

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-758**

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

## Clinical Pharmacology/Biopharmaceutics Review

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NDA	21-758
Submission Date	12/17/2004
Brand Name	<u>                    </u>
Generic Name	Fluocinonide
Reviewer	Lei Zhang, Ph.D.
Team Leader	Raman K. Baweja, Ph.D.
OCPB Division	DPE III
OND Division	DDDDP (HFD-540)
Applicant	Medicis
Relevant IND	IND 61,701
Type of Submission; Code	505 (b)(1); 3S
Formulation; Strength(s)	Cream; 0.1%
Indication	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

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### Memo to File

Submission N-000 (BB) from the Sponsor on December 17, 2004 was to clarify a question from the Reviewer during the review of NDA 21-758. Specifically, the Sponsor clarified that Diprolene ointment, 0.05% was used as a comparator in Study MED 02-005. This has been reviewed and incorporated into the final question-based review (QBR) and individual study reviews. Please refer to these reviews linked to the original submission of April 7, 2004 in DFS.

Lei Zhang, Ph.D. \_\_\_\_\_  
Clinical Pharmacology and Biopharmaceutics Reviewer, DPE III  
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Raman K. Baweja, Ph.D. \_\_\_\_\_  
Clinical Pharmacology and Biopharmaceutics Team Leader, DPE III  
Office of Clinical Pharmacology and Biopharmaceutics

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/s/

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Lei Zhang  
1/27/05 04:16:35 PM  
BIOPHARMACEUTICS

Raman Baweja  
1/27/05 05:31:18 PM  
BIOPHARMACEUTICS

## Clinical Pharmacology/Biopharmaceutics Review

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NDA	21-758
Submission Date	4/7/2004, 10/8/2004, 11/8/2004, 11/15/2004
Brand Name	██████████
Generic Name	Fluocinonide
Reviewer	Lei Zhang, Ph.D.
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### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Fluocinonide is a topical corticosteroid, and as such classical *in vivo* pharmacokinetic studies involving plasma drug measurement are not reliable due to the limitation of current analytical methods and the varying percutaneous absorption of corticosteroids. For a topical corticosteroid, evidence of Hypothalamus-Pituitary-Adrenal (HPA) axis suppression is considered more reliable than traditional plasma sampling, and is used as a surrogate for *in vivo* bioavailability evaluation.

In the current submission, the following studies were submitted to support Human Pharmacokinetics and Bioavailability section:

#### *Vasoconstrictor Assay in Healthy Subjects*

Studies MED00-018, MED01-022, MED02-004, and MED02-005 were designed to evaluate the topical potency of fluocinonide cream, 0.1% for its vasoconstrictor effect in comparison to the currently marketed topical corticosteroids (Temovate®, Psorcon®, Diplorene®, Ultravate®, and Lidex-E®). Study MED00-018 was not reviewed because of its exploratory nature. Study MED01-022 was not reviewed because it was repeated in later studies (the synopsis for this study was attached in Section 4.3.1). Results from studies MED02-004 and MED02-005 suggested a potency for the fluocinonide 0.1% cream formulation that would be in the super-high potency range based on the super- (ultra-) high potency ranking of both Temovate® Cream 0.05% and Ointment 0.05%, Psorcon® Ointment 0.05% and Diprolene® Ointment 0.05%, and the high potency ranking of Lidex-E® Cream 0.05%.

#### *Adrenal Suppression Studies in Clinical Subjects*

HPA axis suppression was evaluated in two studies in adult plaque-type psoriasis patients (Study MP-0201-01) and adult atopic dermatitis patients (Study MP-0201-06).

The HPA axis results from Study MP-0201-01 and MP-0201-06 indicated that the systemic safety based on HPA axis suppression potential is acceptable for the 0.1% fluocinonide cream drug product (BID) in adult plaque-type psoriasis patients, and BID or QD in adult atopic dermatitis patients for up to two weeks under the study conditions. However, the patients in these studies were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible. For Study MP-0201-06, patients with 2-10% BSA were enrolled because fluocinonide is a super-high potent corticosteroid, and the limit of dose is 50 g per week. 1 g of cream usually covers approximately 2% BSA. 50 g per week limited the %BSA to be applied to ~10% (for a BID regimen). Although no clear correlation between %BSA and HPA axis suppression was observed, labeling needs to restrict time duration and area of drug application to limit the risk of HPA axis suppression in patients because of the well-known adrenal suppression effect from corticosteroids and the limitation of the HPA axis suppression testing.

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Lei Zhang, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Pharmaceutical Evaluation III

Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

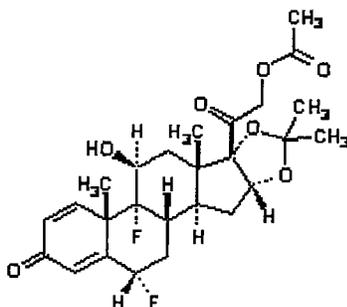
\_\_\_\_\_  
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Clinical Pharmacology Team Leader  
Division of Pharmaceutical Evaluation III  
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## 2 QUESTION BASED REVIEW

### 2.1. General Attributes

#### 2.1.1. What are the highlights of the physicochemical properties of fluocinonide?

The chemical name is 6 alpha, 9 alpha-difluoro-11 beta,21-dihydroxy-16 alpha,17 alphasopropylidenedioxypregna-1,4-diene-3,20-dione 21-acetate. Its chemical formula is C<sub>26</sub>H<sub>32</sub>F<sub>2</sub>O<sub>7</sub>, and its molecular weight is 494.58. The structural formula is shown below:



#### 2.1.2. What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of fluocinonide cream, 0.1% from the Sponsor?

##### Indication:

Fluocinonide Cream, 0.1% is indicated for the relief of the inflammatory and pruritic manifestation of corticosteroid-responsive dermatoses.

##### Dosage and Route of Administration:

Applied topically  daily as directed by the physician. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 60 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

### **Mechanism of Action:**

Like other topical corticosteroids, fluocinonide has anti-inflammatory, antipruritic and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids is unclear. However corticosteroids are thought to act by the induction of phospholipase A<sub>2</sub> inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A<sub>2</sub>.

## **2.2. General Clinical Pharmacology**

### **2.2.1. What studies have been conducted for biopharmaceutic/bioavailability evaluation of the drug product? What are the outcomes of these studies?**

Complete study reports for four vasoconstrictor studies (MED00-018, MED01-022, MED02-004, and MED02-005) and two HPA axis studies (Study 0201-01 and Study MP-0201-06) were included in the submission. One HPA axis study in pediatric patients (Study MP-0201-07) is ongoing at the time of review.

### **Results of Vasoconstriction Study:**

Study MED00-018 was not reviewed because of its exploratory nature. Study MED01-022 was not reviewed because it was repeated in later studies (the synopsis for this study was attached in Section 4.3). Results from Study MED02-004 and Study MED002-05 are listed in Tables 2.2.1.1 and 2.2.1.2. These results suggested a potency for the fluocinonide 0.1% cream formulation that would be in the super- (ultra-) high potency range based on the super-high potency ranking of both Temovate<sup>®</sup> Cream 0.05% and Ointment 0.05%, Psorcon<sup>®</sup> Ointment 0.05% and Diprolene<sup>®</sup> Ointment 0.05%, and the high potency ranking of Lidex-E<sup>®</sup> Cream 0.05%. Details of the vasoconstrictor study are provided in Section 4.2.1 (4.2.1.1 and 4.2.1.2).

**Table 2.2.1.1. Summary of Visual Assessments of Vasoconstriction (MED02-004).**

<b>Code</b>	<b>Product</b>	<b>Potency</b>	<b>Total Score</b>	<b>Mean Score</b>	<b>Mean Rank*</b>
B	Temovate <sup>®</sup> Cream 0.05%	Super High	94	2.6	5.194
E	Fluocinonide 0.1% cream	Test	86	2.4	4.569
F	Fluocinonide 0.2% cream	Test	85	2.4	4.556
D	Lidex-E <sup>®</sup> Cream 0.05%	High	85	2.4	4.486
C	Fluocinonide 0.05% cream	Test	75	2.1	4.181
G	Ultravate <sup>®</sup> 0.05% Cream	Super High	63	1.8	3.486
A	Placebo (fluocinonide cream vehicle)	Test	15	0.4	1.528

\*Mean rank is obtained by ranking the visual assessment scores for all treatments within subject (lowest to highest) and taking the mean of those ranks. Lower rank corresponds to lower visual assessment score.

**Table 2.2.1.2. Summary of Visual Assessments of Vasoconstriction (MED02-005).**

Code	Product	Potency	Total Score	Mean Score	Mean Rank*
A	Temovate <sup>®</sup> Ointment 0.05%	Super High	76	2.1	4.778
D	Psorcon <sup>®</sup> Ointment 0.05%	Super High	76	2.1	4.708
B	Fluocinonide 0.1% ointment	Test	75	2.1	4.681
C	Fluocinonide 0.1% cream	Test	72	2.0	4.514
F	Diprolene <sup>®</sup> Ointment 0.05%	Super High	65	1.8	4.097
E	Lidex-E <sup>®</sup> Cream 0.05%	High	51	1.4	3.347
G	Placebo (fluocinonide ointment vehicle)	Test	12	0.3	1.875

\*Mean rank is obtained by ranking the visual assessment scores for all treatments within subject (lowest to highest) and taking the mean of those ranks. Lower rank corresponds to lower visual assessment score.

**Results of HPA Axis Suppression Studies:**

Study MP-0201-01 is a Phase 2 study that evaluated the potential of fluocinonide 0.1% cream to suppress the HPA axis, as compared to the marketed corticosteroid, Lidex (fluocinonide 0.05% cream) when applied twice daily (*bid*) for 14 days in subjects with plaque-type psoriasis (10-50% BSA). Study MP-0201-06 is a Phase 3 study that evaluated the efficacy and safety of fluocinonide 0.1% cream in the treatment of atopic dermatitis (2-10% BSA) when applied topically twice daily or once daily for 2 weeks. A subset of patients in this study were evaluated for HPA axis suppression potential.

Results from Study MP-0201-01 and Study MP-0201-06 are summarized in Tables 2.2.1.3 and 2.2.1.4. Details of the HPA axis suppression studies are provided in Section 4.2.2 (4.2.2.1 and 4.2.2.2).

**Table 2.2.1.3. Comparison between 0.1%  (fluocinonide) cream BID and 0.05% Lidex (fluocinonide) cream BID treatment groups (MP-0201-01).**

	HPA Axis Suppression at Week 2	Total Weight of Application (g) (Mean)	% BSA at Baseline (Mean ± SD) (Range)	Baseline 30-min Post-Stimulation Serum Cortisol Level (µg/dL) (Mean ± SD)	Week 2 30-min Post-Stimulation Serum Cortisol Level (µg/dL) (Mean ± SD)
<b>0.1%  (Fluocinonide) (N=18)</b>	2/18 (11.1 %)	59-117 (95)	19.6 ± 10.9 (10-50)	26.3 ± 3.9	26.4 ± 6.6
<b>0.05% Lidex (Fluocinonide) Cream BID (N=19)</b>	1/19 (5.3%)	31-114 (75)	14.8 ± 5.9 (10-32)	26.7 ± 4.0	27.5 ± 5.3

**Table 2.2.1.4. Comparison between 0.1% **██████████** (fluocinonide) cream QD and 0.1% **██████████** (fluocinonide) cream BID treatment groups (MP-0201-06).**

	HPA Axis Suppression at Wk 2	Weight per Application (g) (Mean ± SD)	% BSA at Baseline (Mean ± SD) (Range)
<b>0.1% <b>██████████</b> (Fluocinonide) Cream QD (N=17)</b>	1/17 (5.9%)	1.5 ± 1.3	4.7 ± 2.3 (2-10)
<b>0.1% <b>██████████</b> (Fluocinonide) Cream BID (N=14)</b>	0/14 (0%)	1.3 ± 0.9	5.1 ± 1.8 (3-10)

The HPA axis results from these two studies indicated that the systemic safety based on HPA axis suppression potential is acceptable for the 0.1% **██████████** (fluocinonide) cream drug product (BID) in adult plaque-type psoriasis patients, and BID or QD in adult atopic dermatitis patients for up to two weeks under the study conditions. However, the patients in these studies were not necessarily tested under the maximal usage conditions, i.e., they did not have as a high percentage of BSA of the diseased skin as possible. For Study MP-0201-06, patients with 2-10% BSA were enrolled because fluocinonide is a super-high potent corticosteroid, and the limit of dose is 50 g per week. 1 g of cream usually covers approximately 2% BSA. 50 g per week limited the %BSA to be applied to ~10% (for a BID regimen). Mean %BSA in Study MP-0201-01 was 15-20% and in Study MP-0201-06 was 5%. Although no clear correlation between %BSA and HPA axis suppression was observed, labeling needs to restrict the time of duration and area of drug application to limit the risk of HPA axis suppression in patients because of the well-known adrenal suppression effect from corticosteroids and the limitation of the HPA axis suppression testing.

## 2.5 General Biopharmaceutics

### 2.5.1. What is formulation (quantitative composition) of 0.1% **██████████** (fluocinonide) cream?

Table 2.5.1.1 shows the composition of the drug product. The formulation is different from that of previous Lidex 0.05% cream.

**Appears This Way  
On Original**

**Table 2.5.1.1. Composition of the Drug Product, Fluocinonide 0.1% Cream**

Component	Function	Raw Material Code	% w/w	Testing Standard	Typical Vendor
Propylene glycol, USP	Solvent for active			USP	[REDACTED]
Dimethyl isosorbide				Patheon	
[REDACTED] PEG stearate)				Patheon	
Glyceryl monostearate NF				NF	
Purified water, USP				USP	
Carbopol 980				NF	
Diisopropanolamine				Patheon	
Fluocinonide, micronized, USP				Patheon	
Citric acid, USP				USP/NF	

**2.5.2. Are there any differences between clinical and to-be-marketed formulations?**

All batches utilized in the clinical and human biopharmaceutic studies to support this application were made with the to-be-marketed formula (LB-0094 and MPC 6051-13-01AX).

**3 DETAILED LABELING RECOMMENDATIONS**

Recommendations for changes to the proposed labeling are provided below (only affected sections relating to Clinical Pharmacology are listed).

**CLINICAL PHARMACOLOGY**

[REDACTED]

7 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

## 4.2 Individual Study Reviews

### 4.2.1 Vasoconstrictor Study

#### 4.2.1.1. Study MED02-004: A Randomized, Evaluator-blinded, Within-subject, Single-center Evaluation of the Vasoconstrictive Properties of Fluocinonide 0.05%, 0.1%, and 0.2% Creams in Normal Healthy Volunteers

Study Rationale: Topical corticosteroids produce a localized skin-blanching response when applied to skin, caused by constriction of the superficial blood vessels of the skin. The degree of skin blanching assessed by visual scoring is a measure of the inherent potency of the drug and its capacity to diffuse through the stratum corneum. The vasoconstrictor assay is the most widely used surrogate test to assess the potency of topical corticosteroids.

Objectives: The objective of this study was to evaluate the relative vasoconstrictive potential of fluocinonide 0.05%, 0.1%, and 0.2% creams and their vehicle cream, compared with Temovate® Cream, Ultravate® 0.05% Cream and Lidex-E® 0.05% Cream.

Study Site: \_\_\_\_\_

Investigator: \_\_\_\_\_

Study Period: April 11, 2002 to April 18, 2002

Study Design: This was a 2-day, randomized, evaluator-blinded, within-subject, single-center study. Thirty-six healthy volunteers (18-60 years) enrolled and completed the study (Appendix, Table A1). Seven products were evaluated: 3 on one forearm and 4 on the other.

On Day 1, each subject had four 1 cm<sup>2</sup> test sites identified on each ventral forearm. A single application of approximately 10 mg of each study medication was applied in accordance with a computer-generated randomization code. Test sites were protected using a raised, perforated guard that was secured to the arm with nonocclusive tape. Subjects were instructed to keep the test sites dry, and were scheduled to return the following day.

On Day 2, 16 hours following study medication applications, the subjects removed the protective guards at home and gently washed the test sites with mild soap and water. Upon return to the clinic, 2 hours later (18 hours after the study medication applications), an experienced evaluator performed the Visual Assessment of Vasoconstriction (skin-blanching) and assessed the skin at each site based on a 4-point scale (0-3):

- 0 = no blanching; no change from surrounding area
- 1 = mild blanching; slight or indistinct outline at application site
- 2 = moderate blanching; discernible outline at application site
- 3 = marked blanching; distinct outline at application site

Safety was assessed based on concurrent medical conditions, concomitant therapies and adverse events.

Duration of treatment: 16 hours

Investigational product:

Identification: Fluocinonide 0.05% cream (code C)

Active ingredient: Fluocinonide micronized USP

Batch number: 718

Identification: Fluocinonide 0.1% cream (code E)

Active ingredient: Fluocinonide micronized USP

Batch number: 719

*(Reviewer's Note: The batch used in the study, although an earlier small scale batch, is the same in both quantity and quality as the final clinical batch used in pivotal Phase 2 and 3 clinical studies.)*

Identification: Fluocinonide 0.2% cream (code F)

Active ingredient: Fluocinonide micronized USP

Batch number: 720

Note: Due to the small quantities of fluocinonide formulations required for evaluation, only Batch numbers (and not Lot numbers) were assigned, according to the SOP of the manufacturer.

Comparator:

Identification: Lidex-E® Cream 0.05% (code D)

Active ingredient: Fluocinonide USP

Lot number: RAB044

Identification: Temovate® Cream 0.05% (code B)

Active ingredient: Clobetasol propionate

Lot number: IE288

Identification: Ultravate® Cream 0.05% (code G)

Active ingredient: Halobetasol propionate

Lot number: 14P038

Identification: Fluocinonide cream vehicle (code A)

Active ingredient: None

Batch number: 717

Results:

Total vasoconstriction scores ranged from 15 (placebo) through 94 (Temovate®), with mean scores ranging from '0.4' (0 = no blanching) at the placebo treatment site to '2.6' (3 = marked blanching) at the Temovate® treatment site (Table 1).

**Table 1. Summary of Visual Assessments of Vasoconstriction (MED02-004).**

Code	Product	Potency	Total Score	Mean Score	Mean Rank*
B	Temovate <sup>®</sup> Cream 0.05%	Super High	94	2.6	5.194
E	Fluocinonide 0.1% cream	Test	86	2.4	4.569
F	Fluocinonide 0.2% cream	Test	85	2.4	4.556
D	Lidex-E <sup>®</sup> Cream 0.05%	High	85	2.4	4.486
C	Fluocinonide 0.05% cream	Test	75	2.1	4.181
G	Ultravate <sup>®</sup> 0.05% Cream	Super High	63	1.8	3.486
A	Placebo (fluocinonide cream vehicle)	Test	15	0.4	1.528

\*Mean rank is obtained by ranking the visual assessment scores for all treatments within subject (lowest to highest) and taking the mean of those ranks. Lower rank corresponds to lower visual assessment score.

Analysis of the mean rank of the visual assessment of vasoconstriction assay (VCA) scores indicated that fluocinonide 0.1% cream and fluocinonide 0.2% cream were similar to Lidex-E<sup>®</sup> Cream and Temovate<sup>®</sup>, and they were significantly more active than the vehicle cream ( $p < 0.001$ ) (Table 1 and Appendix, Table A2). The VCA responses of fluocinonide 0.05% cream was significantly less than that of Temovate<sup>®</sup> 0.05% Cream ( $p = 0.005$ ). In addition, the VCA responses of fluocinonide 0.1% cream and fluocinonide 0.2% cream were significantly greater than that of Ultravate<sup>®</sup> 0.05% Cream ( $p = 0.003$ ), while fluocinonide 0.05% cream was similar to Ultravate<sup>®</sup> 0.05% Cream.

#### Discussion and Conclusions:

This study compared the relative potency of new formulations of fluocinonide 0.05%, 0.1%, and 0.2% creams and their vehicle in comparison to Temovate<sup>®</sup> Cream 0.05% (Class 1, super high potency), Ultravate<sup>®</sup> 0.05% Cream (Class 1, super high potency), and Lidex-E<sup>®</sup> Cream 0.05% (Class 2, high potency) FDA-approved, currently marketed topical corticosteroids with rankings established using the vasoconstrictor assay. The fluocinonide 0.1% cream formulation demonstrated potency similar to that of Temovate<sup>®</sup> 0.05% Cream (super high potency) and significantly greater than that of Ultravate<sup>®</sup> 0.05% Cream (super high potency). Interestingly, Lidex-E<sup>®</sup> Cream 0.05%, a highly potent corticosteroid, showed comparable potency to Temovate<sup>®</sup> Cream 0.05% (super high potency) and was more potent than Ultravate 0.05% Cream (super high potency) in this study. These results suggest that 0.1% fluocinonide cream formulation has activity in the super high potency category, and can be classified as Class 1. There was no increase in potency from 0.1% cream to 0.2% cream.

**Appendix (MED02-004)**

**Table A1. Summary of Demographics**

Age (years)	
N	36
Mean (SD)	38.4 (11.2)
Median	36.6
Range	18.0 - 60.3
Sex, n(%)	
Female	27 ( 75.0%)
Male	9 ( 25.0%)
Race, n(%)	
White	21 ( 58.3%)
Asian/Pacific Islander	7 ( 19.4%)
Hispanic/Latino	6 ( 16.7%)
Black	1 ( 2.8%)
American/Alaskan Native	1 ( 2.8%)

**Table A2. Summary of Visual Assessments of Vasoconstriction**

Product (Cream)	Total Score	Mean Rank**	COMPARISONS***						
			A	B	C	D	E	F	G
B) Temovate 0.05%	94	5.184	<.001*	—	0.005*	0.050*	0.083	0.076	<.001*
E) Fluocinonide 0.1%	86	4.569	<.001*	0.083	0.279	0.816	—	0.969	0.003*
F) Fluocinonide 0.2%	85	4.556	<.001*	0.076	0.297	0.847	0.969	—	0.003*
D) Lidex 0.05%	85	4.488	<.001*	0.050*	0.395	—	0.816	0.847	0.006*
C) Fluocinonide 0.05%	75	4.181	<.001*	0.005*	—	0.395	0.279	0.297	0.054
G) Ultravate 0.05%	63	3.486	<.001*	<.001*	0.054	0.006*	0.003*	0.003*	—
A) Vehicle	15	1.528	—	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*

\* p-Value is significant at the 0.05 level.

\*\* Mean rank is obtained by ranking the visual assessment scores for all treatments within subject (lowest to highest) and taking the mean of those ranks. Lower rank corresponds to lower visual assessment score.

\*\*\* p-Values are obtained using a Friedman analysis.

**4.2.1.2. Study MED02-005: A Randomized, Evaluator-blinded, Within-subject, Single-center Evaluation of the Vasoconstrictive Properties of Fluocinonide 0.1% Cream and 0.1% Ointment in Normal Healthy Volunteers**

Objectives: The objective of this study was to evaluate the relative vasoconstrictive potential of Fluocinonide 0.1% cream and 0.1% ointment and the vehicle ointment, compared with Temovate® Ointment 0.05%, Psorcon® Ointment 0.05%, Diprolene® Ointment 0.05% and Lidex-® E 0.05% Cream: FDA-approved and marketed reference drugs

Study Site: \_\_\_\_\_

Investigator: \_\_\_\_\_

Study Period: June 10, 2002 to June 20, 2002

Study Design: This was a 2-day, randomized, evaluator-blinded, within-subject, single-center study. Thirty-six healthy volunteers (18-60 years) enrolled and completed the study (Appendix, Table A1) (Reviewer's Note: *It appears that majority of the 36 subjects who enrolled in Study MED02-004 were re-enrolled in this study.*) Seven products were evaluated: 3 on one forearm and 4 on the other.

Reviewer's Note: *This study adopted the same study design as MED02-004. The rest of the study design is not repeated in this review. Please refer to individual study review for Study MED02-004 for details.*

Duration of treatment: 16 hours

Investigational product:

Identification: Fluocinonide 0.1% cream (code C)  
Active ingredient: Fluocinonide micronized USP  
Batch number: 719

Identification: Fluocinonide 0.1% ointment (code B)  
Active ingredient: Fluocinonide micronized USP  
Batch number: 730

Note: Due to the small quantities of fluocinonide formulations required for evaluation, only Batch numbers (and not Lot numbers) were assigned according to the SOP of the manufacturer.

Comparator:

Identification: Lidex-E® Cream 0.05% (code E)  
Active ingredient: Fluocinonide USP  
Lot number: RAD030

Identification: Temovate® Ointment 0.05% (code A)  
Active ingredient: Clobetasol propionate  
Lot number: IH374

Identification: Psorcon® Ointment 0.05% (code D)  
Active ingredient: Diflorasone diacetate  
Lot number: 0012FSR

Identification: Diprolene® Ointment 0.05% (code F)  
Active ingredient: Betamethasone dipropionate  
Lot number: THYA502

Identification: Fluocinonide ointment vehicle (code G)  
Active ingredient: None  
Lot number: 729

Results:

Total vasoconstriction scores ranged from 12 (placebo) through 76 (Temovate® and Psorcon®), with mean scores ranging from '0.3' (0 = no blanching) at the placebo site to '2.1' (2 = moderate blanching) at the Temovate®, Psorcon® and, fluocinonide 0.1% ointment sites (Table 1).

**Table 1. Summary of Visual Assessments of Vasoconstriction (MED02-005)**

Code	Product	Potency	Total Score	Mean Score	Mean Rank*
A	Temovate® Ointment 0.05%	Super High	76	2.1	4.778
D	Psorcon® Ointment 0.05%	Super High	76	2.1	4.708
B	Fluocinonide 0.1% ointment	Test	75	2.1	4.681
C	Fluocinonide 0.1% cream	Test	72	2.0	4.514
F	Diprolene® Ointment 0.05%	Super High	65	1.8	4.097
E	Lidex-E® Cream 0.05%	High	51	1.4	3.347
G	Placebo (fluocinonide ointment vehicle)	Test	12	0.3	1.875

\*Mean rank is obtained by ranking the visual assessment scores for all treatments within subject (lowest to highest) and taking the mean of those ranks. Lower rank corresponds to lower visual assessment score.

Statistical comparison of the mean rank scores of fluocinonide 0.1% ointment and fluocinonide 0.1% cream showed no significant between-treatment differences, and both treatments ranked significantly higher than placebo ( $p < 0.001$ ) and Lidex-E® Cream 0.05% ( $p \leq 0.004$ ) (Table 1 and Appendix, Table A2). In addition both fluocinonide 0.1% ointment and fluocinonide 0.1% cream showed no significant between-treatment differences when compared to Temovate® Ointment 0.05%, Psorcon® Ointment 0.05%, or Diprolene® Ointment 0.05%.

Discussion and Conclusions:

This study compared the relative potency of new formulations of Fluocinonide 0.1% cream and 0.1% ointment and the vehicle ointment in comparison to Temovate® Ointment 0.05% (Class 1, super high potency), Psorcon® Ointment 0.05% (Class 1, super high potency), Diprolene® Ointment 0.05% (Class 1, super high potency), and Lidex® E 0.05% Cream (Class 2, high potency): FDA approved, marketed topical corticosteroids with rankings established using the vasoconstrictor assay. The results of this study suggest a potency for the fluocinonide 0.1% ointment and fluocinonide 0.1% cream formulations that would be in the super high potency range based on the ultra high potency ranking of Temovate® Ointment 0.05%, Psorcon® Ointment 0.05%, and Diprolene® Ointment 0.05% and the high potency ranking of Lidex-E® Cream 0.05%.

## Appendix (MED02-005)

### Table A1. Summary of Demographics

Age (years)	
N	36
Mean (SD)	39.6 (11.5)
Median	38.7
Range	18.2 - 60.5
Sex, n(%)	
Female	27 ( 75.0%)
Male	9 ( 25.0%)
Race, n(%)	
White	21 ( 58.3%)
Hispanic/Latino	7 ( 19.4%)
Asian/Pacific Islander	6 ( 16.7%)
Black	1 ( 2.8%)
American/Alaskan Native	1 ( 2.8%)

### Table A2. Summary of Visual Assessments of Vasoconstriction

Product	Total Score	Mean Rank**	COMPARISONS***						
			A	B	C	D	E	F	G
A) Tamovate Oint. 0.05%	76	4.778	—	0.809	0.512	0.863	<.001*	0.092	<.001*
D) Psorcon Oint. 0.05%	76	4.708	0.863	0.545	0.629	—	<.001*	0.130	<.001*
B) Fluocinonide 0.1% Oint	75	4.681	0.609	—	0.679	0.945	0.001*	0.148	<.001*
C) Fluocinonide 0.1% Crm	72	4.514	0.512	0.679	—	0.629	0.004*	0.301	<.001*
F) Diprolene Oint. 0.05%	65	4.087	0.092	0.148	0.301	0.130	0.064	—	<.001*
E) Lidex E 0.05% Crm	51	3.347	<.001*	0.031*	0.004*	<.001*	—	0.064	<.001*
G) Ointment Vehicle	12	1.875	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	—

\* p-Value is significant at the 0.05 level.

\*\* Mean rank is obtained by ranking the visual assessment scores for all treatments within subject (lowest to highest) and taking the mean of those ranks. Lower rank corresponds to lower visual assessment score.

\*\*\* p-Values are obtained using a Friedman analysis.

## 4.2.2 HPA Axis Suppression Study

### 4.2.2.1. Study MP-0201-01: A Randomized, Parallel, Open-Label, Adrenal Suppression Study of Fluocinonide 0.1% Cream as compared to Fluocinonide 0.05% Cream (Lidex®) in Subjects with Plaque-Type Psoriasis

**Objectives:** The objective of the study was to evaluate the potential of fluocinonide 0.1% cream to suppress the HPA axis, as compared to the marketed corticosteroid, Lidex (fluocinonide 0.05% cream) when applied twice daily (*bid*) for 14 days by subjects with plaque-type psoriasis.

**(Reviewer's Note:** In the protocol and study report, the Sponsor defined normal HPA axis function as 1) an early morning serum cortisol level >5 µg/dL, 2) serum cortisol levels >18 µg/dL approximately 30 minutes following stimulation, and 3) with an increase over basal levels ≥ 7

NDA 21-758

██████████<sup>4</sup> (Fluocinonide) Cream, 0.1%  
Original NDA Review

*µg/dL, in response to 0.25 mg cosyntropin administered by intravenous (IV) injection. In the FDA draft guidance, only one criterion, i.e., serum cortisol level > 18 µg/dL 30-min post-stimulation is recommended as the indication for normal HPA axis function. Therefore, the Reviewer used a 30-min post-stimulation level ≤ 18 µg/dL as the definition for HPA axis suppression to review the HPA axis data for this study.)*

Study Sites: Five study sites in the U.S.

Investigators: \_\_\_\_\_

Study Period: December 30, 2002 to March 12, 2003

Study Design: This was a multi-center, randomized, multiple-dose, comparator-controlled, open-label study of the investigational product (fluocinonide 0.1% cream) and Lidex® 0.05% in subjects with clinically diagnosed plaque-type psoriasis (≥ 10% of total body surface area). Qualified subjects had a normally functioning HPA axis, as defined by serum cortisol levels >18 µg/dL, approximately 30 minutes following stimulation in response to 0.25 mg cosyntropin administered by intravenous (IV) injection. The analytical lab responsible for cortisol assays was blinded to the treatment assignments.

A total of 37 subjects (>18 years old) were screened and enrolled in the study. Subjects were randomized to 1 of 2 treatment groups, fluocinonide 0.1% cream (18 subjects) or Lidex® 0.05% (19 subjects), applied topically *bid* for 2 weeks (Appendix, Table A1). Dosage was 3.5 g per application or 7 g daily, to achieve an exposure of approximately 50 g per week. Blood samples for serum cortisol levels were collected pre- and post- stimulation with cosyntropin at screening (-1 wk), Baseline (Week 0), and Week 2. At the end of the 14-day treatment period, any subject with HPA axis suppression was re-tested at Week 4 and weekly thereafter until 1 of the 2 control levels (pre- or post- stimulation) was within normal limits.

Safety assessments included serum cortisol levels before and after stimulation with cosyntropin, fasting blood glucose levels, skin safety evaluations (signs and symptoms of skin atrophy), vital signs, weight, and evaluation of any adverse events (AEs) reported during the study. Efficacy assessments were made at Week 2 and Week 4. This review will focus on HPA axis suppression as indicated by post-stimulation cortisol levels.

Duration of treatment: 2 weeks

Investigational product:

Fluocinonide Cream (0.1%): Lot Number: R0044D001

Manufactured by: Patheon, Inc, 2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9

Comparator:

Lidex® (fluocinonide cream 0.05%): Lot Number: RAB045

Manufactured by: Patheon, Inc, 2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9

**Results:**

The total weight of investigational medication used for fluocinonide 0.1% BID treatment group ranged from 59 g – 117 g with a mean of 95 g. Subjects randomized to fluocinonide 0.05% BID treatment group used 31 g – 114 g of medication, with a mean of 75 g. Total drug applied (in terms of weight) and %BSA at Baseline were slightly higher for the 0.1% treatment group (~30%) in this study (Table 1). Subjects 6, 12, 27 and 29 missed 1 application of fluocinonide 0.05% and subject 4 missed 2 applications of fluocinonide 0.05%. Subjects 11 and 37 missed 1 application of fluocinonide 0.1% and subjects 5 and 15 missed 2 applications of fluocinonide 0.1% during the study treatment period. Because the missed doses were not considered to have a significant impact on the overall exposure to the drug, these subjects were included in the final HPA axis evaluation.

Serum cortisol level data are listed in Appendix Tables A2 and A3. At the Week 2 visit, 2 subjects (Subject 20 and 37, 2 out of 18, 11.1%) in the 0.1% fluocinonide group and 1 subjects (Subject 23, 1 out of 19, 5.3%) in the 0.05% Lidex (fluocinonide) group met the criterion for HPA axis suppression (Table 1). At the Week 4 visit (2 weeks post treatment), 1 subject (Subject 17) in the 0.1% fluocinonide met the HPA axis suppression criterion who did not show suppression at Week 2. No clear correlation between %BSA and HPA axis suppression was observed (Appendix, Table A4).

**Table 1. Comparison between 0.1% fluocinonide cream BID and 0.05% Lidex (fluocinonide) cream BID treatment groups.**

	HPA Axis Suppression at Week 2	Total Weight of Application (g) (Mean)	% BSA at Baseline (Mean ± SD) (Range)	Baseline 30-min Post-Stimulation Serum Cortisol Level (µg/dL) (Mean ± SD)	Week 2 30-min Post-Stimulation Serum Cortisol Level (µg/dL) (Mean ± SD)
<b>0.1% Fluocinonide cream BID (N=18)</b>	2/18 (11.1 %)	59-117 (95)	19.6 ± 10.9 (10-50)	26.3 ± 3.9	26.4 ± 6.6
<b>0.05% Lidex (Fluocinonide) cream BID (N=19)</b>	1/19 (5.3%)	31-114 (75)	14.8 ± 5.9 (10-32)	26.7 ± 4.0	27.5 ± 5.3

**Discussion and Conclusions:**

The evidence of systemic availability of fluocinonide in the 0.1% product was provided by using HPA axis suppression as a pharmacodynamic endpoint. Under the conditions provided in this study in adult patients with plaque-type psoriasis (≥10% BSA), 0.1% fluocinonide treatment group showed a higher rate of HPA axis suppression than the approved 0.05% fluocinonide treatment group (11% vs. 5%) following BID dosing for two weeks. This result is anticipated

because more drug is applied at the same dosing interval for the 0.1% drug product. The HPA axis results obtained from this study suggest that the systemic safety based on HPA axis suppression is acceptable for the 0.1% fluocinonide drug product (BID for two weeks) in adult plaque-type psoriasis patients. However, the patients in this study were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible (BSA range 10-50%, mean 19.6%). Although no clear correlation between %BSA and HPA axis suppression was observed from this study, labeling needs to restrict the time of duration and area of drug application to limit the risk of HPA axis suppression in patients because of well-known adrenal suppression effect of topical corticosteroids and the limitation of the study (e.g., small number of patients).

### Appendix (MP-0201-01)

**Table A1. Demographic summary by treatment groups (MP-0201-01)**

	Fluocinonide 0.05% N = 19	Fluocinonide 0.1% N = 18
Age (yr)		
mean ± SD	45.4 ± 14.2	46.6 ± 14.0
range	20 - 68	21 - 71
Gender - n(%)		
male	13 (68%)	11 (61%)
female	6 (32%)	7 (39%)
Race - n(%)		
Caucasian	16 (84%)	16 (89%)
Asian	1 (5%)	0
Hispanic	1 (5%)	2 (11%)
Other	1 (5%)	0
Height (in)		
mean ± SD	67.9 ± 4.99	68.3 ± 3.58
range	58 - 76	62 - 76
Weight (lbs)		
mean ± SD	196 ± 43.0	202 ± 53.4
range	106 - 279	118 - 329
Duration of disease (yrs)		
mean ± SD	17.9 ± 16.3	16.0 ± 13.8
range	1 - 49	1 - 42
BSA involvement (%)		
mean ± SD	14.8 ± 5.86	19.6 ± 10.9
range	10 - 32	10 - 50

Subjects 6, 12, 27 and 29 missed 1 application of fluocinonide 0.05% and subject 4 missed 2 applications of fluocinonide 0.05%. Subjects 11 and 37 missed 1 application of fluocinonide 0.1% and subjects 5 and 15 missed 2 applications of fluocinonide 0.1% during the study treatment period.

**Table A2. Cortisol Levels in 0.1% fluocinonide treatment group (N=18).**

Treatment Group: Fluocinonide 0.1%

Site	Subject	Visit	---- Pre-stimulation ----			Cosym Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
1	26	SCREENING	8:00	96	14.2	8:01	8:30	37.9	29
		BASELINE	7:55	94	18.1	7:56	8:25	30.0	29
		WEEK 2	8:00	94	14.9	8:01	8:30	35.4	29
1	28	SCREENING	7:55	113	10.7	7:56	8:25	20.3	29
		BASELINE	8:00	100	12.6	8:01	8:30	24.1	29
		WEEK 2	7:55	106	12.4	7:56	8:25	22.6	29
2	1	SCREENING	8:18	89	16.6	8:18	8:49	26.6	31
		BASELINE	7:45	94	14.3	7:45	8:15	25.9	30
		WEEK 2	7:50	97	19.3	7:50	8:20	31.8	30
2	3	SCREENING	7:50	97	14.8	7:50	8:20	22.6	30
		BASELINE	7:35	92	19.1	7:35	8:05	26.8	30
		WEEK 2	7:45	96	18.2	7:45	8:15	23.6	30
		WEEK 4	7:50		15.7	7:50	8:20	24.0	30
2	5	SCREENING	7:40	103	11.4	7:40	8:10	27.1	30
		BASELINE	7:30	105	12.5	7:30	8:00	27.4	30
		WEEK 2	8:13	92	10.2	8:13	8:42	26.6	29
2	8	SCREENING	8:15	97	17.1	8:15	8:45	27.1	30
		BASELINE	8:15	90	19.5	8:15	8:45	27.2	30
		WEEK 2	7:35	97	10.7	7:35	8:05	24.1	30
3	9	SCREENING	8:00	92	14.4	8:02	8:33	23.7	31
		BASELINE	7:46	92	16.6	7:55	8:25	23.8	30
		WEEK 2	8:03	94	16.0	8:12	8:43	23.1	31
3	11	SCREENING	8:05	100	12.5	8:20	8:52	27.1	32
		BASELINE	8:09	110	11.3	8:20	8:54	23.6	32
		WEEK 2	8:20	121	13.8	8:45	9:16	30.6	31

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Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
3	13	SCREENING	8:15	111	15.5	8:46	9:31	25.4	45
		BASELINE	8:27	95	10.8	8:44	9:17	24.0	33
		WEEK 2	8:29	135	19.2	8:57	9:45	35.7	48
3	15	SCREENING	8:27	118	19.2	8:39	9:10	29.8	37
		BASELINE	7:30	107	21.2	7:44	8:15	27.5	31
		WEEK 2	8:11	119	27.3	8:45	9:28	33.7	42
		WEEK 4	8:21		20.4	8:30	9:00	25.6	30
3	33	SCREENING	7:57	101	11.7	8:11	8:46	25.9	35
		BASELINE	7:45	102	12.9	7:49	8:20	36.3	31
		WEEK 2	7:55	105	13.2	8:43	9:20	36.6	37
4	17	SCREENING	7:44	94	20.1	7:45	8:15	25.8	30
		BASELINE	7:14	99	18.1	7:15	7:45	25.7	30
		WEEK 2	7:14	92	17.3	7:15	7:45	23.6	30
		WEEK 4	7:34		14.5	7:35	8:05	12.9	30
		RETEST	7:34		18.4	7:35	8:05	27.0	30
4	20	SCREENING	7:44	149	17.2	7:45	8:15	25.5	30
		BASELINE	7:14	147	18.7	7:15	7:45	28.1	30
		WEEK 2	7:14	139	16.2	7:15	8:15	17.5	60
		WEEK 4	7:54		13.8	7:55	8:25	25.9	30
4	21	SCREENING	7:14	105	13.2	7:15	7:45	21.1	30
		BASELINE	7:14	85	4.9	7:15	7:45	23.1	30
		WEEK 2	7:34	95	2.5	7:35	8:05	19.4	30
		WEEK 4	7:34		1.1	7:35	8:05	24.4	30
		RETEST	7:34		12.5	7:35	8:05	24.3	30
4	24	SCREENING	7:14	90	11.5	7:15	7:45	21.4	30
		BASELINE	7:34	92	10.6	7:35	8:05	18.5	30
		WEEK 2	7:44	91	16.5	7:45	8:15	21.8	30
		WEEK 4	7:34		8.9	7:35	8:05	19.7	30

Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
4	37	SCREENING	7:34	114	14.2	7:35	8:05	34.9	30
		BASELINE	7:44	101	16.8	7:45	8:15	25.2	30
		WEEK 2	7:44	95	19.0	7:45	8:15	13.9	30
		WEEK 4	7:44		21.7	7:45	8:15	35.1	30
5	42	SCREENING	7:53	95	16.3	8:09	8:39	25.0	30
		BASELINE	7:40	85	12.7	7:55	8:25	23.4	30
		WEEK 2	7:50	87	13.3	7:55	8:25	25.6	30
5	45	SCREENING	8:16	83	14.9	8:44	9:10	27.6	26
		BASELINE	8:05	100	14.5	8:10	8:40	32.4	30
		WEEK 2	7:57	87	16.9	8:05	8:35	30.4	30

\* Time diff = Time difference between post-stimulation time and Cosyntropin time (in minutes)

**Table A3. Cortisol Levels in 0.05% fluocinonide (Lidex) treatment group (N=19).**

Treatment Group: Fluocinonide 0.05%

Site	Subject	Visit	---- Pre-stimulation ----		Cocyn Time	Post-stimulation		Time Diff*	
			Time	Glucose Cortisol		Time	Cortisol		
1	25	SCREENING	7:58	90	16.7	8:00	8:30	31.4	30
		BASELINE	8:00	92	17.2	8:01	8:31	30.4	30
		WEEK 2	8:00	90	18.0	8:01	8:30	35.6	29
1	27	SCREENING	7:55	96	17.0	7:57	8:25	27.7	28
		BASELINE	7:55	95	16.1	7:57	8:25	30.5	28
		WEEK 2	8:00	54	15.7	8:01	8:30	28.6	29
1	29	SCREENING	7:55	92	15.3	7:55	8:25	22.7	29
		BASELINE	8:00	86	20.1	8:01	8:30	25.2	29
		WEEK 2	9:50	107	14.3	9:51	10:20	25.5	29
2	2	SCREENING	8:29	98	21.1	8:29	9:00	32.9	31
		BASELINE	7:45	123	26.3	7:45	8:15	30.9	30
		WEEK 2	8:10	100	22.4	8:10	8:40	25.7	30
		WEEK 4	7:55	107	23.5	7:55	8:25	30	30
		RETEST	8:27		19.5	8:27	8:57	29.8	30
2	4	SCREENING	8:25	102	12.1	8:25	8:55	29.9	30
		BASELINE	7:45	104	18.3	7:45	8:15	27.4	30
		WEEK 2	7:55	93	21.6	7:55	8:27	27.6	32
		WEEK 4	7:40		12.4	7:40	8:10	23.3	30
2	5	SCREENING	7:40	99	15.4	7:40	8:10	27.8	30
		BASELINE	7:40	85	15.7	7:40	8:10	27.7	30
		WEEK 2	7:55	117	28.3	7:55	8:25	19.2	30
		WEEK 4	7:45		18.2	7:45	8:15	30.6	30
2	7	SCREENING	7:30	89	11.2	7:30	8:00	23.3	30
		BASELINE	7:50	94	7.7	7:50	8:20	18.4	30
		WEEK 2	7:35	90	14.1	7:35	8:05	21.9	30
3	10	SCREENING	8:00	101	15.1	8:08	8:37	29.3	29
		BASELINE	8:10	99	15.2	8:20	8:50	35.0	30
		WEEK 2	7:37	96	13.9	7:44	8:23	27.0	39

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Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
3	12	SCREENING	7:50	92	13.5	8:02	8:33	25.6	31
		BASELINE	8:06	86	12.3	8:10	8:46	26.3	36
		WEEK 2	7:55	79	17.2	8:30	9:04	30.8	34
3	14	SCREENING	8:11	183	11.6	8:59	9:37	30.8	38
		BASELINE	8:08	196	6.6	8:18	8:53	24.8	35
		WEEK 2	8:21	160	5.5	8:46	9:26	28.3	40
3	16	SCREENING	7:45	100	10.8	7:55	8:33	21.8	38
		BASELINE	7:49	93	7.5	8:03	8:36	20.8	33
		WEEK 2	7:55	103	10.3	7:59	8:30	24.8	31
3	34	SCREENING	7:40	85	19.6	7:53	8:27	26.6	34
		BASELINE	8:17	87	14.8	8:23	9:15	28.3	32
		WEEK 2	8:02	97	17.6	8:04	8:32	27.6	28
4	16	SCREENING	7:59	103	18.2	8:00	8:30	28.1	30
		BASELINE	7:29	100	13.1	7:30	8:00	22.3	30
		WEEK 2	7:34	96	14.1	7:35	8:05	25.5	30
4	19	SCREENING	7:59	133	11.5	8:00	8:30	27.9	30
		BASELINE	7:59	132	8.7	8:00	8:30	25.7	30
		WEEK 2	7:34	130	12.6	7:35	8:05	32.4	30
4	22	SCREENING	7:44	90	14.2	7:45	8:15	23.8	30
		BASELINE	7:44	97	19.6	7:45	8:15	25.3	30
		WEEK 2	7:34	110	30.3	7:35	8:05	38.0	30
		WEEK 4	7:39		8.3	7:40	8:10	26.1	30
4	23	SCREENING		115	22.4			25.0	
		SCREENING	7:29		17.8	7:30	8:00	26.8	30
		BASELINE	7:39	111	22.5	7:40	8:10	24.3	30
		WEEK 2	7:34	110	17.1	7:35	8:05	16.4	30
WEEK 4	7:39		13.9	7:40	8:10	24.8	30		

Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
4	36	SCREENING	7:44	105	11.3	7:45	8:15	21.6	30
		BASELINE	7:54	102	15.9	7:55	8:25	30.9	30
		WEEK 2	7:51	96	11.6	7:55	8:25	24.5	30
5	41	SCREENING	7:40	120	15.0	7:50	8:20	32.8	30
		BASELINE	7:25	122	15.4	7:30	8:00	29.2	30
		WEEK 2	7:45	116	12.7	7:50	8:20	32.8	30
5	44	SCREENING	8:00	100	14.1	8:10	8:40	29.1	30
		BASELINE	8:20	103	12.4	8:25	8:50	23.4	25
		WEEK 2	7:35	94	11.8	7:45	8:15	28.2	30

\* Time diff = Time difference between post-stimulation time and Cosyntropin time (in minutes)

**Table A4. % BSA and HPA axis suppression status for subjects in Study MP-0201-01.**

0.1% Fluocinonide Cream			0.05% Lidex (Fluocinonide) Cream		
Subject No.	%BSA at Baseline	HPA axis Suppression	Subject No.	%BSA at Baseline	HPA axis Suppression
26	17	No	25	13	No
28	39	No	27	17	No
1	12	No	29	10	No
3	25	No	2	32	No
5	15	No	4	18	No
8	20	No	6	11	No
9	10	No	7	28	No
11	13	No	10	12	No
13	24	No	12	14	No
15	12	No	14	15	No
33	11	No	16	17	No
17	29	Yes at Week 4	34	15	No
20	25	Yes at Week 2	18	12	No
21	11	No	19	12	No
24	50	No	22	10	No
37	12	Yes at Week 2	23	12	Yes at Week 2
42	11	No	38	10	No
43	17	No	41	16	No
			44	14	No

**4.2.2.2 Study MP-0201-06: A Randomized, Double-Blind, Parallel-Group, Multicenter, Vehicle-Controlled Study of Fluocinonide 0.1% Cream Once Daily (qd) and Twice Daily (bid) in the Treatment of Atopic Dermatitis**

Objectives: The objective of the study was to evaluate the efficacy and safety of fluocinonide 0.1% cream in the treatment of atopic dermatitis when applied topically twice daily or once daily for 2 weeks.

*(Reviewer's Note: This review will focus on the HPA axis evaluation as part of the safety evaluation for 0.1% fluocinonide cream. This is the same as the review for MP-0201-01, where the Reviewer used a 30-min post-stimulation level  $\leq 18 \mu\text{g/dL}$  as the definition for HPA axis suppression.)*

Study Sites: 24 Study sites in the U.S.

Investigators: \_\_\_\_\_

Study Period: July 28, 2003 to November 4, 2003

Study Design: This was a multicenter, randomized, double-blind, parallel-group, vehicle-controlled study of fluocinonide 0.1% cream in subjects with clinically diagnosed atopic dermatitis (2-10% body surface area).

Subjects were randomized at Baseline to receive either fluocinonide 0.1% cream or its vehicle in a double-blind manner (Appendix, Table A1a). Half of the subjects, randomly selected, were instructed to apply the cream either *qd* in the morning or *qd* in the evening, and half were instructed to apply the cream *bid*, morning and evening, for 14 consecutive days, to all the affected, treatable areas of the skin. At post-Baseline visits, the investigator, blinded to treatment regimens, performed symptom assessments and global evaluations for all the treated areas. Overall symptom scores of erythema, infiltration/papulation, excoriations, and lichenification, the physician's global assessment (PGA), the overall severity of pruritus, and the body surface area (BSA) were re-evaluated at the end of Weeks 1, 2, and 4.

At selected sites, systemic safety was evaluated using cosyntropin stimulation and glucose testing before treatment and at the end of treatment. A subset of 52 subjects (>18 years old) participated in the study for HPA axis evaluation (Appendix, Table A1b): 18 in fluocinonide 0.1% cream QD, 9 in vehicle QD, 16 in fluocinonide 0.1% cream BID and 9 in vehicle BID. Blood samples for serum cortisol levels were collected pre- and post- stimulation with cosyntropin at screening (-1 wk), Baseline (Week 0), and Week 2. At the end of the 14-day treatment period, any subject with HPA axis suppression was re-tested at Week 4 and weekly thereafter until 1 of the 2 control levels (pre- or post- stimulation) was within normal limits.

Duration of treatment: 2 weeks

Investigational product:

Fluocinonide Cream (0.1%): Lot Number: R0044D002

Manufactured by: Patheon, Inc, 2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9

Reference product:

Cream Vehicle: Lot Number: C0059B001

Manufactured by: Patheon, Inc, 2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9

Results:

Serum cortisol level data for each treatment group are listed in Appendix, Tables A2-A5. Subject 180 in 0.1% fluocinonide cream QD treatment group showed HPA axis suppression at the screening (met one of the exclusion criteria). Therefore, data from this subject were excluded. Subject 175 in 0.1% fluocinonide cream BID treatment group did not have the cortisol level at screening and Subject 122 in this group lost follow-up. Therefore, data for these two subjects were excluded from final analysis. Therefore, there were 17 evaluable subjects in the 0.1% fluocinonide cream QD group and 14 evaluable subjects in the 0.1% fluocinonide cream BID group.

At the Week 2 visit, 1 subject (Subject 151, 1 out of 17, 5.9%) in the 0.1% fluocinonide cream QD treatment group and no subject (0 out of 14, 0%) in the 0.1% fluocinonide cream BID treatment group met the criterion for HPA axis suppression (Table 1). No subject in either

vehicle group (QD and BID) showed HPA axis suppression (0 out of 9, Appendix, Tables A4 and A5). Subject 151 returned to normal HPA axis at the Week 4 visit (2 weeks post treatment). %BSA for Subject 151 was 4% (Appendix, Table A6).

The total weight of investigational medication used for fluocinonide 0.1% cream QD treatment group ranged from 2.4 g – 80.1 g for subjects that had normal HPA axis function at the screening (Appendix, Table A6). Subjects in the fluocinonide 0.1% cream BID treatment group used 12.7 g – 98 g of medication (Appendix, Table A7). Mean drug applied per application (in terms of weight) and % BSA at Baseline were similar between the two treatment groups in this study (Table 1).

**Table 1. Comparison between 0.1% fluocinonide cream QD and 0.1% fluocinonide cream BID treatment groups.**

	HPA Axis Suppression at Wk 2	Weight per Application (g) (Mean ± SD)	% BSA at Baseline (Mean ± SD) (Range)
<b>0.1% Fluocinonide Cream QD (N=17)</b>	1/17 (5.9%)	1.5 ± 1.3	4.7 ± 2.3 (2-10)
<b>0.1% Fluocinonide cream BID (N=14)</b>	0/14 (0%)	1.3 ± 0.9	5.1 ± 1.8 (3-10)

Discussion and Conclusions:

Under the conditions provided in this study in adult patients with atopic dermatitis (2-10% BSA), 0.1% fluocinonide cream QD treatment group showed a higher rate of HPA axis suppression than the 0.1% fluocinonide cream BID treatment group (6% vs. 0%) following dosing for two weeks. The HPA axis results obtained from this study suggest that the systemic safety based on HPA axis suppression is acceptable for the 0.1% fluocinonide drug product (either QD or BID for two weeks) in adult atopic dermatitis patients.

It needs to be pointed out that the patients in this study were not necessarily tested under the maximal usage conditions, i.e., they did not have as high a percentage of BSA of the diseased skin as possible. In this study, patients with 2-10% BSA were enrolled because fluocinonide is a super-high potent corticosteroid; the limit of dose is 50 g per week. 1 g of cream usually covers approximately 2% BSA. 50 g per week limited the %BSA to be applied to ~10% (for a BID regimen). Labeling needs to restrict time duration and area of drug application to limit the risk of HPA axis suppression in patients because of the well-known adrenal suppression effect from corticosteroids and the limitation of the HPA axis suppression testing.

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Appendix (MP-0201-06)

Table A1a. Demographic summary by treatment groups (MP-0201-06)

	Fluocinonide 0.1% <i>qd</i> N = 109	Vehicle <i>qd</i> N = 50	Fluocinonide 0.1% <i>bid</i> N = 102	Vehicle <i>bid</i> 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 (yrs)</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

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**Table A1b. Demographic summary for all subjects who had HPA axis testing (MP-0201-06)**

	ONCE DAILY		TWICE DAILY	
	Fluocinonide	Vehicle	Fluocinonide	Vehicle
Age				
N	18	9	16	9
Mean	43.4	54.9	39.1	48.1
Standard Deviation	15.8	18.9	18.9	14.8
Median	42.9	62.7	37.0	47.9
Range	19.7 - 72.4	24.2 - 73.1	18.0 - 72.2	28.5 - 71.2
< 40	8 (44.4)	2 (22.2)	9 (56.3)	3 (33.3)
40 - <65	8 (44.4)	3 (33.3)	5 (31.3)	4 (44.4)
>= 65	2 (11.1)	4 (44.4)	2 (12.5)	2 (22.2)
Gender - n (%)				
MALE	10 (55.6)	3 (33.3)	8 (50.0)	3 (33.3)
FEMALE	8 (44.4)	6 (66.7)	8 (50.0)	6 (66.7)
Race - n (%)				
CAUCASIAN	18 (100)	7 (77.8)	14 (87.5)	7 (77.8)
BLACK	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
ASIAN	0 (0.0)	1 (11.1)	2 (12.5)	2 (22.2)
Duration of Disease (years)				
N	18	9	16	9
Mean	14.0	19.3	16.5	21.7
Standard Deviation	11.8	23.4	17.2	17.4
Median	9.0	5.0	11.5	15.0
Range	0.7 - 37.5	2.0 - 62.0	1.4 - 60.0	3.0 - 50.0
Duration of Current Episode (months)				
N	18	9	16	9
Mean	1.7	2.7	4.0	1.5
Standard Deviation	2.4	3.6	9.2	1.6
Median	0.4	2.0	1.5	0.8
Range	0.1 - 7.0	0.1 - 11.0	0.1 - 38.0	0.2 - 5.0
BSA Involvement at Screening (%)				
N	18	9	16	9
Mean	5.0	5.6	5.4	4.6
Standard Deviation	2.6	2.2	2.1	2.1
Median	4.5	5.0	5.0	5.0
Range	2 - 10	3 - 9	3 - 10	2 - 7

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**Table A2. Cortisol Levels in 0.1% flucinonide QD treatment group (N=18).**

Treatment Group: FLUCCINONIDE QD									
Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff'
			Time	Glucose	Cortisol		Time	Cortisol	
8	176	SCREEN	8:21	96	6.3	8:22	8:52	29.4	30
		WEEK 2	8:29	94	7.6	8:30	9:00	34.7	30
8	180	SCREEN	8:20	69	20.7	8:21	8:51	10.1	30
		WEEK 2	8:24	65	4.0	8:25	8:55	20.7	30
		WEEK 4	8:14	69	9.8	8:15	8:45	17.8	30
8	350	SCREEN	8:30	114	15.2	8:31	9:05	22.8	34
		WEEK 2	8:22	97	21.0	8:23	8:55	25.2	32
		WEEK 4	8:15	106	17.1	8:16	8:46	25.7	30
8	351	SCREEN	8:19	90	12.4	8:20	8:50	22.4	30
		WEEK 2	8:12	96	9.6	8:13	8:45	20.6	32
10	151	SCREEN	7:40	97	12.3	7:50	8:20	25.3	30
		WEEK 2	7:30	83	21.1	7:40	8:12	11.4	32
		WEEK 4	7:30	78	12.9	7:40	8:15	20.9	35
10	154	SCREEN	7:40	163	33.1	7:50	8:25	35.5	35
		WEEK 2	8:10	63	19.9	8:20	8:50	29.9	30
10	157	SCREEN	8:30	66	24.1	8:40	9:15	46.2	35
		WEEK 2	8:00	66	22.8	8:05	8:43	34.9	38
10	161	SCREEN	8:20	98	11.2	8:30	9:10	36.8	40
		WEEK 2	8:30	97	6.4	8:40	9:15	34.5	35
15	2	SCREEN	8:00	94	6.9	8:00	8:30	22.5	30
		WEEK 2	8:05	67	21.2	8:05	8:35	28.0	30
		WEEK 4	8:00	67	26.4	8:00	8:30	36.3	30
15	6	SCREEN	8:27	112	11.0	8:27	8:59	25.0	32
		WEEK 2	8:08	111	32.6	8:08	8:38	35.7	30

Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
15	279	SCREEN	8:30	67	23.0	8:30	9:00	31.6	30
		WEEK 2	8:17	67	23.8	8:17	8:47	29.8	30
		WEEK 4	8:28	78	20.8	8:28	9:00	31.1	32
15	281	SCREEN	8:30	92	20.9	8:30	9:01	31.1	31
		WEEK 2	7:45	96	17.4	7:45	8:15	32.4	30
23	117	SCREEN	8:03	116	10.3	8:11	8:42	22.4	31
		WEEK 2	8:20	109	16.2	8:50	9:20	23.3	30
23	120	SCREEN	8:02	93	24.4	8:20	8:50	29.5	30
		WEEK 2	8:00	89	15.7	8:10	8:40	27.6	30
23	123	SCREEN	8:25	97	18.0	9:00	9:30	36.8	30
		WEEK 2	8:15	100	13.3	8:20	8:50	28.6	30
24	131	SCREEN	7:29	67	17.5	7:30	8:00	20.9	30
		WEEK 2	7:14	90	22.6	7:15	7:45	32.9	30
24	132	SCREEN	7:29	100	22.7	7:30	8:00	29.1	30
		WEEK 2	7:04	104	15.2	7:05	7:35	23.5	30
24	133	SCREEN	7:14	84	19.3	7:15	7:45	32.2	30
		WEEK 2	7:14	95	21.6	7:15	7:45	32.5	30

\* Time diff = Time difference between post-stimulation time and Cosyntropin time (in minutes)

**Table A3. Cortisol Levels in 0.1% fluocinonide BID treatment group (N=16).**

Treatment Group: FLUOCINONIDE BID									
Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
8	175	SCREEN	8:09			8:10	8:40		30
		WEEK 2	8:09	77	17.7	8:10	8:40	24.4	30
8	177	SCREEN	8:10	83	14.3	8:11	8:41	27.7	30
		WEEK 2	8:14	82	15.9	8:15	8:45	29.0	30
8	353	SCREEN	8:24	100	26.0	8:25	8:55	30.6	30
		WEEK 2	8:23	83	23.4	8:24	8:56	28.8	31
		WEEK 4	8:29	87	21.1	8:30	9:05	35.5	35
10	163	SCREEN	7:36	91	30.2	7:55	8:25	38.9	30
		WEEK 2	8:00	81	28.4	8:10	8:40	33.3	30
		WEEK 4	7:50	78	29.1	8:00	8:30	29.1	30
		UNSCH	7:30	86	28.9	7:40	8:15	36.0	35
10	166	SCREEN	8:00	86	20.6	8:10	8:43	26.4	33
		WEEK 2	7:30	80	16.8	7:40	8:16	26.7	35
10	169	SCREEN	7:30	88	6.6	7:40	8:16	23.8	35
		WEEK 2	7:15	107	14.6	7:25	8:00	27.3	36
10	162	SCREEN	8:15	113	8.3	8:20	8:40	23.8	20
		WEEK 2	8:00	78	12.6	8:10	8:45	24.7	35
15	1	SCREEN	8:16	94	27.7	8:16	8:46	36.6	30
		WEEK 2	8:16	85	32.3	8:16	8:47	40.1	32
15	3	SCREEN	8:20	93	24.0	8:20	8:50	29.0	30
		WEEK 2	7:59	90	16.4	7:59	8:30	24.0	31
15	280	SCREEN	8:00	84	18.9	8:00	8:30	29.8	30
		WEEK 2	7:58	75	10.4	7:58	8:30	27.4	32

Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
15	282	SCREEN	8:27	87	16.0	8:27	8:58	22.6	31
		WEEK 2	8:20	92	23.0	8:20	8:50	29.0	30
23	118	SCREEN	8:00	102	11.2	8:05	8:35	36.5	30
		WEEK 2	8:10	110	11.2	8:15	8:45	32.6	30
23	119	SCREEN	8:01	92	22.7	8:15	8:46	32.9	31
		WEEK 2	8:10	90	17.8	8:15	8:47	31.5	32
23	122	SCREEN	8:25	80	8.9	8:31	9:02	23.2	31
24	127	SCREEN	7:44	90	18.1	7:46	8:15	24.9	30
		WEEK 2	7:15	115	22.1	7:16	7:46	35.4	30
24	129	SCREEN	7:44	132	26.3	7:45	8:15	33.4	30
		WEEK 2	7:14	102	21.4	7:15	7:45	30.3	30

\* Time diff = Time difference between post-stimulation time and Cosyntropin time (in minutes)

**Table A4. Cortisol Levels in Vehicle QD treatment group (N=9).**

Treatment Group: VEHICLE QD

Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
6	179	SCREEN	8:09	104	23.1	8:10	8:40	18.9	30
		WEEK 2	8:25	98	20.0	8:26	8:56	32.5	30
6	352	SCREEN	8:29	61	6.1	8:30	9:00	27.4	30
		WEEK 2	8:29	68	6.3	8:30	9:05	25.2	35
10	155	SCREEN	8:00	68	11.6	8:10	8:45	28.0	35
		WEEK 2	7:15	64	15.1	7:25	7:55	26.6	30
10	158	SCREEN	8:10	82	24.2	8:15	8:45	44.8	30
		WEEK 2	9:00	65	20.1	8:10	8:40	32.4	30
15	4	SCREEN	8:15	99	15.6	8:15	8:45	29.1	30
		WEEK 2	8:29	91	20.2	8:29	9:03	34.1	34
15	277	SCREEN	8:12	67	16.1	8:12	8:42	22.1	30
		WEEK 2	8:20	99	20.1	8:20	8:51	23.2	31
		WEEK 4	8:15	66	19.0	8:15	8:45	25.8	30
23	115	SCREEN	8:00	95	16.5	8:10	8:40	26.5	30
		WEEK 2	8:00	96	14.2	8:40	9:11	27.8	31
23	124	SCREEN	8:15	61	11.6	8:30	9:00	25.0	30
		WEEK 2	8:05	51	13.2	8:10	8:40	25.1	30
24	128	SCREEN	7:44	156	20.2	7:45	8:15	30.5	30
		WEEK 2	7:44	141	26.3	7:45	8:15	29.5	30
		WEEK 4	7:14	157	31.5	7:15	7:45	39.3	30

\* Time diff = Time difference between post-stimulation time and Cosyntropin time (in minutes)

**Table A5. Cortisol Levels in Vehicle BID treatment group (N=9).**

Treatment Group: VEHICLE BID

Site	Subject	Visit	---- Pre-stimulation ----			Cosyn Time	Post-stimulation		Time Diff*
			Time	Glucose	Cortisol		Time	Cortisol	
6	178	SCREEN	8:11	179	10.6	8:12	8:42	47.5	30
		WEEK 2	8:17	119	8.5	8:18	8:50	36.6	32
6	349	SCREEN	8:22	75	14.2	8:23	8:53	25.0	30
		WEEK 2	8:18	79	14.5	8:19	8:49	22.9	30
10	152	SCREEN	7:50	124	14.6	8:00	8:30	30.5	30
		WEEK 2	8:00	116	20.6	8:12	8:45	31.2	33
10	160	SCREEN	7:15	68	12.0	7:30	7:50	20.0	20
		WEEK 2	7:30	79	13.3	7:45	8:15	19.1	30
15	5	SCREEN	8:25	105	19.5	8:25	8:55	28.8	30
		WEEK 2	8:20	102	19.6	8:20	8:50	30.2	30
15	278	SCREEN	7:40	138	14.1	7:40	8:14	21.9	34
		WEEK 2	8:10	128	12.0	8:10	8:43	23.1	33
23	116	SCREEN	8:05	104	10.5	8:17	8:48	18.9	31
		WEEK 2	7:55	112	16.0	8:32	9:03	23.0	31
23	121	SCREEN	8:03	110	17.0	8:13	8:43	29.8	30
		WEEK 2	8:05	116	31.1	8:13	8:41	41.2	26
24	130	SCREEN	7:15	138	14.6	7:16	7:46	28.7	30
		WEEK 2	7:19	124	14.5	7:20	7:50	25.9	30

\* Time diff = Time difference between post-stimulation time and Cosyntropin time (in minutes)

**Table A6. Dosing records and %BSA at Baseline for QD treatment groups.**

----- Group Code=1 Treatment Group=FLUOCINONIDE QD -----

Site No.	Subject No.	Treatment Group	Age	Gender	Total Weight Used (g)	Total No. of Applications	Weight per Application (g)	% BSA at Baseline
8	176	FLUOCINONIDE QD	34.7	M	14.6	14	1.03671	3
8	180	FLUOCINONIDE QD	33.3	M	97.2	15	6.48000	10
8	350	FLUOCINONIDE QD	22.3	F	9.9	16	0.61875	6
8	351	FLUOCINONIDE QD	21.1	F	3.8	15	0.25333	2
10	151	FLUOCINONIDE QD	56.5	M	34.8	15	2.32000	4
10	154	FLUOCINONIDE QD	35.1	F	28.6	14	2.04286	7
10	157	FLUOCINONIDE QD	58.7	F	17.5	15	1.16667	5
10	161	FLUOCINONIDE QD	47.9	M	80.1	15	5.34000	7
15	2	FLUOCINONIDE QD	38.7	M	47.2	14	3.37143	6
15	6	FLUOCINONIDE QD	53.2	M	15.3	16	0.95625	3
15	279	FLUOCINONIDE QD	40.8	F	2.4	17	0.14118	3
15	281	FLUOCINONIDE QD	56.5	F	4.0	15	0.26667	3
23	117	FLUOCINONIDE QD	72.4	F	13.6	16	0.85000	4
23	120	FLUOCINONIDE QD	19.7	F	42.7	17	2.51176	10
23	123	FLUOCINONIDE QD	44.9	M	10.3	15	0.68667	2
24	131	FLUOCINONIDE QD	26.3	M	22.6	14	1.61429	9
24	132	FLUOCINONIDE QD	66.6	M	27.4	15	1.82667	3
24	133	FLUOCINONIDE QD	52.0	M	16.0	15	1.06667	5

----- Group Code=2 Treatment Group=VEHICLE QD -----

Site No.	Subject No.	Treatment Group	Age	Gender	Total Weight Used (g)	Total No. of Applications	Weight per Application (g)	% BSA at Baseline
8	179	VEHICLE QD	71.1	M	20.2	15	1.34667	3
8	352	VEHICLE QD	24.2	F	22.7	16	1.41875	9
10	155	VEHICLE QD	73.1	F	44.0	14	3.14286	6
10	158	VEHICLE QD	70.5	M	67.7	14	4.83671	9
15	4	VEHICLE QD	43.0	F	18.4	16	1.15000	6
15	277	VEHICLE QD	46.0	F	32.4	14	2.31429	5
23	115	VEHICLE QD	32.1	F	26.3	15	1.75333	4
23	124	VEHICLE QD	62.7	F	18.7	15	1.24667	4
24	128	VEHICLE QD	71.4	M	14.1	15	0.94000	4

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**Table A7. Dosing records and %BSA at Baseline for BID treatment groups.**

----- Group Code=3 Treatment Group=FLUOCINONIDE BID -----

Site Subject		Treatment Group	Age	Gender	Total	Total No. of Applications	Weight per	% BSA at Baseline
No.	No.				Weight Used (g)		Application (g)	
8	176	FLUOCINONIDE BID	64.3	M	108.6	29	3.74483	10
8	177	FLUOCINONIDE BID	19.7	F	28.0	29	0.96552	3
8	353	FLUOCINONIDE BID	18.0	F	40.3	29	1.38966	7
10	153	FLUOCINONIDE BID	22.1	F	29.8	28	1.06429	6
10	156	FLUOCINONIDE BID	66.3	M	82.6	29	2.84828	3
10	159	FLUOCINONIDE BID	36.0	M	13.8	27	0.51111	6
10	162	FLUOCINONIDE BID	62.8	M	98.0	29	3.37931	6
15	1	FLUOCINONIDE BID	38.0	F	16.0	27	0.59259	3
15	3	FLUOCINONIDE BID	18.9	M	48.6	27	1.79630	5
15	280	FLUOCINONIDE BID	44.8	F	13.9	29	0.47931	5
15	282	FLUOCINONIDE BID	21.7	F	37.2	29	1.28276	8
23	118	FLUOCINONIDE BID	47.1	M	67.0	29	2.31034	4
23	119	FLUOCINONIDE BID	29.8	M	19.0	29	0.65517	4
23	122	FLUOCINONIDE BID	43.8	F	.0	LOST TO FOLLOW-UP		5
24	127	FLUOCINONIDE BID	20.8	F	12.7	31	0.40968	3
24	129	FLUOCINONIDE BID	72.2	M	34.5	31	1.11290	8

----- Group Code=4 Treatment Group=VEHICLE BID -----

Site Subject		Treatment Group	Age	Gender	Total	Total No. of Applications	Weight per	% BSA at Baseline
No.	No.				Weight Used (g)		Application (g)	
8	178	VEHICLE BID	51.5	M	33.0	31	1.06452	2
8	349	VEHICLE BID	37.5	F	23.6	29	0.81379	6
10	152	VEHICLE BID	71.2	M	30.4	29	1.04828	3
10	160	VEHICLE BID	41.7	F	30.4	31	0.98065	2
15	5	VEHICLE BID	47.9	F	35.0	29	1.20690	5
15	278	VEHICLE BID	28.5	F	39.4	27	1.45926	6
23	116	VEHICLE BID	50.0	F	63.3	29	2.18276	7
23	121	VEHICLE BID	34.6	F	15.0	27	0.55556	7
24	130	VEHICLE BID	70.0	M	24.2	31	0.78065	3

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Draft Labeling

Deliberative Process

#### 4.4 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-758	Brand Name	██████ <sup>TM</sup>	
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Fluocinonide	
Medical Division	DDDDP (HFD-540)	Drug Class	Synthetic Corticosteroids used topically as anti-inflammatory and antipruritic agents	
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	
OCPB Team Leader	Arzu Selen, Ph.D. (Acting)	Dosage Form	Cream, 0.1%	
		Dosing Regimen	██████ daily. Treatment should be restricted to 2 consecutive weeks and amounts less than 60 g/week.	
Date of Submission	4/7/2004	Route of Administration	Topical	
Estimated Due Date of OCPB Review	12/30/2004	Sponsor	Medicis	
PDUFA Due Date	2/12/2005	Priority Classification	New Dosage Form (3-S)	
Division Due Date	1/15/05		IND 61,701	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:	X	2-3	2-3	Systemic exposure to fluocinonide from application of <b>          </b> ™ 0.1% Cream was evaluated in clinical investigations of hypothalamic-pituitary-adrenal axis function.  Study MP-0201-01 (Phase 2) Study MP-0201-06 (Phase 3)  Study MP-0201-07 (Pediatrics) is on-going at the time of submission and results will be submitted as NDA Amendment.
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Vasoconstrictor studies to determine potency</b>		4	2	Study MED-00-018 (multiple-point) Study MED-01-022 (single-point) Study MED-02-004 (single-point) Study MED-02-005 (single-point)

<b>Pediatric development plan</b>				
<b>Literature References</b>	<b>X</b>			
<b>Total Number of Studies</b>		<b>6</b>	<b>4-5</b>	
<b>Fiability and QBR comments</b>				
	<b>"X" if yes</b>	<b>Comments</b>		
<b>Application filable?</b>	<b>X</b>			
<b>Comments sent to firm?</b>		<ul style="list-style-type: none"> <li>Please provide information (including a table in SAS format) regarding doses applied at each application in QD group vs. BID group and % body surface area applied for those patients involved in the HPA axis assessment in Study MP-0201-06.</li> </ul>		
<b>QBR questions (key issues to be considered)</b>		<ul style="list-style-type: none"> <li><b>Were the HPA axis results obtained under maximal usage conditions?</b></li> <li><b>Do the HPA axis results support safe use of this product?</b></li> </ul>		
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>	<b>Lei Zhang, 6/14/2004</b>			
<b>Secondary reviewer Signature and Date</b>	<b>Arzu Selen</b>			

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this page is the manifestation of the electronic signature.**  
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/s/

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Lei Zhang  
1/11/05 04:55:45 PM  
BIOPHARMACEUTICS

Raman Baweja  
1/11/05 06:07:56 PM  
BIOPHARMACEUTICS