CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-152

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	21-152/N-000 (AZ)
Applicant:	GlaxoSmithKline
Name of Drug:	CUTIVATE (fluticasone propionate) lotion 0.05%
Indication:	Atopic dermatitis
Type of Review:	Labeling Resubmission based on AE Letter
Stamp Date:	2/1/05
Medical Reviewer:	Denise Cook, M.D., HFD-540
Statistical Reviewer:	Kathleen Fritsch, Ph.D., HFD-725
Project Manager:	Millie Wright, HFD-540

Background

The Division issued an Approvable (AE) Letter for CUTIVATE (fluticasone propionate) lotion, 0.05% listing various chemistry, non-clinical, and clinical deficiencies. This review focuses on the Sponsor's proposed changes to the labeling dealing with the clinical studies. For a complete review of the applicable data, refer to the original statistical review for NDA 21-152 dated 12/1/04.

Clinical Studies Section

Text from the AE Letter:

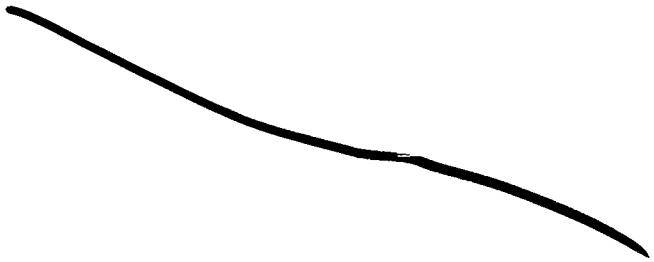
> **CLINICAL STUDIES**: CUTIVATE Lotion applied once daily was superior to vehicle in the treatment of atopic dermatitis in two studies. The two studies enrolled 438 patients with atopic dermatitis aged 3 months and older, of which 169 patients were selected as having clinically significant signs of erythema, infiltration/papulation, and erosion/oozing/crusting at baseline. Table 1 presents the percentage of patients who completely cleared of erythema, infiltration/papulation, and erosion/oozing/crusting at Week 4 out of those patients with clinically significant baseline signs.

Table 1 – Complete Clearance Rate

	CUTIVATE Lotion	**Vehicle**
Study 1	9/45 (20%)	0/37 (0%)
Study 2	7/44 (16%)	1/43 (2%)

Sponsor's Counterpropsal:

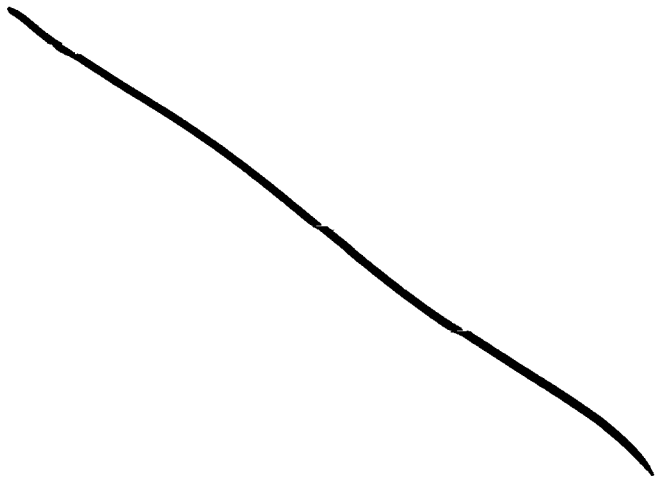
[redacted]



Reviewer Comments
This reviewer recommends retaining the wording from the AE letter and not incorporating any of the Sponsor's proposed changes. The endpoint "50% of lesions cleared plus improvement or no change in ≥75% of remaining lesions for erythema infiltration/papulation and erosion/oozing/crusting" was never agreed upon by the Division. A related endpoint "*at least* 50% of lesions cleared plus improvement or no worsening on *all* scores for erythema, *scaling*, erosion/oozing/crusting, infiltration/papulation, and *pruritus* was discussed at the Pre-NDA meeting as a possible way to salvage the data from these clinical studies that did not include an appropriate Investigator's Global Assessment. However, upon review of the data, this post-hoc endpoint was not considered sufficiently clinically relevant.

Because of the entry criteria did not specify a minimum level of acute signs and symptoms, and the way the baseline severity data was collected with multiple sign and symptom scores on multiple body regions, there are many ways to attempt to distinguish those subjects with mild versus moderate to severe baseline signs. The Division has proposed one cutoff point, and the Sponsor has counterproposed a different cutoff point. The Division made efforts to minimize bias due to the post hoc selection of subjects by having a clinical reviewer not involved with the original review define the cutoff. This reviewer recommends keeping the Division's cutoff point.

HPA Axis Suppression Data
Text from the AE Letter:



Reviewer Comments

- This reviewer recommends acknowledging that 42 subjects completed the study but that the Division considers 40 subjects to be evaluable due to 2 subjects who applied less than 90% of scheduled applications.
- If suppression was defined differently in the studies with CUTIVATE cream (e.g. [redacted]), then it may be appropriate to note that suppression has been observed without providing the details about the number of suppressions observed, as the cream data would not be directly comparable to the lotion data.

Kathleen Fritsch, Ph.D.
Mathematical Statistician, Biometrics III

concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Orig. NDA 21-152/N-000 (AZ)
HFD-540/Wilkin
HFD-540/Luke
HFD-540/Cook
HFD-540/Wright
HFD-700/Anello
HFD-700/Dubey
HFD-725/Huque
HFD-725/Lin
HFD-725/Alosh
HFD-725/Fritsch

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/s/

Kathleen Fritsch
3/16/05 12:41:21 PM
BIOMETRICS

Mohamed Alosh
3/16/05 04:19:00 PM
BIOMETRICS
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	21-152 / N-000 (RS)
Drug Name:	Cutivate [redacted]fluticasone propionate[redacted] 0.05%
Indication(s):	Atopic dermatitis
Applicant:	GlaxoSmithKline
Dates:	Submitted: March 12, 2004 PDUFA: January 12, 2005
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistics Reviewer:	Kathleen Fritsch, Ph.D.
Concurring Reviewer:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatologic and Dental Drug Products (HFD-540)
Clinical Team:	Michael Albert, M.D., Markham Luke, M.D. (TL)
Project Manager:	Millie Wright

Keywords: post hoc/prospective analyses, EASI score, atopic dermatitis

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1 Executive Summary

1.1 Conclusions and Recommendations

The sponsor conducted two Phase 3 studies for Cutivate (fluticasone propionate) [redacted] 0.05%, but they were not designed according to the Division's recommendations for assessing efficacy in the treatment of atopic dermatitis. The primary efficacy endpoint specified in the protocol was based on the EASI score rather than an investigator's global assessment. In addition, many subjects in these studies were enrolled with very minimal acute signs of atopic dermatitis. A medical officer not directly involved in the review defined a subpopulation of subjects meeting certain minimum baseline criteria (referred to in this review as the MBLC population) that is used in many reviewer analyses. Less than 40% of enrolled subjects were included in the MBLC population.

Analyses by the reviewers of the proportion of subjects who achieve clearance of erythema, infiltration/papulation, and erosion/oozing/crusting in the MBLC population indicate that the data do provide evidence that fluticasone is efficacious in the treatment of atopic dermatitis. The clearance rates among subjects with moderate to severe acute signs of atopic dermatitis at baseline (MBLC) were 20% (9/45) in Study 3 and 16% (7/44) in Study 4 for fluticasone subjects versus 0% (0/37) in Study 3 and 2% (1/43) in Study 4 for vehicle patients. Since this analysis is post hoc, the p-values cannot be used in a strict sense to test for efficacy, though the p-values for this analysis are less than 0.05 in both studies. Although results in patients with moderate to severe disease at baseline may be of primary clinical interest, additional supporting evidence is provided by the fact that the treatment effect for the complete clearance rate among the mild subjects at baseline is approximately the same as for moderate to severe subjects. The complete clearance rates for the mild subjects who were not in the MBLC population were 38% (25/65) for fluticasone versus 12% (9/73) for vehicle in Study 3 and 37% (25/67) for fluticasone versus 6/64 (9%) for vehicle.

The studies met the statistical objectives for which they were designed, and results are consistent across studies and among subjects with different baseline severities. However, since the studies' endpoints and inclusion criteria did not match the recommendations of the Division and the clinical objectives of interest, it is difficult to conclusively state whether the sponsor's studies adequately address the important clinical questions related to efficacy and safety.

1.2 Brief Overview of Clinical Studies

The sponsor conducted two identical Phase 3 studies in subjects with atopic dermatitis, Study FPL30003 and Study FPL30004. Study 3 enrolled 220 subjects, 110 fluticasone and 110 vehicle, and Study 4 enrolled 218 subjects, 111 fluticasone and 107 vehicle. More than half (55%) of the subjects were pediatric with 26% of the subjects under 3 years. Subjects applied treatment once daily for four weeks. The protocol defined the

primary efficacy endpoint as at least a 75% reduction in EASI from baseline. Subjects were enrolled into the studies based on their score on the Rajka/Langeland scale.

1.3 Statistical Issues and Findings

The primary reviewer analysis of the subjects in Studies 3 and 4 who met the minimum baseline criteria (MBLC) and cleared of erythema, infiltration/papulation, and erosion/oozing/crusting is presented in Table 1. The two studies have comparable treatment effects. Interpreting the p-values from this analysis is difficult since both the endpoint and the subset of subjects included in the analysis were defined post hoc. The p-values may be useful for indicating that the treatment effect is reasonably large relative to the remaining sample size and variability, however, it is not possible to say that these p-values alone provide adequate statistical significance of a treatment effect. These results can only be interpreted within the full context of the available data.

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

Studies 3 and 4 were not designed to directly answer the clinical questions of interest to the Division regarding efficacy for atopic dermatitis. The sponsor was advised of the Division's recommendations regarding study design at an End of Phase 2 meeting held in May 1998. The following features of Studies 3 and 4 make it challenging to assess the efficacy of fluticasone in the treatment of atopic dermatitis.

1. The inclusion criteria did not address the baseline severity of the key signs of atopic dermatitis. Many subjects had minimal signs of acute atopic dermatitis (erythema, infiltration/papulation, and erosion/oozing/crusting) at baseline.
2. The piecemeal nature of the assessments for the EASI score makes it difficult to reconstruct a global picture of a subject's severity at any point in the trial.
3. Any attempt to match the available data from the trial to the Division's recommendations for assessing efficacy is necessarily post hoc, making it difficult to assess statistical significance.

However, even with all of the disagreements between the sponsor and the Agency regarding study design, in the full body of evidence, the following features of Studies 3 and 4 help support the claim that fluticasone is effective in the treatment of atopic dermatitis

1. The clearance rate analysis based on the minimum baseline criteria (MBLC) subpopulation indicates that there is still some evidence of a treatment effect in this subpopulation, even with the reduced sample size. The minimum baseline criteria were selected by a medical officer not directly involved with the review to minimize potential bias.
2. The difference in clearance rate between fluticasone and vehicle does not appear to be greatly affected by the baseline severity (refer to Table 15 on page 17 which

divides subjects into quartiles based on their baseline sum score). The difference between subjects appears to decrease slightly as the baseline sum score increases, however it stays at generally the same magnitude. The key feature is that as the baseline sum score increases, the number of subjects with that score or higher quickly decreases. Once a subset of subjects is selected based on baseline severity, the primary issue is whether the selected subset of subjects has enough members remaining to draw any valid conclusions.

3. The two studies provide very similar results and are consistent with each other.
4. For the endpoint (EASI) and subject population defined in the protocols, the studies demonstrate a statistically significant treatment effect in favor of fluticasone.

2 Introduction

2.1 Overview

Cutivate (fluticasone propionate) is currently marketed in two dosage forms, Cutivate cream, 0.05% and Cutivate ointment, 0.005%. Both products were approved in 1990 and both are indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The current application is for a new dosage form of the 0.05% concentration, Cutivate emulsion, 0.05% (also referred to as Cutivate lotion). This application, NDA 21-152, was originally submitted on December 13, 1999 and was withdrawn by the sponsor five months into the review cycle on May 25, 2000 for the "company's commercial decision not to market this product". The current submission contains essentially the same materials that were submitted in 1999.

The sponsor conducted two identical Phase 3 studies in subjects with atopic dermatitis, Study FPL30003 and Study FPL30004. Study 3 enrolled 220 subjects, 110 fluticasone and 110 vehicle, and Study 4 enrolled 218 subjects, 111 fluticasone and 107 vehicle. More than half (55%) of the subjects were pediatric with 26% of the subjects under 3 years. Subjects applied treatment once daily for four weeks. All study centers were located in the United States.

2.2 Data Sources

The datasets for this application are archived at \\CDSESUB1\2004-08-03\crt\datasets in folders fpl30003 and fpl30004. The primary datasets used in this review were assess1.xpt and outcomes.xpt.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoint Discussions

Studies FPL30003 and FPL30004 are identical randomized, double-blind, vehicle-controlled studies evaluating fluticasone propionate lotion 0.05% in the treatment of atopic dermatitis. Subjects applied study medication once daily for four weeks.

Investigators evaluated subjects at baseline, Day 15 (Week 2), and Day 29 (Week 4). The protocol specified that subjects whose lesions were 100% cleared on Day 15 were to stop treatment and complete all end of treatment procedures.

The studies were designed to enroll approximately equal numbers of pediatric and adult patients. At the start of the study, subjects were stratified by age group, and the age strata were 3 months to 2 years, 3 to 5 years, and ≥18 years. Pediatric and adult subjects were enrolled at separate centers, except for one center in Study 4 that enrolled both pediatric and adult subjects. Approximately four months after enrollment began, the sponsor amended the protocol to additionally permit enrollment of pediatric subjects ages 6 to 17 years after the sponsor believed adequate enrollment in the lowest ages had been achieved. After the protocol amendment, the stratification within the pediatric age group was dropped and all pediatric subjects were randomized using subject numbers from either of the original pediatric strata.

To assess disease severity at baseline, subjects were evaluated on the Rajka/Langeland severity scale. The scale measures extent of disease, time course, and intensity of itching. The full scale is presented in Table 26 in the Appendix. The possible values for the total score range from 3 to 9. Subjects were required to have a minimum score of 5 at baseline and were classified as either moderate (score 5 – 7) or severe (score 8 – 9). At the End of Phase 2 Meeting, held May 7, 1998, the FDA advised the sponsor that the signs of erythema, papulation/edema, and erosion/oozing/crusting should be used for the inclusion criteria and that enrolled subjects should have acute eczema. The use of the Rajka/Langeland severity scale is inconsistent with the FDA's End of Phase 2 advice.

The primary efficacy endpoint defined in the protocol was at least a 75% reduction from baseline in the EASI (Eczema and Severity Index) score. The EASI score incorporates assessments of erythema, infiltration/papulation, pruritus, lichenification, and body area. Assessments are recorded separately for the four body regions: head and neck, trunk, upper limbs, and lower limbs, and each sign and symptom is assessed on a 4-point scale. Possible EASI scores range from a minimum of 0 to a maximum of 72. Additional evaluations included a dynamic Investigator Global Evaluation (IGE) and assessments of scaling and erosion/oozing/crusting. The IGE was defined as

0 = Cleared – 100% of lesions have cleared
1 = Almost Cleared – 90% of lesions have cleared
2 = Marked Clearing – 50% of lesions have cleared
3 = Modest Clearing – Less than 50% of lesions have cleared
4 = No Change – Unchanged from baseline EASI
5 = Exacerbation – Worse than baseline EASI

The primary endpoint specified in the protocol was different from the endpoint recommended by the FDA at the End of Phase 2 Meeting. The FDA advised the sponsor at the End of Phase 2 Meeting to define the primary efficacy endpoint as achieving clear or almost clear on a global evaluation. The FDA further stated that the global evaluation should reflect the end of study severity state, not be a comparison to baseline, and should incorporate the signs of erythema, papulation/edema, and erosion/oozing/crusting.

The secondary efficacy endpoint specified in the protocol was a combination of the IGE and the reduction in EASI. A successful outcome was defined as at least 50% of lesions have cleared (score ≤2 on the IGE) and the reduction from baseline EASI is at least 75%. The protocol stated that the primary and secondary efficacy endpoints would be analyzed using a continuity-corrected chi-square test adjusting for investigator sites.

At the Pre-NDA meeting held April 19, 1999, the FDA reiterated that since the EASI score is derivative and obscures primary information it would not be appropriate as the primary endpoint. The reviewers also recommended an endpoint that could be computed from the data collected in Studies 3 and 4. The endpoint defined success as having at least 50% of lesions cleared (IGE ≤2) and having no worsening on the scores for erythema, infiltration/papulation, scaling, erosion/oozing/crusting, and pruritus.

Signs and symptoms were assessed individually in four body areas (head/neck, trunk, upper limbs, and lower limbs) in Studies 3 and 4. The sponsor interpreted the FDA's recommendation that the five signs and symptoms should improve or not worsen as a subject would need to have at least 15 of the 20 assessments (5 signs/symptoms × 4 body areas) improve or not change from baseline with no more than 5 of the 20 assessments worsening (hereafter referred to as "sponsor pre-NDA success"). The sponsor wrote the study reports using "sponsor pre-NDA success" as the primary endpoint. The study reports do not contain any analyses of the protocol-specified "EASI success" endpoint. After the sponsor submitted to the FDA their interpretation of the pre-NDA meeting endpoint discussion, the FDA responded (fax dated August 13, 1999) that their intention was that *all* sign and symptom assessments must improve or not change with none of them getting worse. The sponsor included the analysis of ≥50% clear + improvement or no change on 20/20 assessments as supplements to the study reports (hereafter referred to as "FDA pre-NDA success").

The sponsor analyzed the pre-NDA success rates using the Cochran-Mantel-Haenszel (CMH) test stratified on center. This is consistent with the analysis specified in the protocol for the EASI success endpoint. This reviewer also used the CMH test for all reviewer analyses of success rates. The Breslow-Day test was used to assess for homogeneity among investigators. The sponsor did not specify a plan for pooling small centers or pool any centers in the analyses. However, since some centers only enrolled one or two subjects, this reviewer pooled centers with fewer than 8 subjects per treatment arm for the analyses.

The protocol defined the ITT population as all subjects who applied at least one dose of study medication. At the End of Phase 2 and Pre-NDA meetings, the FDA advised the sponsor that the ITT population should be defined as all subjects randomized and dispensed study treatment, and the sponsor used this definition in the study reports. One subject in Study 4 was randomized, but was not dispensed treatment and thus excluded from the ITT population. The ITT population in Study 3 included 220 subjects, 110 on each arm. The ITT population in Study 4 included 218 subjects, 111 fluticasone and 107 vehicle.

3.1.2 Baseline Disease Severity

Subjects were enrolled in the studies based on their scores for the Rajka/Langeland scale. The scale measures extent of disease, time course, and intensity of itching. The full scale is presented in Table 26 in the Appendix. The possible values for the total score range from 3 to 9. Subjects were required to have a minimum score of 5 at baseline and were classified as either moderate (score 5 – 7) or severe (score 8 – 9). The distribution of the Rajka/Langeland baseline scores are presented in Table 2.

Table 2 – Baseline Rajka/Langeland Severity Score (ITT)

	Study 3		Study 4	
	Fluticasone N=110	Vehicle N=110	Fluticasone N=111	Vehicle N=107
5 – 7 (Moderate)	77 (70%)	79 (72%)	87 (78%)	85 (79%)
8 – 9 (Severe)	33 (30%)	31 (28%)	24 (22%)	22 (21%)

Source: Vol. 16, pg. 86, and Vol. 20, pg. 84.

However, as the Rajka/Langeland scale primary measures chronicity of atopic dermatitis rather than acuteness of signs of atopic dermatitis, many subjects were enrolled with very mild scores on signs such as erythema, infiltration/papulation, and erosion/oozing/ crusting. Because the study did not include a static global evaluation of disease severity, the only available assessments of disease severity are the individual sign and symptom scores assessed within each of the four body regions (head/neck, trunk, upper limbs, and lower limbs) that are the components of the EASI score. Through discussions with the clinical team, the reviewers decided to assess baseline severity through the scores for erythema, infiltration/papulation, and erosion/oozing/crusting, which is the advice provided to the sponsor at the End of Phase 2 meeting. One component of severity is assessed through the sum score for the three signs over the four body regions. Since each sign is assessed from 0 to 3, the sum score has a range of 0 to 36. In Study 3 the baseline sum scores ranged from 2 to 32 and in Study 4 the baseline sum scores ranged from 1 to 29. The median baseline sum score was 9 in each study. The distribution of the sum scores is presented in Table 3.

Table 3 – Distribution of the Baseline Sum Score (ITT)

	Study 3		Study 4	
Baseline Sum Score[a]	Fluticasone N=110	Vehicle N=110	Fluticasone N=111	Vehicle N=107
1-3	6 (6%)	9 (8%)	7 (6%)	6 (6%)
4-6	28 (26%)	26 (24%)	22 (20%)	20 (19%)
7-9	22 (20%)	31 (28%)	27 (24%)	33 (31%)
10-12	21 (19%)	17 (16%)	25 (23%)	22 (21%)
13-15	15 (14%)	7 (6%)	12 (11%)	13 (12%)
16-18	11 (10%)	10 (9%)	7 (6%)	6 (6%)
19-21	4 (4%)	3 (3%)	5 (5%)	5 (5%)
22-24	2 (2%)	6 (6%)	1 (1%)	2 (2%)
25-27	0	0	3 (3%)	1 (1%)
28-30	1 (1%)	0	2 (2%)	0
31-33	0	1 (1%)	0	0
34-36	0	0	0	0

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

Many subjects enrolled in Studies 3 and 4 had low baseline sum scores, and as these studies were designed to evaluate treatment in moderate to severe subjects, the clinical reviewer noted that many of the subjects with mild baseline signs and symptoms may not be appropriate candidates for these clinical trials. Since the Agency and the sponsor did not come to agreement regarding the baseline severity scale for inclusion at the protocol stage, any subsetting of subjects based on baseline severity at the review stage is necessarily post hoc and somewhat arbitrary. Because the review team was too familiar with the data to derive an objective criterion to subset subjects, a medical officer who is not involved in the review of this NDA submission was asked to define clinically meaningful minimum baseline criteria that could be applied to the available signs and symptoms scores. The selected minimum baseline criteria (MBLC) were a total baseline sum score of 10 or greater (for erythema, infiltration/papulation, and erosion/oozing/ crusting), and 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 may be in different body areas). Less than half of the enrolled subjects met the MBLC with 37% of subjects in Study 3 and 40% of subjects in Study 4 meeting the criteria.

3.1.3 Subject Disposition

Study 3 enrolled 220 subjects, 110 to each arm. Study 4 enrolled 219 subjects, 111 fluticasone and 108 vehicle. One vehicle subject in Study 4 with an allergy to parabens (a component of the medication) was randomized, but this violation of the inclusion criterion was discovered before the subject was dispensed medication. This subject is excluded from the ITT population since no medication was dispensed. The ITT population in Study 4 includes 218 subjects, 111 fluticasone and 107 vehicle. The protocol permitted subjects who were clear at Day 15 to exit the study as successes, and 9 subjects in Study 3 and 7 subjects in Study 4 were exited early due to treatment success.

The primary reason for discontinuation was lack of efficacy and was much more prevalent on the vehicle arm than the fluticasone arm. Of the vehicle subjects, 19% in Study 3 and 21% in Study 4 discontinued for lack of efficacy compared to 3% in Study 3 and 2% in Study 4 who discontinued due to lack of efficacy on the fluticasone arm. The other reasons for discontinuation involved fewer subjects and were fairly balanced across treatment arms. The reasons for study discontinuation are listed in Table 4.

Table 4 – Reason for Study Discontinuation (All Randomized)

	Study 3		Study 4	
	Fluticasone	Vehicle	Fluticasone	Vehicle
Number of Subjects	110	110	111	108
Subjects who Stopped Treatment at Day 15 due to Success	7	2	7	0
Subjects who Discontinued	11 (10%)	29 (26%)	10 (9%)	36 (33%)
Reasons for Discontinuation				
Adverse Experience	2 (2%)	5 (5%)	2 (2%)	3 (3%)
Consent Withdrawn	1 (<1%)	1 (<1%)	1 (<1%)	0
Lost to Follow-up	4 (4%)	1 (<1%)	3 (3%)	2 (2%)
Protocol Violation	1 (<1%)	0	1 (<1%)	6 (6%)
Lack of Efficacy	3 (3%)	21 (19%)	2 (2%)	23 (21%)
Other[a]	0	1 (<1%)	1 (<1%)	2 (2%)

[a] Includes abnormal baseline labs, ineligibility determined before application, and scheduling conflict.
Source: Vol. 16, pg. 79 and Vol. 20, pg. 77.

The reasons for study discontinuation in the MBLC population are listed in Table 5. Most of the percentages are similar to the all randomized population, except that the proportion of vehicle subjects who discontinued due to lack of efficacy is even higher in the MBLC population than the all randomized population (27-42% versus 19-21%), especially in Study 4. This may simply indicate that subjects assigned to vehicle with more severe disease at baseline were more likely to drop out due to lack of efficacy than those with less severe disease.

Table 5 – Reason for Study Discontinuation (MBLC)

	Study 3		Study 4	
	Fluticasone	Vehicle	Fluticasone	Vehicle
Number of Subjects	45	37	44	43
Subjects who Stopped Treatment at Day 15 due to Success	2	0	2	0
Subjects who Discontinued	5 (11%)	14 (38%)	5 (11%)	24 (56%)
Reasons for Discontinuation				
Adverse Experience	1 (2%)	3 (8%)	1 (2%)	1 (2%)
Consent Withdrawn	1 (2%)	0	1 (2%)	0
Lost to Follow-up	1 (2%)	1 (3%)	1 (2%)	0
Protocol Violation	0	0	1 (2%)	4 (9%)
Lack of Efficacy	2 (4%)	10 (27%)	1 (2%)	18 (42%)
Other (Scheduling conflict)	0	0	0	1 (2%)

Source: Reviewer analysis.

3.1.4 Baseline Demographics

The treatment arms were comparable with regards to baseline demographics for both studies. Both studies enrolled approximately equal numbers of male and female subjects. More than half (55%) of the subjects were pediatric with 26% of the subjects under 3 years. Seventeen subjects were over the age of 65. Most subjects were Caucasian (75%) or black (14%). Table 6 presents the baseline demographic data for the ITT population. If only the subjects that met the reviewer's MBLC are considered, the distribution of the subjects at baseline is similar to that of the ITT population. Table 7 presents the baseline demographic data for the MBLC population. Approximately the same ratio of subjects was pediatric (56%) as in the ITT, with 31% under 3 years. The distribution of race and age were also similar in the MBLC and ITT.

Table 6 – Baseline Demographic Data (ITT)

		Study 3		Study 4	
		Fluticasone N=110	Vehicle N=110	Fluticasone N=111	Vehicle N=107
Sex	Male	54 (49%)	49 (45%)	50 (45%)	55 (51%)
	Female	56 (51%)	61 (55%)	61 (55%)	52 (49%)
Age	3m – 2y	33 (30%)	33 (30%)	27 (24%)	22 (21%)
	3y – 5y	14 (13%)	11 (10%)	28 (25%)	28 (26%)
	6y – 16y	11 (10%)	11 (10%)	10 (9%)	14 (13%)
	17y – 65y	50 (45%)	53 (48%)	40 (36%)	36 (34%)
	> 65y	2 (2%)	2 (2%)	6 (5%)	7 (7%)
Race	Caucasian	78 (71%)	80 (73%)	86 (77%)	85 (79%)
	Black	19 (17%)	19 (17%)	9 (8%)	13 (12%)
	Asian	4 (4%)	4 (4%)	5 (5%)	3 (3%)
	Hispanic	9 (8%)	6 (5%)	2 (2%)	3 (3%)
	Other	0 (0%)	1 (1%)	9 (8%)	3 (3%)

Source: Vol. 16, pg. 83 and Vol. 20, pg. 81.

Table 7 – Baseline Demographic Data (MBLC)

		Study 3		Study 4	
		Fluticasone N=45	Vehicle N=37	Fluticasone N=44	Vehicle N=43
Sex	Male	20 (44%)	12 (32%)	18 (41%)	24 (56%)
	Female	25 (56%)	25 (68%)	26 (59%)	19 (44%)
Age	3m – 2y	15 (33%)	14 (38%)	14 (32%)	10 (23%)
	3y – 5y	8 (18%)	4 (11%)	8 (18%)	10 (23%)
	6y – 16y	3 (7%)	2 (5%)	3 (7%)	4 (9%)
	17y – 65y	19 (42%)	15 (41%)	16 (37%)	15 (35%)
	> 65y	0 (0%)	2 (5%)	3 (7%)	4 (9%)
Race	Caucasian	32 (71%)	28 (76%)	31 (70%)	34 (79%)
	Black	7 (16%)	6 (16%)	4 (9%)	5 (12%)
	Asian	2 (4%)	1 (3%)	3 (7%)	1 (2%)
	Hispanic	4 (9%)	2 (5%)	2 (5%)	1 (2%)
	Other	0 (0%)	0 (0%)	4 (9%)	2 (5%)

Source: Reviewer analysis.

3.1.5 Major Protocol Violations

Subjects with major protocol violations were excluded from the per protocol population. The major violations included insufficient washout, less than 2 weeks treatment, applying less than 75% of doses, and using prohibited concomitant medications. More vehicle than fluticasone subjects had major protocol violations and this was primarily due to more vehicle subjects who treated for less than two weeks or applied less than 75% of doses. The number of subjects with major protocol violations and the breakdown by violation for subjects meeting the MBLC are presented in Table 8 and Table 9 respectively. The sponsor's definition of "applied less than 75% of doses" is not fully defined. The protocol states that patients who do not receive at least 75% of required applications will be excluded from the per protocol population. This definition is repeated in the study reports. However, within the data sets themselves, the protocol violation is defined as "applied <75% of study medication by Day 15".

Table 8 – Number of Subjects with Major Protocol Violations (MBLC)

	Fluticasone	Vehicle
Study 3	8/45 (18%)	16/37 (43%)
Study 4	6/44 (14%)	21/43 (49%)

Source: Reviewer analysis

Table 9 – Major Protocol Violations (MBLC)

	Violation	Fluticasone	Vehicle
Study 3	Insufficient Washout	2/45 (4%)	1/37 (3%)
	< 2 Weeks Treatment	4/45 (9%)	12/37 (32%)
	< 75% of Doses	2/45 (4%)	4/37 (11%)
	Concomitant Meds	2/45 (4%)	4/37 (11%)
Study 4	Insufficient Washout	0/44 (0%)	0/43 (0%)
	< 2 Weeks Treatment	2/44 (5%)	20/43 (47%)
	< 75% of Doses	1/44 (2%)	11/43 (26%)
	Concomitant Meds	4/44 (9%)	4/43 (9%)

Note: A subject may have had more than 1 major protocol violation.
Source: Reviewer analysis

3.1.6 Primary Efficacy Endpoint

3.1.6.1 Protocol-Defined Primary Endpoint – 75% Reduction in EASI

The primary efficacy endpoint specified in the protocol was at least a 75% reduction in the EASI score from baseline to Week 4. The EASI score incorporates assessments of erythema, infiltration/papulation, pruritus, lichenification, and body area. Assessments are recorded separately for the four body regions: head and neck, trunk, upper limbs, and

lower limbs, and each sign and symptom is assessed on a 4-point scale. In Study 3, 63% of fluticasone and 21% of vehicle subjects had at least a 75% reduction in EASI score, and this difference is statistically significant ($p < 0.0001$). The results in Study 4 were similar, with 59% of fluticasone and 18% of vehicle subjects achieving at least a 75% reduction in EASI score ($p < 0.0001$). The results are similar if only the subjects meeting the MBLC are included in the analysis. Full results are presented in Table 10.

Table 10 – At Least 75% Reduction in EASI from Baseline to Week 4 (ITT, MBLC)

	ITT			MBLC[a]		
	Fluticasone	**Vehicle**	**p-value**	**Fluticasone**	**Vehicle**	**p-value**
Study 3	69/110 (63%)	23/110 (21%)	<0.0001	20/45 (60%)	6/37 (16%)	<0.0001
Study 4	65/111 (59%)	19/107 (18%)	<0.0001	26/44 (59%)	8/43 (19%)	<0.0001

[a] Subjects must have a total baseline sum score of 10 or greater for erythema, infiltration/papulation, and erosion/oozing/crusting, and 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 may be in different body areas.)
Source: Reviewer analysis.

The Division has not accepted the EASI score as the primary endpoint in the past and the sponsor was advised at the End of Phase 2 meeting that the primary efficacy endpoint should be defined as clear or almost clear on an investigator's global. After further discussions at the pre-NDA meeting regarding the Division's unwillingness to accept the EASI endpoint, the sponsor did not include any results in the study report based on the EASI endpoint. The analyses presented here were re-created by this reviewer based on the definitions in the protocol.

One interesting caveat regarding the EASI endpoint is that three subjects (two in Study 3 and one in Study 4, all on the vehicle arm) discontinued the study early due to lack of efficacy but were still classified as successes at their last visit. The EASI scores for the three subjects are listed in Table 11. All three subjects are included as successes in Table 10. One subject (52005-030024) had a 91% reduction in EASI at the time of discontinuation but was nonetheless discontinued due to lack of efficacy. The success classification for the second subject (08046-035046), however, may be due to a data recording error. Subject 08046-035046 was recorded as having positive scores for erythema, infiltration/papulation, and pruritus at the final visit and an investigator's global score of 'worsened', but all of the body area scores were recorded as 0, causing the EASI score to equal 0. Thus the final EASI score of 0 appears to be the result of a data recording error. Since this subject received vehicle and keeping this subject as a success on the EASI endpoint only reduces the magnitude of the treatment effect and is not in favor of fluticasone, this reviewer has elected to keep this subject as a treatment success in Table 10. In addition, Subject 04412-049018 discontinued treatment after two weeks, but still returned for a final visit at Week 4. While the subject's status had not improved during the first two weeks on vehicle treatment, the subject improved sufficiently during the last two weeks off treatment to achieve at least 75% reduction in EASI by the end of the study. Thus only one of the three subjects who discontinued due to lack of efficacy

and yet were classified as a success appears to have actually met the criterion at the time the investigator decided to discontinue the subject.

Table 11 – Subjects who Discontinued due to Lack of Efficacy but who had at least 75% Reduction in EASI

Study	Subject	Treatment	Baseline EASI	Final EASI	% Reduction	Investigator's Global
3	52005-030024	Vehicle	16.0	1.5	91%	Almost Cleared (90%)
3	08046-035046	Vehicle	8.1	0.0[a]	100%	Worsened
4	04412-049018	Vehicle	29.2	6.7[b]	77%	Marked Clearing (50%)

[a] Subject 035046 was scored as having erythema, infiltration/papulation, and pruritus at the final evaluation (some worse than baseline), but the body surface area scores were recorded as 0 in all regions causing an EASI score of 0.
[b] Subject 049018 was discharged due to lack of efficacy and stopped treatment at Day 14 with an EASI score of 26.8 and an IGE of 'No Change'. Subject returned, however, for evaluation on Day 27 with an EASI score of 6.7 and an IGE of 'Marked Clearing'.

3.1.6.2 Pre-NDA Discussions – Disease Improvement

At the pre-NDA meeting held April 19, 1999, the Division again advised the sponsor that they had not accepted the EASI score as the primary endpoint for establishing efficacy. At the meeting, the reviewers recommended an alternative endpoint that could be computed from the data collected in the study. This endpoint was defined as achieving at least 50% improvement ('marked clearing', 'almost cleared', or 'cleared' on the investigator's global) plus improvement or no worsening from baseline on all scores for erythema, scaling, erosion/oozing/crusting, infiltration/papulation, and pruritus. The results of this analysis are presented in Table 12. The treatment effect is statistically significant with 73% of fluticasone subjects in Study 3 and 53% of fluticasone subjects in Study 4 achieving a successful outcome compared with 26% and 22% of vehicle subjects for the two studies. The results based only on the patients meeting the minimum baseline criteria are similar to those for the whole ITT population with 69% and 52% of fluticasone subjects versus 19% and 21% of vehicle subjects achieving FDA pre-NDA success for the two studies respectively.

Table 12 – Treatment Success (FDA Pre-NDA Definition) (ITT, MBLC)

	ITT			MBLC		
	Fluticasone	**Vehicle**	**p-value**	**Fluticasone**	**Vehicle**	**p-value**
Study 3	80/110 (73%)	29/110 (26%)	<0.0001	31/45 (69%)	7/37 (19%)	<0.0001
Study 4	59/111 (53%)	23/107 (22%)	<0.0001	23/44 (52%)	9/43 (21%)	0.0022

Treatment success defined as at least 50% improvement on the IGE + improvement or no change on all scores for erythema, scaling, erosion/oozing/crusting, infiltration/papulation, and pruritus.
Source: Reviewer analysis.

The component variables for FDA pre-NDA success (≥50% improvement on the IGE and no worsening on the 20 scores for erythema, scaling, erosion/oozing/crusting, infiltration/papulation, and pruritus) are presented in Table 27 in the Appendix. A subject's success on the FDA definition appears to be largely driven by whether the subject achieved at least 50% reduction on the IGE, at least in Study 3 (the effect is less pronounced in Study 4). Most subjects who had at least 50% reduction on the IGE also had no worsening sign and symptom scores.

Although this endpoint was suggested by the FDA at the pre-NDA meeting, and it appears to be able to distinguish between treatment arms, a 50% improvement on the IGE plus no worsening in signs or symptoms is a weaker endpoint than clear or almost clear, which is the Division's standard. It is not clear whether this endpoint would correspond to a clinician's or patient's idea of a successful outcome of treatment.

3.1.6.3 Reviewer Analyses – Disease Clearance

Because of the difficulties with clinically interpreting the results of the EASI analysis and the pre-NDA success analysis, the clinical and statistical reviewers agreed to analyze the endpoint defining success as achieving clearance of erythema, infiltration/papulation, and erosion/oozing/crusting in all body areas. This definition is slightly stricter than the Division's standard (and End of Phase 2 recommendation) of defining success as clear or almost clear from an investigator's global, however the definition avoids the difficulties with defining "almost clear" from the available data. The results of this analysis for the ITT and MBLC populations are presented in Table 13 and the results for the per protocol population are presented in Table 14. Clearance rates are higher in the full ITT population than in the MBLC population, however, this is true for both fluticasone and vehicle. The treatment difference between the two arms is roughly the same (14-23%) in both the ITT and MBLC populations. For the full ITT population, about 30% of fluticasone and 8% of vehicle patients achieved clearance. For the subjects meeting the MBLC, 16-20% of fluticasone and 0-2% of vehicle subjects achieved clearance. The results for the per protocol population are similar. Many more vehicle subjects than fluticasone subjects were excluded from the per protocol population due to the fact that many more vehicle subjects discontinued the study early due to lack of efficacy, though the point estimates in the ITT and per protocol populations are similar.

Table 13 – Clear of Erythema, Infiltration/Papulation, and Erosion/Oozing/ Crusting at Week 4 (ITT, MBLC)

	ITT			MBLC[a]		
	Fluticasone	**Vehicle**	**p-value**	**Fluticasone**	**Vehicle**	**p-value**
Study 3	34/110 (31%)	9/110 (8%)	<0.0001	9/45 (20%)	0/37 (0%)	0.0102
Study 4	32/111 (29%)	7/107 (7%)	<0.0001	7/44 (16%)	1/43 (2%)	0.0410

[a] Subjects must have a total baseline sum score of 10 or greater for erythema, infiltration/papulation, and erosion/oozing/crusting, and 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 may be in different body areas.)
Source: Reviewer analysis

Table 14 – Clear of Erythema, Infiltration/Papulation, and Erosion/Oozing/ Crusting at Week 4 (PP, MBLC-PP)

	PP			MBLC-PP[a]		
	Fluticasone	**Vehicle**	**p-value**	**Fluticasone**	**Vehicle**	**p-value**
Study 3	29/88 (33%)	9/74 (12%)	0.0015	7/37 (19%)	0/21 (0%)	0.1591
Study 4	28/95 (29%)	6/69 (9%)	0.0007	7/38 (18%)	1/22 (5%)	0.1382

[a] Subjects must be in both the MBLC per protocol population.
Source: Reviewer analysis.

Interpreting the results of Studies 3 and 4 is a difficult task. Although the studies have strong consistent results for the analyses defined in the protocol, the Division needs to be convinced that fluticasone demonstrates efficacy on a clinically relevant endpoint within a clinically appropriate population. Although the MBLC was selected by a medical officer not directly involved with the review to promote objectivity, it is clear that many other reasonable criteria could have been selected instead. It is not sufficient to simply look at the p-value for the analysis that appears to best address the relevant clinical concerns from the available data. Instead, it is important to assess the consistency of the treatment effect from a variety of angles.

To explore how the clearance rate is related to the baseline sum score, subjects were divided into quartiles based on their baseline sum score. Table 15 presents the clearance rates by baseline quartile grouping. As might be expected, the subjects with lower baseline sum scores are the more likely to achieve clearance than subjects with higher baseline sum scores, but this is true for both fluticasone and vehicle subjects. For the studies combined, the treatment difference does decrease as the quartiles increase, going from 32% in the first quartile to 16% in the fourth quartile. Although the treatment effect is decreasing as the baseline sum score increases, this may be in part to a "floor" effect. That is, since the success rate can go no lower than 0, once the success rate for vehicle approaches 0, if the success rate for fluticasone continues to decrease, the treatment difference between fluticasone and vehicle must decrease.

Table 15 – Clearance Rate by Baseline Sum Score Quartile

Quartile	Study 3		Study 4		Combined	
(Sum Range)	Flutic.	Vehicle	Flutic.	Vehicle	Flutic.	Vehicle
Q_1 (1 – 6)	15/34 (44%)	7/35 (20%)	15/29 (52%)	3/26 (12%)	30/63 (48%)	10/61 (16%)
Q_2 (7 – 9)	8/22 (36%)	1/31 (3%)	6/27 (22%)	3/32 (9%)	14/49 (29%)	4/63 (6%)
Q_3 (10 – 13)	5/26 (19%)	1/21 (5%)	9/32 (28%)	1/27 (4%)	14/58 (24%)	2/48 (4%)
Q_4 (14+)	6/28 (21%)	0/23 (0%)	2/23 (9%)	0/22 (0%)	8/51 (16%)	0/45 (0%)

Source: Reviewer analysis

3.1.7 Additional Efficacy Issues

3.1.7.1 Dropout Rates

A clear difference between the treatment arms was the dropout rate due to lack of efficacy, with 27-42% of vehicle subjects in the MBLC population discontinuing due to lack of efficacy versus about 3% of fluticasone subjects. Since these dropouts comprise a large proportion of the subjects, it is worth considering their impact on the efficacy conclusions. As discussed in Section 3.1.6.1 (Table 11) above, one subject who discontinued vehicle treatment after two weeks due to lack of efficacy was still followed to Week 4 and showed continued improvement after stopping treatment, so it is possible that other subjects who were not followed could have also shown some improvement after discontinuing. Since out of the two studies, only one vehicle subject meeting the MBLC who completed the full treatment completely cleared, it seems unlikely that subjects who had been discontinued after two weeks due to lack of efficacy would clear. However, if a sensitivity analysis is conducted where one vehicle subject in each study who discontinued due to lack of efficacy is counted as cleared rather than a failure, the treatment effect p-values in the MBLC population would roughly double, changing to 0.0392 from 0.0147 in Study 3 and changing to 0.0835 from 0.0410 in Study 4.

3.1.7.2 Week 2 Clearance Rates

Only a few patients achieved complete clearance of erythema, infiltration/papulation, and erosion/oozing/crusting by Week 2, however, clearance occurred more often among fluticasone subjects than vehicle subjects. Clearance rates at Week 2 are presented in Table 16. The p-values in Table 16 are from Fisher's exact test due to the low success rates and many empty cells.

Table 16 – Clear of Erythema, Infiltration/Papulation, and Erosion/Oozing/ Crusting at Week 2 (ITT, MBLC)

	ITT			MBLC		
	Fluticasone	**Vehicle**	**p-value[a]**	**Fluticasone**	**Vehicle**	**p-value[a]**
Study 3	8/110 (7%)	3/110 (3%)	0.2146	1/45 (2%)	0/37 (0%)	>0.999
Study 4	11/111 (9%)	0/107 (0%)	0.0007	3/44 (7%)	0/43 (0%)	0.2414

[a] P-values are from Fisher's exact test
Source: Reviewer analysis.

3.1.7.3 Efficacy Results by Center

There are no obvious differences in the clearance rates among the centers, considering the relatively small samples sizes within centers. Clearance rates by center are presented in Table 17. There does appear to be some variation among the centers with regards to baseline severity, as some centers had most of their subjects meet the MBLC (e.g. 18/22 in Center 04412) while another center had no subjects meeting the MBLC (0/18 in Center 52676). Centers enrolled exclusively either pediatric or adult patients, with the exception of Center 54097 in Study 4 which enrolled both pediatric and adult patients.

Table 17 – Clearance Rates by Center

Study 3		ITT		MBLC	
Center	**Type**	**Fluticasone**	**Vehicle**	**Fluticasone**	**Vehicle**
00363	Adult	1/6 (17%)	0/7 (0%)	0/3 (0%)	0/4 (0%)
03806	Ped.	11/21 (52%)	3/20 (15%)	1/5 (20%)	0/11 (0%)
04739	Adult	8/22 (36%)	4/22 (18%)	1/7 (14%)	0/9 (0%)
05817	Adult	1/11 (9%)	1/12 (8%)	0/3 (0%)	--
08046	Ped.	4/10 (40%)	1/10 (10%)	3/8 (38%)	0/2 (0%)
08693	Ped.	0/1 (0%)	0/1 (0%)	0/1 (0%)	--
42612	Ped.	2/9 (22%)	0/9 (0%)	1/4 (25%)	0/4 (0%)
52005	Ped.	4/11 (36%)	0/12 (0%)	1/3 (33%)	0/1 (0%)
54096	Adult	1/13 (8%)	0/14 (0%)	1/6 (17%)	0/4 (0%)
54149	Ped.	1/4 (25%)	0/2 (0%)	0/3 (0%)	0/2 (0%)
54923	Ped.	1/2 (50%)	0/1 (0%)	1/2 (50%)	--

Study 4		ITT		MBLC	
Center	**Type**	**Fluticasone**	**Vehicle**	**Fluticasone**	**Vehicle**
04412	Adult	1/11 (9%)	0/11 (0%)	1/8 (13%)	0/10 (0%)
04551	Ped.	0/1 (0%)	--	0/1 (0%)	--
43091	Ped.	7/12 (58%)	0/12 (0%)	0/2 (0%)	0/5 (0%)
44452	Adult	2/9 (22%)	0/8 (0%)	0/1 (0%)	--
52676	Adult	3/10 (30%)	0/8 (0%)	--	--
52970	Ped.	3/22 (14%)	3/22 (14%)	1/9 (11%)	0/7 (0%)
54097	Both	8/20 (40%)	0/19 (0%)	5/13 (38%)	0/11 (0%)
54275	Ped.	4/14 (29%)	1/14 (7%)	0/8 (0%)	1/6 (17%)
54808	Ped.	4/12 (33%)	3/13 (23%)	0/2 (0%)	0/4 (0%)

Source: Reviewer analysis.

Per the clinical reviewer, the submission is not clear on the size of payments made to Center 52970 [redacted] in Study 4. The clinical reviewer requested a sensitivity analysis excluding subjects from Center 52970. Table 18 presents the results of the analysis of the clearance rate in the MBLC population with and without the subjects from Center 52970. The results from Center 52970 are very similar to the results from the remaining centers with 11% of fluticasone and 0% of vehicle subjects achieving clearance at Center 52970 versus 17% of fluticasone and 3% of vehicle subject achieving clearance at the other centers. Center 52970 enrolled about 18% of the subjects in the MBLC population.

Table 18 – Sensitivity Analysis of the Clearance Rate Excluding Center 52970 [redacted] Study 4) (MBLC)

	Fluticasone	**Vehicle**
All centers except 52970	6/35 (17%)	1/36 (3%)
Center 52970	1/9 (11%)	0/7 (0%)
Total	7/44 (16%)	1/43 (2%)

Source: Reviewer analysis.

3.2 *Evaluation of Safety*

3.2.1 Extent of Exposure

Because of the higher percentage of vehicle subjects who dropped out, the percentage of fluticasone subjects who treated for 4 weeks was higher than for vehicle subjects, although the majority of vehicle subject also treated for about 4 weeks. The median number of days treated was 28 days for both arms in both studies. The numbers of subjects with various treatment durations, divided roughly into weeks, are presented in Table 19 and Table 20 for the ITT and MBLC populations.

Table 19 – Treatment Duration (ITT)

	Study 3		Study 4	
	Flutic. N=110	Vehicle N=110	Flutic. N=111	Vehicle N=107
< 12 days	2 (2%)	12 (11%)	3 (3%)	18 (17%)
12 – 18 days	12 (11%)	15 (14%)	10 (9%)	11 (10%)
19 – 25 days	6 (5%)	6 (5%)	2 (2%)	3 (3%)
26 – 32 days	79 (72%)	72 (65%)	91 (82%)	68 (64%)
> 32 days	9 (8%)	4 (4%)	3 (3%)	5 (5%)

Source: Table 12, Vol. 16, pg. 96, and Vol. 20, pg. 99.

Table 20 – Treatment Duration (MBLC)

	Study 3		Study 4	
	Flutic. N=45	Vehicle N=36	Flutic. N=43	Vehicle N=43
< 12 days	2 (4%)	3 (8%)	2 (5%)	14 (33%)
12 – 18 days	5 (11%)	8 (22%)	3 (7%)	7 (16%)
19 – 25 days	3 (7%)	3 (8%)	1 (2%)	2 (5%)
26 – 32 days	29 (64%)	22 (28%)	36 (84%)	20 (47%)
> 32 days	6 (13%)	0 (0%)	1 (2%)	0 (0%)

Source: Reviewer analysis.

3.2.2 Adverse Events

About 30-40% of subjects experienced adverse events during the trial and the adverse events were fairly equally distributed between the fluticasone and vehicle arms. The most common adverse events were the common cold, upper respiratory infections, and fever. The adverse events occurring in at least 3% of subjects are presented in Table 21. A small percentage of subjects experienced treatment related adverse events on their skin and appendages. Treatment related adverse events are presented in Table 22. Burning and stinging of skin was the most commonly reported treatment related adverse event, affecting 4 fluticasone and 3 vehicle subjects.

Table 21 – Number of Subjects with Adverse Events (>3% in any arm)

	Study 3		Study 4	
	Fluticasone N=110	Vehicle N=110	Fluticasone N=111	Vehicle N=107
All Adverse Events	44 (40%)	41 (37%)	33 (30%)	41 (38%)
Burning and stinging of skin	3 (3%)	1 (<1%)	1 (<1%)	2 (2%)
Pruritus	1 (<1%)	1 (<1%)	2 (2%)	4 (4%)
Skin infection	0 (0%)	3 (3%)	0 (0%)	0 (0%)
Common cold	6 (5%)	5 (5%)	3 (3%)	0 (0%)
Ear infection	1 (<1%)	3 (3%)	2 (2%)	0 (0%)
Nasal sinus infection	2 (2%)	1 (<1%)	0 (0%)	3 (3%)
Rhinitis	1 (<1%)	3 (3%)	0 (0%)	0 (0%)
Upper resp. tract infection	4 (4%)	4 (4%)	2 (2%)	3 (3%)
Normal tooth eruption	2 (2%)	3 (3%)	0 (0%)	0 (0%)
Vomiting	0 (0%)	2 (2%)	3 (3%)	0 (0%)
Cough	4 (4%)	2 (2%)	3 (3%)	4 (4%)
Influenza	5 (5%)	0 (0%)	0 (0%)	1 (<1%)
Headache	3 (3%)	3 (3%)	1 (<1%)	2 (2%)
Fever	7 (6%)	3 (3%)	1 (<1%)	5 (5%)
Seasonal allergy	0 (0%)	0 (0%)	2 (2%)	3 (3%)

Source: Table 19, Vol. 16, pg. 105-107, and Vol. 20, pg. 104-105.

Table 22 – Number of Subjects with Drug-Related Adverse Events

	Study 3		Study 4	
	Fluticasone N=110	Vehicle N=110	Fluticasone N=111	Vehicle N=107
Burning and stinging of skin	3 (3%)	1 (<1%)	1 (<1%)	2 (2%)
Exacerbation of atopic derm.	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Contact dermatitis	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Irritant contact dermatitis	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Pruritus	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Pustule(s) on arm(s)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Rash	1 (<1%)	2 (2%)	0 (0%)	0 (0%)
Folliculitis of leg(s)	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Skin infection	0 (0%)	3 (3%)	0 (0%)	0 (0%)

Source: Table 20, Vol. 16, pg. 108, and Vol. 20, pg. 106.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

The clearance rate for fluticasone was higher than for vehicle in all demographic subgroups. The treatment effect appears to be fairly consistent across subgroups. Clearance rates by subgroup are presented in Table 23 for Study 3 and in Table 24 for Study 4.

Table 23 – Clearance Rate by Subgroup (Study 3)

Study 3		ITT		MBLC	
		Fluticasone	Vehicle	Fluticasone	Vehicle
Gender	Male	18/54 (33%)	2/49 (4%)	2/20 (10%)	0/12 (0%)
	Female	16/56 (29%)	7/61 (11%)	7/25 (28%)	0/25 (0%)
Race	Caucasian	24/78 (31%)	5/80 (6%)	7/32 (22%)	0/28 (0%)
	Black	5/19 (26%)	3/19 (16%)	1/7 (14%)	0/6 (0%)
	Other	5/13 (38%)	1/11 (9%)	1/6 (17%)	0/3 (0%)
Age	3 mos. – 2 yrs	12/33 (36%)	3/33 (9%)	2/15 (13%)	0/14 (0%)
	3 – 5 yrs	7/14 (50%)	0/11 (0%)	4/8 (50%)	0/4 (0%)
	6 – 16 yrs	4/11 (36%)	1/11 (9%)	1/3 (33%)	0/2 (0%)
	17 – 64 yrs	9/50 (18%)	5/53 (9%)	2/19 (11%)	0/15 (0%)
	65+ years	2/2 (100%)	0/2 (0%)	0/0	0/2 (0%)

Source: Reviewer analysis.

Table 24 – Clearance Rate by Subgroup (Study 4)

Study 4		ITT		MBLC	
		Fluticasone	Vehicle	Fluticasone	Vehicle
Gender	Male	14/50 (28%)	3/55 (5%)	2/18 (11%)	0/24 (0%)
	Female	18/61 (30%)	4/52 (8%)	5/26 (19%)	1/19 (5%)
Race	Caucasian	25/86 (29%)	5/85 (6%)	5/31 (16%)	1/34 (3%)
	Black	4/9 (44%)	0/13 (0%)	1/4 (25%)	0/5 (0%)
	Other	3/16 (19%)	2/9 (22%)	1/9 (11%)	0/4 (0%)
Age	3 mos. – 2 yrs	8/27 (30%)	1/22 (5%)	1/14 (7%)	0/10 (0%)
	3 – 5 yrs	7/28 (25%)	4/28 (14%)	1/8 (13%)	1/10 (10%)
	6-16 yrs	5/10 (50%)	2/14 (14%)	1/3 (33%)	0/4 (0%)
	17-64 yrs	10/40 (25%)	0/36 (0%)	4/16 (25%)	0/15 (0%)
	65+ years	2/6 (33%)	0/7 (0%)	0/3 (0%)	0/4 (0%)

Source: Reviewer analysis.

4.2 Other Special/Subgroup Populations

Not Applicable.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

It is difficult to interpret the results of Studies 3 and 4 as they were not designed to assess atopic dermatitis in the way that the Division finds the most clinically useful, nor did the studies enroll subjects with the severity of disease that the Division believes is most relevant. The studies enrolled subjects based on their scores for extent of disease (body surface area), course (months of remission per year), and intensity of itching. Subjects were not required to have any particular level of erythema, infiltration/papulation, or erosion/oozing/crusting at baseline. For the population enrolled and the protocol specified endpoint, the studies met the statistical objectives for which they were designed. That is, a statistically significantly higher proportion of subjects using fluticasone lotion than vehicle lotion had at least a 75% reduction in EASI score from baseline to Week 4.

However, of key interest is whether the studies can provide adequate evidence of a treatment effect with regards the subpopulation and endpoints of interest to the Division. The Division needs to be convinced that the effect seen in Studies 3 and 4 corresponds to a clinical outcome of interest in an appropriate population.

As was discussed in the End of Phase 2 meeting, the Division recommends assessing efficacy with a global evaluation incorporating erythema, infiltration/papulation, and erosion/oozing/crusting. Subjects should have moderate to severe disease at baseline and be clear or almost clear at the end of the study to be counted as a success. The studies did not incorporate a global evaluation based on the three key signs of atopic dermatitis, but the studies did assess the three signs individually in four separate body regions (head/neck, trunk, upper limbs, and lower limbs). These 12 individual assessments provide the available information on disease severity which most closely corresponds to the information that would have been obtained from a static global assessment, and are thus the focus of most of the reviewer analyses. The reviewer analyses focused on a subset of enrolled patients who may be considered to have at least moderate disease in terms of the three key signs and counted as successes those subjects who achieved complete clearance of the three signs.

The analysis of the subjects who met the minimum baseline criteria (MBLC) and cleared of erythema, infiltration/papulation, and erosion/oozing/crusting is presented in Table 25. The two studies have comparable treatment effects for this analysis. Interpreting the p-values from this analysis is difficult since both the endpoint and the subset of subjects included in the analysis were defined post hoc. The p-values may be useful for indicating that the treatment effect is reasonably large relative to the remaining sample size and variability, however, it is not possible to say that these p-values alone provide adequate statistical significance of a treatment effect. These results can only be interpreted within the full context of the available data.

Table 25 – 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.

Studies 3 and 4 were not designed to directly answer the clinical questions of interest to the Division regarding efficacy for atopic dermatitis. The sponsor was advised of the Division's recommendations regarding study design at an End of Phase 2 meeting held in May 1998. The following features of Studies 3 and 4 make it challenging to assess the efficacy of fluticasone in the treatment of atopic dermatitis.

1. The inclusion criteria did not address the baseline severity of the key signs of atopic dermatitis. Many subjects had minimal signs of acute atopic dermatitis (erythema, infiltration/papulation, and erosion/oozing/crusting) at baseline.

2. The piecemeal nature of the assessments for the EASI score makes it difficult to reconstruct a global picture of a subject's severity at any point in the trial.
3. Any attempt to match the available data from the trial to the Division's recommendations for assessing efficacy is necessarily post hoc, making it difficult to assess statistical significance.

However, even with all of the disagreements between the sponsor and the Agency regarding study design, in the full body of evidence, the following features of Studies 3 and 4 help support the claim that fluticasone is effective in the treatment of atopic dermatitis

1. The clearance rate analysis based on the minimum baseline criteria (MBLC) subpopulation indicates that there is still evidence of a treatment effect in this subpopulation, even with the reduced sample size. The minimum baseline criteria were selected by a medical officer not directly involved with the review to minimize potential bias.
2. The difference in clearance rate between fluticasone and vehicle does not appear to be greatly affected by the baseline severity (refer to Table 15 on page 17 which divides subjects into quartiles based on their baseline sum score). The difference between subjects appears to decrease slightly as the baseline sum score increases, however it stays at generally the same magnitude. The key feature is that as the baseline sum score increases, the number of subjects with that score or higher quickly decreases. Once a subset of subjects is selected based on baseline severity, the primary issue is whether the selected subset of subjects has enough members remaining to draw any valid conclusions.
3. The two studies provide very similar results and are consistent with each other.
4. For the endpoint (EASI) and subject population defined in the protocols, the studies demonstrate a statistically significant treatment effect in favor of fluticasone.

5.2 Conclusions and Recommendations

Since Studies 3 and 4 were not designed according to the Division's recommendations for assessing efficacy in treating atopic dermatitis, the Agency must determine whether the key clinical information can be gleaned from the available data. Many subjects in these studies were enrolled with very minimal acute signs of atopic dermatitis. Less than 40% of enrolled subjects met the minimum baseline criteria selected by the reviewers as a clinically relevant definition of acute moderate to severe atopic dermatitis. Analyses by the reviewers of the proportion of subjects who achieve clearance of erythema, infiltration/papulation, and erosion/oozing/crusting in the MBLC population indicate that the data do provide evidence that fluticasone is efficacious in the treatment of atopic dermatitis. However, it is very difficult to draw conclusions from studies where the endpoints of clinical interest were not directly examined in the studies, as we lose the benefits of pre-specified analyses.

Appendix

Table 26 – Rajka/Langeland Severity Grading Scale

Extent of Disease **Infants:** Under 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** 1 = less than 9% of the body area involved 2 = More than 9% and less than 36% of the body are involved 3 = More than 36% of the body are involved
Course 1 = More than 3 months of remission during a year 2 = Less than 3 months remission during a year 3 = Continuous course
Intensity 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
Total (Extent + Course + Intensity)

Source: Vol. 18, pg. 30

Table 27 – Component Variables for FDA Pre-NDA Success (ITT, MBLC)

	Fluticasone			Vehicle		
	≥50% Improv.	No Scores Worsening	Treatment Success[a]	≥50% Improv.	No Scores Worsening	Treatment Success[a]
Study 3						
ITT	83/110 (75%)	92/110 (86%)	80/110 (73%)	35/110 (32%)	49/110 (45%)	29/110 (26%)
MBLC	31/45 (69%)	38/45 (84%)	31/45 (69%)	9/37 (24%)	15/37 (41%)	7/37 (19%)
Study 4						
ITT	73/111 (66%)	66/111 (59%)	59/111 (53%)	29/107 (27%)	45/107 (42%)	23/107 (22%)
MBLC	29/44 (65%)	26/44 (59%)	23/44 (52%)	9/43 (21%)	15/43 (35%)	9/43 (21%)

[a] Treatment success defined as at least 50% improvement on the IGA + improvement or no change on all scores for erythema, scaling, erosion/oozing/crusting, infiltration/papulation, and pruritus.
Source: Reviewer analysis.

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Kathleen Fritsch
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Mohamed Alosh
12/1/04 01:40:53 PM
BIOMETRICS
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