by the FDA for use in the United States.

**Methodology:** This was a single-center, double-blind, intra-subject, single-exposure study on healthy adult male and female subjects that compared the skin-blanching (vasoconstriction) potentials of the investigational articles using visual assessment. Potential subjects were screened for vasoconstriction responsiveness using a single dose application of Locoid Lipocream® (hydrocortisone butyrate 0.1%) without occlusion on normal skin of the upper ventral arm (two sites). Individuals who met all inclusion and exclusion criteria and demonstrated a 1 (one) value score or greater visual vasoconstriction score on either screen test site were qualified for enrollment into the treatment phase of the study.

The following test articles were used in the study:

- *Hydrocortisone butyrate 0.1% lotion (#R6546)*
- *Hydrocortisone butyrate 0.1% lotion (#R6539)*
- *Hydrocortisone butyrate 0.1% lotion vehicle (#R7173)*
- *Hydrocortisone butyrate 0.1% lotion vehicle (#R7380)*
- *Locoid Lipocream® (hydrocortisone butyrate 0.1%) (Class 5 – mid strength)*

- *Hytone® 2.5% (hydrocortisone) lotion (Class 7 – mild strength)*
- *Diprolene AF® (betamethasone dipropionate) cream (Class 2 – potent strength)*

For study conduct, 36 healthy subjects had seven 1-cm<sup>2</sup> sites on both forearms evaluated for vasoconstriction response to as many as seven different formulations following a single dose application duration of 16 hours. Approximately 5.5 mg of each study medication or vehicle treatments was applied to the designated site. The test site was protected using a Hill Top chamber without dish secured to the arm with a non-occlusive tape. Sixteen hours after the study medication application, study personnel removed the protective guards and cleaned the test sites. Two hours after removal of medication visual assessment of the test sites were performed. Pharmacodynamic responses to the topical corticosteroids pre-dose, and following dose removal, were assessed by visual score using the following scale:

*0- no visible response*

*1- weak blanching – skin is somewhat paler than surrounding skin*

*2- moderate blanching – skin is white compared to surrounding skin*

*3- strong blanching – skin is very white compared to surrounding skin*

Evaluators were blinded to the test articles and had been trained in their respective tasks. Every effort was made to have the visual scores conducted by a single evaluator throughout the study. Pre-dose visual score assessments were conducted to ensure that all test sites were free of obvious differences in skin color or for the presence of a skin condition, scar tissue, tattoo or discoloration that would interfere with placement of test sites, or their assessments. If a defect was observed, the subject was excluded from the study if the test site(s) could not be placed such that the defect was avoided.

*Safety:* Subjects were observed and queried for the occurrence of adverse events throughout the study.

**Statistical Methods:** Visual scores were tabulated and collated to site and test article. The data was analyzed for differences among treatments. Within this analysis, Ryan-Einot-Gabriel-Welsch Multiple Range Test was employed as the multiple comparison tests of choice to determine pair-wise treatment differences.

### **Results:**

The following tables summarize the results of the analyses performed on the pharmacodynamic parameters.

Treatment	N	Mean	Sum
Hydrocortisone butyrate lotion 0.1%	36	0.44	16
Hydrocortisone butyrate lotion 0.1%	36	0.61	22
Vehicle® A	36	0.28	10
Vehicle® B	36	0.28	10
Locoid® Lipocream® Cream	36	1.11	40
Hytone® Hydrocortisone Lotion	36	0.14	5
Diprolene AF®	36	0.72	26

A review of the scores shows a high range of intra-subject variability and the sponsor comments that variability is well known in human assays and no technical issues causing the variable results were identified.

**Safety Results:** According to the sponsor, there was one adverse event, unrelated to the test articles, reported during the study. No serious adverse events were reported. The relationships of the adverse events to the test articles were determined to be “Unlikely”.

**Discussion:** According to the above visual scores and by sponsor’s statistical analysis, Locoid® Lipocream Cream (Hydrocortisone butyrate 0.1%) was significantly more vasoconstrictive than the remaining treatments. That is contrary to the standard potency classification of corticosteroids where Locoid® Lipocream Cream belongs to Class 5 – mid strength category. Additionally, Diprolene AF® Cream (Betamethasone dipropionate 0.05%) being the Class 2 – potent strength category showed substantially lower vasoconstrictive score than Locoid® Lipocream Cream. Another surprise was Hytone® Lotion was found to be less vasoconstrictive than both hydrocortisone butyrate lotion 0.1% A and B vehicles which did not contain any corticosteroids. On the other hand, Locoid® Lipocream Cream was as expected significantly more vasoconstrictive than vehicle A, Vehicle B and Hytone® Lotion (Hydrocortisone 2.5%). Vasoconstriction for both Hydrocortisone butyrate lotion 0.1% A and B were significantly greater than Hytone® Lotion. No other pair-wise comparisons were significantly different.

**Comments:**

*The outcome does not provide definitive potency ranking for either of the test article formulations; also, in absence of pair-wise comparisons between the test products, it is not possible to conclude that the test products are of similar potency. At least the mean scores from two test formulations appear different (0.44 and 0.61). The only inference that can be drawn from the data is that potency of the test products fall between the Locoid Lipocream (mid-potency) and Hytone (low-potency) reference products. Because of the findings that contradicted the established potency ranking for various products as discussed on Page 8, the data are not considered reliable.*

---

**NDA: 22-076/Study 01-097**

**Study Dates: June, 2005**

**A Randomized, Blinded, Single-Center Evaluation of the Vasoconstrictive Properties of 0.1% Hydrocortisone Butyrate Lotion in Normal Healthy Volunteers**

---

**Objectives:**

1. The primary objective of this study was to determine the potency ranking of 0.1% hydrocortisone butyrate lotion using visual (primary) assessment and chromameter (secondary) assessment of the vasoconstriction response to four (4) other topical corticosteroid formulations of different potency ranking.
2. The secondary objective of this study was to evaluate the relative vasoconstriction potency of the 0.1% hydrocortisone butyrate lotion to four commercially available 0.1% hydrocortisone butyrate formulations (Solution, Cream, Ointment and Lipocream) using visual (primary) assessment and chromameter (secondary) assessment of the vasoconstriction response.

**Methodology:** This was a double-blind, intra-subject, single-exposure study on healthy adult male and female subjects that compared the skin-blanching (vasoconstriction) potentials of the investigational articles using chromameter and visual assessment. Potential subjects were screened for vasoconstriction responsiveness using a single dose application of Locoid<sup>®</sup> Cream (hydrocortisone butyrate 0.1%) without occlusion on normal skin of the upper ventral arm (two sites). Individuals who met all inclusion and exclusion criteria and demonstrated a 1 (one) value score or greater visual vasoconstriction score on either screen test site qualified for enrollment into the treatment phase of the study.

One hundred eighteen (118) potential subjects (male and female) were screened for vasoconstriction responsiveness. Those subjects who demonstrated vasoconstriction

responsiveness and passed all other inclusion and exclusion criteria qualified for study enrollment into the treatment phase of this study. A total of thirty-six (36) male and female subjects were enrolled for study conduct and had five 4-cm<sup>2</sup> sites on both forearms evaluated for vasoconstriction response to the following topical steroid formulations following a single dose application duration of 16 hours. Two additional sites on each forearm remained untreated to serve as control sites. The study conduct was initiated in the afternoon of Study Day 1 and the subjects were sequestered overnight in the study facility for dose removal and site assessments on Study Day 2.

*Hydrocortisone butyrate lotion 0.1% (R6546) by Ferndale Laboratories, Inc.*  
*Locoid® Cream (Hydrocortisone butyrate 0.1%) by Ferndale Laboratories, Inc.*  
*Locoid® Lipocream Cream (Hydrocortisone butyrate 0.1%) by Ferndale Laboratories, Inc.*  
*Locoid® Ointment (Hydrocortisone butyrate 0.1%) by Ferndale Laboratories, Inc.*  
*Locoid® Solution (Hydrocortisone butyrate 0.1%) by Ferndale Laboratories, Inc.*  
*Clobex™ (Clobetasol propionate) Lotion 0.05% by DPT Laboratories, Ltd.*  
*Hytone® Lotion (Hydrocortisone 2.5%) by Dermik Laboratories, Inc.*  
*Cutivate® Cream (Fluticasone propionate 0.05%) by GSK Consumer Healthcare LP*  
*Cutivate® Ointment (Fluticasone propionate 0.005%) by GSK Consumer Healthcare LP*

Pharmacodynamic responses to the topical corticosteroids pre-dose, and following dose removal, were assessed by visual score and by chromameter measurement. Evaluators were blinded to the test articles and had been trained in their respective tasks. Every effort was made to have the visual scores conducted by a single evaluator throughout the study. Pre-dose visual score assessments were conducted to ensure that all test sites were free of obvious differences in skin color or for the presence of a skin condition, scar tissue, tattoo or discoloration that would interfere with placement of test sites, or their assessments. If a defect was observed, the subject was excluded from the study if the test site(s) could not be placed such that the defect was avoided.

Vasoconstriction response was evaluated by visual score and by chromameter measurement at pre-dose, and at 2 hours after dose removal. Degree of vasoconstriction, graded visually and by chromameter two hours after test article removal. Visual score, which was the primary assessment, was determined as follows:

- 0- No pallor; no change from surrounding area
- 1- Mild pallor; slight or indistinct within application site
- 2- Moderate pallor; discernible but diffuse within application site
- 3- Moderate pallor; clean, distinct within application site
- 4- Intense pallor; clean, distinct within application site

The chromameter was Minolta Inc, Model CR300, which automatically collected three back-to-back readings to obtain the internally calculated mean.

Both visual and chromameter scores were tabulated and collated to site and test article. The final assessment for each site was first corrected for that site's baseline reading (site

baseline), then corrected for the mean of the non-dosed control sites (baseline corrected control site mean). The final values were then used for the product comparison evaluation. The data was then partitioned by objective (by arm) and by assessment (visual vs. chromameter), and evaluated for differences between the test formulations. For Objective #1 (comparison to different topical corticosteroid formulations), the mean results across subjects for the test formulation were correlated to the known ranking of the reference formulations. The test formulation was then evaluated (ranked) for its placement among the reference formulations. For Objective #2 (comparison to the different types of formulation which all contain hydrocortisone butyrate), the mean results across subjects for each test formulation were compared for equivalency to the test formulation.

The data was analyzed for differences among treatments. Within this analysis, Ryan-Einot-Gabriel-Welsch Multiple Range Test was employed as the multiple comparison tests of choice to determine pair-wise treatment differences.

*Safety:* Subjects were observed and queried for the occurrence of adverse events throughout the study.

**Results:**

The following tables summarize the results of the analyses performed on the pharmacodynamic parameters.

**Objective 1: Visual Score Data**

Score	Test Article	R.E.G.W
0.0000	E – Hytone <sup>®</sup> 2.5% Lotion (VII)	W
		W
0.0000	CONTROL	W
0.5278	D – Cutivate <sup>®</sup> Cream (V)	X
		X
0.8056	B – Hyd. Butyrate Lotion (Test)	X
1.5833	A – Clobex <sup>™</sup> Lotion (I)	Y
2.0833	C – Cutivate <sup>®</sup> Ointment (III)	Z

**Objective 1: Chromameter Data**

Score	Teat Article	R.E.G.W
0.1386	E – Hytone <sup>®</sup> 2.5% Lotion (VII)	X
		X
0.0003	CONTROL	X
-0.9061	D – Cutivate <sup>®</sup> Cream (V)	Y
		Y
-1.0242	B – Hyd. Butyrate Lotion (Test)	Y
-2.4569	A – Clobex <sup>™</sup> Lotion (I)	Z
		Z
-2.5394	C – Cutivate <sup>®</sup> Ointment (III)	Z

(Test Articles with similar letter values are not statistically different. Test articles are ranked in order, top to bottom, from lowest to highest potency)

Based on the statistical results of the Ryan-Einot-Gabriel-Welsch Multiple Range Test using the visual data (primary assessment), the test product, hydrocortisone butyrate lotion 0.1%, by Ferndale Laboratories, Inc. is not statistically different from Treatment D, Cutivate<sup>®</sup> Cream, 0.05%, a Class 5 (mid-strength) topical corticosteroid. Further, the results indicate that the hydrocortisone butyrate lotion 0.1% test formulation is statistically different from the Class 7 mild potency ranked steroid formulation Hytone<sup>®</sup> 2.5% Lotion, and from the higher potency ranked steroid formulations Clobex<sup>™</sup> Lotion and Cutivate<sup>®</sup> Ointment (Class 3 – potent). Based on these findings, the hydrocortisone butyrate 0.1% test formulation demonstrates a vasoconstriction response consistent with those products classified within the Class 5 – mid potency topical corticosteroids. This is supported by the statistical results using the chromameter data (secondary assessment).

The applicant concluded that Locoid<sup>®</sup> lotion is not statistically different from Cutivate<sup>®</sup> cream, is statistically different from Hytone<sup>®</sup> lotion, Clobex<sup>®</sup> lotion, and Cutivate<sup>®</sup> ointment, and therefore “demonstrates a vasoconstriction response consistent with those products classified as class 5 topical corticosteroids. It is noted that the study was unable to rank the potency for Hytone Lotion.

**Objective 2: Visual Score Data**

Score	Test Article	R.E.G.W
0.0000	CONTROL	X
0.4306	G – Locoid <sup>®</sup> Ointment	Y
		Y
0.6806	J – Locoid <sup>®</sup> Solution	Y
1.0139	H – Locoid <sup>®</sup> Cream	Z
		Z
1.1528	I – Locoid <sup>®</sup> Lipocream	Z
		Z
1.2083	B – Hyd. Butyrate Lotion (Test)	Z

**Objective 2: Chromameter Data**

Score	Test Article	R.E.G.W
-0.0014	CONTROL	W
-0.8831	G – Locoid <sup>®</sup> Ointment	X
		X
-1.1328	J – Locoid <sup>®</sup> Solution	X Y
		Y
-1.4597	H – Locoid <sup>®</sup> Cream	Z Y
		Z Y
-1.6389	I – Locoid <sup>®</sup> Lipocream	Z Y
		Z
-1.8528	B – Hyd. Butyrate Lotion (Test)	Z

(Test Articles with similar letter values are not statistically different. Test articles are ranked in order, top to bottom, from lowest to highest potency)

According to the applicant, based on the statistical results of the Ryan-Einot-Gabriel-Welsch Multiple Range Test using the visual data (primary assessment), the test product, hydrocortisone butyrate lotion 0.1%, by Ferndale Laboratories, Inc. is not statistically different from Treatment H, Locoid<sup>®</sup> Cream, 0.1%, by Ferndale Laboratories, Inc. or Treatment I, Locoid<sup>®</sup> Lipocream, 0.1%, by Ferndale Laboratories, Inc. This is supported by the statistical results using the chromameter data (secondary assessment).

**Safety Results:** According to the sponsor, two (2) subjects experienced a total of two (2) adverse events over the course of the study. Adverse events were mild to moderate in severity. No serious adverse events were reported. The relationships of the adverse events to the test articles were determined to be “Unlikely”.

**Comments:**

*In general more occlusive topical formulations of the same drug i.e., ointment versus cream, lotion etc. are associated with more skin blanching which translates into higher (more potent) potency ranking; e.g., Cyclocort ointment 0.1% is a class 2 corticosteroid whereas Cyclocort cream 0.1% belongs to class 3. However, in Sponsor' objective 2 data, the more occlusive vehicle formulation (i.e., Locoid ointment) demonstrated lower potency than all other Locoid formulations.*

*The ordinal rankings of the formulations are not consistent. Unlike study 01-036, which found Locoid® Lipocream to be more potent than Locoid® lotion, this study found a greater mean blanching score for the lotion (although not statistically significant, according to the applicant).*

*It is not clear how visual scoring for the same formulation under 2 different objectives can be so different. The mean score for Locoid® lotion for Objective 2 (1.2083) was greater than that found for Objective 1 (0.8056), although the methods and scoring were identical. There was no explanation for this difference reported by the applicant*

*Similarly the above inconsistency was seen in chrommometer data as well. The mean score for Locoid® lotion for Objective 2 (-1.8528) was greater than that found for Objective 1 (-1.0242), although the methods and scoring were identical. There was no explanation for this difference reported by the applicant.*

*The appropriateness of presenting results solely as means (rather than medians) and without a pre-specified equivalence margin between test articles and a study powered to detect this difference, it is not clear to this reviewer that lack of evidence of a difference between test articles should be taken as evidence of blanching equivalence.*

*The applicant makes the following claim in section 12.3 of proposed labeling:*

*While this statement may be supported by the same ordinal ranking of Locoid® lotion with Cutivate cream and Locoid cream, this claim contradicts findings from study 01-036, which was not able to show a statistically significant difference between hydrocortisone butyrate lotion 0.1% and Diprolene AF®, a class 2 (potent) topical corticosteroid.*

**b(4)**

*No other approved Locoid product has potency ranking information on the label. Due to inconsistencies observed in ordinal rankings described above, reliance of data from study 03-097 is questionable. The reviewer does not recommend putting any language in terms of potency ranking in the labeling.*

**NDA: 22-076/Study 104**

**Study Dates: Sep, 04 –Feb, 06**

**An Open Label Adrenal Suppression Study of Hydrocortisone Butyrate Lotion 0.1% Used 3x Daily in Pediatric Subjects Aged 3 Months to Less than 18 Years With Moderate to Severe Atopic Dermatitis**

---

**Objectives:**

The objective of this study was to investigate the adrenal suppression potential of hydrocortisone butyrate lotion 0.1% used three times daily on diseased skin in pediatric subjects aged 3 months to less than 18 years diagnosed with moderate to severe atopic dermatitis following up to 4 weeks of treatment by monitoring adrenal function [as determined by Cortrosyn® Stimulation Testing (CST)], hematology, serum chemistry, vital signs, urinalysis, and adverse events.

**Methodology:**

This was a multicenter (10 centers), open-label study where a sample size of approximately 72 subjects to ensure that 15 evaluable subjects for each age cohort complete the study was planned. Male and female subjects, age 3 months to less than 18 years, with moderate to severe atopic dermatitis affecting a minimum of 25% body surface area and met the criteria described by Hanifin and Rajka were enrolled. Eighty-four (84) of the 90 subjects enrolled passed the screening criteria and continued into the treatment phase of the study.

There were four age cohorts:

- Cohort 1: 12 years to less than 18 years.(n=19).
- Cohort 2: 6 years to less than 12 years (n=25).
- Cohort 3: 2 years to less than 6 years (n=21).
- Cohort 4: 3 months to less than 2 years (n=19).

Forty-three of the 84 subjects (51%) were male and 41/84 subjects (49%) were female. The average weight of these subjects was 70.40 pounds and the average height was 46.58 inches. The average percent body surface area affected was 46.3%.

Looid® Lotion, 0.1%, (Batch Number: 04065A ) was applied topically 3 times daily for 3 to 4 weeks, depending on improvement of the condition.

Study medication was applied three times daily to affected areas without occlusive dressing at approximately equally spaced intervals during the waking hours. Ideally, applications were spaced at 6-hour intervals. The investigator reviewed the affected areas and reinstructed the subject or the subject's caregivers on dosing. Affected areas were treated as they appeared. Treatment to affected areas which had cleared since the previous visit was discontinued. An affected area was defined as any area with lesions that had signs of atopic dermatitis such as erythema, induration/papulation, lichenification, excoriation, or oozing/crusting or any area that had been identified by the subject and/or subject's parent(s) or legal guardian(s) as having pruritus.

All affected areas were treated except those on the peri-ocular area, scalp, perioral area, perinasal area, diaper area of those who wore diapers or those areas deemed clinically inappropriate for treatment in the opinion of the investigator (e.g., surgical incisions). Affected areas to be treated were clearly documented on a body diagram at the Baseline Visit. Affected areas were treated three times daily (t.i.d.) as prescribed by the physician until the next visit.

Study medication was applied as a thin film and massaged into the skin until evenly distributed and no study medication remained visible. This ensured that study medication was applied at the rate of approximately 1 mg lotion/cm<sup>2</sup> which delivered 1 µg hydrocortisone butyrate/cm<sup>2</sup>.

Subjects dosed at up to:

- 15 g/day for subjects aged 3 months to < 2 years,
- 21 g/day for subjects aged 2 years to < 6 years,
- 30 g/day for subjects aged 6 years to < 12 years,
- 36 g/day for subjects aged 12 years to 18 years.

Dosing was measured by dispensing a dollop of study medication, the size of a shelled peanut, onto the fingertip. This amount is typically sufficient to cover an area of 9 x 9 inches (24 x 24 cm<sup>2</sup>). This is approximately equal to the area of a sheet of letter-sized paper. The first dose was applied under the supervision of the medical staff.

The table below provides an estimate of the number of 2 oz bottles of study medication that would be sufficient to dose a subject of a specific age cohort with 25% or 75% BSA involvement for one week.

Estimated number of 2 oz. bottles for treatment

Cohort	Age	If 25% BSA bottles/week	If 75% BSA bottles/week
1	12 y < 18 y	2	5
2	6 y to < 12 y	2	4
3	2 y to < 6 y	1	3
4	3 mo to < 2 y	1	2

Subjects were instructed to dose three times daily for 4 weeks (Day 29). The exception was if the subject's condition was assessed as clear (PGA = 0) prior to Day 29 at a scheduled visit, the subject either completed the Final Visit activities (if the CST could be completed within the specified time period) or the subject was instructed to return to the clinic the following day and the activities scheduled for the Final Visit were performed at that time.

#### Cortrosyn® Stimulation Test (CST)

A Cortrosyn® Stimulation Test was performed at Screening Visit (7 to 14 days prior to the Baseline Visit) and at the Final Visit. Subjects who had abnormal adrenal function at

the Final Visit had their adrenal function reassessed every 4 weeks using the CST until post-stimulation adrenal function returned to normal (cortisol level  $>18 \mu\text{g/dL}$ ). Potential subjects with prestimulation cortisol levels less than  $5 \mu\text{g/dL}$  or post-stimulation levels  $\leq 18 \mu\text{g/dL}$  at screening were not enrolled. If there was evidence of adrenal suppression, CST was performed every 4 weeks until axis function was normalized. The endpoint was considered Day  $29 \pm 1$  day or earlier if the subject was assessed as clear (PGA=0) at a prior scheduled visit. If assessed as clear, the final visit would occur within 2 days thereafter.

Cortrosyn<sup>®</sup> (0.125mg for subjects aged 3 months to less than 3 years and 0.25mg for subjects aged 3 to 18 years) was administered, and followed by a second blood draw for total cortisol evaluation 30 minutes later. The preferred route for administration of the Cortrosyn<sup>®</sup> was intravenous and every effort was made to ensure intravenous administration of Cortrosyn<sup>®</sup> throughout the study. However, if this was unachievable, intramuscular administration was permitted. Following the post-stimulation blood draw, it was recommended that subjects remain in the clinic for an additional 30 minutes to monitor for any allergic reactions that could be associated with the administration of Cortrosyn<sup>®</sup>.

If there was laboratory evidence of adrenal suppression at the Final Visit, this was to be considered an adrenal adverse event and was documented on the CRF. For these subjects, post-study CST testing was performed every 4 weeks until axis function was documented as returning to normal. CST testing was performed between 7 am and 9 am at the same time as the Screening Visit test  $\pm$  one (1) hour.

#### Efficacy:

- Individual signs of erythema, induration/papulation, excoriation, lichenification, and oozing/crusting, were assessed at the Baseline and Days 8, 22, and 29 on a scale of 0 (none) to 3 (severe).
- Pruritus was assessed at the Baseline Visit and on Days 8, 22, and 29.
- Overall %BSA affected by the disease was determined by the investigator or a qualified designee at the Baseline Visit and on Days 8, 22, and 29.
- Overall disease condition was assessed and documented at Baseline and on Days 8, 22, and 29 using a Physician's Global Assessment Scale ranging from 0 (clear) to 4 (severe).

Subjects who were assessed as clear (PGA = 0) at an interim evaluation completed the study and had all evaluations for the Final Day 29 visit completed at that time.

#### Safety:

- Vital signs (temperature, blood pressure, respiration rate, and pulse) were recorded at screening and final visit.
- A Cortrosyn<sup>®</sup> Stimulation Test was performed at the Screening Visit (7 to 14 days prior to the Baseline Visit) and at the Final Visit. A subject was considered to have

evidence of adrenal suppression at the end of treatment if the serum cortisol level 30 minutes after Cortrosyn<sup>®</sup> administration was less than or equal to 18µg/dL.

Standard safety laboratory tests including serum chemistry panel and hematology including a complete blood count with differentials was performed at the Screening and Final Visit. Urinalysis and urine pregnancy testing was performed at the Screening Visit.

**Results:**

**Adrenal Suppression**

At Screening, pre-stimulation cortisol levels averaged 14.64 µg/dL compared to 12.97 µg/dL at the End of Treatment which resulted in a mean change of -1.57µg/dL. At Screening, post-stimulation cortisol levels averaged 28.20 µg/dL compared to 24.26 µg/dL at the End of Treatment which resulted in a mean change of -3.67µg/dL. Change from pre-stimulation to post-stimulation resulted in an increase in cortisol levels of 13.56 µg/dL at Screening and 11.30 µg/dL at the End of Treatment. Seven of 82 subjects (9%) demonstrated laboratory evidence of adrenal suppression at the End of Treatment evaluation. These results are summarized in the following Tables. In no case did any of these seven subjects demonstrate clinical signs or symptoms of adrenal suppression. The distribution of subjects who were suppressed at the end of treatment (Day 29) by age cohort was: 2 of 19 subjects aged 3 months to <2 years old, 1 of 21 subjects aged 2 years to <6 years old, 3 of 25 subjects aged 6 years to <12 years old, and 1 of 19 subjects aged 12 years to <18 years. Laboratory evidence of adrenal suppression resolved without difficulty in all subjects, as documented by normal post-stimulation cortisol levels at their first post treatment follow-up visit for 6 of 7 subjects (~ 4 weeks after the End of Treatment). The seventh subject (6-90) continued to show signs of suppression at the 4-week follow-up with a post-stimulation cortisol level of 16.4µg/dL but with a normal post-stimulation cortisol approximately 8 weeks after the End of Treatment. Two subjects did not have an End of Treatment CST performed for administrative or technical reasons. Subject 3-60 was lost to follow-up following the Day 15 evaluation. The second subject (4-34, aged 2.38 years old), experienced difficulty with venous access (three failed attempts) and the child's mother requested that further attempts be stopped.

**Table 1: Summary of Safety: Adrenal Axis Suppression at End of Treatment (Safety Subjects)**

	<u>Screening</u>	<u>End of Treatment</u>	<u>Change from Screening<sup>a</sup></u>
Pre-Stimulation			
Cortisol Concentration (µg/dL)			
n	84	82	82
Mean	14.64	12.97	-1.57

STD	5.79	5.94	7.31
Post-Stimulation			
Cortisol Concentration (µg/dL)			
n	84	82	82
Mean	28.20	24.26	-3.67
STD	6.67	7.45	8.45

Cortisol Concentration (µg/dL)	Change from Pre-Stimulation to Post-Stimulation	
	<u>Screening</u>	<u>End of Treatment</u>
n	84	82
Mean	-13.56	-11.30
STD	5.71	5.40

Number of Subjects (%)  
with Adrenal Suppression<sup>b</sup> 7 ( 9%)

<sup>a</sup> Change from screening was calculated as End of Treatment cortisol concentration minus Screening cortisol concentration.

<sup>b</sup> Adrenal suppression is defined as a serum cortisol level 30 minutes after Cortrosyn<sup>®</sup> administration less than or equal to 18 µg/dL.

Note: No imputations were made for missing data.

Table 2: Summary of Safety: Serum Cortisol Levels (µg/dL) (Safety Subjects) (Page 1 of 4)

**3 months to <2 Years**

Subject	Age (Years)	Baseline %BSA	Screening		End of Treatment		Follow-Up 1		Days Out from EOT
			Pre	Post	Pre	Post	Pre	Post	
002-081	1.44								
003-061	1.60								
<del>003-062</del>	1.73								
003-125	1.12								
004-033	1.78								
004-037	1.33								
005-018	1.44								
005-079	0.57								
005-080	1.95								
005-097	0.50								
005-098	1.80								
005-121	0.72								
006-087	1.18								
006-089	0.80								
006-090	1.01								
FU2*									

b(4)

009-048 1.39  
 010-109 0.37  
 010-111 1.37  
 010-112 0.76

b(4)

**2 years to <6 Years**

<u>Subject</u>	<u>Age (Years)</u>	<u>Baseline %BSA</u>	<u>Screening</u>		<u>End of Treatment</u>		<u>Follow-Up 1</u>		<u>Days Out from EOT</u>
			<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	
002-010	4.07								
002-012	2.77								
003-058	3.52								
003-059	4.14								
003-060	4.95								
003-064	5.12								
004-034	2.38								
004-035	2.32								
004-036	3.41								
004-038	2.08								
004-040	5.43								
004-101	4.56								
004-104	5.14								
005-020	2.37								
005-022	3.34								
005-073	2.96								
005-074	3.65								
005-095	2.30								
005-096	3.64								
009-043	2.15								
009-047	4.56								

b(4)

Table 2 (Contd) : Summary of Safety: Serum Cortisol Levels (µg/dL) (Safety Subjects) (Page 2 of 4)

**2 years to <6 Years**

<u>Subject</u>	<u>Age (Years)</u>	<u>Baseline %BSA</u>	<u>Screening</u>		<u>End of Treatment</u>		<u>Follow-Up 1</u>		<u>Days Out from EOT</u>
			<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	
002-010	4.07								
002-012	2.77								
003-058	3.52								
003-059	4.14								
003-060	4.95								
003-064	5.12								
004-034	2.38								
004-035	2.32								
004-036	3.41								
004-038	2.08								
004-040	5.43								
004-101	4.56								
004-104	5.14								
005-020	2.37								
005-022	3.34								
005-073	2.96								

b(4)

005-074	3.65
005-095	2.30
005-096	3.64
009-043	2.15
009-047	4.56

b(4)

**6 years to <12 Years**

002-009	8.54
002-011	8.25
002-014	10.13
002-015	8.96
002-016	10.88
003-057	10.84
004-039	7.45
004-099	11.55
004-100	7.44
004-102	7.50
004-103	9.37
005-019	8.84
005-021	10.57
005-023	8.87
005-075	6.03
005-076	6.60
006-050	10.60
006-052	10.23
006-085	6.62
006-086	8.98
008-025	9.86
009-042	6.95
009-044	7.05
009-045	9.71
009-046	6.80

b(4)

Table 2 (Contd.) : Summary of Safety: Serum Cortisol Levels (µg/dL) (Safety Subjects) (Page 4 of 4)

**12 years to <18 Years**

<u>Subject</u>	<u>Age (Years)</u>	<u>Baseline %BSA</u>	<u>Screening</u>		<u>End of Treatment</u>		<u>Follow-Up 1</u>		<u>Days Out from EOT</u>
			<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	<u>Pre</u>	<u>Post</u>	
001-001	12.39								
001-003	14.10								
002-013	12.35								
002-082	15.40								
002-083	16.92								
002-084	14.96								
005-017	17.73								
005-024	12.63								
005-077	15.61								
005-078	15.51								
006-049	12.62								
006-051	13.55								
006-053	12.68								
006-054	14.33								
006-055	14.51								
006-056	16.33								

b(4)

006-073 17.85  
006-074 16.76  
009-041 12.88

b(4)

ND = Not Done

\* Subject 006-090 required a second follow-up visit. Days Out is calculated as Days Out from Follow-Up 1.

Of the remaining 84, subjects, 83 (98.8%) completed the study and one (003-060, Cohort 3) was lost to followup. An additional subject (004-034) has the final CST result as "ND" (not done), leaving 82 evaluable subjects. Seven of 82 subjects (8.5%) developed adrenal suppression, including the following:

- Cohort 1: 12 years to less than 18 years.(n=19) – 1 subject (5.3%).
- Cohort 2: 6 years to less than 12 years (n=25) – 3 subjects (12.0%).
- Cohort 3: 2 years to less than 6 years (n=19). – 1 subject (5.3%).
- Cohort 4: 3 months to less than 2 years (n=19) – 2 subjects (10.5%)

All subjects recovered adrenal function by the next test (one month after treatment discontinuation), except for one subject in Cohort 4, a 1.01-year-old boy who did not recover adrenal function until two months following treatment discontinuation. Adrenally suppressed subjects had a mean baseline BSA of 66.7% (range, 35% to 90%). Seventeen of 21 subjects (81%) with BSA > 66.7% were not suppressed. BSA of the two suppressed subjects in the youngest age cohort (Cohort 1, 3 months to <2 years) was 75% and 90%; six subjects in the same cohort with BSAs of 95%, 93%, 85%, 80%, 75%, and 70% were not suppressed. The number of suppressed subjects in each cohort ranged from one to three.

Safety and efficacy:

Safety and efficacy data are being evaluated by Dr. Kenneth A. Katz of HFD-540. According to the sponsor, the results of this study demonstrated the safety and efficacy of the study medication. The study medication was well tolerated. Few adverse events were reported during the study all of which were mild to moderate. Most were not considered related to study medication.

#### CONCLUSIONS:

*In a study of pediatric subjects with moderate-to-severe atopic dermatitis, seven of 82 subjects (8.5%) developed adrenal suppression. There was no clear signal that rates of suppression depended on extent of disease or age of subject. However, the product labeling should indicate that adrenal suppression may occur during use of Locoid® lotion, and therefore should be used for the minimum time necessary to accomplish the treatment objective, which may even be less than 4 weeks.*

**Sponsor's Proposed Label:**

13 Page(s) Withheld

           Trade Secret / Confidential (b4)

  x   Draft Labeling (b4)

           Draft Labeling (b5)

           Deliberative Process (b5)

*Withheld Track Number: Clin Pharm/Bio-   1*

Office of Clinical Pharmacology and Biopharmaceutics

**New Drug Application Filing and Review Form**

General Information About the Submission

	Information		Information
NDA Number	22-076	Brand Name	Locoid® Lotion
OCPB Division (I, II, III)	III	Generic Name	Hydrocortisone butyrate 0.1% lotion
Medical Division	540	Drug Class	Corticosteroids
OCPB Reviewer	Tapash K. Ghosh	Indication(s)	Atopic dermatitis
OCPB Team Leader	Sue-Chih Lee	Dosage Form	Topical lotion
		Dosing Regimen	bid
Date of Submission	7/20/06	Route of Administration	Topical
Estimated Due Date of OCPB Review	04/14/07	Sponsor	Ferndale
PDUFA Due Date	5/20/07	Priority Classification	3S
Division Due Date	5/01/07		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:	X	3	3	Vasoconstrictor Assay studies (2) HPA Axis Suppression study (1)
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		3	3	
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<i>Application filable ?</i>	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<i>Comments sent to firm ?</i>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>	<b>Does Locoid® Lotion have adequate systemic safety?</b>			

Other comments or information not included above	
Primary reviewer Signature and Date	<i>Tapash Ghosh</i>
Secondary reviewer Signature and Date	<i>Sue-Chih Lee</i>

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Tapash Ghosh  
5/3/2007 04:12:02 PM  
BIOPHARMACEUTICS

Sue Chih Lee  
5/4/2007 08:15:41 PM  
BIOPHARMACEUTICS