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RESEARCH**

APPLICATION NUMBER:

21-152

MEDICAL REVIEW

NDA 21-152 N-000 RZ
Cutivate Lotion
Clinical Team Leader Review

Indication: Atopic Dermatitis
Submitted: February 1, 2005
PDUFA Due Date: April 1, 2005
Review Date: March 14, 2005
Revised Date: March 21, 2005

Background:

See prior Clinical Team Leader Secondary Review dated January 12, 2005 and prior discipline reviews for this NDA.

The NDA application (21-152) for Cutivate Lotion was given an approvable action on January 12, 2005. Outstanding Clinical issues included:

- 1) Labeling discussion – A revised proposed label from the Agency was sent to the applicant on December 16, 2004. However, no response was received from the applicant to accept the proposed label until this submission. On January 6, 2005, the Agency had received correspondence stating the applicant's commitment to further labeling negotiations with the Division.
- 2) Pediatric studies in the 3 month to 1 year age group – Review of the original submission stated that "Of significant note, the safety and efficacy studies had relatively few patients in the 3 months to 1 year age group, a group of patients in which atopic dermatitis does occur." In the action letter of January 12, 2005, the applicant was asked to present plans to evaluate the safety (both local and systemic, to include laboratory tests) and systemic availability of this product for the treatment of ~~atopic dermatitis~~ atopic dermatitis in patients age 3 months to 1 year.
- 3) The applicant was asked to present plans to evaluate the long term safety of the product when used in humans as per ICH E1A.

Additional Pharmacology/Toxicology and Chemistry/Manufacturing/Controls information also remain outstanding (see items 4, 5(a) through 5(j) in the January 12, 2005 letter). Further, the Agency asked, "When you respond to the above deficiencies, please also include a safety update as described in 21 CFR 314.50(d)(5)(vi)(v). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level."

Review:

This submission, received February 1, 2005, was deemed to be a complete response to the Approvable letter of January 12, 2005.

The applicant responds to the specific issues outlined in the January 12, 2005 letter. This review includes review of proposed labeling changes.

A) Product Name –

The current application desired that the product be named CUTIVATE (fluticasone propionate 0.05%, however this was discussed further with the applicant and it was agreed that “Lotion” is preferred by the Agency in place of [redacted] and should be used in the proprietary name. The designation [redacted] is not acceptable [redacted] lotions with regard to viscosity. See also CMC review. On discussion with the applicant on the March 10, 2005, the CMC review team, Clinical, and the applicant came to agreement that the product should have the proprietary name of CUTIVATE Lotion.

Further, as there were concerns regarding the suffix [redacted] (see DMETS review of July 8, 2004) this suffix will not be used.

The labeling will be adjusted accordingly.

B) Clinical Pharmacology section –

The applicant proposes two changes to the Clinical Pharmacology section of the labeling. The first to re-insert text previously included in other fluticasone propionate labels: “Although fluticasone propionate has a weak affinity for the progesterone receptor and virtually no affinity for the mineralocorticoid, estrogen or androgen receptors, the clinical relevance as related to safety is not fully known.” This statement appears to be appropriate and inform as to factors relevant to the safe use of this drug product. This reviewer would recommend that this statement be re-inserted.

The second item is regarding the subsection named “Special Population (Pediatric).” The applicant would like to insert the statement that [redacted]

[redacted]

C) Clinical Trials section –

This section should remain unchanged from the last action letter sent by the Agency.

The complete clearance rate was used as an Agency endpoint that provides meaningful information for labeling. Lesser efficacy evaluations such as that proposed by the applicant of a percentage of patients who achieved a success criterion of 50% of lesions cleared plus improvement or no change in at least 75% of remaining lesions appears contrived and is not clinically compelling.

D) PRECAUTIONS section –

1) General –

The paragraphs on the pediatric HPA axis study were proposed to be modified by the applicant. These revisions were reviewed, and after discussion with the

Biostatistics and Clinical Pharmacology reviewers, the following language is proposed:

“Forty-two pediatric patients (4 months to < 6 years of age) with moderate to severe atopic eczema who were treated with CUTIVATE Lotion for at least 3 to 4 weeks were assessed for HPA axis suppression and 40 of these subjects applied at least 90% of applications. None of the 40 evaluable subjects suppressed, where the sole criterion for HPA axis suppression is a plasma cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Although HPA axis suppression was observed in 0 of 40 pediatric patients (upper 95% confidence bound is 7.2%), the occurrence of HPA axis suppression in any patient and especially with longer use cannot be ruled out. In other studies with fluticasone propionate topical formulations, adrenal suppression has been observed.”

2) Pediatric Use -

The applicant proposes to delete the majority of the Pediatric Use section as proposed by the Agency. This reviewer recommends that this section be retained as was proposed in the January 12, 2005 action letter. However, the second paragraph detailing the study in 40 patients for HPA axis suppression could be modified to reflect the changes from the general Precautions section.

3) Geriatric Use -

E) Post-marketing commitments –

- 1) The applicant “recognizes that, although there were patients less than 12 months of age included in both the pivotal and safety studies performed in support of the application, the number of patients were relatively low.” Despite this, the applicant has “no plans to further evaluate the safety of CUTIVATE...in children under the age of 12 months.”

Taking into consideration the Pediatric Research and Equity Act of 2003, the applicant should commit to conduct a post-marketing study to evaluate the safety (both local and systemic, to include laboratory tests) and systemic bioavailability of this product for the treatment of atopic dermatitis in patients ages 3 months to 1 year.

The timing of the study (which may be negotiable with the applicant prior to commitment) could be as follows:

Study Protocol submission	By September 1, 2005
Study Start Date	By March 1, 2006
Final Report Submission	By March 1, 2007

- 2) The applicant “has determined that there is no concern that this drug would cause late developing adverse drug events or cause adverse drug events that increase in severity or frequency over time. Therefore, the ongoing safety of

CUTIVATE...will be monitored through the [applicant's] safety reporting process where adverse event reports (from spontaneous, clinical studies, literature sources, etc.) are collected and submitted to the FDA in accordance with 21 CFR 314.80 and 21 CFR 314.81. The safety of CUTIVATE (fluticasone propionate) has been established through the work submitted in [this] NDA and the approved NDAs for Cream (NDA 19-958) and Ointment (NDA 19-957), supplemented by millions of exposures ([REDACTED] packs sold in the US alone) since launch of the approved products in 1990."

This argument appears to be reasonable and this reviewer agrees that a need for long-term safety studies could be waived for this product given the preponderance of safety information supporting the moiety.

F) Pharmacology Toxicology Concern: Photoco-carcinogenic Potential Study-

The Division requested that the applicant submit their plan for conduct of a study to determine the photoco-carcinogenic potential of Cutivate Lotion. The applicant was referred to the guidance document titled "Guidance for Industry – Photosafety Testing" published in May 2003. The applicant considered "the data submitted to NDA 21-152 to be sufficient to appropriately evaluate the photoco-carcinogenic potential of CUTIVATE...and as such, considers photocarcinogenicity testing to be unnecessary."

The photoco-carcinogenic potential study continues to be recommended by the review team (see Pharmacology/Toxicology Review and Evaluation by Dr. Barbara Hill).

G) Safety Update:

Under Attachment X (page 84) in the submission, the applicant addresses the concern outlined in the January 12, 2005 action letter regarding the need for a revised safety update. The safety update and attachments were reviewed and determined to mostly consist of non-serious adverse events or likely unrelated events. Of specific interest to this reviewer is a case of HPA "disorder" for an unknown formulation of fluticasone propionate (US Case ID A0132778A from November 16, 2000). Little further detail was provided on this case.

This case and other case line listings do not appear to provide additional concerns for labeling at this time, however. It is recommended that the original Adverse Events section of labeling communicated with the applicant on January 12, 2005 be used.

Conclusion:

It is recommended that this application be Approvable, with final approval pending the applicant's acceptance of the Agency's proposed labeling and the commitments to conduct post-marketing studies for pediatric patients less than 1 year of age and for photoco-carcinogenicity evaluation. Changes to specific sections should be made to the draft label as discussed above.

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

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/s/

Markham Luke
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Clinical TL Review for Cutivate Lotion - NDA complete
response to Approvable letter of January 12, 2005.

Jonathan Wilkin
3/30/05 06:21:02 PM
MEDICAL OFFICER

**NDA 21-152 N-000 Cutivate Lotion
Clinical Team Leader Secondary Review**

Indication: Atopic Dermatitis
Submitted: March 12, 2004
PDUFA due date: January 12, 2004
Review date: December 22, 2004
Revised date: January 12, 2005

While the primary clinical reviewer has conducted a careful review of this NDA submission, the Clinical Team Leader disagrees with the recommendation for non-Approval. Although the two clinical studies were not conducted in a manner recommended by the Agency, both the Applicant's analysis and the Agency's sensitivity analysis on a population selected on the basis of entry severity indicate that the drug product Cutivate Lotion is superior to vehicle as demonstrated in two independent clinical studies. The clinical studies, the dermal and systemic safety studies, and the post-marketing safety assessment of other products containing the active ingredient, fluticasone propionate, provide sufficient basis to evaluate the safety of this drug. The Clinical Team Leader recommends that the NDA be approvable with a post-marketing commitment as outlined in the conclusion (regarding pediatric studies).

Patients were not recruited as would reflect actual use of this product in clinical conditions, but rather according to their background chronicity of disease. This concern is circumvented by ensuring via statistical analysis that the patient allocation was equal to both arms in each study (which was indeed the case – see Dr. Fritsch's review). In addition, the primary endpoint for efficacy is not a valid endpoint to be used in assessing the efficacy of a drug for treatment of atopic dermatitis. This was informed to the Applicant, but the advice was not followed. However, Agency analysis that was performed used the stringent criteria of zero or "completely clear" in a subset of patients with more severe disease according to components of EASI.

Regulatory History

The Applicant submitted two identically designed Phase 3 studies that were conducted in subjects with atopic dermatitis, Studies FPL30003 (Study 3) and FPL30004 (Study 4). It was discussed at the End-of-Phase 2 Meeting on May 7, 1998 that the primary efficacy variable should be an Investigator's Global Evaluation (IGE) of disease severity at the end of treatment. Further, review of the submitted protocol resulted in comments faxed to the Applicant on March 17, 1999 that stated the Agency did not agree with the use the proposed Eczema Area and Severity Index (EASI – a composite score) as the primary efficacy endpoint, nor did the Agency agree with the use of the Rajka/Langeland Severity Grading Scale (a measure of chronic eczema severity that does not account for acute severity) for baseline determination. Baseline entry criteria and evaluation should use the same acute severity scale as the primary efficacy endpoint. These concerns were reiterated to the Applicant on April 19th, 1999 at the pre-NDA meeting: "EASI is a derivative and obscures the primary information. Therefore, treatment success defined by the EASI score, an unvalidated tool, would not be

appropriate. Using the EASI score as a tertiary variable in the trials would be more appropriate...” However, at the same meeting, the Agency agreed that derivation of an efficacy endpoint may be performed by the Agency: “The latter efficacy variable would be derived from some of the components of the EASI score tabulated separately.” This is not the preferable route for product development.

The two clinical studies submitted to the NDA used both EASI scoring for the primary endpoint and the Rajka/Langeland Scale for determination of entry criteria. The original application was withdrawn shortly after submission, but resubmitted largely unchanged for this review cycle.

Clinical Efficacy

The Applicant has chosen to pursue an alternative strategy to drug development from what was advised by the Agency. The careful statistical analysis and review by the Agency Biostatistician suggest that there may be sufficient evidence of efficacy from the conducted studies. Study 3 enrolled 220 patients, 110 Cutivate Lotion and 110 vehicle; Study 4 enrolled 218 patients, 111 Cutivate Lotion and 107 vehicle. The protocol had defined clinical success as at least a 75% reduction in EASI from baseline. However, baseline enrollment was not dependent on a severity cut-off for acute atopic dermatitis using EASI. Instead, enrollment was based on the Rajka/Langeland scale. Thus, the studies that were conducted with EASI were not designed to evaluate the aspects of atopic dermatitis that would be of interest to the Agency or to practicing dermatologists who would be using such a product. So, even though the Applicant achieved statistical significance using criteria chosen a priori for success, that analysis was by itself not meaningful and would not be sufficiently informative for labeling. Because of this, a re-analysis was performed using sparse or parsimonious criterion, i.e., completely clear, as chosen by members of the clinical team at FDA. This analysis is admittedly more stringent due to the requirement that the patients completely clear in order to be a success, however, this stringency is needed to accommodate the lack of acceptable inclusion criteria and the difficulty of finding “almost clear” using EASI.

This concern with regard to the need for acute evaluation of the severity of the patients at baseline resulted in clinical discussion and selection of minimum baseline criteria (MBLC) with regard to atopic dermatitis disease severity. Further, the success endpoint for that subset of enrolled patients would be those patients that cleared (score of 0) of erythema, infiltration/papulation, and erosion/oozing/crusting. Early in the review process for this submission, the review team agreed to the different primary analysis that would provide useful clinical information from the studies conducted. This was agreed to prior to implementation of such an analysis (see Biostatistics review for details).

The resulting table for this analysis for the two studies is presented below:

Table 1 – Clearance Rate (MBLC)

	Fluticasone	Vehicle	p-value
Study 3	9/45 (20%)	0/37 (0%)	0.0102
Study 4	7/44 (16%)	1/43 (2%)	0.0410

Source: Reviewer analysis (see Biostatistics review by Dr. Kathy Fritsch)

While the original study and these data were not intended to be used in such a fashion, the analysis supports a modicum of efficacy with Cutivate Lotion that is higher than that of vehicle. With point estimates for success obtained for clearing of disease from baseline from 16% and 20% for the active arm, the Applicant achieved statistical significance with the more clinically relevant endpoint for the conducted studies.

A key concern is that if EASI is indeed an unacceptable endpoint, can endpoints that are derived from components of EASI become valid? As mentioned above, the score required for a success is complete clearing, an unambiguous score that would be a success in largely any other evaluation scale.

The primary clinical reviewer has indicated that there were several protocol violations, which if excluded would bring question to the statistical significance of the study results. Key concerns were the use of concomitant medication and the length of time for treatment. While this concern is valid with regard to evaluating the overall efficacy, statistical significance is determined using the ITT or intent-to-treat population. Further, the protocol violations were in both arms, but more so in the vehicle arm (likely due to the relatively low efficacy or even irritating nature of the lotion vehicle). See Biostatistics review for further discussion of the per-protocol analysis.

It must be stressed that any future drug development plan for atopic dermatitis should not use EASI for later stage studies as this scale is a composite score that has many permutations that are not useful for the medical practitioner. No patient with atopic dermatitis in day-to-day practice is assessed using this scale. Further, the evaluation of atopic dermatitis should be done for the acute disease. Baseline determination for study eligibility and patient assessment should be via an Investigator's Global Evaluation.

Both the biostatistics review and the primary clinical reviewer are correct in the assertion that the Agency analysis using a different inclusion criteria is post-hoc. Agency agreement to conduct such an analysis was implied in the minutes of the pre-NDA meeting held on April 19, 1999. Thus, efficacy derived from such an analysis, which was conducted in a careful manner by the Agency biostatistician and clinical reviewer provides valid efficacy data for the following key reasons:

- 1) Two studies were conducted with signals that were consistent.
- 2) The Sponsor owns other approved products in which the active is in different vehicles at the same or lower concentrations.
- 3) There was agreement at the Pre-NDA meeting, which would not likely be offered in the future, i.e. a post-hoc evaluation. In general, post-hoc evaluations offer little regulatory utility.

Clinical Safety

The safety of Cutivate Lotion was assessed by the Applicant in the two pivotal safety and efficacy studies, as well as, the dermal safety and HPA axis suppression studies. On review of these studies by the Agency, no safety events were evident to disqualify the use of Cutivate Lotion in an Rx setting. Of significant note, the safety and efficacy studies had relatively few patients in the 3 months to 1 year age group, a group of patients in which atopic dermatitis does occur.

It is also important to stress that even though none of the 40 evaluable patients in the HPA axis study were suppressed, there is sufficient concern for HPA axis suppression

given what is known about other drug products containing the active corticosteroid ingredient. Further, the upper 95% confidence bound for 0 out of 40 is 7.2%.

Labeling for this product should reflect these concerns.

The primary medical reviewer's concerns regarding outcome in exposed pregnancies does not warrant further evaluation for this drug in the Clinical TL's opinion. There is information from this class of corticosteroid compounds that would suggest no reason for additional concern for fluticasone. No new non-compendial excipients are used in the product formulation that would raise additional concern for teratogenicity.

Drug Name

The Clinical Team Leader recommends that this product have the proprietary name of "Cutivate Lotion" as was originally proposed by the Applicant with the original NDA submission. The concerns regarding the suffix [REDACTED]

[REDACTED] see DMETS review dated July 8, 2004). [REDACTED]

[REDACTED] See also CMC review and letter from CMC to Applicant on this matter. It would be better to have a more specific term to inform the practitioner as to substantivity of the drug product.

Therefore, "Cutivate Lotion" is recommended as the name for this product.

Conclusion

In summary, it is recommended that Cutivate Lotion be approvable for marketing with labeling changes as suggested by the Agency. Additionally, in one post-marketing study, the Applicant should further evaluate the safety (both local and systemic) of use of this product in the 3 month to 1 year age group in at least 45 evaluable patients with atopic dermatitis affecting at least 25% of the body. Such an evaluation could include biopharmaceutic measurements of levels of the drug substance and metabolites and additional laboratory work as indicated to be needed (see also page 68 of primary clinical review).

Wording for the post-marketing commitment from Clinical could be as follows: [REDACTED] evaluate the safety (both local and systemic – including laboratory tests) and systemic availability of this product for the treatment of [REDACTED] atopic dermatitis in patients age 3 months to 1 year."

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

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/s/

Markham Luke

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MEDICAL OFFICER

Clinical TL secondary review. Recommendation for Approval with a
post-marketing commitment.

Jonathan Wilkin

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MEDICAL OFFICER

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Medical Officer's Review of NDA 21-152

Clinical Reviewer: Michael Albert, M.D.

Generic Name: Fluticasone propionate lotion 0.05%

Proposed Trade Name: _____

Pharmacological Category: Topical Corticosteroid

Indication: Inflammatory and Pruritic Manifestations of Atopic Dermatitis

Dosage Form: Lotion

Route of Administration: Topical

Dates: Correspondence: March 11, 2004
CDER Stamp Date: March 12, 2004
Review Completed (in DFS): December 22, 2004
PDUFA Goal Date: January 12, 2005
(This review was entered again into DFS, without revision, on January 6, 2005)

Sponsor: GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ 07054

Review Division: Division of Dermatologic and Dental Drug Products (HFD-540)

Team Leader: Markham Luke, M.D., Ph.D.

Division Director: Jonathan K. Wilkin, M.D.

Project Manager: Millie Wright

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The two phase 3 studies (FPL30003, FPL30004) submitted to support the efficacy of fluticasone propionate lotion were seriously flawed from a clinical standpoint.

The phase 3 studies were designed to study patients with [REDACTED] atopic dermatitis. However, the sponsor did not follow Agency recommendations regarding inclusion criteria, and most patients enrolled had mild or even minimal disease (based on an assessment by the Agency for this submission). These patients should not have been candidates for the studies and make interpretation of the results extremely problematic. In addition, major protocol violations occurred in a high percentage of patients; approximately 25% of patients in each study were reported by the sponsor to have had at least one major protocol violation. An additional flaw in these studies was the use of the Eczema Area and Severity Index score and a dynamic Investigator's Global Evaluation to measure treatment effect, contrary to the recommendations made by the Agency.

During the review of this NDA, the Agency conducted a post-hoc analysis to attempt to determine efficacy in the subset of patients who might have met inclusion criteria for [REDACTED] based on the clinical signs recommended by the Agency for disease assessment. A total of only 38% of patients in phase 3 studies met the minimum baseline criteria used for inclusion in this analysis. The results of such a post-hoc analysis, not pre-specified in the protocol, need to be interpreted with caution. Because such an analysis cannot take the place of adequately conducted prospective clinical trials with appropriate inclusion criteria and efficacy endpoints, it can be viewed as supportive only and is not necessarily sufficient to serve as the basis for demonstrating drug efficacy from a clinical perspective. In any case, the results of this analysis were not definitive; although there was an efficacy signal, the difference between the vehicle and active groups did not reach statistical significance in either study when protocol violations were taken into account.

C. Safety

Safety testing was inadequate for this drug product. As noted above, the majority of patients in phase 3 studies (FPL30003, FPL30004) were determined by an Agency analysis to have mild or minimal disease. Patients with more severe disease would be expected to apply more lotion, have increased drug absorption, and be more susceptible to certain adverse events.

[REDACTED] Salient safety findings are summarized here and detailed in greater depth in this review; however, a larger patient population is needed to accurately determine the drug's safety profile.

Burning and stinging was the most commonly reported drug-related adverse event in phase 3 studies. Because there was no appreciable difference in burning and stinging or pruritus between the vehicle and fluticasone groups, it appears that vehicle ingredients may be responsible. The vehicle formulation contains 10% propylene glycol, which is known to be a potential irritant. Among adverse events occurring with greater frequency in the active treatment arm was influenza; five cases of influenza were reported in

patients receiving fluticasone propionate and no cases were reported in the vehicle group. All reported influenza cases occurred in patients in the 17 - 65 year age group. A serious adverse event that occurred in phase 3 studies was an episode of eczema herpeticum in a 33-year-old male receiving fluticasone propionate lotion. The causal role of fluticasone in this episode is uncertain; the investigator did not consider it drug related.

In the HPA axis suppression study (FPL10005), no patients met the currently recommended Division criterion for HPA axis suppression (the sole criterion for suppression being a 30-minute post-stimulation serum cortisol level of ≤ 18 $\mu\text{g/dL}$). The sponsor's consultant pediatric endocrinologist and reviewers from the Agency's Division of Metabolic and Endocrine Drug Products agreed that 2 patients in this study may have sustained partial suppression of the HPA axis, although this was not considered to be of likely clinical significance. Nonetheless, recommendations made by the reviewers from the Agency's Division of Metabolic and Endocrine Drug Products include cosyntropin stimulation testing before and after exposure to fluticasone propionate lotion 0.05% for ≥ 21 - 28 days.

Plasma fluticasone levels were also measured in patients ≥ 2 years of age in the sponsor's HPA axis suppression study. A total of 13 (62%) of 21 patients had measurable plasma fluticasone at the end of treatment. Three patients had fluticasone levels over 300 pg/mL , with one patient having a level of 819.81 pg/mL . No information was obtained for patients < 2 years of age.

Laboratory evaluations were performed in pediatric patients in the HPA axis suppression study as well. One notable finding was that in patients in the 3 month - 3 year age group, AST levels were elevated in 14 (74%) of 19 patients at baseline and 19 (95%) of 20 patients at the end-treatment visit. It is unclear why such a high percentage of patients had an elevated AST both at the baseline and the end-of-treatment assessments. One 4-month-old male patient had marked elevations of both AST and ALT during the study. His baseline values were elevated, with an AST of 113 U/L (normal range 11-36 U/L), and an ALT of 110 U/L (normal range 6-43 U/L). The end-of-treatment AST for this patient was 366 U/L, and the ALT was 523 U/L. This finding was initially coded as possibly drug related but based on follow-up was eventually assessed as not drug related. AST elevations occurring during the study were not high in other patients. Although the Agency had requested that clinical laboratory evaluations be performed in at least 30 patients in the lowest age group (3 months - 3 years), the study included fewer than 20 evaluable subjects in this age group.

In the repeat insult patch test study (FPL10003), the majority of subjects (57%) exhibited a grade 1 reaction (excluding patients who had a tape reaction alone) at some time during the study. Semi-occlusive patch conditions may have contributed to this high rate of irritancy. A total of 8 (4%) of 204 subjects exhibited a grade 1 reaction during the challenge phase. The lotion contains imidurea, methylparaben, propylparaben, and propylene glycol, which are known contact sensitizers. Fluticasone propionate may also act as a sensitizer, but has been previously described as having a low sensitization potential.

A consultation was made to the Office of Drug Safety to review postmarketing adverse events for other fluticasone-containing dermatologic products. Nineteen cases of adverse events for Cutivate Cream 0.05% and Cutivate Ointment 0.005% were summarized in their review. Reported systemic adverse events included: immunosuppression/Pneumocystis carinii pneumonia/leucopenia/thrombocytopenia; hyperglycemia/glycosuria; Cushing syndrome; generalized body edema/blurred vision; and acute urticarial reaction (edema, urticaria, pruritus, and throat swelling). A causal role of Cutivate in most cases could not be determined because of the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information.

D. Dosing

No dose-ranging studies were performed for fluticasone propionate lotion with respect to concentration, dosing, or treatment duration. Once daily dosing only was studied in phase 3 trials, and twice daily dosing was studied in the open-label HPA axis suppression study, which did not evaluate efficacy. Patients were scheduled for 2 – 4 weeks of treatment in phase 3 trials, and 3 – 4 weeks of treatment in the HPA axis suppression study.

E. Special Populations

The number of patients with moderate to severe atopic dermatitis who were exposed to the drug under labeled conditions is insufficient to adequately evaluate gender, race and age effects on efficacy or safety.

**Appears This Way
On Original**

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This NDA is for fluticasone propionate lotion 0.05%.

Because the formulation was referred to as a lotion in the sponsor's study reports for this NDA, it will be referred to as such in this review. The drug is a synthetic fluorinated glucocorticosteroid for topical dermatologic use. Fluorine molecules introduced to the steroid structure increase the potency of glucocorticoid activity. The proposed indication is for "inflammatory and pruritic manifestations of atopic dermatitis." The initial

B. State of Armamentarium for Indication(s)

Many fluorinated and non-fluorinated topical corticosteroid formulations, such as creams, ointments, lotions, and solutions are available for the indication of corticosteroid-responsive dermatoses (this includes atopic dermatitis, which is a form of eczema). Topical corticosteroid lotions currently available for the indication of corticosteroid-responsive dermatoses include: flurandrenolide lotion 0.05%; amcinonide lotion 0.1%; desonide lotion 0.05%; triamcinolone acetonide lotion 0.025%; triamcinolone acetonide lotion 0.1%; betamethasone dipropionate lotion 0.05%; mometasone furoate lotion 0.1%; and hydrocortisone lotion 2.5%.

Cutivate (fluticasone propionate cream) Cream, 0.05%, and Cutivate (fluticasone propionate ointment) Ointment, 0.005%, are medium potency topical corticosteroid formulations that are currently marketed for the indication of corticosteroid-responsive dermatoses. Both Cutivate Cream and Cutivate Ointment were approved by FDA in 1990.

C. Important Milestones in Product Development

Pre-IND Meeting (1) - October 22, 1997

The Agency clinical guidance included the following:

[REDACTED]

- The use of birth control during the proposed vasoconstrictor study should reflect what is going to be included in the product labeling.

[REDACTED]

Sponsor Meeting (Follow-up to Pre-IND) - December 15, 1997

The Agency clinical guidance included the following:

[REDACTED]

- A hypothalamic-pituitary-adrenal (HPA) axis suppression study in pediatric patients could substitute for an HPA axis suppression study in adults if no evidence of adrenal suppression was observed in pediatric patients.

End-of-Phase 2 Meeting - May 7, 1998

The Agency clinical guidance included the following:

- The primary efficacy variable should be an Investigator's Global Evaluation of disease severity. The global evaluation should have a morphological definition that reflects the disease severity at the end of the study – not a comparison to baseline (i.e. the global evaluation should be static). For eczema, the morphological scale should incorporate the signs of erythema; papulation/edema; and erosion/oozing/crusting. These should be the signs used for inclusion criteria. The patients should be those with acute eczema.
- The Investigator's Global Evaluation should be dichotomized. Success should be defined as patients who fall into the categories of clear or almost clear (at least 50% of the patient's lesions fall into one of these two morphologically described categories).
- Clinical trials, including an HPA axis suppression study and pivotal trials, should include pediatric patients down to the age group of expected use.

[REDACTED]

IND 54,894/SN:011, 012/Reviewer's Comments - faxed to the sponsor March 17, 1999
The Agency clinical guidance included the following:

- The Agency did not agree with the use of the Rajka/Langland Severity Grading Scale for determining eligibility for the study. This scale does not distinguish acute from chronic eczema nor does it allow one to easily distinguish the severity of eczema. Instead, inclusion criteria should include clinical signs of eczema: erythema; papulation/edema; and erosion/crusting/oozing.
- The Agency did not agree with the use of the Eczema Area and Severity Index (EASI) as the primary efficacy variable. It is difficult to gain a sense of the overall severity of disease from EASI because it is a composite score.
- The primary efficacy variable should be an Investigator's Global Evaluation of patient severity status at the end of treatment. Furthermore, this global evaluation should be static (i.e. end-of-treatment status instead of improvement from baseline).
- Success should be defined as clear or almost clear under the Investigator's Global Evaluation with at least 50% of the patient's lesions falling into one of these two morphologically described categories.
- Adult safety data cannot be extrapolated to children. Safety assessments for systemic effects of fluticasone propionate lotion (i.e. serum chemistries and hematology) should be assessed in the pediatric population as well as the adult population.
- Two trials assessing the efficacy and safety of fluticasone propionate lotion in the treatment of eczema will not lead to labeling consistent with the treatment of corticosteroid-responsive dermatoses.
- The Agency emphasized in summary statements that: "This phase 3 protocol has major deviations from the recommendations discussed in that [End-of-Phase 2] meeting."

Pre-NDA Meeting - April 19, 1999

The Agency clinical guidance included the following:

- Two phase 3 studies should have an appropriate number of patients to detect a 95% confidence interval in order to properly evaluate the active drug product for safety. That number is usually at least 300 patients exposed to the active drug under labeled conditions.
- EASI is derivative and obscures the primary information. Treatment success defined by the EASI score is not appropriate. Success might be defined as patients with at least 50% of the lesions totally cleared and the remaining lesions

improved for the signs and symptoms of EASI. However, lichenification and body surface area would not be included in this tabulation.

- Because the lotion formulation will be for the indication of atopic dermatitis, the HPA axis suppression study should concentrate on enrolling patients with atopic dermatitis, not psoriasis.
- Demographic subgroup analysis should be further subdivided to the following [age expressed nominally]: 3 mos - 2 yrs; 3 yrs - 5 yrs; 6 yrs - 16 yrs.
- Adult safety data cannot be extrapolated downward to infancy. A significant safety review issue will be any signs of glucose intolerance or electrolyte imbalance in infants and toddlers. Data should be available to address this issue in at least 30 patients in the lowest age group

NDA Submission - December 13, 1999

NDA Withdrawal - May 25, 2000

- The NDA was withdrawn by the sponsor six months into the review process.

NDA Re-submission - March 11, 2004

- A Pre-NDA Meeting prior to re-submission was offered by the Agency but was declined by the sponsor.

D. Other Relevant Information

The sponsor states: "Fluticasone propionate emulsion formulation is not yet commercially available in any country. A market application has not previously been submitted to any regulatory authority." (Sponsor's NDA submission, Volume 1, p. 19.)

E. Important Issues with Pharmacologically Related Agents

Safety concerns for topical corticosteroids include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency upon withdrawal of treatment. Systemic adverse events may also include Cushing syndrome, hyperglycemia, and glucosuria. Local adverse events that may occur with topical corticosteroids include irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

Labeling for Cutivate Cream states:

Labeling for Cutivate Ointment states: "A concentrated fluticasone propionate ointment, 0.05% (10 times that of the marketed fluticasone propionate ointment 0.005%)

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry

The sponsor states: "Cutivate (fluticasone propionate) Lotion 0.05% is a white to off-white smooth lotion packaged in 60-mL white bottles with white flip-top closures."

The formulations used in the sponsor's submitted studies are shown in Table 1. Formula C represents the sponsor's proposed market formulation.

**Table 1
Formulations of Cutivate Lotion**

Component	Formula A	Formula B	Formula C (Sponsor's Proposed Market Formulation)
	Quantity (% w/w)	Quantity (% w/w)	Quantity (% w/w)
Fluticasone Propionate	0.05	0.05	0.05
Cetostearyl Alcohol, NF			
Isopropyl Myristate, NF			
Dimethicone 360, NF			
Cetostearyl			
Propylene Glycol, USP			
Imidurea, NF			
Methylparaben, NF			
Propylparaben, NF			
Citric Acid (Anhydrous), USP			
Citric Acid (Hydrous), USP			
Sodium Citrate, USP			
Dibasic Sodium Phosphate, USP			
Purified Water, USP			

Source: Sponsor's NDA submission, Volume 1, CMC Summary, p. 29.

Formulations A and B were used in studies FPLA1001 and FPL10002. Formula C was used in studies FPL10003, FPL10005, FPL30003, and FPL30004.

The reader is referred to the chemistry review by Dr. Allan Fenselau for a comprehensive review of chemistry-related issues.

Consultant Reviews

Consults from the Office of Drug Safety and the Division of Metabolic and Endocrine Drug Products are discussed in the safety section of this review.

III. Human Pharmacokinetics and Pharmacodynamics

The sponsor conducted two vasoconstrictor studies: FPLA1001 and FPL10002. Study FPLA1001 compared the blanching potential of two fluticasone propionate lotion 0.05% formulations to the following: their respective vehicles; Cutivate (fluticasone propionate) Cream 0.05%; Temovate (clobetasol propionate) Cream 0.05%; Elocon (mometasone furoate) Lotion 0.1%; and Hytone (hydrocortisone) Lotion 2.5%. A total of 33 healthy volunteer subjects completed the study. The sponsor's efficacy conclusions stated:

"Three efficacy endpoints were used: 2-hour blanching, AUC, and mean blanching...Consistent potency rankings were obtained across all three efficacy endpoints for both populations. Temovate and Elocon were the most potent, Lotion 1 [fluticasone propionate 0.05%], Lotion 2 [fluticasone propionate 0.05%], and Cutivate [Cream], were the next most potent, and Vehicles 1 and 2 and Hytone were the least potent. Statistical comparisons of each of the fluticasone propionate lotions against its vehicle showed that, in the intent-to-treat population, Lotion 1 was statistically different from its vehicle on all three efficacy endpoints and Lotion 2 was statistically different from its vehicle on one of three endpoints (2 hour blanching)." (Sponsor's NDA submission, Volume 11, p. 37.)

The sponsor initiated study FPL10002 as a bioequivalence vasoconstrictor study comparing the blanching effect of two formulations of fluticasone propionate lotion 0.05% and Cutivate Cream 0.05%. Fifteen healthy volunteer female subjects received study drug. The first part of the study was designed to determine the dose duration needed to attain half of the maximum response (ED_{50}) for Cutivate Cream 0.05%, and to make a preliminary assessment of comparability of blanching for fluticasone propionate lotion 0.05%. The duration of application ranged from 15 – 300 minutes, and skin blanching was assessed at 0, 2, 4, 6, 8, 10, 19, 21, and 24 hours after drug removal. The second part of the study was designed to test the bioequivalence of the two lotion formulations compared to Cutivate Cream. However, the second part of the study was not performed. The sponsor indicated that an acceptable dose-model was not obtainable from either the chromometer or visual results in part 1 of the study:

"Large variability was observed in the Chroma Meter results, which were likely due to fluctuations of skin tone in the absence of significant vasoconstrictor response (poor signal to noise ratio). The extremely low visual response and small areas under the curve are consistent with the low vasoconstrictor effect elicited by the durations used in the study. Consequently, no valid conclusions could be drawn regarding the comparison of the reference cream and the two test drugs." (Sponsor's NDA submission, Volume 12, p. 7.)

Reviewer's Comment: The final to-be-marketed formulation was not tested in studies FPLA1001 and FPL10002.

Study FPL10005 was an HPA axis suppression study in pediatric subjects, aged 3 months to 6 years, diagnosed with moderate to severe eczema. This study is discussed in the safety section of this review.

The reader is referred to the clinical pharmacology and biopharmaceutics review of Dr. Abimbola Adebawale for a comprehensive review of these studies.

IV. Description of Clinical Data and Sources

A. Overall Data

Data sources included the sponsor's NDA submission and the sponsor's submissions under IND 54,894. Consults were obtained for this NDA from the Office of Drug Safety and the Division of Metabolic and Endocrine Drug Products. Agency biostatistical analyses cited in this review were performed by Dr. Kathleen Fritsch, a biostatistical reviewer. See also the chemistry review of Dr. Allan Fenselau, the clinical pharmacology and biopharmaceutics review of Dr. Abimbola Adebawale, and the statistical review of Dr. Kathleen Fritsch.

B. Tables Listing the Clinical Trials

Table 2
Phase 1 Studies

Study Number	Study Objective	Treatment Arms	Number of Subjects	Initiation and Completion Dates
FPLA1001	Vasoconstrictor assay	Two formulations of fluticasone lotion 0.05%, Cutivate (fluticasone propionate) Cream 0.05%, Temovate (clobetasol propionate) Cream	33	February 2, 1998 - February 13, 1998

		0.05%, Elocon (mometasone furoate) Lotion 0.01% Hytone (hydrocortisone) Lotion 2.5%, Two vehicle lotions		
FPL10002	Bioequivalence vasoconstrictor assay	Two formulations of fluticasone lotion 0.05%, Cutivate (fluticasone propionate) Cream 0.05%	15	February 2, 1998 - February 6, 1998 (Terminated Early)
FPL10003	Contact sensitization and irritation study	Fluticasone propionate lotion 0.05%, Vehicle lotion	231	May 29, 1998 - July 17, 1998
FPL10005	HPA axis suppression study	Fluticasone propionate lotion 0.05%	44	November 11, 1998 - April 14, 1999

Source: Sponsor's NDA submission, Volume 10, p. 36.

**Table 3
Phase 3 Studies**

Study Number	Study Objective	Treatment Arms	Number of Patients	Initiation and Completion Dates
FPL30003	Evaluation of safety and efficacy	Fluticasone lotion 0.05%, Vehicle lotion	220	November 20, 1998 - April 12, 1999
FPL30004	Evaluation of safety and efficacy	Fluticasone lotion 0.05%, Vehicle lotion	219	November 13, 1998 - April 21, 1999

Source: Sponsor's NDA submission, Volume 10, p. 36.

Reviewer's Comment: No studies of fluticasone propionate lotion were conducted after April 1999.

C. Postmarketing Experience

This formulation of fluticasone propionate has not been approved in any country. A consult from the Office of Drug Safety relating to postmarketing adverse events for other dermatologic products containing fluticasone propionate is summarized in the safety section of this review.

V. Clinical Review Methods

A. How the Review was Conducted

The two phase 3 trials were reviewed in detail for information about both the efficacy and safety of fluticasone propionate lotion. Phase 1 trials FPL10003 and FPL10005 were reviewed for information on safety. Studies FPLA1001 and FPL1002 are also included in the review of drug safety; however, drug exposure was minimal in these phase 1 trials and the to-be-marketed formulation was not used.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Investigation of clinical sites by the Division of Scientific Investigations was not requested for this NDA submission.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appear to have been conducted in accordance with accepted ethical standards, and the sponsor states such in the NDA submission.

D. Evaluation of Financial Disclosure

The sponsor disclosed ten investigators or subinvestigators who received a payment above \$25,000; all were at the clinical site of [REDACTED]. The principal investigator was Dr. [REDACTED].

Financial disclosure forms list the following payments to investigators and sub-investigators:

**Table 4
Sponsor's Financial Disclosure**

Investigator or Sub-Investigator Name	Study	Total Payment ¹
[REDACTED]	[REDACTED]	40,000.00
[REDACTED]	[REDACTED]	41,000.00 ²
[REDACTED]	[REDACTED]	40,000.00

The sponsor did not follow Agency recommendations regarding inclusion criteria, and many patients were enrolled who had minimal to mild disease. These patients should not have been candidates for the studies and make interpretation of the results extremely problematic. It should be noted that these studies were not designed to study mild disease, and patients with minimal disease would not have been appropriate candidates in any case.

Another significant flaw of the studies was the high percentage of patients who had major protocol violations. By the sponsor's determination, approximately 25% of patients in each study had at least one major protocol violation. For example, approximately 10% of patients in both studies also used interfering concomitant medications during the study. The actual number of major protocol violations is slightly higher than reported by the sponsor because they did not include all patients who received < 75% study drug applications at 4 Weeks, or patients who were treated beyond 32 days (the range of treatment duration was up to 48 days) - both of which were in violation of the protocol. Moreover, protocol violations disproportionately occurred in the vehicle groups, particularly premature discontinuation of treatment. As discussed in this review, this introduces potential bias into the intent-to-treat analyses.

An additional flaw in these studies was the use the Eczema Area and Severity Index (EASI) score and a dynamic Investigator's Global Evaluation to measure treatment effect, contrary to the recommendations made by the Agency.

During the review of this NDA, the Agency conducted a post-hoc analysis to attempt to determine efficacy in the subset of patients who might have met inclusion criteria for moderate to severe disease based on the Agency's recommended parameters for disease assessment. Less than 40% of patients in phase 3 studies met the minimum baseline criteria used for inclusion in this analysis. Moreover, this attempt to determine disease severity was made retrospectively based on certain separate components of the sponsor's EASI score and other clinical scales, because an Investigator's Global Evaluation was not performed at baseline. Although this appeared to be the best method to attempt a meaningful analysis of these studies, it is far from ideal. The results of such a post-hoc analysis, not pre-specified in the protocol and including only a subset of patients, need to be interpreted with caution. Because such an analysis cannot take the place of an adequately conducted prospective clinical trial, with appropriate inclusion criteria and efficacy endpoints, it can be viewed as supportive only and is not necessarily sufficient to serve as the basis for demonstrating drug efficacy from a clinical perspective. The results were not definitive, and the difference between the vehicle and active groups did not reach statistical significance in either study when protocol violations were taken into account.

B. General Approach to Review of the Efficacy of the Drug

The efficacy evaluation of fluticasone propionate lotion 0.05% is based on a detailed review of the two phase 3 trials, FPL30003 and FPL30004. Table 5 provides an overview of those trials:

**Table 5
Overview of Phase 3 Trials**

Study	Site	Initiation and Completion Dates	Total Subjects Treated (Pediatric/Adult)¹	Patients/Treatment	Duration of Treatment²	Measurement Time Points
FPL30003	11 Sites in the United States	November 20, 1998 – April 12, 1999	220 (113/107)	110 Fluticasone propionate 0.05% lotion 110 Vehicle lotion	Up to 4 weeks	Baseline, Day 15, Day 29
FPL30004	11 Sites in the United States; 9 sites enrolled patients	November 13, 1998- April 21, 1999	218 ³ (129/89)	111 Fluticasone propionate 0.05% lotion 107 Vehicle lotion	Up to 4 weeks	Baseline, Day 15, Day 29

Source: Sponsor's NDA submission, Volume 10, p. 36.

¹Pediatric patients were defined as patients < 17 years of age.

²Study treatment was defined in the protocol to be completed after 4 weeks or at the end of 2 weeks if 100% cleared of disease.

³An additional pediatric patient was enrolled in the vehicle group but did not receive at least one dose of study drug.

C. Detailed Review of Trials by Indication

Pivotal Trials for Atopic Dermatitis

Reviewer's Comment: The two pivotal trials, FPL30003 and FPL30004, were identical in design but differed in site locations. Atopic dermatitis was the only indication studied in either trial. Both studies were designed to study patients with moderate to severe atopic dermatitis.

Pivotal Study 1: Protocol Number FPL30003

Title: "A Multicenter, Randomized, Double-Blind, Parallel Group, Vehicle-Controlled Study of the Efficacy and Safety of Fluticasone Propionate Lotion 0.05% Applied Once Daily for Four Weeks in the Treatment of Adult and Pediatric Subjects with Moderate to Severe Atopic Dermatitis."

Investigators

**Table 6
Investigators
Study FPL30003**

Name	Location	Pediatric Patients Enrolled Vehicle/Active/Total	Adult Patients Enrolled Vehicle/Active/Total
		10/10/20	0/0/0
		9/9/18	0/0/0
		12/11/23	0/0/0
		1/1/2	0/0/0
		0/0/0	12/11/23
		0/0/0	22/22/44
		2/4/6	0/0/0
		20/21/41	0/0/0
		1/2/3	0/0/0
		0/0/0	14/13/27
		0/0/0	7/6/13

Source: Sponsor's NDA submission, Volume 16, p. 78.

Objective/Rationale

To evaluate the safety and efficacy of fluticasone propionate lotion 0.05% applied once daily for up to 4 weeks compared to vehicle lotion, in adult and pediatric patients with moderate to severe atopic dermatitis.

Overall Study Design

The study was a multicenter, randomized, vehicle-controlled, double-blinded trial. Patients were 3 months of age or older. Planned enrollment was approximately 200 patients, with 100 patients – 50 adults and 50 children – in each treatment group. Patients who met eligibility criteria were randomized in a 1:1 ratio to receive either fluticasone propionate lotion 0.05% or vehicle lotion. At the pediatric study sites, patients were initially stratified by age into two groups: ≥ 3 months to < 3 years of age, and ≥ 3 years to < 6 years of age. Stratification was subsequently discontinued following a protocol amendment to permit enrollment of patients aged 6 to 18. Patients were assigned a subject number in chronological order of enrollment at each study site; the subject number corresponded to a specific set of pre-packaged medication for one of the two treatment regimens.

Study drug was applied in the evening on a daily basis, as described below. Patients were evaluated at Day 1 (baseline), Day 15, and Day 29. Patients were scheduled for 4 weeks of treatment; however, any patient whose lesions were 100% clear at Day 15 had end-treatment evaluations performed at that time.

Protocol

Inclusion Criteria

The sponsor considered a patient eligible for inclusion in the study only if they met the following criteria:

- Patient was male or non-pregnant, non-lactating female. A female was eligible to participate if she was (a) of non-childbearing potential (defined as physiologically incapable of becoming pregnant, including any female who was pre-menarchal or post-menopausal), or (b) if she had a negative pregnancy test at the screening visit and used complete abstinence or other effective form of birth control (specified in the protocol).
- Patient was 3 months of age or older.
- Patient presented with signs/symptoms of moderate to severe atopic dermatitis as determined by a score of > 4 on the Rajka/Langeland Severity Grading Scale (see Table 7).
- A signed and dated written informed consent was obtained from the patient or parent/guardian prior to study participation.

Reviewer's Comment: As noted above, the initial inclusion criterion for age was ≥ 3 months to < 6 years of age, or ≥ 18 years of age. The protocol was later amended to include patients aged 3 months or older. The amendment was implemented only at those sites enrolling pediatric patients. The sponsor stated that the rationale for this change was that adequate enrollment in the lower age range had been achieved.

Table 7
The Rajka/Langeland Severity Grading Scale

<u>Extent of disease</u>	
Infants (younger than one year of age)	
	1 = Less than approximately 18% of the skin involved
	2 = More than 18%; less than 54%
	3 = More than 54%
Childhood and Adults (older than one year of age)	
	1 = Less than 9% of the body area involved
	2 = More than 9% and less than 36% of the body area involved
	3 = More than 36% of the body area involved
<u>Course</u>	
	1 = More than 3 months of remission during a year
	2 = Less than 3 months of remission during a year
	3 = Continuous course
<u>Intensity</u>	
	1 = Mild itch, only exceptionally disturbing sleep
	2 = Itch is more than score 1; less than score 3
	3 = Severe itch, usually disturbing night's sleep
<u>Definition of Severity Scores (sum of above scores)</u>	
Mild	3 – 4
Moderate	5 – 7
Severe	8 – 9

Source: Sponsor's NDA submission, Volume 16, p. 25.

Reviewer's Comment: The Agency did not agree with the sponsor's use of the Rajka/Langeland Severity Grading Scale to determine study eligibility. The sponsor was advised at the End-of-Phase-2 Meeting that they should enroll patients with acute disease into pivotal studies. This was again strongly emphasized in the Agency's clinical reviewer's comments about submitted phase 3 protocols (comments were from Dr. Denise Cook, with concurrence from Dr. Susan Walker and Dr. Jonathan Wilkin). These comments were faxed to the sponsor on March 17, 1999, and stated:

"The division does not agree with the use of the Rajka/Langeland Severity Grading Scale. In the End-of-Phase 2 Meeting on May 7, 1998 with the sponsor, it was recommended that the clinical signs of eczema would be erythema, papulation/edema, and erosion/crusting/oozing with an ordinal grading scale that would contain these signs and that these signs would be used for the inclusion criteria. The patients enrolled in the study were also to have acute eczema for which these signs are the most predictive. The Rajka/Langeland Severity Grading Scale does not distinguish acute from chronic eczema nor does it allow one to easily distinguish severity of eczema."

Exclusion Criteria

The sponsor excluded the following patients from phase 3 studies:

- Patients with a history of adverse response to fluticasone propionate or any other topical or systemic steroid therapy.
- Patients who were immunocompromised.
- Patients with atopic dermatitis who required the use of other concomitant therapies during the course of the study.
- Patients who had significant endocrinological disorders that would either interfere with assessment of study results or contraindicate treatment with potent corticosteroids (e.g. insulin-dependent diabetes mellitus).
- Patients who had an unstable concurrent disease other than the condition to be treated in the study.
- Patients who used any topical treatments that have a known beneficial effect on atopic dermatitis within 1 week prior to the start of the study.
- Patients who used topical or systemic antihistamines within 3 days prior to the start of the study.
- Patients who used any other systemic medications for atopic dermatitis or other disease which could interfere with assessment of study results, within 4 weeks prior to the start of the study.
- Patients who used concomitant medications which could interfere with interpretation of study results (e.g. antihistamines).
- Patients whose atopic dermatitis appeared to be spontaneously improving without treatment.
- Patients who had any condition contraindicating treatment with corticosteroids (e.g. cutaneous infection, pre-existing skin atrophy).
- Patients who had been involved in an investigational drug study within 4 weeks prior to the start of the trial, or were involved in a concurrent study.
- Patients with a history of alcoholism, drug abuse, psychosis, antagonistic personality, poor motivation, or emotional or intellectual problems which would

likely limit validity or consent to participate in the study, or pediatric patients with a parent/guardian who had any of the above conditions.

- Patients who had a physical illness or disability or lived in a geographical location which would have likely prevented regular attendance at study visits.

Withdrawal Criteria

The protocol stated: "A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time." (Sponsor's NDA submission, Volume 18, p. 39.)

Procedures and Observations

Adult patients received up to four 60 ml bottles of fluticasone propionate lotion 0.05% or vehicle lotion per 2-week period, whereas pediatric patients received up to three 60 ml bottles per 2-week period. The number of bottles patients actually received was determined at the investigator's discretion based on the body surface area to be treated. The initial dose of study drug was to be applied at the research facility. The patient or parent/guardian was instructed on the amount of lotion to use, as well as the body surface areas to treat. Following the first dose, treatment was to be applied by the patient or parent/guardian/family member approximately 24 hours apart each evening. Study drug was to be applied to all affected areas of the body except the "eyelids, perioral area, nostrils, or diaper area." Study drug was not to be applied to areas where corticosteroid treatment was contraindicated, such as sites of infection or atrophy. Any new areas of disease were to be treated. The patient was not to have a bath or shower within 2 hours after application of study medication.

Table 8 lists the assessments that were to be made throughout the trial:

Table 8
Study Assessments
Study FPL30003

Parameter	Day 1	Day 15	Day 29 or Discontinuation
Inclusion/Exclusion Criteria	X		
Informed Consent	X		
Medical History	X		
Physical Examination	X		
Rajka/Langeland Severity Grading (used as inclusion criterion)	X		
Modified EASI Assessment	X	X	X
Additional Sign Scoring	X	X	X
Investigator Global Evaluation of Treatment Outcome		X	X
Patient's/Parent's Evaluation of Treatment Response		X	X
Dermatology-Specific Quality of Life Assessment ¹	X		X

Laboratory Tests ¹	X		X ²
Atrophy and Pigmentation Assessments	X	X	X
Adverse Events Assessment		X	X
Application of First Dose	X		
Drug Dispensing	X	X	
Drug Return and Accountability		X	X

Source: Sponsor's NDA submission, Volume 18, p. 58.

¹Adult patients only.

²Repeat laboratory tests were scheduled for patients who had abnormalities at Day 29. If a patient was discontinued because of a laboratory abnormality, they were to return for a follow-up laboratory test 2 weeks later.

Efficacy Endpoints

The protocol specified: "The primary efficacy variable will be the calculated percent reduction from baseline in the modified Eczema Area and Severity Index (EASI), using a 75% reduction as the minimum requirement for successful therapy." (Sponsor's NDA submission, Volume 18, p. 35.) The sponsor's modified EASI scale and method for calculating the EASI score are illustrated in Tables A.1 and A.2 in the Appendix.

Reviewer's Comment: *The Agency did not agree with the use of EASI as the primary efficacy variable because it is difficult to gain a sense of disease severity from this composite score. This was conveyed to the sponsor in the Agency's clinical reviewer's comments about the submitted phase 3 protocols.*

The primary efficacy variable was changed to the following at the time of NDA submission:

"The primary efficacy variable is a combination of the Investigator Global Assessment of the percentage of lesions cleared, plus severity assessments for each of five primary signs and symptoms (erythema, scaling, infiltration/papulation, erosion/oozing/crusting, and pruritus) in each of the four body regions (head/neck, trunk, upper limbs, lower limbs), for a total of 20 individual assessments. Treatment Success was defined as: at least 50% of lesions cleared **and** improvement or no change from baseline in $\geq 75\%$ of the severity scores (20 assessments) for the remaining (uncleared) lesions." (Sponsor's NDA Volume 10, page 73).

Reviewer's Comment: *The Agency recommended at the Pre-NDA Meeting that treatment success be defined as patients with at least 50% of lesions cleared and improvement or no change in 100% of the severity scores. The sponsor states in the NDA submission that this analysis was performed retrospectively, after the study blind had been broken.*

The primary efficacy population was the intent-to-treat population, which consisted of all patients who were randomized to treatment and who were dispensed study medication. The second analysis population was the per-protocol population "consisting of all subjects who were at least 75% compliant with the study medication regimen (received at

least 75% of required applications) as instructed by the investigator." (Sponsor's NDA submission, Volume 18, p. 41.)

The sponsor's Investigator Global Assessment of the percentage of lesions cleared was scored as follows:

Table 9
Investigator Global Assessment

Score	Description
0 = Cleared	100% of the lesions cleared
1 = Almost Cleared	90-99% of the lesions cleared
2 = Marked Clearing	50-89% of the lesions cleared
3 = Modest Clearing	< 50% of the lesions cleared
4 = No Change	Unchanged from baseline
5 = Exacerbation	Worse than baseline

Source: Sponsor's NDA submission, Volume 16, p. 31.

Reviewer's Comment: The Investigator Global Assessment scale is a dynamic scale, which is subject to recall bias. At the End-of-Phase-2 Meeting and in the subsequent clinical reviewer's comments about the submitted phase 3 protocols, the sponsor was advised that the Investigator Global Assessment should be a static scale, i.e. not based on a comparison to the baseline evaluation, but an assessment of observed disease status. Specifically, the clinical reviewer's comments, faxed to the sponsor on March 17, 1999, stated the following:

"The sponsor is referred to the minutes from the end-of-phase 2 meeting on May 7, 1998 for recommendations by the division for the design of phase 3 pivotal clinical trials for fluticasone propionate lotion in the treatment of eczema. This phase 3 protocol has major deviations from the recommendations discussed in that meeting. Again, along with the above deficiencies, the division recommended that the primary efficacy variable should be 'Investigator's Global Evaluation of the patient severity status' at the end of treatment. Further, it was recommended that this global evaluation should be static (i.e. end of treatment status instead of improvement compared to baseline). The division also recommended that success be defined as clear or almost clear under the global evaluation with at least 50% of the patient's lesions falling into one of these two morphologically described categories."

The scoring for evaluated signs and symptoms was based on the sponsor's grading scales shown in Table 10:

Table 10
Sponsor Grading Scales of Signs and Symptoms

Erythema

<p>0 = No evidence of redness compared to surrounding skin 1 = Patchy pink coloration, barely noticeable 2 = Easily noticeable redness 3 = Bright intense redness</p>
<p><u>Infiltration/Papulation</u></p> <p>0 = Lesions smooth and impalpable, not discernible to touch 1 = Few isolated areas palpable to touch 2 = Most lesions papulated or swollen above surrounding skin 3 = Extensive swelling and marked thickening</p>
<p><u>Scaling</u></p> <p>0 = No evidence of scaling 1 = Mainly fine, superficial scales; lesions at least partially covered 2 = Powdery scales; lesions at least partially covered 3 = Large areas of powdery scales virtually entire surface of lesion covered; rough surface</p>
<p><u>Erosion/Oozing/Crusting</u></p> <p>0 = No evidence of scaling, oozing, or surface changes 1 = Mild degree scaling with minimal oozing 2 = Few small fissures (cracks) with moderate crusting and/or oozing 3 = Lesions weeping and crusted with multiple cracks on surface possible</p>
<p><u>Pruritus</u></p> <p>0 = No itching 1 = Occasional itch, not interfering with daily activity 2 = Fairly persistent itch, partially tolerated; sometimes interferes with daily activities and disturbs sleep 3 = Intolerable, constant itch, interferes often with daily activities and disturbs sleep</p>
<p><u>Lichenification</u></p> <p>0 = Smooth skin particularly in flexural areas 1 = Minimal lines and epidermal thickening 2 = Thickened areas with deeper lines that involve greater than 50% of flexural areas 3 = Extensive skin markings and thickening extending beyond the flexural unit</p>
<p><u>Body Surface Area Score</u></p> <p>0 = 0% area affected 1 = 1-9% area affected 2 = 10-29% area affected 3 = 30-49% area affected 4 = 50-69% area affected 5 = 70-89% area affected 6 = 90-100% area affected</p>

Source: Sponsor's NDA submission, Volume 16, p. 31-3.

Reviewer's Comment: *The Agency recommended that the Investigator's Global Evaluation include signs of erythema, infiltration/papulation, and erosion/oozing/crusting. Pruritus has been considered a secondary efficacy variable by the Agency.*

An additional evaluation was patient assessment of response to treatment. Adult patients were asked to rate the response treatment as: excellent, good, fair, or poor. Parents or guardians rated the response for pediatric patients.

Results of Study FPL30003

A total of 220 patients in 11 study sites were enrolled in the study: 110 patients in the fluticasone group and 110 in the vehicle group. A total of 107 patients in the study were adults (≥ 17 years old) and 113 were pediatric patients (< 17 years old). Table 11 lists the study patient populations:

**Table 11
Patient Populations
Study FPL30003**

Study Population	Vehicle Lotion N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110 (%)	Total N=220 (%)
Enrolled	110 (100)	110 (100)	220 (100)
Intent-to-Treat	110 (100)	110 (100)	220 (100)
Sponsor's Per-Protocol	74 (67)	88 (80)	162 (74)

Source: Sponsor's NDA submission, Volume 10, p. 78.

Reviewer's Comment: The protocol stated that patients in the per-protocol population should have received at least 75% of required applications. However, the sponsor included in their per-protocol population, patients who received 75% of applications at Week 2 (and not necessarily Week 4), even if they were not completely clear of disease at Week 2. Also, the protocol defined the window for the final visit to be from Day 26 to Day 32 of the study. However, the sponsor included in their per-protocol population, patients who received more than 32 days of treatment. In analyses below, the Agency defined a per-protocol population that excluded patients whose final visit was before Day 21 (unless they were completely clear of disease at Week 2) or after Day 32.

Patient disposition, per the sponsor's analysis, is illustrated in Table 12:

**Table 12
Patient Disposition at End of Study
Study FPL30003 (Intent-to-Treat Population)**

Disposition	Vehicle Lotion N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110 (%)	Total N=220 (%)

Completed Study	81 (74)	99 (90)	180 (82)
Prematurely Discontinued	29 (26)	11 (10)	40 (18)
Reason for Discontinuation			
Adverse Event	5 (5)	2 (2)	7 (3)
Consent Withdrawn	1 (<1)	1 (<1)	2 (<1)
Lost to Follow-up	1 (<1)	4 (4)	5 (2)
Protocol Violation	0	1 (<1)	1 (<1)
Lack of Efficacy/Exacerbation	21 (19)	3 (3)	24 (11)
Other	1 (<1)	0	1 (<1)

Source: Sponsor's NDA submission, Volume 10, p. 76.

Reviewer's Comment: A substantial number of enrolled patients did not complete the study. Importantly, an asymmetry occurred with 26% of vehicle patients discontinued early compared to 10% of fluticasone patients. This was largely driven by "lack of efficacy/exacerbation" for which 19% of vehicle patients were discontinued early compared to only 3% of fluticasone patients. This is a surprisingly high percentage of patients given that this was only a 4-week study. Furthermore, only 1 patient was noted to be discontinued at the patient's or parent's request in the sponsor's line listings (NDA Volume 10, p. 232-8). A similar rate of early discontinuation occurred in study FPL30004, discussed below.

Although discontinued patients are considered treatment failures in a "last observation carried forward" analysis, it cannot be known what the clinical outcome of these patients would have been had they remained in the study and been assessed at the protocol's pre-specified Week 4 endpoint. Therefore, the high rate of early discontinuation in this study and the disproportionately high rate in the vehicle group, represent potential sources of bias in the intent-to-treat analyses of these pivotal studies. Importantly, discontinuation of vehicle patients at Week 2 might obscure the true difference between the treatment groups at the pre-specified Week 4 endpoint if there is a difference in the rate of treatment effect between vehicle and active drug. This is clinically plausible if the vehicle acts as an emollient, which might lead to a more gradual improvement over a 4-week period. In addition, bias is introduced by the high discontinuation rate in the vehicle group because spontaneous improvement may occur in atopic dermatitis based on natural waxing and waning of the disease course. Therefore, from a clinical perspective, it is important that the analysis of the per-protocol population be considered in addition to the intent-to-treat population when analyzing these studies.

The sponsor indicates that 10 patients enrolled in violation of 12 inclusion/exclusion criteria. The violations were as follows: use of a topical treatment known to be beneficial for atopic dermatitis within 1 week of study initiation (3 fluticasone propionate patients, 2 vehicle patients); use of systemic medication for atopic dermatitis within 4 weeks of study initiation (3 fluticasone patients); use of concomitant medication during the study that would interfere with the interpretation of study results (1 fluticasone patient; 1 vehicle patient); use of topical or systemic antihistamines within 3 days of study initiation (1 fluticasone patient), and unacceptable contraceptive method (1 vehicle patient).

A total of 58 patients (28%) in the study were considered by the sponsor to have had a major protocol violation. They occurred disproportionately in the vehicle group (33%), but the rate was also high in the fluticasone group (20%). The sponsor's list of major protocol violations that occurred in the study are summarized in the following table:

Table 13
Major Protocol Violations
Study FPL30003 (All Patients Enrolled)

	Vehicle Lotion N=110 (%)	Fluticasone Propionate Lotion 0.05% N =110 (%)	Total N=220 (%)
Patients with One or More Major Protocol Violations	36 (33)	22 (20)	58 (26)
Protocol Violation			
Insufficient Washout	3 (3)	6 (5)	9 (4)
Treated < 2 Weeks	25 (23)	7 (6)	32 (15)
Subject Applied < 75% of Medication ¹	9 (8)	4 (4)	13 (6)
Interfering Concomitant Medication	11 (10)	9 (8)	20 (9)

Source: Sponsor's NDA submission, Volume 10, p. 115.

¹The sponsor determined this at Week 2, not Week 4.

***Reviewer's Comment:** A high percentage of patients had major protocol violations in this study. The sponsor should have also included treatment past 32 days as a major protocol violation.*

Consistent with Table 12, a disproportionate number of patients receiving vehicle (23%) were treated for less than 2 weeks in violation of the protocol, compared to patients receiving fluticasone propionate (6%).

Table 14 summarizes the treatment duration of patients in the study:

Table 14
Treatment Duration
Study FPL30003 (Intent-to-Treat Population)

Treatment Duration	Vehicle Lotion N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110

		(%)
< 12 days	12 (11)	2 (2)
12 - 18 days	15 (14)	12 (11)
19 - 25 days	6 (5)	6 (5)
26 - 32 days	72 (65)	79 (72)
> 32 days ¹	4 (4)	9 (8)

Source: Sponsor's NDA submission, Volume 10, p. 117; Volume 16, p. 338-44.

¹The range was up to 44 days.

Patient demographics for this study are summarized in Table 15:

Table 15
Demographic Characteristics of Study Patients
Study FPL30003 (Intent-to-Treat Population)

Variable	Vehicle Lotion N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110 (%)	Total N=220 (%)
Age			
≥ 3 mos and < 3 yrs	33 (30)	33 (30)	66 (30)
≥ 3 yrs and < 6 yrs	11 (10)	14 (13)	25 (11)
≥ 6 yrs and < 17 yrs	11 (10)	11 (10)	22 (10)
≥ 17 yrs and ≤ 65 yrs	53 (48)	50 (45)	103 (47)
> 65 yrs	2 (2)	2 (2)	4 (2)
Gender			
Male	49 (45)	54 (49)	103 (47)
Female	61 (55)	56 (51)	117 (53)
Race			
White	80 (73)	78 (71)	158 (72)
Black	19 (17)	19 (17)	38 (17)
Asian	4 (4)	4 (4)	8 (4)
Hispanic	6 (5)	9 (8)	15 (7)
Other	1 (<1)	0	1 (<1)

Source: Sponsor's NDA submission, Volume 16, p. 83.

Baseline scores for the Rajka/Langeland Severity Grading Scale for the vehicle and fluticasone groups are shown in Table A.3 in the Appendix.

Baseline and end-of-treatment scores for signs and symptoms are illustrated in Tables A.4 and A.5 in the Appendix.

As discussed above, the clinical signs recommended by the Agency to be used to determine disease severity and eligibility for enrollment were erythema, edema/papulation, and erosion/oozing/crusting. These were not used by the sponsor to

determine eligibility for enrollment. However, baseline assessments did include scores for these clinical signs (if infiltration is considered equivalent to edema) in each of four body areas: head/neck, trunk, upper limbs, and lower limbs. The score was graded 0 - 3 for each sign in each body area (see Table 10). Therefore, the total cumulative score for any sign ranged from 0 - 12, and the combined score of the three signs from 0 - 36. The combined baseline scores for these three clinical signs are shown in Table 16:

Table 16
Distribution of the Baseline Severity Sum Score
Study FPL30003 (Intent-to-Treat Population)

Baseline Sum Score ¹	Vehicle N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110 (%)
1-3	9 (8)	6 (5)
4-6	26 (24)	28 (25)
7-9	31 (28)	22 (20)
10-12	17 (15)	21 (19)
13-15	7 (6)	15 (14)
16-18	10 (9)	11 (10)
19-21	3 (3)	4 (4)
22-24	6 (5)	2 (2)
25-27	0	0
28-30	0	1 (1)
31-33	1 (1)	0
34-36	0	0

Source: Agency Biostatistical Analysis.

¹ Combined baseline scores for erythema, infiltration/papulation, and erosion/oozing/crusting over head/neck, trunk, upper limbs, and lower limbs (possible range is 0 to 36).

Reviewer's Comment: *The study was ostensibly in patients with moderate to severe atopic dermatitis. However, this was based on the Rajka/Langeland Severity Grading Scale, which relies only on chronicity of disease, pruritus and body surface area. As discussed above, the Agency did not agree with the use of this scale. The above table illustrates that if disease severity is determined based on the Agency's criteria of erythema, edema/papulation, and erosion/oozing/crusting, many patients actually had mild or minimal disease. A majority of patients (55%) scored less than 10 at baseline out of a possible score of 36, and 31% of patients scored 6 or less. It should be noted that for the scales used, scores of 1 for individual signs of symptoms might be considered roughly equivalent to "almost clear"; for example, a score of 1 for erythema indicated "patchy pink coloration, barely noticeable." Moreover, only 17 (8%) of 220 patients scored above 18 out of 36.*

In summary, most enrolled patients apparently did not have significant enough disease to warrant inclusion into this study based on the Agency's recommended inclusion criteria. This makes evaluation of both the efficacy and safety of fluticasone propionate lotion based on the results of the sponsor's phase 3 studies extremely difficult.

The sponsor used a primary efficacy endpoint that defined success as: (a) at least 50% of lesions cleared, and (b) improvement or no change from baseline in 100% of the severity scores of the uncleared lesions for the five signs/symptoms of erythema, infiltration/papulation, scaling, erosion/oozing/crusting, and pruritus. The sponsor's analysis, using this definition for success, is shown in Table 17:

Table 17
Summary of Treatment Success by Sponsor's Analysis
Study FPL30003

Population	Vehicle	Fluticasone Propionate Lotion 0.05%	p value ¹
Intent-to-Treat	29/110 (26%)	80/110 (73%)	≤ 0.001
Sponsor's Per-Protocol	25/74 (34%)	67/88 (76%)	≤ 0.001

Source: Sponsor's NDA submission, Volume 10, p. 80-1.

¹Cochran-Mantel-Haenszel Test.

***Reviewer's Comment:** This analysis includes patients with minimal or mild disease (see discussion above). Also, the sponsor's primary efficacy endpoint includes a dynamic scale and is, therefore, dependent on comparison to baseline disease.*

The Agency performed a post-hoc analysis which attempted to evaluate only those patients whose disease was severe enough (based on signs of acute atopic dermatitis) to warrant inclusion in a study of moderate to severe atopic dermatitis. In this analysis, the three clinical signs of acute disease that had been recommended by the Agency as inclusion criteria were utilized: erythema, papulation/infiltration (considering infiltration equivalent to edema for the purpose of the analysis), and erosion/crusting/oozing. For the Agency's analysis, patients were required to have: (a) a combined score of 10 or greater out of 36 and (b) a minimum score of at least 2 for any two of the three signs in at least 1 of the 4 body areas (the scores of 2 could be in different body areas for different signs). Because scores of 1 were common at baseline, and this approximated "almost clear," the endpoint used was complete clearance. These criteria were chosen by an experienced medical officer in the Division (Dr. Denise Cook). The results of this analysis are shown in Table 18:

Table 18
Summary of Treatment Success by Agency's Analysis
Study FPL30003

Population	Vehicle	Fluticasone Propionate Lotion 0.05%	p value ¹
Intent-to-Treat	0/37 (0%)	9/45 (20%)	0.0102
Sponsor's Per-Protocol	0/21 (0%)	7/37 (19%)	0.1591
Agency's Per-Protocol ²	0/21 (0%)	6/30 (20%)	0.1483

Source: Agency Biostatistical Analysis.

¹Cochran-Mantel-Haenszel Test.

²The Agency excluded from the sponsor's per-protocol population those patients whose final visit was prior to Day 21 (unless they were completely clear of disease at the Day 15 visit) or after Day 32.

Reviewer's Comment: Only 82 (37%) of 220 patients in the intent-to-treat population met the Agency's minimum criteria for inclusion. In addition, there were only 58 patients (26%) in the sponsor's per-protocol population, and 51 (23%) in the Agency's per-protocol population.

A serious flaw in this study was the high number of protocol violations. There is not a statistically significant difference between the treatment groups when this is taken into account and either the sponsor's or Agency's per-protocol population is used.

Two successes in the fluticasone intent-to-treat population were lost in both the Agency's and sponsor's per-protocol populations. Both patients used concomitant antibiotic treatment during the study. This is a significant protocol violation because of the possible role staphylococcal and streptococcal antigens may play in atopic dermatitis.

One success in the fluticasone group received 34 days of treatment. This patient was included in the sponsor's intent-to-treat population and per-protocol population, but excluded from the Agency's per-protocol population.

It should be noted that this post-hoc analysis, while informative, is not a substitute for a prospective study using a pre-specified static Investigator's Global Evaluation as recommended by the Agency. As such it should be viewed as supportive only and is not necessarily sufficient to serve as the basis for demonstrating drug efficacy from a clinical perspective.

The following table shows the number of patients who had a major protocol violation, as identified by the sponsor, for patients meeting the Agency's minimum baseline criteria:

Table 19
Major Protocol Violations
Study FPL30003 (Patients Meeting Agency's Minimum Baseline Criteria)

	Vehicle Lotion N=37 (%)	Fluticasone Propionate Lotion 0.05% N=45 (%)	Total N=82 (%)
Patients with One or More Major Protocol Violations	16 (43)	8 (18)	24 (29)
Protocol Violation			
Insufficient Washout	1 (3)	2 (4)	3 (4)
Treated < 2 Weeks	12 (32)	4 (9)	16 (20)
Subject Applied < 75% of Medication ¹	4 (11)	2 (4)	6 (7)
Interfering Concomitant Medication	4 (11)	2 (4)	6 (7)

Source: Agency Biostatistical Analysis (Modification of Sponsor's Table: NDA submission, Volume 10, p. 115).

¹The sponsor determined this at Week 2, not Week 4.

Reviewer's Comment: Table 19 illustrates the high percentage of patients meeting the Agency's minimum baseline criteria who had at least one major protocol violation: 43% of patients in the vehicle group, 18% of patients in the fluticasone group, and 29% overall.

Table 20 summarizes the treatment duration of patients in the study who met the Agency's minimum baseline criteria:

Table 20
Treatment Duration
Study FPL30003 (Patients Meeting Agency's Minimum Baseline Criteria)

Treatment Duration	Vehicle Lotion N=36 (%)	Fluticasone Propionate Lotion 0.05% N=45 (%)
< 12 days	3 (8)	2 (4)
12 - 18 days	8 (22)	5 (11)
19 - 25 days	3 (8)	3 (7)
26 - 32 days	22 (61)	29 (64)
> 32 days	0 (0)	6 (13)

Source: Agency Biostatistical Analysis (Modification of Sponsor's Table: NDA submission, Volume 10, p. 117.)

The protocol listed as the secondary efficacy variable, the combined "EASI success (minimum of 75% reduction) with Investigator Global Evaluation of Treatment Outcome or percent lesions cleared (minimum of 50% of lesions cleared)." The Agency did not

agree with the use of the EASI scale and this will not be considered here. Also, the tertiary efficacy variable of the severity score of scaling and erosion/oozing/crusting will not be considered separately. These signs are included in the primary efficacy variable used by the sponsor, and erosion/oozing/crusting is included as one of the clinical signs in the Agency's analysis (see above). The protocol also listed as a tertiary efficacy endpoint, "the subject's/parent's evaluation of response to treatment, rated at all post-baseline visits." The results of the sponsor's analysis of this endpoint at the end of treatment are listed in Table A.6 in the Appendix.

Pivotal Study 2: Protocol Number FPL30004

Title: "A Multicenter, Randomized, Double-Blind, Parallel Group, Vehicle-Controlled Study of the Efficacy and Safety of Fluticasone Propionate Lotion 0.05% Applied Once Daily for Four Weeks in the Treatment of Adult and Pediatric Subjects with Moderate to Severe Atopic Dermatitis."

Investigators

**Table 21
Investigators
Study FPL30004**

Name	Location	Pediatric Patients Enrolled Vehicle/Active/Total	Adult Patients Enrolled Vehicle/Active/Total
		0/0/0	9/10/19
		22/21/43	0/1/1
		13/12/25	0/0/0
		11/12/23	1/0/1
		0/1/1	0/0/0
		0/0/0	8/9/17
		0/0/0	11/11/22
		4/5/9	15/15/30
		14/14/28	0/0/0

Source: Sponsor's NDA submission, Volume 16, p. 78.

Objective/Rationale

To evaluate the safety and efficacy of fluticasone propionate lotion 0.05% applied once daily for up to 4 weeks compared to vehicle lotion, in adult and pediatric patients with moderate to severe atopic dermatitis.

Overall Study Design

Studies FPL30003 and FPL30004 were replicate studies, identical in design but including different sites.

Protocol

The protocol for study FPL30004 was identical to study FPL30003.

Results of Study FPL30004

A total of 219 patients in nine study sites were enrolled in the study. Of these, 218 patients received study drug and were included in the sponsor's intent-to-treat population: 111 in the fluticasone group and 107 in the vehicle group. A total of 89 patients were adults and 129 were pediatric patients. The intent-to-treat population and per-protocol population were defined as in study FPL30003. Study patient populations and disposition of patients are shown in the following tables:

**Table 22
Patient Populations
FPL30004**

Study Population	Vehicle Lotion N=108 (%)	Fluticasone Propionate Lotion 0.05% N= 111 (%)	Total N=219 (%)
Enrolled	108 (100)	111 (100)	219 (100)
Intent-to-Treat	107 (>99)	111 (100)	218 (>99)
Per-Protocol	69 (64)	95 (86)	164 (75)

Source: Sponsor's NDA submission, Volume 10, p. 78.

**Table 23
Patient Disposition at End of Study
FPL30004 (Intent-to-Treat Population)**

Disposition	Vehicle Lotion N=107 (%)	Fluticasone Propionate Lotion 0.05% N=111 (%)	Total N=218 (%)
Completed Study	72 (67)	101 (91)	173 (79)
Prematurely Discontinued	35 (33)	10 (9)	45 (21)
<u>Reason for Discontinuation</u>			
Adverse Event	3 (3)	2 (2)	5 (2)
Consent Withdrawn	0	1 (<1)	1 (<1)

Lost to Follow-up	2 (2)	3 (3)	5 (2)
Protocol Violation	6 (6)	1 (<1)	7 (3)
Lack of Efficacy/Exacerbation	23 (21)	2 (2)	25 (11)
Other	2 (<1)	1 (<1)	2 (<1)

Source: Sponsor's NDA submission, Volume 10, p. 76.

Reviewer's Comment: *As in study FPL30003, a substantial number of enrolled patients did not complete this 4-week study. The asymmetry of early patient discontinuation also occurred in this study, with 33% of vehicle patients discontinued early compared to 9% of fluticasone patients. Again, this was largely driven by "lack of efficacy/exacerbation" for which 21% of vehicle patients were discontinued early, compared to only 2% of fluticasone patients. For only 1 patient was the study discontinuation noted to be at the patient's request in the sponsor's line listings (NDA Volume 10 p. 239-245). As discussed above, this early discontinuation represents a potential source of bias in the intent-to-treat analyses of phase 3 studies.*

One patient enrolled in the vehicle group was determined by the sponsor to have violated inclusion/exclusion criteria. The patient had a known allergy to parabens, a component of the fluticasone propionate formulation.

The sponsor reported a total of 55 patients (25%) who had a major protocol violation in this study. The sponsor's list of major protocol violations are summarized in Table 24:

**Table 24
Major Protocol Violations
Study FPL30004 (All Patients Enrolled)**

	Vehicle Lotion N=108 (%)	Fluticasone Propionate Lotion 0.05% N=111 (%)	Total N=219 (%)
Patients with One or More Major Protocol Violations	39 (36)	16 (14)	55 (25)
Protocol Violation			
Insufficient Washout Treated Less Than 2 Weeks	1 (<1)	0	1 (<1)
Subject Applied < 75% of Medication ¹	30 (28)	5 (5)	35 (16)
Interfering Concomitant Medication	17 (16)	4 (4)	21 (10)
	12 (11)	11 (10)	23 (11)

Source: Sponsor's NDA submission, Volume 10, p. 116.

¹The sponsor determined this at Week 2, not Week 4.

Reviewer's Comment: A total of 25% of all enrolled patients were reported by the sponsor to have had at least one major protocol violation. More patients with major protocol violations were in the vehicle group (36%) than the fluticasone group (14%). As in study FPL30003, the sponsor did not include treatment past 32 days as a major protocol violation.

Table 25 summarizes the treatment duration of patients in the study:

**Table 25
Treatment Duration
Study FPL30004 (Intent-to-Treat Population)**

Treatment Duration	Vehicle Lotion N=107 (%)	Fluticasone Propionate Lotion 0.05% N=111 (%)
< 12 days	18 (17)	3 (3)
12 - 18 days	11 (10)	10 (9)
19 - 25 days	3 (3)	2 (2)
26 - 32 days	68 (64)	91 (82)
> 32 days ¹	5 (5)	3 (3)

Source: Sponsor's NDA submission, Volume 10, p. 118; Volume 20 p. 330-7.

¹The range was up to 48 days.

A summary of baseline demographic data for the study is shown in Table 26:

**Table 26
Demographic Characteristics of Study Patients
Study FPL30004 (Intent-to-Treat Population)**

Variable	Vehicle Lotion N=107 (%)	Fluticasone Propionate Lotion 0.05% N=111 (%)	Total N=218 (%)
<u>Age</u>			
≥ 3 mos and < 3 yrs	22 (21)	27 (24)	49 (22)
≥ 3 yrs and < 6 yrs	28 (26)	28 (25)	56 (26)
≥ 6 yrs and < 17 yrs	14 (13)	10 (9)	24 (11)
≥ 17 yrs and ≤ 65 yrs	36 (34)	40 (36)	76 (35)
> 65 yrs	7 (7)	6 (5)	13 (6)
<u>Gender</u>			
Male	52 (49)	61 (55)	113 (52)
Female	55 (51)	50 (45)	105 (48)
<u>Race</u>			

White	85 (79)	86 (77)	171 (78)
Black	13 (12)	9 (8)	22 (10)
Asian	3 (3)	5 (5)	8 (4)
Hispanic	3 (3)	2 (2)	5 (2)
Other	3 (3)	9 (8)	12 (6)

Source: Sponsor's NDA submission, Volume 20, p. 81.

Baseline scores using the Rajka/Langeland Severity Grading Scale are shown in Table A.7 in the Appendix. As noted, the Agency did not agree with the use of this scale to measure disease severity.

Baseline and end-of-treatment scores for signs and symptoms are listed in Tables A.8 and A.9 in the Appendix.

As described in the results section for study FPL30003, baseline severity was determined in a post-hoc analysis by the Agency. This was based on the clinical signs recommended by the Agency to be used to determine disease severity and eligibility for enrollment: erythema, infiltration/papulation, and erosion/oozing/crusting. These were scored at baseline for each of four body areas. Baseline severity based on the sum of these scores is shown in the following table:

Table 27
Distribution of the Baseline Severity Sum Score
Study FPL30004 (Intent-to-Treat Population)

Baseline Sum Score¹	Vehicle N=107 (%)	Fluticasone Propionate 0.05% Lotion N=111 (%)
1-3	6 (6)	7 (6)
4-6	20 (19)	22 (20)
7-9	33 (31)	27 (24)
10-12	22 (21)	25 (23)
13-15	13 (12)	12 (11)
16-18	6 (6)	7 (6)
19-21	5 (5)	5 (5)
22-24	2 (2)	1 (1)
25-27	1 (1)	3 (3)
28-30	0	2 (2)
31-33	0	0
34-36	0	0

Source: Agency Biostatistical Analysis.

¹Baseline score for erythema, infiltration/papulation, or erosion/oozing/crusting over head/neck, trunk, upper limbs, and lower limbs (possible range is 0 to 36).

Reviewer's Comment: As in study FPL30003, many patients in study FPL30004 had mild or minimal disease based on the Agency's analysis of disease severity. A majority of patients (53%) scored less than 10 out of a possible score of 36 at baseline, and 25% of patients scored 6 or less. Only 19 (9%) of 218 patients had a sum score above 18. Therefore, many patients were enrolled who should not have been candidates for this study of moderate to severe atopic dermatitis.

The sponsor's primary efficacy assessment was the same as in study FPL30003. The sponsor defined success as: (a) at least 50% lesions cleared, and (b) improvement or no change from baseline in 100% of the severity scores of the uncleared lesions for the five signs/symptoms of erythema, infiltration/papulation, scaling, erosion/oozing/crusting, and pruritus. The results of the sponsor's analysis, using this definition for success, are illustrated in Table 28:

Table 28
Summary of Treatment Success by Sponsor's Analysis
Study FPL30004

Population	Vehicle	Fluticasone Propionate Lotion 0.05%	p value ¹
Intent-to-Treat	23/107 (22%)	59/111 (53%)	≤ 0.001
Sponsor's Per-Protocol	20/69 (29%)	52/95 (55%)	≤ 0.001

Source: Sponsor's NDA submission, Volume 10, p. 80-1.

¹Cochran-Mantel-Haenszel Test.

Reviewer's Comment: This analysis includes patients with minimal or mild disease (see discussion above). Also, the sponsor's primary efficacy endpoint includes a dynamic scale and is, therefore, dependent on comparison to baseline disease.

The Agency conducted the same post-hoc analysis as for study FPL30003, excluding patients with mild or minimal disease based on the signs of acute atopic dermatitis recommended by the Agency: erythema, infiltration/papulation, and erosion/oozing/crusting. As discussed above, for inclusion in the analysis patients were required to have: (a) a combined score of 10 or greater, out of 36, and (b) a minimum score of at least 2 for any two of the three signs in at least 1 of the 4 body areas (the scores of 2 could be in different body areas for different signs). The endpoint used for success was complete clearance because scores of 1 were common, and this approximated "almost clear." The results of this analysis are shown in Table 29:

Table 29
Summary of Treatment Success by Agency's Analysis
Study FPL30004

Population	Vehicle	Fluticasone Propionate Lotion 0.05%	p value ¹
Intent-to-Treat	1/43 (2%)	7/44 (16%)	0.0410
Sponsor's Per-Protocol	1/22 (5%)	7/38 (18%)	0.1382
Agency's Per-Protocol ²	1/21 (5%)	6/35 (17%)	0.1645

Source: Agency Biostatistical Analysis.

¹Cochran-Mantel-Haenszel Test.

²The Agency excluded patients from the sponsor's per-protocol population whose final visit was prior to Day 21 (unless they were completely clear of disease at the Day 15 visit) or after Day 32.

Reviewer's Comment: As in study FPL30003, the number of patients meeting the minimum post-hoc criteria was small, relative to the original size of the study. Only 87 (40%) of 218 patients in the intent-to-treat population met the Agency's minimum criteria for inclusion. Moreover, there were only 60 patients (28%) in the sponsor's per-protocol population, and 56 (26%) in the Agency's per-protocol population.

As was observed in study FPL30003, there is not a statistically significant difference between the treatment groups when protocol violations are taken into account.

One treatment success in the fluticasone group was a patient who received a total of 37 days of treatment (39 day treatment duration with two days of missed applications). This patient was included in the sponsor's intent-to-treat population and per-protocol population, but excluded from the Agency's per-protocol population.

Five of the seven successes in the fluticasone group were from one clinical site

Table 30 shows the number of patients who had a major protocol violation, as identified by the sponsor, for patients meeting the Agency's minimum baseline criteria:

**Table 30
Major Protocol Violations
Study FPL30004 (Patients Meeting Agency's Minimum Baseline Criteria)**

	Vehicle Lotion N=43 (%)	Fluticasone Propionate Lotion 0.05% N=44 (%)	Total N=87 (%)
Patients with One or More Major Protocol Violations	21 (49)	8 (18)	29 (33)

Protocol Violation			
Insufficient Washout	0	0	0
Treated < 2 Weeks	20 (47)	2 (5)	22 (25)
Subject Applied < 75% of Medication ¹	11 (26)	1 (2)	12 (14)
Interfering Concomitant Medication	4 (9)	4 (9)	8 (9)

Source: Agency Biostatistical Analysis (Modification of Sponsor's Table: NDA submission, Volume 10, p. 116).

¹The sponsor determined this at Week 2, not Week 4.

Reviewer's Comment: A total of 49% of patients in the vehicle group, 18% of patients in the fluticasone group, and 33% of patients overall had one or more major protocol violation.

The following table summarizes the treatment duration of patients in the study who met the Agency's minimum baseline criteria:

Table 31
Treatment Duration
Study FPL30004 (Patients Meeting Agency's Minimum Baseline Criteria)

Treatment Duration	Vehicle Lotion N=43 (%)	Fluticasone Propionate Lotion 0.05% N=43 (%)
< 12 days	14 (33)	2 (5)
12 - 18 days	7 (16)	3 (7)
19 - 25 days	2 (5)	1 (2)
26 - 32 days	20 (47)	36 (84)
> 32 days	0 (0)	1 (2)

Source: Agency Biostatistical Analysis (Modification of Sponsor's Table: NDA submission, Volume 10, p. 118.)

Secondary and tertiary endpoints listed in the protocol were the same as in study FPL30003. The results of the sponsor's analysis of the subject's/parent's evaluation of response to treatment at end-treatment are listed in Table A.6 in the Appendix.

D. Efficacy Conclusions

From a clinical perspective, the efficacy of fluticasone propionate lotion 0.05% to treat moderate to severe atopic dermatitis has not been adequately demonstrated in the sponsor's pivotal trials. As revealed in this review, phase 3 studies were seriously flawed from a clinical standpoint. Importantly, the sponsor did not follow Agency recommendations regarding inclusion criteria, and the majority of patients who were enrolled had minimal to mild disease. These patients should not have been candidates for

these studies. Also, a high percentage of patients had major protocol violations; by the sponsor's determination, approximately 25% of patients in each study had one or more major protocol violations. In addition, these studies used the Eczema Area and Severity Index score and a dynamic Investigator's Global Evaluation to measure treatment effect, contrary to the recommendations made by the Agency. During the review of this NDA, the Agency conducted a post-hoc analysis to attempt to determine efficacy in the subset of patients who might have met inclusion criteria for moderate to severe disease based on the clinical signs recommended by the Agency for disease assessment. A total of only 38% of patients in phase 3 studies met the minimum baseline criteria used for inclusion in this analysis. Because such an analysis cannot take the place of an adequately conducted prospective clinical trial, it can be viewed as supportive only and is not necessarily sufficient to serve as the basis for demonstrating drug efficacy from a clinical perspective. The results of this analysis were not definitive, and the difference between the vehicle and active groups did not reach statistical significance in either study when protocol violations were taken into account. The evidence for efficacy provided from these flawed studies does not meet the standard necessary for drug approval from a clinical perspective.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Fluticasone propionate lotion 0.05% has not been sufficiently studied in patients with moderate to severe atopic dermatitis to determine that this drug has an acceptable safety profile. Only 89 (40%) of 221 patients in the fluticasone group in the combined phase 3 studies met the Agency's minimum baseline criteria (discussed in the efficacy section) for having disease considered severe enough to warrant inclusion in the studies of moderate to severe atopic dermatitis. Safety results in patients with mild or minimal disease cannot be extrapolated to patients with moderate to severe disease because those with more severe disease would be expected to apply more drug, have increased drug absorption, and be more susceptible to certain adverse events, such as infection and systemic adverse events (not necessarily related to HPA axis suppression). Even combining the safety data from these 89 patients with the data from 44 patients enrolled in the open-label HPA axis suppression study (FPL10005), the total number of patients with moderate to severe disease exposed to the active drug under labeled conditions is insufficient for drug approval. At the Pre-NDA Meeting, the Agency recommended at least 300 patients be exposed to the drug under labeled conditions. Specific safety issues identified in this review are discussed in detail below and summarized in section VII (E).

B. Description of Patient Exposure

Six studies are included in the review of safety. There are four phase 1 studies (FPLA1001, FPL10002, FPL10003, FPL10005), and two phase 3 studies (FPL30003, FPL30004).

Phase 1 Studies:

**Table 32
Patient Exposure: Summary of Phase 1 Studies**

	Study			
	FPLA1001 ¹	FPL10002 ^{1,2}	FPL10003 ³	FPL10005
<u>Objective</u>	Vasoconstrictor assay	Bioequivalence assay	Contact sensitization and irritation study	HPA axis suppression study
<u>Design</u>	Randomized, double-blind, single-center study	Randomized, double-blind, single-center study	Randomized, double-blind, vehicle-controlled, single-center study	Open-label, multicenter study
<u>Location</u>	United States	United States	United States	United States
<u>Treatment Groups</u>	Two formulations of fluticasone lotion 0.05%, Cutivate (fluticasone propionate) Cream 0.05%. Temovate (clobetasol propionate) Cream 0.05%, Elocon (mometasone furoate) Lotion 0.01%, Hytone (hydrocortisone) Lotion 2.5%, Two vehicle lotions	Two fluticasone propionate lotion formulations, Cutivate (fluticasone propionate) Cream 0.05%	Fluticasone propionate lotion 0.05%. Vehicle lotion	Fluticasone propionate lotion 0.05%
<u>Enrolled</u>	33 healthy adults	15 healthy adult females	231 healthy adults	44 pediatric patients with eczema
<u>Dose</u>	10 µl non-occluded drug	10 µl non-occluded drug	0.2 ml semi-occluded drug	Twice daily application of amount necessary to cover ≥ 35% body surface area
<u>Number of Doses per Study Time Frame</u>	A single application at baseline	Treatments applied to different forearm sites for a duration of 15 – 300 minutes	Every 48 hours for up to 14 applications	Study drug was applied twice daily for 3 to 4 weeks
<u>Number of Visits</u>	4 visits – 1 screening, then 3 consecutive daily visits	2 visits – 1 screening visit then 1 visit for a 24 hour period	Up to 22 visits	5 or 6 visits
<u>Measurement Time points</u>	2, 3, 6, 8 and 24 hours after drug removal	0, 2, 4, 6, 8, 10, 19, 21, and 24 hours after drug	Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27, 41, 43, 45. Also days 55, 57,	Days 0, 8, 15, 22, 29. Also follow-up as needed

			58, 59 if rechallenge necessary	
<u>Measurements Related to Safety</u>	Adverse events	Adverse events	Sensitization, irritation, adverse events	Cosyntropin stimulation test, chemistry and hematology laboratory evaluations, adverse events vital signs, atrophy, pigmentation changes

Source: Sponsor's NDA submission, Volume 10, p.183; Volume 11, p. 20.

¹The sponsor's proposed market formulation of fluticasone propionate lotion 0.05% was not tested.

²Part 1 only of the study was completed.

³Twelve applications were scheduled unless rechallenge was necessary.

Extent of Exposure, Phase 1

Studies FPLA1001, FPL10002, and FPL10003 used applications of 2 cm² in size. In studies FPLA1001 and FPL10002, the drug was not under occlusion, whereas in FPL10003, semi-occlusion was used. In FPLA1001, a 10 µl application was used for eight study drugs, which included two formulations of fluticasone propionate lotion 0.05%. In FPL10002, 10 µl of fluticasone propionate cream was applied to seven separate 2 cm² areas of the arm, and 10 µl was applied to one 2 cm² of the arm. In FPL10003, patients were scheduled for 12 patch applications of 0.2 ml to a 2 cm² area (with the possibility of up to 14 applications if rechallenge was considered necessary). The initial 11 applications were made over an approximately 24 day induction phase. Following a 2-week rest period, an additional application was made in the challenge phase of the study.

Reviewer's Comment: *Exposure to fluticasone was minimal in studies FPLA1001 and FPL1002. Also, the proposed market formulation was not used in these studies. In study FPL1002 only part one of the study, in which subjects were exposed to fluticasone propionate cream, was completed.*

In study FPL10005, patients were required to have eczema lesions covering a minimum of 35% of their body surface area to be eligible for enrollment. During the study, patients were to continue to apply study drug to a minimum of 35% body surface area for at least 3 weeks, regardless of healing status. Subjects ≥ 3 months and < 3 years of age received up to two 60 mL bottles per week of fluticasone propionate lotion. Subjects ≥ 3 years and < 6 years of age received up to three 60 ml bottles per week. Drug usage was determined by weighing returned medication bottles. A total of 44 patients were enrolled with 42 patients completing the study – 33 (75%) receiving 4 weeks of treatment and 9 (20%) receiving 3 weeks of treatment. The sponsor states that the mean number of days that patients were treated was 27.6 days (± 3.6 days). A total of 35 (80%) of 44 patients returned all medication bottles. The mean amount of drug used over the study period was 197.0 grams (± 114.5 grams) in patients for whom all medication bottles were returned. The sponsor indicates that the average full bottle weight of a 60 ml tube of fluticasone

propionate lotion was 75.0 grams. If the weight of the returned bottle was more than 36.8 grams, the amount used was considered by the sponsor to be zero for that tube.

Demographic Characteristics, Phase 1

Baseline demographic information for these studies is displayed in Table 33.

**Table 33
Demographics Characteristics of Study Patients
Phase 1 Studies (Intent-to-Treat Population)**

Variable	FPLA1001	FPL10002	FPL10003	FPL10005
N	33	15	231	44
<u>Gender</u>				
Female	27 (82%)	15 (100%)	172 (74%)	22 (50%)
Male	6 (18%)	0	59 (26%)	22 (50%)
<u>Ethnic Origin</u>				
White	33 (100%)	15 (100%)	205 (89%)	18 (41%)
Black	0	0	5 (2%)	15 (34%)
Other	0	0	21 (9%)	11 (25%)
<u>Age (years)</u>				
Mean	43.2	39.6	48.8	2.6
Range	20-66	22-50	18.2-75.6	0.3-5.9

Source: Sponsor's NDA submission, Volume 10, p.184.

Subject Accountability, Phase 1

Patient disposition for phase 1 studies is summarized in Table 34:

**Table 34
Patient Disposition at End of Study
Phase 1 Studies (Intent-to-Treat Population)**

	FPLA1001	FPL10002 (Part 1 of Study Only) ¹	FPL10003	FPL10005
Enrolled	33	15	231	44
Completed Study	33	15	204	42
Prematurely Discontinued	0	0	27	2
<u>Reason for Discontinuation</u>				
Adverse Event	0	0	5	0
Consent Withdrawn	0	0	20	0
Lost to Follow-up	0	0	0	1
Protocol Violation	0	0	2	1

Source: Sponsor's NDA submission, Volume 10, p.184.

¹A separate enrollment of 60 - 80 patients was planned for Part 2. Part 2 of the study was never initiated.

Phase 3 Studies:

The sponsor has pooled safety data for the two replicate phase 3 studies, FPL30003 and FPL30004.

Summary of Phase 3 Studies

An overview of phase 3 trials is provided in Table 5. Treatment arms were fluticasone lotion 0.05% and vehicle lotion. Dosing was once daily application. Safety measurements included adverse events, chemistry and hematology laboratory evaluations (in patients \geq 17 years of age only), signs of cutaneous atrophy, and pigmentation changes.

Extent of Exposure, Phase 3

The sponsor indicates that for patients receiving fluticasone propionate lotion, the mean duration of treatment was 26.8 days (\pm 6.2, range 2 to 48), whereas patients receiving vehicle had a mean duration of treatment of 23.5 days (\pm 8.6, range 3 to 39). A total of 182 (82%) of 221 patients receiving fluticasone propionate lotion completed 4 weeks or more of treatment, and 149 (69%) of 217 of patients receiving vehicle completed 4 weeks or more of treatment. Twenty-seven patients (12%) in the fluticasone propionate lotion group and 56 patients (26%) in the vehicle group received 2 weeks or less of treatment. Tables summarizing the treatment duration for these studies, including for those patients meeting the Agency's minimum baseline criteria, are in the efficacy section of this review (see Tables 14, 20, 25, 31).

Reviewer's Comment: As discussed in the efficacy section, a significant number of enrolled patients were discontinued early, in violation of the protocol.

In studies FPL30003 and FPL30004, the sponsor measured medication use based on the number of bottles dispensed to patients. Pediatric patients could use up to three 60 ml bottles every 2 weeks, and adult patients could use up to four bottles every 2 weeks. Therefore, the maximum use over 4 weeks was six bottles for pediatric patients and eight bottles for adults. A summary of fluticasone propionate lotion use is shown in the following table:

**Table 35
Fluticasone Propionate Lotion Used
Phase 3 Studies (Intent-to-Treat Population Assigned to Active Study Drug)**

Number of Bottles of Fluticasone Propionate Lotion Used ¹	FPL30003 Pediatric (N=58)	FPL30003 Adult (N=52)	FPL30004 Pediatric (N=65)	FPL30004 Adult (N=46)
0.00	0	0	0	0
0.25	1	1	0	1
0.50	3	5	1	1

0.75	2	2	4	1
1.00	5	3	6	1
1.25	8	3	4	4
1.50	3	7	12	4
1.75	2	5	5	1
2.00	7	3	5	2
2.25	1	1	8	3
2.50	5	3	3	2
2.75	2	0	2	2
3.00	8	3	4	2
3.25	2	1	1	1
3.50	4	3	0	2
3.75	1	2	2	3
4.00	1	2	2	3
4.25	1	1	0	3
4.50	0	0	2	3
4.75	1	1	0	0
5.00	0	0	1	0
5.25	0	0	1	0
5.50	1	2	1	1
5.75	0	0	0	0
6.00	0	3	1	0
6.25	0	0	0	0
6.50	0	0	0	0
6.75	0	0	0	0
7.00	0	0	0	1
7.25	0	0	0	0
7.50	0	0	0	0
7.75	0	0	0	1
8.00	0	0	0	4
> 8.00	0	1	0	0

Source: Sponsor's NDA submission, Volume 16, p.97; Volume 20, p. 96.

¹One bottle contained 60 ml of drug. Subjects dispensed drug for which the amount used was unknown were assumed by the sponsor to have used the whole bottle.

Reviewer's Comment: *The sponsor submitted usage data except in terms of total bottles used. The treatment time was variable per patient.*

As illustrated in the Table 35, a total of 68 (55%) of 123 pediatric patients and 44 (45%) of 98 adult patients used two bottles or less during the study. This reflects, in part, the fact that many patients enrolled into these studies had mild or minimal disease. Note also that the sponsor's assumption that the whole bottle was used, when the amount used was unknown, tends to overestimate usage.

Demographic Characteristics, Phase 3

Demographic characteristics for studies FPL30003 and FPL30004 are shown individually in Tables 15 and 26. Pooled baseline demographic characteristics for phase 3 studies are listed below:

Table 36
Demographics Characteristics of Study Patients
Pooled Phase 3 Studies (Intent-to-Treat Population)

Variable	FPL30003 and FPL3004 N=438 (%)
Gender	
Female	230 (53)
Male	208 (47)
Race	
White	329 (75)
Black	60 (14)
Hispanic	20 (5)
Asian	16 (4)
Other	13 (3)
Age	
≥ 3 months and < 3 years	115 (26)
≥ 3 years and < 6 years	81 (18)
≥ 6 years and < 17 years	46 (11)
≥ 17 years and ≤ 65 years	179 (41)
> 65 years	17 (4)

Source: Sponsor's NDA submission, Volume 10, p. 224.

Reviewer's Comment: *Note that references to the age groups in these studies correspond with the definitions in this table. However, for ease of reading, "<" and "≥" will be omitted in the text below.*

Subject Accountability, Phase 3

A total of 438 of 439 patients enrolled in phase 3 studies received at least one dose of study drug and are included in the sponsor's safety population. For end-of-study patient disposition, see Tables 12 and 23 in the efficacy section.

C. Methods and Specific Findings of Safety Review

This safety review of fluticasone propionate lotion 0.05% includes adverse events by body system; systemic safety as measured by HPA axis suppression testing and clinical laboratory evaluations; cutaneous atrophy and pigmentation changes; and cutaneous irritancy and allergenicity.

Adverse Events, Phase 1

Few adverse events were reported for phase 1 studies FPLA1001 and FPL10002, which had minimal drug exposure. In study FPLA1001, two adverse events were reported: a patient developed blisters at the site of the protective guard for the application site, and

another patient developed tooth pain. Neither adverse event was considered by investigators to be related to the study drug. A total of 13 adverse events were reported in 12 patients for study FPL10003 (contact sensitization and irritation study). These included three subjects who developed a rash of moderate severity. Five subjects in study FPL10003 withdrew because of adverse events. The subjects included three who experienced rash, one with cervical cancer, and one who experienced streptococcal pharyngitis. No adverse events in the study were considered by investigators to be related to study drug.

Adverse events for these three phase 1 studies are summarized in Table 37:

Table 37
Summary of Adverse Events
Studies FPLA1001, FPL10002, and FPL10003 (Intent-to-Treat Population)

	FPLA1001	FPL10002	FPL10003
Total Number of Subjects	33	15	231
Subjects with Adverse Events	2 (6%)	3 (20%)	12 (5%)
Total Adverse Events	2	3	13
Skin-Related Adverse Events	1 Blisters	0	3 Rash
All Other Adverse Events	1 Tooth pain	2 Headache 1 Diarrhea	1 Cervical Cancer 1 Tooth infection 1 Cough 3 Infection 4 Headache

Source: Sponsor's NDA submission, Volume 10, p.188.

Reviewer's Comment: It is possible that the rash occurring on the back in subjects in study FPL10003 was a generalized reaction to patch testing ("hyperirritable skin").

The final phase 1 study was the HPA axis study, FPL10005 (study results are discussed separately below). In this study, a total of 49 adverse events occurred in 28 (64%) of 44 patients. Of these, 12 were skin-related adverse events occurring in 11 patients. Dry skin at multiple sites was reported in 3 patients and stinging at the application site in 2 patients. The remaining skin-related adverse events were each reported once: folliculitis, rash (not further defined), scabies, urticaria, hematoma, excoriation, and tinea (not further defined). Of non-skin-related adverse events, the most frequent were respiratory infections and ear infections. One adverse event was considered severe: a streptococcus infection in a 5-year-old girl. This reportedly resolved after 9 days and was not considered related to study drug.

Six of the adverse events occurring in 6 patients (14%) were reported by the sponsor to be related to study drug. These were all skin related: dry skin at multiple sites in 3 patients; stinging at the application site in 2 patients; and excoriations in 1 patient. All

events resolved by the end of the study. No patients withdrew from the study because of adverse events.

Adverse events for study FPL10005 are summarized in Table 38:

Table 38
Summary of Adverse Events by Body System
Study FPL10005 (Intent-to-Treat Population)

Body System	Number of Patients Age 3 mos - 3 yrs (N = 26)	Number of Patients Age 3 yrs - 6 yrs (N = 18)	Total Number of Patients (N = 44)
Any Adverse Event	18 (69%)	10 (56%)	28 (64%)
Skin			
Acute Urticaria	1 (4%)	0	1 (2%)
Dry Skin of Multiple Sites	3 (12%)	0	3 (7%)
Folliculitis	0	1 (6%)	1 (2%)
Rash	1 (4%)	0	1 (2%)
Scabies	0	1 (6%)	1 (2%)
Tinea	0	1 (6%)	1 (2%)
Ear Nose and Throat			
Common Cold	1 (4%)	2 (11%)	3 (7%)
Ear Infection	1 (4%)	0	1 (2%)
Otitis	4 (15%)	0	4 (9%)
Rhinitis	1 (4%)	0	1 (2%)
Sore Throat	1 (4%)	0	1 (2%)
Upper Respiratory Tract Infection	7 (27%)	4 (22%)	11 (25%)
Lower Respiratory			
Bronchitis	1 (4%)	0	1 (2%)
Cough	2 (8%)	0	2 (5%)
Wheeze	1 (4%)	1 (6%)	2 (5%)
Non-Site Specific			
Fever	2 (8%)	0	2 (5%)
General Congestion	1 (4%)	0	1 (2%)
Pain	1 (4%)	0	1 (2%)
Streptococcus	0	1 (6%)	1 (2%)
Viral Syndrome	1 (4%)	0	1 (2%)
Drug Interaction, Overdose and Trauma			
Excoriation	1 (4%)	0	1 (2%)
Hematoma	0	1 (6%)	1 (2%)
Stinging at Application Sites	1 (4%)	1 (6%)	2 (5%)
Gastrointestinal			
Diarrhea	1 (4%)	0	1 (2%)
Vomiting	0	1 (6%)	1 (2%)
Hepatobiliary Tract and Pancreas			
Increased Liver Function Test	1 (4%)	0	1 (2%)

Source: Sponsor's NDA submission, Volume 14, p. 87-9.

Reviewer's Comment: There was no vehicle arm for comparison in this open-label study.

Serious Adverse Events and Deaths, Phase 1

The sponsor reported that there were "no serious adverse events or deaths in any of the four Phase 1 studies." (Sponsor's NDA submission, Volume 10, p. 190.)

Pregnancies, Phase 1

The sponsor reported no pregnancies for phase 1 studies.

Adverse Events, Phase 3

Table 39 summarizes adverse events that occurred in $\geq 1\%$ of patients – either in the vehicle or fluticasone arm – in pooled phase 3 studies (FPL30003, FPL30004).

Table 39
Summary of Adverse Events by Body System: All Patients
Pooled Phase 3 Studies (Intent-to-Treat Population)

Body System	Vehicle Lotion N = 217	Fluticasone Propionate Lotion N = 221
Any Adverse Event	82 (38%)	77 (35%)
Skin		
Burning and Stinging	3 (1%)	4 (2%)
Pruritus	5 (2%)	3 (1%)
Rash	3 (1%)	2 (<1%)
Skin Infection	3 (1%)	0
Ear, Nose, Throat		
Common Cold	5 (2%)	9 (4%)
Ear Infection	3 (1%)	3 (1%)
Nasal Sinus Infection	4 (2%)	2 (<1%)
Rhinitis	3 (1%)	1 (<1%)
Upper Respiratory Tract Infection	7 (3%)	6 (3%)
Gastrointestinal		
Normal Tooth Eruption	3 (1%)	2 (< 1%)
Diarrhea	0	3 (1%)
Vomiting	2 (<1%)	3 (1%)
Lower Respiratory		
Cough	6 (3%)	7 (3%)
Influenza	0	5 (2%)
Wheeze	3 (1%)	0
Neurology		
Headache	5 (2%)	4 (2%)
Non-Site Specific		
Fever	8 (4%)	8 (4%)
Seasonal Allergy	3 (1%)	2 (<1%)

Source: Sponsor's NDA submission, Volume 10, p. 249-52.

Reviewer's Comment: A serious limitation for adverse event and other safety data in phase 3 studies is that many patients enrolled in the studies had mild or minimal disease.

Only 89 (40%) of 221 patients in the fluticasone group in the combined studies met the Agency's minimum baseline criteria (see efficacy section) for having disease considered severe enough to warrant inclusion in the study. Because patients with more severe disease would likely apply more lotion, have greater drug absorption, and be more susceptible to certain adverse events, such as infection or systemic adverse events, conclusions based on these data cannot be generalized with confidence.

The number of patients with at least one adverse event in the study was similar in the fluticasone (35%) and vehicle (38%) groups. There was not an appreciable difference in adverse events between the fluticasone and vehicle groups for most adverse events. An exception was that five cases of influenza were reported in patients receiving fluticasone propionate and no cases were reported in patients in the vehicle group. All reported influenza cases occurred in patients aged 17 – 65.

It should be noted that patients in these studies were instructed not to treat eyelids, nostrils, the perioral area or the diaper area.

Adverse events were also summarized based on patient age. The following two tables list adverse events that occurred in $\geq 1\%$ of patients in either the vehicle or fluticasone propionate treatment arms in the youngest age groups: 3 months – 3 years of age, and 3 years – 6 years of age.

Table 40
Summary of Adverse Events by Body System: Patients 3 Months - 3 Years of Age
Pooled Phase 3 Studies (Intent-to-Treat Population)

Body System	Vehicle Lotion N = 55	Fluticasone Propionate Lotion N = 60
Any Adverse Event	28 (51%)	21 (35%)
Skin		
Burning and Stinging	1 (2%)	1 (2%)
Dermatitis	1 (2%)	0
Pruritus	0	1 (2%)
Rash	1 (2%)	0
Skin Infection	1 (2%)	0
Ear, Nose, Throat		
Cold Symptoms	1 (2%)	0
Common Cold	4 (7%)	2 (3%)
Ear Infection	3 (5%)	3 (5%)
Otitis	1 (2%)	1 (2%)
Otitis Media	2 (4%)	1 (2%)
Nasal Sinus Infection	1 (2%)	1 (2%)
Sinusitis	1 (2%)	0
Sneezing	0	1 (2%)
Rhinitis	2 (4%)	1 (2%)
Upper Respiratory Tract Infection	4 (7%)	1 (2%)
Gastrointestinal		
Normal Tooth Eruption	3 (5%)	2 (3%)

Diarrhea	0	1 (2%)
Vomiting	1 (2%)	1 (2%)
Gastrointestinal Gaseous Symptom	1 (2%)	0
Gingivalgia	1 (2%)	0
Loose Stools	1 (2%)	0
Teething Pain	0	1 (2%)
Lower Respiratory		
Bronchitis	0	1 (2%)
Cough	2 (4%)	1 (2%)
Restrictive Lung Disease	1 (2%)	0
Wheeze	3 (5%)	0
Psychiatry		
Fussy	0	1 (2%)
Non-Site Specific		
Candida	0	1 (2%)
Erythema Infectiosum	0	1 (2%)
Fever	5 (9%)	3 (5%)
Pain	1 (2%)	0
Redness	1 (2%)	0
Seasonal Allergy	0	1 (2%)

Source: Sponsor's NDA submission, Volume 10, p. 253-4.

Table 41
Summary of Adverse Events by Body System: Patients 3 Years - 6 Years of Age
Pooled Phase 3 Studies (Intent-to-Treat Population)

Body System	Vehicle Lotion N = 39	Fluticasone Propionate Lotion N = 42
Any Adverse Event	15 (38%)	17 (40%)
Skin		
Burning and Stinging	1 (3%)	1 (2%)
Pruritus	0	1 (2%)
Rash	1 (3%)	1 (2%)
Skin Infection	2 (5%)	0
Drug Interaction Overdose and Trauma		
Fractured Upper Limb(s)	1 (3%)	0
Injury to Finger(s)	1 (3%)	0
Ear, Nose, Throat		
Common Cold	1 (3%)	2 (5%)
Earache	1 (3%)	0
Nasal Congestion	0	2 (5%)
Otitis Media	0	1 (2%)
Nasal Sinus Infection	1 (3%)	0
Rhinitis	1 (3%)	0
Upper Respiratory Tract Infection	1 (3%)	2 (5%)
Sore Throat	0	1 (2%)
Streptococcal Pharyngitis	0	1 (2%)
Gastrointestinal		
Diarrhea	0	2 (5%)
Vomiting	0	1 (2%)

Nausea	0	1 (2%)
Lower Respiratory		
Bronchitis	0	1 (2%)
Cough	3 (8%)	4 (10%)
Chest Congestion	1 (3%)	0
Non-Site Specific		
Fever	1 (3%)	4 (10%)
Seasonal Allergy	1 (3%)	1 (2%)
General Congestion	1 (3%)	0
Streptococcus	0	1 (2%)
Varicella	0	1 (2%)
Viral Syndrome	1 (3%)	0

Source: Sponsor's NDA submission, Volume 10, p. 255.

Reviewer's Comment: Adverse events occurred commonly in the younger age groups, including those affecting the ear, nose, and throat, and respiratory system. However, there was not a pattern of increased adverse events in patients treated with fluticasone propionate lotion compared to patients treated with vehicle. Fever was reported more commonly in the fluticasone group for patients aged 3 - 6 years; this was not observed for the 3 month - 3 year age group.

A total of 46 patients were enrolled in the age group of 6 to 17 years. Of these, 18 (39%) patients experienced adverse events: 12 patients (48%) in the vehicle group and 6 patients (29%) in the fluticasone group. The most commonly reported adverse event was headache, which occurred in 3 patients in the vehicle group and 1 patient in the fluticasone group. No other adverse event was reported in more than 2 patients in either the vehicle or fluticasone groups.

A total of 57 (32%) of 179 patients aged 17 years to 66 years experienced adverse events in phase 3 studies. A total of 26 patients (29%) were in the vehicle group and 31 patients (34%) were in the fluticasone group. The most common adverse event was a common cold, which occurred in 5 patients in the fluticasone group and no patients in the vehicle group.

For the age group > 65 years of age, only 17 patients were enrolled. Three adverse events were recorded in this age group: 1 patient from the vehicle group experienced pruritus; 1 patient in the fluticasone group experienced an upper respiratory tract infection; and 1 patient in the fluticasone group experienced back pain.

In phase 3 studies, 19 patients (4%) experienced at least one adverse event that was considered by investigators to be related to study drug. These are listed in Table 42:

Table 42
Summary of Adverse Events Related to Study Drug
Pooled Phase 3 Studies (Intent-to-Treat Population)

Adverse Event	Vehicle	Fluticasone
---------------	---------	-------------

	Lotion N = 217	Propionate Lotion N = 221
Total Number of Patients with One or More Drug-Related Adverse Events	11	8
Rash	2	1
Pustule on Arm	0	1
Burning and Stinging	3	4
Pruritus	1	1
Exacerbation of Atopic Dermatitis	1	0
Skin Infection	3	0
Irritant Contact Dermatitis	1	0
Contact Dermatitis	1	0
Folliculitis of Leg	0	2

Source: Sponsor's NDA submission, Volume 10, p. 271.

Reviewer's Comment: Burning and stinging was the most commonly reported drug-related adverse event. Because there was no appreciable difference in burning and stinging or pruritus between the vehicle and fluticasone groups, it appears that the vehicle ingredients may be responsible in most cases. The vehicle formulation contains 10% propylene glycol, which is a known potential irritant. Similarly, the two episodes of contact dermatitis were in the vehicle group, indicating an irritant or allergic response to vehicle ingredients. Both cases of folliculitis occurred in the fluticasone group; folliculitis is a known local adverse event that may occur with topical corticosteroid use.

The sponsor states that 12 patients were withdrawn from phase 3 studies because of an adverse event – 4 patients in the fluticasone treatment group, and 8 patients in the vehicle group. Nine of these adverse events were considered related to study drug. One additional patient, a 42-year-old male in the fluticasone group, stopped study drug but completed the study. He developed a mild rash that resolved within one day without medication. The investigator considered the event drug related. Patients withdrawn because of an adverse event are summarized in Table 43:

Table 43
Summary of Patients Withdrawn Because of an Adverse Event
Pooled Phase 3 Studies (Intent-to-Treat Population)

Subject	Treatment Group	Adverse Event	Investigator Considered Possibly or Definitely Drug Related	Outcome
1-year-old male	Fluticasone	Moderate burning/stinging, pruritus	Yes	Resolved within 13 days without medication
7-year-old female	Fluticasone	Severe urticaria	No	Resolved within 10 days without medication

33-year-old male	Fluticasone	Eczema herpeticum	No	Resolved within 29 days with multiple medications including acyclovir ¹
4-year-old female	Fluticasone	Severe burning/stinging	Yes	Resolved within 1 day without medication
16-year-old male	Vehicle	Mild rash	Yes	Resolved within 4 days without medication
2-year-old female	Vehicle	Moderate burning/stinging	Yes	Resolved within 1 day without medication
11-year-old male	Vehicle	Exacerbation of atopic dermatitis	Yes	Resolved within 11 days without medication
2-year-old female	Vehicle	Moderate skin infection	Yes	Resolved within 27 days with erythromycin and topical mupirocin
4-year-old female	Vehicle	Moderate skin infection and rash	Yes	Infection resolved within 22 days with erythromycin and topical mupirocin. Rash unresolved at end of study and patient lost to follow-up.
53-year-old male	Vehicle	Severe foot infection	No	Resolved within 24 days with amoxicillin
44-year-old female	Vehicle	Severe contact dermatitis	Yes	Had not resolved at discontinuation and patient lost to follow-up
38-year-old male	Vehicle	Moderate burning/stinging	Yes	Resolved within 28 days without medication

Source: Sponsor's NDA submission, Volume 10, p. 203-4.

¹See description under serious adverse events below.

Reviewer's Comment: It is notable that moderate or severe burning and stinging was significant enough to require discontinuation in 1 adult and 3 pediatric patients.

The patient with eczema herpeticum is discussed under "serious adverse events" below.

Serious Adverse Events and Deaths, Phase 3

One patient was reported to have a serious adverse event during phase 3 studies. A 33-year-old male in the fluticasone treatment group in study FPL30004, developed a severe event of eczema herpeticum (widespread cutaneous infection with herpes simplex virus). The patient was noted at baseline to have atopic dermatitis affecting > 54% of his skin. A case narrative provided by the sponsor describes the episode:

"Approximately one day after initiating treatment, the subject developed bumps on his skin. On the third day after initiating treatment, the subject phoned the investigator and reported that he had developed weeping bumps on his face. The subject was advised over the phone to discontinue study drug. The subject was seen in clinic four days later. The blisters were umbilicated and bloody. The subject was afebrile. He was diagnosed with eczema herpeticum and treated with acyclovir, betamethasone, prednisone, mupirocin

ointment, Theraplex lotion, Aveeno baths, and Vaseline...The event resolved within 1 month. In the investigator's opinion, the events were unrelated to the use of study drug and caused by a rare complication of atopic eczema." (Sponsor's NDA submission, Volume 20, p. 68.)

Reviewer's Comment: Eczema herpeticum may occur in patients with active atopic dermatitis. Whether fluticasone propionate lotion played a role in the development or course of eczema herpeticum in this patient is uncertain.

There were no deaths reported in phase 3 studies

Pregnancies, Phase 3

There were no pregnancies reported in phase 3 studies.

Reviewer's Comment: At both the Pre-IND Meeting on October 22, 1997, and the End-of-Phase 2 Meeting on May 7, 1998, the sponsor was advised that if females of child-bearing potential were required to use birth control in order to be eligible for studies of fluticasone propionate lotion, then this should be reflected in labeling for the product. In a letter to the Agency of August 11, 1998, the sponsor argued that women of childbearing potential needed to use an acceptable form of contraception to participate in clinical trials for fluticasone propionate lotion. This was an eligibility requirement for phase 3 (and earlier) studies. This should be reflected in labeling. Were this drug product approved, postmarketing information regarding the outcome of pregnancies in women who use this product during pregnancy should be sought to address the issue of possible risks of treatment during this time.

Systemic Safety: HPA Axis Suppression Study and Plasma Fluticasone Levels

Study FPL10005 was performed to evaluate the safety of a 3 or 4 week course of fluticasone propionate lotion 0.05% in patients aged 3 months to 6 years. The effect of fluticasone propionate lotion on HPA axis function was assessed by a cosyntropin stimulation test. In children ≥ 2 years old, plasma levels of fluticasone were also measured. Other safety parameters included hematology and chemistry laboratory evaluations, and clinical signs of skin atrophy and pigmentation changes at the application site (these are discussed separately below).

Reviewer's Comment: The sponsor stated that the decision not to measure plasma fluticasone levels in children less than 2 years of age was based experience from an HPA axis study for fluticasone cream. Specifically, the sponsor states that in that study "some IRBs [Institutional Review Boards] were not comfortable with a large volume of blood being drawn from infants and some of the investigational sites did not have the technical proficiency to collect this volume of blood from small peripheral veins." (Sponsor's NDA submission, Volume 14, p. 18.)

Study Design

The study was a multicenter, phase 1, open-label study. The study included six study sites and enrolled 44 patients diagnosed with moderate to severe eczema. Investigators are listed in Table 44.

Table 44
Investigators
Study FPL10005

Investigator Number	Name	Location	Patients Enrolled
			1
			1
			18
			22
			1
			1

Source: Sponsor's NDA submission, Volume 15, p. 125-6.

Reviewer's Comment: *Although the study included six study sites, only two enrolled more than a single patient.*

Inclusion criteria required that patients be 3 months to 6 years of age at the time of the screening visit; have eczema or psoriasis covering $\geq 35\%$ body surface area; and have disease that was stable or worsening. Patients were required to have a combined severity score of at least 6 based on a grading scale of 0 – 3 for any three of the following eight signs and symptoms: erythema, pruritus, papulation, induration, oozing/crusting, scaling, excoriation, and lichenification. The grading scale was as follows: 0 = absent; 1 = mild; 2 = moderate; 3 = severe.

Reviewer's Comment: *Although the protocol allowed enrollment of patients with psoriasis, the sponsor states that all 44 patients had a diagnosis of eczema at baseline. However, it should be noted that patients enrolled in this study may not necessarily have had atopic dermatitis, which is a form of "eczema" or "eczematous dermatitis." Severity scores should also have been based on clinical signs recommended by the Agency for phase 3 studies (erythema, edema/papulation, and erosion/oozing/crusting).*

Thirteen patients received chronic treatment (> 4 weeks continuously) with topical steroids within 4 weeks of baseline, in violation of eligibility criteria. Another patient had a 5-day course of prednisolone therapy within 3 months of baseline. However, as the sponsor notes, these treatments might tend to result in a more stringent test than expected.

Patients who had an abnormal baseline cosyntropin stimulation test could be discontinued or kept in the study, at the investigator's discretion. The study was designed to obtain data for a minimum of 20 – 32 evaluable patients, with approximately half being 3 months to 3 years of age.

Patients used fluticasone propionate lotion 0.05%, two times a day for 3 or 4 weeks; those patients who were 100% clear at 2 weeks were to receive 3 weeks of treatment, and patients who were < 100% clear at 2 weeks were to receive 4 weeks of treatment. Patients were to continue to treat at least 35% body surface area, even if the affected area fell to less than 35%. The eyelids, nostrils, diaper area, and perioral area were not treated.

Two cosyntropin stimulation tests were given – one at baseline and one at the end of treatment. The end-of-treatment cosyntropin stimulation test was given after either 3 or 4 weeks, to correspond with the time when treatment was stopped. Patients aged 3 months to 3 years received intravenous injections of 0.125 mg cosyntropin. Patients aged 3 years to 6 years received intravenous injections of 0.25 mg cosyntropin. A blood sample was obtained for analysis of serum cortisol prior to cosyntropin administration (scheduled at 8:00 a.m.) and 30 minutes after cosyntropin administration. Cortisol was reportedly assayed using a fluorescence polarization immunoassay.

Reviewer's Comment:

However, demonstrating adrenal suppression based on a serum cortisol level of $\leq 18 \mu\text{g/dL}$ obtained 30 minutes post-stimulation, is consistent with the current Division recommendation.

Results: Cosyntropin Stimulation Test

Of a total of 44 enrolled patients, 42 completed end-treatment cosyntropin stimulation tests. Of these, 24 patients were 3 months to 3 years of age, and 18 patients were 3 years to 6 years of age.

The sponsor reported that the mean sum of the severity scores for all patients was 14.6 (± 2.7) out of 24 for the eight signs and symptoms considered. The mean percent body surface area to be treated at baseline was 65%.

Table 45 summarizes the results of cosyntropin stimulation testing in this study for the 24 patients in the 3 month – 3 year age group, who completed the study. Normal adrenal response to the cosyntropin stimulation test was defined as a post-stimulation cortisol level of $> 18.0 \mu\text{g/dL}$.

Table 45
Serum Cortisol Levels
Study FPL10005: Patients 3 Months – 3 Years of Age

Subject #	Age (year-month)	Total Drug Used ¹ (g)	Serum Cortisol ($\mu\text{g/dL}$)							
			Screening Visit			End of Treatment (Week 3 – 4)				
			Pre-stimulation	Post-stimulation	Change	Pre-stimulation	Post-stimulation	Change		

5023	1-2	125.1	11.9	37.7	25.8	13.1	29.0	15.9
5004	1-8	292.2	7.3	30.0	22.7	6.5	28.3	21.8
5005	1-7	129.2	6.0	31.8	25.8	7.6	34.3	26.7
5006	0-11	188.4	7.4	29.3	21.9	11.7	39.6	27.9
5007	0-7	421.7	12.2	35.0	22.8	8.2	39.7	31.5
5008	1-0	184.9	23.1	32.9	9.8	8.9	21.1	12.2
5019	0-9	247.9	12.6	46.6	34.0	8.0	25.0	17.0
5020	2-3	277.2	22.8	34.9	12.1	14.5	27.0	12.5
5021	1-3	Unknown	19.1	35.0	15.9	16.1	36.1	20.0
5022	2-7	Unknown	18.5	45.9	27.4	28.4	52.3	23.9
5031	1-6	240.7	12.7	36.4	23.7	10.2	40.7	30.5
5032	1-10	121.4	16.3	40.2	23.9	8.3	26.5	18.2
5011	2-2	245.8	9.8	32.9	23.1	8.2	28.8	20.6
5012 ²	1-3	212.9	12.0	39.6	27.6	15.0	41.5	26.5
5015	1-4	101.2	11.9	35.5	23.6	21.8	48.0	26.2
5017	0-4	69.2	6.1	39.6	33.5	18.2	59.7	41.5
5018	2-5	66.1	16.3	37.6	21.3	8.1	27.3	19.2
5025	1-3	33.5	20.5	42.9	22.4	11.9	34.4	22.5
5026 ³	0-5	176.6	10.4	44.4	34.0	12.6	31.7	19.1
5027	2-6	92.5	11.1	36.9	25.8	12.7	43.6	30.9
5028	0-11	103.6	11.4	32.1	20.7	14.2	29.2	15.0
5029	0-11	41.0	9.4	39.9	30.5	14.3	41.6	27.3
5013	0-6	299.8	8.0	31.0	23.0	6.1	31.9	25.8
5009 ²	0-5	437.8	30.4	51.8	21.4	2.9	27.7	24.8

Source: Sponsor's NDA submission, Volume 14, p. 210-41.

¹Drug usage is considered unknown if all medication bottles were not returned.

²Patient missed more than 10% of scheduled applications of study medication.

³End-treatment cosyntropin stimulation test was after only 19 days.

Reviewer's Comment: As indicated in Table 45, 2 patients missed more than 10% of scheduled applications, and 1 patient had her end-of-treatment cosyntropin stimulation test after only 19 days.

Results of cosyntropin stimulation testing for the 18 patients in the 3 year to 6 year age group, who completed the study, are shown in the following table:

Table 46
Serum Cortisol Levels
Study FPL10005: Patients 3 Years – 6 Years of Age

Subject #	Age (year-month)	Total Drug Used ¹ (g)	Serum Cortisol (µg/dL)					
			Screening Visit			End of Treatment (Week 3 – 4)		
			Pre-stimulation	Post-stimulation	Change	Pre-stimulation	Post-stimulation	Change
6001	3-6	Unknown	29.6	32.2	2.6	25.8	32.3	6.5
6003	4-2	Unknown	18.0	39.2	21.2	14.3	32.7	18.4

6004	3-8	156.2	14.5	37.6	23.1	11.8	33.9	22.1
6005	5-11	208.5	5.6	32.3	26.7	11.8	35.5	23.7
6006	4-6	328.4	10.4	41.0	30.6	15.6	32.6	17.0
6007	4-4	207.5	17.1	30.7	13.6	22.0	40.5	18.5
6008	4-10	258.4	7.5	19.1	11.6	15.6	23.8	8.2
6011	4-3	97.6	17.2	28.6	11.4	31.2	37.0	5.8
6012	3-10	Unknown	17.0	31.9	14.9	8.8	30.5	21.7
6015	4-0	Unknown	13.1	40.4	27.3	14.7	31.7	17.0
6016	3-10	Unknown	5.6	30.5	24.9	3.8	25.1	21.3
6017	5-2	177.7	14.2	33.8	19.6	8.4	27.3	18.9
6018	4-9	96.5	21.8	32.3	10.5	10.4	33.5	23.1
6025	5-11	Unknown	6.2	27.7	21.5	6.8	24.3	17.5
6026	3-3	88.6	13.1	36.9	23.8	12.1	34.4	22.3
6027	3-3	190.7	7.7	36.3	28.6	9.2	31.8	22.6
6028	5-2	462.1	6.8	27.4	20.6	4.6	25.5	20.9
6029	4-4	116.4	9.1	29.1	20.0	4.5	22.5	18.0

Source: Sponsor's NDA submission, Volume 14, p. 210-41.

¹Drug usage is considered unknown if all medication bottles were not returned.

The sponsor consulted a pediatric endocrinologist, _____

_____ to interpret the data. The sponsor states that Dr. _____ identified 2 patients – 5008 and 6029 – who showed decreases in end-treatment plasma cortisol levels for both pre- and post-testing. (These patients are indicated in bold type in the above tables.) The sponsor summarized Dr. _____ findings as follows:

"While the post-stimulation plasma cortisol levels were above the defined criteria for normal adrenal responsiveness, it was suspected that these subjects could be demonstrating mild partial suppression. It was further noted that these subjects demonstrated moderate to severe disease involving extensive body surface areas (80%, subject 5008; 75%, subject 6029). Overall, these findings were not considered to be clinically relevant with regard to the subjects' ability to mount an adrenal response, and the endocrinologist concluded that HPA axis suppression with fluticasone lotion when applied twice a day for 3-4 weeks is likely to be a rare event." (Sponsor's NDA submission, Volume 14, p. 44.)

Division of Metabolic and Endocrine Drug Products Consultation:

A consultation was obtained from the Agency's Division of Metabolic and Endocrine Drug Products (DMEDP) to review the findings of the HPA axis suppression study (see above). The reviewer, Dr. Robert S. Perlstein, with concurrence from the DMEPD Division Director, Dr. David Orloff, states the following commentary/conclusions (italics are from the original; underlining omitted):

"Recent review of the literature and safety databases by the DDDDP [Division of Dermatologic and Dental Drug Products] (presented at an October 2003 Advisory Committee) indicates that treatment of various dermatological disorders with topical

glucocorticoid formulations may result in clinically significant suppression of the HPA axis, especially when potent halogenated/fluorinated glucocorticoid formulations are applied to large BSAs [body surface areas] in children.

"In that context, it is therefore plausible that the 2 patients described [by the sponsor's consultant pediatric endocrinologist]...may have sustained *partial* suppression of the HPA axis after exposure to Cutivate, a topical, *fluorinated* glucocorticoid formulation.

"I also agree with the Sponsor's endocrinology consultant that these findings are most *likely* not clinically significant – in that the stimulated serum cortisol of these 2 children remained above 18 µg/dL. However, it should be noted that, *on occasion*, patients who stimulate normally in response to Cortrosyn, manifest abnormal responses during the 'gold standard' maneuver for evaluating the integrity of the HPA axis, the insulin tolerance test (ITT).

"I further agree with the Sponsor's overall conclusion that clinically significant suppression of the HPA axis appears to occur infrequently when relatively large amounts of Cutivate lotion 0.05% are applied to large BSAs for 21-28 days in children (aged 3 months to 5 years) with moderate to severe eczema."

The recommendations of Dr. Perlstien and Dr. Orloff are as follows:

"A CST [cosyntropin stimulation test] should be performed before and after exposure to Cutivate (for ≥ 21-28 days).

"In the event a stimulated serum cortisol < 18 µg/dL is observed following exposure to a course of Cutivate (*unlikely*), serial CSTs should be performed at appropriate intervals. Until the stimulated serum cortisol exceeds 18 µg/dL, empiric coverage with stress doses of a rapidly acting glucocorticoid should be administered during intercurrent serious illness/stress and a medalert bracelet/wallet card should be given to the patient.

"In the event potential *partial* suppression of the HPA axis is observed (as in the case of 2 patients during this study), there are 2 possible courses of action. *My first choice* would be to recommend empiric or prn (if the clinical circumstances indicate possible adrenal insufficiency) administration of stress doses of a rapidly acting glucocorticoid during intercurrent serious illness/stress, and use of a medalert identifier, *for at least one year after discontinuation of the course of Cutivate lotion*. (The more conservative option [more invasive and much less feasible/practical and therefore my second choice] would be to perform an ITT. If the serum cortisol during the ITT is appropriate, then partial adrenal insufficiency is essentially ruled out. On the other hand, if the ITT result is abnormal, empiric coverage with stress doses of a rapidly acting glucocorticoid should be administered during intercurrent serious illness/stress and a medalert bracelet/wallet card should be given to the patient until the ITT result normalizes.)"

Results: Plasma Fluticasone Levels

Plasma fluticasone levels were measured in patients ≥ 2 years of age in study FPL10005. The lower limit of quantification for the assay was 20 pg/mL. However, the sponsor states that for a few samples, the lower limit of quantification was 100 pg/mL because of insufficient sample volume.

A total of 21 patients had fluticasone levels measured. Two (10%) of 21 patients had measurable serum fluticasone levels at baseline. The sponsor states: "Neither of these subjects' parents had reported recent use of fluticasone. Sample contamination was the most likely explanation, possibly occurring during the blood drawing procedure." (Sponsor's NDA submission, Volume 14, p. 49.)

Reviewer's Comment: The sponsor did not indicate how sample contamination might have occurred. The blood draw for serum cortisol was scheduled prior to drug dispensing in the protocol.

Thirteen (62%) of 21 patients had measurable fluticasone at the end of treatment. The median level was 59.7 pg/mL. The highest end-treatment value was 819.8 pg/mL; this level occurred in a 3-year-old male treated for 28 days, with application to 35-40% body surface area. The patient did not have HPA axis suppression based on the cosyntropin stimulation test.

Of the 2 patients determined by the sponsor's pediatric endocrinologist to have evidence of possible partial HPA axis suppression, one was less than 2 years of age and, therefore, was not tested for plasma fluticasone. The other did not have measurable levels; however, the lower limit of quantification in this case was indicated to be 100 pg/mL because of insufficient sample volume.

Treatment information for the 13 patients with detectable serum fluticasone levels are summarized in Table 47:

Table 47
Patients with Detectable Plasma Fluticasone at End of Treatment
Study FPL10005

Subject	Age (yr-mo)	Sex	End-Treatment Fluticasone Plasma Level (pg/mL)	% Body Surface Area Treated at Baseline	Sum of Severity Scores at Baseline ¹	Total Drug Used ² (g)	Treatment Duration (wks)	End-Treatment Post-Stimulation Cortisol (μ g/dL)
6001	3-6	M	819.81	35	17	Unknown	4	32.3
5020	2-3	M	25.24	92	19	277.2	4	27.0
6003	4-2	F	309.63	60	14	Unknown	4	32.7
6004	3-8	F	115.15	60	12	156.2	4	33.9
6005	5-11	F	59.68	51	14	208.5	4	35.5
6006	4-6	F	42.82	83	14	328.4	4	32.6

6007	4-4	F	36.39	43	14	207.5	4	40.5
6008	4-10	F	67.30	70	14	258.4	3+	23.8
5011	2-2	F	70.13	60	16	245.8	4	28.8
6015	4-0	M	366.67	65	17	Unknown	5	31.7
6016	3-10	M	34.14	85	18	Unknown	4	25.1
6017	5-2	M	20.46	38	10	177.7	3+	27.3
6027	3-3	M	57.99	85	14	190.7	4	31.8

Source: Sponsor's NDA submission, Volume 14, p. 50.

¹Out of a maximum score of 24.

²Drug usage is considered unknown if all medication bottles were not returned.

Reviewer's Comment: *Three patients had serum fluticasone levels over 300 pg/mL, with one of these having a level of 819.81 pg/mL. The sponsor reported that their analysis indicated no relationship of fluticasone level to cosyntropin stimulation test results.*

The reader is also referred to the clinical pharmacology and biopharmaceutics review of Dr. Abimbola Adebawale for a review of this study.

Systemic Safety: Chemistry and Hematology Laboratory Evaluation

Laboratory Evaluation Phase 1

In study FPL10005, chemistry and hematology laboratory values were assessed at baseline and the end-of-treatment visits. Laboratory values were classified as shifting to low, normal, high or remaining unchanged between baseline and the end of treatment. Results are summarized in the Tables A.10 and A.11 in the Appendix.

Reviewer's Comment: *In patients in the 3 month - 3 year age group, AST levels were elevated in 14 (74%) of 19 patients at baseline and 19 (95%) of 20 patients at the end-of-treatment visit. However, with the exception of patient 5017 (described below), AST elevations occurring during the study were not high (10 U/L or less). It is unclear why such a high percentage of patients had an elevated AST both at the baseline and the end-of-treatment assessments. AST elevations were not generally associated with other hepatic panel laboratory abnormalities. A total of 4 (21%) of 19 patients in the 3 month - 3 year age group had an elevated ALT at baseline, and 2 (10%) of 20 patients had an elevated ALT at the end-of-treatment visit. Similarly, elevations were not observed for alkaline phosphatase or bilirubin (see Table A.11). Laboratory changes of AST were not considered drug related by investigators. AST laboratory values for patients in the 3 month - 3 year age group are summarized in Table 48.*

Table 48
Summary of AST (SGOT) Values at Baseline and End of Treatment
Study FPL10005: Patients Aged 3 Months to 3 Years

Subject #	Age (year-month)	AST (U/L) ¹	AST (U/L) ¹	Change
-----------	------------------	------------------------	------------------------	--------

		(Baseline)	(End-Treatment)	
5023	1-2	39	40	1
5003	1-8	36	39	3
5004	1-8	-	-	-
5005	1-7	-	-	-
5006	0-11	-	35	-
5007	0-7	-	48 ²	-
5008	1-0	88	59	-29
5019	0-9	35	43	8
5020	2-3	35	36	1
5021	1-3	40	38	-2
5022	2-7	43	44	1
5031	1-6	39	-	-
5032	1-10	40	42	2
5011	2-2	30	35	5
5012	1-3	56	-	-
5015	1-4	40	-	-
5017	0-4	113	366 ³	253
5018	2-5	41	42	1
5025	1-3	47	-	-
5026	0-5	32	42	10
5027	2-6	28	35	7
5028	0-11	-	54	-
5029	0-11	44	43	-1
5013	0-6	43	53	10
5009	0-5	-	40	-

Source: Sponsor's NDA submission, Volume 14, p. 325-430.

¹The normal range for AST was variably listed either as 11-36 U/L or 9-34 U/L.

²Follow-up laboratory AST value was 37 (9 days post-treatment).

³Follow-up laboratory AST values were 89 (7 days post-treatment); 407 (17 days post-treatment); and 37 (31 days post-treatment).

Three patients were coded by investigators as having clinically significant laboratory results. These were not considered related to treatment. One patient (5017) was a 4-month-old male. He had elevated liver enzymes at baseline (AST 113 U/L, normal range 11-36 U/L; ALT 110 U/L, normal range 6-43 U/L) that had increased at the end-of-treatment visit (AST 366 U/L, ALT 523 U/L). The end-of-treatment test result was coded as possibly drug related by the investigator. The values had decreased at 7 days post-treatment (AST 89 U/L, ALT 119 U/L) and then had increased again at a second follow-up visit, 17 days post-treatment (AST 407 U/L, ALT 584 U/L). The condition was considered "resolved" at a follow-up visit, 31 days post-treatment (AST 37 U/L, ALT 34 U/L). The elevated liver enzymes were reported as an adverse event and assessed as not drug related at this time. The sponsor did not provide an explanation for the likely cause of the patient's condition. Line listings for this patient indicate no concurrent medical conditions, and his concomitant medications were EMLA cream as a topical anesthetic, cosyntropin and Eucerin moisturizer.

The second patient was a 7-month-old female (5007) who had a decreased bicarbonate level of 14.4 mEq/L (normal range 17-30.6 mEq/L) at the end of treatment. This was assessed by the investigator to be the result of concurrent disease (unspecified). This laboratory measurement was normal (20.8 mEq/L) at a follow-up assessment nine days later.

The final patient coded by investigators as having a clinically significant laboratory result at baseline was a 1-year-old female (5005). This patient had a white blood count of $3.79 \times 10^3/\mu\text{L}$ (normal range $6-11 \times 10^3/\mu\text{L}$) at baseline that was considered by the investigator to be related to concurrent disease (unspecified). This laboratory measurement had returned to within the normal range ($8.16 \times 10^3/\mu\text{L}$) at the final visit.

The sponsor's medical monitor also rated 2 patients as having abnormal baseline laboratory test results. A 1-year-old female (5012) had an elevated AST (56 U/L) and ALT (74 U/L) at baseline. No end-of-treatment values were available because attempts to draw blood were reportedly unsuccessful at that time. The other patient, a 3-year-old male (6016), had a hemoglobin value of 8.9 g/dL at baseline (normal range 11-14.5 g/dL). This was related to Hemophilia A, diagnosed at birth. The end-of-treatment value was 9.3 g/dL.

The sponsor concluded: "There were no clinically significant laboratory abnormalities (chemistry/hematology) or changes in laboratory values suggesting specific safety concerns. In addition, laboratory data did not show any classical corticosteroid-induced systemic effects, such as lymphopenia, eosinopenia, neutrophilia, hyperglycemia, and electrolyte imbalances." (Sponsor's NDA submission, Volume 10, p. 160.)

Reviewer's Comment: At the Pre-NDA Meeting, April 19, 1999, the Agency recommended that laboratory values for electrolyte imbalance and glucose intolerance be evaluated in at least 30 patients in the lowest age group (i.e. 3 months – 3 years). However, laboratory evaluations were performed in fewer than 20 evaluable patients in the 3 month – 3 year age group. Therefore, additional laboratory data should be collected for patients in this age group. A hepatic panel laboratory test should also be included. As noted above, 1 patient showed a high elevation of liver enzymes during the study. This was initially considered by the investigator to be possibly drug related, although based on follow-up, it was ultimately assessed not to be drug related.

Laboratory Evaluation Phase 3

In the phase 3 studies FPL30003 and FPL30004, chemistry and hematology laboratory values were assessed at baseline and the end of treatment in patients who were ≥ 17 years of age. A total of 6 (7%) of 91 patients in the fluticasone group had shifted to a high serum glucose value at the end of the study. However, this was comparable to the vehicle group in which 10 (11%) of 91 patients shifted to a high serum glucose value. Shifts were also comparable for the liver enzymes, AST and ALT. For AST, a total of 1 (1%) of 92 patients in the fluticasone group shifted to a high value at the end of treatment, compared to 3 (3%) of 95 patients in the vehicle group. For ALT, 4 (4%) of 92 patients

shifted to a high value in the fluticasone group, compared to 2 (2%) of 95 patients in the vehicle group.

One patient had a laboratory value coded by investigators as clinically significant. A 43-year-old woman had a baseline CBC with differential, which showed an eosinophil percentage of 5.3% (normal range, 0 - 6.8%). At the end of treatment (Day 29) this had increased to 11.2%. The value had returned to within the normal range (3.6%) at a follow-up visit on Day 43. This was considered by the investigator as unlikely to be related to study drug.

Local Safety: Atrophy and Pigmentation Changes

In the phase 1 study, FPL10005, and phase 3 studies, atrophy and pigmentation changes were assessed at baseline and at subsequent visits.

Atrophy

In these three studies, the following signs were evaluated to determine the presence or absence of atrophic changes of the skin: telangiectasia, loss of elasticity, purpura, dusky erythema, and striae. Investigators used "2X magnification" to rate each sign using the following scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. The investigator was also asked to evaluate if the sign was indicative of cutaneous atrophy.

In study FPL10005, one patient exhibited mild facial telangiectasia at baseline and at subsequent study visits; however, this did not worsen in severity during the study and was not considered by the investigator to be indicative of atrophy.

In the phase 3 studies, 3 patients were noted to have signs of atrophy at baseline. Two of these patients received treatment with fluticasone propionate and one with vehicle. The patient treated with fluticasone propionate was noted to have telangiectasia at the site of pre-existing striae of the antecubital fossae on the Day 15 visit. However, the investigator did not consider it to be drug related; the sponsor states that this area was not treated with study medication, in accordance with the protocol (Sponsor's NDA submission, Volume 10, p. 207). No other patients developed signs of atrophy.

Reviewer's Comment: Cutaneous atrophy and telangiectasia are known adverse events associated with the use of topical corticosteroids. Clinical signs of atrophy were not observed in patients in these studies, except in patients in whom they were present at baseline. Treatment in these studies was from 2 – 4 weeks; the risk of atrophy and telangiectasia would be expected to increase with longer duration of treatment.

Pigmentary Changes

In study FPL10005, a total of 7 (16%) of 44 patients were observed to have abnormal pigmentation present in lesional skin at baseline. Pigmentation changes in lesional skin were recorded at each subsequent visit; the highest prevalence was at day 15 with changes observed in 4 (10%) of 39 patients. These changes were all considered by investigators to be post-inflammatory hypopigmentation. Three patients had post-

inflammatory hypopigmentation of lesional skin at their final visit; in 2 of these patients pigmentary change had not been present at baseline.

In phase 3 studies, 17 (4%) of 438 patients had post-baseline pigmentation changes that were not present at baseline. Of these, 10 (5%) of 221 were in a fluticasone group and 7 (3%) of 217 were in a vehicle group. The sponsor states: "All observed, post-baseline, pigmentation events were distributed similarly between the treatment groups and considered part of the normal healing process." (Sponsor's NDA submission, Volume 10, p. 207.)

Reviewer's Comment: Pigmentary change is a known adverse event associated with the use of topical corticosteroids. However, post-inflammatory hyper- or hypopigmentation may also occur secondary to inflammation from atopic dermatitis. It is possible that fluticasone propionate treatment played a role in the formation of pigmentation changes in certain patients. However, these changes were seen in both the fluticasone and vehicle groups during phase 3 studies, so investigators may have been correctly concluded in most cases this was the result of evolving disease. One limitation to this safety data is that a grading scale was not used to measure the severity of pigmentary changes in these studies.

Local Safety: Cutaneous Irritation and Sensitization

A repeat insult patch test study, FPL10003, was performed to investigate the irritation and contact sensitization potential of fluticasone propionate 0.05% lotion after multiple applications.

Study Design

A total of 231 healthy volunteer subjects, who were 18 years of age or older and met eligibility criteria, were enrolled into this single-center, double-blinded study. Subjects served as their own controls and the trial medications were fluticasone propionate lotion 0.05% and vehicle lotion.

The study was divided into a 3-week induction phase, a 2-week rest period, and a one-application challenge phase. During the induction phase, 0.2 ml each of study drug and vehicle were applied under a 2 x 2 cm semi-occlusive patch to the upper left or right quadrant of the back. The areas were identified with a surgical marker so that subsequent patches could be placed at the same sites. Eleven patch applications were performed during the induction phase – on days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22 and 24. Patches were applied on day 27 if any of the prior scheduled applications were missed. At each visit the patch test site was examined for irritation using the following scale:

- 0 = None (no reaction)
- 1 = Mild erythema without edema
- 2 = Erythema with mild edema
- 3 = Erythema with infiltration, raised spreading reaction beyond the borders of the patch site, with or without vesiculation

4 = Erythema with large vesiculo-bullous reaction
Letter codes were used for additional notations.

The induction phase was followed by a 13 – 16 day rest period, and then the challenge phase of the study was performed. Patches were reapplied to the original sites and two adjacent naive sites. Subjects were then evaluated at 48 and 96 hours. The same grading scale and notations used during the induction phase were used for this evaluation. Sensitization was defined in the study as "a reaction score of 2 or greater as documented in the sensitization reaction scale in at least one of the two challenge readings and confirmed by rechallenge." (Sponsor's NDA submission, Volume 13, p. 30.) If necessary, a rechallenge phase was scheduled after a second rest phase to retest patients who had an ambiguous response during the challenge phase.

Results

A total of 204 (88%) of 231 subjects completed the study, receiving 12 patch applications as specified in the protocol. The reasons for premature discontinuation of 27 subjects were stated as: withdrawal of consent (20 subjects), adverse events (5 subjects), and protocol violation (2 subjects).

A total of 131 (57%) of 231 subjects were observed to have a response graded as 1 at some time during the test (excluding patients who had a tape reaction alone). No subjects had a response graded greater than 1. The sponsor conducted an analysis of cumulative irritancy potential. Cumulative irritancy index was defined as the mean of irritation scores received during the induction phase. The cumulative irritancy index (\pm SD) was reported to be 0.09 ± 0.16 for the fluticasone group and 0.20 ± 0.25 for the vehicle group.

Of 204 subjects evaluated for sensitization in the challenge phase of the study, 8 subjects had a grade 1 reaction at either the original or naive sites. Six subjects had a response at the 48 hour reading only, and 2 subjects had a response at both the 48 and 96 hour reading. One of these subjects had an additional reading at 120 hours, with no residual response observed. Because sensitization was defined in this study as a reaction score of 2 or greater in at least one of the challenge readings with confirmation by rechallenge, no subjects were considered by the sponsor to have shown evidence of sensitization.

Reviewer's Comment: *Irritancy reactions secondary to fluticasone propionate lotion 0.05% or vehicle were mild, with no subjects observed to have a grade 2 or higher reaction. Nevertheless, they occurred commonly, with a majority of subjects (57%) experiencing a grade 1 reaction of mild erythema without edema (excluding subjects who had a tape reaction alone) at some point during the study. Semi-occlusive patch conditions may have contributed to the high frequency of this response. The sponsor's cumulative irritancy index was lower in the fluticasone propionate 0.05% lotion group compared to the vehicle group, perhaps suggesting the corticosteroid may have suppressed the irritant response to the vehicle to some extent.*

Although no subjects experienced sensitization using the criteria defined by the sponsor, 8 (4%) of 204 subjects did show a grade 1 reaction during the challenge phase. The

lotion contains imidurea, methylparaben and propylparaben as preservatives, which are known sensitizers. It also contains cetylstearyl alcohol, isopropyl myristate and propylene glycol, which may act as sensitizers. Fluticasone propionate may also act as a sensitizer, but has been described as having a low sensitization potential. It is, therefore, likely that allergic contact dermatitis would be observed with fluticasone propionate 0.05% lotion in larger postmarketing studies.

Although the Agency at the End-of-Phase 2 Meeting had raised the possibility of skin stripping of the stratum corneum as a means of evaluating allergenicity in patients with compromised epidermal integrity, this was not performed.

Photoallergy and phototoxicity testing may apparently be waived because the sponsor provided data indicating that fluticasone propionate lotion 0.05% does not absorb light in the 290 – 700 nm range. See the pharmacology /toxicology review by Dr. Barbara Hill for discussion on the need for photocarcinogenicity studies.

Office of Drug Safety Consultation

Cutivate (fluticasone propionate) Cream, 0.05% and Cutivate (fluticasone propionate) Ointment, 0.005% are currently approved dermatologic products. A review of postmarketing adverse events for these products was requested from the Office of Drug Safety, including adverse events related to adrenal suppression, Cushing syndrome, eczema herpeticum, herpes simplex, influenza, and other notable adverse events.

A total of 35 cases of adverse events in the AERS database were reviewed by the Office of Drug Safety reviewer, Dr. Renan A. Bonnel, with concurrence from the Division Director, Dr. Mark Avigan. This report states: "Sixteen cases were excluded for various reasons and the remaining 19 cases are summarized in this safety review." In nine of the reviewed cases, the reported events were localized reactions, which included: severe pruritus, periorbital edema, aggravation of skin rash, burning, and skin pigmentation. Six reports were of systemic reactions, including: immunosuppression/Pneumocystis carinii pneumonia (PCP)/leucopenia/thrombocytopenia; hyperglycemia/glycosuria; Cushing syndrome; generalized body edema/blurred vision; acute urticarial reaction (edema, urticaria, pruritus, and throat swelling); and agitation/fatigue. The other four reports were of lack of efficacy. No cases of eczema herpeticum, herpes simplex, or influenza were identified. There were no reported fatalities.

The report stated: "In general most events were labeled, and unlabeled events were few in number. The exact causal role of Cutivate in most cases could not be determined due to the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information."

Four-Month Safety Update

The sponsor's 4-month safety update did not have any new data for fluticasone propionate lotion.

Postmarketing adverse events were reported for Cutivate Ointment and Cutivate Cream; these were listed without narratives. The presence or absence of a causal relationship to the drug was not categorized for these adverse events. Postmarketing adverse events for Cutivate Cream and Cutivate Ointment in the AERS database were reviewed by the Office of Drug Safety. (See Office of Drug Safety Consultation above).

D. Adequacy of Safety Testing

Safety testing was inadequate in phase 3 studies. The two combined phase 3 studies included a total of 221 patients who received fluticasone propionate lotion. However, many patients had mild or minimal disease. Specifically, only 89 (40%) of these patients met the minimum baseline inclusion criteria for disease severity that the Agency developed for a post-hoc analysis of the studies (see discussion in the efficacy section of this review). Therefore, the overall safety results cannot be generalized with confidence to patients with moderate to severe disease. Patients with more severe disease would be expected to apply more lotion, have increased drug absorption, and be more susceptible to certain adverse events.

Phase 3 studies included laboratory evaluations for patients under age 17. As the Division noted at the Pre-NDA Meeting, adult safety data cannot be extrapolated downward to infancy. Subsequently, study FPL10005 did include laboratory evaluation in children 3 months - 6 years of age. At the Pre-NDA Meeting, the Division had recommended that data on glucose intolerance and electrolyte imbalance be assessed in at least 30 patients in the lowest age group (3 months - 3 years). However, the study included fewer than 20 evaluable subjects in this age group. Additional laboratory testing should be performed in patients in this age group. This should include a hepatic panel because one 4-month-old patient in that study had a very high elevation of hepatic enzymes, although this was ultimately not considered to be drug related by the investigator.

The HPA axis suppression study (FPL10005) included a safety population of 44 patients. A total of 42 patients completed the study: 24 patients aged 3 months to 3 years, and 18 patients aged 3 years to 6 years of age. The study assessed treatment for a minimum of 3 weeks to at least 35% of body surface area (regardless of healing status). The sponsor indicates that the mean number of days that patients were treated was 27.6 (\pm 3.6 days), and that the mean percent body surface area to be treated at baseline was 65%.

Plasma fluticasone levels were evaluated in 21 patients. This was not measured in patients less than 2 years of age, so no information was obtained for this age group.

Testing for irritation and contact sensitization in study FPL10003 included 231 subjects and appears to have been adequate.

E. Summary of Critical Safety Findings and Limitations of Data

As discussed in this review, safety testing was inadequate for this drug product. A serious limitation of the safety data relates to the high percentage of patients in phase 3 studies with mild or minimal disease. Patients with more severe disease would be expected to apply more drug, have increased drug absorption, and be more susceptible to certain adverse events such as infection and systemic adverse events. The total number of patients with moderate to severe atopic dermatitis who were exposed to the active drug under labeled conditions was insufficient for drug approval.

In the HPA axis suppression study, no patients met the current Division criterion for HPA axis suppression. The sponsor's consultant pediatric endocrinologist and the reviewers from the Agency's Division of Metabolic and Endocrine Drug Products agreed that 2 patients may have sustained partial suppression of the HPA axis following exposure to fluticasone propionate lotion 0.05%; however this was considered unlikely to be of clinical significance. Recommendations made by the reviewers from the Agency's Division of Metabolic and Endocrine Drug Products, include cosyntropin stimulation testing before and after exposure to fluticasone propionate lotion 0.05% for ≥ 21 - 28 days. Other recommendations are listed above (see Division of Metabolic and Endocrine Drug Products Consultation).

Plasma fluticasone levels were measured in patients ≥ 2 years of age in the sponsor's HPA axis suppression study. A total of 13 (62%) of 21 patients had measurable fluticasone at the end of treatment. Three patients had fluticasone levels over 300 pg/mL, with one of these having a level of 819.81 pg/mL. No data was obtained for patients < 2 years of age.

In patients in the 3 month - 3 year age group in the HPA axis suppression study, AST levels were elevated in 14 (74%) of 19 patients at baseline and 19 (95%) of 20 patients at the end-treatment visit. It is unclear why such a high percentage of patients had an elevated AST both at the baseline and the end-treatment assessments. One 4-month-old patient had marked elevations of AST and ALT during the study. This was initially coded as possibly drug related but based on follow-up was eventually assessed as not drug related. The AST elevations occurring during the study were not high in other patients.

The number of patients in the 3 month - 3 year age group who received clinical laboratory evaluation was inadequate. Although the Agency had requested that clinical laboratory evaluation be performed in at least 30 patients in the lowest age group (3 months - 3 years), the study included fewer than 20 evaluable subjects in this age group.

A serious adverse event that occurred in phase 3 studies was an episode of eczema herpeticum in a 33-year-old male receiving fluticasone propionate lotion. It is uncertain whether fluticasone played a causal role in the development of this adverse event; the investigator did not consider it drug related.

There was not an appreciable difference in adverse events between the fluticasone propionate and vehicle groups for most adverse events reported in phase 3 studies.

Among those adverse events in which there was a notable difference in frequency between the treatment groups was influenza; five cases of influenza were reported in patients receiving fluticasone propionate and no cases were reported in the vehicle group. All reported influenza cases occurred in patients in the 17 - 65 year age range.

Burning and stinging was the most commonly reported drug-related adverse event. Because there was no appreciable difference in burning and stinging, or pruritus between the vehicle and fluticasone groups, it appears that the vehicle ingredients may be responsible. The vehicle formulation contains 10% propylene glycol, which is a known potential irritant.

Clinical signs of atrophy were not observed in patients using fluticasone propionate lotion, except in patients in whom they were present at baseline. Treatment was from 2 - 4 weeks; the risk of atrophy and telangiectasia would be expected to increase with a longer duration of treatment. Pigmentation changes were observed in some patients using fluticasone propionate lotion. Although this may have resulted from evolving atopic dermatitis, it is possible that fluticasone treatment played a role in the formation of pigmentary changes in certain patients.

In the repeat insult patch test, the majority of subjects (57%) exhibited a grade 1 reaction at some time during the study. Semi-occlusive patch conditions may have contributed to this high rate of irritancy. A total of 8 (4%) of 204 subjects exhibited a grade 1 reaction during the challenge phase. In addition to propylene glycol, the lotion contains imidurea, methylparaben and propylparaben as preservatives, which are known contact sensitizers. Fluticasone propionate may also act as a sensitizer, but has previously been described as having a low sensitization potential.

A consultation was made to the Office of Drug Safety to review postmarketing adverse events for other fluticasone-containing dermatologic products. Nineteen cases of adverse events for Cutivate Cream 0.05% and Cutivate Ointment 0.005% were summarized in their review. Reported systemic adverse events included: immunosuppression/Pneumocystis carinii pneumonia/leucopenia/thrombocytopenia; hyperglycemia/glycosuria; Cushing syndrome; generalized body edema/blurred vision; and acute urticarial reaction (edema, urticaria, pruritus, and throat swelling). The causal role of fluticasone propionate could not be determined in most cases because of the concomitant use of topical corticosteroids, confounding medical conditions, and insufficient clinical information.

In a letter to the Agency of August 11, 1998, the sponsor argued that women of childbearing potential needed to use an acceptable form of contraception to participate in clinical trials for fluticasone propionate lotion 0.05%. Therefore, were this drug product approved (and contraception had been similarly required in additional phase 3 studies), this should be reflected in labeling. In addition, postmarketing information regarding the outcome of pregnancies in women who used this product during pregnancy should be obtained.

VIII. Dosing, Regimen, and Administrative Issues

No dose-ranging studies were performed for fluticasone propionate lotion with respect to drug concentration, dosing, or treatment duration. A fluticasone propionate concentration of 0.05% only was studied. Once daily dosing only was studied in phase 3 trials, although patients used twice daily dosing in the HPA axis suppression study. Patients were scheduled for 2 – 4 weeks of treatment in phase 3 trials, and 3 – 4 weeks of treatment in the open-label HPA axis suppression study. The proposed indication is for once daily dosing for up to 4 weeks.

Reviewer's Comment: *As discussed, reviewers for the Agency's Division of Metabolic and Endocrine Drug Products recommended that a cosyntropin stimulation test be performed before and after exposure to fluticasone propionate lotion 0.05% for ≥ 21 -28 days. Their recommendations in the event of abnormal results for this test are also summarized above.*

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor submitted an analysis of treatment success in phase 3 studies by gender subgroups of the intent-to-treat populations. The sponsor states: "Success rates for males and females were similar to each other and to the ITT populations in both studies and demonstrated the superior efficacy of fluticasone lotion over vehicle." (Sponsor's NDA submission, Volume 10, p. 87). However, the sponsor's analysis included many patients with minimal or mild disease (per the Agency's analysis). Also, the sponsor's analysis uses a primary endpoint with a dynamic scale – "at least 50% of lesions cleared and improvement or no change from baseline in $\geq 75\%$ of severity scores of remaining lesions." (Sponsor's NDA submission, Volume 10, p. 87.)

Tables 49 and 50 show success rates by gender in the phase 3 studies using the Agency's post-hoc analysis (see efficacy section for a description of this analysis) for the intent-to-treat and per-protocol populations respectively:

Table 49
Summary of Treatment Success by Gender: Agency's Analysis
Studies FPL30003 and FPL30004 (Intent-to-Treat Population)

Gender	Study FPL30003		Study FPL30004	
	Vehicle	Fluticasone Propionate Lotion 0.05%	Vehicle	Fluticasone Propionate Lotion 0.05%
Male	0/12	2/20	0/24	2/18
Female	0/25	7/25	1/19	5/26

Source: Agency Biostatistical Analysis.

Table 50
Summary of Treatment Success by Gender: Agency's Analysis
Studies FPL30003 and FPL30004 (Per-Protocol Population¹)

Gender	Study FPL30003		Study FPL30004	
	Vehicle	Fluticasone Propionate Lotion 0.05%	Vehicle	Fluticasone Propionate Lotion 0.05%
Male	0/7	2/14	0/12	2/14
Female	0/14	4/16	1/9	4/21

Source: Agency Biostatistical Analysis.

¹Agency's per-protocol population used, which excluded from the sponsor's per-protocol population those patients whose final visit was prior to Day 21 (unless they were completely clear of disease at the Day 15 visit) or after Day 32.

Reviewer's Comment: *The number of patients meeting the Agency's minimum baseline criteria for moderate to severe atopic dermatitis is insufficient to adequately evaluate gender effects. As illustrated in the tables above, the size of the population decreases even further when patients with major protocol violations are excluded.*

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Demographic characteristics of patients in phase 3 studies are listed in Tables 15 and 26. Tables 51 and 52 show success rates by race and age in the phase 3 studies using the Agency's post-hoc analysis (see efficacy section for a description of this analysis) for the intent-to-treat and per-protocol populations:

Table 51
Summary of Treatment Success by Race and Age: Agency's Analysis
Studies FPL30003 and FPL30004 (Intent-to-Treat Population)

	Study FPL30003		Study FPL30004	
	Vehicle	Fluticasone Propionate Lotion 0.05%	Vehicle	Fluticasone Propionate Lotion 0.05%
<u>Race</u>				
White	0/28	7/32	1/34	5/31
Black	0/6	1/7	0/5	1/4
Other ¹	0/3	1/6	0/4	1/9
<u>Age</u>				
≥ 3 mos and < 3 yrs	0/14	2/15	0/10	1/14
≥ 3 yrs and < 6 yrs	0/4	4/8	1/10	1/8
≥ 6 yrs and < 17 yrs	0/2	1/3	0/4	1/3
≥ 17 yrs and ≤ 65 yrs	0/15	2/19	0/15	4/16

> 65 yrs	0/2	0/0	0/4	0/3
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Source: Agency Biostatistical Analysis.

¹Combines groups classified by the sponsor as Hispanic, Asian, and Other.

Table 52
Summary of Treatment Success (Agency's Analysis) by Race and Age Studies
FPL30003 and FPL30004 (Per-Protocol Population¹)

	Study FPL30003		Study FPL30004	
	Vehicle	Fluticasone Propionate Lotion 0.05%	Vehicle	Fluticasone Propionate Lotion 0.05%
Race				
White	0/13	5/19	1/16	4/24
Black	0/5	0/5	0/4	1/3
Other ²	0/3	1/6	0/1	1/8
Age				
≥ 3 mos and < 3 yrs	0/6	2/10	0/4	1/11
≥ 3 yrs and < 6 yrs	0/2	3/6	1/5	1/7
≥ 6 yrs and < 17 yrs	0/2	0/1	0/3	0/1
≥ 17 yrs and ≤ 65 yrs	0/11	1/13	0/6	4/13
> 65 yrs	--	--	0/3	0/3

Source: Agency Biostatistical Analysis.

¹Agency's per-protocol population used, which excluded from the sponsor's per-protocol population those patients whose final visit was prior to Day 21 (unless they were completely clear of disease at the Day 15 visit) or after Day 32.

²Combines groups classified by the sponsor as Hispanic, Asian, and Other.

Demographic characteristics of patients in phase 1 studies are listed in Table 33.

Reviewer's Comment: *The number of patients meeting the Agency's minimum baseline criteria for moderate to severe atopic dermatitis is insufficient to adequately evaluate race and age effects. The size of the population decreases further if patients with major protocol violations are excluded.*

C. Evaluation of Pediatric Program

A total of 242 (55%) of 438 patients in phase 3 studies were pediatric patients. However, only 95 pediatric patients in these studies met the Agency's minimum baseline criteria (51 in the fluticasone group and 44 in the vehicle group). The size of the population decreases further if patients with major protocol violations are excluded.

All 44 patients enrolled in open-label study FPL10005 were ≤ 6 years old at the time of the screening visit.

Reviewer's Comment: *Evaluation of the safety and efficacy of fluticasone propionate in the pediatric population cannot be adequately performed based on phase 3 studies because many patients enrolled had minimal or mild disease in those studies.*

D. Comments on Data Available or Needed in Other Populations

Additional study of the safety and efficacy of fluticasone propionate lotion 0.05% needs to be performed in both adult and pediatric patients with moderate to severe atopic dermatitis. In addition, analyses of gender, age, and race/ethnicity effects should be based on a larger patient population.

X. Conclusions and Recommendations

A. Conclusions

NDA 21-152 is Not Approvable from a clinical standpoint. The efficacy of fluticasone propionate lotion 0.05% to treat [REDACTED] atopic dermatitis when used once daily for up to 4 weeks has not been adequately demonstrated in the sponsor's pivotal trials, which were seriously flawed. Similarly, the drug has not been sufficiently studied in patients with [REDACTED] atopic dermatitis to accurately determine the drug's safety profile.

B. Recommendations

It is recommended that a Not Approvable action be taken for this NDA.

For approval of fluticasone lotion 0.05%, it is recommended the sponsor conduct pivotal clinical trials which follow recommendations previously made by the Agency and discussed at length in this review. Importantly, this includes enrolling patients with moderate to severe atopic dermatitis based on signs of acute disease. Safety data should be obtained on a significantly larger number of patients with moderate to severe atopic dermatitis who are exposed to the active drug under labeled conditions (300 patients was recommended at the Pre-NDA Meeting). It is also recommended that the primary efficacy variable be an Investigator's Global Evaluation at the end of treatment. The Investigator's Global Evaluation should be a static, dichotomized scale. In addition, it is important that the number of protocol violations be minimized as far as is possible. Additional laboratory evaluations should be performed for patients in the youngest age group (3 months - 3 years of age). The sponsor should submit protocols for Agency review, preferably as a Special Protocol Assessment request, prior to initiation of the studies.

XI. Appendix

Table A.1
Sponsor's Modified Eczema Area and Severity Index (EASI)
Part A: Parameters

<p>1. Erythema 0 = no evidence of redness compared to surrounding skin 1 = patchy pink coloration, barely noticeable 2 = easily noticeable redness 3 = bright intense redness</p>
<p>2. Infiltration/Papulation 0 = lesions smooth and impalpable, not discernable to touch 1 = few isolated areas palpable to touch 2 = most lesions papulated or swollen above surrounding skin 3 = extensive swelling and marked thickening</p>
<p>3. Pruritus (Assessed by interview of the subject/parent) 0 = no itching 1 = occasional itch, not interfering with daily activity 2 = fairly persistent itch, partially tolerated; sometimes interferes with daily activities and disturbs sleep 3 = intolerable, constant itch, interferes often with daily activities and disturbs sleep</p>
<p>4. Lichenification 0 = smooth skin particularly in flexural areas 1 = minimal lines and epidermal thickening 2 = thickened areas with deeper lines that involve greater than 50% of flexural areas 3 = extensive skin markings and thickening extending beyond the flexural unit</p>
<p>5. Body Area Score for each region 0 = 0% area affected 1 = 1-9% area affected 2 = 10-29% area affected 3 = 30-49% area affected 4 = 50-69% area affected 5 = 70-89% area affected 6 = 90-100% area affected</p>

Source: Sponsor's NDA submission, Volume 18, p. 32.

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Table A.2
Sponsor's Modified Eczema Area and Severity Index (EASI)
Part B: Method of Calculating of Score

Regional Assessment for two populations: ≥ 7 years old and < 7 years old	Head/Neck	Trunk	Upper Limbs	Lower Limbs
	≥ 7 (10% BSA)	≥ 7 (30% BSA)	≥ 7 (20% BSA)	≥ 7 (40% BSA)
	< 7 (20% BSA)	< 7 (30% BSA)	< 7 (20% BSA)	< 7 (30% BSA)
1. Sum of Scores (Erythema + Infiltration/Papulation + Pruritus + Lichenification) multiplied by Body Surface Area score for each region (see Table A.1)				
2. Regional Multiplication Factor for subjects 7 years or older OR	x 0.1	x 0.3	x 0.2	x 0.4
3. Regional Multiplication Factor for subjects under 7 years of age	x 0.2	x 0.3	x 0.2	x 0.3
4. Total of each region (row 1 x row 2) OR (row 1 x row 3)				
5. EASI Score	Head Total +	Trunk Total +	Upper Limbs Total +	Lower Limbs Total

Source: Sponsor's NDA submission, Volume 18, p. 33.

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Table A.3
Rajka/Langland Score (Baseline)
Study FPL30003 (Intent-to-Treat Population)

Parameter	Vehicle Lotion N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110 (%)	Total N=220 (%)
Mean Rajka/Langland Score	6.8	6.8	6.8
Extent of Disease			
Age < 1 year	6 (5)	12 (11)	18 (8)
Less than 18% of body area involved	3	6	9
Greater than 18% and less than 54% of body area involved	3	5	8
Greater than 54% of body area involved	0	1	1
Age > 1 year	104 (95)	98 (89)	202 (92)
Less than 9% of body area involved	34	34	68
Greater than 9% and less than 36% of body area involved	46	48	94
Greater than 36% of body area involved	24	16	40
Course			
More than 3 months of remission during a year	4 (4)	4 (4)	8 (4)
Less than 3 months of remission during a year	13 (12)	11 (10)	24 (11)
Continuous course	93 (85)	95 (86)	188 (85)
Intensity			
Mild itch, only exceptionally disturbing sleep	16 (15)	17 (15)	33 (15)
Itch is more than score 1; less than score 3	63 (57)	54 (49)	117 (53)
Severe itch, usually disturbing night's sleep	31 (28)	39 (35)	70 (32)

Source: Sponsor's NDA submission, Volume 16, p. 85-6.

Table A.4
Summary of Investigator Assessment of Signs and Symptoms at Baseline
Study FPL30003

Parameter	Vehicle Lotion N=110 (%)				Fluticasone Propionate Lotion 0.05% N=110 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erythema								
0	48 (44)	50 (45)	20 (18)	31 (28)	48 (44)	39 (35)	14 (13)	35 (32)
1	37 (34)	34 (31)	40 (36)	36 (33)	32 (29)	37 (34)	39 (35)	30 (27)
2	19 (17)	22 (20)	38 (35)	35 (32)	27 (25)	31 (28)	52 (47)	39 (35)
3	6 (5)	4 (4)	12 (11)	8 (7)	3 (3)	3 (3)	5 (5)	6 (5)
Infiltration/Papulation								
0	55 (50)	52 (47)	24 (22)	33 (30)	59 (54)	46 (42)	15 (14)	36 (33)
1	40 (36)	40 (36)	40 (36)	39 (35)	34 (31)	43 (39)	48 (44)	34 (31)
2	14 (13)	16 (15)	37 (34)	31 (28)	17 (15)	19 (17)	45 (41)	36 (33)
3	1 (<1)	2 (2)	9 (8)	7 (6)	0	2 (2)	2 (2)	4 (4)
Pruritus								
0	45 (41)	46 (42)	16 (15)	28 (25)	47 (43)	37 (34)	13 (12)	36 (33)
1	29 (26)	30 (27)	37 (34)	27 (25)	27 (25)	26 (24)	35 (32)	23 (21)
2	26 (24)	27 (25)	39 (35)	34 (31)	26 (24)	34 (31)	38 (35)	27 (25)
3	10 (9)	7 (6)	18 (16)	21 (19)	10 (9)	13 (12)	24 (22)	24 (22)
Scaling								
0	57 (52)	57 (52)	33 (30)	41 (37)	56 (51)	45 (41)	22 (20)	36 (33)
1	31 (28)	32 (29)	33 (30)	27 (25)	41 (37)	47 (43)	45 (41)	36 (33)
2	17 (15)	15 (14)	35 (32)	31 (28)	10 (9)	14 (13)	32 (29)	30 (27)
3	5 (5)	6 (5)	9 (8)	11 (10)	3 (3)	4 (4)	11 (10)	8 (7)

(Table Continued on Next Page)

Table A.4 (Continued)
Summary of Investigator Assessment of Signs and Symptoms at Baseline
Study FPL30003

Parameter	Vehicle Lotion N=110 (%)				Fluticasone Propionate Lotion 0.05% N=110 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erosion, Oozing, Crusting								
0	89 (81)	92 (84)	53 (48)	61 (55)	83 (75)	87 (79)	58 (53)	67 (61)
1	15 (14)	13 (12)	28 (25)	27 (25)	18 (16)	20 (18)	32 (29)	23 (21)
2	6 (5)	5 (5)	25 (23)	14 (13)	9 (8)	2 (2)	17 (15)	17 (15)
3	0	0	4 (4)	8 (7)	0	1 (<1)	3 (3)	3 (3)
Lichenification								
0	63 (57)	63 (57)	30 (27)	40 (36)	65 (39)	56 (51)	21 (19)	41 (37)
1	36 (33)	39 (35)	38 (35)	39 (35)	36 (33)	44 (40)	51 (46)	41 (37)
2	10 (9)	7 (6)	35 (32)	24 (22)	7 (6)	8 (7)	32 (29)	24 (22)
3	1 (<1)	1 (<1)	7 (6)	7 (6)	2 (2)	2 (2)	6 (5)	4 (4)
Body Area Score								
0	41 (37)	43 (39)	14 (13)	27 (25)	41 (37)	33 (30)	8 (7)	32 (29)
1	36 (33)	20 (18)	32 (29)	24 (22)	32 (29)	32 (29)	39 (35)	23 (21)
2	21 (19)	24 (22)	32 (29)	26 (24)	19 (17)	20 (18)	35 (32)	30 (27)
3	3 (3)	6 (5)	10 (9)	7 (6)	11 (10)	11 (10)	11 (10)	6 (5)
4	3 (3)	8 (7)	8 (7)	10 (9)	4 (4)	9 (8)	8 (7)	8 (7)
5	5 (5)	6 (5)	9 (8)	11 (10)	1 (<1)	4 (4)	6 (5)	9 (8)
6	1 (<1)	3 (3)	5 (5)	5 (5)	2 (2)	1 (<1)	3 (3)	2 (2)

Source: Sponsor's NDA submission, Volume 16, p. 90-1.

Table A.5
Summary of Investigator Assessment of Signs and Symptoms at End of Treatment
Study FPL30003

Parameter	Vehicle Lotion N=107 (%)				Fluticasone Propionate Lotion 0.05% N=107 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erythema								
0	64 (60)	63 (59)	31 (29)	36 (34)	85 (79)	81 (76)	63 (59)	65 (61)
1	24 (22)	26 (24)	39 (36)	41 (38)	15 (14)	20 (19)	33 (31)	32 (30)
2	16 (15)	16 (15)	28 (26)	24 (22)	7 (7)	6 (6)	11 (10)	10 (9)
3	3 (3)	2 (2)	9 (8)	6 (6)	0	0	0	0
Infiltration/Papulation								
0	65 (61)	65 (61)	32 (30)	43 (40)	92 (86)	85 (79)	67 (63)	73 (68)
1	32 (30)	29 (27)	40 (37)	36 (34)	12 (11)	17 (16)	32 (30)	26 (24)
2	10 (9)	12 (11)	28 (26)	24 (22)	3 (3)	4 (4)	6 (6)	7 (7)
3	0	1 (<1)	7 (7)	4 (4)	0	1 (<1)	2 (2)	1 (<1)
Pruritus								
0	62 (58)	62 (58)	37 (35)	45 (42)	86 (80)	90 (84)	74 (69)	83 (78)
1	21 (20)	17 (16)	27 (25)	23 (21)	17 (16)	11 (10)	21 (20)	14 (13)
2	13 (12)	16 (15)	25 (23)	23 (21)	3 (3)	5 (5)	10 (9)	6 (6)
3	11 (10)	12 (11)	18 (17)	16 (15)	1 (<1)	1 (<1)	2 (2)	4 (4)
Scaling								
0	66 (62)	67 (63)	37 (35)	45 (42)	95 (89)	89 (83)	74 (69)	75 (70)
1	29 (27)	32 (30)	40 (37)	38 (36)	10 (9)	16 (15)	27 (25)	28 (26)
2	10 (9)	4 (4)	25 (23)	17 (16)	2 (2)	2 (2)	5 (5)	3 (3)
3	2 (2)	4 (4)	5 (5)	7 (7)	0	0	1 (<1)	1 (<1)

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Table A.5 (Continued)
Summary of Investigator Assessment of Signs and Symptoms at End of Treatment
Study FPL30003

Parameter	Vehicle Lotion N=107 (%)				Fluticasone Propionate Lotion 0.05% N=107 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erosion, Oozing, Crusting								
0	95 (89)	93 (87)	64 (60)	73 (68)	101 (94)	103 (96)	93 (87)	95 (89)
1	11 (10)	9 (8)	22 (21)	16 (15)	3 (3)	3 (3)	9 (8)	8 (7)
2	1 (<1)	5 (5)	14 (13)	14 (13)	3 (3)	1 (<1)	3 (3)	2 (2)
3	0	0	7 (7)	4 (4)	0	0	2 (2)	2 (2)
Lichenification								
0	71 (66)	72 (67)	34 (32)	47 (44)	87 (81)	86 (80)	66 (62)	75 (70)
1	29 (27)	28 (26)	42 (39)	39 (36)	18 (17)	17 (16)	29 (27)	22 (21)
2	7 (7)	7 (7)	24 (22)	18 (17)	2 (2)	4 (4)	11 (10)	7 (7)
3	0	0	7 (7)	3 (3)	0	0	1 (<1)	3 (3)
Body Area Score								
0	52 (49)	54 (50)	23 (21)	35 (33)	79 (74)	75 (70)	54 (50)	59 (55)
1	33 (31)	23 (21)	35 (33)	28 (26)	19 (18)	19 (18)	38 (36)	30 (28)
2	14 (13)	12 (11)	26 (24)	23 (21)	4 (4)	4 (4)	8 (7)	9 (8)
3	2 (2)	10 (9)	9 (8)	6 (6)	1 (<1)	5 (5)	3 (3)	5 (5)
4	2 (2)	2 (2)	6 (6)	5 (5)	2 (2)	3 (3)	0	1 (<1)
5	3 (3)	4 (4)	4 (4)	6 (6)	2 (2)	1 (<1)	4 (4)	3 (3)
6	1 (<1)	2 (2)	4 (4)	4 (4)	0	0	0	0

Source: Sponsor's NDA submission, Volume 16, p. 102-3.

Table A.6
Summary of Patient's/Parent's Assessment of Response to Treatment, End of Treatment (Intent-to-Treat Population)

Assessment	FPL30003			FPL30004		
	Vehicle N=110 (%)	Fluticasone Propionate Lotion 0.05% N=110 (%)	p-value ¹	Vehicle N=107 (%)	Fluticasone Propionate Lotion 0.05% N=111 (%)	p- value ¹
Excellent	17 (15%)	56 (51%)		8 (7%)	53 (48%)	
Good	21 (19%)	27 (25%)		20 (19%)	19 (17%)	
Fair	22 (20%)	16 (15%)		26 (24%)	20 (18%)	
Poor	47 (43%)	8 (7%)		50 (47%)	16 (14%)	
			< 0.001			< 0.001

Source: Sponsor's NDA submission, Volume 10, p. 84.

¹Cochran-Mantel-Haenszel Chi-Square Test on total distribution.

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Table A.7
Rajka/Langland Score (Baseline)
Study FPL30004 (Intent-to-Treat Population)

Parameter	Vehicle Lotion N=107 (%)	Fluticasone Propionate Lotion 0.05% N=111 (%)	Total N=218 (%)
Mean Rajka/Langland Score	6.5	6.5	6.5
Extent of Disease			
<u>Age < 1 year</u>	5 (5)	5 (5)	10 (5)
Less than 18% of body area involved	1	1	2
Greater than 18% and less than 54% of body area involved	2	2	4
Greater than 54% of body area involved	2	2	4
<u>Age > 1 year</u>	102 (95)	106 (95)	208 (95)
Less than 9% of body area involved	41	43	84
Greater than 9% and less than 36% of body area involved	45	46	91
Greater than 36% of body area involved	16	17	33
Course			
More than 3 months of remission during a year	5 (5)	5 (5)	10 (5)
Less than 3 months of remission during a year	16 (15)	17 (15)	33 (15)
Continuous course	86 (80)	89 (80)	175 (80)
Intensity			
Mild itch, only exceptionally disturbing sleep	32 (30)	37 (33)	69 (32)
Itch is more than score 1; less than score 3	47 (44)	46 (41)	93 (43)
Severe itch, usually disturbing night's sleep	28 (26)	28 (25)	56 (26)

Source: Sponsor's NDA submission, Volume 20, p. 83-4.

Table A.8
Summary of Investigator Assessment of Signs and Symptoms at Baseline
Study FPL30004

Parameter	Vehicle Lotion N=107 (%)				Fluticasone Propionate Lotion 0.05% N=111 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erythema								
0	53 (50)	43 (40)	15 (14)	18 (17)	49 (44)	36 (32)	18 (16)	18 (16)
1	30 (28)	37 (35)	45 (42)	30 (28)	38 (34)	51 (46)	44 (40)	42 (38)
2	17 (16)	26 (24)	44 (41)	49 (46)	21 (19)	20 (18)	42 (38)	42 (38)
3	7 (7)	1 (<1)	3 (3)	10 (9)	3 (3)	4 (4)	7 (6)	9 (8)
Infiltration/Papulation								
0	60 (56)	43 (40)	21 (20)	20 (19)	58 (52)	39 (35)	22 (20)	21 (19)
1	26 (24)	46 (43)	45 (42)	42 (39)	32 (29)	51 (46)	49 (44)	43 (39)
2	18 (17)	18 (17)	38 (36)	38 (36)	19 (17)	20 (18)	34 (31)	41 (37)
3	3 (3)	0	3 (3)	7 (7)	2 (2)	1 (<1)	6 (5)	6 (5)
Pruritus								
0	59 (55)	49 (46)	19 (18)	18 (17)	55 (50)	39 (35)	18 (16)	20 (18)
1	14 (13)	20 (19)	32 (30)	28 (26)	21 (19)	38 (34)	44 (40)	34 (31)
2	25 (23)	30 (28)	47 (44)	50 (47)	26 (23)	24 (22)	34 (31)	39 (35)
3	9 (8)	8 (7)	9 (8)	11 (10)	9 (8)	10 (9)	15 (14)	18 (16)
Scaling								
0	58 (54)	52 (49)	25 (23)	22 (21)	60 (54)	49 (44)	29 (26)	28 (25)
1	31 (29)	35 (33)	46 (43)	38 (36)	31 (28)	41 (37)	44 (40)	40 (36)
2	15 (14)	19 (18)	31 (29)	37 (35)	16 (14)	18 (16)	27 (24)	31 (28)
3	3 (3)	1 (<1)	5 (5)	10 (9)	4 (4)	3 (3)	11 (10)	12 (11)

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Table A.8 (Continued)
Summary of Investigator Assessment of Signs and Symptoms at Baseline
Study FPL30004

Parameter	Vehicle Lotion N=107 (%)				Fluticasone Propionate Lotion 0.05% N=111 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erosion, Oozing, Crusting								
0	87 (81)	87 (81)	65 (61)	66 (62)	88 (79)	81 (73)	66 (59)	65 (59)
1	11 (10)	16 (15)	30 (28)	19 (18)	12 (11)	20 (18)	22 (20)	22 (20)
2	7 (7)	2 (2)	12 (11)	20 (19)	9 (8)	10 (9)	22 (20)	18 (16)
3	2 (2)	2 (2)	0	2 (2)	2 (2)	0	1 (<1)	6 (5)
Lichenification								
0	64 (60)	56 (52)	26 (24)	28 (26)	64 (58)	57 (51)	31 (28)	30 (27)
1	33 (31)	42 (39)	51 (48)	49 (46)	35 (32)	43 (39)	48 (43)	45 (41)
2	6 (6)	9 (8)	29 (27)	25 (23)	11 (10)	10 (9)	22 (20)	29 (26)
3	4 (4)	0	1 (<1)	5 (5)	1 (<1)	1 (<1)	10 (9)	7 (6)
Body Area Score								
0	48 (45)	35 (33)	13 (12)	14 (13)	45 (41)	31 (28)	14 (13)	17 (15)
1	27 (25)	27 (25)	32 (30)	25 (23)	30 (27)	35 (32)	39 (35)	32 (29)
2	15 (14)	21 (20)	32 (30)	28 (26)	20 (18)	21 (19)	27 (24)	25 (23)
3	8 (7)	12 (11)	16 (15)	19 (18)	7 (6)	13 (12)	12 (11)	11 (10)
4	2 (2)	9 (8)	12 (11)	13 (12)	4 (4)	7 (6)	12 (11)	17 (15)
5	5 (5)	3 (3)	2 (2)	8 (7)	1 (<1)	3 (3)	5 (5)	7 (6)
6	2 (2)	0	0	0	4 (4)	1 (<1)	2 (2)	2 (2)

Source: Sponsor's NDA submission, Volume 20, p. 89-90.

Table A.9
Summary of Investigator Assessment of Signs and Symptoms at End of Treatment
Study FPL30004

Parameter	Vehicle Lotion N=102 (%)				Fluticasone Propionate Lotion 0.05% N=108 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erythema								
0	53 (52)	56 (55)	27 (26)	28 (27)	83 (77)	71 (66)	62 (57)	51 (47)
1	23 (23)	20 (20)	35 (34)	28 (27)	23 (21)	29 (27)	28 (26)	38 (35)
2	19 (19)	22 (22)	30 (29)	37 (36)	2 (2)	7 (6)	13 (12)	14 (13)
3	7 (7)	4 (4)	10 (10)	9 (9)	0	1 (<1)	5 (5)	5 (5)
Infiltration/Papulation								
0	61 (60)	59 (58)	28 (27)	29 (28)	91 (84)	73 (68)	70 (65)	54 (50)
1	25 (25)	26 (25)	39 (38)	37 (36)	15 (14)	28 (26)	25 (23)	36 (33)
2	11 (11)	15 (15)	30 (29)	29 (28)	2 (2)	6 (6)	13 (12)	16 (15)
3	5 (5)	2 (2)	5 (5)	7 (7)	0	1 (<1)	0	2 (2)
Pruritus								
0	69 (68)	62 (61)	39 (38)	38 (37)	95 (88)	77 (71)	75 (69)	70 (65)
1	11 (11)	20 (20)	26 (25)	27 (26)	8 (7)	23 (21)	21 (19)	20 (19)
2	14 (14)	11 (11)	25 (25)	23 (23)	4 (4)	7 (6)	9 (8)	13 (12)
3	8 (8)	9 (9)	12 (12)	14 (14)	1 (<1)	1 (<1)	3 (3)	5 (5)
Scaling								
0	63 (62)	64 (63)	42 (41)	36 (35)	85 (79)	70 (65)	69 (64)	55 (51)
1	24 (24)	23 (23)	31 (30)	31 (30)	18 (17)	23 (21)	23 (21)	29 (27)
2	11 (11)	12 (12)	22 (22)	23 (23)	3 (3)	8 (7)	7 (6)	14 (13)
3	4 (4)	3 (3)	7 (7)	12 (12)	2 (2)	7 (6)	9 (8)	10 (9)

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Table A.9 (Continued)
Summary of Investigator Assessment of Signs and Symptoms at End of Treatment
Study FPL30004

Parameter	Vehicle Lotion N=102 (%)				Fluticasone Propionate Lotion 0.05% N=108 (%)			
	Head/ Neck	Trunk	Upper Limbs	Lower Limbs	Head/ Neck	Trunk	Upper Limbs	Lower Limbs
Erosion, Oozing, Crusting								
0	85 (83)	84 (82)	69 (68)	62 (61)	105 (97)	96 (89)	86 (80)	83 (77)
1	11 (11)	10 (10)	13 (13)	18 (18)	2 (2)	8 (7)	16 (15)	12 (11)
2	6 (6)	7 (7)	17 (17)	13 (13)	1 (<1)	4 (4)	6 (6)	10 (9)
3	0	1 (<1)	3 (3)	9 (9)	0	0	0	3 (3)
Lichenification								
0	64 (63)	62 (61)	32 (31)	35 (34)	93 (86)	79 (73)	73 (68)	63 (58)
1	26 (25)	26 (25)	43 (42)	38 (37)	13 (12)	26 (24)	22 (20)	30 (28)
2	8 (8)	13 (13)	17 (17)	18 (18)	2 (2)	3 (3)	10 (9)	12 (11)
3	4 (4)	1 (<1)	10 (10)	11 (11)	0	0	3 (3)	3 (3)
Body Area Score								
0	49 (48)	46 (45)	22 (22)	19 (19)	77 (71)	59 (55)	54 (50)	44 (41)
1	26 (25)	20 (20)	26 (25)	31 (30)	19 (18)	24 (22)	27 (25)	27 (25)
2	14 (14)	17 (17)	28 (27)	24 (24)	9 (8)	15 (14)	10 (9)	13 (12)
3	6 (6)	11 (11)	10 (10)	11 (11)	0 (0)	5 (5)	8 (7)	9 (8)
4	2 (2)	6 (6)	12 (12)	7 (7)	1 (<1)	0	3 (3)	6 (6)
5	3 (3)	2 (2)	3 (3)	9 (9)	1 (<1)	2 (2)	3 (3)	6 (6)
6	2 (2)	0	1 (<1)	1 (<1)	1 (<1)	3 (3)	3 (3)	3 (3)

Source: Sponsor's NDA submission, Volume 20, p. 101-2.

Table A.10
Summary of Hematology Laboratory Abnormalities at Baseline and End of Treatment
Study FPL10005

Test	Result	Age 3mos-3 yrs		Age 3yrs-6yrs		Total	
		Baseline	End-Treatment	Baseline	End-Treatment	Baseline	End-Treatment
Hemoglobin	n	15	17	17	18	32	35
	Low	0	0	1	3	1	3
	Normal	15	17	16	15	31	32
	High	0	0	0	0	0	0
Platelets	n	15	17	17	18	32	35
	Low	0	0	2	2	2	2
	Normal	11	10	14	15	25	25
	High	4	7	1	1	5	8
RBC	n	15	17	17	18	32	35
	Low	0	0	0	0	0	0
	Normal	14	14	17	18	31	32
	High	1	3	0	0	1	3
Hematocrit	n	15	16	17	18	32	34
	Low	1	0	1	2	2	2
	Normal	13	16	16	16	29	32
	High	1	0	0	0	1	0
White Blood Cells	n	15	17	17	18	32	35
	Low	4	1	1	0	5	1
	Normal	7	15	16	17	23	32
	High	4	1	0	1	4	2
Neutrophils	n	14	8	17	18	31	26
	Low	7	3	1	3	8	6
	Normal	7	4	16	15	23	19
	High	0	1	0	0	0	1
Neutrophils (%)	n	15	17	17	18	32	35
	Low	11	11	7	11	18	22
	Normal	4	6	10	7	14	13
	High	0	0	0	0	0	0
Lymphocytes	n	14	8	17	18	31	26
	Low	4	1	1	1	5	2
	Normal	10	7	16	16	26	23
	High	0	0	0	1	0	1
Lymphocytes (%)	n	15	17	17	18	32	35
	Low	0	0	0	0	0	0
	Normal	4	7	12	10	16	17
	High	11	10	5	8	16	18
Monocytes	n	14	8	17	18	31	26
	Low	0	0	0	1	0	1
	Normal	14	6	17	17	31	23
	High	0	2	0	0	0	2
Monocytes (%)	n	15	17	17	18	32	35
	Low	2	1	0	1	2	2
	Normal	13	12	17	17	30	29
	High	0	4	0	0	0	4

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Table A.10 (Continued)
Summary of Hematology Laboratory Abnormalities at Baseline and End of Treatment
Study FPL10005

Test	Result	Age 3mos-3 yrs		Age 3yrs-6yrs		Total	
		Baseline	End-Treatment	Baseline	End-Treatment	Baseline	End-Treatment
Eosinophils	n	14	8	17	18	31	26
	Low	0	0	0	0	0	0
	Normal	9	6	11	14	20	20
	High	5	2	6	4	11	6
Eosinophils (%)	n	15	17	17	18	32	35
	Low	0	0	0	0	0	0
	Normal	11	15	10	11	21	26
	High	4	2	7	7	11	9
Basophils	n	14	8	17	18	31	26
	Low	0	0	0	0	0	0
	Normal	14	8	17	17	31	25
	High	0	0	0	1	0	1
Basophils (%)	n	15	17	17	18	32	35
	Low	0	0	0	0	0	0
	Normal	15	17	17	18	32	35
	High	0	0	0	0	0	0
Bands	n	14	8	17	18	31	26
	Low	0	0	0	0	0	0
	Normal	14	8	17	18	31	26
	High	0	0	0	0	0	0
Bands (%)	n	15	17	17	18	32	35
	Low	0	0	0	0	0	0
	Normal	15	17	17	18	32	35
	High	0	0	0	0	0	0

Source: Sponsor's NDA submission, Volume 14, p. 96-9.

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Table A.11
Summary of Chemistry Laboratory Abnormalities at Baseline and End of Treatment
Study FPL10005

Test	Result	Age 3mos-3yrs		Age 3yrs-6yrs		Total	
		Baseline	End-Treatment	Baseline	End-Treatment	Baseline	End-Treatment
Alkaline Phosphatase	n	19	19	18	18	37	37
	Low	0	0	0	0	0	0
	Normal	18	19	18	18	36	37
	High	1	0	0	0	1	0
AST (SGOT)	n	19	20	18	18	37	38
	Low	0	0	0	0	0	0
	Normal	5	1	9	11	14	12
	High	14	19	9	7	23	26
ALT (SGPT)	n	19	20	18	18	37	38
	Low	0	0	0	0	0	0
	Normal	15	18	18	18	33	36
	High	4	2	0	0	4	2
Glucose	n	19	20	18	18	37	38
	Low	5	6	2	0	7	6
	Normal	14	13	16	18	30	31
	High	0	1	0	0	0	1
Total Protein	n	19	20	18	18	37	38
	Low	0	0	0	0	0	0
	Normal	18	15	15	14	33	29
	High	1	5	3	4	4	9
Albumin	n	19	20	18	18	37	38
	Low	2	0	1	1	3	1
	Normal	17	20	16	17	33	37
	High	0	0	1	0	1	0
Serum Sodium	n	15	18	18	18	33	36
	Low	0	0	0	0	0	0
	Normal	15	18	17	18	32	36
	High	0	0	1	0	1	0
Serum Potassium	n	15	17	18	18	33	35
	Low	0	0	0	0	0	0
	Normal	14	16	18	18	32	34
	High	1	1	0	0	1	1
Serum Chloride	n	15	18	18	18	33	36
	Low	0	0	0	0	0	0
	Normal	15	18	18	18	33	36
	High	0	0	0	0	0	0
Serum Bicarbonate	n	15	18	18	18	33	36
	Low	2	2	1	1	3	3
	Normal	13	16	17	17	30	33
	High	0	0	0	0	0	0
Phosphorus	n	19	19	18	18	37	37
	Low	0	0	0	0	0	0
	Normal	17	18	18	17	35	35
	High	2	1	0	1	2	2

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Table A.11 (Continued)
Summary of Chemistry Laboratory Abnormalities at Baseline and End of Treatment
Study FPL10005

Test	Result	Age 3mos-3yrs		Age 3yrs-6yrs		Total	
		Baseline	End-Treatment	Baseline	End-Treatment	Baseline	End-Treatment
Serum Uric Acid	n	19	20	18	18	37	38
	Low	1	0	1	0	2	0
	Normal	18	20	17	18	35	38
	High	0	0	0	0	0	0
Urea Nitrogen	n	19	20	18	18	37	38
	Low	0	0	0	0	0	0
	Normal	19	20	18	18	37	38
	High	0	0	0	0	0	0
Creatinine	n	19	20	18	18	37	38
	Low	0	0	0	0	0	0
	Normal	19	20	17	16	36	36
	High	0	0	1	2	1	2
Calcium (EDTA)	n	19	20	18	18	37	38
	Low	0	0	0	0	0	0
	Normal	18	19	16	16	34	37
	High	1	1	2	2	3	1
Total Bilirubin	n	14	19	16	16	30	35
	Low	0	0	0	0	0	0
	Normal	14	19	16	16	30	35
	High	0	0	0	0	0	0

Source: Sponsor's NDA submission, Volume 14, p. 103-6.

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/s/

Michael Albert
1/6/05 03:02:31 PM
MEDICAL OFFICER

Markham Luke
1/6/05 03:56:07 PM
MEDICAL OFFICER
Please also see Clinical TL summary/secondary review.

Jonathan Wilkin
1/12/05 12:37:59 PM
MEDICAL OFFICER
See Clinical Team Leader Secondary Review

Date of Consultation Request From HFD-540/DDDDP (Medical Team Leader - Dr. Markham Luke (301-827-2052); Biopharmaceutics Reviewer - Dr. Abi Adebawale (301-827-2078); and Project Manager - Millie Wright (301-827-2084): 8/2/04

Date Consultation Request Received by this Medical Officer: 8/20/04

NDA 21,152 (presently being reviewed by DDDDDP - User Fee Date 1/10/05)

Sponsor - GlaxoSmithKline, Inc.

Generic Name of Drug: Fluticasone Propionate Lotion 0.05% (a topical fluorinated glucocorticoid formulation)

Trade Name of Drug: Cutivate

Sponsor's Proposed Indication for Cutivate in Children and Adults: Treatment of ~~_____~~

Date of Consultation by HFD-510/DMEDP (Medical Officer - Dr. Robert Perlstein): 9/10/04

Sources Utilized by DMEDP Medical Officer: Copy of Study Report for Protocol FPL10005 - "An Open Label Adrenal Suppression Study of Fluticasone Propionate Lotion 0.05% Used Twice Daily in Pediatric Subjects Aged 3 Months to 5 Years with Moderate to Severe Eczema or Psoriasis"

A. Rationale for Study: In that topically administered glucocorticoid therapy can be systemically absorbed, the potential exists for suppression of the hypothalamic-pituitary-adrenal (HPA) axis (as well as iatrogenic Cushing's syndrome).

B. Primary Objectives of Protocol/Hypothesis: To evaluate the integrity of the HPA axis after a 21-28 day course of twice daily fluticasone propionate lotion 0.05% in children aged 3 months to 5 years utilizing Cosyntropin (Cortrosyn, ACTH₁₋₂₄) Stimulation Testing (CST).

C. Abbreviated Protocol Design: Open label safety study. Forty two children with moderate to severe eczema were treated for 21-28 days with Cutivate. Patients who had received systemic glucocorticoid therapy within 6 months were excluded. CST was performed at baseline and after completion of Cutivate therapy. During the CST, serum cortisol levels were determined pre-stimulation and 30 minutes after an intravenous bolus injection of 250 µg of Cosyntropin. A normal response was appropriately defined as a post-stimulation value >18 µg/dL. Plasma fluticasone levels were measured in children >2 years of age to assess systemic absorption and relationship to CST results.

D. Abbreviated Summary of CST Results:

The mean body surface area (BSA) treated was 65±15.3% and the mean amount of drug used during the study was ~195-200 grams.

The mean pre-stimulation and post-stimulation serum cortisol levels at baseline and end-treatment were normal and not significantly different (baseline mean pre-stimulation = 13.2 µg/dL, baseline mean post-stimulation = 35.3 µg/dL [range, 19.1-51.8 µg/dL], end-treatment mean pre-stimulation = 12.4 µg/dL, end-treatment mean post-stimulation = 33.3 µg/dL [21.1-59.7 µg/dL]). All patients had end-treatment post-stimulation serum cortisol levels >18 µg/dL.

When the responsiveness of individual patients was assessed, the Sponsor's consulting endocrinologist identified 2 patients whose pre- and post-stimulation serum cortisol levels were clearly lower at end-treatment compared with baseline. He concluded that these 2 patients may have developed mild, partial suppression of the HPA axis as a consequence of Cutivate exposure. However, he also concluded that these findings were not clinically relevant.

Subject		Pre-stimulation	Post-stimulation
5008	Baseline	23.1	32.9
	End-Treatment	8.9	21.1
6029	Baseline	9.1	29.1
	End-Treatment	4.5	22.5

Serum levels of fluticasone did not correlate with the CST results.

E. Questions Posed by DDDDP:

Does DMEDP agree with the conclusions of the Sponsor's endocrinology consultant? More specifically, does DMEDP agree that the results of CST indicates the development of mild, partial adrenal suppression in 2 children (out of 42 completers) after treatment with Cutivate for 21-28 days?

F. DMEDP Commentary/Conclusions:

- Recent review of the literature and safety databases by the DDDDP (presented at an October 2003 Advisory Committee) indicates that treatment of various dermatological disorders with topical glucocorticoid formulations may result in clinically significant suppression of the HPA axis, especially when potent halogenated/fluorinated glucocorticoid formulations are applied to large BSAs in children.
- In that context, it is therefore plausible that the 2 patients described in Section D. above (with decreased end-

treatment pre-stimulation and Cortrosyn-stimulated levels of serum cortisol) may have sustained partial suppression of the HPA axis after exposure to Cutivate, a topical, fluorinated glucocorticoid formulation.

- I also agree with the Sponsor's endocrinology consultant that these findings are most likely not clinically significant - in that the stimulated serum cortisols of these 2 children remained above 18 µg/dL. However, it should be noted that, on occasion, patients who stimulate normally in response to Cortrosyn, manifest abnormal responses during the "gold standard" maneuver for evaluating the integrity of the HPA axis, the insulin tolerance test (ITT).
- I further agree with the Sponsor's overall conclusion that clinically significant suppression of the HPA axis appears to occur infrequently when relatively large amounts of Cutivate lotion 0.05% are applied to large BSAs for 21-28 days in children (aged 3 months to 5 years) with moderate to severe eczema.

F. DMEDP Recommendations Regarding the Cutivate NDA Submission:

- A CST should be performed before and after exposure to Cutivate (for ≥21-28 days).
- In the event a stimulated serum cortisol <18 µg/dL is observed following exposure to a course of Cutivate (unlikely), serial CSTs should be performed at appropriate intervals. Until the stimulated serum cortisol exceeds 18 µg/dL, empiric coverage with stress doses of a rapidly acting glucocorticoid should be administered during intercurrent serious illness/stress and a medalert bracelet/wallet card should be given to the patient.
- In the event potential partial suppression of the HPA axis is observed (as in the case of 2 patients during this study), there are 2 possible courses of action. My first choice would be to recommend empiric or prn (if the clinical circumstances indicate possible adrenal insufficiency) administration of stress doses of a rapidly acting glucocorticoid during intercurrent serious illness/stress, and use of a medalert identifier, for at least 1 year after discontinuation of the course of Cutivate lotion. (The more conservative option [more invasive and much less feasible/practical and therefore my second choice] would be to perform an ITT. If the serum cortisol during the ITT is appropriate, then partial adrenal insufficiency is essentially ruled out. On the other hand, if the ITT result is abnormal, empiric coverage with stress doses of a rapidly acting glucocorticoid should be administered during intercurrent serious illness/stress and a medalert bracelet/wallet card should be given to the patient until the ITT result normalizes.)

The contents of this consultation have been discussed with the DMEDP Division Director, Dr. David Orloff.

If I can be of further assistance, please free to contact me by email or at 301-827-9082.

Robert S. Perlstein MD, FACP, FACE
Medical Officer
DMEDP

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

/s/

Robert Perlstein
9/15/04 05:20:16 PM
MEDICAL OFFICER

David Orloff
9/15/04 05:24:17 PM
MEDICAL OFFICER