

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-758**

**STATISTICAL REVIEW(S)**



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

### CLINICAL STUDIES

**NDA/Serial Number:** 21-758 / N-000

**Drug Name:** ™ (flucicort) cream, 0.1%

**Indication(s):** Treatment of Corticosteroid responsive dermatoses

**Applicant:** Medicis

**Date(s):** Submitted: April 7, 2004  
Received: April 12, 2004  
Draft Review Completed: November 1, 2004  
Final Review Completed: January 4, 2005

**Review Priority:** Standard Review

**Biometrics Division:** Division of Biometrics III (HFD-725)

**Statistical Reviewer:** Fraser Smith, Ph.D., Mathematical Statistician

**Concurring Reviewers:** Mohamed Alish, Ph.D., Statistics Team Leader

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

**Clinical Team:** Brenda Vaughan, M.D.: Medical Reviewer  
Markham Luke, M.D., Ph.D.: Medical Team Leader

**Project Manager:** Melinda Harris: Regulatory Project Manager

## TABLE OF CONTENTS

	Page
<b>List of Tables .....</b>	<b>3</b>
<b>1. EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1 Conclusions and Recommendations .....	5
1.2 Brief Overview of Clinical Studies .....	5
1.3 Statistical Issues and Findings .....	6
<b>2. Introduction .....</b>	<b>11</b>
2.1 Overview .....	11
2.2 Data Sources .....	12
<b>3. Statistical Evaluation .....</b>	<b>12</b>
3.1 Evaluation of Efficacy .....	12
3.1.1 Methods for Statistical Analysis of Efficacy Data .....	12
3.1.2 Study Design .....	13
3.1.3 Subject Disposition .....	14
3.1.4 Demographics .....	15
3.1.5 Primary Efficacy Analysis .....	18
3.1.5.1 Robustness of Primary Analysis .....	18
3.1.6 Secondary Efficacy Analyses for Study MP-0201-05 .....	19
3.1.7 Secondary Efficacy Analyses for Study MP-0201-06 .....	25
3.2 Evaluation of Safety .....	31
3.2.1 Medication Compliance and Exposure .....	31
3.2.2 Adverse Events .....	33
3.2.2.1 Adverse Events in Study MP-0201-05 .....	33
3.2.2.2 Adverse Events in Study MP-0201-06 .....	35
<b>4. Findings in Special/Subgroup Populations .....</b>	<b>41</b>
4.1 Gender, Age, and Race .....	41
4.2 Other Special/Subgroup Populations .....	44

<b>5. Summary and Conclusions</b> .....	<b>49</b>
5.1 Statistical Issues and Collective Evidence .....	49
5.2 Conclusions and Recommendations .....	51

## LIST OF TABLES

	Page
Table 1 Primary Efficacy Endpoint – Computation of Treatment Success based on dichotomized PGA scores for overall lesion severity at the end of Week 2 .....	7
Table 2 Overall Symptom Severity Scores .....	8
Table 3 Subject Disposition: Study MP-0201-05 .....	14
Table 4 Subject Disposition: Study MP-0201-06 .....	15
Table 5 Demographic summary at Baseline by treatment group: Study MP-0201-05 .....	16
Table 6 Demographic summary at Baseline by treatment group: Study MP-0201-06 .....	17
Table 7 Primary Efficacy Endpoint – Computation of Treatment Success based on dichotomized PGA scores for overall lesion severity at the end of Week 2 .....	18
Table 8 PGA scores for Overall Lesion Severity: Study MP-0201-05 .....	19
Table 9 Overall Symptom Severity Scores: Study MP-0201-05 .....	21
Table 10 PGA scores for Overall lesion severity: Study MP-0201-06 .....	25
Table 11 Overall Symptom Severity scores: Study MP-0201-06 .....	27
Table 12 Medication Compliance and Exposure: Study MP-0201-05 .....	31
Table 13 Medication Compliance and Exposure: Study MP-0201-06 .....	32
Table 14 Number (%) of subjects with AEs overall and by body system: Study MP-0201-05 .....	33
Table 15 Summary of Treatment Emergent Adverse Events by Severity: Study MP-0201-05 .....	34
Table 16 Number (%) of subjects with AEs overall and by body system: Study MP-0201-06 .....	35
Table 17 Summary Of Treatment Emergent Adverse Events, By Severity: Study MP-0201-06 .....	36
Table 18 Summary of HPA axis suppression: Study MP-0201-06 .....	37
Table 19 Mean increase in serum cortisol levels after cosyntropin stimulation: Study MP-0201-06 .....	38
Table 20 Subjects with HPA axis suppression by criterion of HPA axis suppression at baseline and end of Week 2: Study MP-0201-06 .....	38
Table 21 Mean % BSA and Mean Grams Used by Treatment Group and HPA axis suppression using the FDA criterion of post-stimulation cortisol levels $\leq 18$ $\mu\text{g/dL}$ .....	39
Table 22 Pearson Correlations (r) between HPA axis suppression and % BSA and Mean Grams Used	

· using the FDA criterion of post-stimulation cortisol levels $\leq 18 \mu\text{g/dL}$ .....	40
Table 23 Summary of HPA axis suppression at Week 2 (end of treatment) using the FDA Definition: Studies MP-0201-01 and MP-0201-06 .....	40
Table 24 Treatment success rates by gender, age and race .....	41
Table 25 Summary of Primary Endpoint by Subgroup Statistical Test Results: Study MP-0201-05 .....	42
Table 26 Summary of Primary Endpoint by Subgroup Statistical Test Results: Study MP-0201-06 .....	43
Table 27 Primary efficacy endpoint – Comparison of treatment success based on dichotomized PGA scores for overall lesion severity at end of Week 2 .....	44
Table 28 Treatment success rates by site: Study MP-0201-05 .....	45
Table 29 Treatment Success Rates by Site: Study MP-0201-06 .....	46
Table 30 Site numbers for common investigators .....	48
Table 31 Study MP-0201-05 Summary of Primary Endpoint Statistical Test Results, Stratified by Center .....	48

Appears This Way  
On Original

## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

In the psoriasis patients in study MP-0201-05, 31% of the twice-daily fluocinonide treatment group and 18% of the once-daily fluocinonide treatment group were treatment successes at Week 2 compared to only 6-7% of the vehicle controls. [REDACTED] (fluocinonide) 0.1% cream was shown to be statistically superior to vehicle in the treatment of psoriasis when used once- or twice-daily for two weeks. Twice-daily fluocinonide treatment was also shown to be superior to once-daily fluocinonide treatment in this patient population.

In contrast to psoriasis, there were no differences between once-daily and twice-daily fluocinonide treatment in patients with atopic dermatitis. Almost 60% of the once-daily and twice-daily fluocinonide patients were treatment successes at Week 2 compared to only 12% of the once-daily and 19% of the twice-daily vehicle controls. Fluocinonide was shown to be statistically superior to vehicle in the treatment of atopic dermatitis in adults when used once or twice-daily for two weeks.

[REDACTED]

Similar trends were observed in the per protocol populations for the treatment of psoriasis and atopic dermatitis.

Hypothalamus-pituitary-adrenal (HPA) axis suppression data were collected for only 16% (51/314) of the patients enrolled in study MP-0201-06. Even using HPA axis suppression data from an additional 37 patients in study MP-0201-01, there was insufficient power to rule out the possibility that fluocinonide may put patients at increased risk for HPA axis suppression.

### 1.2 Brief Overview of Clinical Studies

The applicant conducted two pivotal Phase III double-blind multicenter vehicle-controlled studies of the efficacy and safety of fluocinonide 0.1% cream for the purpose of obtaining a claim for the treatment of corticosteroid-responsive dermatoses; one study was in adult patients with psoriasis (MP-0201-05) and the second study was in adult patients with atopic dermatitis (MP-0201-06). Fluocinonide 0.1% cream was applied topically once-daily (qd) or twice-daily (bid) for 2 weeks.

The primary objective of the two pivotal studies was to compare the efficacy of twice-daily fluocinonide 0.1% cream to twice-daily vehicle control based on the dichotomized physician's static

global assessment (PGA) of overall lesion severity at the end of treatment (Week 2) where a 'treatment success' at Week 2 was defined as a subject who had a PGA score of 0 (cleared) or 1 (almost cleared). If the results of this comparison were statistically significant, once-daily fluocinonide 0.1% cream was compared to a once-daily vehicle control. If this comparison was statistically significant, then the twice-daily and once-daily regimens of fluocinonide were compared.

The primary population for analyses of clinical efficacy was the Intent-to-Treat (ITT) population of all treated subjects, including those subjects for whom only incomplete data were available.

Subjects in MP-0201-05 and MP-0201-06 were centrally randomized so there would be a planned enrollment of 100 in each of the 2 active treatment groups and 50 in each of the 2 vehicle treatment groups in each study.

In each study, a pre-determined computer-generated randomization schedule assigned each contiguous block of 6 subjects to the 4 treatment groups in random order, in the ratio of 2:2:1:1. Study products were issued to the investigational sites in blocks of 6, in order to balance treatment assignment within sites. All sites were encouraged to complete at least 18 subjects in study MP-0201-05 and 12 subjects in study MP-0201-06.

## **OTHER SUPPORTIVE STUDIES**

MP-0201-01 was a Phase II randomized, parallel, open-label adrenal suppression study of fluocinonide 0.1% cream and fluocinonide 0.05% cream (Lidex<sup>®</sup>) in subjects with plaque-type psoriasis. There were 37 subjects enrolled at 5 study centers in the USA; 19 in the fluocinonide 0.05% treatment group and 18 in the fluocinonide 0.1% treatment group. The subjects were 18 years of age or older with clinically diagnosed plaque-type psoriasis involving  $\geq 10\%$  of their total body surface area (BSA) who were supposed to have normal HPA axis function at the time of enrollment.

## **1.3 Statistical Issues and Findings**

### **Primary Efficacy Results**

The actual enrollment in study MP-0201-05 was 323 subjects at 15 study centers in the United States: 107 in the fluocinonide qd group, 107 in the fluocinonide bid group, 54 in the vehicle once-daily group, and 55 in the vehicle twice-daily group.

The actual enrollment in study MP-0201-06 was 313 subjects at 24 study centers in the United States: 109 in the qd fluocinonide group, 102 in the bid fluocinonide group, 50 in the qd vehicle group, and 52 in the bid vehicle group.

**Table 1 Primary Efficacy Endpoint – Computation of Treatment Success based on dichotomized PGA scores for overall lesion severity at the end of Week 2**

Indication / Population	Once-Daily Regimen			Twice-Daily Regimen			Fluocinonide qd vs bid p-value <sup>1</sup>
	Fluocinonide 0.1%	Vehicle	p-value <sup>1</sup>	Fluocinonide 0.1%	Vehicle	p-value <sup>1</sup>	
<b>Psoriasis</b>							
ITT	19/107 (18%)	4/54 (7%)	0.043	33/107 (31%)	3/55 (6%)	<0.001	0.025
Per Protocol	18/90 (20%)	4/43 (9%)	0.071	31/97 (32%)	3 / 47 (6%)	<0.001	0.060
<b>Atopic Dermatitis</b>							
ITT	64/109 (59%)	6/50 (12%)	<0.001	58/102 (57%)	10/52 (19%)	<0.001	0.837
Per Protocol	54/87 (62%)	6/36 (17%)	<0.001	52/88 (59%)	5/41 (12%)	<0.001	0.884

Source: Table 9.1 in the Clinical Study Report, Volume 7, Item 8, pages 55 and 1947

Note: All percentages are rounded. Treatment success was defined as a PGA score of 0 (cleared) or 1 (almost cleared).

<sup>1</sup>p-values using pairwise Mantel-Haenszel statistics, stratified on investigational site

Using the dichotomized PGA of overall lesion severity at the end of treatment (Week 2), studies MP-0201-05 and MP-0201-06 demonstrated a statistically significant effect of fluocinonide in the treatment of psoriasis and atopic dermatitis in adults when applied twice-daily or once-daily for two weeks.

Compared to the twice-daily regimen, fluocinonide was significantly less effective when used once-daily for two weeks for the treatment of psoriasis; 31% of the patients who applied fluocinonide twice-daily had a treatment success compared to only 18% of the patients who applied it once-daily.

In contrast to psoriasis, there were no differences between once-daily and twice-daily fluocinonide treatment in patients with atopic dermatitis. Almost 60% of the once-daily and twice-daily fluocinonide patients were treatment successes at Week 2 compared to only 12% of the once-daily and 19% of the twice-daily vehicle controls.

Similar trends were observed in the per protocol populations for the treatment of psoriasis and atopic dermatitis. Due to the smaller sample sizes, some of the p-values for the per protocol population were not statistically significant but were still close to being statistical significant.

## Secondary Efficacy Results

Secondary efficacy parameters included Physician's Global Assessment (PGA) of Overall Lesion Severity, Symptom Severity Ratings (including Induration, Erythema, Scaling and Total IES Score for Psoriasis and Erythema, Induration/Papulation, Excoriations, Lichenification and Total Score for Atopic Dermatitis), Pruritus Ratings and Percent Body Surface Area (BSA).

**Table 2 Overall Symptom Severity Scores  
 (Mean  $\pm$ SD, ITT Population)**

	<b>Fluocicor 0.1%, qd N = 107</b>	<b>Vehicle Qd N = 54</b>	<b>Fluocicor 0.1%, bid N = 107</b>	<b>Vehicle bid N = 55</b>
<b>Psoriasis</b>				
<b>Total IES:</b>				
<b>Screen/Baseline</b>	9.43 $\pm$ 0.86	9.50 $\pm$ 0.88	9.51 $\pm$ 0.95	9.49 $\pm$ 0.88
<b>Week 1</b>	6.68 $\pm$ 2.36*	7.63 $\pm$ 1.99	5.66 $\pm$ 2.42*†	7.27 $\pm$ 2.41
<b>Week 2</b>	5.49 $\pm$ 2.49*	6.63 $\pm$ 2.33	4.47 $\pm$ 2.62*†	6.35 $\pm$ 2.72
<b>Week 4</b>	6.36 $\pm$ 2.79	6.88 $\pm$ 2.55	4.86 $\pm$ 2.59*†	7.08 $\pm$ 2.57
<b>Atopic Dermatitis</b>				
<b>Total Score:</b>				
<b>Screen/Baseline</b>	8.06 $\pm$ 1.20	8.16 $\pm$ 1.31	7.97 $\pm$ 1.29	8.08 $\pm$ 1.47
<b>Week 1</b>	4.97 $\pm$ 2.30*	6.60 $\pm$ 2.10	4.23 $\pm$ 2.22*†	6.12 $\pm$ 2.35
<b>Week 2</b>	3.36 $\pm$ 2.37*	5.98 $\pm$ 2.61	2.99 $\pm$ 2.21*	5.60 $\pm$ 2.39
<b>Week 4</b>	4.65 $\pm$ 3.13	5.07 $\pm$ 2.70	3.32 $\pm$ 2.62*†	5.17 $\pm$ 2.89

Source: Table 9.3 in the Clinical Study Report, Volume 7, Item 8, pages 58, 1950

\*p < 0.05 fluocicor vs. corresponding vehicle

†p < 0.05 fluocicor qd vs. bid

‡p < 0.05 vehicle qd vs. bid

In psoriasis and atopic dermatitis patients, total scores were significantly lower in twice-daily and once-daily fluocicor treatment groups at Weeks 1 and 2 than their corresponding vehicle controls. Total scores were also significantly lower in twice-daily fluocicor patients than their corresponding vehicle controls at Week 4. In addition, total scores were significantly lower in twice-daily fluocicor patients than in once-daily fluocicor patients.

Similar trends were apparent for many of the other secondary efficacy parameters (with the possible exception of percent body surface area in study MP-0201-05 where there were no statistically significant fluocicor treatment effects at any week). In most cases the maximum treatment effect was observed at Week 2 in both studies and the magnitude of the treatment effect of the twice-daily dose of fluocicor was larger than that of the once-daily regimen.

## Safety Results

### Most Common Adverse Events in Psoriasis Patients

For the psoriasis indication, the incidence of overall adverse event rates ranged from 11% in the once-daily fluocinonide treatment group to 19% in the once-daily vehicle controls.

Nervous system disorders were the most prevalent adverse event in fluocinonide patients, reported in 4% of the fluocinonide patients and 2% of the vehicle controls.

Skin and subcutaneous tissue disorders had the highest incidence rates in the vehicle controls. These adverse events were reported in 9% of the vehicle controls and only 1% of the fluocinonide patients.

Other adverse events that occurred in a small number of fluocinonide and vehicle control patients ( $\geq 2$  subjects in a group) included gastrointestinal disorders, general disorders and administration site conditions, and respiratory, thoracic and mediastinal disorders. Musculoskeletal and connective disorders and eye disorders occurred in 1% of the fluocinonide patients and none of the vehicle controls.

### Most Common Adverse Events in Patients with Atopic Dermatitis

The percentage of subjects with adverse events ranged from 25% in the once-daily fluocinonide treatment group to 34% in the once-daily vehicle controls.

Respiratory, thoracic and mediastinal disorders were the most frequently reported adverse event in fluocinonide patients, occurring in 7% of the fluocinonide patients and 8% of the vehicle controls.

Skin and subcutaneous tissue disorders were the most prevalent adverse event in the vehicle controls, reported in 16% of the vehicle controls and only 5% of the fluocinonide patients.

Other adverse events that occurred in fluocinonide and vehicle control patients ( $\geq 2$  subjects in a group) included nervous system disorders, musculoskeletal and connective disorders, general disorders and administration site conditions, gastrointestinal disorders, blood and lymphatic system disorders and infections and infestations.

### Severe Adverse Events (SAEs) in Psoriasis Patients

In study MP-0201-05 SAEs were only reported in <1% of the fluocinonide patients and 5% of the vehicle controls in patients. No deaths were reported in the study.

#### Severe Adverse Events (SAEs) in Patients with Atopic Dermatitis

In study MP-0201-06, SAEs were only reported in the once-daily regimen; 2% of the fluocinonide patients and 4% of the vehicle controls reported having a severe adverse event. No deaths were reported in the study.

#### HPA axis suppression in Patients with Atopic Dermatitis

In study MP-0201-06 the number of subjects with suppressed (abnormal) HPA axis at Week 2 (end of treatment) appeared to be almost the same as the number of subjects with suppressed HPA axis at screening in each treatment group. Approximately 30% of the fluocinonide patients and 15% of the vehicle controls had HPA axis suppressions at screening and Week 2 (end of treatment). Using the FDA definition of post-stimulatin cortisol levels  $\leq 18$   $\mu\text{g/dL}$  only 1 patient had HPA axis suppression at screening and Week 2. These were different patients, but both patients were in the fluocinonide 0.1%, qd treatment group.

HPA axis suppression data were collected for only 16% (51/314) of the patients enrolled in study MP-0201-06. The sample size was too small to make any definitive conclusions about whether patients who use fluocinonide are at increased risk for HPA Axis suppression. Even for the comparison between the 18 vehicle controls in study MP-0201-06 and the 70 fluocinonide patients in studies MP-0201-01 and MP-0201-06, the power to detect a statistically significant difference at the two-sided 0.05 level was only 1% assuming a true incidence of 0.1% in the vehicle controls and 5% in the fluocinonide treatment group.

**Appears This Way  
On Original**

## 2. INTRODUCTION

### 2.1 Overview

#### Study Objectives and Design

MP-0201-05 was a phase III, randomized, double-blind, controlled, multicenter vehicle-controlled study of the efficacy and safety of fluocinonide 0.1% Cream in the Treatment of Plaque-Type Psoriasis when applied topically once-daily (qd) or twice-daily (bid) for 2 weeks.

MP-0201-06 was a phase III, randomized, double-blind, controlled, multicenter vehicle-controlled study of the efficacy and safety of fluocinonide 0.1% Cream in the Treatment of Atopic Dermatitis when applied topically once-daily (qd) or twice-daily (bid) for 2 weeks.

Subjects in MP-0201-05 and MP-0201-06 were centrally randomized so there would be a planned enrollment of 100 in each of the 2 active treatment groups and 50 in each of the 2 vehicle treatment groups in each study.

In each study, a pre-determined computer-generated randomization schedule assigned each contiguous block of 6 subjects to the 4 treatment groups in random order, in the ratio of 2:2:1:1. Study products were issued to the investigational sites in blocks of 6, in order to balance treatment assignment within sites. All sites were encouraged to complete at least 18 subjects in study MP-0201-05 and 12 subjects in study MP-0201-06.

#### OTHER SUPPORTIVE STUDIES

MP-0201-01 was a Phase II randomized, parallel, open-label adrenal suppression study of fluocinonide 0.1% cream and fluocinonide 0.05% cream (Lidex<sup>®</sup>) in subjects with plaque-type psoriasis. There were 37 subjects enrolled at 5 study centers in the USA; 19 in the fluocinonide 0.05% treatment group and 18 in the fluocinonide 0.1% treatment group. The subjects were 18 years of age or older with clinically diagnosed plaque-type psoriasis involving  $\geq 10\%$  of their total body surface area (BSA) who were supposed to have normal HPA axis function at the time of enrollment.

## 2.2 Data Sources

The datasets for this application are archived at

\\Cdsub1\n21758\N\_000\2004-04-07\CRT\DATASETS\MP0201-01

\\Cdsub1\n21758\N\_000\2004-04-07\CRT\DATASETS\MP0201-05

\\Cdsub1\n21758\N\_000\2004-04-07\CRT\DATASETS\MP0201-06 and

\\Cdsub1\n21758\N\_000\2004-07-21.

The primary datasets used in the efficacy review of study MP-0201-05 were ratings, xpop, and medstat while the primary datasets used in the review of MP-0201-06 were adrating, xpop and medstat. The primary datasets used to review HPA axis suppression in study MP-0201-01 were labdata, hpa, and product while the primary datasets used to review similar data from study MP-0201-06 were labdata, hpa and hpadose.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

The applicant evaluated two dosing regimens in Phase 3 trials, once-daily and twice-daily for 2 weeks. Each dosing regimen was evaluated in two Phase 3 trials; one for the indication of psoriasis and the other for atopic dermatitis. The applicant is pursuing labeling for corticosteroid responsive dermatoses which includes the 2 separate indications.

#### 3.1.1 Methods for Statistical Analysis of Efficacy Data

The primary efficacy measure in study MP-0201-05 was:

- The dichotomized physician's static global assessment (PGA) of overall lesion severity at the end of treatment (Week 2). A 'treatment success' at Week 2 was defined as a subject who had a PGA score of 0 (cleared) or 1 (almost cleared).

The primary efficacy measure in study MP-0201-06 was:

- The dichotomized physician's static global assessment (PGA) of overall disease severity at the end of treatment (Week 2). A 'treatment success' at Week 2 was defined as a subject who had a PGA score of 0 (clearing) or 1 (almost clearing) of the atopic dermatitis lesions.

The primary population for analyses of clinical efficacy was the Intent-to-Treat (ITT) population of all treated subjects, including those subjects for whom only incomplete data were available.

Additional analyses were performed in the Per Protocol (PP) population, excluding subjects who discontinued treatment prematurely, interrupted treatment, or were otherwise noncompliant to protocol requirements. A rationale for subject exclusion from the PP population for each excluded subject was assigned and documented prior to unblinding of the treatment codes.

The Safety Population included all patients exposed to at least one dose of study medication.

The sample sizes of 100 and 50 for active and vehicle had 80% power to detect a treatment difference in success rates of 25% assuming a 50% success for active treatment. The comparison between the active treatments with 100 patients per group had 80% power to detect a 20% difference between groups.

Secondary analyses for both studies compared mean PGA and symptom severity scores, mean pruritus ratings, and percent body surface area (BSA) affected at Weeks 1, 2 and 4.

### 3.1.2 Study Design

Studies MP-0201-05 and MP-0201-06 were randomized, double-blind, multi-center Phase 3 studies of the safety and efficacy of fluocinonide cream versus vehicle in the treatment of psoriasis (study MP-0201-05 ) and atopic dermatitis (study MP-0201-06). Subjects applied the study treatment either once-daily or twice-daily for two weeks.

Subjects in study MP-0101-05 had to be experiencing the clinical signs and symptoms of plaque-type psoriasis at the start of the study, with a minimum total symptom score of "9" (induration, erythema, scaling), a physician static global assessment of overall lesion severity of at least "3" (moderate), and involved BSA of at least 2% but no more than 10%.

Subjects in study MP-0101-06 had to be experiencing the clinical signs and symptoms of atopic dermatitis at the start of the study, with a minimum total symptom score of "7" (erythema, infiltration/population, excoriations, lichenification), at least mild Pruritus, a physician static global assessment of overall lesion severity of at least "3" (moderate), and involved BSA of at least 2% but

no more than 10%.

Subjects in both studies were required to make 4 visits to the study site (Screening/Baseline [Day 1], Week 1, Week 2 and Week 4). At Baseline, qualified subjects were randomized to 1 of 4 treatment groups, fluocinonide 0.1% cream *qd*, fluocinonide 0.1% cream *bid*, vehicle cream *qd*, or vehicle cream *bid*. Study medication was dispensed, and subjects self-administered the medication at home *qd* or *bid* as assigned for 14 days. Subjects returned to the study site at the end of Weeks 1, 2, and 4 for the investigator to perform the designated evaluations, review treatment compliance, and concomitant therapy, and to collect information regarding adverse events (AEs). Each subject participated for 4 weeks.

The main criteria for inclusion in either study were male or female subjects, 18 years of age or older, with clinically diagnosed psoriasis (study MP-0201-05) or atopic dermatitis (study MP-0201-06) involving at least 2% but no more than 10% of their total BSA.

### 3.1.3 Subject Disposition

**Table 3 Subject Disposition: Study MP-0201-05**

	Once-daily		Twice-daily	
	Fluocinonide N=107	Vehicle N=54	Fluocinonide N=107	Vehicle N=55
<b>Discontinued Study</b>	9 (8%)	6 (11%)	5 (5%)	3 (6%)
<b>Adverse Event</b>	1 (1%)	2 (4%)	0 (0%)	1 (2%)
<b>Subject's Request</b>	3 (3%)	1 (2%)	1 (1%)	2 (4%)
<b>Lost to Follow-Up</b>	5 (5%)	2 (4%)	3 (3%)	0 (0%)
<b>Other</b>	0 (0%)	1 (2%)	1 (1%)	0 (0%)

Source: Post-text Table 2 of the Clinical Study Report, Volume 7, Item 8, Page 78.

The actual enrollment in study MP-0201-05 was 323 subjects at 15 study centers in the United States: 107 in the fluocinonide *qd* group, 107 in the fluocinonide *bid* group, 54 in the vehicle once-daily group, and 55 in the vehicle twice-daily group.

Discontinuation rates ranged from 5% in the fluocinonide twice-daily treatment group to 11% in the once-daily vehicle controls. Reasons for discontinuations primarily included adverse events, subject's request and lost to follow-up.

Discontinuations due to adverse events occurred in 1% of the once-daily fluocinonide patients and 4% of the corresponding vehicle controls. Discontinuation rates for the twice-daily regimens were approximately half of the corresponding once-daily rates.

**Table 4 Subject Disposition: Study MP-0201-06**

	Once-daily		Twice-daily	
	Fluocinonide N=109	Vehicle N=50	Fluocinonide N=102	Vehicle N=52
<b>Discontinued Study</b>	4 (4%)	6 (12%)	6 (6%)	6 (12%)
<b>Adverse Event</b>	1 (1%)	2 (4%)	1 (1%)	1 (2%)
<b>Protocol Violation</b>	0 (0%)	0 (0%)	0 (0%)	1 (2%)
<b>Subject's Request</b>	1 (1%)	1 (2%)	1 (1%)	2 (4%)
<b>Lost to Follow-Up</b>	2 (2%)	1 (2%)	4 (4%)	2 (4%)
<b>Other</b>	0 (0%)	2 (4%)	0 (0%)	0 (0%)

Source: Post-Text Table 2 of the Clinical Study Report, Volume 7, Item 8, Page 1969

The actual enrollment in study MP-0201-06 was 313 subjects at 24 study centers in the United States: 109 in the qd fluocinonide group, 102 in the bid fluocinonide group, 50 in the qd vehicle group, and 52 in the bid vehicle group.

In both regimens approximately 5% of the fluocinonide subjects discontinued treatment compared to 12% of the vehicle controls. Reasons for discontinuations primarily included adverse events, subject's request and lost to follow-up.

Discontinuations due to adverse events ranged from 1% of the once-daily and twice-daily fluocinonide patients to 4% in the once-daily vehicle controls.

### 3.1.4 Demographics

Demographic data in the ITT Population are shown in Table 5 and 6 for studies MP-0201-05 and MP-0201-06. Baseline characteristics were generally comparable in the four treatment groups in both studies.

The mean age in study MP-0201-05 was approximately 50 years of age and ranged from 19 to 90 years. Approximately 55% of the subjects were female. Approximately 90% of the subjects were

Caucasian, <5% were Black, <2% were Asian, and <5% were Hispanic. The mean height was 68 inches and the mean weight was approximately 195 lbs. The mean duration of disease was approximately 17 years while the duration of current episode was approximately 10 months. The percent of BSA involvement was approximately 5%.

**Table 5 Demographic summary at Baseline by treatment group: Study MP-0201-05**

	Fluocinonide 0.1%, qd	Vehicle qd	Fluocinonide 0.1%, bid	Vehicle bid
	N = 107	N = 54	N = 107	N = 55
<b>Age (years)</b>				
mean ± SD	49.0 ± 15.0	50.4 ± 16.6	50.3 ± 14.3	46.4 ± 12.7
Range	20 - 90	20 - 84	20 - 78	19 - 78
<b>Gender – n(%)</b>				
Male	60 (56)	22 (41)	55 (51)	34 (62)
Female	47 (44)	32 (59)	52 (49)	21 (38)
<b>Race - n(%)</b>				
•    Caucasian	96 (90)	48 (89)	100 (94)	50 (91)
•    Black	2 (2)	3 (6)	4 (4)	2 (4)
•    Asian	2 (2)	0	2 (2)	1 (2)
•    Native American	0	1 (2)	0	0
•    Hispanic	5 (5)	2 (4)	1 (1)	2 (4)
•    Other	2 (2)	0	0	0
<b>Height (inches)</b>				
mean ± SD	67.5 ± 4.4	67.4 ± 4.1	67.4 ± 3.6	68.3 ± 4.9
Range	56 - 78	58 - 77	60 - 75	58 - 77
<b>Weight (lbs)</b>				
mean ± SD	190.1 ± 43.8	192.4 ± 44.9	198.5 ± 61.3	197.0 ± 53.3
Range	110 - 295	95 - 300	104 - 526	110 - 338
<b>Duration of disease (years)</b>				
mean ± SD	17.2 ± 14.3	16.6 ± 14.3	16.2 ± 12.4	18.3 ± 14.7
Range	0.5 - 60.0	0.8 - 53.0	0.8 - 58.0	0.8 - 58.0
<b>Duration of current episode (months)</b>				
mean ± SD	10.7 ± 13.6	9.9 ± 11.0	9.0 ± 10.8	11.3 ± 14.3
Range	0.1 - 60.0	0.3 - 53.0	0.1 - 55.0	0.3 - 58.0
<b>BSA involvement (%)</b>				
mean ± SD	5.4 ± 2.7	5.0 ± 2.7	4.9 ± 2.6	5.1 ± 2.7
Range	2 - 10	2 - 10	2 - 10	2 - 10

Source: Table 7-1 of the Clinical Study Report, Volume 7, Item 8, Page 52

In the ITT Population, the mean age in study MP-0201-06 was approximately 40 years of age and ranged from 18 to 79 years. Approximately 50-60% of the subjects were female. The percentage of Caucasians was higher in the twice-daily fluocinonide treatment group than in the corresponding controls. However there were no statistically significant treatment by race interactions and treatment effects did not appear to be confounded by race (see Section 4.1).

The mean duration of disease was approximately 17 years in each treatment group. The standard deviations for duration of current episode were almost twice as large as the means. Consequently, mean durations of current episode varied considerably, from 2 episodes in the twice-daily vehicle controls to almost 6 episodes in the once-daily vehicle controls. The percent of BSA involvement was approximately 5% in each treatment group.

**Table 6 Demographic summary at Baseline by treatment group: Study MP-0201-06**

	Fluocinonide 0.1%, qd N = 109	Vehicle qd N = 50	Fluocinonide 0.1%, bid N = 102	Vehicle bid N = 52
<b>Age (yr)</b>				
mean ± SD	40.9 ± 13.0	43.7 ± 16.5	42.9 ± 15.7	43.7 ± 13.0
Range	19 – 76	18 – 76	18 - 79	20 – 71
<b>Gender – n(%)</b>				
Male	44 (40)	22 (44)	52 (51)	22 (42)
Female	65 (60)	28 (56)	50 (49)	30 (58)
<b>Race - n(%)</b>				
•    Caucasian	81 (74)	39 (78)	82 (80)	31 (60)
•    Black	17 (16)	5 (10)	10 (10)	12 (23)
•    Asian	0	1 (2)	3 (3)	3 (6)
•    Native American	0	0	1 (1)	1 (2)
•    Hispanic	11 (10)	5 (10)	6 (6)	5 (10)
<b>Duration of disease (years)</b>				
mean ± SD	17.2 ± 14.6	16.8 ± 16.5	17.8 ± 16.8	17.2 ± 15.1
Range	0.1 – 52.0	0.9 - 62.0	0.9 –64.0	1.0 - 57.0
<b>Duration of current episode (months)</b>				
mean ± SD	3.8 ± 7.3	5.6 ± 12.0	4.2 ± 8.3	2.4 ± 4.4
Range	0.1 – 40.0	0.1 - 50.0	0.1 –41.0	0.1 - 20.0
<b>BSA involvement (%)</b>				
mean ± SD	5.6 ± 2.8	5.5 ± 2.3	5.5 ± 2.6	4.9 ± 2.6
Range	2 – 10	2 – 10	2 - 10	2 -10

Source: Table 7-1 of the Clinical Study Report, Volume 7, Item 8, Page 1943

### 3.1.5 Primary Efficacy Analysis

In summarizing the efficacy results, the primary comparisons were ordered hierarchically to control the Type I error; the qd regimen was tested against its vehicle only if the bid regimen test against its vehicle was statistically significant. A statistical comparison between once-daily and twice-daily applications was made if both of the comparisons between fluocinonide and the corresponding vehicle controls were statistically significant.

**Table 7 Primary Efficacy Endpoint – Computation of Treatment Success based on dichotomized PGA scores for overall lesion severity at the end of Week 2**

Indication / Population	Once-Daily Regimen			Twice-Daily Regimen			Fluocinonide qd vs bid p-value <sup>1</sup>
	Fluocinonide 0.1%	Vehicle	p-value <sup>1</sup>	Fluocinonide 0.1%	Vehicle	p-value <sup>1</sup>	
<b>Psoriasis</b>							
ITT	19/107 (18%)	4/54 (7%)	0.043	33/107 (31%)	3/55 (6%)	<0.001	0.025
Per Protocol	18/90 (20%)	4/43 (9%)	0.071	31/97 (32%)	3 / 47 (6%)	<0.001	0.060
<b>Atopic Dermatitis</b>							
ITT	64/109 (59%)	6/50 (12%)	<0.001	58/102 (57%)	10/52 (19%)	<0.001	0.837
Per Protocol	54/87 (62%)	6/36 (17%)	<0.001	52/88 (59%)	5/41 (12%)	<0.001	0.884

Source: Table 9.1 in the Clinical Study Report, Volume 7, Item 8, pages 55 and 1947

Note: All percentages are rounded. Treatment success was defined as a PGA score of 0 (cleared) or 1 (almost cleared).

<sup>1</sup>p-values using pairwise Mantel-Haenszel statistics, stratified on investigational site

Study MP-0201-05 demonstrated a statistically significant effect of fluocinonide in the treatment of psoriasis in adults when applied twice-daily or once-daily for two weeks. Compared to twice-daily use, fluocinonide was significantly less effective when used once-daily for the treatment of psoriasis (p=0.025); 31% of the patients who applied fluocinonide twice-daily had a treatment success compared to only 18% of the patients who applied it once-daily.

Study MP-0201-06 demonstrated a statistically significant effect of fluocinonide in the treatment of atopic dermatitis in adults when applied once or twice-daily for two weeks. The difference between the once-daily and twice-daily regimens of fluocinonide was not statistically significant.

#### 3.1.5.1 Robustness of Primary Analysis

Similar trends for the treatment of psoriasis and atopic dermatitis were observed in the per protocol population.

For psoriasis, only the difference between the twice-daily application of flucicor and its corresponding vehicle control was statistically significant - this was most likely due to the smaller sample size in the per protocol population.

Both once-daily and twice-daily applications of flucicor were superior to the vehicle control for the treatment of atopic dermatitis in adults.

### 3.1.6 Secondary Efficacy Analyses for Study MP-0201-05

**Table 8 PGA scores for Overall Lesion Severity: Study MP-0201-05  
 (Mean ± SD, ITT Population)**

	Flucicor 0.1%, qd N = 107	Vehicle qd N = 54	Flucicor 0.1%, bid N = 107	Vehicle bid N = 55
Screen/Baseline Visit	3.19 ± 0.46	3.13 ± 0.34	3.21 ± 0.47	3.25 ± 0.52
Week 1	2.64 ± 0.70*	2.85 ± 0.60	2.35 ± 0.78*†	2.91 ± 0.67
Week 2	2.30 ± 0.80*	2.76 ± 0.80	1.99 ± 0.97*†	2.69 ± 0.79
Week 4	2.47 ± 0.88	2.76 ± 0.72	2.17 ± 1.02*†	2.77 ± 0.76

Source: Table 9-2 of the Clinical Study Report, Volume 7, Item 8, Page 56

\*p < 0.05 flucicor vs. corresponding vehicle

†p < 0.05 flucicor qd vs. bid

Mean PGA Scores of Overall Lesion Severity are displayed in Figure 2 of the Clinical Study Report and in Table 8.

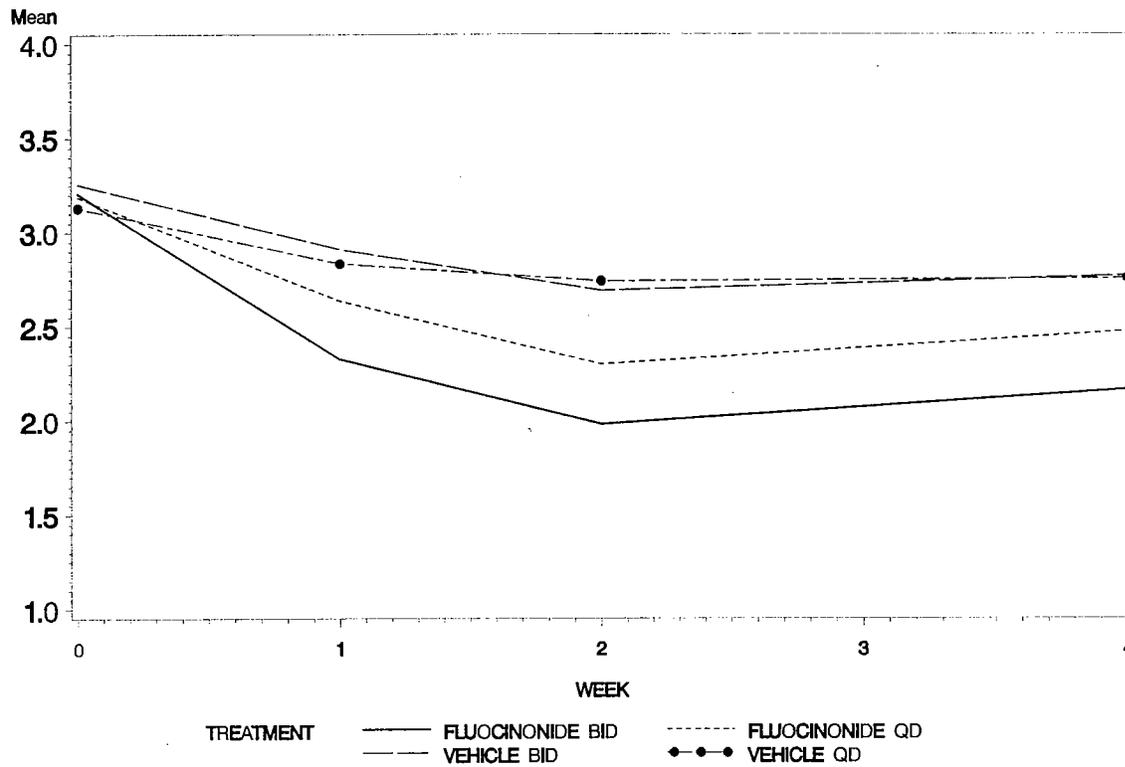
There were statistically significant differences for qd and bid flucicor compared to corresponding control regimens at Weeks 1 and 2.

There was also a statistically significant difference in favor of bid flucicor compared to the bid controls at Week 4.

There were statistically significant differences favoring bid flucicor over qd flucicor at Weeks 1, 2 and 4.

Appears This Way  
 On Original

Figure 2 Physicians Global Assessment of Overall Lesion Severity - ITT Population



Source: Study MP-0201-05, Figure 2 of the Clinical Study Report, Volume 7, Item 8, Page 57

Appears This Way  
On Original

**Table 9 Overall Symptom Severity Scores: Study MP-0201-05  
(Mean ± SD, ITT Population)**

	Fluocicore 0.1%, qd N = 107	Vehicle qd N = 54	Fluocicore 0.1%, bid N = 107	Vehicle bid N = 55
<b>Induration:</b>				
Screen/Baseline	3.13 ± 0.41	3.13 ± 0.48	3.15 ± 0.47	3.25 ± 0.48
Week 1	2.22 ± 0.87*	2.52 ± 0.77	1.83 ± 0.94*†	2.51 ± 0.96
Week 2	1.81 ± 0.89*	2.20 ± 0.83	1.40 ± 1.04*†	2.05 ± 1.04
Week 4	2.12 ± 1.00	2.20 ± 0.96	1.61 ± 0.99*†	2.35 ± 0.95
<b>Erythema:</b>				
Screen/Baseline	3.12 ± 0.41	3.15 ± 0.41	3.06 ± 0.41	2.95 ± 0.36‡
Week 1	2.28 ± 0.82*	2.59 ± 0.66	2.05 ± 0.77*†	2.44 ± 0.76
Week 2	1.90 ± 0.89*	2.33 ± 0.89	1.67 ± 0.82*	2.27 ± 0.87
Week 4	2.17 ± 0.90	2.45 ± 0.79	1.72 ± 0.91*†	2.35 ± 0.81
<b>Scaling:</b>				
Screen/Baseline	3.18 ± 0.45	3.22 ± 0.50	3.31 ± 0.46†	3.29 ± 0.46
Week 1	2.18 ± 0.95*	2.52 ± 0.86	1.79 ± 0.96*†	2.33 ± 1.02
Week 2	1.78 ± 0.99*	2.09 ± 0.94	1.39 ± 1.01*†	2.02 ± 1.11
Week 4	2.07 ± 1.07	2.22 ± 1.03	1.54 ± 0.93*†	2.38 ± 1.09
<b>Total IES:</b>				
Screen/Baseline	9.43 ± 0.86	9.50 ± 0.88	9.51 ± 0.95	9.49 ± 0.88
Week 1	6.68 ± 2.36*	7.63 ± 1.99	5.66 ± 2.42*†	7.27 ± 2.41
Week 2	5.49 ± 2.49*	6.63 ± 2.33	4.47 ± 2.62*†	6.35 ± 2.72
Week 4	6.36 ± 2.79	6.88 ± 2.55	4.86 ± 2.59*†	7.08 ± 2.57

Source: Table 9-3 of the Clinical Study Report, Volume 7, Item 8, Page 58

\*p < 0.05 fluocicore vs. corresponding vehicle

†p < 0.05 fluocicore qd vs. bid

‡p < 0.05 vehicle qd vs. bid

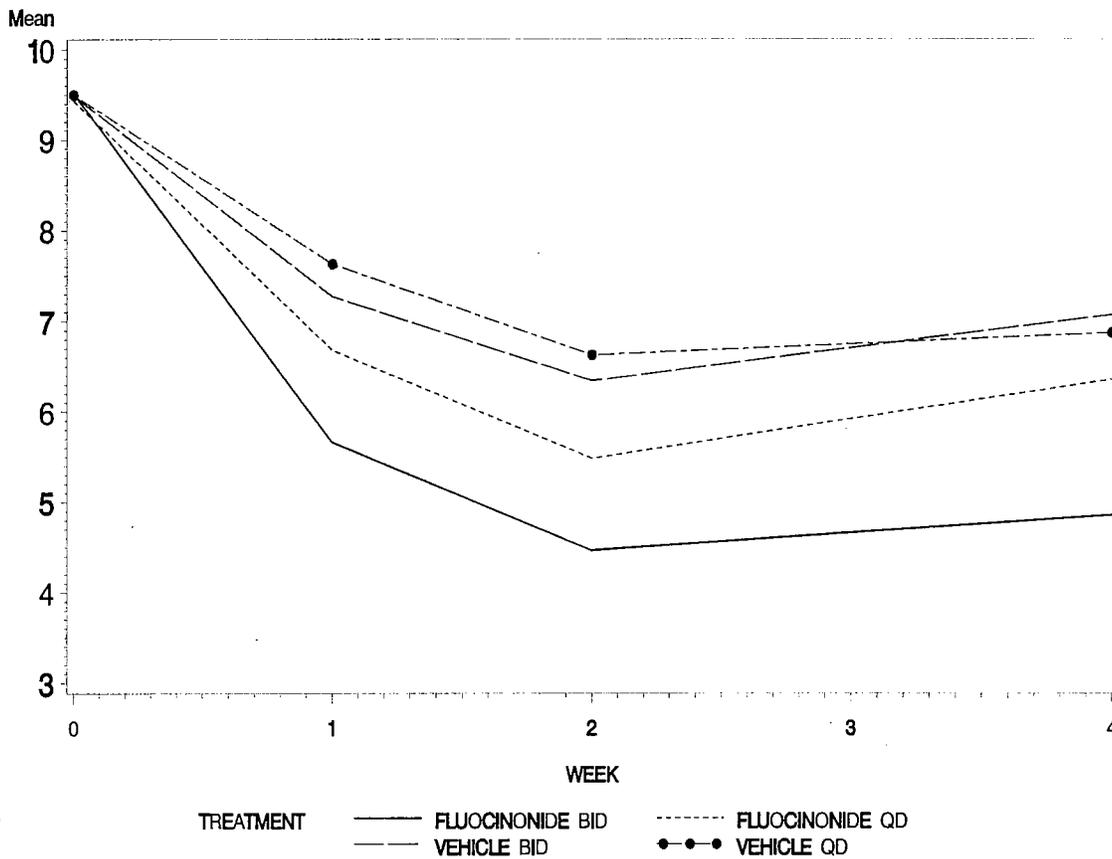
Mean Total IES Scores in the ITT Population are shown in Figure 6 of the Clinical Study Report and in Table 9. Similar trends were observed for each of the components of the total score (induration, erythema, scaling).

There were statistically significant differences in favor of qd and bid fluocicore treatment groups compared to corresponding regimens of the control at Weeks 1 and 2.

There was also a statistically significant difference in favor of bid fluocicore compared to the bid controls at Week 4.

There were statistically significant differences favoring bid fluocicore over qd fluocicore at Weeks 1, 2 and 4.

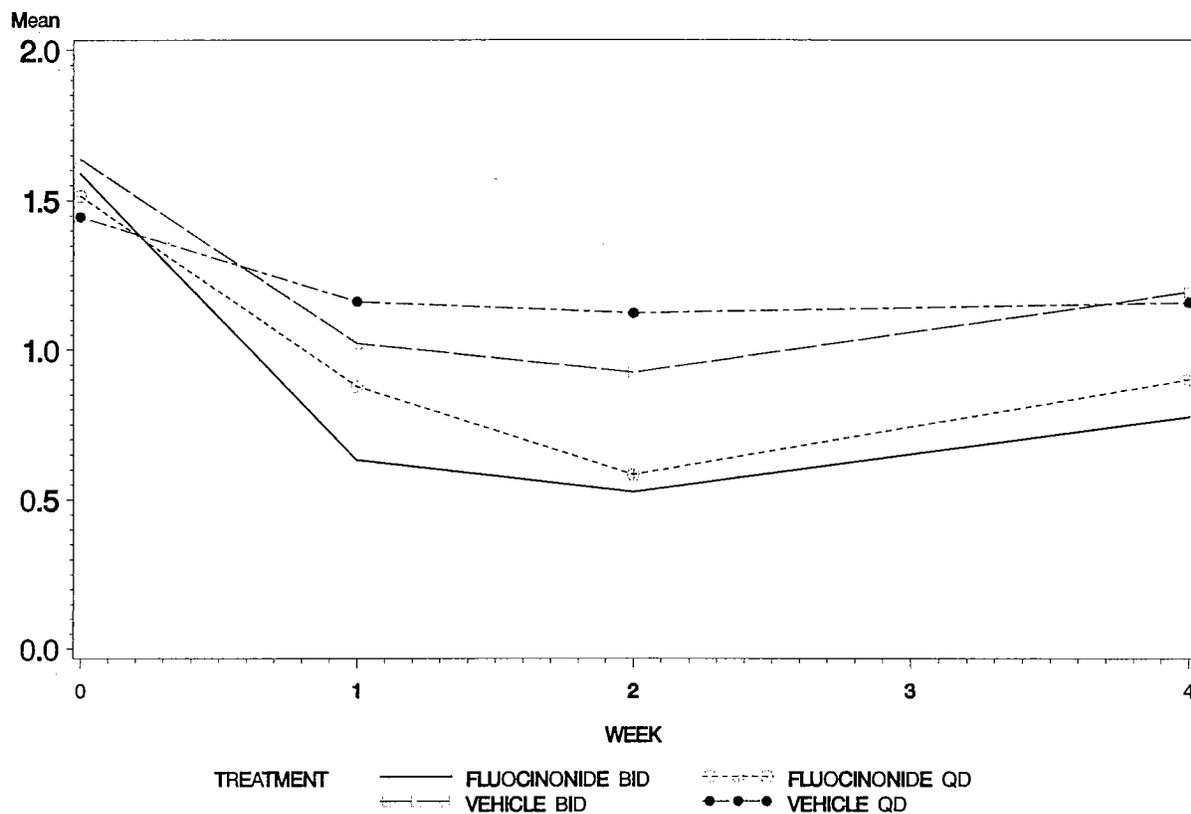
Figure 6 Symptom Severity Ratings - Total IES Scores in ITT Population



Source: Study MP-0201-05, Figure 6 of the Clinical Study Report, Volume 7, Item 8, Page 60

Appears This Way  
On Original

Figure 7 Subject's Overall Rating of Pruritus – ITT Population

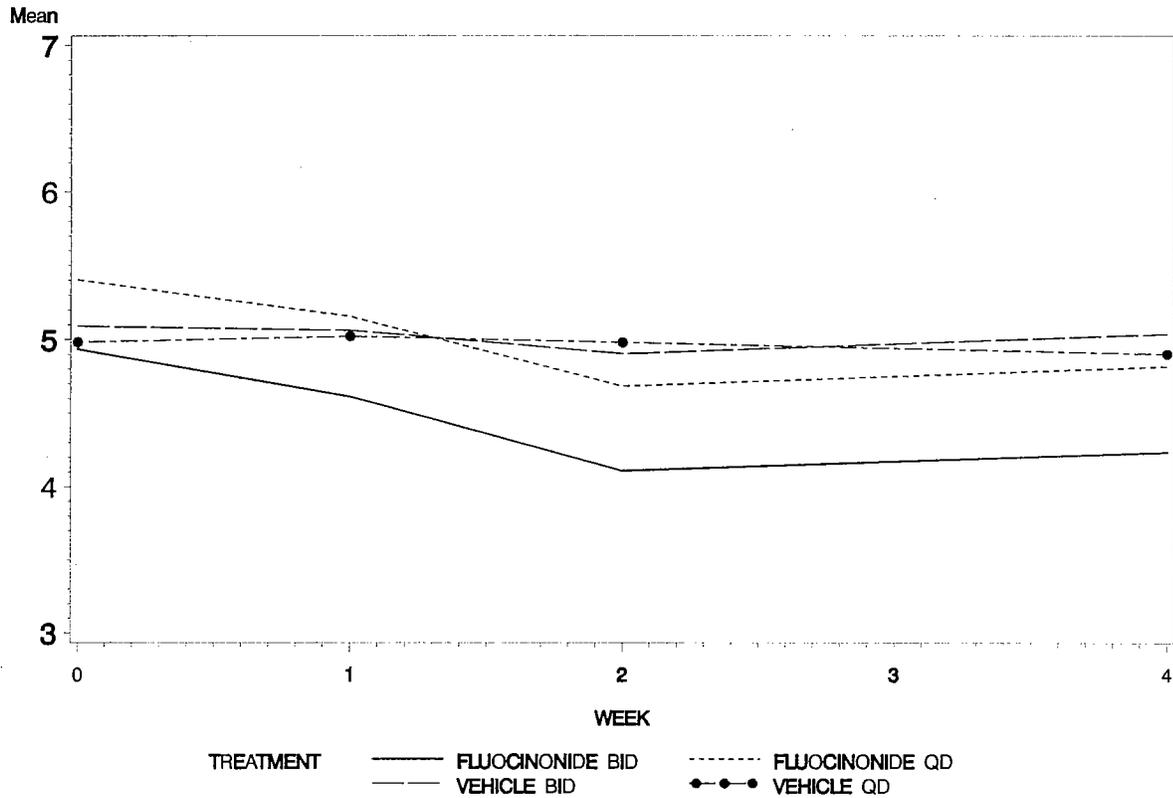


Source: Study MP-0201-05, Figure 7 of the Clinical Study Report, Volume 7, Item 8, Page 61

Similar trends were also observed for mean subject's overall rating of pruritus in the ITT population (Figure 7 of the Clinical Study Report). The maximum treatment effect occurred at Week 2 with Week 4 means returning to higher levels.

Appears This Way  
On Original

Figure 8 Percent BSA Affected – ITT Population



Source: Study MP-0201-05, Figure 8 of the Clinical Study Report, Volume 7, Item 8, Page 62

The mean percent body surface area affected in each treatment group at each week is shown in Figure 8 of the Clinical Study Report. There were no statistically significant treatment differences observed in % BSA at any week.

Appears This Way  
On Original

### 3.1.7 Secondary Efficacy Analyses for Study MP-0201-06

**Table 10 PGA scores for Overall lesion severity: Study MP-0201-06  
 (Mean ± SD, ITT Population)**

	<b>Fluocinonide 0.1%, qd N = 109</b>	<b>Vehicle qd N = 50</b>	<b>Fluocinonide 0.1%, bid N = 102</b>	<b>Vehicle bid N = 52</b>
<b>Screen/Baseline Visit</b>	3.14 ± 0.35	3.12 ± 0.33	3.12 ± 0.32	3.15 ± 0.36
<b>Week 1</b>	2.22 ± 0.83*	2.76 ± 0.66	2.00 ± 0.87*†	2.60 ± 0.75
<b>Week 2</b>	1.56 ± 0.99*	2.54 ± 0.81	1.42 ± 0.95*	2.37 ± 0.84
<b>Week 4</b>	2.02 ± 1.11	2.23 ± 0.94	1.60 ± 1.07*†	2.15 ± 1.03

Source: Table 9-2 of the Clinical Study Report, Volume 7, Item 8, Page 1949

\*p < 0.05 fluocinonide vs. corresponding vehicle

†p < 0.05 fluocinonide qd vs. bid

Mean PGA scores of overall lesion severity are displayed in Figure 2 of the Clinical Study Report and in Table 10.

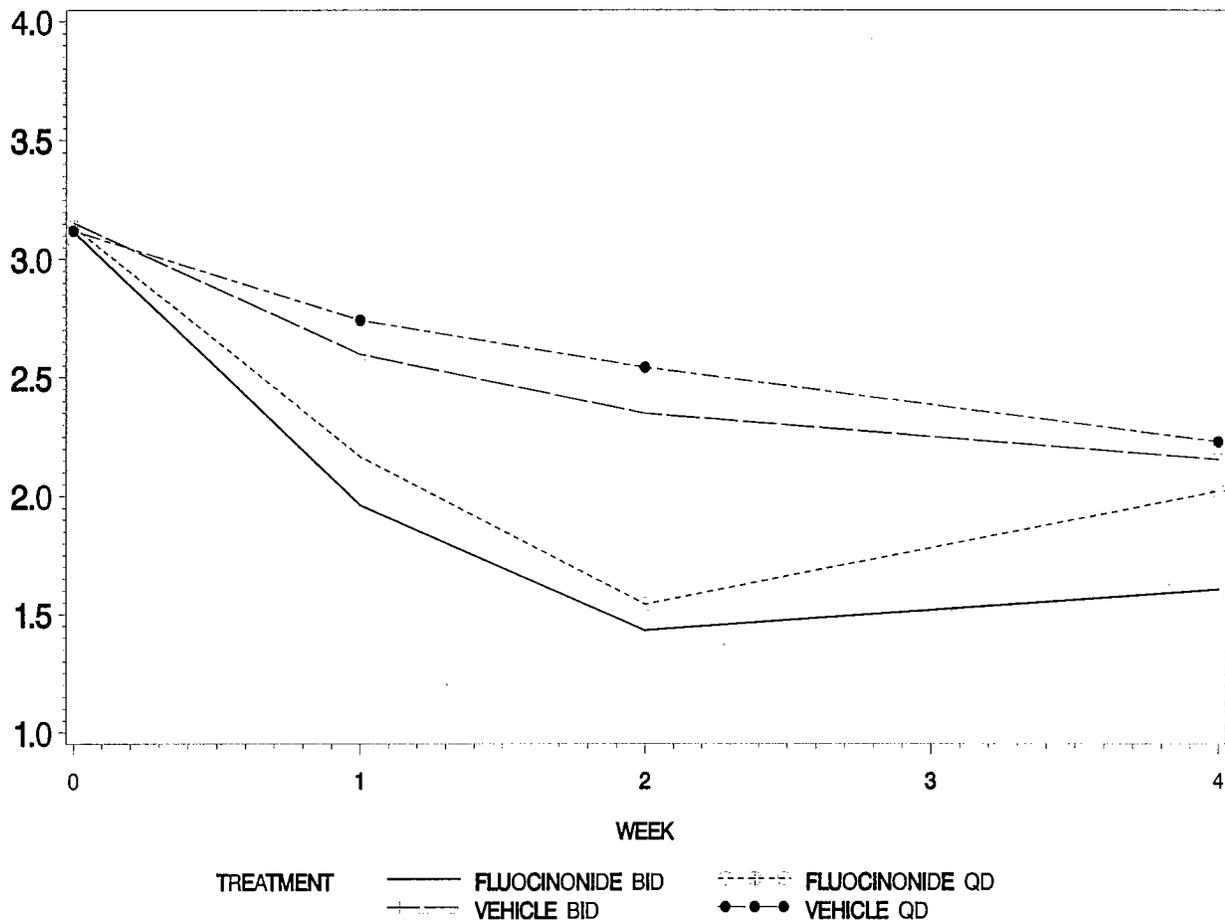
There were statistically significant differences in favor of qd fluocinonide and bid fluocinonide treatment groups compared to corresponding regimens of the control at Weeks 1 and 2.

There was also a statistically significant difference in favor of bid fluocinonide compared to the bid controls at Week 4.

There were statistically significant differences favoring bid fluocinonide over qd fluocinonide at Weeks 1 and 4.

**Appears This Way  
 On Original**

Figure 2 Physicians Global Assessment of overall lesion severity - ITT population



Source: Study MP-0201-06, Figure 2 of the Clinical Study Report, Volume 7, Item 8, Page 1948

Appears This Way  
On Original

**Table 11 Overall Symptom Severity scores: Study MP-0201-06  
 (Mean ± SD, ITT Population)**

	Fluciclonide 0.1%, qd N = 109	Vehicle qd N = 50	Fluciclonide 0.1%, bid N = 102	Vehicle bid N = 52
<b>Erythema::</b>				
Screen/Baseline	2.05 ± 0.42	2.12 ± 0.39	2.05 ± 0.41	2.06 ± 0.46
Week 1	1.33 ± 0.61*	1.82 ± 0.52	1.28 ± 0.65*	1.65 ± 0.56
Week 2	1.02 ± 0.67*	1.70 ± 0.61	0.94 ± 0.67*	1.58 ± 0.64
Week 4	1.25 ± 0.84	1.34 ± 0.78	1.04 ± 0.75*	1.39 ± 0.65
<b>Induration/Population:</b>				
Screen/Baseline	2.17 ± 0.52	2.10 ± 0.42	2.09 ± 0.38	2.13 ± 0.49
Week 1	1.34 ± 0.77*	1.72 ± 0.67	1.14 ± 0.73*†	1.60 ± 0.66
Week 2	0.89 ± 0.83*	1.62 ± 0.78	0.77 ± 0.73*	1.46 ± 0.64
Week 4	1.28 ± 0.85	1.34 ± 0.78	0.92 ± 0.82*†	1.39 ± 0.86
<b>Excoriations:</b>				
Screen/Baseline	1.79 ± 0.67	1.98 ± 0.65	1.83 ± 0.63	1.88 ± 0.73
Week 1	0.94 ± 0.73*	1.50 ± 0.91	0.71 ± 0.75*†	1.33 ± 0.86
Week 2	0.53 ± 0.73*	1.34 ± 0.94	0.45 ± 0.73*	1.25 ± 0.84
Week 4	0.99 ± 1.00	1.09 ± 0.83	0.58 ± 0.80*†	1.15 ± 0.89
<b>Lichenification:</b>				
Screen/Baseline	2.06 ± 0.64	1.96 ± 0.57	2.00 ± 0.61	2.00 ± 0.66
Week 1	1.36 ± 0.81	1.56 ± 0.70	1.10 ± 0.70*†	1.54 ± 0.78
Week 2	0.92 ± 0.81*	1.32 ± 0.84	0.82 ± 0.76*	1.31 ± 0.88
Week 4	1.13 ± 0.91	1.30 ± 0.76	0.78 ± 0.81*†	1.24 ± 0.92
<b>Total Score:</b>				
Screen/Baseline	8.06 ± 1.20	8.16 ± 1.31	7.97 ± 1.29	8.08 ± 1.47
Week 1	4.97 ± 2.30*	6.60 ± 2.10	4.23 ± 2.22*†	6.12 ± 2.35
Week 2	3.36 ± 2.37*	5.98 ± 2.61	2.99 ± 2.21*	5.60 ± 2.39
Week 4	4.65 ± 3.13	5.07 ± 2.70	3.32 ± 2.62*†	5.17 ± 2.89

Source: Table 9.3 of the Clinical Study Report, Volume 7, Item 8, Page 1950

\*p < 0.05 fluciclonide vs. corresponding vehicle

†p < 0.05 fluciclonide qd vs. bid

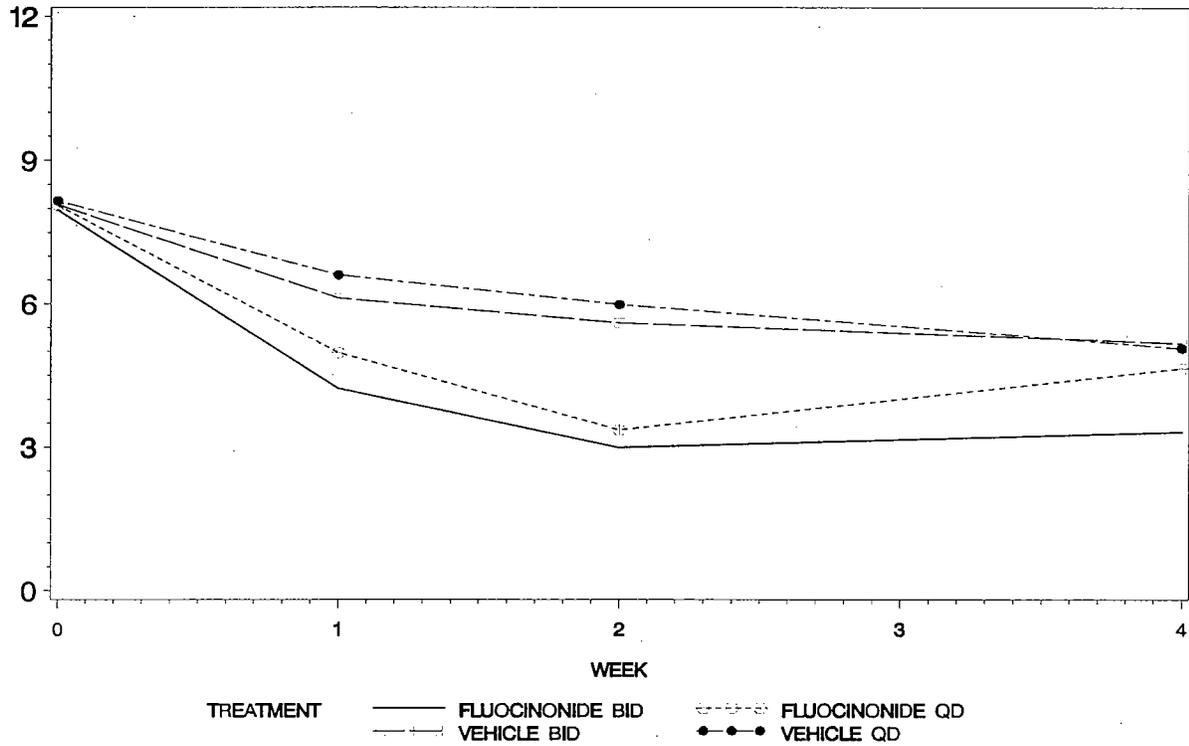
Mean symptom severity ratings (total scores) for each treatment are plotted by week in Figure 7 of the Clinical Study Report. The maximum treatment effect was observed at Week 2. Similar trends were observed for each of the components of the total score (erythema, induration/population, excoriations, lichenification).

There were statistically significant differences in favor of qd fluciclonide and bid fluciclonide treatment groups compared to corresponding regimens of the control at Weeks 1 and 2.

There was a statistically significant difference in favor of bid fluciclonide compared to the bid controls at Week 4.

There were statistically significant differences favoring bid fluocinonide over qd fluocinonide at Weeks 1 and 4.

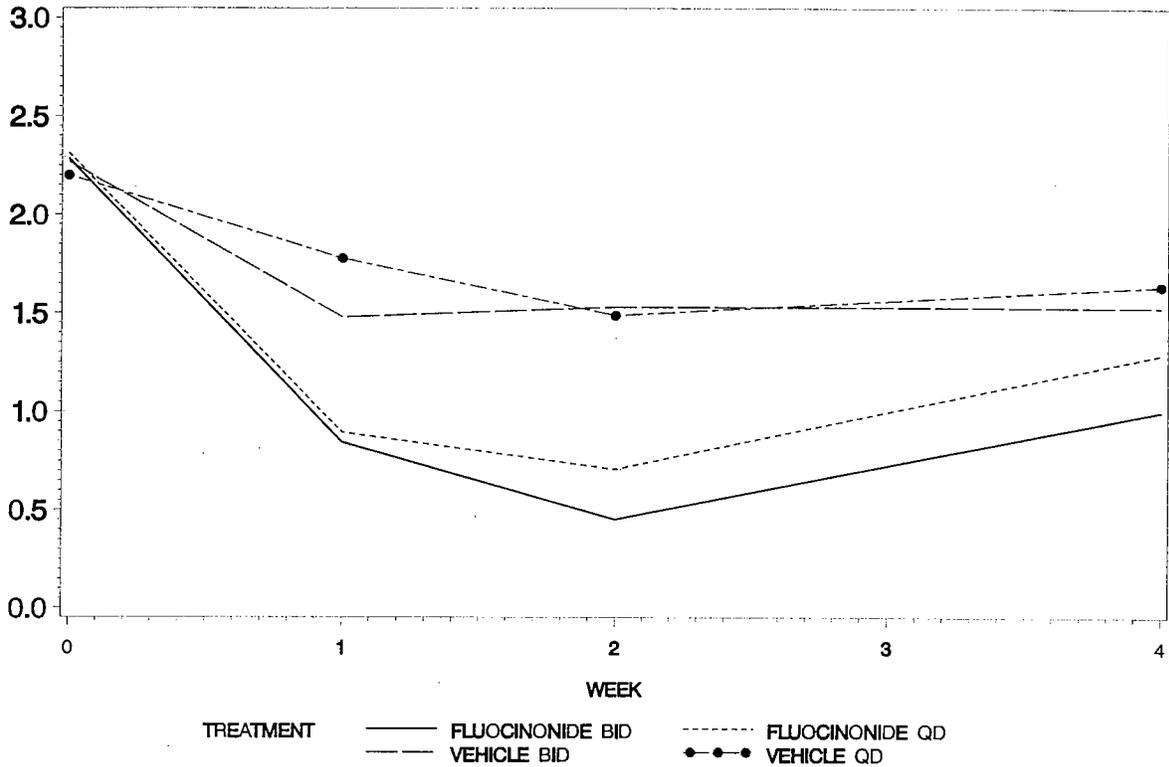
Figure 7      Symptom severity ratings - total scores in ITT population



Source: Study MP-0201-06, Figure 7 of the Clinical Study Report, Volume 7, Item 8, Page 1953

Appears This Way  
On Original

Figure 8 Subject's overall rating of pruritus – ITT population

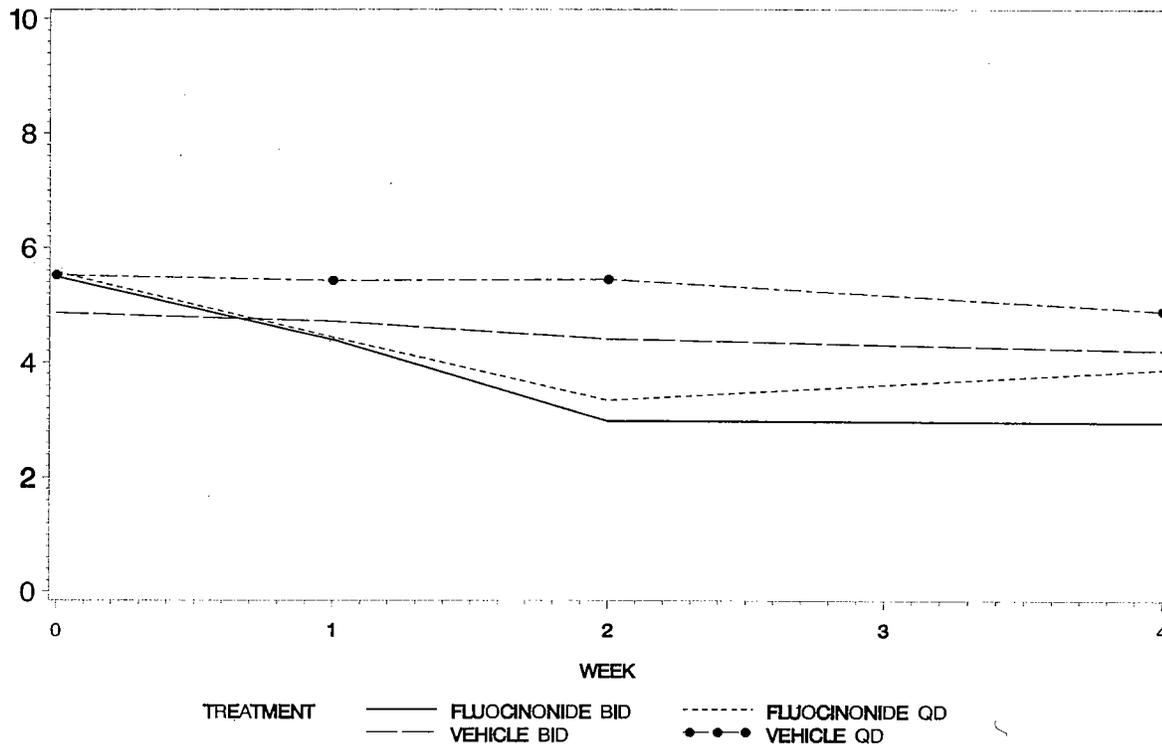


Source: Study MP-0201-06, Figure 8 of the Clinical Study Report, Volume 7, Item 8, Page 1954

Similar trends were also observed for mean subject's overall rating of pruritus in the ITT population (Figure 8 of the Clinical Study Report). The maximum treatment effect occurred at Week 2 with Week 4 means returning to higher levels.

Appears This Way  
On Original

Figure 9 Percent BSA affected – ITT population



Source: Study MP-0201-06, Figure 9 of the Clinical Study Report, Volume 7, Item 8, Page 1954

The mean percent body surface area affected in each treatment group at each week is shown in Figure 9 of the Clinical Study Report. There were statistically significant treatment differences between bid and qd fluciclonide and the corresponding vehicle control groups at Week 2.

There were also statistically significant differences between qd fluciclonide and the qd control at Week 1, bid fluciclonide and the corresponding control at Week 4 and between qd fluciclonide and bid fluciclonide at Week 4 in favor of bid fluciclonide.

## 3.2 Evaluation of Safety

### 3.2.1 Medication Compliance and Exposure

**Table 12 Medication Compliance and Exposure: Study MP-0201-05  
 (All Treated Subjects)**

	<b>Fluocinonide 0.1%, qd N = 107</b>	<b>Vehicle qd N = 54</b>	<b>Fluocinonide 0.1%, bid N = 107</b>	<b>Vehicle bid N = 55</b>
<b>Total Duration of Treatment (days)</b>				
N	100	49	103	53
mean ± SD	15 ± 1	15 ± 1	15 ± 1	15 ± 2
Range	8 - 20	12 - 20	11 - 22	8 - 19
<b>Total Weight of Study Medication Used (grams)</b>				
N	103	49	104	51
mean ± SD	39 ± 30	34 ± 29	47 ± 31	54 ± 41
Range	1 - 117	2 - 123	2 - 117	2 - 156
<b>Total Number of Applications</b>				
N	100	49	103	53
mean ± SD	15 ± 2	15 ± 1	29 ± 3	28 ± 5
Range	8 - 20	11 - 20	18 - 42	2 - 37

Source: Study MP-0201-05, Post-text Table 4 of the Clinical Study Report, Volume 7, Item 8, page 110.

In study MP-0201-05, the mean exposure time was 15 days in each treatment group. Exposure times ranged from 8-22 days.

The mean total weight of study medication used was lowest in the once-daily vehicle control (34 grams) and highest in the twice-daily vehicle control (54 grams).

The mean total number of applications was approximately 15 in both of the once-daily treatment groups and approximately twice as large in the twice-daily treatment groups.

**Table 13 Medication Compliance and Exposure: Study MP-0201-06  
 (All Treated Subjects)**

	<b>Fluocinonide 0.1%, qd N = 109</b>	<b>Vehicle qd N = 50</b>	<b>Fluocinonide 0.1%, bid N = 102</b>	<b>Vehicle bid N = 52</b>
<b>Total Duration of Treatment (days)</b>				
N	106	46	96	47
mean ± SD	15 ± 1	15 ± 1	15 ± 2	16 ± 1
Range	13 - 21	9 - 18	3 - 22	13 - 20
<b>Total Weight of Study Medication Used (grams)</b>				
N	107	49	97	51
mean ± SD	29 ± 25	33 ± 26	42 ± 31	40 ± 29
Range	0 - 109	4 - 100	4 - 152	3 - 120
<b>Total Number of Applications</b>				
N	106	46	96	47
mean ± SD	15 ± 2	15 ± 1	29 ± 3	30 ± 3
Range	13 - 21	9 - 18	5 - 43	22 - 39

Source: Study MP-0201-06, Post-text Table 4, Clinical Study Report, Volume 7, Item 8, Page 2019.

In study MP-0201-06, the mean exposure time was approximately 15 days in each treatment group. Exposure times ranged from 3-22 days.

The mean total weight of study medication used was lowest in the once-daily fluocinonide treatment group (29 grams) and highest in the twice-daily fluocinonide treatment group (42 grams).

The mean total number of applications was approximately 15 in the two once-daily treatment groups and approximately twice as large in the twice-daily treatment groups.

**Appears This Way  
 On Original**

### 3.2.2 Adverse Events

#### 3.2.2.1 Adverse Events in Study MP-0201-05

**Table 14 Number (%) of subjects with AEs overall and by body system: Study MP-0201-05 (≥ 2 subjects in a group)**

	<b>Fluocinonide 0.1%, <i>qd</i> n (%)</b>	<b>Vehicle cream, <i>qd</i> n (%)</b>	<b>Fluocinonide 0.1%, <i>bid</i> n (%)</b>	<b>Vehicle cream, <i>bid</i> N (%)</b>
<b>Subjects studied</b>				
total no. of subjects	107 (100)	54 (100)	107 (100)	55 (100)
total no. of subjects with AEs	12 (11)	10 (19)	15 (14)	9 (16)
<b>Body system affected</b>				
Skin and subcutaneous tissue Disorders	2 (2)	4 (7)	1 (1)	6 (11)
Nervous system disorders	3 (3)	2 (4)	5 (5)	0
Gastrointestinal disorders	2 (2)	2 (4)	2 (2)	1 (2)
General disorders and administration site conditions	1 (1)	2 (4)	1 (1)	3 (6)
Respiratory, thoracic and mediastinal disorders	2 (2)	1 (2)	3 (3)	1 (2)
Musculoskeletal and connective tissue disorders	1 (1)	0	2 (2)	0
Eye disorders	0	0	2 (2)	0

Source: Table 10-2 of the Clinical Study Report, Volume 7, Item 8, Page 63

#### Most Common Adverse Events

For the psoriasis indication, the incidence of overall adverse event rates ranged from 11% in the once-daily fluocinonide treatment group to 19% in the once-daily vehicle controls.

Nervous system disorders were the most prevalent adverse event in fluocinonide patients, reported in 4% of the fluocinonide patients and 2% of the vehicle controls.

Skin and subcutaneous tissue disorders had the highest incidence rates in the vehicle controls. These adverse events were reported in 9% of the vehicle controls and only 1% of the fluocinonide patients.

Other adverse events that occurred in a small number of fluocinonide and vehicle control patients (≥2 subjects in a group) included gastrointestinal disorders, general disorders and administration site

conditions, and respiratory, thoracic and mediastinal disorders. Musculoskeletal and connective disorders and eye disorders occurred in 1% of the fluocinonide patients and none of the vehicle controls.

**Table 15 Summary of Treatment Emergent Adverse Events by Severity:  
 Study MP-0201-05  
 (All Treated Subjects)**

	<b>Fluocinonide 0.1%, qd</b>	<b>Vehicle qd</b>	<b>Fluocinonide 0.1%, bid</b>	<b>Vehicle bid</b>
<b>Overall Number of Subjects</b>	107 ( 100)	54 ( 100)	107 ( 100)	55 ( 100)
<b>Subjects with AE(s)</b>				
<b>Mild</b>	7 ( 6.5)	7 (13.0)	13 (12.1)	5 ( 9.1)
<b>Moderate</b>	5 ( 4.7)	3 ( 5.6)	2 ( 1.9)	2 ( 3.6)
<b>Severe</b>	1 ( 0.9)	3 ( 5.6)	0 ( 0.0)	2 ( 3.6)

Source: Post-text Table 14-3 of the Clinical Study Report, Volume 7, Item 8, Page 175

In study MP-0201-05 severe adverse events occurred in <1% of the fluocinonide patients and 5% of the vehicle controls. No deaths were reported in the study.

Appears This Way  
 On Original

### 3.2.2.2 Adverse Events in Study MP-0201-06

**Table 16 Number (%) of subjects with AEs overall and by body system: Study MP-0201-06 (≥ 2 subjects in a group)**

	Fluocinonide 0.1%, <i>qd</i> n (%)	Vehicle cream, <i>qd</i> n (%)	Fluocinonide 0.1%, <i>bid</i> n (%)	Vehicle cream, <i>bid</i> n (%)
<b>Subjects studied</b>				
Total no. of subjects	109 (100)	50 (100)	102 (100)	52 (100)
Total no. of subjects with AEs	27 (25)	17 (34)	27 (27)	15 (29)
<b>Body system</b>				
<b>Respiratory, thoracic and Mediastinal disorders</b>	9 (8)	3 (6)	6 (6)	5 (10)
Nasal congestion	3 (3)	0	1 (1)	0
Nasopharyngitis	2 (2)	1 (2)	1 (1)	0
Bronchitis NOS	2 (2)	0	0	1 (2)
<b>Skin and subcutaneous tissue Disorders</b>	6 (6)	11 (22)	5 (5)	5 (10)
Application site burning	3 (3)	6 (12)	3 (3)	3 (6)
Skin fissures	0	2 (4)	0	0
<b>Nervous system disorders</b>	6 (6)	2 (4)	4 (4)	2 (4)
Headache	5 (5)	2 (4)	4 (4)	2 (4)
<b>Musculoskeletal and connective tissue disorders</b>	5 (5)	1 (2)	5 (5)	1 (2)
<b>General disorders and administration site conditions</b>	3 (3)	3 (6)	2 (2)	1 (2)
<b>Gastrointestinal disorders</b>	2 (2)	0	5 (5)	1 (2)
Nausea	1 (1)	0	2 (2)	0
Toothache	1 (1)	0	2 (2)	0
<b>Blood and lymphatic system Disorders</b>	2 (2)	0	1 (1)	0
Lymphadenopathy	2 (2)	0	0	0
<b>Infections and infestations</b>	0	0	2 (2)	1 (2)

Source: Table 10-1 of the Clinical Study Report, Volume 7, Item 8, Page 1956

NOS = Not otherwise specified

Note: All percentages are rounded.

#### Most Common Adverse Events

The percentage of subjects with adverse events ranged from 25% in the once-daily fluocinonide treatment group to 34% in the once-daily vehicle controls.

Respiratory, thoracic and mediastinal disorders were the most frequently reported adverse event in fluocinonide patients, occurring in 7% of the fluocinonide patients and 8% of the vehicle controls.

Skin and subcutaneous tissue disorders were the most prevalent adverse event in the vehicle controls, reported in 16% of the vehicle controls and only 5% of the fluocinonide patients.

Other adverse events that occurred in fluocinonide and vehicle control patients ( $\geq 2$  subjects in a group) included nervous system disorders, musculoskeletal and connective disorders, general disorders and administration site conditions, gastrointestinal disorders, blood and lymphatic system disorders and infections and infestations.

**Table 17 Summary Of Treatment Emergent Adverse Events, By Severity: Study MP-0201-06  
(All Treated Subjects)**

	<b>Fluocinonide 0.1%, qd</b>	<b>Vehicle qd</b>	<b>Fluocinonide 0.1%, bid</b>	<b>Vehicle bid</b>
<b>Overall Number of Subjects</b>	109 ( 100)	50 ( 100)	102 ( 100)	52 ( 100)
<b>Subjects with AE(s)</b>				
<b>Mild</b>	23 (21.1)	9 (18.0)	16 (15.7)	12 (23.1)
<b>Moderate</b>	6 ( 5.5)	7 (14.0)	13 (12.7)	5 ( 9.6)
<b>Severe</b>	2 ( 1.8)	2 ( 4.0)	0 ( 0.0)	0 ( 0.0)

Source: Post-text Table 13-3 of the Clinical Study Report, Volume 7, Item 8, Page 2098

In study MP-0201-06, severe adverse events were only reported in the once-daily regimen; 2% of the fluocinonide patients and 4% of the vehicle controls reported having a severe adverse event. No deaths were reported in the study.

Appears This Way  
On Original

**Table 18 Summary of HPA axis suppression: Study MP-0201-06  
 (ITT population)**

	<b>Fluocinonide 0.1%, <i>qd</i> n (%)</b>	<b>Vehicle cream, <i>qd</i> n (%)</b>	<b>Fluocinonide 0.1%, <i>bid</i> n (%)</b>	<b>Vehicle cream, <i>bid</i> n (%)</b>
Number of subjects studied	18 (100)	9 (100)	16 (100)	9 (100)
Number of subjects with normal HPA axis at screen/baseline	13/18 (72)	7/9 (78)	10/15 <sup>†</sup> (67)	9/9 (100)
Number of subjects with suppressed (abnormal) HPA axis at screen/ baseline	5/18 (28)	2/9 (22)	5/15 <sup>†</sup> (33)	0/9 (0)
Number of subjects with suppressed HPA axis at Week 2 (end of treatment)	6/18 (33)	2/9 (22)	4/15 (27)	1/9 (11)
Number of subjects with normal HPA axis at screen/ baseline but suppressed at Week 2 ( end of treatment)	5/13 (39)	1/7 (14)	1/9 (11)	1/9 (11)
Number of subjects with abnormal HPA axis at screen/ baseline and not suppressed at Week 2/4 (end of treatment / follow-up)	3/5 (60)	1/2 (50)	4/5 (80)	0 (0)
Number of subjects with normal HPA axis at screen/ baseline but suppressed at Week 2 and returned to normal at Week 4/follow-up visit*	4/4*	1/1*	1/1*	0*
Number of subjects with abnormal HPA axis at screen/ baseline but suppressed at Week 2 (no follow-up data)	1	0	0	1

Source: Post-Text Table 14 and Listing 4.3

Note: All percentages are rounded.

\* Only limited data are available for subjects meeting the criteria for HPA axis suppression at Week 2 and those who underwent testing at Week 4 or at a subsequent follow-up study visit.

<sup>†</sup> One subject (Subject 175) had no results for HPA axis data at screen/baseline visit.

Source: Table 10-2 of the Clinical Study Report, Volume 7, Item 8, Page 1959

In study MP-0201-06, 6 out of 18 (33%) of the once-daily fluocinonide patients met the applicant's criteria of hypothalamus-pituitary-adrenal (HPA) axis suppression at Week 2 (end of treatment) and 5 out of 18 (28%) met the criteria at screening.

Four out of 15 (27%) of the twice-daily fluocinonide patients met the applicant's criteria of HPA axis suppression at Week 2 (end of treatment) and 5 out of 15 (33%) met the criteria at screening.

Two of the 9 patients (22%) in the once-daily vehicle controls met the applicant's criteria of HPA axis suppression at screening and Week 2 (end of treatment).

One of the 9 patients (11%) in the twice-daily vehicle controls met the applicant's criteria of HPA axis suppression at Week 2 (end of treatment) and none of the twice-daily vehicle controls (0%) met the criteria at screening.

**Table 19 Mean increase in serum cortisol levels after cosyntropin stimulation: Study MP-0201-06 (ITT population)**

	Fluocinonide 0.1%, <i>qd</i>	Vehicle cream, <i>Qd</i>	Fluocinonide 0.1%, <i>bid</i>	Vehicle cream, <i>bid</i>
Number of subjects tested	18	9	15	9
Screen/ Baseline visit	11.1 ± 8.6	11.7 ± 7.5	10.7 ± 5.8	13.8 ± 9.1
Week 2 (all subjects)	10.8 ± 8.5	11.0 ± 4.7	10.8 ± 4.6	11.4 ± 6.5
Week 2 (subjects not meeting criteria for HPA axis suppression at Screen/Baseline visit (n))	10.5 ± 9.9 (13)	11.9 ± 4.2 (7)	12.4 ± 4.9 (9)	11.4 ± 6.5 (9)

Source: Table 10-3 of the Clinical Study Report, Volume 7, Item 8, Page 1960

Mean increases in serum cortisol levels after cosyntropin stimulation were similar in the qd and bid treatment groups at screening at Week 2 (Table 19). The applicant concluded that there appeared to be no advantage of qd dosing to reduce the incidence of HPA axis suppression but that it is reasonable to assume that a lower drug exposure by qd dosing would provide the greatest potential safety margin.

**Table 20 Subjects with HPA axis suppression by criterion of HPA axis suppression at baseline and end of Week 2: Study MP-0201-06 (ITT population)**

	Pre-stimulation cortisol levels ≤ 5 µg/dL	Post-stimulation cortisol levels	
		≤ 18 µg/dL	Increase over basal levels < 7 µg/dL
Number and % of subjects (subject number)			
Screen/Baseline Visit			
Fluocinonide 0.1%, <i>qd</i>	0	1/18 (180) or 6%	4/18 (120, 131, 132, 154) or 22%
Vehicle <i>qd</i>	0	0	2/9 (179, 277) or 22%
Fluocinonide 0.1%, <i>bid</i>	0	0	5/16 (3, 127, 156, 282, 353,) or 31%
Vehicle <i>bid</i>	0	0	0
Week 2			
Fluocinonide 0.1%, <i>qd</i>	1/18 (180) or 6%	1/18 (151) or 6%	4/18 (2, 6, 279, 350) or 22%
Vehicle <i>qd</i>	0	0	2/9 (128, 277) or 22%
Fluocinonide 0.1%, <i>bid</i>	0	0	4/16 (153, 175, 282, 353) or 25%
Vehicle <i>bid</i>	0	0	1/9 (160) or 11%

Source: Table 10-4 of the Clinical Study Report, Volume 7, Item 8, Page 1960

The majority of patients with HPA axis suppression had post-stimulation cortisol levels increases over basal levels < 7 µg/dL (Table 20). Among the bid regimen in this group, there were higher proportion of fluocinonide patients with HPA axis suppression than corresponding vehicle controls but the difference between fluocinonide and vehicle controls was larger at screening (31% vs. 0%) than it was at Week 2 (25% vs. 11%).

The FDA Draft Guidance for Industry on the Use of Cosyntropin Stimulation Testing to Assess for Corticosteroid-Induced Adrenal Suppression During Drug Development recommends using post-stimulation ≤ 18 µg/dL to indicate adrenal suppression. Using this criterion, only 1 patient in the

fluocinonide once-daily treatment group had HPA axis suppression at Screening and Week 2 (patient 180 at Screening and patient 151 at Week 2).

**Table 21 Mean % BSA and Mean Grams Used by Treatment Group and HPA axis suppression using the FDA criterion of post-stimulation cortisol levels  $\leq 18 \mu\text{g/dL}$  Week 2 (ITT population)**

Study Treatment Group	HPA Axis Suppression	% BSA		Total Grams used	
		n	mean	n	mean
<b>MP-0201-01 (Psoriasis)</b>					
Fluocinonide 0.05%, bid	No	18	15	17	77
	Yes	1	12	1	51
Fluocinonide 0.1%, bid	No	16	20	16	95
	Yes	2	19	2	91
<b>MP-0201-06 (Atopic Dermatitis)</b>					
Fluocinonide 0.1%, qd	No	17	5	17	27
	Yes	1	4	1	35
Vehicle <i>qd</i>	No	9	6	9	29
Fluocinonide 0.1%, bid	No	15	5	15	43
Vehicle <i>bid</i>	No	9	5	9	33

It was hypothesized that patients with greater Mean Percent Body Surface Area (% BSA) and Total Grams Used would be more likely to develop HPA axis suppressions. Given the small number of patients with HPA axis suppression it is difficult to make definitive conclusions about the effect of %BSA and total grams used. However mean % BSA and mean total grams used appear to be just as high in patients who did not have HPA Axis Suppression as they did for patients who did.

Appears This Way  
 On Original

**Table 22 Pearson Correlations (r) between HPA axis suppression and % BSA and Mean Grams Used using the FDA criterion of post-stimulation cortisol levels  $\leq$  18  $\mu$ g/dL**

**Week 2 (ITT population)**

Study Treatment Group	r (HPA, % BSA)			r (HPA, Total Grams used)		
	n	r	p-value	n	r	p-value
<b>MP-0201-01 (Psoriasis)</b>						
Fluocinonide 0.05%, bid	19	-0.12	0.64	18	-0.24	0.34
Fluocinonide 0.1%, bid	18	-0.04	0.88	18	-0.08	0.75
<b>MP-0201-06 (Atopic Dermatitis)</b>						
Fluocinonide 0.1%, qd	18	-0.10	0.70	18	+0.07	0.77

Pearson correlation coefficients between HPA axis suppression and % BSA and total grams used are also very small and were not statistically significant.

**Table 23 Summary of HPA axis suppression at Week 2 (end of treatment) using the FDA Definition: Studies MP-0201-01 and MP-0201-06 (ITT population)**

<b>Study MP-0201-06</b>	<b>Fluocinonide 0.1%, qd</b>	<b>Vehicle cream, qd</b>	<b>Fluocinonide 0.1%, bid</b>	<b>Vehicle cream, bid</b>
Number of subjects (Percentage)	1/18 (6%)	0/9 (0%)	0/15 (0%)	0/9 (0%)
95% Confidence Interval	(0%, 27%)		(0%, 22%)	(0%, 34%)
<b>Study MP-0201-01</b>	<b>Fluocinonide 0.05%, bid</b>		<b>Fluocinonide 0.1%, bid</b>	
Number of subjects (Percentage)	1/19 (5%)		2/18 (11%)	
95% Confidence Interval	(0%, 26%)		(0%, 35%)	
<b>Studies MP-0201-01 and MP-0201-06 combined</b>	<b>Fluocinonide 0.05% bid, 0.1% bid or qd</b>	<b>Vehicle Cream qd or bid</b>		
Number of subjects (Percentage)	4/70 (6%)	0/18 (0%)		
95% Confidence Interval	(0%, 14%)	(0%, 19%)		

The percentages of patients with HPA Axis suppressions using the FDA definition were calculated in the table above, along with corresponding exact 95% confidence intervals. Given the small sample sizes the confidence intervals were extremely wide indicating the lack of precision of the estimates.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Age, and Race

The percentage of treatment success rates by gender, race and age category for each study are shown below. Since the minimum age was 19 in fluocinonide subjects in study MP-0201-06 there were no results available for pediatric patients with atopic dermatitis.

**Table 24 Treatment success rates by gender, age and race**

#### Study MP-0201-05

	Fluocinonide bid			Fluocinonide qd			Vehicle bid			Vehicle qd		
	x	n	x/n	x	n	x/n	x	n	x/n	x	n	x/n
<b>Gender</b>												
Females	17	52	0.33	11	47	0.23	2	21	0.10	3	32	0.09
Males	16	55	0.29	8	60	0.13	1	34	0.03	1	22	0.05
<b>Age (yr)</b>												
<50	15	49	0.31	11	59	0.19	2	33	0.06	3	28	0.11
≥50-64	12	40	0.30	6	34	0.18	1	17	0.06	0	13	0
≥65	6	18	0.33	2	14	0.14	0	5	0	1	13	0.07
<b>Race</b>												
Caucasians	32	100	0.32	18	96	0.19	3	50	0.06	4	48	0.08
Other	1	7	0.14	1	11	0.09	0	5	0	0	6	0

#### Study MP-0201-06

	Fluocinonide bid			Fluocinonide qd			Vehicle bid			Vehicle qd		
	x	n	x/n	x	n	x/n	x	n	x/n	x	n	x/n
<b>Gender</b>												
Females	28	50	0.56	38	65	0.58	7	30	0.23	5	28	0.18
Males	30	52	0.58	26	44	0.59	3	22	0.14	1	22	0.05
<b>Age</b>												
<50	38	67	0.57	47	83	0.57	7	32	0.22	4	35	0.11
≥50-64	16	24	0.67	14	20	0.70	3	18	0.17	2	8	0.25
≥65	4	11	0.36	3	6	0.50	0	2	0	0	7	0
<b>Race</b>												
Caucasians	44	82	0.54	49	81	0.60	6	31	0.19	5	39	0.13
Other	14	20	0.70	15	28	0.54	4	21	0.19	1	11	0.09

There were no statistically significant treatment by gender, treatment by race or treatment by age interactions in either study in either regimen (qd or bid). Fluctuations of treatment effects within these subgroups can therefore probably all be attributed to chance.

**Table 25 Summary of Primary Endpoint by Subgroup Statistical Test Results:  
 Study MP-0201-05  
 (Intent to Treat Population)**

**Fluocinonide 0.1%, bid vs Vehicle Cream bid**

Subgroup	M-H Odds Ratio (95% LB, 95% UB) <sup>1</sup>	Breslow-Day Homogeneity Tests		
		Chi-Square	df	p-value
Gender	0.13 ( 0.04, 0.46)	0.69	1	0.406
Age (<50, ≥50)	0.13 ( 0.04, 0.44)	0.06	1	0.806
Race	0.13 ( 0.04, 0.45)	0.11	1	0.738

**Fluocinonide 0.1%, qd vs Vehicle Cream qd**

Subgroup	M-H Odds Ratio (95% LB, 95% UB) <sup>1</sup>	Breslow-Day Homogeneity Tests		
		Chi-Square	df	p-value
Gender	0.33 ( 0.10, 1.04)	0.005	1	0.945
Age (<50, ≥50)	0.37 ( 0.12, 1.16)	0.57	1	0.449
Race	0.37 ( 0.12, 1.15)	0.23	1	0.630

<sup>1</sup> Adjusted Odds Ratio based on Success Rates of Vehicle Control / Fluocinonide.

Appears This Way  
 On Original

**Table 26 Summary of Primary Endpoint by Subgroup Statistical Test Results:  
Study MP-0201-06  
(Intent to Treat Population)**

**Fluocinonide 0.1%, bid vs Vehicle Cream bid**

Subgroup	M-H Odds Ratio (95% LB, 95% UB) <sup>1</sup>	Breslow-Day Homogeneity Tests		
		Chi-Square	df	p-value
Gender	0.18 ( 0.08, 0.40)	0.73	1	0.394
Age (<50, ≥50)	0.18 ( 0.08, 0.40)	0.31	1	0.580
Race	0.17 ( 0.07, 0.38)	0.65	1	0.420

**Fluocinonide 0.1%, qd vs Vehicle Cream qd**

Subgroup	M-H Odds Ratio (95% LB, 95% UB) <sup>1</sup>	Breslow-Day Homogeneity Tests		
		Chi-Square	df	p-value
Gender	0.10 ( 0.04, 0.25)	1.82	1	0.178
Age (<50, ≥50)	0.09 ( 0.04, 0.24)	0.03	1	0.852
Race	0.09 ( 0.04, 0.24)	0.007	1	0.934

<sup>1</sup> Adjusted Odds Ratio based on Success Rates of Vehicle Control / Fluocinonide.

Appears This Way  
On Original

## 4.2 Other Special/Subgroup Populations

### By Center Discussion

- Centers were comparable in size (no unusually large centers) – Ranges: 8-35 (Study 05), 4-30 (Study 06)
- The two studies were run simultaneously
- No center had an unusually large treatment effect
- 7 centers were common between the two studies. After eliminating the common investigators from both studies the p-values were still significant. (Study 05: BID p=0.0038, QD p=0.0314; Study 06: BID p<0.001, QD p<0.001).
- The primary analysis was less significant for duplicate centers (see table below)
- Recommendation regarding DSI Audit: No centers are obvious choices for DSI audit. If a DSI audit is desired Dr. **██████** (Study 05, Center 9 and Study 06, Center 17) had consistently good results in both studies and enrolled a medium number of patients.

**Table 27 Primary efficacy endpoint – Comparison of treatment success based on dichotomized PGA scores for overall lesion severity at end of Week 2 (ITT Population)**

Indication/ Type of Center <sup>2</sup>	Once-Daily Regimen			Twice-Daily Regimen			Fluocinonide qd vs bid
	Fluocinonide 0.1%	Vehicle	p-value <sup>1</sup>	Fluocinonide 0.1%	Vehicle	p-value <sup>1</sup>	p-value <sup>1</sup>
<b>Psoriasis</b>							
Duplicate	8/47 (17%)	3/24 (13%)	0.487	16/51 (31%)	2/26 (8%)	0.018	0.101
Single	11/60 (18%)	1/30 (3%)	0.031	17/56 (30%)	1/29 (3%)	0.004	0.132
<b>Atopic Dermatitis</b>							
Duplicate	15/28 (54%)	3/14 (21%)	0.031	11/27 (41%)	1/15 (7%)	0.015	0.232
Single	49/81 (60%)	3/36 (8%)	<0.001	47/75 (63%)	9/37 (24%)	<0.001	0.745

Source: Table 9.1 in the Clinical Study Report, Volume 7, Item 8, pages 55 and 1947

Note: All percentages are rounded. Treatment success was defined as a PGA score of 0 (cleared) or 1 (almost cleared).

<sup>1</sup>p-values using pairwise Mantel-Haenszel statistics, stratified on investigational site

<sup>2</sup>Analyses using duplicate centers in the two studies vs. those using single centers that are in only one study

Appears This Way  
 On Original

The percentages of treatment success rates by site for each study are shown below. The center-adjusted p-values compare fluocinonide to the vehicle control in each regimen.

**Table 28 Treatment success rates by site: Study MP-0201-05**

Site	Fluocinonide 0.1%, bid			Fluocinonide 0.1%, qd			Vehicle bid			Vehicle qd		
	x	n	x/n	x	n	x/n	x	n	x/n	x	n	x/n
1	2	11	0.18	0	12	0.00	0	6	0.00	0	6	0.00
2	5	8	0.63	2	7	0.29	0	4	0.00	0	3	0.00
3	1	8	0.13	0	7	0.00	1	4	0.25	1	3	0.33
4	0	2	0.00	0	4	0.00	0	1	0.00	0	1	0.00
5	1	9	0.11	1	9	0.11	0	5	0.00	0	5	0.00
6	4	6	0.67	4	6	0.67	1	3	0.33	1	4	0.25
7	1	7	0.14	1	8	0.13	0	4	0.00	0	4	0.00
8	0	6	0.00	0	7	0.00	0	3	0.00	0	4	0.00
9	3	5	0.60	1	4	0.25	0	3	0.00	1	2	0.50
10	3	9	0.33	2	10	0.20	1	5	0.20	0	5	0.00
11	1	7	0.14	0	8	0.00	0	4	0.00	0	4	0.00
12	2	8	0.25	1	6	0.17	0	3	0.00	0	3	0.00
13	2	5	0.40	1	4	0.25	0	2	0.00	0	3	0.00
14	4	8	0.50	5	8	0.63	0	4	0.00	1	4	0.25
15	4	8	0.50	1	7	0.14	0	4	0.00	0	3	0.00
<b>Total</b>	<b>33</b>	<b>107</b>	<b>0.31</b>	<b>19</b>	<b>107</b>	<b>0.18</b>	<b>3</b>	<b>55</b>	<b>0.05</b>	<b>4</b>	<b>54</b>	<b>0.07</b>
<b>p-value<sup>1</sup></b>	<b>&lt;0.001</b>			<b>0.043</b>								

<sup>1</sup>Center-stratified p-values comparing fluocinonide to the vehicle control in each regimen

Appears This Way  
 On Original

**Table 29 Treatment Success Rates by Site: Study MP-0201-06**

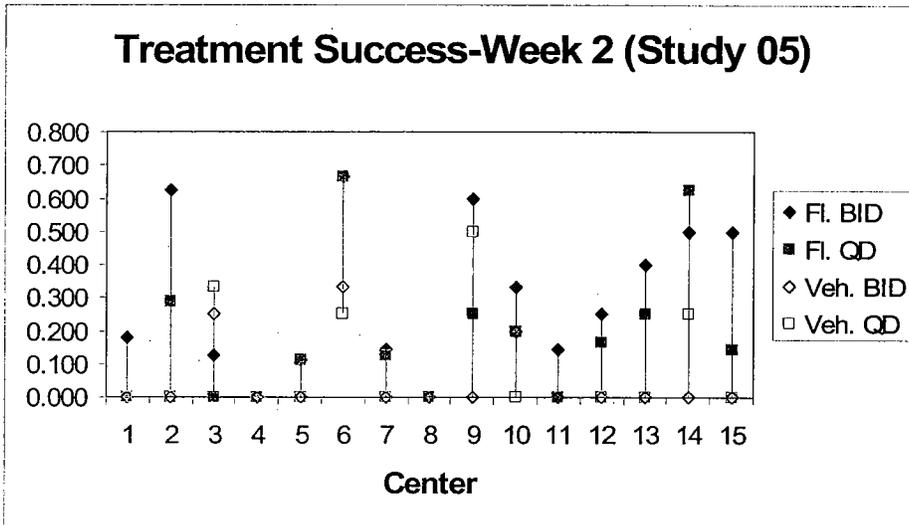
Site	Fluociclonide 0.1%, bid			Fluociclonide 0.1%, qd			Vehicle bid			Vehicle qd		
	x	n	x/n	x	n	x/n	x	n	x/n	x	n	x/n
1	2	7	0.29	4	7	0.57	0	4	0.00	0	3	0.00
2	2	4	0.50	1	6	0.17	0	2	0.00	0	2	0.00
3	5	6	0.83	4	6	0.67	1	2	0.50	0	2	0.00
4	1	2	0.50	2	2	1.00	0	1	0.00	0	1	0.00
5	1	3	0.33	3	4	0.75	0	1	0.00	0	2	0.00
6	0	5	0.00	1	4	0.25	0	3	0.00	0	2	0.00
7	1	2	0.50	1	3	0.33	0	1	0.00	0	1	0.00
8	1	3	0.33	0	4	0.00	0	2	0.00	0	2	0.00
9	5	6	0.83	6	6	1.00	1	3	0.33	1	3	0.33
10	2	4	0.50	3	4	0.75	0	2	0.00	0	2	0.00
11	1	3	0.33	2	4	0.50	0	1	0.00	0	2	0.00
12	7	7	1.00	6	7	0.86	3	4	0.75	2	4	0.50
14	7	10	0.70	4	10	0.40	1	5	0.20	0	5	0.00
15	4	4	1.00	3	4	0.75	0	2	0.00	1	2	0.50
16	3	4	0.75	3	3	1.00	0	2	0.00	0	1	0.00
17	3	5	0.60	3	4	0.75	0	2	0.00	0	2	0.00
18	6	7	0.86	4	8	0.50	1	4	0.25	0	4	0.00
19	0	1	0.00	2	2	1.00	0	1	0.00	0	0	----
20	0	3	0.00	1	2	0.50	1	1	1.00	0	1	0.00
21	0	3	0.00	1	4	0.25	0	2	0.00	1	2	0.50
22	1	2	0.50	1	3	0.33	1	1	1.00	0	1	0.00
23	1	3	0.33	3	3	1.00	0	2	0.00	1	2	0.50
24	1	2	0.50	1	3	0.33	0	1	0.00	0	1	0.00
25	4	6	0.67	5	6	0.83	1	3	0.33	0	3	0.00
<b>Total</b>	<b>58</b>	<b>102</b>	<b>0.569</b>	<b>64</b>	<b>109</b>	<b>0.59</b>	<b>10</b>	<b>52</b>	<b>0.19</b>	<b>6</b>	<b>50</b>	<b>0.12</b>
<b>p-value<sup>1</sup></b>			<b>&lt;0.001</b>			<b>&lt;0.001</b>						

<sup>1</sup>Center-stratified p-values comparing fluciclonide to the vehicle control in each regimen

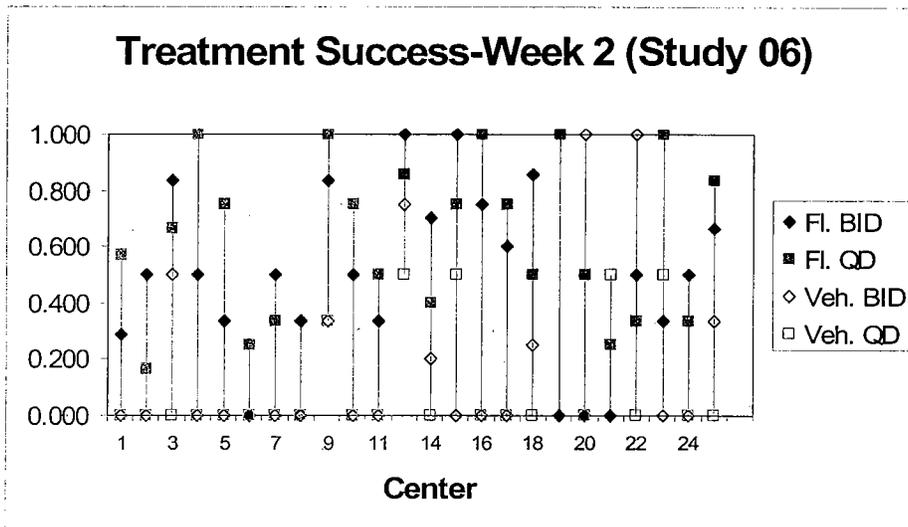
Appears This Way  
 On Original

**Plots of Treatment Successes at Week 2 by Center**

**Study MP-0201-05**



**Study MP-0201-06**



**Table 30 Site numbers for common investigators**

Investigator	Study 05 Site #	Study 06 Site #
	3	6
	5	8
	6	9
	9	17
	11	23
	12	24
	15	21

There were no statistically significant treatment by center interactions in either study in either regimen (qd or bid). Fluctuations of treatment effects within these sites can therefore probably all be attributed to chance.

**Table 31 Study MP-0201-05 Summary of Primary Endpoint Statistical Test Results, Stratified by Center**

**Fluocinonide 0.1% vs Vehicle Cream  
 (Intent to Treat Population)**

**Study MP-0201-05**

Regimen	M-H Odds Ratio (95% LB, 95% UB) <sup>1</sup>	Breslow-Day Homogeneity Tests		
		Chi-Square	df	p-value
Twice-Daily	0.11 ( 0.03, 0.42)	9.1	10	0.526
Once-Daily	0.30 ( 0.09, 1.02)	9.4	8	0.309

**Study MP-0201-06**

Regimen	M-H Odds Ratio (95% LB, 95% UB) <sup>1</sup>	Breslow-Day Homogeneity Tests		
		Chi-Square	df	p-value
Twice-Daily	0.14 ( 0.06, 0.34)	7.6	11	0.753
Once-Daily	0.08 ( 0.03, 0.22)	8.2	11	0.697

<sup>1</sup> Center-stratified Odds Ratio based on Success Rates of Vehicle Control / Fluocinonide.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The applicant conducted two pivotal Phase III double-blind vehicle-controlled studies for the purpose of obtaining a claim for corticosteroid-responsive dermatoses; one study was in adult patients with psoriasis (MP-0201-05) and the second study was in adult patients with atopic dermatitis (MP-0201-06).

#### Primary Efficacy Results

Using the dichotomized PGA of overall lesion severity at the end of treatment (Week 2), studies MP-0201-05 and MP-0201-06 demonstrated a statistically significant effect of fluocinonide in the treatment of psoriasis and atopic dermatitis in adults when applied once-daily or twice-daily for two weeks.

In the psoriasis patients in study MP-0201-05, 31% of the twice-daily fluocinonide treatment group and 18% of the patients randomized to the once-daily fluocinonide treatment group were treatment successes at Week 2 compared to only 6-7% of the vehicle controls. ████████ (fluocinonide) 0.1% cream was shown to be statistically superior to vehicle in the treatment of psoriasis when used twice-daily or once-daily for two weeks. Twice-daily fluocinonide treatment was also shown to be superior to once-daily fluocinonide treatment.

In patients with atopic dermatitis (study MP-0201-06), almost 60% of the once-daily and twice-daily fluocinonide patients were treatment successes at Week 2 compared to only 12% of the once-daily and 19% of the twice-daily vehicle controls. Fluocinonide was shown to be statistically superior to vehicle in the treatment of atopic dermatitis in adults when used once or twice-daily for two weeks.

#### Secondary Efficacy Results

Secondary efficacy parameters included Physician's Global Assessment (PGA) of Overall Lesion Severity, Symptom Severity Ratings (including Induration, Erythema, Scaling and Total IES Score for Psoriasis and Erythema, Induration/Papulation, Excoriations, Lichenification and Total Score for Atopic Dermatitis), Pruritus Ratings and Percent Body Surface Area (BSA).

In psoriasis and atopic dermatitis patients, total scores were significantly lower in twice-daily and once-daily fluocinonide treatment groups at Weeks 1 and 2 than their corresponding vehicle controls. Total scores were also significantly lower in twice-daily fluocinonide patients than their corresponding vehicle controls at Week 4. In addition, total scores were significantly lower in twice-daily fluocinonide patients than in once-daily fluocinonide patients.

Similar trends were apparent for many of the other secondary efficacy parameters (with the possible exception of percent body surface area in study MP-0201-05 where there were no statistically significant fluocinonide treatment effects at any week). In most cases the maximum treatment effect was observed at Week 2 in both studies and the magnitude of the treatment effect of the twice-daily dose of fluocinonide was larger than that of the once-daily regimen.

#### Most Common Adverse Events in Psoriasis Patients

For the psoriasis indication, the incidence of overall adverse event rates ranged from 11% in the once-daily fluocinonide treatment group to 19% in the once-daily vehicle controls.

Nervous system disorders were the most prevalent adverse event in fluocinonide patients, reported in 4% of the fluocinonide patients and 2% of the vehicle controls.

Skin and subcutaneous tissue disorders had the highest incidence rates in the vehicle controls. These adverse events were reported in 9% of the vehicle controls and only 1% of the fluocinonide patients.

#### Most Common Adverse Events in Patients with Atopic Dermatitis

The percentage of subjects with adverse events ranged from 25% in the once-daily fluocinonide treatment group to 34% in the once-daily vehicle controls.

Respiratory, thoracic and mediastinal disorders were the most frequently reported adverse event in fluocinonide patients, occurring in 7% of the fluocinonide patients and 8% of the vehicle controls.

Skin and subcutaneous tissue disorders were the most prevalent adverse event in the vehicle controls, reported in 16% of the vehicle controls and only 5% of the fluocinonide patients.

#### Severe Adverse Events (SAEs) in Psoriasis Patients

In study MP-0201-05 SAEs occurred in <1% of the fluocinonide patients and 5% of the vehicle controls. No deaths were reported in the study.

### Severe Adverse Events (SAEs) in Patients with Atopic Dermatitis

In study MP-0201-06, SAEs were only reported in the once-daily regimen; 2% of the fluocinonide patients and 4% of the vehicle controls reported having a severe adverse event. No deaths were reported in the study.

### HPA axis suppression in Patients with Atopic Dermatitis

In study MP-0201-06 the number of subjects with suppressed (abnormal) HPA axis at Week 2 (end of treatment) appeared to be almost the same as the number of subjects with suppressed HPA axis at screening in each treatment group. Approximately 30% of the fluocinonide patients and 15% of the vehicle controls had HPA axis suppressions at screening and Week 2 (end of treatment). Using the FDA definition of post-stimulatin cortisol levels  $\leq 18 \mu\text{g/dL}$  only 1 patient had HPA axis suppression at screening and Week 2. These were different patients, but both patients were in the fluocinonide 0.1%, qd treatment group.

HPA axis suppression data were collected for only 16% (51/314) of the patients enrolled in study MP-0201-06. The sample size was too small to make any definitive conclusions about whether patients who use fluocinonide are at increased risk for HPA Axis suppression. Even for the comparison between the 18 vehicle controls in study MP-0201-06 and the 70 fluocinonide patients in studies MP-0201-01 and MP-0201-06, the power to detect a statistically significant difference at the two-sided 0.05 level was only 1% assuming a true incidence of 0.1% in the vehicle controls and 5% in the fluocinonide treatment group.

## **5.2 Conclusions and Recommendations**

██████████ (fluocinonide) 0.1% cream was shown to be statistically superior to vehicle in the treatment of psoriasis when used twice-daily or once-daily for two weeks. Twice-daily fluocinonide treatment was also shown to be superior to once-daily fluocinonide treatment in psoriasis patients. Thirty-one percent (31%) of the twice-daily fluocinonide treatment group and 18% of the patients randomized to the once-daily fluocinonide treatment group were treatment successes at Week 2 compared to only 6-7% of the vehicle controls.

Fluocinonide was shown to be statistically superior to vehicle in the treatment of atopic dermatitis in adults when used once or twice-daily for two weeks. Almost 60% of the once-daily and twice-daily fluocinonide patients were treatment successes at Week 2 compared to only 12% of the once-daily and 19% of the twice-daily vehicle controls. Since the minimum age of fluocinonide subjects enrolled in this study was 19, no conclusions could be reached about the effectiveness of fluocinonide in pediatric patients with atopic dermatitis.

HPA axis suppression data were collected for only 16% (51/314) of the patients enrolled in study MP-0201-06. Even using HPA axis suppression data from an additional 37 patients in study MP-0201-01, there was insufficient power to rule out the possibility that fluocinonide may put

patients at increased risk for HPA axis suppression.

Appears This Way  
On Original

Appears This Way  
On Original

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

/s/

-----  
Fraser Smith  
1/5/05 03:59:09 PM  
BIOMETRICS

Mohamed Alesh  
1/6/05 08:34:43 AM  
BIOMETRICS  
Concur with review