

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-076**

**MEDICAL REVIEW(S)**

**Secondary Lead Medical Officer Clinical Review  
NDA 22-076 Locoid (hydrocortisone butyrate) Lotion, 0.1%**

May 11, 2007

The Dermatology Clinical Team Leader agrees with the Primary Clinical Review for NDA 22-076 that Locoid (hydrocortisone butyrate) Lotion, 0.1% is recommended for approval for the treatment of mild-to-moderate atopic dermatitis. However, specific issues and recommendations proposed in the Primary Review warrant further discussion with alternative consideration for action. In addition, specific issues raised by other discipline reviews impact the clinical application and will be discussed in this review with recommendations provided.

**Team Leader Clinical Review Recommendations**

*Clinical Risk Management Activity* - The Primary Clinical Review recommends that “the applicant be required, for one year following approval, to submit quarterly reports detailing adverse events (AEs) possibly related to photosafety.” This recommendation for requirement is not necessary to be conveyed as the standard submissions for adverse events would be sufficient for this product. New NDA approvals routinely require quarterly submissions for the first three years and then annually, thereafter. The routine clinical review for these submissions should include evaluation of phototoxicity-related adverse events.

*Required Phase 4 Commitments* - The Clinical Team Leader does not agree with the Primary Clinical Review recommendation that “the applicant be required to conduct the following studies...as discussed in EOP2 and pre-NDA meetings, studies to fulfill ICH E1a guidelines for numbers of subjects exposed for long-term safety.”

The Primary Clinical Reviewer proposes that, “These studies should include 300 and 100 subjects between 3 months and 18 years of age with atopic dermatitis using Locoid® 0.1% lotion twice daily for six and 12 months, respectively, and should assess endpoints including adrenal suppression, effects on growth, topical steroid-specific AEs, and development of skin malignancies.”

- a) Hydrocortisone butyrate is a known molecular entity with previous topical products available as cream, ointment, and solution with original NDA approval dates from March 31, 1982.
- b) The new formulation of Locoid Lotion does not contain any new excipients that warrant safety concern.
- c) The target indication for atopic dermatitis is a subset of the broader indication for corticosteroid responsive dermatosis (the labeled indication for the other Locoid products).
- d) The submitted study on HPA-axis suppression using cosyntropin stimulation testing with a positive determination for suppression is sufficient for

labeling. Further study for long-term study of HPA axis study is redundant and not without risk to subjects. The information to be gained by such study is minimal at best.

- e) Effects on growth by topical corticosteroids are currently labeled. Studies on growth suppression by topical corticosteroids have previously been a topic of discussion at a joint NDAC/DODAC meeting (March 24, 2004). At that meeting, it was discussed and agreed upon by the committee members that no such study was required for OTC use of topical corticosteroids. The logic provided at that discussion also applies to Rx use of topical corticosteroids.
- f) No safety signal has emerged upon rigorous review by the Division of Drug Risk Evaluation of cutaneous malignancies associated with topical corticosteroid use. This includes description on page 33 of the Primary Clinical Review that between 1/1/00 and 8/31/05 over 24,000 patients were estimated to have been treated with one of the Locoid dosage forms. Only minor adverse events were reported. While the Agency continues to request non-clinical dermal carcinogenicity studies with topical corticosteroids (as per routine) to inform for labeling, no information has been provided that would provide impetus for long-term clinical study.
- g) Discussion at the EOP2 and pre-NDA meeting did not state that post-marketing studies will be needed. Rather, as always, an assessment will be made at the time of NDA review with regard to the need for these studies. Applicants are recommended to provide their own assessment or any information from studies that may address long-term safety as per ICH E1a.

For these reasons, it is recommended that no post-marketing commitment with regard to longer term studies to evaluate the chronic use of the new Locoid Lotion product is required.

*Recommendations for Labeling: Mechanism of Action* - The Primary Clinical Review recommends modification to the Mechanism of Action section of the label for Locoid. Please see page 86 of the Primary Clinical Review. A working group to discuss class labeling for all corticosteroid products, topical, oral, injected, and inhaled is in the process of standardizing corticosteroid labeling. Consideration needs to be given to standardization and fair balance, as well as, the scientific validity of any new language for the Mechanism of Action section. Therefore, at this time, the current wording for Mechanism of Action, which is currently the standard for the class, should remain in place.

#### **Clinical Team Leader Recommendations with Regard to CMC**

*Lotion vs. Cream Nomenclature* – Locoid (hydrocortisone butyrate) Lotion, 0.1% is an \_\_\_\_\_ formulation that is a “white to off-white smooth homogeneous lotion.” The CMC Review expressed concern that the product in question is not a lotion, but rather a cream. According to the CMC Review, this product is not a liquid and cannot be readily poured. Further, rheology testing by the applicant confirms that this

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product may meet the specifications for a cream with reference to the CDER Data Standards Manual. The sponsor argues that rheology testing may be similar to other currently approved lotion products.

From <http://www.fda.gov/cder/dsm/DRG/drg00201.htm>, "The definitions for Lotion, Cream, Ointment, and Paste were revised on June 21, 2006 to include information that would assist the user in differentiating between these dosage forms. These changes were the result of discussions during an FDA Advisory Committee with an open public forum, scientific studies that were published in refereed pharmaceutical journals, and internal discussions by Agency personnel, including the usual adherence to the criteria that are specified in MaPP 7600.4." Currently, the CDER Data Standards Manual defines lotion as "An emulsion, liquid dosage form. This dosage form is generally for external application to the skin." Of note this change was made after the initiation of clinical studies submitted to NDA 22-076. The definition prior to June 21, 2006 was "The term, lotion has been used to categorize many topical suspensions, solutions, and emulsions intended for application to the skin."

Communication with the sponsor regarding whether this product was a cream or a lotion were not actively pursued until the NDA filing letter. No reference to this question was made at either the pre-IND or End-of-Phase 2 meeting. Of note, lack of discussion with CDER with regard to a regulatory topic does not obviate enforcement of such regulation. However, the Clinical Team Leader points out that it is not clear that this applicant was aware of the issue. In fact, during discussions with the applicant, the applicant pointed out that there is, currently, two marketed cream formulations of Locoid. The applicant was specifically targeting a Lotion formulation for development. Thus, this issue is a major concern for the applicant.

In evaluating the information at hand, based on currently available regulatory standards, the Clinical Team Leader recommends that the description of this product as a lotion be allowed. The following are reasons for this departure from the recommendation in the CMC review:

- 1) Not all standards currently agree with the CDER Data Standards Manual, e.g. the U.S. Pharmacopeia. Thus, the regulatory standard is in transition.
- 2) The clinical studies and product development was conducted for the most part when the CDER Data Standards did not reflect the current thinking.
- 3) The applicant has placed the product in a lotion type bottle and the majority of product (approximately 80%) can be retrieved with minimal effort.

*Product Dispensing – Testing* (conducted by CDER) demonstrated that approximately 20% of the product cannot be retrieved from the provided to-be-marketed container without additional effort, e.g. vigorous shaking. This issue is not an approvability issue nor is this Team Leader aware that the Agency has taken any prior action to address this issue. Product retrieval may be an inherent marketing problem for some products to which consumers may readily adapt.

#### **Pharmacology/Toxicology Recommendation for Post-marketing Study**

The Clinical Team Leader agrees with the recommendation that a non-clinical dermal carcinogenicity be conducted with Locoid Lotion, 0.1% as a post-marketing

commitment. Please see Pharmacology/Toxicology Review for details and specifics for this recommendation.

**Conclusion**

The Clinical Team Leader recommends that Locoid (hydrocortisone butyrate) Lotion, 0.1% be approved for the treatment of atopic dermatitis with labeling as discussed and agreed upon with the sponsor.

Markham C. Luke, M.D., Ph.D.  
Lead Medical Officer, Dermatology

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

5/17/2007 09:40:20 AM

MEDICAL OFFICER

Secondary Clinical Review. See also Primary Clinical Review.

Stanka Kukich

5/17/2007 12:09:40 PM

MEDICAL OFFICER

Concur with the recommendation that Locoid (hydrocortisone butyrate) Lotion  
0.1% be approved for the treatment of mild  
to moderate atopic dermatitis in patients 3 months  
of age and older

## CLINICAL REVIEW

Application Type: NDA  
Submission Number: 22-076  
Submission Code: N000 / 505(b)(1)

Letter Date: 2006-06-26  
Stamp Date: 2006-06-28  
PDUFA Goal Date: 2007-05-20

Reviewer Name: Kenneth A. Katz, M.D., M.Sc., M.S.C.E.  
Through: Markham C. Luke, M.D., Ph.D.  
Review Completion Date: 2007-03-19

Established Name: Hydrocortisone butyrate 0.1% lotion  
(Proposed) Trade Name: Locoid® lotion  
Therapeutic Class: Topical corticosteroid  
Applicant: Ferndale Laboratories, Inc.

Priority Designation: S

Formulation: Lotion  
Dosing Regimen: Twice daily

Indication: \_\_\_\_\_

(proposed by applicant)

Intended Population: Patients three months of age and older

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**1. EXECUTIVE SUMMARY****1.1 Recommendation on Regulatory Action**

This reviewer recommends approval of Locoid® lotion<sup>1</sup> for the treatment of mild-to-moderate atopic dermatitis, with revisions to the applicant's proposed labeling.

**1.2 Recommendation on Postmarketing Actions****1.2.1 Risk Management Activity**

This reviewer recommends that the applicant be required, for one year following approval, to submit quarterly reports detailing adverse events (AEs) possibly related to photosafety. These recommendations result from a potential phototoxicity signal seen in a photoallergenicity study of Locoid® lotion.

**1.2.2 Required Phase 4 Commitments**

This reviewer recommends that the applicant be required to conduct the following studies: (1) carcinogenicity study, as per pharm/tox review team recommendations; and (2) as discussed in EOP2 and pre-NDA meetings, studies to fulfill ICH E1a guidelines for numbers of subjects exposed for long-term safety. These studies should include 300 and 100 subjects between 3 months and 18 years of age with atopic dermatitis using Locoid® 0.1% lotion twice daily for six and 12 months, respectively, and should assess endpoints including adrenal suppression, effects on growth, topical steroid-specific AEs, and development of skin malignancies.

**1.2.3 Other Phase 4 Requests**

No other phase 4 requests were deemed necessary.

**1.3 Summary of Clinical Findings**

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<sup>1</sup> Note: The nomenclature of the formulation of this product is still under discussion (see section 3.1, which includes a comment from this reviewer on dosage form nomenclature issues for this product). In this review, this product is referred to as "lotion," although a final determination regarding appropriate nomenclature is pending and the "lotion" designation may change.

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#### 1.3.1 Brief Overview of Clinical Program

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 because (1) atopic dermatitis is largely a pediatric disease and (2) the study included subjects with eczema, which may or may not be due to atopic dermatitis. 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.

#### 1.3.2 Efficacy

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.

#### 1.3.3 Safety

In two phase 3 studies, AEs observed did not raise significant safety concerns with four weeks of twice daily use.

In four phase 1 dermal safety studies (primary irritancy, cumulative irritancy, contact sensitization, and photoallergenicity), there were no concerning signals for irritancy or contact sensitization. One subject in the photoallergenicity study experienced a possible reaction to Locoid® lotion (but not vehicle lotion). Absorption spectrum data subsequently submitted to the Agency and reviewed by the pharm/tox review team demonstrated no significant absorption by the drug product in the range of \_\_\_\_\_ In this reviewer's opinion, these data, combined with extensive clinical experience with other Locoid® formulations that does not indicate any issues surrounding photosafety, suggest that the probability of true photosafety concerns with Locoid® lotion is minimal. This small probability can be addressed by requiring (for one year after approval) quarterly reporting of potential photosafety reactions in the postmarketing phase. b(4)

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.

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#### 1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is twice daily topical use for no longer than four weeks in patients three months of age or older.

#### 1.3.5 Drug-Drug Interactions

No drug-drug interactions were studied, and none were deemed necessary.

#### 1.3.6 Special Populations

Subjects less than three months of age were not studied in the clinical development program. Because age correlates with volume-to-mass ratio, children may be more susceptible to systemic toxicity, including HPA axis suppression, than adults. Labeling for Locoid® 0.1% lotion should include precautions regarding the risk of systemic absorption of topical corticosteroids in young patients, similar to the labeling that accompanies other approved topical corticosteroids, and should include that safety and efficacy had not been demonstrated for patients less than 3 months of age.

## 2. INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The product is an \_\_\_\_\_ formulation containing 0.1% hydrocortisone butyrate as the active ingredient. The established name is hydrocortisone butyrate. The proposed trade name is Locoid® lotion. Hydrocortisone butyrate is currently marketed in other 0.1% formulations, including Locoid® solution, cream, and ointment, and Locoid Lipocream®. The pharmacological class is topical corticosteroid. The proposed indication is \_\_\_\_\_

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\_\_\_\_\_” The frequency of dosing used in phase 3 trials was twice daily.

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### 2.2 Currently Available Treatment for Indications

Multiple therapies and other approaches are currently used to treat atopic dermatitis, including bathing and emollients; avoidance of irritant and allergic triggers, topical corticosteroids in cream, foam, gel, lotion, and ointment formulations, topical calcineurin inhibitors in cream and ointment formulations, oral antihistamines, systemic anti-inflammatory agents (including oral corticosteroids), and ultraviolet light (Eczematous eruptions in childhood. In: Paller AS, Mancini AJ, editors. Hurwitz Clinical Pediatric Dermatology. Philadelphia: Elsevier Saunders; 2006. p.49-84). Of note, lotion formulations are often favored for use in the pediatric population, due to ease of application and coating of the affected area (Strober BE, Washenik K, Shupack JL. Principles of Topical Therapy. In: Freedberg IM, Eisen AZ, Wolff, et al., editors: Fitzpatrick's

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Dermatology in General Medicine, 6<sup>th</sup> ed. New York: McGraw-Hill; 2003. p. 2319-23.).

**2.3 Availability of Proposed Active Ingredient in the United States**

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.” There have been no major safety concerns or labeling changes with other Locoid® formulations and no discontinuations for safety or marketing reasons.

Of note, the original intended indication in the clinical development program was \_\_\_\_\_

This indication is typically supported by one study each in atopic dermatitis \_\_\_\_\_  
However, for reasons discussed in section 2.5, the sponsor proposed changing the indication to atopic dermatitis during a 1/20/04 Guidance Meeting. \_\_\_\_\_

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**2.4 Important Issues With Pharmacologically Related Products**

Systemic adverse effects of topical corticosteroids are rarely seen but include Cushing’s syndrome, hyperglycemia, osteopathy, adrenocortical suppression, decreased growth rate, edema, hypocalcemia, hypertension, posterior subcapsular cataracts, and glaucoma. More frequently experienced local adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura, and less frequently experienced adverse effects include hypertrichosis, pigmentary alterations, delayed wound healing, exacerbation of skin infections, and contact sensitization reactions (Hengge UR, et al. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 2006;54:-15).

**2.5 Presubmission Regulatory Activity**

The IND (64,845) was initially submitted 5/21/02, with the intended indication \_\_\_\_\_

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The following focuses on important clinical issues discussed during the pre-marketing phase:

**Guidance Meeting (1/20/04):**

1. Adrenal suppression data required in NDA.
2. Applicability of “eczema” subjects in Study 03-074 for a corticosteroid-responsive dermatosis indication is not clear, and atopic dermatitis is primarily a pediatric disease, rendering 03-074 supportive but not pivotal.
3. Outstanding biostatistical issues with study 03-074 (definition of success as a 1-

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point, not 2-point, change; imputing success at study end for subjects cleared at day 14; lack of clear a priori statistical analysis plan; concerns regarding pooling and potential for results at an extreme site to drive efficacy results).

Additionally, during discussion at this meeting regarding issues surrounding the acceptability of 03-074 and the need for pediatric studies in atopic dermatitis, the sponsor proposed seeking an indication only for atopic dermatitis, rather than \_\_\_\_\_ as originally intended. Limiting the clinical development program to atopic dermatitis was deemed acceptable by the Agency during the EOP2 meeting, described below.

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**End of phase 2 (EOP2) meeting (3/29/04):**

1. Design of Study 04-103 is suitable for indication of atopic dermatitis \ \_\_\_\_\_
2. Adequate number of subjects with moderate atopic dermatitis is necessary to support mild-to-moderate atopic dermatitis indication
3. Adequate number of 3-month-old to 2-year-old subjects is necessary
4. Dosing should be twice daily. All subjects should be assessed at study end (Day 28)
5. Global assessment scale should be used as primary endpoint.
6. Protocol 04-103 may be adequate as the sole phase 3 superiority study if results are robust and convincing with regard to efficacy
7. Adrenal suppression testing should involve 3-month-old to 18-year-old subjects
8. ICH E1A issues can be addressed as a post-marketing commitment

b(4)

**Pre-NDA meeting (1/5/06):**

1. Data regarding photoabsorption spectrum should be submitted to the NDA
2. Long-term safety(ICH E1a concerns) may be addressed as a post-marketing study
3. Clinical studies appear adequate to support NDA filing.

Dosage form nomenclature, including specifications for dosage forms, was not a subject of sponsor-Agency discussions until after the NDA was submitted.

**2.6 Other Relevant Background Information**

No other background information was reviewed.

**3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

**3.1 CMC (and Product Microbiology, if Applicable)**

A complete CMC review is pending as of 4/24/07. The CMC review team has expressed

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concerns regarding the following issues during the course of the review:

1. Dosage form nomenclature. Per definitions set forth in the CDER Data Standards Manual (<http://www.fda.gov/cder/dsm/DRG/drg00201.htm>), the product is more appropriately classified as a cream, rather than a lotion, formulation, according to the CMC review team. As noted in section 2.5, dosage form nomenclature, including specifications for dosage forms, was not a subject of sponsor-Agency discussions until after the NDA was submitted.

*Reviewer comment: Formulations of topical drug products matter to physicians and, therefore, to patients. Physicians are trained to consider dosage formulation in making prescribing decisions. For example, in a chapter entitled "Principles of Topical Therapy" in a major American dermatology textbook, the authors state as follows (emphasis added):*

*After correctly diagnosing a cutaneous disease, the dermatologist must consider a myriad of options in formulating an effective treatment plan. Sensible topical drug therapy involves not only the selection of an appropriate agent, but also a thoughtful consideration of the areas of the body affected, the state of the diseased skin, the concentration of the drug in a suitable vehicle (i.e., ointment, cream, lotion, etc.), the method of application, and a defined duration of use that both maximized efficacy and minimizes adverse side effects. Behind each of the aforementioned considerations are basic principles that help guide the practitioner toward a rational plan of therapy (Strober BE, et al., 2003).*

*The authors state the following regarding the clinical utility of cream formulations (to which they also refer as water-in-oil emulsions): "Water-in-oil emulsions are less greasy, spread easily on the skin, and provide a protective film of oil that remains on the skin as an emollient, while the slow evaporation of the water phase provides a cooling effect" (Strober BE, et al., 2003).*

*By contrast, the authors state the following regarding the clinical utility of lotion formulations (to which they also refer as suspensions) (emphasis added): "The applied lotion leaves the skin feeling cooler via evaporation of the aqueous component. Lotions are easier to apply and allow for uniform coating of the affected area, and are often the favorite preparation in treating children" (Strober BE, et al., 2003). Of note, atopic dermatitis primarily affects the pediatric population, which might be adversely affected by the labeling of a non-lotion formulation as a lotion.*

*Other widely used dermatology textbooks also note the importance of formulation in prescribing topical drug products, including the greater utility of lotions and creams in treating hairy and hairless areas, respectively (Warner M, Camisa C. Topical Corticosteroids. In: Wolverton SE, editor. Comprehensive Dermatologic Drug Therapy. Philadelphia: W.B. Saunders Company; 2001. p. 548-77; Lipsker D, Kragballe K, Fogh K, Saurat J-H. Other Topical Medications. In: Bologna JL, Jorizzo JL, Rapini RP. Dermatology. London: Mosby; 2003. p. 2055-70.).*

*Of note, however, the dermatology textbooks cited above do not provide technical definitions of dosage formulations. In this reviewer's experience, dosage forms are understood by clinicians by gestalt interpretations with some gradations (e.g., "thin" vs. "thick" creams) rather than by technically rigorous specifications. Inconsistent*

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*application of dosage form nomenclature to products currently on the market may make the "correct" dosage form of this product a matter of debate among clinicians. In this reviewer's opinion, to help resolve such debates and to ensure that physicians are best able to prescribe the most appropriate dosage form for their patients, it would be generally clinically advantageous for topical products (including this one) to be correctly classified in a standard nomenclature, to the extent that regulatory authority allows doing so.*

2. Particle size distribution. There are concerns with the methods used to perform this assay.
3. Homogeneity. There is a concern that homogeneity testing, including testing for particle size distribution, be included in the bulk batch testing protocol.

Please see the CMC review for a full discussion of these issues.

**3.2 Animal Pharmacology/Toxicology**

The pharmacology/toxicology reviewer has deemed the NDA approvable from a pharmacological/toxicological perspective, with approval conditional on the applicant's agreement to (1) conduct a dermal carcinogenicity study with Locoid® lotion as a phase 4 commitment, and (2) changes in the proposed labeling.

**4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY****4.1 Sources of Clinical Data**

The only sources of clinical data reviewed were those submitted as part of the NDA application.

**4.2 Tables of Clinical Studies**

Clinical studies conducted to support this NDA are shown below:

**Table 1. Clinical studies conducted to support NDA 22-076 (Locoid® lotion)**

Study number	Title	Subjects enrolled
<b>Phase 1 studies</b>		
<i>Dermal safety studies</i>		
01-029	Human repeated insult patch test	282
02-043	21-day cumulative irritation study	44
02-044	Primary irritation patch study in humans	15
04-108	A 6-week, randomized, controlled study to evaluate the potential of hydrocortisone butyrate lotion 0.1% to induce a photoallergic skin reaction in healthy volunteers, using a controlled photopatch test design	23

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<i>Vasoconstrictor studies</i>		
01-036	Vasoconstrictor study to rank the relative potency of hydrocortisone butyrate lotion 0.1% with respect to approved topical corticosteroid preparations in human volunteers	37
03-097	A randomized, blinded, single-center evaluation of the vasoconstrictive properties of 0.1% hydrocortisone butyrate lotion in normal healthy volunteers	36
Phase 2 study		
04-101	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	90
Phase 3 studies		
03-074	A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis or eczema in adults	301
04-103	A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate lotion 0.1% in the treatment of mild to moderate atopic dermatitis in pediatric subjects aged 3 months to less than 18 years	284

**4.3 Review Strategy**

All clinical studies submitted in the NDA were reviewed for safety. Both phase 3 studies were reviewed for efficacy as well as safety. Vasoconstrictor studies were reviewed for safety as well as potency.

**4.4 Data Quality and Integrity**

No issues were identified as part of the NDA review with the data quality and integrity.

**4.5 Compliance with Good Clinical Practices**

The studies were conducted in compliance with Good Clinical Practices.

**4.6 Financial Disclosures**

Financial disclosure was complete and did not raise any concerns.

**5. CLINICAL PHARMACOLOGY**

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### 5.1 Pharmacokinetics

Pharmacokinetic data were not collected as part of the clinical development program. Please see the clinical pharmacology review.

### 5.2 Pharmacodynamics

The draft clinical pharmacology review recommended approval of the NDA, with changes to labeling. Please also see this reviewer's reviews of the two vasoconstrictor studies in sections 10.1.8 and 10.1.9, below.

### 5.3 Exposure-Response Relationships

Exposure-response relationships were not assessed in this NDA.

## 6. INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The proposed indication is “

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#### 6.1.1 Methods

Efficacy and safety data from two phase 3 studies, 04-103 (pivotal) and 03-074 (supportive), were used to support the proposed indication. The clinical rationale for considering study 03-074 supportive is discussed in section 1.3.1, above.

#### 6.1.2 General Discussion of Endpoints

##### Study 04-103

The primary efficacy endpoint defined success as a score corresponding to a PGA score of “clear” or “almost clear” and a reduction of at least two points from baseline PGA score. The PGA scale for study 04-103 was defined as follows:

**Table 2. PGA scale used in study 04-103**

Score	Category	Definition
0	Clear	No signs of inflammatory atopic dermatitis (AD)

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1	Almost clear	Faint, barely detectable erythema and/or trace residual elevation in limited areas; neither excoriation nor oozing/crusting are present
2	Mild	Light pink erythema and slightly perceptible elevation; excoriation, if present, is mild
3	Moderate	Dull red, clearly distinguishable erythema and clearly perceptible elevation but not extensive; excoriation or oozing/crusting, if present, are mild to moderate
4	Severe	Deep/dark red erythema, and marked and extensive elevation; excoriation and oozing/crusting are present

Source: Mod 5, Vol 10, Page 35

*Reviewer comment: An endpoint using this type of scale and this definition of success is one typically accepted by the Agency in atopic dermatitis studies, as discussed in the EOP2 Meeting and Guidance Meeting in 2004.*

The secondary endpoint was the change in pruritus score from baseline to Day 29. Pruritus was scored as follows:

**Table 3. Pruritus scale used in study 04-103**

Score	Category	Definition
0	None	None
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching/discomfort which is not disturbing sleep
3	Severe	Bothersome itching/scratching/discomfort which is disturbing sleep

Source: Mod 5, Vol 10, Page 38

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**Study 03-074**

The primary efficacy endpoint defined success as either:

1. A PGA score of 0 ("clear") or 1 ("just perceptible") on Days 14 and 21 (if achieved, treatment was discontinued and the subject discharged from the study); or
2. A PGA score of 0 or 1 at Day 28.

The PGA scale was defined as follows:

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**Table 4. PGA scale used in study 03-074**

Score	Category	Definition
0	Clear	No inflammatory signs of atopic dermatitis
1	Just perceptible	Just perceptible erythema, and just perceptible infiltration/population
2	Mild	Mild erythema, and mild population/infiltration
3	Moderate	Moderate erythema, and moderate population/infiltration
4	Marked	More pronounced erythema, and more pronounced population/infiltration
5	Severe	Severe erythema, and severe population/infiltration
6	Extreme	Severe erythema, and severe population/infiltration with oozing/crusting

Source: Mod 5, Vol 3, Page 38

*Reviewer comment: This definition of success deviates from the typical definition accepted by the Agency in that it does not require a reduction of at least two points from baseline. This preference for defining success (0 or 1 and 2-point reduction) for study 03-074 was communicated to the sponsor at the 1/20/04 Guidance Meeting. Additionally, variable assessment (i.e., at week 3 or 4) was raised as a potentially problematic biostatistical issue at the Guidance Meeting on 1/20/04, and resolution of this issue did not occur in the EOP2 meeting on 3/29/04. This issue further adds to clinical issues regarding this study discussed above (i.e., the inclusion of "eczema" patients and the study of adult patients in a primarily pediatric disease), giving more support to the Agency's consideration of 03-074 as a supportive rather than pivotal study. Additionally, it is noted that data on a pruritus endpoint collected in this study was not formally analyzed statistically by the applicant, nor was a formal statistical analysis for this endpoint pre-specified in the protocol*

**6.1.3 Study Design**

Study 04-103 was a randomized, double-blind study of Locoid® lotion and vehicle in subjects with atopic dermatitis. Subjects ages 3 months to 18 years with mild to moderate atopic dermatitis (Physician's Global Assessment [PGA] score 2 or 3) affecting at least 10% BSA were enrolled. Randomization was 1:1 for Locoid® and vehicle lotions. The study enrolled 284 subjects (139 in the Locoid® lotion group, 145 in the vehicle lotion group) at 15 centers in the USA. Subjects applied study medication to affected areas twice daily for up to four weeks. In the event that a subject's PGA score was 0 at Day 22, treatment was discontinued and the subject scheduled to return on Day 29 for final assessment.

Study 03-074 was also a randomized, double-blind study of Locoid® and vehicle lotions. It enrolled adult subjects (ages 18 years or older) with mild to moderate atopic dermatitis or eczema (PGA score  $\geq 2$ ). There was no minimal BSA requirement. Randomization was 1:1 for Locoid® and vehicle lotions. Of 301 enrolled subjects, 151 were treated with Locoid® lotion and 150 were treated with vehicle lotion. Subjects applied study medication twice

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daily for either three or four weeks. If a subject had a PGA score of 0 at both Day 14 and Day 21 visits, then treatment was discontinued and this visit was the final visit. Subjects applied study medication to affected areas twice daily for up to four weeks; otherwise, treatment continued until the final visit and assessment at Day 28. Efficacy endpoints assessed at the Day 28 visit included PGA score, pruritus, signs of atopic dermatitis overall and by body region, and BSA involvement.

**6.1.4 Efficacy Findings**

Study 04-103

The primary-endpoint efficacy analysis for study 04-103 is shown below.

**Table 5. Study 04-103: primary efficacy endpoint, ITT analysis**

	<b>Locoid® lotion (n=139)</b>	<b>Vehicle (n=145)</b>	<b>p-value<sup>a</sup></b>
Number (%) successes	68 (49%)	35 (24%)	<0.0001

<sup>a</sup> Calculated using CMH test, stratified by pooled sites

Source: FDA biostatistical review

According to the biostatistical review, two sensitivity analyses using different methods of imputing missing data as well as a per-protocol analysis demonstrated a statistically significant difference in favor of Locoid® lotion. Efficacy results over time tended to favor Locoid® lotion, and the success rate of both arms appeared relatively consistent across pooled sites.

*Reviewer comment; Based on these analysis, this study demonstrated the clinical and statistical superiority of Locoid® lotion over vehicle lotion when used twice daily for four weeks in pediatric subjects with mild to moderate atopic dermatitis.*

Primary-endpoint efficacy analyses by subgroups – including gender, race, and age, and baseline disease severity – were consistent with the overall findings favoring Locoid® lotion over vehicle, as discussed in the review of the study report in section 10.1.1, below.

The secondary-endpoint efficacy analysis for study 04-103 is shown below.

**Table 6. Study 04-103: secondary endpoint (change from baseline in pruritus), ITT**

<b>Change from baseline</b>	<b>Locoid® lotion (n=139)</b>	<b>Vehicle (n=145)</b>	<b>p-value<sup>a</sup></b>
-2	1 (<1%)	1 (<1%)	<0.001
-1	1 (<1%)	12 (8%)	
0	25 (18%)	50 (34%)	
1	43 (31%)	48 (33%)	
2	56 (40%)	29 (20%)	
3	13 (9%)	5 (3%)	

<sup>a</sup> Calculated using CMH test

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Source: FDA biostatistical review

According to the biostatistical review, a statistically similar result, also favoring Locoid® lotion, was obtained with analysis of these data using an analysis of variance model (mean[SD] in Locoid® lotion arm 1.37 [0.96] vs 0.74 [1.01] in vehicle arm,  $p < 0.0001$ ).

*Reviewer comment: For reasons discussed above, in this reviewer's opinion these pruritus data have limited regulatory utility and should not be included in product labeling.*

### Study 03-074

The primary efficacy analysis for study 03-074 is shown below.

**Table 7. Study 03-074: primary efficacy endpoint, ITT**

	<b>Locoid® lotion (n=151)</b>	<b>Vehicle (n=150)</b>	<b>p-value<sup>a</sup></b>
Number (%) successes	84 (56%)	49 (33%)	<0.0001

<sup>a</sup> Calculated using CMH test, stratified by pooled sites

Source: FDA biostatistical review

According to the biostatistical review, three sensitivity analyses were performed, including one that required at least a 2-point reduction from baseline PGA score as part of the definition of success. The other two sensitivity analyses each used a different method to imputed missing observations at Day 28. All three sensitivity analyses demonstrated statistically significant superiority of Locoid® lotion over vehicle. Results were also consistent across study centers.

*Reviewer comment: These findings support the results of the pivotal study, 04-103.*

### 6.1.5 Clinical Microbiology

Not applicable.

### 6.1.6 Efficacy Conclusions

The pivotal phase 3 study, 04-103, demonstrated that Locoid® lotion, used by pediatric subjects with atopic dermatitis ages 3 months to 18 years twice daily for four weeks, was clinically and statistically significantly superior to vehicle lotion. Results of study 03-074 support this finding.

## 7. INTEGRATED REVIEW OF SAFETY

## Clinical Review

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## 7.1 Methods and Findings

### 7.1.1 Deaths

There were no deaths.

### 7.1.2 Other Serious Adverse Events

#### Study 04-103

There was one serious AE (SAE) in the vehicle arm (n=145, 0.7%). A 1.47-year-old boy was discontinued from the study on Day 14 due to lack of efficacy. He was provided alternate therapy for atopic dermatitis. One week later he presented at a local health facility with acute eczema exacerbation of moderate intensity. The event resolved three days later. The applicant considered the relationship to study drug unassessable.

*Reviewer comment: This reviewer concurs that the relationship is unassessable.*

#### Study 03-074

There were two SAEs, one each in the active (n=151; 0.7%) and vehicle (n=150, 0.7%) arms. The sponsor considered neither to be related to the study drug. In one, a 69-year-old man randomized to vehicle lotion was admitted to a hospital on Day 27 with acute gallbladder disease. He underwent a cholecystectomy and subsequently returned to complete the study. In the other, a 70-year-old woman randomized to receive Locoid® lotion was admitted to a hospital on Day 21 with acute bronchitis. She was discharged after six days but did not return to the study.

*Reviewer comment: In this reviewer's opinion, it is unlikely that these SAEs were related to vehicle or Locoid® lotion, respectively.*

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

The overall profile of dropouts is shown below for studies 04-103, 03-074, and 04-101.

**Table 8. Study 04-103 – dropout profile**

	Locoid® lotion	Vehicle	Total
Number of subjects	139	145	284
Number completed	132	120	252
Number prematurely discontinued	7 (5.0%)	25 (17.2%)	32 (11.3%)
Reason for premature discontinuation			
Subject request	2	7	9

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Subject non-compliance	0	0	0
Lost to follow-up	5	5	10
Lack of efficacy	0	6	6
Adverse event	0	5	5
Other <sup>a</sup>	0	2	2

<sup>a</sup>In the vehicle group, one subject was discontinued after being removed from the care of her mother by social services, and one withdrew consent due to family problems.

Source: Table 10.1.2, mod 5, vol 10, page 48

**Table 9. Study 03-074 – dropout profile**

	Locoid® lotion	Vehicle	Total
Number of subjects	151	150	301
Number completed	136	116	252
Number prematurely discontinued	15 (9.9%)	34 (22.7%)	49 (16.3%)
Reason for premature discontinuation			
Subject request	2	10	12
Subject non-compliance	0	1	1
Lost to follow-up	8	9	17
Lack of efficacy	0	8	8
Adverse event	2	4	6
Other <sup>a</sup>	3	2	5

<sup>a</sup>In the Locoid® group, two subjects did not meet inclusion criterion #4 (PGA≥2), one had recurring cellulitis. In the vehicle group, one subject took an exclusionary medication and one had conflicts with work schedules.

Source: Table 10.1.2, mod 5, vol 3, page 52

**Table 10. Study 04-101 – dropout profile**

	Locoid® lotion
Number of subjects	90
Number completed	83
Number prematurely discontinued	7 (8.4%)
Reason for premature discontinuation	
Subject request	0
Subject non-compliance	0
Lost to follow-up	1
Lack of efficacy	0
Adverse event	0
Other <sup>a</sup>	6

<sup>a</sup>Three subjects were screen failures due to post-stimulation cortisol values. One subject required use of excluded medications. Two subjects did not have Cosyntropin® tests done due to unsuccessful blood draw attempts.

Source: Table 10.1.2, mod 5, vol 20, page 40

*Reviewer comment: In both phase 3 studies a higher percentage of subjects in the vehicle arm discontinued prematurely. Compared to the Locoid® lotion arm, the numbers of discontinuations in both studies due to subject request, lack of efficacy and AEs were*

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*higher in the vehicle arm. The number lost to follow-up was the same in each arm in study 04-103 and was one greater in the vehicle-treated arm in study 03-074. Dropouts were not related to AEs or lack of efficacy in study 04-101. In summary, these data do not suggest significant safety concerns.*

#### 7.1.3.2 Adverse events associated with dropouts

##### Study 04-103

There were no subjects in the Locoid® arm and five in the vehicle arm who discontinued prematurely due to application-site-related AEs, as follows:

- A 9.8 year old girl was discontinued after five days due to a rash on the back, arms, and legs.
- A 4.4-year-old boy was discontinued after 21 days due to burning.
- A 1.0-year-old boy was discontinued after seven days due to persistent erythema in application areas.
- A 2.1-year-old boy was discontinued after 10 days due to itching and stinging.
- An 11.7-year-old girl was discontinued after three days due to itching and burning.

*Reviewer comment: In this reviewer's opinion, the most likely cause of these events is undertreated atopic dermatitis.*

##### Study 03-074

There were two subjects in the Locoid® arm who discontinued prematurely due to an adverse event, as follows:

- A 21-year-old woman (#118) had a positive pregnancy test.
- A 70-year-old woman (#397) developed acute bronchitis, for which she was hospitalized. This serious adverse event is also described above.

*Reviewer comment: In this reviewer's opinion it is unlikely that either of these AEs was related to the study drug.*

There were four subjects in the vehicle arm who discontinued prematurely due to AEs, as follows:

- A 24-year-old man (#122) developed worsening pruritus.
- A 68-year-old man (#123) developed tinea.
- A 53-year-old woman (#153) experienced an eczema flare at the application site.
- A 20-year-old woman (#322) developed urticaria.

*Reviewer comment: In this reviewer's opinion, the most likely cause of the pruritus and eczema flare is undertreated atopic dermatitis, and it is unlikely that tinea or hives were related to the study drug vehicle.*

##### Study 04-101

There were no dropouts associated with AEs.

#### 7.1.3.3 Other significant adverse events

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Numbers of AEs reported, Numbers of subjects reporting one or more AEs, and the relationship of AEs to clinical trial materials for studies 04-103, 03-074, and 04-101 are shown below.

**Table 11. AEs in study 04-103, 03-074, and 04-101**

	Study 04-103		Study 03-074		Study 04-101
	Locoid® (n=139)	Vehicle (n=145)	Locoid® (n=151)	Vehicle (n=150)	Locoid® (n=90)
Number of events reported	69	85	38	52	59
Number of subjects reporting ≥1 adverse event	48 (35%)	56 (39%)	27(18%)	34 (23%)	31 (37%)
Relationship to study drug					
Unassessable	3 (4%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
None	61 (88%)	62 (73%)	34 (89%)	46 (88%)	44 (75%)
Possible	5 (7%)	6 (7%)	2 (5%)	6 (12%)	2 (3%)
Probable	0 (0%)	7 (8%)	2 (5%)	0 (0%)	9 (15%)
Certain	0 (0%)	9 (11%)	0 (0%)	0 (0%)	4 (7%)

**Study 04-103**

In study 04-103, AEs possibly related to Locoid® included application site burning (n=1), application site pruritus (n=1), and acne infantile (n=1).

*Reviewer comment: In applicant's Table 14.5.3.3, Mod 5, Vol 10, Page 141, some of these events appear to be double-counted, with the system organ class (SOC) heading and the preferred term for a single event each being counted.*

AEs possibly related to the vehicle included application site burning (n=1), application site dermatitis (n=2), application site folliculitis (n=1), diarrhea (n=1), and generalized rash (n=1). AEs probably related to vehicle included application site burning (n=1), application site pruritus (n=3), application site erythema (n=2), and application site inflammation (n=1). AEs certainly related to vehicle included application site burning (n=6), application site pruritus (n=2), and application site irritation (n=1).

**Study 03-074**

AEs possibly related to Locoid® lotion included application site burning (n=2). AEs probably related included application site burning (n=2).

AEs possibly related to vehicle include application site dermatitis/eczema (n=2), application site pruritus (n=2), acne (n=1), and urticaria (n=1).

**Study 04-101**

AEs possibly related to Locoid® include application site burning (n=2). AEs probably related include adrenal suppression (n=4) and application site burning (n=5).

*Reviewer comment: Application site-related AEs are discussed in section 7.1.4, below.*

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### 7.1.4 Other Search Strategies

This reviewer sought to identify all application site-related AEs in phase 3 studies, regardless of the applicant's assessment of causality. This was done by summing the number of relevant AEs that were listed in summary tables under the SOC term "general disorders and administration site conditions." Relevant AEs under this SOC included preferred terms beginning with the words "application site" and followed by any of the following: "burning," "pruritus," "dermatitis," "erythema," "eczema," "inflammation," or "irritation." The results are as follows:

**Table 12. Application site-related AEs in phase 3 studies**

	Study 04-103		Study 03-074		Studies 04-103 and 03-074 combined	
	Locoid® lotion (n=139)	Vehicle (n=145)	Locoid® lotion (n=151)	Vehicle (n=150)	Locoid® lotion (n=290)	Vehicle (n=295)
Number of application site-related AEs (%)	2 (1.4%)	20 (13.8%)	5 (3.3%)	7 (4.7%)	7 (2.4%)	27 (9.2%)

Sources: Table 14.5.3.1, Mod 5, Vol 10, Page 134; Table 14.3.2.1, Mod 5, Vol 3, Page 138

*Reviewer's comment: These data could be summarized in the package insert. For application site-related AEs, there were numerically fewer in the Locoid® lotion group and numerically more in the vehicle group in the pediatric study compared to the adult study. The reason for this difference is not clear. The proportion of these events is higher in the vehicle compared to Locoid® lotion arm in both studies, possibly because (1) an AE might actually represent persistence or worsening of disease in the vehicle group, which was "undertreated" for atopic dermatitis, and/or (2) the hydrocortisone butyrate in the Locoid® arm could have treated some of these AEs, rendering them subclinical.*

### 7.1.5 Common Adverse Events

#### 7.1.5.1 Eliciting adverse events data in the development program

In phase 2 and 3 studies, at each visit investigators asked a subject (or parent/guardian) a non-specific question (e.g., 'Have you noticed any change in your medical condition since your last visit?') There were four, three or four, and three weekly visits for each subject after a baseline visit in studies 04-103, 03-074, and 04-101, respectively.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse event categorization and preferred terms were appropriate. MedDRA classification was used.

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NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

**7.1.5.3 Incidence of common adverse events**

Common AEs, defined as those occurring in  $\geq 1\%$  of exposed subjects, included AEs classified under the SOC heading “general disorders and administration site conditions” (discussed in section 7.1.4), “infections and infestations,” “respiratory, thoracic and mediastinal disorders,” “gastrointestinal disorders,” and “skin and subcutaneous tissue disorders.” AEs under SOC headings besides the “general disorders and administration site conditions” represent relatively common events, particularly in a pediatric population, for which a background rate such as that seen in the study might be expected.

*Reviewer comment: These data do not suggest a signal for a common adverse event of Locoid® lotion. Of note, none of the well-described side effects of topical corticosteroids (see section 2.4) were noted in these studies, though a 4-week course may be too brief for these to develop. Additionally, these phase 3 studies did not assess laboratory evidence of adrenal suppression, investigated in study 04-101.*

**7.1.5.4 Common adverse event tables**

The following tables show AEs occurring at rates of 5% or more for a SOC term or preferred term in either study arm in phase 3 studies.

**Table 13. Study 04-103: Common AEs (rate  $\geq 5\%$ ), ITT**

Adverse event	Locoid® (n=139)	Vehicle (n=145)
General disorders and administration site conditions	7 (5%)	25 (17%)
Application site burning	1 (1%)	8 (6%)
Pyrexia	5 (4%)	7 (5%)
Infections and infestations	25 (18%)	22 (15%)
Nasopharyngitis	7 (5%)	9 (6%)
Respiratory, thoracic and mediastinal disorders	8 (6%)	12 (8%)

Source: Table 14.5.3.1, Mod 5, Vol 10, page 132-4.

**Table 14. Study 03-074: Common AEs (rate  $\geq 5\%$ ), ITT**

Adverse event	Locoid® (n=151)	Vehicle (n=150)
General disorders and administration site conditions	7 (5%)	6 (4%)
Infections and infestations	14 (9%)	13 (9%)

Source: Table 14.3.2.1, Mod 5, Vol 3, page 137-9.

**Table 15. Pooled phase 3 studies (04-103 and 03-074): Common AEs (rate  $\geq 5\%$ ), ITT**

Adverse event	Locoid® (n=290)	Vehicle (n=295)
General disorders and administration site conditions	14 (5%)	31 (11%)
Respiratory, thoracic and mediastinal disorders	10 (3%)	15 (5%)
Infections and infestations	39 (13%)	35 (12%)

Source: Mod 5, Vol 26, page 16-7

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Locoid lotion (hydrocortisone butyrate 0.1% lotion)

*Reviewer comment: See section 7.1.4 for a discussion of general disorders and administration site conditions, including application site reactions. All other common AEs are consistent with background rates that would be expected in pediatric and adult populations. Of note, phase 3 studies did not assess HPA axis suppression, which is discussed below.*

The following tables show AEs occurring at rates of 1% or more (and >1 subject) for a SOC term or preferred term in either study arm.

**Table 16. Study 04-103: AEs with rate  $\geq$  1% and >1 subject, ITT**

Adverse event	Active (n=139)	Vehicle (n=145)
General disorders and administration site conditions	7 (5%)	25 (17%)
Application site burning	1 (1%)	8 (6%)
Pyrexia	5 (4%)	7 (5%)
Application site pruritus	1 (1%)	5 (3%)
Application site dermatitis	0 (0%)	2 (1%)
Application site erythema	0 (0%)	2 (1%)
Infections and infestations	25 (18%)	22 (15%)
Nasopharyngitis	7 (5%)	9 (6%)
Upper respiratory tract infection	6 (4%)	4 (3%)
Croup infectious	0 (0%)	2 (1%)
Ear infection	4 (3%)	1 (1%)
Gastroenteritis viral	3 (2%)	1 (1%)
Pharyngitis streptococcal	2 (1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	8 (6%)	12 (8%)
Cough	3 (2%)	4 (3%)
Nasal congestion	3 (2%)	4 (3%)
Pharyngolaryngeal pain	1 (1%)	3 (2%)
Sinus congestion	1 (1%)	2 (1%)
Rhinorrhea	2 (1%)	1 (1%)
Gastrointestinal disorders	5 (4%)	6 (4%)
Diarrhea	2 (1%)	2 (1%)
Teething	2 (1%)	2 (1%)
Vomiting	1 (1%)	2 (1%)
Skin and subcutaneous tissue disorders	5 (4%)	4 (3%)
Rash	0 (0%)	2 (1%)
Urticaria	2 (1%)	1 (1%)

Source: Table 14.5.3.1, Mod 5, Vol 10, page 132-4.

*Reviewer comment: Of note, infantile acne and skin depigmentation were each reported by one subject in the active arm (1% for each reaction) and no subjects in the vehicle arm in this study. In this reviewer's opinion, these reactions could be related to Locoid® lotion.*

**Table 17. Study 03-074: AEs with rate  $\geq$  1% and >1 subject, ITT**

Adverse event	Active (n=151)	Vehicle (n=150)
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Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

General disorders and administration site conditions	7 (5%)	6 (4%)
Application site burning	4 (3%)	0 (0%)
Application site dermatitis	0 (0%)	2 (1%)
Application site eczema	0 (0%)	2 (1%)
Application site pruritus	1 (1%)	2 (1%)
Infections and infestations	14 (9%)	13 (9%)
Influenza	1 (1%)	3 (2%)
Nasopharyngitis	6 (4%)	4 (3%)
Injury, poisoning and procedural complications	2 (1%)	2 (1%)
Musculoskeletal and connective tissue disorders	4 (3%)	4 (3%)
Nervous system disorders	2 (1%)	2 (1%)

Source: Table 14.3.2.1, Mod 5, Vol 3, page 137-9.

**Table 18. Pooled phase 3 studies (04-103 and 03-074): Common AEs (rate  $\geq$  1%), ITT**

Adverse event	Active (n=290)	Vehicle (n=295)
General disorders and administration site conditions	14 (5%)	31 (11%)
Application site burning	5 (2%)	8 (3%)
Pyrexia	5 (2%)	7 (2%)
Application site pruritus	2 (1%)	7 (2%)
Application site dermatitis	0 (0%)	4 (1%)
Application site erythema	0 (0%)	3 (1%)
Application site eczema	0 (0%)	3 (1%)
Skin and subcutaneous tissue disorders	5 (2%)	12 (4%)
Rash	0 (0%)	2 (1%)
Acne	0 (0%)	2 (1%)
Urticaria	2 (1%)	3 (1%)
Infections and infestations	39 (13%)	35 (12%)
Respiratory, thoracic and mediastinal disorders	10 (3%)	15 (5%)
Gastrointestinal disorders	6 (2%)	7 (2%)
Musculoskeletal and connective tissue disorders	4 (1%)	5 (2%)
Injury, poisoning and procedural complications	6 (2%)	5 (2%)

Source: Mod 5, Vol 26, page 16-7.

*Reviewer comment: In this reviewer's opinion, rates of these common AEs appear consistent with background rates that would be expected in pediatric and adult populations. Consistent with this interpretation, with the exception of rates of "general disorders and administration site conditions," which were more common in the vehicle arms, rates of other AE categories are roughly equivalent in the two arms!*

**7.1.5.5 Identifying common and drug-related adverse events**

AEs experienced by  $\geq$ 1% of subjects in pooled phase 3 trials are shown below, classified by applicant-assessed certainty of relationship with the study drug.

**Table 19. AEs of  $\geq$ 1% frequency – applicant-assessed relationship to study drug**

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NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

Adverse event	Number (%) of AEs assessed as possible, probable, or certain	
	Locoid® lotion (n=290)	Vehicle (n=295)
General disorders and administration site conditions	5 (1.7%)	19 (6.4%)
Application site burning	5 (1.7%)	8 (2.7%)
Application site pruritus	1 (0.3%)	6 (2.0%)
Application site dermatitis	0 (0%)	3 (1.0%)
Skin and subcutaneous tissue disorders	1 (<1%)	4 (1%)

Source: Mod 5, Vol 26, Page 18

*Reviewer comment: Rates of AEs classified under the “general disorders and administration site conditions” SOC were higher in the vehicle arm. However, as discussed above, this may reflect elements of disease being incorrectly assessed as AEs or irritation by vehicle that was treated by the hydrocortisone butyrate in Locoid® lotion.*

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were conducted.

7.1.6 Less Common Adverse Events

There were numerous other AEs that occurred in <1% and ≤1 subject. Of note, infantile acne and skin depigmentation were each reported by one subject in the active arm (1% for each reaction) and no subjects in the vehicle arm in the pediatric study (04-103). In this reviewer’s opinion, these reactions could be related to Locoid® lotion.

7.1.7 Laboratory Findings

~~7.1.7.1~~ Overview of laboratory testing in the development program

Laboratory testing was not done as part of phase 3 studies. Laboratory testing was done as part of the HPA axis suppression study, 04-101, which is discussed in section 7.1.12.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values  
Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data  
Not applicable.

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Locoid lotion (hydrocortisone butyrate 0.1% lotion)

*7.1.7.3.1 Analyses focused on measures of central tendency*

Not applicable.

*7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Not applicable.

*7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities*

Not applicable.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs before and after treatment were assessed in study 04-101, which is discussed in Section 7.1.12, below, and in study 03-074, discussed in this section. In study 04-103, vital signs were collected only prior to treatment.

*Reviewer comment: The major concern would be an excess number of subjects in the Locoid lotion arm who developed hypertension, which is a feature of Cushing's syndrome and, therefore, might represent a systemic effect of a topically applied corticosteroid.*

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Study 03-074, discussed in this section, was a vehicle-controlled study. Study 04-101, discussed in section 7.1.12, below, did not include a control group.

7.1.8.3 Standard analyses and explorations of vital signs data

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Locoid lotion (hydrocortisone butyrate 0.1% lotion)

**7.1.8.3.1 Analyses focused on measures of central tendencies**

Analyses of vital signs that focused on measures of central tendencies (e.g., means, standard deviations) were not performed. More relevant analyses – i.e., those that focus on individual subjects whose vital signs were out of normal ranges – are discussed below.

**7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal**

Vital sign data for subjects in study 03-074 are shown in Table 20.

**Table 20. Vital sign data from study 03-074, focusing on abnormal values, shifts from normal to abnormal, or shifts from abnormal to normal.**

		Active (n=151)		Vehicle (n=150)	
		#	% subjects	#	% subjects
<b>Systolic BP</b>					
Static during study	Low-low	0	0.0	0	0.0
	High-high	3	2.0	8	5.33
	Total	3	2.0	8	5.33
Changes during study	High-normal	6	4.0	10	6.7
	Normal-high	4	2.7	8	5.3
	Low-normal	0	0.0	0	0.0
	Normal-low	0	0.0	0	0.0
Total		10	6.6	18	12.0
<b>Diastolic BP</b>					
Static during study	Low-low	1	0.7	0	0.0
	High-high	0	0.0	1	0.7
	Total	1	0.7	1	0.7
Changes during study	High-normal	4	2.7	7	4.7
	Normal-high	5	3.3	4	2.7
	Low-normal	3	2.0	1	0.7
	Normal-low	0	0.0	3	2.0
Total		12	8.0	15	10.0
<b>Pulse</b>					
Static during study	Low-low	2	1.3	2	1.3
	High-high	1	0.7	1	0.7
	Total	3	2.0	3	2.0
Changes during study	High-normal	0	0.0	0	0.0
	Normal-high	1	0.7	1	0.7
	Low-normal	3	2.0	3	2.0
	Normal-low	3	2.0	3	2.0
Total		7	4.6	7	4.7
<b>Respiratory rate</b>					
Static during study	Low-low	0	0.0	0	0.0
	High-high	9	6.0	11	7.3

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		Total	9	6.0	11	7.3
Changes during study	High-normal	6	4.0	3	2.0	
	Normal-high	1	0.7	3	2.0	
	Low-normal	1	0.7	0	0.0	
	Normal-low	0	0.0	0	0.0	
		Total	8	5.3	6	4.0
<b>Temperature</b>						
Static during study	Low-low	17	11.3	28	18.7	
	High-high	0	0.0	0	0.0	
		Total	17	11.3	28	18.7
Changes during study	High-normal	1	0.7	1	0.7	
	Normal-high	0	0.0	1	0.7	
	Low-normal	24	15.9	27	18.0	
	Normal-low	24	15.9	25	16.7	
	High-low	2	1.3	0	0.0	
	Low-high	0	0.0	1	0.7	
		Total	51	33.8	55	36.7

Source: Table 2, Response to 2/21/07 Request for Information (stamp date 3/15/07)

*Reviewer comment: There do not appear to be excess numbers of subjects with persistent or new-onset hypertension in the Locoid lotion arm. Other vital sign abnormalities appear equally balanced, in general, between the two arms. In this reviewer's opinion, these findings are reassuring from a safety perspective.*

**7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities**

A line-by-line examination of data from subjects with abnormal vital signs, provided in Attachment A of the applicant's Response to 2/21/07 Request for Information (stamp date 3/15/07), did not suggest a concerning pattern of vital-sign outliers. There were no dropouts for vital sign abnormalities.

**7.1.8.4 Additional analyses and explorations**

Additional analyses and explorations were not performed.

**7.1.9 Electrocardiograms (ECGs)**

ECG testing was not performed in the clinical development program.

**7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results**

Not applicable.

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

*7.1.9.3.1 Analyses focused on measures of central tendency*

Not applicable.

*7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Not applicable.

*7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities*

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Immunogenicity was not assessed in the clinical development program and was not needed.

7.1.11 Human Carcinogenicity

Carcinogenicity was not assessed in the clinical development program and was not needed. As stated in section 1.2.2 (Required Phase 4 Commitments), this reviewer recommends that development of skin malignancies should be assessed as part of a required phase 4 commitment to study long-term clinical safety. Additionally, as stated in section 3.2 (Animal Pharmacology/Toxicology), the pharmacology/toxicology reviewer has recommended that a nonclinical dermal carcinogenicity study be conducted as a phase 4 commitment.

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#### 7.1.12 Special Safety Studies

Main findings of special safety studies are described below. Detailed discussion can be found in the review of individual study reports (section 10.1), below.

##### Study 01-129: Human repeated insult patch test study

This 3-week contact sensitization study was completed by 217 subjects

*Reviewer comment: There was no indication of contact sensitization from Locoid® lotion or vehicle, in this reviewer's opinion.*

##### Study 02-043: 21-day cumulative irritation study

Thirty-three subjects completed this study.

*Reviewer comment: There was no concerning irritation signal, in this reviewer's opinion.*

##### Study 02-044: Primary irritation patch study in humans

Eleven subjects completed this study.

*Reviewer comment: There was no concerning irritation signal, in this reviewer's opinion.*

##### Study 04-108: A 6-week, randomized, controlled study to evaluate the potential of hydrocortisone butyrate lotion 0.1% to induce a photoallergic skin reaction in healthy volunteers, using a controlled photopatch test design

This study was terminated early, after nonclinical data demonstrated that the drug product did not significantly absorb in the \_\_\_\_\_ The pharm/tox review team concurred with this interpretation of the data. However, of the 18 subjects completing the study prior to termination, one may have had a photosensitivity reaction to Locoid® lotion (but not to vehicle).

*Reviewer comment: Because of the negative absorption data and extensive clinical experience with other marketed Locoid® formulations, it is this reviewer's opinion that photosafety could be reasonably monitored in the post-marketing phase by requiring quarterly reports of possible photosensitivity reactions for one year following approval.*

##### Study 04-101: 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.

Of 82 subjects completing the study, seven (8.5%) developed laboratory evidence of adrenal suppression, which resolved in one month for six subjects and in two months for one subject.

*Reviewer comment: These data, discussed in detail below, should be included in product labeling.*

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

There have been no reports of abuse of the product in this clinical development program, and topical corticosteroids have no known potential for abuse.

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**7.1.14 Human Reproduction and Pregnancy Data**

No studies in pregnant women were performed as part of this clinical development program. Other Locoid® formulations are pregnancy class C.

**7.1.15 Assessment of Effect on Growth**

Assessment of effect on growth was not conducted in the clinical development program. Phase 3 studies lasted four weeks only.

*Reviewer comment: In this reviewer's opinion, assessment of effect on growth could be included in postmarketing studies necessary to fulfill ICH E1a guidelines on long-term safety.*

**7.1.16 Overdose Experience**

There were no reports of overdose during the clinical development program.

**7.1.17 Postmarketing Experience**

According to the applicant, Hydrocortisone butyrate was first approved for marketing in September 1970 in The Netherlands and Ireland and has been subsequently introduced in a variety of dosage forms in over 80 countries worldwide. No marketing authorizations have been withdrawn or suspended, except for marketing reasons. There have been no photosafety concerns regarding other Locoid® 0.1% formulations. A safety update covering 1/1/00 through 8/31/05 was prepared by the successor to the innovator company, Astellas Pharma Europe BV, which showed that over — patients were estimated to have been treated with one of the Locoid® dosage forms during this period. A total of 36 adverse experiences were reported worldwide during this period. There were no deaths. Most AEs related to application site reactions or other skin reactions. Non-skin-related serious AEs included three cases of clonus, three cases of erysipelas, two cases of wheezing, and one case each of dysphonia and hoarseness.

b(4)

*Reviewer comment: These data do not indicate a concerning safety signal.*

**7.2 Adequacy of Patient Exposure and Safety Assessments**

**7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

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NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

## 7.2.1.1 Study type and design/patient enumeration

A total of 1047 subjects had some exposure to Locoid® lotion, as shown below:

**Table 21. Subject exposure to study drug, by study type and duration**

Study	Title	# subjects	Dosing	Duration
<b>Phase 1</b>				
01-029	Human repeated insult patch test	217	9 48-hour applications	18 days
01-036	Vasoconstrictor study to rank the relative potency of hydrocortisone butyrate lotion 0.1% with respect to approved topical corticosteroid preparations in human volunteers	37	Single application	16 hours
03-097	A randomized, blinded, single-center evaluation of the vasoconstrictive properties of 0.1% hydrocortisone butyrate lotion in normal healthy volunteers	36	Single application	16 hours
02-043	21-day cumulative irritation study	44	24-hour applications	21 days
02-044	Primary irritation patch study in humans	15	24-hour applications	2 days
04-108	A 6-week, randomized, controlled study to evaluate the potential of hydrocortisone butyrate lotion 0.1% to induce a photoallergic skin reaction in healthy volunteers, using a controlled photopatch test design	23	Twice-weekly applications for three weeks; 10-17 day rest period; one-day application as challenge	6 weeks
<b>Phase 2</b>				
04-101	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	90	TID	29 days
<b>Phase 3</b>				
03-074	A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis or eczema in	301	BID	3-4 weeks

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Locoid lotion (hydrocortisone butyrate 0.1% lotion)

	adults			
04-103	A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate lotion 0.1% in the treatment of mild to moderate atopic dermatitis in pediatric subjects aged 3 months to less than 18 years	284	BID	3-4 weeks

Source: Mod 5, Vol 1, page 1-2.

*Reviewer comment: Adequacy of exposure is discussed below, in section 7.2.3.***7.2.1.2 Demographics**

In the pediatric study (04-103, ITT population, n=284), the subjects' mean age was 7.14 years (SD 5.2 years, range 0.3-17.8 years). Subjects 3 months of age to less than two years old comprised 21.4% of the total, while 25.4% were between two and six years old, 29.9% were between six and 12 years old, and 23.2% were between 12 and 18 years old. There were 143 males and 141 females. Racially, 65% were white, 32% black or African American, 5% Asian, 1% Native Hawaiian or Pacific Islander, and 1% American Indian or Alaska Native. Ethnically, 8% were Hispanic/Latino and 92% not Hispanic/Latino.

For the adult study (03-074, ITT population, n=301), the mean age of all subjects was 42.65 years (SD 15.9 years, range 18.1-86.2 years). There were 37% males and 63% females. Racially, 76% were white, 20% black or African American, 3% Asian, 0% Native Hawaiian or Pacific Islander, and 1% American Indian or Alaska Native. Ethnically, 13% were Hispanic/Latino and 87% not Hispanic/Latino.

**7.2.1.3 Extent of exposure (dose/duration)**

The planned extent of exposure in phase 3 studies was twice daily topical application for four weeks. In the HPA axis study, it was three times daily for four weeks.

**7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety****7.2.2.1 Other studies**

Not applicable.

**7.2.2.2 Postmarketing experience**

See section 7.1.17 for a discussion of postmarketing experience with other Locoid® formulations.

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7.2.2.3 Literature

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

In this reviewer's opinion, the overall clinical experience appears adequate to assess safety and effectiveness of short-term (i.e., four-week) treatment in subjects over 3 months of age. The overall clinical experience with hydrocortisone butyrate 0.1% lotion compared to guidelines set forth in ICH E1a is shown below.

**Table 22. Overall clinical experience with Locoid® lotion and ICH E1a guidelines**

Duration of exposure	Number of subjects recommended in ICH E1a guidelines	Number of subjects in clinical experience with Locoid® lotion (% of ICH E1a-recommended total)
6 months	300-600	0 (0%)
12 months	100	0 (0%)
"Short term"	1500	1047 <sup>a</sup>

<sup>a</sup> See section 7.2.1.1.

*Reviewer comment: As discussed in prior meetings with the applicant and as recommended by this reviewer in section 1.2.2., longer term studies (i.e., 6 and 12 months) should be conducted in the postmarketing phase. The safety and effectiveness of use for more than four weeks is not established, which should be reflected in product labeling.*

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal and in vitro testing was deemed adequate for marketing. Please see the pharmacology/toxicology review, which (this reviewer anticipates) will recommend a postmarketing carcinogenicity study.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was deemed adequate to assess short-term safety and efficacy.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

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Locoid lotion (hydrocortisone butyrate 0.1% lotion)

**7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study**

Not applicable.

**7.2.8 Assessment of Quality and Completeness of Data**

The data provided were complete and of adequate quality to conduct the safety review.

**7.2.9 Additional Submissions, Including Safety Update**

In a letter to the Agency dated 1/31/07, the applicant stated that no additional safety data have become available since the original NDA submission.

**7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

Clinical trial data support the safety of using Locoid® lotion in patients as young as 3 months who have mild to moderate atopic dermatitis. The most common treatment-related AEs included adrenal suppression and application-site reactions. An important limitation is that the clinical development program only studied use of Locoid® lotion up to four week's duration, whereas atopic dermatitis is a chronic condition. The product labeling should reflect these two treatment-related side effects as well as the duration-limited nature of the safety database.

**7.4 General Methodology**

**7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence**

**7.4.1.1 Pooled data vs. individual study data**

This reviewer examined individual study data from the two phase 3 studies as well as pooled data from these two studies presented in the applicant's Integrated Summary of Safety.

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#### 7.4.1.2 Combining data

Data for Locoid® arms and vehicle arms were combined in the applicant's ISS.

#### 7.4.2 Explorations for Predictive Factors

##### 7.4.2.1 Explorations for dose dependency for adverse findings

Only one concentration, 0.1%, was studied.

##### 7.4.2.2 Explorations for time dependency for adverse findings

The treatment period for all clinical studies was four weeks or less. No explorations were performed for time-dependency within this narrow window of time. Labeling should reflect that the safety and efficacy of use for longer than four weeks have not been evaluated or established. Some adverse effects of topical steroids (e.g., HPA axis suppression, telangiectasias, striae, atrophy, effects on growth) may be dose and time dependent, which should be reflected in product labeling.

##### 7.4.2.3 Explorations for drug-demographic interactions

This reviewer examined whether the frequency of HPA axis suppression differed by age cohort in study 04-101. There is no indication that the frequency correlated directly or indirectly with age.

##### 7.4.2.4 Explorations for drug-disease interactions

A subgroup analysis of efficacy in study 04-103 (see section 10.1.1, below) by disease severity showed that Locoid® was superior to vehicle in subjects with either mild or moderate disease.

##### 7.4.2.5 Explorations for drug-drug interactions

Explorations for drug-drug interactions were not performed.

#### 7.4.3 Causality Determination

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Clinical trial data indicate that Locoid® lotion may cause adrenal suppression and application site reactions. The label should adequately address these concerns.

## **8. ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

There are no concerns with the twice-daily dosing regimen and the topical administration of Locoid® lotion for a maximum of four weeks' duration, which is similar to the regimens and administrations of other currently marketed Locoid® formulations.

### **8.2 Drug-Drug Interactions**

No drug-drug interactions were studied in the clinical development program.

### **8.3 Special Populations**

Clinical studies did not include subjects less than 3 months of age. The lack of safety and efficacy data for patients in this age range should be reflected in product labeling.

### **8.4 Pediatrics**

Atopic dermatitis is primarily a pediatric disease. The safety and efficacy of Locoid® lotion was adequately demonstrated in the clinical development program for patients over 3 months of age.

### **8.5 Advisory Committee Meeting**

Not applicable.

### **8.6 Literature Review**

Eczematous eruptions in childhood. In: Paller AS, Mancini AJ, editors. Hurwitz Clinical Pediatric Dermatology. Philadelphia: Elsevier Saunders; 2006. p. 49-84

Franz TJ. Pharmacokinetics and the skin. In: Bologna JL, et al, editors. London: Mosby;

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2003. p. 1975-8.

Hengge UR, et al. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol* 2006;54:-15.

Lipsker D, Kragballe K, Fogh K, Saurat J-H. Other Topical Medications. In: Bologna JL, Jorizzo JL, Rapini RP. *Dermatology*. London: Mosby; 2003. p. 2055-70.

Schimmer BP, Parker KL. Adrenocorticotrophic hormone; Adrenocortical steroids and their synthetic analogs; Inhibitors of the synthesis and actions of adrenocortical hormones. In: Brunton LL, et al. *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*. 11<sup>th</sup> ed. New York: McGraw-Hill; 2006.

Strober BE, Washenik K, Shupack JL. Principles of Topical Therapy. In: Freedberg IM, Eisen AZ, Wolff, et al., editors. *Fitzpatrick's Dermatology in General Medicine*, 6<sup>th</sup> ed. New York: McGraw-Hill; 2003. p. 2319-23.

Valencia IC, Kerdel FA. Topical glucocorticoids. In: Freedberg IM, et al, editors. *Fitzpatrick's Dermatology in General Medicine*. 6<sup>th</sup> ed. New York: McGraw-Hill; 2003. p. 2324-8.

Warner M, Camisa C. Topical Corticosteroids. In: Wolverton SE, editor. *Comprehensive Dermatologic Drug Therapy*. Philadelphia: W.B. Saunders Company; 2001. p. 548-77.

### **8.7 Postmarketing Risk Management Plan**

The applicant should be required to submit quarterly reports of AEs possibly related to photosafety for one year following approval.

### **8.8 Other Relevant Materials**

~~No other materials were reviewed for this NDA.~~

## **9. OVERALL ASSESSMENT**

### **9.1 Conclusions**

### **9.2 Recommendation on Regulatory Action**

This reviewer recommends approval with revised labeling and postmarketing

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commitments.

**9.3 Recommendation on Postmarketing Actions****9.3.1 Risk Management Activity**

In addition to annual reports required for all NDAs, the applicant should be required to submit to the Agency quarterly summaries of AEs possibly related to photosafety for one year following approval.

**9.3.2 Required Phase 4 Commitments**

This reviewer recommends that the applicant be required to conduct the following studies: (1) carcinogenicity study, as per pharm/tox review team recommendations; and (2) as discussed in EOP2 and pre-NDA meetings, studies to fulfill ICH E1a guidelines for numbers of subjects exposed for long-term safety, studies of 300 and 100 subjects between 3 months and 18 years of age with atopic dermatitis using HCB 0.1% lotion twice daily for six and 12 months, respectively. These studies should capture data on the following parameters:

- HPA axis function, using Cosyntropin testing, measured several times during the course of the study, with follow-up for subjects who experience HPA axis suppression to determine the time required until return of normal HPA axis function;
- Growth velocity, using the Guidance Document entitled "Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children" to help inform the design and conduct of the study;
- Topical steroid-specific adverse effects (including striae, telangiectasia, atrophy, and pigmentary change), assessed by clinical examination several times during the course of the study, with follow-up for subjects who experience these AEs to determine whether they are reversible;
- Other AEs occurring during the course of the study (e.g., infections, malignancies).

**9.3.3 Other Phase 4 Requests**

This reviewer has no other phase 4 requests.

**9.4 Labeling Review**

Please see the appended line-by-line labeling review for details.

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**9.5 Comments to Applicant**

There are no additional comments to be conveyed to the sponsor other than the phase 4 commitments needed for pharmacology/toxicology and the changes to the proposed label.

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## 10. APPENDICES

### 10.1 Review of Individual Study Reports

**10.1.1 Study 04-103:** A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate lotion 0.1% in the treatment of mild to moderate atopic dermatitis in pediatric subjects aged 3 months to less than 18 years

**Trial design:**

Study sites: 14, USA

Number of subjects: 284 (139 to Locoid® lotion arm, 145 to vehicle arm)

Study period: 10/19/04 to 9/20/05

Objectives:

Primary: To evaluate efficacy of twice daily application of hydrocortisone butyrate lotion 0.1% as compared to vehicle in subjects aged 3 months to less than 18 years diagnosed with mild to moderate atopic dermatitis.

Secondary: To evaluate the safety of that treatment by evaluating the reported and observed AEs.

Study design: Multi-center, randomized, double-blind, placebo-controlled study of pediatric subjects with atopic dermatitis

Diagnosis and main criteria for inclusion:

1. Subject (male or female) was 3 months to less than 18 years of age.
2. Subject presented with a clinical diagnosis of stable and mild to moderate atopic dermatitis as defined by the criteria per Hanifin and Rajka involving at least 10% of the body.

*Reviewer comment: These criteria are well-known and have been used in previous studies of atopic dermatitis in approved NDAs.*

3. Subject's severity of atopic dermatitis according to PGA (see below) was 2 (mild) or 3 (moderate).
4. With the exception of the disease being studied, the subject was in general good health in the opinion of the investigator.
5. The subject and parent(s)/legal guardian(s) agreed to the requirements and restrictions of the study and appeared for all the required examinations.
6. Female subjects of child-bearing potential (FOCBP) were willing to submit to a urine pregnancy test at baseline and at the final visit.
7. Subject's parent/legal guardian signed a written, IRB-approved, informed consent prior to admission into the study and was able to understand that consent form. Subjects 7 years or older must have provided written assent.
8. Subject used the same type of soap, moisturizers, lotions, creams, ointments, sunscreens or other skin products, and hair products (e.g., shampoo, etc.) for at least 2 weeks prior to the baseline visit and agreed to continue usage with the same products and with similar frequency for the entire study.

Exclusion criteria:

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4. Hypersensitivity to any component of study medication.
5. Subject required any topical or systemic medications or was using topical inflammatory dermatoses therapies that could have affected the course of their atopic dermatitis during the study period. Stable maintenance therapy ( $\geq 30$  days of use prior to enrollment) of oral antihistamines and corticosteroid-containing nasal sprays and antibiotics for acne treatment were allowed.
6. Subject had extensive disease which could not be reasonably controlled, in the opinion of the investigator, with topical corticosteroid therapy.
7. Subject used systemic corticosteroids, immunomodulators, or anti-metabolites within 30 days prior to enrollment with the exception of inhalers.
8. Subject used ultraviolet light therapy within 30 days prior to entering the study.
9. Subject used topical therapies for atopic dermatitis treatment including but not limited to corticosteroids, immunomodulators, calcipotriene or other vitamin D preparations, retinoids, antihistamines, or antibiotics within 14 days prior to entering the study.
10. Subject desired excessive or prolonged UV exposure during the study.
11. Subject used systemic antibiotic therapy within 7 days prior to entering study (except for acne therapy, as per criterion 2)
12. Subject was immunocompromised.
13. Subject was pregnant or lactating
14. Subject had other conditions that would interfere with the evaluation of the study medication.
15. Subject was treated with another investigation device or drug within 30 days prior to study enrollment, or was participating or intended to participate in another concurrent clinical trial.

Duration of treatment: twice daily for 4 weeks.

Criteria for evaluation:

Primary efficacy variable: Success, defined as a PGA score scale of 0 or 1 at Day 29 and a 2-point PGA reduction from baseline.

Secondary efficacy: Change in pruritus from baseline to Day 29

Other efficacy: change in percentage BSA, change from baseline in severity of erythema, induration/population, lichenification, excoriation, oozing/crusting, and pruritus at each post-baseline evaluation, Eczema Area and Severity Index (EASI)

How measured:

**Table 22. PGA scale, study 04-103**

Score	Category	Definition
0	Clear	No signs of inflammatory atopic dermatitis (AD)
1	Almost clear	Faint, barely detectable erythema and/or trace residual elevation in limited areas; neither excoriation nor oozing/crusting are present
2	Mild	Light pink erythema and slightly perceptible elevation; excoriation, if present, is mild
3	Moderate	Dull red, clearly distinguishable erythema and clearly perceptible elevation but not extensive; excoriation or oozing/crusting, if present, are mild to moderate
4	Severe	Deep/dark red erythema, and marked and extensive elevation; excoriation and oozing/crusting are present

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**Table 23. Pruritus scale, study 04-103**

Score	Category	Definition
0	None	None
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching/discomfort which is not disturbing sleep
3	Severe	Bothersome itching/scratching/discomfort which is disturbing sleep

**Table 24. Scales to measure signs of atopic dermatitis, study 04-103**

<b>Erythema (E)</b>		
0	None	None
1	Mild	Faintly detectable erythema: very light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red
<b>Induration/papulation (I/P)</b>		
0	None	None
1	Mild	Barely perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
<b>Excoriations (Ex)</b>		
0	None	None
1	Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions
<b>Lichenification (L)</b>		
0	None	None
1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern
<b>Oozing/crusting (O)</b>		
0	None	None
1	Mild	Evidence of exudation
2	Moderate	Serous brown, yellow or green, exudations and/or drying of the discharge.
3	Severe	Many dry scabs and/or exudations.

**BSA involvement:**

The percentage of each body region (head/neck; upper limbs; trunk; lower limbs) was determined and then multiplied by the weighted value for that region (0.1; 0.2; 0.3; and 0.4, respectively). Scores were then summed to calculate the total BSA involvement.

**EASI computation:**

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Each of four body regions was evaluated and individual scores assigned to each sign (erythema, induration/population, excoriation, and lichenification, each on a 4-point scale.) These sign scores were summed and multiplied by the Percent Involvement Score, as follows:

**Table 25. Percent body involvement scores, study 04-103**

Score	% of body region affected
0	0%
1	1% - < 10%
2	≥10% - <30%
3	≥30% - <50%
4	≥50% - <70%
5	≥70% - <90%
6	≥90% - 100%

These scores were then multiplied by the weighted value assigned to that body region, with head/neck, upper limbs, trunk, and lower limbs having values of 0.1, 0.2, 0.3, and 0.4, respectively.

The sum of EASI scores by body region gave the EASI total, which ranged from 0 to 72. Percent change from baseline to the final visit was then calculated.

*Reviewer comment: EASI has not had regulatory utility in DDDP as an endpoint assessment.*

**Safety evaluation:**

All AEs were recorded. Topical steroid-specific evaluations were done at every study visit (excluding day 15) for the presence or absence of telangiectasias, skin atrophy, and striae.

**Statistical methods:**

The primary endpoint was analyzed with the Cochran-Mantel-Haenszel (CMH) test, stratified by investigational centers.

**Study population:****Table 26. Subject demographics and baseline characteristics, study 04-103, ITT**

	Locoid® lotion	Vehicle lotion	Total
Number of subjects	139	145	284
Age (years): overall			
Mean	7.31	6.97	7.14
S.D.	5.32	5.09	5.20
Range	0.3-17.8	0.4-17.6	0.3-17.8
Age (years): 3 mths to < 2 yrs (n)	22	17	39
Mean	0.96	1.21	1.08
S.D.	0.48	0.46	0.48
Range	0.3-1.9	0.4-1.9	0.3-1.9
Age (years): 2 yrs to <6 yrs (n)	21	31	52
Mean	3.77	3.30	3.51
S.D.	1.13	1.00	1.08
Range	2.1-5.7	2.1-5.2	2.1-5.7

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Age (years): 6 yrs to < 12 yrs (n)	34	34	68
Mean	8.69	8.74	8.72
S.D.	1.73	1.58	1.67
Range	6.2-11.6	6.0-11.9	6.0-11.9
Age (years): 12 yrs to <18 yrs	27	23	50
Mean	14.44	14.91	14.65
S.D.	1.73	1.58	1.67
Range	12.2-17.8	12.0-17.6	12.0-17.8
Gender			
Male	64 (46%)	79 (54%)	143 (50%)
Female	75 (54%)	66 (46%)	141 (50%)
Race <sup>a</sup>			
White	92 (66%)	93 (64%)	185 (65%)
Black or African American	40 (29%)	52 (36%)	92 (32%)
Asian	9 (6%)	4 (3%)	13 (5%)
Native Hawaiian or Pacific Islander	0 (0%)	2 (1%)	2 (1%)
American Indian or Alaska Native	2 (1%)	2 (1%)	4 (1%)
Ethnicity			
Hispanic/Latino	12 (9%)	10 (7%)	22 (8%)
Not Hispanic/Latino	127 (91%)	135 (93%)	262 (92%)

<sup>a</sup>Subjects could report more than one category, so total may be > 100%.

Source: Table 14.2.1.1, Mod 5, Vol 10, Page 74.

The mean age in this study was just over 7 years across treatment groups. Subjects ranged in age from 3 months to nearly 18 years of age. There were more subjects in the Locoid® arm in the youngest and oldest age cohorts, an equal number in the second-oldest age cohort, and more subjects in the vehicle arm in the second-youngest age cohort. Overall, the gender distribution was equal, with somewhat more males in the Locoid® arm and somewhat more females in the vehicle arm. Racially, almost two-thirds of subjects were white, and there were somewhat more subjects indicating black or African American in the vehicle arm. There were very few subjects who were Asian, Native Hawaiian or Pacific Islander, or American Indians or Alaska Natives. Ethnically, slightly less than 10% of subjects were Hispanic or Latino.

**Table 27. Baseline PGA characteristics, study 04-103, ITT**

	Locoid® lotion (n=139)	Vehicle lotion (n=145)	Total (n=284)
PGA score			
Clear	0 (0%)	0 (0%)	0 (0%)
Almost clear	0 (0%)	0 (0%)	0 (0%)
Mild	65 (47%)	69 (48%)	134 (47%)
Moderate	74 (53%)	75 (52%)	149 (52%)
Severe	0 (0%)	1 (1%)	1 (<1%)

Only one subject, in the vehicle arm, was classified as Severe by PGA score, and none were clear or almost clear. A comparable proportion in each group was mild or moderate.

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**Subject disposition:****Table 28. Subject enrollment, evaluability, and discontinuation, study 04-103**

	Locoid® lotion (n=139)	Vehicle (n=145)	Total (n=284)
Number completed (%)	132 (95.0%)	120 (82.8%)	252 (88.7%)
Reason for premature discontinuation			
Subject request	2	7	9
Subject non-compliance	0	0	0
Lost to follow up	5	5	10
Lack of efficacy	0	6	6
Adverse event	0	5	5
Other <sup>a</sup>	0	2	2

<sup>a</sup>One subject was discontinued after being removed from the care of her mother by social services, and another was discontinued after consent was withdrawn by the parent due to family problems. Source: Table 10.1.2, Mod 5, Vol 10, Page 48

A greater proportion of subjects discontinued in the vehicle compared to the Locoid® arm, due to a greater number of subject requests, lack of efficacy, AEs, and other reasons. An equal number (five) in each arm were lost to follow up, and no subject was discontinued due to non-compliance. See below for discussion of AEs related to drop outs.

**Study conduct:****Table 29. Protocol deviations leading to disqualification from per protocol analysis, study 04-103**

	Locoid® lotion (n=139)	Vehicle (n=145)	Total (n=284)
Number of subjects with deviations (%)	35 (25.2%)	40 (27.6%)	75 (26.4%)
Deviation			
Missed final visit	7	14	21
Final visit outside visit window of ±2 days	7	11	18
Not compliant with dosing regimen <sup>a</sup>	2	4	6
Prohibited concomitant medication	18	10	28
Inappropriate enrollment (failed inclusion criteria)	1	1	2

<sup>a</sup>Compliance was defined as not missing more than four consecutive doses and having applied at least 75 of the expected applications and not applying more than 125% of expected applications.

*Reviewer comment: A greater proportion of subjects in the vehicle compared to Locoid® arm had protocol deviations in all categories except prohibited concomitant medication (10 vs. 18) and inappropriate enrollment (1 vs. 1). Even if the prohibited concomitant medications were effective atopic dermatitis treatments, however, given that the primary efficacy endpoint so favored Locoid® it is unlikely that these deviations would have affected the overall trial outcome.*

**Efficacy results:**

**Primary efficacy endpoint:** Dichotomized PGA score at Day 29 (0 or 1 score and 2-point reduction in score from baseline needed for success)

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**Table 30. Primary efficacy endpoint, study 04-103, ITT**

	<b>Locoid® lotion (n=139)</b>	<b>Vehicle (n=145)</b>	<b>p-value<sup>a</sup></b>
Number (%) successes	68 (49%)	35 (24%)	<0.0001

<sup>a</sup> Calculated using CMH test, stratified by pooled sites

Source: FDA biostatistical review

This analysis concurred with the applicant's analysis, as presented in Table 11.4.11, Mod 5, Vol 10, Page 53. As discussed in section 6.1.4, results of sensitivity and per protocol analyses also favored Locoid® lotion over vehicle.

Subgroup analyses by gender, age, and race, and by baseline PGA and percentage BSA, were consistent with the overall results, as shown below:

**Table 31. Primary efficacy endpoint results by gender, age, and race, study 04-103**

			<b>Locoid® lotion N=139</b>	<b>Vehicle N=145</b>
Gender	Male	Total	64	79
		Success (%)	37 (58%)	21 (27%)
	Female	Total	75	66
		Success (%)	31 (41%)	14 (21%)
Race	White	Total	88	87
		Success (%)	46 (52%)	22 (25%)
	Black	Total	40	51
		Success (%)	17 (43%)	12 (24%)
	Asian	Total	9	3
		Success (%)	5 (56%)	0 (0%)
	Pacific Islander	Total	0	2
		Success (%)	0 (0%)	1 (50%)
	American Indian	Total	2	2
		Success (%)	0 (0%)	0 (0%)
Age	3 months - < 2 years	Total	32	29
		Success (%)	19 (59%)	5 (17%)
	2 years - < 6 years	Total	32	40
		Success (%)	16 (50%)	9 (23%)
	6 years - < 12 years	Total	38	47
		Success (%)	24 (63%)	13 (28%)
	12 years - < 18 years	Total	37	29
		Success (%)	9 (24%)	8 (28%)

Source: FDA biostatistical review

**Table 32. Primary efficacy results by baseline disease severity (PGA and % BSA), study 04-103**

		<b>Locoid® lotion N=139</b>	<b>Vehicle N=145</b>

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Baseline PGA	2	Total	65	69
		Success (%)	25 (38%)	20 (29%)
	3	Total	74	75
		Success (%)	43 (58%)	14 (19%)
	4	Total	0	1
		Success (%)	0 (0%)	1 (100%)
Baseline % BSA	≤20	Total	75	72
		Success (%)	34 (45%)	20 (28%)
	>20	Total	64	73
		Success (%)	34 (53%)	15 (21%)

Source: FDA biostatistical review

**Secondary efficacy endpoint:** Change in pruritus from baseline to Day 29**Table 33. Secondary endpoint (pruritus), study 04-103, ITT**

Change from baseline	Locoid® lotion (n=139)	Vehicle (n=145)	p-value <sup>a</sup>
-2	1 (<1%)	1 (<1%)	<0.001
-1	1 (<1%)	12 (8%)	
0	25 (18%)	50 (34%)	
1	43 (31%)	48 (33%)	
2	56 (40%)	29 (20%)	
3	13 (9%)	5 (3%)	

<sup>a</sup> Calculated using CMH test

Source: FDA biostatistical review

**Other efficacy endpoints (based on applicant's analysis):****Table 34. EASI, percent change from baseline, study 04-103, ITT**

	Locoid® lotion (n=139)	Vehicle (n=145)	p-value
EASI, percent change from baseline (mean, S.D.)	74.5 (37.5)	41.5 (53.4)	<0.001

Additional efficacy endpoints, including signs of atopic dermatitis and BSA, were presented graphically in the application, with means at each timepoint appearing to favor Locoid® lotion over vehicle. Formal statistical analyses of these endpoints were not presented.

**Safety results:**

There were no deaths reported in this study.

There was one serious adverse event in the vehicle arm (n=145, 0.7%), with relationship to study drug considered unassessable by the sponsor and by this reviewer. This event involved a 1.47-year-old boy in the vehicle-lotion arm who was discontinued from the study on Day 14 due to

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lack of efficacy. He was provided alternate therapy for atopic dermatitis. One week later he presented at a local health facility with acute eczema exacerbation of moderate intensity. The event resolved three days later.

The percentage of subjects in each treatment group who experienced at least one adverse event was 35% in the Locoid® arm and 39% in the vehicle arm. There were no subjects in the Locoid® arm and five in the vehicle arm who discontinued prematurely due to AEs, as follows:

- A 9.8 year old girl was discontinued after five days due to a rash on the back, arms, and legs.
- A 4.4-year-old boy was discontinued after 21 days due to burning.
- A 1.0-year-old boy was discontinued after seven days due to persistent erythema in application areas.
- A 2.1-year-old boy was discontinued after 10 days due to itching and stinging.
- A 11.7-year-old girl was discontinued after three days due to itching and burning.

*Reviewer comment: In this reviewer's opinion, the most likely cause of these events is undertreated atopic dermatitis.*

Topical steroid-specific evaluations: no telangiectasia, skin atrophy, or striae were reported.

**Conclusions:**

Locoid® lotion was significantly more effective than vehicle lotion in treating atopic dermatitis in pediatric subjects in this pivotal study. The adverse event profile was reasonable.

**10.1.2 Study 03-074:** A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis or eczema in adults

**Trial design:**

Study sites: 20, USA

Number of subjects: 301 (151 to Locoid® arm, 150 to vehicle arm)

Study period: 8/19/03 to 3/24/04

Objectives: To demonstrate the therapeutic efficacy and safety of a 3- or 4-week course of twice daily application of hydrocortisone butyrate 0.1% lotion as compared to vehicle in subjects ages 18 years and over diagnosed with mild to moderate atopic dermatitis or eczema

Study design: Multi-center, randomized, double-blind, placebo-controlled study of adults subjects with atopic dermatitis or eczema

**Diagnosis and main criteria for inclusion:**

4. Subject signed a written, IRB-approved, informed consent prior to admission into the study and was able to understand that consent form.
5. Male or female subjects 18 years of age or older.

*Reviewer comment: Atopic dermatitis is primarily a pediatric disease, and this inclusion criterion requires the enrollment of adults. This is one of the reasons the Agency previously decided to consider this study as supportive, rather than pivotal.*

6. Subject had a clinical diagnosis of mild to moderate atopic dermatitis or eczema based on the Rajka-Langeland Grading of the Severity of Atopic Dermatitis.

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*Reviewer comment: The inclusion of "eczema" is problematic, since this diagnosis could include discrete disease entities such as atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, nummular dermatitis, and potentially other disease entities. This is one of the reasons the Agency previously decided to consider this study as supportive, rather than pivotal.*

7. Subject must have had a PGA score of 2 or greater.
8. The subject's disease must have been present for at least three months and must have been clinically stable at the time of enrollment
9. The subject must have used the same type and brand of soap, moisturizers, lotions, creams, ointments, sunscreens or other skin products, and hair products (e.g., shampoo, etc.) for at least 2 weeks prior to the baseline visit and agree to continue usage with the same products and with similar frequency for the entire study.
10. The subject must have used the same type of vitamins and nutritional supplements for at least 2 weeks prior to the baseline visit and agreed to continue usage with the same product for the entire study.
11. The subject was not to begin the use of any topical medications, vitamins or nutritional products of any kind other than the study treatment unless approved by the investigator.
12. Subject(s) must have understood and agreed to the requirements of the study, abided by the restrictions, and appeared for all the required examinations.

#### Exclusion criteria:

1. The subject had a known hypersensitivity to any component of the study medication.
2. The subject had a history of adverse response to topical or systemic steroid therapy.
3. The subject had extensive disease that required the use of concomitant therapy or whose disease could not be reasonably controlled with topical corticosteroid treatment. This included vesicular and/or pustular eczema.
4. The subject had primary bacterial or viral skin lesions (such as erysipelas, varicella, vaccinia, herpes simplex, etc.) or had obvious infected secondary lesions that, in the opinion of the investigator, would affect the clinical assessments.
5. The subject had significant endocrinology disorders that could interfere with the assessment of study results or that required contraindicated treatment with potent corticosteroids (e.g., insulin-dependent diabetes).
6. Subject had an unstable concomitant disease other than the condition to be treated in this study.
7. The subject's condition appeared to be spontaneously improving without treatment.
8. The subject had a malignant disease that had not been in remission for at least 5 years (excluding non-melanoma skin cancers).
9. The subject required any medications (topical or systemic) that could affect the course of their atopic dermatitis or eczema during the study period.
10. The subject's condition had been stabilized with use of topical steroid within two (2) weeks of the study.
11. The subject had started the use of inhaled steroids less than 30 days prior to the start of the study.
12. The subject had used systemic steroids within 30 days of the study.
13. The subject had used therapy such as immunomodulators, cyclosporine, methotrexate, PUVA within 30 days of the study.
14. The subject had been on a stable dose/regimen of antihistamines for less than 30 days prior to baseline.

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- 15. The subject was immunocompromised.
- 16. The subject had been involved in another investigational study within 30 days prior to screening.
- 17. The subject was on a special diet that could alter their atopic dermatitis or eczema.
- 18. The subject was pregnant or lactating.
- 19. The subject was considered unreliable or incapable, based on the investigator interview, and may not have used the medication as instructed, and/or complied in keeping scheduled appointments and adhered to other aspects of the protocol.

Duration of treatment: twice daily for 3 or 4 weeks.

Criteria for evaluation:

Primary efficacy variable: Dichotomized PGA at Day 28, with success defined as PGA score of 0 or 1 at Day 28. Subjects who discontinued at Day 21 due to a confirmed clear (PGA 0 at both Day 14 and Day 21) were also considered a success at Day 29. Last observation carried forward was used to impute missing data.

*Reviewer comment: Unlike the pediatric study (04-103), this study did not require a minimum 2-point reduction in PGA scale as part of the definition of success. Additionally, the potential for a 3- or 4-week course of treatment was problematic for statistical assessment, as noted in previous discussions with the sponsor, and is contributes to the decision to consider this study as supportive rather than pivotal. Post hoc analyses that required a minimum 2-point PGA reduction from baseline were performed, however.*

Secondary efficacy: Dichotomized PGA at Day 21 and percent change in EASI scores at Days 21 and 28.

How measured:

**Table 35. PGA scale, study 03-074**

Score	Category	Definition
0	Clear	No inflammatory signs of atopic dermatitis
1	Just perceptible	Just perceptible erythema, and just perceptible infiltration/population
2	Mild	Mild erythema, and mild population/infiltration
3	Moderate	Moderate erythema, and moderate population/infiltration
4	Marked	More pronounced erythema, and more pronounced population/infiltration
5	Severe	Severe erythema, and severe population/infiltration
6	Extreme	Severe erythema, and severe population/infiltration with oozing/crusting

*Reviewer comment: This study used a 7-point scale, as opposed to the 5-point scale used in the pediatric study (04-103). The difference lies mainly in the higher numbers, which are more subdivided in this 7-point scale. The relevance of distinguishing between these degrees of more severe disease is not clear for a product intended to treat mild-to-moderate atopic dermatitis.*

EASI, pruritus, signs of atopic dermatitis, and BSA involvement:

These measures were scored in the same way as in the pediatric study (04-103), described above.

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**Safety evaluation:**

All AEs were reported. Vital signs (blood pressure, heart rate, temperature, and respiratory rate) were performed at baseline and end of treatment. Topical steroid-specific evaluations were not explicitly performed.

*Reviewer comment: This differed from the pediatric study (04-103), in which end-of-study vital signs were not measured and topical steroid-specific evaluations were explicitly performed.*

**Statistical methods:**

Statistical significance was based on two-sided hypothesis testing resulting in p-values of 0.05 or less.

**Study population:****Table 36. Subject demographics and baseline characteristics, study 03-074, ITT**

	Locoid® lotion	Vehicle lotion	Total
Number of subjects	151	150	301
Age (years)			
Mean	41.72	43.58	42.65
S.D.	15.88	5.93	15.91
Range	18.1-83.8	18.7-86.2	18.1-86.2
Gender			
Male	45 (30%)	65 (43%)	110 (37%)
Female	106 (70%)	85 (57%)	191 (63%)
Race			
White	115 (76%)	115 (77%)	230 (76%)
Black or African American	31 (21%)	29 (19%)	60 (20%)
Asian	5 (3%)	3 (2%)	8 (3%)
Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native	0 (0%)	3 (2%)	3 (1%)
Ethnicity			
Hispanic/Latino	16 (11%)	22 (15%)	38 (13%)
Not Hispanic/Latino	135 (89%)	128 (85%)	263 (87%)

Source: Table 14.1.2, Mod 5, Vol 3, Page 83.

The mean age in this study was approximately 43 years, with a range of 18 to 86 years. There were more women than men enrolled, particularly in the Locoid® group. Most subjects were white, with about one-fifth black or African-American and very few, if any, members of other racial categories. Overall, 13% of subjects were Hispanic or Latino.

**Table 37. Baseline PGA characteristics, study 03-074, ITT**

	Locoid® lotion (n=151)	Vehicle lotion (n=150)	Total (n=301)
PGA score			
Clear	0 (0%)	0 (0%)	0 (0%)
Just perceptible	2 (1%)	0 (0%)	2 (1%)
Mild	40 (26%)	39 (26%)	79 (26%)
Moderate	85 (56%)	80 (53%)	165 (55%)

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Marked	18 (12%)	25 (17%)	43 (14%)
Severe	3 (2%)	5 (3%)	8 (3%)
Extreme	3 (2%)	1 (1%)	4 (1%)

Source:

*Reviewer comment: Most subjects had mild or moderate disease. There appear to be too few subjects with more severe disease to establish labeling information for more severe disease categories.*

**Subject disposition:****Table 38. Subject enrollment, evaluability, and discontinuation, study 03-074**

	Locoid® lotion (n=151)	Vehicle (n=150)	Total (n=301)
Number completed (%)	136 (90.1%)	116 (77.3%)	252 (62.8%)
Reason for premature discontinuation			
Subject request	2	10	12
Subject non-compliance	0	1	1
Lost to follow up	8	9	17
Lack of efficacy	0	8	8
Adverse event	2	4	6
Other <sup>a</sup>	3	2	5

<sup>a</sup>Two subjects in the Locoid® group did not have a PGA score of 2 or higher (inclusion criterion 4). Another subject in the Locoid® arm had recurring cellulitis. In the vehicle group, one subject took an exclusionary medication and another had work-schedule conflicts.

Source: Table 10.1.2, Mod 5, Vol 3, Page 52.

A greater proportion of subjects in the vehicle compared to Locoid® arm discontinued treatment, with most of the excess discontinuations due to subject request, lack of efficacy, or AEs (see below for discussion of AEs related to drop outs).

**Study conduct:****Table 39. Protocol deviations resulting in disqualification from the per protocol population, study 03-074**

	Locoid® (n=151)	Vehicle (n=150)	Total (n=301)
Number of subjects with deviation (%)	29 (19.2%)	34 (22.7%)	73 (24.3%)
Deviation			
Lost to follow up	8	9	17
Missed final visit	4	6	10
Final visit outside visit window of ±2 days	10	7	17
Not compliant with dosing regimen <sup>a</sup>	2	16	18
Prohibited concomitant medication	1	2	3
Discontinued due to a non-treatment related AE	2	2	4
Inappropriate enrollment (failed inclusion criteria)	2	2	4

<sup>a</sup> Compliance is defined as not missing more than four consecutive doses and taking at least 75% of doses up to and including the final visit.

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Source: Table 10.2.1, Mod 5, Vol 3, Page 53.

A greater proportion of subjects in the vehicle compared to Locoid® arm had protocol deviations, most markedly in the category of deviations from compliance with the dosing regimen (16 vs. 2). A difference in rate of compliance in the Locoid® vs. vehicle arms in this randomized, blinded study suggests differential effectiveness of the two therapies, which is reflected in the study outcome.

Efficacy results:

**Primary efficacy endpoint:** Dichotomized PGA score

Primary efficacy analysis, ITT population, applicant's analysis<sup>2</sup>

	<b>Locoid® lotion (n=139)</b>	<b>Vehicle lotion (n=145)</b>	<b>P-value</b>
PGA at Day 29			
Success	84 (56%)	49 (33%)	<0.001
Failure	67 (44%)	101 (67%)	

Source: Table 11.4.1.1, Mod 5, Vol 3, Page 55

Note: For this primary analysis, subjects with PGA 0 at Day 14 and Day 21 were considered successes at Day 21 and discharged from the study.

Analysis of dichotomized PGA score at Day 28 with a 2-point minimum reduction as an additional requirement for success

**Table 40. Primary efficacy endpoint analysis, study 03-074**

	<b>Locoid® lotion (n=151)</b>	<b>Vehicle (n=150)</b>	<b>p-value<sup>a</sup></b>
Number (%) successes	84 (56%)	49 (33%)	<0.0001

<sup>a</sup> Calculated using CMH test, stratified by pooled sites

Source: FDA biostatistical review

Other efficacy endpoints analyzed by the applicant favored Locoid® lotion. Because study 03-074 is considered supportive rather than pivotal, these analyses were not confirmed by FDA biostatistical reviewers.

Safety results:

There were no deaths reported in this study.

There were two serious AEs, which were not considered to be related to the study drug by the sponsor or by this reviewer. The first event involved a 69-year-old man randomized to vehicle lotion who was admitted to a hospital on Day 27 with acute gallbladder disease. He underwent a cholecystectomy and subsequently returned to complete the study. The second involved a 70-year-old woman randomized to receive Locoid® lotion who was admitted to a hospital on Day 21 with acute bronchitis. She was discharged after six days but did not return to the study.

<sup>2</sup> Await FDA biostat analysis for confirmation

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The percentage of subjects in each treatment group who experienced at least one adverse event was 18% in the Locoid® arm and 23% in the vehicle arm. There were two subjects in the Locoid® arm who discontinued prematurely due to an adverse event, as follows:

- A 21-year-old woman (#118) had a positive pregnancy test.
  - A 70-year-old woman (#397) developed acute bronchitis, for which she was hospitalized.
- This serious adverse event is also described above.

*Reviewer comment: In this reviewer's opinion it is unlikely that either of these AEs was related to the study drug.*

There were four subjects in the vehicle arm who discontinued prematurely due to AEs, as follows:

- A 24-year-old man (#122) developed worsening pruritus.
- A 68-year-old man (#123) developed tinea.
- A 53-year-old woman (#153) experienced an eczema flare.
- A 20-year-old woman (#322) developed hives.

*Reviewer comment: In this reviewer's opinion, the most likely cause of the pruritus and eczema flare is undertreated atopic dermatitis, and it is unlikely that tinea or hives were related to the study drug vehicle.*

No telangiectasia, skin atrophy, or striae were reported in this study.

**Conclusions:**

Locoid® lotion was significantly more effective than vehicle lotion with a reasonable adverse event profile in this supportive study of adult subjects with atopic dermatitis or eczema.

**10.1.3 Study 04-101:** 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

NOTE: The protocol for this study was deemed acceptable by the Agency in a SPA in May 2004.

**Trial design:**

Study sites: 10 (one of which enrolled no subjects), USA

Number of subjects: 84 (all to Locoid® lotion arm)

Study period: 9/22/04 to 2/22/06

Objective: 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 AEs.

Study type: Multi-center, open-label study

**Inclusion criteria:**

1. Subject was (male or female) between 3 months and 18 years of age (not yet reached his or her 18<sup>th</sup> birthday at the time of enrollment).

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2. Subject presented with a clinical diagnosis of stable moderate to severe atopic dermatitis involving at least 25% of the body as defined by the criteria per Hanifin and Rajka.

*Reviewer comment: As noted above, these criteria are widely used, and their use in previous studies has been accepted by the Agency.*

3. White dermatographism/delayed blanch.

4. Subject's severity of atopic dermatitis was such that the rating for the overall disease severity was moderate to severe on the Physician's Global Assessment scale (PGA = 3 or 4).

*Reviewer comment: The PGA scale was the same as that used in Study 04-103, described above.*

5. With the exception of the disease being studied, the subject was in general good health in the opinion of the investigator.
6. Parent(s) or legal guardian(s) agreed to the requirements and restrictions of the study and agreed to appear for all the required examinations.
7. Females of childbearing potential (FOCBP) were willing to submit to a urine pregnancy test at the Screening, Baseline, and Final Visits.
8. Parent(s) or legal guardian(s) provided written, informed consent prior to admission into the study. If the subject was 7 years of age or older, he or she provided assent.

#### Exclusion criteria:

1. Subject had a known hypersensitivity to any component of the study medication.
2. Subject required any topical or systemic medications or was using topical inflammatory dermatoses therapies as detailed in the Concomitant Medications section that could have affected the course of their atopic dermatitis during the study period. As a stable maintenance therapy (30 days or more of use prior to enrollment), oral antihistamines for treatment of bronchial asthma or allergic rhinitis and antibiotics for treatment of acne were allowed but were documented in the CRF.
3. Subject used systemic corticosteroids, immunomodulators, PUVA light therapy or antimetabolites, within four (4) weeks prior to entering the study.
4. Subject used topical inflammatory dermatoses therapies (corticosteroids, anthralin, topical vitamin D, tar, tacrolimus, pimecrolimus, etc.) exclusive of emollients, or received UVB light therapy within two (2) weeks prior to entering the study.
5. Subject was treated with another investigational device or drug within 30 days prior to study enrollment or was participating in a clinical trial at the time of enrollment or intended to participate in a clinical trial concurrent with this study.
6. Subject had abnormal adrenal function or adrenal insufficiency. Adrenal function was assessed at Screening and reviewed at the Baseline Visit. Subjects who were subsequently determined to have abnormal function were withdrawn.
7. Subject was pregnant or lactating.

#### Study design:

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).

CST was performed at screening (7 to 14 days prior to baseline) between 7 am and 9 am with post-stimulation blood draw being completed within 30 minutes and by 9 am. Administration was 0.125 mg for subjects < 3 years old and 0.25 mg for others. The preferred route of

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administration was intravenous; if unachievable, intramuscular administration was permitted. A post-stimulation cortisol level 30 minutes after administration of  $\leq 18 \mu\text{g/dL}$  indicated adrenal suppression. Potential subjects with pre-stimulation 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.

Treatment administration: Three times daily with up to 36, 30, 21, and 15 g/day of Locoid® lotion for Cohorts 1, 2, 3, and 4, respectively.

Criteria for evaluation:

Safety:

1. Primary endpoint: number of subjects with adrenal suppression as determined by CST at Day 29.
2. Vital signs (temperature, blood pressure, respiration rate, and pulse) were recorded at screening and final visit.
3. Topical steroid specific evaluations (telangiectasia, skin atrophy, and burning/stinging), noted as present or absent, at screening, interim, and final visits.
4. Chemistry and hematology panel at screening and final visit. Urine pregnancy test if appropriate at screening, baseline, and final visits. Urinalysis and optional RAST testing at screening visit only.

Efficacy (all assessed at baseline and Days 8, 22, and 29):

1. Individual signs of erythema, induration/population, excoriation, lichenification, and oozing/crusting.

*Reviewer comment: The scales for assessing these features were the same as those used in Study 04-103, described above.*

2. Pruritus
3. Overall percentage BSA
4. Overall disease condition using PGA (as defined above)

Statistical methods: Descriptive statistics were used.

Study population:

**Table 41. Subject demographics and baseline PGA and BSA involvement, study 04-101, evaluable population**

	Locoid® (n=84)
Age (years) overall	
Mean	7.09
S.D.	5.19
Range	0.4-17.9
Gender	
Male	43 (51%)
Female	41 (49%)
Race <sup>a</sup>	

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White	42 (50%)
Black or African American	39 (46%)
Asian	4 (5%)
Native Hawaiian or Pacific Islander	1 (1%)
American Indian or Alaska Native	1 (1%)
<b>Ethnicity</b>	
Hispanic/Latino	4 (5%)
Not Hispanic/Latino	80 (95%)
<b>PGA score</b>	
Clear	0 (0%)
Almost clear	0 (0%)
Mild	0 (0%)
Moderate	67 (80%)
Severe	17 (20%)
<b>Percent body surface involvement</b>	
Mean	46.3%
S.D.	23.4%
Range	25.0%-98.5%

Source: Table 14.2.2, Mod 5, Vol 20, page 54-5.

The mean age was approximately 7 years, similar to that in the pediatric phase 3 study (04-103). Both genders were nearly equally represented. White and black or African Americans were well-represented (the latter more so than in the phase 3 pediatric trial), with only a few subjects from other racial categories. Most subjects were not Hispanic or Latino. Subjects had moderate or severe atopic dermatitis with relatively extensive BSA involvement.

**Subject disposition:**

Of 90 subjects enrolled, 6 (6.4%) were excluded from the safety analyses due to failure to pass screening (3 due to post-stimulation cortisol values, one due to use of excluded medication, and 2 due to unsuccessful attempts at blood draws). Of the remaining 84, subjects, 83 (98.8%) completed the study and one (003-060, Cohort 3) was lost to follow-up. An additional subject (004-034) has the final CST result as "ND" (not done), leaving 82 evaluable subjects.

A standard of 75% compliance with the per-protocol number of applications of study medication was used to determine dosing compliance. Two subjects were not compliant by this definition; one subjects received 65% of applications, and the other was 54% compliant.

**Efficacy data:**

PGA scores over the course of Study 04-101

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Physician's Global	Baseline	Day 8	Day 15	Day 22	Day 29
n	84	83	82	81	83
Clear	0 ( 0%)	0 ( 0%)	5 ( 6%)	8 ( 10%)	20 ( 24%)
Almost Clear	0 ( 0%)	14 ( 17%)	17 ( 21%)	18 ( 22%)	20 ( 24%)
Mild	0 ( 0%)	33 ( 40%)	34 ( 41%)	33 ( 41%)	22 ( 27%)
Moderate	67 ( 80%)	32 ( 39%)	24 ( 29%)	21 ( 26%)	21 ( 25%)
Severe	17 ( 20%)	4 ( 5%)	2 ( 2%)	1 ( 1%)	0 ( 0%)
Not Reported	0	1	2	3	1

Note: Last observation carried forward was used to impute missing data for subjects who completed the study prior to Day 29 due to complete clearing. No other imputations were made for missing data.

Source: Table 14.3.1, Mod 5, Vol 20, page 56.

Descriptive data presented suggest improvement over the course of the study in the mean scores of all atopic dermatitis signs, BSA involvement, and severity of pruritus.

### Safety data:

#### Adrenal suppression:

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.

*Reviewer comment: Eighty-two rather than 84 is used as the denominator for calculating the overall percentage of subjects with adrenal suppression because two subjects had CST results listed as "ND" at the final visit, both in Cohort 3. A conservative estimate of the rate of suppression might consider a worst-case scenario, in which both subjects are assumed to be suppressed, yielding a rate of 9/84, or 10.7%. Additionally, line listings of subjects' exposure to Locoid® lotion in this study indicate that ten subjects (003-060 [on whom final CST was not performed], 004-099, 005-019, 005-023, 005-076, 005-078, 005-096, 006-051, 006-085, and 006-087) had exposures of less than 30 days (range, 13 to 27 days), including two, five, two, and one subject in Cohort 1, 2, 3, and 4, respectively. The protocol did allow for discontinuation of Locoid® lotion for subjects who cleared (PGA=0) prior to 28 days, with final CST performed within two days of the "clear" visit. One of these subjects (005-096, a 3.64-year-old boy in Cohort 3 exposed for 15 days) developed adrenal suppression. Limiting the calculation to those subjects who had 4 weeks of exposure to Locoid® lotion and who had final CSTs (n=73), the rate of adrenal suppression was 6/73, or 8.2%, which does not differ markedly from 7/82, or 8.5%. In this reviewer's opinion, these data suggest that product labeling should indicate that (1) adrenal suppression may occur prior to 4 weeks of use, and (2) Locoid® lotion should be*

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*used for the minimum time necessary to accomplish the treatment objective, even if less than 4 weeks.*

To help assess whether there was any association between HPA axis suppression and total weight of medication used or percent compliance, the applicant was asked to provide these data for the subjects overall and for the seven subject with HPA axis suppression. These data are shown in Table 42.

**Table 42. Total weight of medication used and percent compliance for subjects with HPA axis suppression and subjects overall, study 04-101**

Subject (age in years)	Total weight used (g)	Percent compliance
02-013 (12.4)	292.7	65.5
03-061 (1.6)	367.3	103.6
05-021 (10.6)	533.1	104.8
05-075 (6.0)	535.5	103.6
05-096 (3.6)	214.9	97.6
06-090 (1.0)	414.0	107.1
09-045 (9.7)	659.1	100.0
Overall mean $\pm$ SD	228.2 $\pm$ 151.7	99.5 $\pm$ 9
Overall median, min, max	210, 19, 679	101, 54, 119

*Reviewer comment: All subjects with HPA axis suppression used more than the mean and median weight of medication. Four of the seven used an amount more than one standard deviation greater than the mean. Compliance did not appear to differ from that of subjects overall. In this reviewer's opinion, though not formally analyzed statistically, suggest that there may be an association between amount of medication use and HPA axis suppression. To address this concern, in this reviewer's opinion, labeling should state that safety of use for greater than four weeks is not known, and that the medication should be discontinued as soon as control is achieved.*

Listings of individual subject data, by cohort, are shown in Tables 31, 32, 33, and 34.

**Table 43. Cohort 1 (12 years to <18 years) adrenal suppression data, study 04-101**

**Clinical Review**

Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

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

b(4)

Source: Table 14.4.1.2, Mod 5, Vol 20, page 64.

**Table 44. Cohort 2 (6 years to <12 years) adrenal suppression data, study 04-101**

<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>	
002-009	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)

Source: Table 14.4.1.2, Mod 5, Vol 20, page 63.

**Table 45. Cohort 3 (2 years to <6 years) adrenal suppression data, study 04-101**

**Clinical Review**

Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

<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)

Source: Table 14.4.1.2, Mod 5, Vol 20, page 62.

**Table 46. Cohort 4 (3 months to <2 years) adrenal suppression data, study 04-101**

<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>	
002-081	1.44								
003-061	1.60								
003-062	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	4.18								
006-089	0.80								
006-090	1.01								
FU2*									
009-048	1.39								
010-109	0.37								
010-111	1.37								
010-112	0.76								

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.

Source: Table 14.4.1.2, Mod 5, Vol 20, page 61.

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Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

**Vital sign data:**

There did not appear to be a concerning pattern or signal regarding vital sign data, in this reviewer's opinion.

**Topical steroid specific evaluation data :**

Table 36. Topical-steroid-specific evaluation data from Study 04-101

	<u>Baseline</u>	<u>Day 8</u>	<u>Day 15</u>	<u>Day 22</u>	<u>Day 29</u>
<b>Telangiectasia</b>					
Absent	83 ( 99%)	82 ( 99%)	81 ( 99%)	75 ( 99%)	75 ( 99%)
Present	1 ( 1%)	1 ( 1%)	1 ( 1%)	1 ( 1%)	1 ( 1%)
Not Reported	0	1	2	8	8
<b>Skin Atrophy</b>					
Absent	84 (100%)	83 (100%)	82 (100%)	76 (100%)	76 (100%)
Present	0 ( 0%)	0 ( 0%)	0 ( 0%)	0 ( 0%)	0 ( 0%)
Not Reported	0	1	2	8	8
<b>Burning/Stinging</b>					
Absent	80 ( 95%)	80 ( 96%)	80 ( 98%)	76 (100%)	76 (100%)
Present	4 ( 5%)	3 ( 4%)	2 ( 2%)	0 ( 0%)	0 ( 0%)
Not Reported	0	1	2	8	8

Note: No imputations were made for missing data. The protocol specified recording the presence/absence of striae not burning/stinging. Any reports of striae are included in the adverse events listings.

Source: Table 14.4.3, Mod 5, Vol 20, page 66.

*Reviewer comment: Burning/stinging may be due to application site reactions or to atopic dermatitis. Because telangiectasia was assessed dichotomously, as present or absent, it is not clear whether the pre-existing telangiectasia changed at all over the course of the study.*

**AEs:**

Ten of 90 subjects (11%) reported 13 AEs. None were serious. Two (and only two) AEs of adrenal suppression were reported, although seven subjects experienced suppression, as shown above. Other AEs potentially related to the study drug, in this reviewer's opinion, include skin infection (n=1) and skin fissures (n=1).

**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.*

**10.1.4 Study 01-129: Human repeated insult patch test****Trial design:**

**Study sites:** 1, USA

**Number of subjects:** 282

**Study period:** 2/17/03 to 3/17/03

**Objective:** To investigate the potential of hydrocortisone butyrate 0.1% lotion to induce allergic contact dermatitis by 48-hour repetitive applications to the skin.

**Study population:** Single-center, double-blinded study in healthy adult subjects. The

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Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

investigators screened 323 subjects and enrolled 282 of them, of whom 65 withdrew for reasons unrelated to the study, leaving 217 evaluable subjects.

**Study design:**

**Induction/irritation phase:** Each subject received nine approximately 48-hour applications of approximately 0.2 ml of the following test articles to the right and left back during over approximately three weeks:

- A: Clindamycin phosphate 1%
- B: Vehicle for clindamycin phosphate 1%
- C: 4% lidocaine cream
- D: Vehicle for 4% lidocaine cream
- E: 5% lidocaine cream
- F: Vehicle for 5% lidocaine cream
- G: Hydrocortisone butyrate lotion 0.1%
- H Vehicle for hydrocortisone butyrate lotion 0.1%
- I: Distilled water (negative control)
- J: Sodium lauryl sulfate 0.1% w/v in distilled water (positive control)

Tests sites were visually evaluated three times per week for reactions at approximately 48 hours (or 72 hours over weekends) after patch applications.

**Rest period:** 14-17 days, during which no patches were applied.

**Challenge phase:** The test articles above were applied to a naïve, uninvolved skin site on the right and left superior lateral arm of each subject for approximately 48 hours and evaluated at approximately 48 and 96 hours after application.

**Results:**

There were no reactions to Locoid® lotion or its vehicle.

Four subjects experienced reactions to other test articles (one each to A and E; one to both B, E; one to both C and E) that were possibly indicative of allergic contact dermatitis and were rechallenged. An additional 51 subjects (23.5%) had reactions to J and were not re-challenged. During the re-challenge phase, reactions indicative of contact dermatitis were experienced by three subjects, one to 4% lidocaine cream and two to 5% lidocaine cream.

*Reviewer comment: The number of subjects exceeds the number typically accepted by DDDP for contact sensitization studies (i.e., 200). In this reviewer's opinion, the results indicate very low contact sensitization potential for hydrocortisone butyrate 0.1% lotion, including the vehicle (upper bound of a 95% confidence interval using the exact binomial method is 1.7%, according to an analysis performed at this reviewer's request by the biostatistical reviewer). The study design appears adequate. The occurrence of positive reactions to J (more commonly a producer of irritant rather than allergic contact dermatitis) and to several other test articles is reassuring regarding study design and conduct.*

There were no serious AEs and no AEs that were deemed by the applicant to be related to the test materials (with the exception of reactions to tape used to hold patches in place).

**10.1.5 Study 0-2-043: 21-day cumulative irritation study****Trial design:**

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Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

Study sites: 1, USA

Number of subjects: 44

Study period: 7/15/02 to 8/7/02

Objective: To investigate the potential of the test articles to induce cutaneous irritation during 21 days of continuous exposure.

Study population: Single-center, double-blinded study in healthy adult subjects. The investigators screened 47 subjects and enrolled 44 of them, of whom 11 withdrew for reasons unrelated to the study.

Study design: Each subject received 21 consecutive, approximately 24-hour patch applications of 0.2 ml of the following test articles to the right and left arms:

- A: Hydrocortisone butyrate #R6539 (alternative formulation)
- B: Hydrocortisone Butyrate vehicle #R7380 (alternative formulation vehicle)
- C: Hydrocortisone Butyrate #R6546 (to-be-marketed [TBM] formulation)
- D: Hydrocortisone butyrate vehicle #R7173 (TBM formulation vehicle)
- E: Distilled water (negative control)
- F: 0.1% sodium lauryl sulfate w/v

Subjects were instructed to keep the patches on and dry for approximately 24 hours, remove patches 30 to 60 minutes prior to the next visit, and not use other products on the test sites. The grading scale was as follows:

- 0: No evidence of irritation
- 1: Minimal erythema, barely perceptible
- 2: Definite erythema, readily visible; or minimal edema; or minimal papular response
- 3: Erythema and papules
- 4: Definite edema
- 5: Erythema, edema and papules
- 6: Vesicular eruption
- 7: Strong reaction spreading beyond test site

Additionally, letters could be appended to these scores to classify effects on superficial layers of the skin, as follows:

- A: Slight glazed appearance
- B: Marked glazing
- C: Glazing with peeling and cracking
- F: Glazing with fissures
- G: Film of dried serous exudate covering all or portion of the patch site
- H: Small petechial erosions and/or scabs

Any site with score  $\geq 3$  or F, G, or H was not re-patched for the remainder of the study, and a residual score of 3 was carried out for the remainder of the study. Sites demonstrating severe tape irritation from the patch adhesive were dropped and the data for that test article on that subject removed from the final analysis. If/when a maximum score was reached, a grade 3 was entered for all subsequent scoring dates ("converted" score) and a residual score was carried in parentheses for the remainder of the test.

Results:

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NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

**Table 47. Group cumulative mean irritation scores, study 02-043**

Group	Test article	Number of subjects	Mean	SD
A	Hydrocortisone butyrate #R6539 (alternative formulation)	32	9.8	8.2
B	Hydrocortisone Butyrate vehicle #R7380 (TBM formulation vehicle)	31	4.5	7.2
C	Hydrocortisone Butyrate #R6546 (TBM formulation)	31	10.7	10.4
D	Hydrocortisone butyrate vehicle #R7173 (alternative formulation vehicle)	29	3.0	3.2
E	Distilled water (negative control)	33	4.5	5.9
F	0.1% sodium lauryl sulfate w/v	33	53.4	3.2

Source: Mod 5, Vol 26, Page 138.

The applicant's analysis showed the following:

- Test articles A, B, C, and D demonstrated less irritation than F;
- Test article B was significantly less irritating than A
- Test article D was significantly less irritating than C
- No statistically significant difference was found between A and C.

*Reviewer comment: In this reviewer's opinion, the utility of these statistical comparisons, in a study not powered to detect differences and where an irritancy signal may potentially be masked by a comparison of group means or medians, is limited.*

**Table 48. Irritation scores at Day 21, study 02-043**

Group	Test article	Reaction level			
		1	2	3	4
A	Hydrocortisone butyrate #R6539 (alternative formulation)	7	9	9	0
B	Hydrocortisone Butyrate vehicle #R7380 (TBM formulation vehicle)	6	0	3	0
C	Hydrocortisone Butyrate #R6546 (TBM formulation)	11	8	4	8
D	Hydrocortisone butyrate vehicle #R7173 (alternative formulation vehicle)	10	1	1	0
E	Distilled water (negative control)	1	1	1	0
F	0.1% sodium lauryl sulfate w/v	0	0	0	33

Source: Attachment A, Applicant's Response to 2/7/07 Request for Information (stamp date 3/15/07).

*Reviewer comment: There appear to be a greater number of level 4 reactions ("definite edema") with the Locoid lotion TBM formulation compared to all other test articles except the positive control. While these results in and of themselves may be concerning, the very low frequency of application site reactions seen in phase 2 and phase 3 studies is reassuring regarding the irritancy of Locoid lotion.*

There were four AEs (none serious) reported, none of which was deemed related to the test

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Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)  
articles.

**10.1.6 Study 02-044: Primary irritation patch study in humans**

**Trial design:**

Study sites: 1, USA

Number of subjects: 15

Study period: 7/8/02 to 7/12/02

Objective: To investigate the potential of two hydrocortisone butyrate 0.1% lotions (#R6539 and #R6546) and their corresponding vehicles (#R7380 and #R7173) to cause cutaneous irritation after two successive 24-hour occluded patch applications.

Study population: Single-center, double-blinded study in 15 healthy adult subjects.

Study design: Each subject received two successive approximately 24-hour applications of 0.2 ml each of the following test articles to the superior lateral arm:

- A: Hydrocortisone butyrate #R6539 (alternative formulation)
- B: Hydrocortisone Butyrate vehicle #R7380 (alternative formulation vehicle)
- C: Hydrocortisone Butyrate #R6546 (TBM formulation)
- D: Hydrocortisone butyrate vehicle #R7173 (TBM formulation vehicle)
- E: 0.1% sodium lauryl sulfate w/v
- F: Distilled water (negative control)

Evaluations (n=4) occurred after each application and 24 and 48 hours after the second.

The grading system is as follows, with scores for erythema, edema, papules and vesicles were marked as present only if they involved 25% or more of the patch site; identifiable reaction(s) involving less than 25% of the site were documented on the scoring sheet.

- 0: No visible reaction and/or erythema
- 0.5: Slight, confluent or patchy erythema
- 1: Mild reaction – macular erythema (faint, but definite pink)
- 2: Moderate reaction – macular erythema (definite redness, similar to a sunburn)
- 3: Strong to severe reaction – macular erythema (very intense redness)

Letter grades could also be appended to a numerical grade, as follows:

- E: Edema – swelling, spongy feeling when palpated
- P: Papules – red, solid, pinpoint elevations, granular feeling
- V: Vesicles – small elevation containing serous fluid (blister-like), diameter 5 mm or less
- B: Bulla reaction – fluid-filled lesion greater than 0.5 cm in diameter
- S: Spreading – evidence of the reaction beyond the test site
- W: Weeping – result of a vesicular or bulla reaction – serous exudate – clear fluid oozing or covering patch site
- I: Induration – solid, elevated, hardened, thickening skin reaction
- L: Test patch worn less than 23 hours
- XC: Additional comments appear below or on the following page
- Finally, superficial observations could be appended to a numerical and/or letter grade, as follows:

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NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

G: Glazing

- Y: Peeling
- C: Scab, dried film of serous exudate of vesicular or bulla reaction
- D: Hyperpigmentation (reddish-brown discoloration of test site)
- H: Hypopigmentation (loss of visible pigmentation at test site)
- F: Fissuring – grooves in the superficial layers of the skin

Group means for each evaluation time are shown in Table xx:

**Table 49. Group means for each evaluation time, study 02-044**

Group	Test article	Evaluation			
		1	2	3	4
A	Hydrocortisone butyrate #R6539 (alternative formulation)	0.15	0.08	0.23	0
B	Hydrocortisone Butyrate vehicle #R7380 (TBM formulation vehicle)	0.12	0.15	0.15	0.12
C	Hydrocortisone Butyrate #R6546 (TBM formulation)	0.08	0.15	0.23	0
D	Hydrocortisone butyrate vehicle #R7173 (alternative formulation vehicle)	0.19	0.12	0	0
E	0.1% sodium lauryl sulfate w/v	1.46	1.80	1.58	1.40
F	Distilled water (negative control)	0	0.12	0.04	0

Source: Table 1, Mod 5, Vol 26, Page 81

*Reviewer comment: In this reviewer's opinion, the utility of these comparisons, in a study not powered to detect differences and where an irritancy signal may potentially be masked by a comparison of group means or medians, is limited.*

**Table 50. Irritation scores at second evaluation (after second application), study 02-044**

Group	Test article	Subjects with each score level								
		0	0.5	1	1.5	2	2.5	3	3.5	4
A	Hydrocortisone butyrate #R6539 (alternative formulation)	11	2	0	0	0	0	0	0	0
B	Hydrocortisone Butyrate vehicle #R7380 (TBM formulation vehicle)	9	4	1	0	0	0	0	0	0
C	Hydrocortisone Butyrate #R6546 (TBM formulation)	10	2	1	0	0	0	0	0	0
D	Hydrocortisone butyrate vehicle #R7173 (alternative formulation vehicle)	10	3	0	0	0	0	0	0	0
E	0.1% sodium lauryl sulfate w/v	1	3	2	0	7	0	0	0	0
F	Distilled water (negative control)	10	3	0	0	0	0	0	0	0

*Reviewer comment: This analysis does not suggest a concerning irritancy signal for the TBM formulation of Locoid lotion.*

Of three AEs, none were serious and all were unrelated to the test articles.

**10.1.7 Study 04-108:** A 6-week, randomized, controlled study to evaluate the potential of hydrocortisone butyrate lotion 0.1% to induce a photoallergic skin reaction in healthy volunteers, using a controlled photopatch test design

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NDA 22-076/000

Locoid lotion (hydrocortisone butyrate 0.1% lotion)

**Trial design:**

Study sites: 1, USA

Number of subjects: 23

Study period: 4/11/05 to 5/21/05

**Objective:** To evaluate the potential of hydrocortisone butyrate lotion 0.1% to induce a photoallergic skin reaction in healthy volunteers, using a controlled photopatch test design

NOTE: This study was initiated in April 2005 after the sponsor could not dissolve the formulation in common solvents and therefore was unable to demonstrate a lack of relevant absorption. Subsequently, the sponsor was able to dissolve the formulation in \_\_\_\_\_ Peak absorption occurred at \_\_\_\_\_, corresponding to absorption of the drug substance, with slight shoulder absorption at \_\_\_\_\_ attributed to the presence of \_\_\_\_\_ (peak absorption \_\_\_\_\_), which are commonly used in topical formulations. The sponsor then concluded that the drug product did not absorb in the \_\_\_\_\_ of interest and terminated the study. The applicant also states that there have been no photosafety concerns regarding other Locoid® products.

b(4)

*Reviewer comment: According to the pharm/tox review team, the applicant's conclusion regarding the absorption spectrum is supported by the submitted data. Review of postmarketing data submitted in the application did not reveal any possible photosafety events.*

Study population: Single-center, double-blinded study in 23 healthy adult subjects, of whom 18 completed the study.

Study design:

Induction phase: The following test articles were applied under non- or semi-occlusive patch conditions to 2-cm x 2-cm areas twice weekly for 3 weeks:

- Hydrocortisone butyrate lotion 0.1%
- Clindamycin phosphate gel 1%/benzoyl peroxide cream 5%
- Hydrocortisone butyrate lotion 0.1% vehicle
- Clindamycin phosphate gel 1% vehicle
- Benzoyl peroxide cream 5% vehicle

Rest period: 2 weeks; no patches applied.

Challenge phase: One-time applications of patches, followed by irradiation. An untreated irradiated site served as a control.

Results:

Two subjects showed possible evidence of photo-mediated sensitization to hydrocortisone butyrate and its vehicle, as follows:

- Subject 002, who is Caucasian, reacted in the irradiated site to hydrocortisone butyrate lotion 0.1%, its vehicle, and control with "moderate erythema" in the challenge phase. This subject did not show evidence of irritant reactions for hydrocortisone butyrate lotion 0.1% or its

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vehicle during the induction phase. This subject also reacted in both irradiated and non-irradiated sites to benzoyl peroxide cream 5% vehicle with "mild, but definite" "moderate," and "marked/severe" erythema, respectively, at 0, 24, and 48 hours (with this last reaction continuing to 72 hours). (The subject was not phototested to clindamycin phosphate gel 1%/benzoyl peroxide cream 5% or clindamycin phosphate gel 1% vehicle due to previous strong irritant reactions.) Because this subject had the same reaction at the hydrocortisone butyrate lotion and vehicle sites as the subject had at the control site, the applicant asserts, the reaction was due to irradiation, not to the product.

- Subject 006, who is Caucasian, reacted in the irradiated site to hydrocortisone butyrate lotion 0.1% with "mild, but definite" erythema at 24 hours only and did not react to its vehicle. This subject also reacted in the irradiated site of benzoyl peroxide cream 5% vehicle with "mild, but definite" erythema at 24 hours and in both irradiated and non-irradiated sites to clindamycin phosphate gel 1% vehicle with "mild" erythema at 0 hours, increasing to "moderate" erythema at 24, 48, and 72 hours. The subject did not react in control sites. The subject was not phototested to clindamycin phosphate gel 1%/benzoyl peroxide cream 5% due to previous strong irritant reactions.

*Reviewer comment: In this reviewer's opinion, because Subject 002 had comparable reactions to hydrocortisone butyrate lotion 0.1%, its vehicle, and control, it is a reasonable assumption that this subject experienced a photoreaction at all three sites, independent of the drug or its vehicle. Subject 006's reaction to hydrocortisone butyrate lotion 0.1% suggests a phototoxic or photoallergic reaction. (Of note, a phototoxicity study was not performed. Although the applicant does not specifically state the reason for this, it is likely because of the absorption-spectrum findings were thought to obviate the need for such testing. Additionally, it is noted that the applicant did not list subject 006 as having had a photosensitivity reaction.) However, subject 006 did not react to hydrocortisone butyrate lotion 0.1% vehicle. Therefore, the putative agent acting as the photoallergen or phototoxin for this subject is the hydrocortisone butyrate 0.1% itself. According to the applicant (as discussed above), there have been no photosafety concerns regarding other Locoid® 0.1% formulations. In this reviewer's opinion, this post-marketing experience, combined with the absorption-spectrum data discussed above, renders less concerning the results from subject 006 alone and do not raise a public health concern regarding photosafety that would require additional pre-marketing testing. However, in this reviewer's opinion, for the first year after approval the sponsor should be required to submit summaries of any AEs potentially related to photosafety in quarterly safety reports.*

AEs (n=3) were deemed unrelated or unlikely to be related to the study product.

**10.1.8 Study 01-036:** Vasoconstrictor study to rank the relative potency of hydrocortisone butyrate lotion 0.1% with respect to approved topical corticosteroid preparations

#### **Trial design:**

Study sites: I, USA

Number of subjects: 37 (36 included in analysis)

Study period: 7/15/02 to 8/9/02

Objective: To rank the relative potency of hydrocortisone butyrate lotion 0.1% with respect to

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Kenneth A. Katz, M.D., M.Sc., M.S.C.E.

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Locoid lotion (hydrocortisone butyrate 0.1% lotion)

approved topical corticosteroid preparations

Study population: Single-center, double-blinded study in 37 healthy adult subjects with demonstrated capacity to exhibit vasoconstriction in response to topical application of a reference-listed drug (Locoid Lipocream®).

Study design: Approximately 5.5 mg of each test article (at approximately 7 mg/cm<sup>2</sup>) was applied to one of seven 1-cm-diameter test sites on the ventral forearms for 16 hours. Test articles included the following:

- Hydrocortisone butyrate 0.1% lotion (#R6546) (TBM formulation)
- Hydrocortisone butyrate 0.1% lotion (#R6539) (alternative formulation)
- Hydrocortisone butyrate 0.1% lotion vehicle (#R7173) (TBM vehicle)
- Hydrocortisone butyrate 0.1% lotion vehicle (#R7380) (alternative vehicle)
- Locoid Lipocream® (hydrocortisone butyrate 0.1%)
- Hytone® 2.5% (hydrocortisone) lotion
- Diprolene AF® (betamethasone dipropionate) cream

*Reviewer comment: According to a standard U.S. dermatology textbook (Valencia IC, Kerdel FA. Topical glucocorticoids. In: Freedberg IM, et al. Fitzpatrick's Dermatology in General Medicine. 6<sup>th</sup> ed. New York: McGraw-Hill; 2003. p. 2324-8), potency rankings of the topical corticosteroids used in this study are shown below. There are seven classes, with class 1 the most potent:*

- Locoid® Lipocream hydrocortisone butyrate cream 0.1% 2 – class 5 (mid-strength)
- Hytone® 2.5% hydrocortisone lotion – class 7 (mild)
- Diprolene® AF cream – class 2 (potent)

Criteria for evaluation:

Blanching: Degree of vasoconstriction, graded visually two hours after test article removal, as follows:

- 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

Safety: Current medical conditions, concomitant therapies, AEs

Blanching data:

**Table 51. Mean blanching scores, study 01-036**  
(n=36 subjects for all)

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

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The applicant's analysis showed that there was significantly greater blanching with Locoid® Lipocream than with all other treatment groups. Diprolene® AF cream's blanching was significantly greater than vehicle A, vehicle B, and Hytone®. The mean blanching scores for both hydrocortisone butyrate 0.1% lotions were significantly greater than Hytone®. There were no other statistically significant differences for any other pair-wise comparisons.

*Reviewer comment: There was no statistically significant difference, according to the sponsor's analysis, between Diprolene AF® cream, a class 2 (potent) topical corticosteroid, and either of the hydrocortisone butyrate lotion 0.1% formulations.*

The applicant concluded that these data do not provide definitive potency rankings for either hydrocortisone butyrate lotion 0.1% formulations, that these formulations are of similar potency, and that they fall between Locoid® Lipocream (mid-potency) and Hytone® (low-potency) reference products. The applicant notes that the findings for the high-potency reference product (Diprolene® AF) and the low-potency reference product (Hytone® cream) are lower than expected. The applicant concludes: "Variability is well known in human assays and no technical issues causing variable results were identified."

*Reviewer comment: Because an equivalency margin between the two hydrocortisone butyrate lotion 0.1% formulations was not pre-specified, it does not seem appropriate to this reviewer to accept the conclusion that these formulations have the same potencies on the basis of these data. Furthermore, the performance of the reference corticosteroids was not as anticipated, raising questions about the overall validity and reliability of the study. To the extent that these data are valid, however, these results indicate that there is no statistically significant difference in potency between hydrocortisone butyrate 0.1% lotion and Diprolene AF®, a class 2 (potent) topical corticosteroid. Therefore, the applicant's potency claim in proposed marketing –*

— is not supported by the data.

b(4)

Safety data:

There was one non-serious adverse event that not related to the test articles.

**10.1.9 Study 03-097:** A randomized, blinded, single-center evaluation of the vasoconstrictive properties of 0.1% hydrocortisone butyrate lotion in normal healthy volunteers

**Trial design:**

Study sites: 1, USA

Number of subjects: 36

Study period: 6/20/05 to 6/23/05.

Objectives:

1. 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 other topical corticosteroid formulations of different potency ranking.
2. To evaluate the relative vasoconstriction potency of the 0.1% hydrocortisone butyrate lotion to four commercially available 0.1% hydrocortisone butyrate formulations (solution, cream,

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ointment and Lipocream) using visual (primary) assessment and chromameter (secondary) assessment of the vasoconstriction response.

Study population: Single-center, double-blinded study in 36 healthy adult subjects with vasoconstrictive responsiveness.

Study design: Each subject had five 4-cm<sup>2</sup> sites on both forearms evaluated for vasoconstriction response to as many as five different topical steroid formulations following a single dose application duration of 16 hours. There were two additional control (untreated) sites on each forearm. Test articles were as follows (with classes and potencies of reference products, based on Valencia 2003, following) for Objective 1 (see above):

- Locoid® lotion hydrocortisone butyrate 0.1% lotion
- Clobex® topical lotion 0.05% clobetasol propionate (cream, ointment, and foam formulations listed as class 1 – superpotent; lotion formulation not listed)
- Cutivate® cream 0.05% fluticasone propionate (class 5 – mid-strength)
- Cutivate® ointment 0.05% fluticasone propionate (class 3 – potent)
- Hytone® lotion 2.5% hydrocortisone – (class 7 – mild)

Test articles were as follows for Objective 2 (see above):

- Locoid® lotion hydrocortisone butyrate 0.1% lotion
- Locoid® ointment 0.1% hydrocortisone butyrate (cream formulation listed as class 5 – mid-strength; ointment formulation not listed)
- Locoid® solution 0.1% (cream formulation listed as class 5 – mid-strength; solution formulation not listed)
- Locoid Lipocream® 0.1% (cream formulation listed as class 5 – mid-strength; Lipocream® formulation not listed)
- Locoid® cream (class 5 – mid-strength)

Blanching: 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.

Statistical analysis:

For both visual and chromameter scores, data were presented as means and analyzed using the Ryan-Einot-Gabriel-Welsch (REGW) Multiple Range Test, which according to the applicant is appropriate as the multiple comparison test of choice to determine pair-wise treatment differences.

*Reviewer comment: The appropriateness of presenting results solely as means (rather than medians) as well as the appropriateness of this statistical test are not clear to this reviewer. Additionally, 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:*

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*In this study, unlike the previous study (01-036), the potent (class 2) steroid Diprolene AF® was not studied. The previous study was not able to differentiate between Locoid lotion and Diprolene AF® in terms of vasoconstriction. Therefore, despite the results of the current study, there are still data that have not been refuted that indicate that Locoid lotion has the same vasoconstrictor potency as a class 2 steroid. On this basis, the applicant's proposed potency claim in labeling is not supported, in this reviewer's opinion.*

b(4)

Safety: AEs occurring during the study.

Blanching data:

NOTE: In the following tables, based on the applicant's analyses, test articles are ranked in order, top to bottom, from lowest to highest potency. Differences in blanching between test articles with similar letter values are not statistically significant, according to the applicant. Standard deviations were not presented in applicant's analysis. For details about topical corticosteroid class, see above. (Note: REGW: Ryan-Einot-Gabriel-Welsch Multiple Range Test.)

**Table 52. Objective 1 – Visual score data, study 03-097**

Mean score	Test article (class)	REGW test
0.0000	Hytone® lotion (7)	W
0.0000	Control	W
0.5278	Cutivate® cream (5)	X
0.8056	Locoid® lotion	X
1.5833	Clobex® lotion (1)	Y
2.0833	Cutivate® ointment (3)	Z

<sup>a</sup> Cream and ointment formulations listed as class 1; see above.

Source: Mod 5, Vol 2, Page 35

**Table 53. Objective 1 – Chromameter data, study 03-097**

Mean score	Test article (class)	REGW test
0.1386	Hytone® lotion (7)	X
0.0003	Control	X
-0.9061	Cutivate® cream (5)	Y
-1.0242	Locoid® lotion	Y
-2.4569	Clobex® lotion (1)	Z
-2.5394	Cutivate® ointment (3)	Z

Source: Mod 5, Vol 2, Page 36

The applicant concluded that Locoid® lotion is not statistically different from Cutivate® cream, is statistically different from Hytone® lotion, Clobex® lotion, and Cutivate® ointment, and therefore “demonstrates a vasoconstriction response consistent with those products classified as class 5 topical corticosteroids.

*Reviewer comment: It is somewhat surprising that in the visual-score analysis, Cutivate® ointment, listed as a class 3 product, was more potent than Clobex® lotion, which contains clobetasol propionate 0.05% (listed as a class 1 product in cream, ointment, and foam*

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formulations). This may be due to the Clobex® vehicle, as vehicles may affect topical corticosteroid potencies (Valencia 2003; Franz TJ. Pharmacokinetics and the skin. In: Bologna JL, et al, editors. London: Mosby; 2003. p. 1975-8). In Objective 2 data shown below, however, a more occlusive vehicle formulation (i.e., ointment) typically associated with higher potency demonstrated lower potency than other formulations.

**Table 54. Objective 2 – Visual score data, study 03-097**

Mean score	Test article (class)	REGW test
0.0000	Control	X
0.4306	Locoid® ointment	Y
0.6806	Locoid® solution	Y
1.0139	Locoid® cream (5)	Z
1.1528	Locoid® Lipocream	Z
1.2083	Locoid® lotion	Z

Source: Mod 5, Vol 2, Page 36

Reviewer comment: 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 noted by the applicant. 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).

**Table 55. Objective 2 – Chromameter data, study 03-097**

Mean score	Test article (class)	REGW test
-0.0014	Control	W
-0.8831	Locoid® ointment	X
-1.1328	Locoid® solution	X Y
-1.4597	Locoid® cream (5)	Z Y
-1.6389	Locoid® Lipocream	Z Y
-1.8528	Locoid® lotion	Z

Source: Mod 5, Vol 2, Page 37

Reviewer comment: 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 noted by the applicant.

The applicant concluded that the blanching induced by Locoid® lotion is not statistically different from that induced by Locoid® cream or Lipocream and is statistically different from that induced by Locoid® ointment and solution.

Reviewer comment: As stated above, this medium-potency 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.

Safety results: There were two non-serious AEs, neither related to the test articles.

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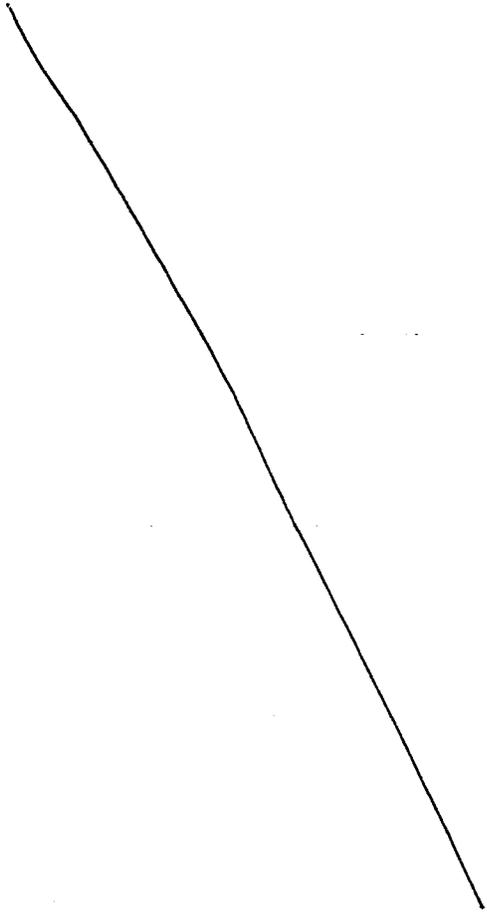
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**10.2 Line-by-Line Labeling Review**

Please refer to the approval letter for the final FDA-approved package insert. The final draft package insert appears below, followed by a comment from this reviewer.



**b(4)**

10 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Kenneth A Katz  
4/24/2007 03:28:11 PM  
MEDICAL OFFICER

Markham Luke  
4/25/2007 10:24:40 AM  
MEDICAL OFFICER

Concur with Approval Recommendation. See Clinical TL secondary review  
regarding other recommendations.

Stanka Kukich  
5/17/2007 09:39:27 AM  
MEDICAL OFFICER

Please see Lead Medical Officer's Secondary Review