

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-758

MEDICAL REVIEW

**Safety Update Review
NDA 21-758**

February 11, 2005

NDA 21-758 was submitted on April 7, 2004. On August 27, 2004, the Agency received a submission labeled Safety Update. However, the text of the cover letter stated: "A 120-day safety update report in accordance with the regulations set forth in 21 CFR 314 & 601, which will also encompass a summary report of all safety data (HPA axis, adverse event, and skin safety) for Cohort 1 will be submitted to the agency on (or about) October 29, 2004 when data will be available for all subjects who completed follow-up."

The October 29, 2004 submission was labeled on its cover letter by the Applicant as "Response to FDA Request for Information Fax". Information included in the submission included a preliminary report regarding an ongoing HPA axis suppression study in pediatric patients. However, the safety update for this drug product was not completely addressed.

On February 11, 2005, in a teleconference with the Applicant, the Agency was informed that there were no outstanding safety issues regarding the IND and the other topical fluocinonide product owned by the Applicant (see also fax from Applicant). A formal submission will be forwarded to the Agency to acknowledge this.

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

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/s/

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SU Review.

Jonathan Wilkin
2/11/05 02:53:54 PM
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NDA 21-758 VANOS (fluocinonide) Cream, 0.1%
Clinical Team Leader Inter-disciplinary Summary

February 10, 2005

The Clinical Team is in agreement regarding the Approval recommendation for VANOS (fluocinonide) Cream, 0.1% for use in the treatment of plaque psoriasis affecting up to 10% (BSA) in patients age 18 years and older. The Applicant has provided adequate information to support both safety and efficacy for the use of this product for the above indication.

Fluocinonide is a corticosteroid drug substance that has been used extensively in previous drug products, including topical cream formulations. However, the 0.1% formulation is a higher concentration of this product than previously available. The currently approved fluocinonide cream is 0.05%.

Clinical Safety

VANOS (fluocinonide) Cream, 0.1% causes HPA axis suppression in adults. Using the cosyntropin stimulation test, serum cortisol levels taken 30 minutes post-stimulation showed adrenal suppression in 2 of 18 subjects using VANOS Cream, 0.1% twice daily for 14 days for the treatment of plaque psoriasis. These patients had a body surface area (BSA) of application that ranged from 10% to 50% with a mean BSA of 19.6%.

The comparative HPA axis study vs. the lower concentration of fluocinonide cream (Lidex Cream, 0.05%) is not conclusive due to the small numbers of patients. However, in that study (MP-0201-01, page 34 of Dr. Brenda Vaughan's comprehensive Medical Officer review), 1 out of 19 subjects using Lidex (fluocinonide) Cream, 0.05% bid for 2 weeks vs. 2 out of 18 subjects using fluocinonide cream 0.1% bid for 2 weeks had HPA axis suppression. In that study, an additional subject using fluocinonide cream 0.1% bid had HPA axis suppression in follow-up testing using the criteria of less than or equal to 18 micrograms per deciliter, but was not suppressed at 2 weeks. Of note, the Applicant proposes that only 1 patient was suppressed as one of the tubes putatively had the pre- and post- stimulation blood tubes switched. It is unclear that there is substantiation for this or whether this was due to laboratory measurements that resulted in the values 19.0 micrograms/deciliter pre- and 13.9 micrograms/deciliter post-. Without such substantiation, it is difficult to agree with such a proposal. The Clinical Team Leader recommends that 2 subjects suppressed out of 18 is a valid representation of the study results.

Other potential systemic safety concerns were evaluated during the clinical studies after 2 weeks of use. No signal emerges regarding blood glucose changes, weight, or blood pressure. There was a slightly greater increase in incidence of nasal congestion and headache in patients in the clinical study who used Tradename Cream

when compared to the vehicle. This is addressed in the proposed label for the product. No growth studies or bone density studies are done for this product.

Due to the short period of safety evaluation, use of this product should be for short-term only (up to 2 weeks) – see Bolded statement under the proposed Dosage and Administration section. “Treatment with VANOS Cream should be limited to 2 consecutive weeks, and amounts greater than 60 g/week should not be used in psoriasis patients.” During labeling discussions, the Applicant further supported the use of up to 60 g/week of medication. In the psoriasis HPA axis suppression study, MP-201-01, the amount of medication used during the two weeks of treatment ranged from 59 to 117 grams with a mean of 95 grams.

Local adverse events observed are similar to that of other topical corticosteroids, so class labeling to that effect would suffice.

A pediatric study to assess HPA axis suppression in children has also been conducted by the Applicant. However, the final study reports for this study was not yet submitted upon closure of the Clinical review. Of interest will also be the local safety of this drug in that population. It was discussed with the Applicant during drug development that the safety of the drug when used in pediatric patients is needed ~~_____~~ for use in atopic dermatitis. Atopic dermatitis is considered to be primarily a pediatric disease so safety in that population will need to be assured ~~_____~~ for that indication.

Further, given that HPA axis suppression was seen in the adult population, the safety of the use of this potent corticosteroids in pediatric patients could require modification to dose and have limits as to amount used. This would need further study if it is to be informed for labeling. This is an important consideration for corticosteroid product development in the pediatric population. Restricting labeling to allow only for use of a corticosteroid product for example to patients greater than age 18 may address pediatric labeling requirements, but does not address the spirit of laws intended to evaluate more carefully the dosing of drugs for pediatric use.

The Medical Officer review (page 44) discussed that “No growth assessment studies have been performed; however, the Applicant is encouraged to explore growth suppression studies if [VANOS] is approved for use in pediatric patients.” Of note, this is not an absolute requirement with topical corticosteroids at this time. It has been discussed by the Division that the effect on growth with topical corticosteroids is difficult to measure at best. Subjects enrolled may discontinue use of drug or use a different topical corticosteroid if their disease shows either treatment improvement or no improvement. It may be sufficient at this time that the labeling for topical corticosteroids for prescription use include information that “linear growth retardation” has been reported in children receiving topical corticosteroids and is a potential side effect of the drug.

The Medical Officer review (page 45) discussed that the “Pediatric subcommittee recommended simultaneous cosyntropin [spelling corrected] testing of all pediatric cohorts; however, the Applicant and Division concurred that sequential cosyntropin testing with a stopping rule was warranted since [VANOS] is a super-potent topical corticosteroid and adrenal suppression was expected.” It is more accurate to say that the Pediatric Advisory Committee discussed sequential vs. simultaneous testing, but did not completely agree as to which is preferable. The key concern with regard to simultaneous testing was the safety of the pediatric subjects. Thus, the Division advocates that for more potent corticosteroids (where both local and systemic safety issues may be a concern) that sequential testing be conducted where the older cohorts are evaluated prior to conducting the study in younger pediatric cohorts. Indeed, this was what was implemented for the HPA axis studies for this drug product.

Clinical Efficacy

Two pivotal Phase 3 clinical studies were conducted. MP-0201-05 was conducted in adult patients with psoriasis. MP-0201-06 was conducted in adult patients with atopic dermatitis. Both of these studies were four-armed studies comparing once-daily application to twice daily application of both the active containing drug product vs. the vehicle.

MP-0201-05 enrolled 107 subjects each in the fluocinonide qd and bid groups, 54 subjects in the vehicle qd group and 55 in the vehicle bid group. MP-0201-06 enrolled 109 subjects in the fluocinonide qd group, 102 subjects in the fluocinonide bid group, 50 subjects in the vehicle qd group and 52 subjects in the vehicle bid group.

The statistical analysis of the efficacy results demonstrated a significant effect of fluocinonide over its vehicle in both of the studies for each of the arms. A nested hypothesis was used to address the two dosage regimens. Having attained some degree of significance with the qd dosing (albeit with $p=0.043$), an additional look at the bid dosing was allowed for without an adjustment for multiplicity. This was pre-specified according to the Biostat team’s review. The bid dosing also achieved statistical significance ($p<0.001$). Further, the bid dosing was superior to the qd dosing ($p=0.025$) – See review by the Agency biostatistician, Fraser Smith. The p-values cited on page 24 of the Medical Officer review (<0.001 and 0.43) apparently are not accurate.

	Tradename Cream, qd	Vehicle Cream, qd	Tradename Cream, bid	Vehicle Cream, bid
Patients cleared	0 (0%)	0 (0%)	6 (6%)	0 (0%)
Patients with treatment success *	19 (18%)	4 (7%)	33 (31%)	3 (6%)

* Treatment success = clear or almost clear

On discussion, the labeling should have a table with this data which should appear in the Clinical Trials section.

It is important to note (as described in Dr. Vaughan's review) that even though the Applicant submitted data for both psoriasis and atopic dermatitis, it was pre-agreed with the Applicant that the sole indication would be psoriasis of pediatric patients are studied with atopic dermatitis. Atopic dermatitis is primarily a disease of pediatric patients, so evaluation and labeling that discusses efficacy and safety in that population is needed. It was pre-agreed that potentially, the efficacy from the adult study in atopic dermatitis could be extrapolated downwards, however, safety could not. A pediatric safety study has been conducted by the Applicant, but final study reports were not submitted to allow for review prior to Agency's taking an action. This data was asked for as part of the Agency's post-marketing commitment requests and agreed upon by the Applicant.

One of the concerns discussed during the review of this drug is that the atopic dermatitis efficacy study did not show a significant difference between once daily and twice daily use. Therefore, for that indication, once daily may be the best choice of dosing for this particular corticosteroid. As an added aspect to this concern, upon the Divisions finding of safety and efficacy for both atopic dermatitis and psoriasis, eligibility for the broader "corticosteroid responsive dermatosis" indication is a possibility. In the event that the safety considerations are worked out for use in atopic dermatitis patients of various ages, a potential Dosage and Administration section for labeling could be:

For atopic dermatitis: Apply a thin layer of VANOS Cream to the affected skin once daily, as directed by a physician."

Of note, Ultravate Cream 0.05% also has once or twice daily use for corticosteroid dermatoses. However, there is not any breakdown regarding the specific corticosteroid responsive dermatoses and dosage.

The Agency recognizes that corticosteroid responsive dermatoses are not a homogenous population of diseases and that drug response for certain products may be different. This Applicant has conducted dose ranging studies in Phase 3 and found that different dosages may be optimal for psoriasis vs. atopic dermatitis. Thus, labeling should so inform.

CMC Concerns

Please see the comprehensive CMC review by Ernest G. Pappas, the Agency CMC reviewer. Late discussion with the Applicant was conducted regarding the dissolution of the drug substance: "When asked during a telephone conference of the physical state of the semi-solid, the firm indicated that fluocinonide drug substance is

completely dissolved, [REDACTED] of the manufacturing process, thereby eliminating the need for a microscopic examination. A compromise was made with the firm to allow a visual examination [REDACTED] manufacturing process, providing a microscopic examination be performed on the first three commercial batches released.”

The tradename of “VANOS” was found to be acceptable by DMETS on February 8, 2005. Two other names submitted by the Applicant were found not be acceptable:
[REDACTED]

Pharmacology/Toxicology Concern

A concern that emerged from the pharmacology toxicology review is a positive genotoxicity signal noted for fluocinonide in the *in vivo* mouse micronucleus assay.

The pharmacology/toxicology reviewer recommended and the Applicant has agreed to conduct a dermal carcinogenicity study with [REDACTED] cream and a study to determine the photoco-carcinogenic potential of [REDACTED] cream as a post-marketing commitment.

Post-Marketing Study Commitments

The applicant commits to conducting a dermal carcinogenicity study with VANOS (fluocinonide) Cream, 0.1%.

Development of dosing formulations:	By August 15, 2005
Development and validation of analytical methodology:	By February 15, 2006
90-day dose range-finding study:	By December 15, 2006
Study protocol submission:	By June 15, 2007
Study start date:	By February 15, 2008
Final report submission:	By August 15, 2011

The applicant commits to conducting a study to determine the photoco-carcinogenic potential of VANOS (fluocinonide) Cream, 0.1%.

90-day dose range-finding study:	By December 15, 2006
Study protocol submission:	By June 15, 2007
Study start date:	By February 15, 2008
Final report submission:	By August 15, 2010

Conclusion

It is recommended that NDA 21-758 be found approvable as a 505(b)1 application for a new drug product. The recommended Indications and Usage section for labeling is as follows:

[REDACTED]



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

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/s/

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MEDICAL OFFICER
Clinical TL Summary. Concur with approval recommendation by MO.

Jonathan Wilkin
2/10/05 07:39:44 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 21-758
Submission Code N

Letter Date April 7, 2004
Stamp Date April 12, 2004
PDUFA Goal Date February 12, 2005

Reviewer Name Brenda E. Vaughan, M.D.
Review Completion Date December 16, 2004

Established Name Fluocinonide
(Proposed) Trade Name
Therapeutic Class Corticosteroid
Applicant Medicis pharmaceutical Corp.

Priority Designation S
Formulation Topical cream
Dosing Regimen Once or twice daily applications.
Indication Relief of the inflammatory and pruritic
manifestations of corticosteroid
responsive dermatoses
Intended Population 18 years of age or older

TABLE OF CONTENTS

EXECUTIVE SUMMARY 4

RECOMMENDATION ON REGULATORY ACTION 4

RECOMMENDATION ON POSTMARKETING ACTIONS..... 4

 Required Phase 4 Commitments 4

SUMMARY OF CLINICAL FINDINGS 5

 Brief Overview of Clinical Program 5

 Efficacy 5

 Safety 6

 Dosing Regimen and Administration 7

 Drug-Drug Interactions 7

 Special Populations 7

2 INTRODUCTION AND BACKGROUND..... 8

 PRODUCT INFORMATION..... 8

 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 8

 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 9

 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 9

 PRESUBMISSION REGULATORY ACTIVITY 9

 OTHER RELEVANT BACKGROUND INFORMATION..... 10

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 10

 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)..... 10

 ANIMAL PHARMACOLOGY/TOXICOLOGY 10

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY..... 10

 SOURCES OF CLINICAL DATA..... 10

 TABLE 1: TABLES OF CLINICAL STUDIES 10

 REVIEW STRATEGY 13

 DATA QUALITY AND INTEGRITY 13

 COMPLIANCE WITH GOOD CLINICAL PRACTICES 13

 FINANCIAL DISCLOSURES 13

5 CLINICAL PHARMACOLOGY 13

 PHARMACOKINETICS 14

 PHARMACODYNAMICS 14

 EXPOSURE-RESPONSE RELATIONSHIPS 14

6 INTEGRATED REVIEW OF EFFICACY 14

 INDICATION 14

 Methods..... 14

 General Discussion of Endpoints 14

 Study Design 15

 Efficacy Findings..... 15

 Clinical Microbiology 24

 Efficacy Conclusions..... 24

7 INTEGRATED REVIEW OF SAFETY..... 24

 METHODS AND FINDINGS..... 24

 METHODS AND FINDINGS..... 25

 Other Serious Adverse Events 35

 Dropouts and Other Significant Adverse Events..... 35

Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 { (fluocinonide) Cream, 0.1%, }

Common Adverse Events	36
TABLE 15 (APPLICANT’S TABLE 8F.12) TREATMENT-EMERGENT ADVERSE EVENTS	36
Laboratory Findings	39
Vital Signs	39
Special Safety Studies	39
3) STUDY MED 02-016 (IRRITANCY STUDY IN 39 SUBJECTS).	41
Human Reproduction and Pregnancy Data	43
Assessment of Effect on Growth.....	44
Overdose Experience.....	44
Postmarketing Experience	44
ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	45
Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	45
8 ADDITIONAL CLINICAL ISSUES	45
DOSING REGIMEN AND ADMINISTRATION.....	45
DRUG-DRUG INTERACTIONS	45
SPECIAL POPULATIONS.....	45
PEDIATRICS.....	45
ADVISORY COMMITTEE MEETING	45
LITERATURE REVIEW	46
POSTMARKETING RISK MANAGEMENT PLAN	46
OTHER RELEVANT MATERIALS	46
9 OVERALL ASSESSMENT	46
CONCLUSIONS.....	46
RECOMMENDATION ON POSTMARKETING ACTIONS.....	47
Required Phase 4 Commitments	47
9.4 LABELING REVIEW	47
9.5 COMMENTS TO APPLICANT	47
APPENDICES	48
LINE-BY-LINE LABELING REVIEW	48

1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

An *Approval* recommendation is being made for use of (fluocinonide) Cream, 0.1%, a topical corticosteroid, applied twice daily for treatment of plaque-type psoriasis affecting up to 10% body surface area (BSA) in patients ≥ 18 years of age.

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.

The Applicant is seeking approval of once daily application of (fluocinonide) Cream, 0.1%, a topical corticosteroid, for relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in adults. Corticosteroid-responsive dermatoses include a broad range of inflammatory and pruritic skin disorders of which the most common are psoriasis and atopic dermatitis. Psoriasis and atopic dermatitis are the disease entities studied in this application as representative of corticosteroid responsive dermatoses.

Since atopic dermatitis is primarily a pediatric disorder and no pediatric patients were studied, the application is only approved for use of (fluocinonide) Cream, 0.1% in adults for treatment of plaque-type psoriasis. Based on the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. This requirement is not waived or deferred since atopic dermatitis is primarily a pediatric disorder and there is substantial potential for use in pediatric patients. Safety studies with use of fluocinonide 0.1% cream in pediatric patients with atopic dermatitis to assess the potential of adrenal suppression are on going at the time of this review and only preliminary data are available.

Recommendation on Postmarketing Actions

Required Phase 4 Commitments



Summary of Clinical Findings

Brief Overview of Clinical Program

The Applicant conducted ten clinical trials in the United States in support of the application. A total of 1,058 subjects have participated in studies of 0.1% fluocinonide concentration. These studies included two Phase 1 studies, one Phase 2 study, two Phase 3 studies, and four supportive studies. Of the 1,058 subjects, 385 were healthy volunteers and 673 were subjects with psoriasis or atopic dermatitis.

In the pooled Phase 2 and Phase 3 studies database, the overall treatment exposure was approximately 15 days, with a range from 3 to 22 days. The Applicant studied two treatment regimens in the Phase 3 studies and subjects in the *qd* treatment arms used a mean of 34.3g of fluocinonide 0.1% cream and 33.3g of vehicle, for an average of 15 applications. Subjects in the *bid* treatment arms used a mean of 75.2g of fluocinonide 0.05%, 48.8g of fluocinonide 0.1% cream, and 46.7g of vehicle, for an average of 29 applications.

Efficacy

The Applicant conducted two pivotal Phase 3 multicenter, double-blind, randomized, vehicle-controlled efficacy and safety studies with use of fluocinonide 0.1% cream. One study each was conducted in adult patients with psoriasis (MP-0201-05) and adult patients with atopic dermatitis (MP-0201-06) to support a claim for treatment of corticosteroid-responsive dermatoses. [REDACTED] (fluocinonide) 0.1% Cream was applied topically once-daily (*qd*) or twice-daily (*bid*) for 2 weeks and patients returned 2 weeks later for a post-treatment assessment.

Although the disease entities studied were different, both study protocols were similar in design. The objective was to evaluate the efficacy and safety of fluocinonide 0.1% cream in the treatment of plaque-type psoriasis and atopic dermatitis when applied topically twice daily or once daily for 2 weeks. Inclusion/exclusion criteria were acceptable for the indication with the exception that both studies were restricted to adults (≥ 18 years of age).

The primary efficacy variable was the dichotomized physician's static global assessment (PGA) of overall lesion severity at the end of treatment (Week 2), with Treatment Success defined as a PGA score of 0 (cleared) or 1 (almost cleared). The secondary efficacy variables included the overall PGA scores, individual symptom scores (induration, erythema, and scaling for Study MP-0201-05 or erythema, infiltration/papulation, excoriations, and lichenification for Study MP-0201-06), total symptom scores, overall severity of pruritus, and body surface area (BSA) of affected treatable areas.

The primary comparison was that of fluocinonide 0.1% cream once daily vs. vehicle, based on data from two studies (MP-0201-05 and MP-0201-06). 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. The fluocinonide 0.1% cream twice

daily regimen was also compared with vehicle based on data from the same two studies (MP-0201-05 and MP-0201-06) in a separate analysis. Once-daily treatment is the regimen proposed by the Applicant. According to the Applicant, the twice-daily regimen is included as part of the support for dose selection and corresponds to labeled dosage for other super-high potency topical corticosteroids (e.g., Temovate®). Greater than 2 weeks usage or more than 60 gram (g) per week are contraindicated due to the risk of adrenal suppression.

In the ITT population, statistical superiority was demonstrated for active over vehicle in both studies (0201-05 and MP-0201-06) for both disease entities (psoriasis and atopic dermatitis) based on PGA of clear or almost clear and both treatment regimens (once daily and twice daily); however, twice (*bid*) dosing frequency was statistically superior ($p < 0.001$) to once daily (*qd*) dosing ($p = 0.43$) in patients with plaque psoriasis. In atopic dermatitis patients, compared to vehicle was statistically significant ($p < 0.001$) for both *qd* and *bid* dosing regimen; however, unlike psoriasis, both *qd* and *bid* treatment regimen were similar to each other in the rate of treatment success. Seven centers were common between two studies; however, according to the Statistical review, elimination of the common investigators from both studies did not impact study results.

Safety

Side effects from topical corticosteroids have been well characterized and can be divided into local side effects and those resulting from systemic absorption. The presence or absence of the seven signs and symptoms of skin atrophy (telangiectasis, skin transparency, loss of elasticity, loss of normal skin markings, skin thinning, striae and bruising) were assessed in the Phase 2 and 3 studies (MP-0201-01, MP-0201-05, and MP-0201-06).

The seven signs and symptoms of skin atrophy were already present at baseline in 17 % (74/433) of patients in the pooled safety database and scores appeared to improve at Week 2. Signs and symptoms of skin atrophy decreased at Week 2 to 9% (39/443); except for telangiectasis which increased slightly at Week 2. The seven signs and symptoms of skin atrophy were absent in the majority of subjects in each treatment arm. In most cases the number of subjects in a treatment arm expressing any of the skin atrophy symptoms decreased slightly throughout the study period. Changes, however, were not significant.

HPA axis suppression was evaluated in Studies MP-0201-01 and MP0201-06 (selected sites only). Studies MP-0201-01 and MP-0201-06 analyzed cortisol levels using two definitions: (1) the protocol definition - a pre-cosyntropin stimulation (basal) serum cortisol level $\leq 5 \mu\text{g/dL}$, a 30- minute post-cosyntropin stimulation level $\leq 18 \mu\text{g/dL}$, or a post- cosyntropin stimulation increase (over basal) $< 7 \mu\text{g/dL}$; (2) a secondary definition - a post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$ as per the FDA Draft Guidance for Industry on the Use of Cosyntropin Stimulation Testing to Assess for Corticosteroid-Induced Adrenal Suppression during drug development.

Using the post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$ criterion to indicate adrenal suppression, two atopic dermatitis patients in the once-daily treatment subgroup

Clinical Review
{Brenda E. Vaughan, M.D.}
{NDA 21-758}
{ (fluocinonide) Cream, 0.1%, }

13% (2/18) patients exhibited abnormal post-stimulation cortisol levels (Study MP-0201-06). In patients with plaque psoriasis, 17% (3/18) patients in the twice daily (fluocinonide 0.1%) Cream study arm and 5% (1/19) in the twice daily Lidex® (fluocinonide 0.05%) Cream study arm exhibited reversible abnormal post-stimulation cortisol levels (Study MP-0201-01).

Dosing Regimen and Administration

Drug-Drug Interactions

No formal drug interaction studies with fluocinonide 0.1% cream have been conducted. No analysis was performed for drug interactions from the data in any of the studies performed.

Special Populations

Safety studies with use of fluocinonide 0.1% cream in pediatric patients to assess the potential of adrenal suppression are on going at the time of this review and only preliminary data are available. As per the guidance obtained at the Pediatric Advisory Committee meeting held on October 29, 2003, it is preferable that all pediatric patients be treated concomitantly (for intermediate or lower strength topical steroids); however, with use of high potency topical steroids sequential cohort testing (12 to <18 years, 6 <12 years, 3 <6 years, and 3 years <3 months) was considered appropriate.

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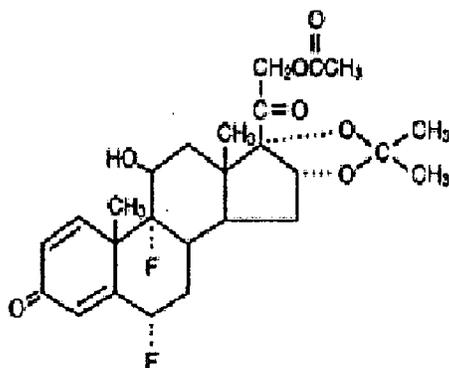
2 INTRODUCTION AND BACKGROUND

Product Information

- Product Description

(flucinonide) Cream 0.1% contains flucinonide, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Flucinonide has the chemical name 6 alpha, 9 alpha-difluoro-11 beta, 21-dihydroxy-16 alpha, 17 alpha-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-acetate. Its chemical formula is $C_{26}H_{32}F_2O_7$ and it has a molecular weight of 494.58.

It has the following chemical structure:



Flucinonide is an almost odorless white to creamy white crystalline powder. It is practically insoluble in water and slightly soluble in ethanol.

Each gram of (flucinonide) Cream contains 1 mg micronized flucinonide in a cream base of propylene glycol, dimethyl isosorbide, glyceryl monostearate and PEG stearate, purified water, Carbopol 980, diisopropanolamine, and citric acid.

Currently Available Treatment for Indications

Topical corticosteroids were first introduced in the early 1950s and are among the most widely used treatment modalities for psoriasis and atopic dermatitis. Corticosteroids have anti-inflammatory, immunosuppressive and antiproliferative properties and are available both OTC

(low potency hydrocortisone 0.05% and 1%) and by prescription. Corticosteroid therapy has become the mainstay for the treatment of atopic dermatitis and psoriasis due to the anti-inflammatory actions. Corticosteroids are often used in conjunction with emollients that help promote hydration of the epidermis. Patients with extensive and severe disease may require oral therapy. Fluocinonide is currently marketed as Lidex® products that are classified as mid and high potency topical corticosteroids.

Other topical therapies for psoriasis include anthralin, tar, retinoids, salicylic acid, calcipotriene (a vitamin D analogue), and tazarotene (a retinoid prodrug). Tacrolimus and pimecrolimus, topical immunosuppressive agents which inhibit T cell activation, have recently been approved for the treatment of atopic dermatitis.

Phototherapy for psoriasis includes ultraviolet (UV) band B (UVB), narrow band UVB, and psoralen, a photosensitizer, plus UV band A (PUVA). Systemic therapies for psoriasis include methotrexate, cyclosporin, and retinoids for severe and/or recalcitrant psoriasis because they induce serious toxicities. Alefacept and other biologics are immunosuppressive agents approved for treatment of moderate-to-severe psoriasis.

Availability of Proposed Active Ingredient in the United States

Fluocinonide is currently marketed as Lidex® products that include fluocinonide 0.05% cream, gel, ointment, and topical solution (rated as Class II topical corticosteroids), and Lidex-E® Emollient cream (rated as a Class III topical corticosteroid).

Important Issues with Pharmacologically Related Products

Side effects of other members of the steroid pharmacologic class have been well characterized and can be divided into local side effects and those resulting from systemic absorption (e.g., suppression of the HPA axis). Side effects from topical corticosteroids are directly related to the potency ranking of the compound and the length of use. Local side effects include atrophy of the skin, striae, purpura, telangiectasia, in addition to the development of perioral dermatitis, and rosacea.

Systemic side effects are also related to the potency of the topical steroid, the site of application, the occlusion, the percentage of the body covered and the length of use. The risk of corticosteroid-induced HPA axis suppression is believed to be increased in children due to a higher skin surface area to body mass ratio.

Presubmission Regulatory Activity

Phase 2 Guidance meeting held on November 27, 2002
End-of-Phase 2 meeting conducted on April 23, 2003,
Pre-NDA Meeting held January 16, 2004
Post Pre-NDA Meeting on February 25, 2004

Other Relevant Background Information

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC (and Product Microbiology, if Applicable)

The Chemistry review has not been completed and according to verbal communications there are some outstanding review issues (not approvalability issues) that are likely to be resolved.

Animal Pharmacology/Toxicology

Although the proposed use is restricted to 2 weeks, the indication is considered chronic and the Applicant has agreed to conduct photoco-carcinogenicity and dermal carcinogenicity studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

Clinical studies conducted by the Applicant and submitted are the source of the review.

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Table 1: Tables of Clinical Studies

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Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 { (fluocinonide) Cream, 0.1%, }

2. Table of all Studies Included in the Integrated Summary of Safety

Table 8F.1 Clinical Studies of Fluocinonide 0.1% Cream

Study No.	Abbreviated Title	Design	Completion Status (Report Date)	Subjects			Treatment			Reference	
				Disease	Number	M/F (G:NG)	Age in years (Mean)	Dose	Frequency		Duration
Phase 1 Studies											
VED 02-015	Sensitivity and Irritation	R, OB, multiple-dose	Complete (8/21/2003)	Healthy adults	226 enrolled 226 R	41/183 (182/143)	19 - 76 (48)	Fluocinonide 0.1% Cream or white petrolatum under occlusion, an amount sufficient to fill a 10 mm Finn Chamber.	8/13 per week for 5 weeks; applications. Challenge treatment 14 days after 5 th treatment	21 days continuous exposure	
VED 02-016	Irritation	R, OB, multiple-dose	Complete (7/19/2002)	Healthy adults	35 enrolled 35 R	8/31 (35/4)	26 - 75 (48)	0.2 g of each product: Fluocinonide 0.1% Cream, Fluocinonide 0.05% ointment, Sodium lauryl sulfate (SLS) or white petrolatum under occlusion.	5 applications each week applications; continuous exposure	21 days (3 consecutive weeks)	
Controlled Phase 2 Studies											
WP-0204-01	Adrenal suppression	R, OB, parallel group	Complete (6/4/2003)	Flaque-Type Psoriasis	37 enrolled 37 R	24/13 (32/5)	20 - 71 (46)	Fluocinonide cream, 0.05% or 0.1%	Orally	14 days	

VC = vehicle-controlled
 OB = open-blind
 OL = open-label
 R = randomized

M = male subjects
 F = female subjects
 CRF = case report form
 VCA = vasoconstriction assay

C = Caucasian subjects
 NC = non-Caucasian
 fm = formulations
 F = fluocinonide
 T = Temovate[®]

Source: Individual Study Reports

Appears This Way
 On Original

Clinical Review

{Brenda E. Vaughan, M.D.}

{NDA 21-758}

{ (fluocinonide) Cream, 0.1%, }

Table 8F.1 Clinical Studies of Fluocinonide 0.1% Cream

Study No.	Abbreviated Title	Design	Completion Status (Report Date)	Subjects			Treatment			Reference	
				Disease	Number	M/F (C/NC)	Age in years (Mean)	Dose	Frequency		Duration
Controlled Phase 3 Studies											
MF-C201-05	Efficacy and safety of F 0.1% Cream, Psoriasis	R, DB, VC, and parallel group	Complete (1/2/2005)	Flaque-Type Psoriasis	323 enrolled 323 R	17 M/152 (254/23)	19-90 (46-50)	F 0.1% cream or vehicle	1x or 2x daily	14 days	
MF-C201-05	Efficacy and safety of F 0.1% Cream, Atopic Dermatitis	R, DB, VC, and parallel group	Complete (1/2004)	Atopic Dermatitis	312 enrolled 312 R	14 M/172 (232/60)	18-75 (41-44)	F 0.1% cream or vehicle	1x or 2x daily	14 days	
Supportive Studies											
MED-C0-018	VCA study comparing various formulations	Multi-point study	Complete - Abbreviated Report (5/2001)	Healthy adults	12	--	20-45	F 0.1% (4 mm, 2 ointment); F 0.05% (2 mm, cream & ointment); T 0.05% (2 mm, cream & ointment); Placebo (2 F excipient mm)	Single 3 mg application of each test article	5 hours	

VC = vehicle-controlled
DB = double-blind
OL = open-label
R = randomized

M = male subjects
F = female subjects
CRF = case report form
VCA = vasoconstriction assay

C = Caucasian subjects
NC = non-Caucasian
TM = formulations
F = fluocinonide
T = Temovate®

Source: Individual Study Reports

Table 8F.1 Clinical Studies of Fluocinonide 0.1% Cream

Study No.	Abbreviated Title	Design	Completion Status (Report Date)	Subjects			Treatment			Reference	
				Disease	Number	M/F (C/NC)	Age in years (Mean)	Dose	Frequency		Duration
MED01-022	VCA study comparing different dose levels of active	Blinded, single-point	Complete 2/5/2004	Healthy adults	36	10/26 (22/14)	20-60 (42)	F: 0.05, 0.1%, 0.075%; Lidex-E® 0.05%; T 0.05%; and Vehicle placebo (cream)	Approximately 10 mg of each test product applied to a 1 cm² area of the forearm; each subject treated with all test products.	One 16-hour exposure	
MED02-004	VCA study comparing different dose levels of active	Blinded, single-point	Complete 2/5/2004	Healthy Adults	36	9/27 (21/15)	18-60 (39)	F: 0.2%, 0.1%, 0.05%; Lidex-E® 0.05%; Ultravate® 0.05%; and Vehicle placebo (cream)	Approximately 10 mg of each test product applied to a 1 cm² area of the forearm; each subject treated with all test products.	One 16-hour exposure	
MED02-005	VCA study comparing different dose levels of active	Blinded, single-point	Complete 2/5/2004	Healthy adults	36	9/27 (21/15)	18-60 (39)	F: 0.1% cream and ointment; Lidex-E® 0.05%; T 0.05%; Psorcon® 0.05%; Diprone® 0.05%; and Vehicle placebo (ointment)	Approximately 10 mg of each test product applied to a 1 cm² area of the forearm; each subject treated with all test products.	One 16-hour exposure	

Clinical Review
{Brenda E. Vaughan, M.D.}
{NDA 21-758}
{ (fluocinonide) Cream, 0.1%, }

Review Strategy

Phase 3 pivotal clinical trials are reviewed for safety and efficacy. Dermal safety, adrenal suppression, and vasoconstrictor studies are being reviewed for safety. Adequacy of adrenal suppression, and vasoconstrictor studies are addressed by Biopharm.

Data Quality and Integrity

DSI audits were not requested.

Compliance with Good Clinical Practices

According to the Applicant, studies were performed in accordance with standard operating procedures of MEDICIS Pharmaceutical Corp. operating at the time of the study. These were designed to ensure adherence to Good Clinical Practices (GCP) and ensure the protection of the subjects, as required by the following directives in operation at the time:

1. International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations (CFR) dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh, 2000).

Financial Disclosures

The Applicant certifies the investigators have not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

5 CLINICAL PHARMACOLOGY

Clinical Pharmacology review is not complete; however, verbal communication indicates that there does not appear to be significant differences between the vasoconstrictor activity of the 0.1% and 0.05% flucocinonide cream formulation. Adrenal suppression is less using the a post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/Dl}$ criterion rather than a pre-cosyntropin stimulation (basal) serum cortisol level $\leq 5 \mu\text{g/dL}$, 30-minute post-cosyntropin stimulation level $\leq 18 \mu\text{g/dL}$, or a post-cosyntropin stimulation increase (over basal) $< 7 \mu\text{g/dL}$ use by the Applicant. (See Clinical Pharmacology for details)

Pharmacokinetics

Pharmacodynamics

Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

Indication

The indication sought is for [REDACTED] daily use of [REDACTED] (flucocinonide .1%) Cream, a topical
[REDACTED]

Reviewer comment:

Based on vasoconstrictor studies submitted with the application, [REDACTED] (flucocinonide .1%) Cream is classified by the Applicant as a super-potent Class 1 corticosteroid; however, blanching scores do not necessarily predict therapeutic success.

Methods

Corticosteroid-responsive dermatoses include a broad range of inflammatory and pruritic skin disorders of which the most common are psoriasis and atopic dermatitis. Psoriasis and atopic dermatitis are the disease entities studied in this application as representative of corticosteroid responsive dermatoses. The Applicant conducted one study each in adult patients with plaque psoriasis (MP-0201-05) and atopic dermatitis MP-0201-06) to demonstrate safety and efficacy with use of flucocinonide 0.1% cream to obtain the treatment of corticosteroid responsive dermatoses labeling claim.

General Discussion of Endpoints

Although the disease entities studied were different, both study protocols were similar in design. The objective was to evaluate the efficacy and safety of flucocinonide 0.1% cream in the treatment of plaque-type psoriasis and atopic dermatitis when applied topically twice daily or once daily for 2 weeks. The primary efficacy variable was the dichotomized physician's static global assessment (PGA) of overall lesion severity at the end of treatment (Week 2), with Treatment Success defined as a PGA score of 0 (cleared) or 1 (almost cleared). The secondary efficacy variables included the overall PGA scores, individual symptom scores (induration, erythema, and scaling [Study MP-0201-05] or erythema, infiltration/papulation, excoriations, and lichenification [Study MP-0201-06] and total symptom scores, overall severity of pruritus, and BSA of affected treatable areas.

The primary comparison was that of flucocinonide 0.1% cream once daily compared to vehicle, based on data of two studies (MP-0201-05 and MP-0201-06). 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. The flucocinonide 0.1%

Clinical Review

{Brenda E. Vaughan, M.D.}

{NDA 21-758}

{XXXXXXXXXX (fluocinonide) Cream, 0.1%, }

cream twice daily regimen was also compared with vehicle based on data from the same two studies (MP-0201-05 and MP-0201-06) in a separate analysis.

The once-daily treatment is the regimen for which this application is submitted. According to the Applicant, the twice-daily regimen is included as part of the support for dose selection and corresponds to labeled dosage for other super-high potency topical corticosteroids (e.g., Temovate®) and greater than 2 weeks usage or more than 60 gram (g) per week are not recommended due to the risk of adrenal suppression.

Study Design

Studies MP-0201-05 and MP-0201-06 were adequate and well-controlled studies; however not independent in that seven centers were common between two studies. Each study was multicenter, randomized, parallel-group, double-blind, vehicle-controlled, clinical trials to assess efficacy and safety of fluocinonide 0.1% cream applied topically once daily or twice daily for 2 weeks in the treatment of psoriasis and atopic dermatitis, respectively. Patients were randomized to 1 of 4 treatment groups.

Investigational product

Fluocinonide Cream (0.1%): MPC 6051-13-01-AX

Lot Number: R0044D001 (Study MP-0201-05, psoriasis study)

Lot Number: R0044D002 (Study MP-0201-06, atopic dermatitis study)

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

The investigational product (0.1% fluocinonide cream) was applied topically once or twice daily for 14 days. It was supplied to the study site in 60 g tubes. Subjects returned to the study site at the end of the 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. Each subject participated for 4 weeks. The extent of rebound assessments were based on the comparison of evaluations between treatments at Week 4, 2 weeks after the cessation of treatment.

Efficacy Findings

Study 1:

Study MP-0201-05

Title of study "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 Plaque-Type Psoriasis".

Study period: First subject randomized: June 3, 2003 Last subject completed: September 12, 2003

A total of 323 subjects with plaque-type psoriasis were enrolled at 15 study centers in the USA at the following study sites:

Site No.	Investigator
01	
03	
04	
05	
06	
07	
08	
09	
10	
11	
12	
13	
14	
15	

Of the 323 subjects enrolled, 107 were treated with fluocinonide 0.1% *qd*, 54 with vehicle *qd*, 107 with fluocinonide 0.1% *bid*, and 55 with vehicle *bid*. Three hundred (300) subjects completed the study and 23 subjects discontinued the study. The reasons for discontinuation were: adverse event (4 subjects), lost to follow-up (10 subjects), subject's request (7 subjects) and other reasons (2 subjects).

Protocol deviations

All subjects randomized to the study received at least one treatment with study drug and were included in the ITT population. A total of 46 subjects were excluded from the PP population due to the following major protocol deviations (e.g., inadequate treatment with study drug (average less than 1 gm study product used, two subjects (subjects #14 and #81) discontinued the study due to product-related adverse events, study visit outside of window (Days 12 – 19), no Week 2 (visit 3) study visit, subjects who did not washout of psoriasis treatments properly, and subjects who used prohibited medications per protocol.

Demographics

Table 2: Demographic Summary

Table 7-1 Demographic summary at Baseline by treatment group

	Fluociconide 01% qd N = 107	Vehicle qd N = 54	Fluociconide 0.1% bid N = 107	Vehicle bid N = 55
Age (years)				
mean ± SD	49.0 ± 15.0	50.4 ± 16.8	50.3 ± 14.3	48.4 ± 12.7
range	20 - 90	20 - 84	20 - 78	19 - 78
Gender - n(%)				
male	60 (56)	22 (41)	55 (51)	34 (62)
female	47 (44)	32 (59)	52 (49)	21 (38)
Race - n(%)				
• Caucasian	86 (80)	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
Height (inches)				
mean ± SD	67.5 ± 4.4	67.4 ± 4.1	67.4 ± 3.6	68.3 ± 4.0
range	56 - 78	58 - 77	60 - 75	58 - 77
Weight (lbs)				
mean ± SD	190.1 ± 43.8	192.4 ± 44.8	199.5 ± 81.3	197.0 ± 53.3
range	110 - 295	95 - 300	104 - 526	110 - 338
Duration of disease (years)				
mean ± SD	17.2 ± 14.3	16.6 ± 14.3	16.2 ± 12.4	18.3 ± 14.7
range	0.5 - 80.0	0.8 - 53.0	0.6 - 58.0	0.8 - 58.0
Duration of current episode (months)				
mean ± SD	10.7 ± 13.6	9.9 ± 11.0	9.0 ± 10.6	11.3 ± 14.3
range	0.1 - 80.0	0.2 - 53.0	0.1 - 55.0	0.3 - 58.0
BSA involvement (%)				
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: Post-Text Table 1

SD = Standard Deviation

Note: all percentages and ranges are rounded

Baseline information was similar between treatment groups. Ages ranged from 19 to 90 years, overall, with means of approximately 46 - 50 years in each treatment group. There were more

male subjects (51% to 62%) than females (38% to 49%) enrolled in all treatment groups except for the qd vehicle group, which had more females than males (41% males, 59% females). Most subjects were Caucasian (> 89%) and had symptoms of the disease for 1 – 60 years prior to the start of the study, with a mean of 16 to 18 years in each treatment group; the average duration of the current episode was 9 to 11 months. The mean percentage of BSA involvement was 5.4% in the fluocinonide 0.1% *qd* group, 5.0% in the vehicle group, *qd* group, 4.9% in the fluocinonide 0.1% *bid* group, and 5.1% in the vehicle group, *bid* group. Overall characteristics were similar in the PP population.

Table 3: (Modified Statistical 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 ¹
	Fluocinonide 0.1%	Vehicle	p-value ¹	Fluocinonide 0.1%	Vehicle	p-value ¹	
Psoriasis							
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

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).

¹p-values using pairwise Mantel-Haenszel statistics, stratified on investigational site

Based on the static dichotomized PGA of overall lesion severity at the end of treatment (Week 2) in the ITT population, statistical superiority over vehicle is demonstrated with use of fluocinonide in the treatment of psoriasis when applied twice-daily or once-daily for two weeks. Although statistical significance is established for active over vehicle for both once and twice daily application frequencies, once daily fluocinonide application was found to be significantly less effective when compared to twice daily applications. In the twice daily study arm 31% (33/107) of the patients compared to 18% (19/107) of the patients in the once-daily study arm were assessed as treatment success. According to the Statistical reviewer, 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 and Rebound Assessment (See Statistical Review for details).

Secondary efficacy variables included the overall PGA scores, individual symptom scores (induration, erythema, and scaling). The symptom severity ratings decreased in both active treatment groups with maximal improvement seen at Week 2 (end of treatment) in ITT population. These improvements were observed for all symptoms (induration, erythema, scaling) as well as in the total IES scores in both the *qd* and *bid* treatment groups, and were statistically significant.

Two weeks after the end of treatment (Week 4 of study), the scores tended to increase towards the levels seen at the screen/baseline visit, but remained significant as compared to the

corresponding vehicle control. Similar results were seen in the PP population. No evidence of rebound (relapse of psoriasis to worse than baseline or transform to life-threatening forms of psoriasis after a response, in a short period of time).

Reviewer comments:

Although statistical significance was demonstrated for active over vehicle treatment success was relatively low with only 18% and 33% of patients achieving a PGA of clear or almost clear. [REDACTED] (fluocinonide) Cream 0.1% is classified by the Applicant as a “super-high potency” corticosteroid based on vasoconstrictor assays; however, it does not appear that blanching scores necessarily predict therapeutic success. Comparative studies should be considered for future development of super-high potency to better assess risk/benefit especially if there is an increased potential for local and systemic (e.g., HPA axis suppression) side effects.

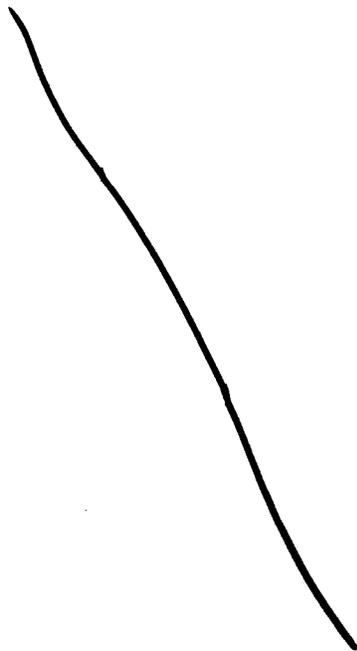
Study 2 **Study MP-0201-06**

Title of study: “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”

Study period: First subject enrolled: July 28, 2003 Last subject completed: November 04, 2003

A total of 313 subjects male and female subjects, 18 years of age or older, with clinically diagnosed atopic dermatitis involving at least 2% but no more than 10% of their total body surface area (BSA) were screened and enrolled at the 24 study sites located in the United States. The study sites are as follows:

Site No.	Investigator
01	
02	
03	
04	
05	
06*	
07	
08*	



09*

10

11

12

14

15

16

17*

18

19

20

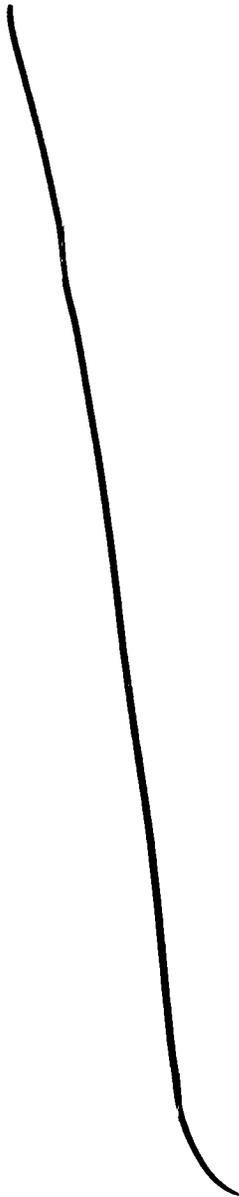
21*

22

23*

24*

25



*Centers common between Studies MP-0201-05 and MP-0201-06.

Adrenal suppression was assessed in a subset of patients at five study sites listed above in the Site and Investigator listings as HPA (See page 33 for details).

Seven centers were common between two studies; however, according to the Statistical review, elimination of the common investigators from both studies did not impact study results. There was no statistically significant treatment by center interactions in either study in either treatment regimen. The Statistical Reviewer concluded that fluctuations of treatment effects within these sites can therefore probably all be attributed to chance.

Baseline

Table 4: Demographic Summary

Table 7-1 Demographic summary at Baseline by treatment group - ITT population

	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
Age (yr)				
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
Gender - n(%)				
male	44 (40)	22 (44)	52 (51)	22 (42)
female	65 (60)	28 (56)	50 (49)	30 (58)
Race - n(%)				
• 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)
Duration of disease (yrs)				
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
Duration of current episode (months)				
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
BSA involvement (%)				
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: Post-Text Table 1; SD = Standard Deviation
 Note: all percentages and ranges are rounded

In general, baseline information was similar between treatment groups. Subject ages ranged from 18 to 79 years, overall, with means of approximately 41 to 44 years in each treatment group. The majority of the subjects were female (56% to 60%), except in the fluocinonide *bid* group (49% female, male 51%) and most were Caucasian ($\geq 60\%$). Subjects had shown symptoms of the disease for 0.1 to 64 years prior to the start of the study, with a mean of 17 to 18 years in each treatment group; the average duration of the current episode was 2.4 to 5.6 months. The mean percentage of BSA involvement was 5.6% in the fluocinonide 0.1% *qd* group, 5.5% in the control vehicle, *qd* group, 5.5% in the fluocinonide 0.1% *bid* group, and 4.9% in the control vehicle, *bid* group. Overall characteristics were similar in the PP population.

Study Results

A total of 109 patients were treated with fluocinonide 0.1% *qd* and 102 with fluocinonide 0.1% *bid*, 50 with vehicle *qd*, and 52 with vehicle *bid*. Of these 313 subjects, 291 subjects completed the study and 22 subjects discontinued the study. The reasons for discontinuation of study were: adverse event (5 subjects), protocol violation (1 subject), subject's request (5 subjects), lost to follow-up (9 subjects) and other reasons (2 subjects).

Table 5: (Modified Statistical Table) 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 <i>qd</i> vs <i>bid</i>	
	Fluocinonide 0.1%	Vehicle p-value ¹	Fluocinonide 0.1%	Vehicle p-value ¹	p-value ¹	p-value ¹
Atopic Dermatitis						
ITT	64/109 (59%)	6/50 (12%) <0.001	58/102 (57%)	10/52 (19%) <0.001	<0.001	0.837
Per Protocol	54/87 (62%)	6/36 (17%) <0.001	52/88 (59%)	5/41 (12%) <0.001	<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).

¹p-values using pairwise Mantel-Haenszel statistics, stratified on investigational site

For the ITT population, treatment success at Week 2 (end of treatment) was achieved for 59% (64/109) subjects in the fluocinonide *qd* group and 57% (58/102) subjects in the fluocinonide *bid* group compared to 12% subjects in the *qd* vehicle control and 19% subjects in the *bid* vehicle control group (fluocinonide vs. vehicle: $p < 0.001$ for both *qd* and *bid* groups). These results indicates that both *qd* and *bid* treatment were superior to vehicle, and similar to each other in the rate of treatment success. Similar results were obtained for the PP population.

In contrast to psoriasis, there were no differences between once-daily and twice-daily fluocinonide treatment in patients with atopic dermatitis. According to the Statistical review, similar trends were observed in the per protocol populations for the treatment of psoriasis and

atopic dermatitis. According to the Statistical review, 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 and Rebound Assessment (See Statistical review for details)

For overall lesion severity in the ITT population, results show significant improvement for both the *qd* and *bid* fluocinonide groups vs. the respective vehicle controls at the end of treatment (Week 2). Rebound was assessed at Week 4 (two weeks after the last dose of study medication) and 31% and 50% subjects in the fluocinonide *qd* and *bid* groups, respectively, compared to 20% subjects in the *qd* vehicle and 30% subjects in the *bid* vehicle group, continued to meet the criteria for treatment success.

Although the Applicant assessed considered overall lesion severity 2 weeks after treatment as rebound, this assessment was a measure of durability of treatment effect. Typically rebound is a phenomenon associated with treatment of psoriasis patients who after a response, in a short period of time, relapse to worse than baseline or transform to life-threatening forms of psoriasis.

Subgroup analysis based on gender and age categories (< 40, 40 to 64, and >65 years) was conducted. According to the Applicant, these data show no evidence of age or gender-related effects on treatment efficacy and treatment success rates in all treatment groups were comparable in all subgroups. The results for the physician's global assessment of overall lesion severity for the PP population were similar to those obtained for the ITT population. However, the number of geriatric patients was small with only 3 patients in the *qd* active study arm and 9 in the *bid* study arms age \geq 65 years of age.

Symptom Severity Ratings (See Statistical review for details)

The symptom severity ratings decreased in both active treatment groups with maximal improvement seen at Week 2 (end of treatment) in the ITT population. These improvements were observed for all symptoms (erythema, induration/papulation, excoriations, lichenification) as well as in the total scores (erythema + induration/papulation + excoriations + lichenification) in both the *qd* and *bid* treatment groups, and were statistically and clinically significant.

Two weeks after the end of treatment (Week 4 of study), the scores tended to increase towards the levels seen at the screen/baseline visit, and remained significant for the fluocinonide *bid* treatment group as compared to the vehicle control. Similar results were seen in the PP population.

The overall rating of pruritus improved at the end of the treatment period (Week 2) in both the *qd* and *bid* treatment groups in ITT population and tended to return towards screen/baseline values at Week 4. Significant differences were observed in % BSA affected in the ITT population at the end of treatment (Week 2) in both the *qd* and *bid* treatment groups compared to the corresponding vehicle groups. There was no significant difference between the *qd* and *bid* fluocinonide treatment groups at Week 2. Similar observations were made for the PP population.

Clinical Microbiology

Not applicable to this application.

Efficacy Conclusions

Based on the dichotomized PGA of overall lesion severity at the end of treatment (Week 2) in the ITT population, statistical superiority was demonstrated for (b) Cream over vehicle in both studies (MP-0201-05 and MP-0201-06) for both disease entities (plaque-type psoriasis and atopic dermatitis) for both treatment regimens (once daily and twice daily); however, twice daily dosing frequency was statistically superior ($p < 0.001$) to once daily dosing ($p = 0.43$) in patients with plaque psoriasis. In atopic dermatitis patients, (b) Cream versus vehicle was statistically significant ($p < 0.001$) for both once and twice dosing regimen; however, there was no significant difference between the *qd* and *bid* fluocinonide treatment groups at Week 2. Seven centers were common between the two studies; however, according to the Statistical review, elimination of the common investigators from both studies did not impact study results.

7 INTEGRATED REVIEW OF SAFETY

Methods and Findings

Fluocinonide 0.1% cream is classified as a super-high potency Class 1 corticosteroid formulation for topical dermatologic use. It has the same active component as the currently marketed Lidex® products (Class 2), and Lidex-E® emollient cream (Class 3), that has been on the market since 1971.

As a class, topical corticosteroids are known to cause cutaneous (e.g., striae, atrophy, acne, purpura, etc.) and systemic side effects (HPA axis suppression, etc.). Topical corticosteroids can be absorbed through normal intact skin and absorption can be influenced by various factors (e.g., vehicle, use of occlusion, percent body surface area of application, site of application, diseased skin, etc.). Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids: they are bound to plasma proteins to varying degrees, metabolized primarily in the liver, and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into bile.

The extent of suppression of the hypothalamic-pituitary-adrenal (HPA) axis by a topical steroid is generally related to the steroid potency, dose administered, body surface area (BSA), and skin barrier function. Manifestations of Cushing's syndrome, hyperglycemia and glucosuria can also be produced in some subjects by systemic absorption of topical corticosteroids. Patients receiving super-potent corticosteroids are advised not to use them for more than 2 weeks at a time, and to treat only small areas at any one time. Since the risk of corticosteroid-induced HPA axis suppression is believed to be increased in children, pediatric use of high and super-high potency products have been restricted.

7.1.5 Common Adverse Events

The presence or absence of the seven signs and symptoms of skin atrophy (telangiectasis, skin transparency, loss of elasticity, loss of normal skin markings, skin thinning, striae and bruising) were assessed in the Phase 2 and 3 studies (MP-0201-01, MP-0201-05, and MP-0201-06).

The seven signs and symptoms of skin atrophy were present at baseline in 17 % (74/433) patients in the pooled safety database and scores appeared to improve at Week 2. Signs and symptoms of skin atrophy decrease at Week 2 to 9% (39/443); except for telangiectasis increased slightly at Week 2. The seven signs and symptoms of skin atrophy were absent in the majority of subjects in each treatment arm. In most cases the number of subjects in a treatment arm expressing any of the skin atrophy symptoms decreased slightly throughout the study period. Changes, however, were not significant.

7.1.5.6 Additional analyses and explorations

Review of literature indicates that systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticoid insufficiency after withdrawal of treatment.

Adrenal Suppression Study (MP-0201-01)

A Phase 2 adrenal suppression study (MP-0201-01) was conducted in patients with plaque psoriasis and a subset of atopic dermatitis patients were tested during conduct of the Phase 3 clinical trial (MP-0201-06). Psoriasis and atopic dermatitis are manifested at different ages of onset with the latter being predominately a pediatric disease; however, the Applicant only studied patients ≥ 18 years of age in the Phase 3 pivotal studies and Phase 2 safety studies. A Phase 2 adrenal suppression study is ongoing at the time of this review.

Methods and Findings

Protocol No. MP-0201-01 (See Biopharm Review for details)

Titled: "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"

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

Study 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.

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. Fasting blood glucose levels were assessed at Screening, Baseline, and Week 2.

Investigational plan

Overall study design

Clinical Review
{Brenda E. Vaughan, M.D.}
{NDA 21-758}
{XXXXXXXXXX (fluocinonide) Cream, 0.1%, }

This was a multi-center, randomized, multiple-dose, comparator-controlled, open-label study of the investigational product (fluocinonide 0.1% cream) and Lidex® Cream 0.05% applied twice daily in subjects with clinically diagnosed plaque-type psoriasis involving $\leq 10\%$ of the total BSA. Study product was not to be applied to lesions of the face, groin, perianal area and axillae and application of any test material under an occlusive dressing was prohibited during the study.

Cortisol levels were analyzed using two definitions: (1) the protocol definition - a pre-cosyntropin stimulation (basal) serum cortisol level $\leq 5 \mu\text{g/dL}$, a 30-minute post-cosyntropin stimulation level $\leq 18 \mu\text{g/dL}$, or a post-cosyntropin stimulation increase (over basal) $< 7 \mu\text{g/dL}$; (2) a second definition - a post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$. 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 level of $\leq 18 \mu\text{g/dL}$ to indicate adrenal suppression.

A total of 3.5 g of investigational product (0.1% fluocinonide cream) was applied to at least 7% of the total BSA twice daily for 14 days. It was supplied to the study site in 60 g tubes.

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

Efficacy assessments

At Week 2 and Week 4, the investigator rated the change in disease severity from Baseline as "improved," "worsened" or "stayed the same." A rating of "worsened" constituted an AE.

Safety assessments

The following safety assessments were made: HPA axis suppression, skin safety evaluations, urine pregnancy testing, and adverse events monitoring.

HPA axis suppression

Measurement of serum cortisol levels pre- and post-stimulation with cosyntropin (0.25 mg) is the standard method used to evaluate adrenal suppression.

Skin safety evaluations

Specific skin safety evaluations were performed at each study visit with regard to all treated lesions by marking as present or absent each of the following 7 signs and symptoms of skin

atrophy: telangiectasis, skin transparency, loss of elasticity, loss of normal skin markings, skin thinning, striae, and bruising.

Urine pregnancy testing

A urine pregnancy test (β -human chorionic gonadotropin, [β -HCG]) was performed on female subjects of childbearing potential prior to enrollment on Day 1 and at the end-of-treatment visit. A positive result on Day 1 excluded the subject from further participation in the study.

Adverse events

At each post-screening visit, information about all local and systemic AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through other means, was collected and recorded on the Adverse Event CRF. Worsening of the primary disease state was recorded as an adverse event.

Study Results

A total of 37 subjects were screened and enrolled into the study: 19 were treated with fluocinonide 0.05% and 18 with fluocinonide 0.1%. All subjects completed the study.

In general, Baseline information was similar between treatment groups. Subject ages ranged from 20-71 years, overall, with means of approximately 46 years in each treatment group. The majority of the subjects were male (>60%) and most were Caucasian (>80%). Subjects had symptoms of the disease for 1 – 49 years prior to the start of the study, with a mean of 18 years in each treatment group. The mean percentage of BSA involvement was 15% in the fluocinonide 0.05% group and 20% in the fluocinonide 0.1% group. Overall characteristics were similar in the evaluable population.

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Table 6: Demographic Summary by Treatment Group
Table 7-1 Demographic summary by treatment group

	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	18.0 ± 13.8
range	1 - 49	1 - 42
BSA involvement (%)		
mean ± SD	14.8 ± 5.86	19.6 ± 10.9
range	10 - 32	10 - 50

Source: Post-Text Table 1

Note: all percentages and ranges are rounded

Dosage

Subjects in both treatment groups applied medication an average of approximately 28 times during the study. The total number of applications ranged from 25 – 31 in the fluocinonide 0.05% group and from 27 – 30 in the fluocinonide 0.1% group. Five subjects in the 0.05% group and 4 subjects in the 0.1% group missed 1 - 2 applications of medication during the treatment period.

The total weight of investigational medication used (fluocinonide 0.1%) ranged from 59 g – 117 g with a mean of 95 g. Subjects randomized to fluocinonide 0.05% used 31 g – 114 g of medication, with a mean of 75 g.

Subject exposure

The mean duration of treatment was 15 days in each treatment group, with a range of 14 – 16 days in the 0.05% group and 14 – 15 days in the 0.1% group.

Efficacy results

Primary efficacy results

According to the Applicant, at the end of the treatment period (Week 2), 100% of subjects in the 0.1% group and 95% of subjects in the 0.05% group showed improvement in their disease severity. By Week 4, 83% and 63% of the fluocinonide 0.1% and 0.05% groups, respectively, had continued to show improvement. None had worsened.

Reviewer comments:

These efficacy results are could be subject to bias in favor of the higher concentration as this was an open labeled safety study. The number of patients is small; however, it does not appear that the higher fluocinonide 0.1% concentration provides a clear advantage to the currently marketed less potent Lidex® (fluocinonide) Cream 0.5% concentration.

Adrenal Suppression Results

Based on the post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$ criterion to define adrenal suppression, three subjects (subject # 17, 20, 37) or 17% (n=18) in the ██████████ study arm and one subject (#23) or 5% (n=19) in the Lidex study arm exhibited reversible abnormal post-stimulation cortisol levels. However in the ██████████ study arm, one subject (# 17) with a Week 2 post stimulation cortisol level of 23.6 $\mu\text{g/dL}$ was considered suppressed based on the per protocol definition of lack of post- cosyntropin stimulation increase (over basal) $< 7 \mu\text{g/dL}$ and would not have been detected based on the $\leq 18 \mu\text{g/dL}$ criterion; however at retest at Week 4, the cortisol level was 12.9 $\mu\text{g/dL}$.

According to per protocol definition of adrenal suppression, at the Week 2 visit, 5 subjects (31%) in the 0.1% group and 2 subjects (13%) in the 0.05% group met the criteria for HPA axis suppression. By the Week 4 visit (2 weeks post treatment), only 1 subject in the 0.1% population still met the criteria. Between-treatment differences were not statistically significant.

Table 7: Subjects with Abnormal Adrenal Suppression Results (Study MP-0201-01)

Study Arm	Subject No.	% Baseline BSA	Amount Used (g) Week 1, Week 2
██████████ (fluocinonide) Cream 0.01% (bid) (N=18)	17*	29%	56 g, 56.7 g
	20	25%	50 g, 45.2 g
	37	12%	52.9 g, 38 g
Lidex (fluocinonide)	23	12%	25.1 g, 25.6 g

Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 { (fluocinonide) Cream, 0.1%, }

Cream 0.05% (bid) (N = 19)			
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* Would not have been detected at Week 2 based on the $\leq 18 \mu\text{g/dL}$

Vital signs

There were no evident changes from Baseline in vital signs (Weight, temperature, pulse, respiration rate, blood pressure) or blood glucose levels.

Skin safety evaluations

The seven signs and symptoms of skin atrophy (telangiectasis, skin transparency, loss of elasticity, loss of normal skin markings, skin thinning, striae and bruising) were absent at all evaluations for all except 1 subject, in the 0.1% group, who presented with bruising at the baseline skin evaluation.

Overall experience of adverse events

The most commonly occurring AEs are presented by body system in Table 10-2, below.

Table 8: (Applicant's Table 10-2) Adverse Events Study MP-0201-01

Table 10-2 Number (%) of subjects with AEs overall and by body system (≥ 2 subjects in a group)

	Fluocinonide 0.05%	Fluocinonide 0.1%
	n (%)	n (%)
Subjects studied		
total no. of subjects	19 (100%)	18 (100%)
total no. of subjects with AEs	10 (53%)	7 (39%)
Body system affected		
Infections and infestations	5 (26%)	0
Musculoskeletal and connective tissue	3 (16%)	2 (11%)
Nervous system	1 (5%)	2 (11%)
Respiratory, thoracic and mediastinal	2 (11%)	2 (11%)
Skin and subcutaneous tissue	1 (5%)	2 (11%)

Source: Post-Text Table 7.1

Overall, 17 subjects, 10 (53%) in the 0.05% group and 7 (39%) in 0.1% group, reported a total of 31 AEs during the study. The incidence of AEs was similar between treatment groups. The most commonly occurring AE was an upper respiratory tract infection that occurred in 5 subjects, all in the 0.05% treatment group. The majority of the AEs were mild or moderate in severity. Only 1 severe AE was reported: a severe eye irritation that was considered unrelated to the study medication.

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Table 9: (Applicant's Table 10-4 Study MP-0201-06, Volume 7, Item 9, Page 1960) Subjects with HPA Axis Suppression

Subjects with HPA axis suppression by criterion of HPA axis suppression at baseline and end of Week 2 – 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 in the Clinical Study Report for Study MP-0201-06, Volume 7, Item 9, Page 1960

The majority of patients with HPA axis suppression had post-stimulation cortisol levels increases over basal levels < 7 µg/dL. 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%).

Deaths and other serious adverse events (SAEs)

No deaths or other serious adverse events occurred during the study.

Other significant adverse events

Of the 31 AEs reported, 3 were considered definitely or probably related to the study medication. Subject 34, in the 0.05% group, experienced mild, intermittent pain of the skin that was considered definitely related to the study medication. Subject 15, in the 0.1% group, experienced mild, intermittent contact dermatitis and mild, intermittent pain of the skin that were both considered probably related to the study medication. Treatment was continued in all cases.

Adrenal Suppression Study (MP-0201-06)

Adrenal suppression was assessed in a subset of atopic dermatitis patients during conduct of the double blind Phase 3 clinical trial (MP-0201-06). There were 16 and 18 subjects tested in the twice daily and once daily fluocinonide 0.1% study arms respectively. In the vehicle arms 18 subjects (9 each) in the twice daily and once daily fluocinonide 0.1% study arms; respectively, were assessed for adrenal suppression.

Based on the post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$ criterion to define adrenal suppression, two subjects (subjects # 180 and #151) in the ██████ once daily study arm met the definition of suppression. However one subject (# 180) with a Week 2 post stimulation cortisol level of $20.7 \mu\text{g/dL}$ would not have been detected based on the $\leq 18 \mu\text{g/dL}$ criteria. This subject was considered suppressed based on the per protocol definition of lack of post-cosyntropin stimulation increase (over basal) $< 7 \mu\text{g/dL}$ and was retested; however, post-stimulation cortisol level was $17.8 \mu\text{g/dL}$ when retested at Week 4; thus, no subsequent retest was performed because this subject met the normal retest criteria based on per protocol definition.

Table 10 (Applicant's Table 10-4)

Table 10-4 Subjects with HPA axis suppression by criterion of HPA axis suppression at baseline and end of Week 2 – ITT population

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

Source : Data Listing 4.3

Based on the post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$ criterion to define adrenal suppression, the subjects in the table that follows were suppressed. MP-0201-06 was a vehicle controlled clinical trial in atopic dermatitis that studied once and twice daily dosing and paradoxically, no evaluable subjects in the twice daily ██████ (fluocinonide) Cream 0.1% as

opposed to the evaluable once daily study arm had an abnormal adrenal suppression test. No evaluable subjects in either vehicle study arms (qd or bid) had an abnormal adrenal suppression test.

Table 11: Summary of patients with abnormal post-cosyntropin stimulation serum cortisol levels ($\leq 18 \mu\text{g/dL}$) (Studies MP-201-01 and MP-201-06)

Study Arm	Subject No.	% Baseline BSA	Amount Used (gm) Week1, Week 2
██████████ (fluocinonide) Cream 0.1% (bid) Study MP-0201-01 (psoriasis) (N = 18)	17*	29%	56 g, 56.7 g
	20	25%	50 g, 45.2 g
	37	12%	52.9 g, 38 g
██████████ (fluocinonide) Cream 0.1% (qd) Study MP-0201-06 (atopic dermatitis) (N = 18)	180*	10%	50.4 g, 46.8 g
	151	4%	21.5 g, 13.3 g
Lidex (fluocinonide) Cream 0.1% (bid) Study MP-0201-01 (psoriasis) (N = 19)	23	12%	25.1 g, 25.6 g

* Would not have been detected at Week 2 based on the $\leq 18 \mu\text{g/dL}$ criterion

It is unclear why Patient 151 with 4% BSA in the once daily application study arm had an abnormal post-cosyntropin stimulation serum cortisol level. Given the small sample size of patients tested for HPA-axis suppression, it is difficult to make definitive conclusions about the risk of adrenal suppression based on % BSA and total grams used. Although adrenal suppression occurred with use of the topical corticosteroids, subsequent testing indicated a return to normal values.

Table 12 (Statistical 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)

Study MP-0201-06	Fluocinonide	Vehicle cream,	Fluocinonide	Vehicle cream,
	0.1%, qd	qd	0.1%, bid	bid
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%)
Study MP-0201-01	Fluocinonide		Fluocinonide	
	0.05%, bid		0.1%, bid	
Number of subjects (Percentage)	1/19 (5%)		2/16 (11)	
95% Confidence Interval	(0%, 26%)		(0%, 35%)	
Studies MP-0201-01 and MP-0201-06	Fluocinonide	Vehicle Cream		

Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 { (fluocinonide) Cream, 0.1%, }

Combined	0.05% bid, 0.1% bid or qd	qd or bid
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 post-cosyntropin stimulation serum cortisol level $\leq 18 \mu\text{g/dL}$ criterion to define adrenal suppression definition were calculated in the Table 12 above by the FDA Statistician, along with corresponding exact 95% confidence intervals.

According to the statistical review, given the small sample sizes the confidence intervals were extremely wide indicating the lack of precision of the estimates. The 95% confidence intervals narrowed considerably when all fluocinonide treatment groups were from the two studies and were compared to the two vehicle controls combined; however, confidence intervals were still quite wide. The HPA-axis sample size was too small to make definitive conclusions.

Table 13:

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

Study Treatment Group	HPA Axis Suppression	% BSA		Total Grams used	
		n	mean	n	mean
MP-0201-01 (Psoriasis)					
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
MP-0201-06 (Atopic Dermatitis)					
Fluocinonide 0.1%, qd	No	17	5	17	27
	Yes	1	4	1	35
Vehicle qd	No	9	6	9	29
Fluocinonide 0.1%, bid	No	15	5	15	43
Vehicle bid	No	9	5	9	33

Class labeling for super-potent corticosteroids advises that only a small area should be treated at any one time due to the increased risk of HPA-axis suppression. In Study MP-0201-01, only patients exposed to active drug were tested. In Study MP-0201-06, both active and vehicle patients were tested and no vehicle patients demonstrated abnormal test results. As previously stated, it is difficult to make definitive conclusions about the risk of adrenal suppression based on % BSA and total grams used due to small sample size.

Deaths

No deaths were reported in any of the Phase 1, 2, 3 or supportive studies.

Other Serious Adverse Events

A total of 3 subjects out of 636 subjects in the Phase 3 studies reported 4 serious adverse events (SAEs) during the studies (1 in the fluocinonide 0.1% *bid* treatment arm, and 2 in the vehicle *bid* treatment arm). One of the three was occurrence of pregnancy in a 36 year old female; however, miscarried in the first trimester of pregnancy. All SAEs were considered unrelated to the study medication.

Dropouts and Other Significant Adverse Events

The majority of TEAEs leading to treatment discontinuation occurred in the vehicle treatment arms: 4% of subjects in the pooled vehicle treatment arms compared to < 1% of subjects in the pooled fluocinonide treatment arms.

7.1.1.1 Overall profile of dropouts

A total of 636 subjects with plaque-type psoriasis or atopic dermatitis were enrolled in Studies MP-0201-05 and MP-0201-06. Of the 636 subjects, 591 subjects completed the study (291 subjects in MP-0201-05 and 300 subjects in MP-0201-06). A total of 45 subjects discontinued the studies. In Study MP-0201-05, 23 subjects discontinued the study as follows: 4 due to adverse events, 10 were lost to follow-up, 7 subjects withdrew consent, and 2 subjects discontinued for other reasons. In Study MP-0201-06, 22 subjects were discontinued from the study: 5 due to adverse events, 1 due to a protocol violation, 5 subjects withdrew consent, 9 were lost to follow-up, and 2 subjects discontinued for other reasons.

7.1.1.2 Adverse events associated with dropouts

A total of 673 subjects were enrolled into the pooled Phase 2 and Phase 3 studies, in a 2:1, fluocinonide 0.1% cream to vehicle, ratio (216 subjects received Fluocinonide 0.1% Cream *qd*, 104 received vehicle *qd*, 227 received fluocinonide 0.1% Cream *bid*, and 107 received vehicle *bid*). Nineteen subjects received Lidex (fluocinonide) 0.05% *bid*, as it was used as a comparator in MP-0201-01 only. Of the 673 enrolled subjects, 45 subjects discontinued the study prematurely. Reasons for discontinuation included AEs, voluntary withdrawal of consent; subject lost to follow-up, protocol violations, and other reasons. The most common reason for discontinuation was lost to follow-up (7 subjects [3%], Fluocinonide 0.1% Cream *qd*; 3 subjects [3%], vehicle *qd*; 7 subjects [3%], Fluocinonide 0.1% Cream *bid*; 2 subjects [2%], vehicle *bid*).

Table 14: (Applicant's Table 8F.5)
Table 8F.5 Subject Disposition: Pooled Phase 2 and Phase 3 Studies

	Once daily Regimen		Twice daily Regimen		
	Fluocinonide 0.1%	Vehicle	Fluocinonide 0.05%	Fluocinonide 0.1%	Vehicle
Enrolled N (%)	216 (100)	104 (100)	19 (100)	227 (100)	107 (100)
Completed study n (%)	203 (94)	92 (89)	19 (100)	216 (95)	98 (92)

Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 {██████ (fluocinonide) Cream, 0.1%, }

Discontinued from the study n (%)	13 (6)	12 (12)	0	11 (5)	9 (8)
Reasons for discontinuation:					
Adverse events n (%)	2 (1)	4 (4)	0	1 (<1)	2 (2)
Withdrawal of consent n (%)	4 (2)	2 (2)	0	2 (1)	4 (4)
Lost to follow-up n (%)	7 (3)	3 (3)	0	7 (3)	2 (2)
Other reasons n (%)	0	3 (3)	0	1 (<1)	0
Protocol violation n (%)	0	0	0	0	1 (1)

Source: Post-text Table 5

Note: Percentages are rounded.

Study MP-0201-05

A total of 6 subjects discontinued the study medication due to adverse events. Of the 6 subjects, one was on active drug (fluocinonide *qd*) group, 3 were in the vehicle control *qd* group and 2 in the vehicle control *bid* group. The adverse event reported for Subject 132 in the fluocinonide *qd* group that resulted in study discontinuation was the worsening of psoriasis after one dose of study medication during the treatment phase of the study.

Study MP-0201-06

A total of 5 subjects discontinued the study medication due to adverse events; 1 in the fluocinonide *qd* group, 2 in the vehicle control *qd* group, 1 in the fluocinonide *bid* group, and 1 in the vehicle control *bid* group. Worsening of atopic dermatitis was the AE resulted in study discontinuation by two subjects (one each in fluocinonide *qd* group and *bid* study arms).

7.1.1.3 Other significant adverse events

Occurrence of pregnancy in a 36 year old female occurred; however, miscarried in the first trimester of pregnancy (Study MP-201-06). One subject, Subject 29, experienced an increase in blood glucose levels from 86 mg/dL at Baseline to 157 mg/dL at Week 2 Study MP-201-01).

Common Adverse Events

7.1.1.4 Common adverse event tables

Table 15 (Applicant's Table 8F.12) Treatment-Emergent Adverse Events

Table 8F.12 TEAEs Reported by > 1% of Subjects and > 1 Subject in Any Treatment Arm: Pooled Phase 2 and Phase 3 Studies

	Fluocinonide 0.1%, pooled (N = 443)	Fluocinonide 0.1% <i>qd</i> (N = 216)	Fluocinonide 0.1% <i>bid</i> (N = 227)	Fluocinonide 0.05% <i>bid</i> (N = 19)	Vehicle, pooled (N = 211)	Vehicle <i>qd</i> (N = 104)	Vehicle <i>bid</i> (N = 107)
Subjects with ≥1 TEAE N (%)	88 (19.9)	39 (18.1)	49 (21.6)	10 (52.6)	51 (24.2)	27 (26.0)	24 (22.4)

Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 { (fluocinonide) Cream, 0.1%, }

Headache	17 (3.8)	8 (3.7)	9 (4.0)	1 (5.3)	6 (2.8)	4 (3.8)	2 (1.9)
Application site burning	9 (2.0)	5 (2.3)	4 (1.8)	0	14 (6.6)	7 (6.7)	7 (6.5)
Naospharyngitis	5 (1.1)	2 (0.9)	3 (1.3)	1 (5.3)	3 (1.4)	2 (1.9)	1 (0.9)
Nasal congestion	4 (0.9)	3 (1.4)	1 (0.4)	0	0	0	0
Application site reaction NOS*	2 (0.5)	1 (0.5)	1 (0.4)	0	3 (1.4)	2 (1.9)	1 (0.9)
Edema peripheral	1 (0.2)	1 (0.5)	0	0	2 (0.9)	2 (1.9)	0
Application site pruritis	1 (0.2)	1 (0.5)	0	0	2 (0.9)	2 (1.9)	0
Skin fissures	0	0	0	0	2 (0.9)	2 (1.9)	0
URI NOS	0	0	0	5 (26.3)	0	0	0

Source: Post-text Table 9

* NOS = not otherwise specified

Table 8F.12 TEAEs Reported by > 1% of Subjects and > 1 Subject in Any Treatment Arm: Pooled Phase 2 and Phase 3 Studies

	Fluocinonide 0.1%, pooled (N = 443)	Fluocinonide 0.1% <i>qd</i> (N = 216)	Fluocinonide 0.1% <i>bid</i> (N = 227)	Fluocinonide 0.05% <i>bid</i> (N = 19)	Vehicle, pooled (N = 211)	Vehicle <i>qd</i> (N = 104)	Vehicle <i>bid</i> (N = 107)
Subjects with ≥1 TEAE N (%)	88 (19.9)	39 (18.1)	49 (21.6)	10 (52.6)	51 (24.2)	27 (26.0)	24 (22.4)
Headache	17 (3.8)	8 (3.7)	9 (4.0)	1 (5.3)	6 (2.8)	4 (3.8)	2 (1.9)
Application site burning	9 (2.0)	5 (2.3)	4 (1.8)	0	14 (6.6)	7 (6.7)	7 (6.5)
Naospharyngitis	5 (1.1)	2 (0.9)	3 (1.3)	1 (5.3)	3 (1.4)	2 (1.9)	1 (0.9)
Nasal congestion	4 (0.9)	3 (1.4)	1 (0.4)	0	0	0	0
Application site reaction NOS*	2 (0.5)	1 (0.5)	1 (0.4)	0	3 (1.4)	2 (1.9)	1 (0.9)
Edema peripheral	1 (0.2)	1 (0.5)	0	0	2 (0.9)	2 (1.9)	0
Application site pruritis	1 (0.2)	1 (0.5)	0	0	2 (0.9)	2 (1.9)	0
Skin fissures	0	0	0	0	2 (0.9)	2 (1.9)	0
URI NOS	0	0	0	5 (26.3)	0	0	0

Source: Post-text Table 9

* NOS = not otherwise specified

Table 8F.12 TEAEs Reported by > 1% of Subjects and > 1 Subject in Any Treatment Arm: Pooled Phase 2 and Phase 3 Studies

Clinical Review
 {Brenda E. Vaughan, M.D.}
 {NDA 21-758}
 { (fluocinonide) Cream, 0.1%, }

	Fluocinonide 0.1%, pooled (N = 443)	Fluocinonide 0.1% <i>qd</i> (N = 216)	Fluocinonide 0.1% <i>bid</i> (N = 227)	Fluocinonide 0.05% <i>bid</i> (N = 19)	Vehicle, pooled (N = 211)	Vehicle <i>qd</i> (N = 104)	Vehicle <i>bid</i> (N = 107)
Subjects with ≥1 TEAE N (%)	88 (19.9)	39 (18.1)	49 (21.6)	10 (52.6)	51 (24.2)	27 (26.0)	24 (22.4)
Headache	17 (3.8)	8 (3.7)	9 (4.0)	1 (5.3)	6 (2.8)	4 (3.8)	2 (1.9)
Application site burning	9 (2.0)	5 (2.3)	4 (1.8)	0	14 (6.6)	7 (6.7)	7 (6.5)
Nasopharyngitis	5 (1.1)	2 (0.9)	3 (1.3)	1 (5.3)	3 (1.4)	2 (1.9)	1 (0.9)
Nasal congestion	4 (0.9)	3 (1.4)	1 (0.4)	0	0	0	0
Application site reaction NOS*	2 (0.5)	1 (0.5)	1 (0.4)	0	3 (1.4)	2 (1.9)	1 (0.9)
Edema peripheral	1 (0.2)	1 (0.5)	0	0	2 (0.9)	2 (1.9)	0
Application site pruritis	1 (0.2)	1 (0.5)	0	0	2 (0.9)	2 (1.9)	0
Skin fissures	0	0	0	0	2 (0.9)	2 (1.9)	0
URI NOS	0	0	0	5 (26.3)	0	0	0

Source: Post-text Table 9

* NOS = not otherwise specified

7.1.1.5 Identifying common and drug-related adverse events

The presence or absence of the 7 signs and symptoms of skin atrophy (telangiectasis, skin transparency, loss of elasticity, loss of normal skin markings, skin thinning, striae and bruising) were captured in the Phase 2 and 3 studies (MP-0201-01, MP-0201-05, and MP-0201-06). However, the seven signs and symptoms of skin atrophy were present at baseline in 17 % (74/433) patients in the pooled safety database and scores appeared to improve at Week 2. Signs and symptoms of skin atrophy decrease at Week 2 to 9% (39/443); except for telangiectasis increased slightly at Week 2. The seven signs and symptoms of skin atrophy were absent in the majority of subjects in each treatment arm. In most cases the number of subjects in a treatment arm expressing any of the skin atrophy symptoms decreased slightly throughout the study period. Changes, however, were not significant.

Most Common AEs

Application site burning was among the most commonly reported treatment related TEAEs. Included in this group (most commonly reported treatment-related TEAEs) were application site burning, application site pruritis and application site reaction. Other AEs (headache, application site burning and nasopharyngitis) were reported by a similar percentage of subjects in the fluocinonide 0.1% cream and vehicle treatment arms. The most commonly reported TEAEs were headache, application site burning and nasopharyngitis. Occurrences of headache and

nasopharyngitis were not considered by the investigator to be causally related to the study treatment.

7.1.1.6 Additional analyses and explorations

Laboratory Findings

7.1.1.7 Overview of laboratory testing in the development program

Blood glucose levels were measured for each subject in Study MP-0201-01 (adrenal suppression study) and measured for subjects at selected sites in MP-0201-06 at the Baseline and Week 2 visits. The mean \pm SD fasting blood glucose levels were 104.6 ± 25.3 mg/dL at Baseline vs. 102.6 ± 15.6 mg/dL at Week 2 (end of treatment) for the Fluocinonide 0.1% Cream group and 105 ± 25.6 mg/dL at Baseline vs. 105 ± 27.9 mg/dL at Week 2 for the fluocinonide 0.05% (Lidex®) group, showing no clinically significant overall changes in fasting blood glucose levels for either treatment group.

One subject, Subject 29, experienced an increase in blood glucose levels from 86 mg/dL at Baseline to 157 mg/dL at Week 2. According to the submission, the change in blood glucose levels over time was too low to be considered a possible manifestation of problems caused by a suppression of the HPA axis. In study MP-0201-06, no significant changes over time in blood glucose levels were noted.

Vital Signs

Weight, temperature, pulse, respiration rate, blood pressure and fasting blood glucose levels were measured in HPA-axis suppression Study MP-0201-06 and there were no evident changes from Baseline in vital signs.

10.6 Other safety evaluations

Special Safety Studies

Safety studies reviewed in this section are: 1) vasoconstrictor, 2) provocative sensitization, 3) irritancy, and 4) adrenal suppression. Based on the finding of no absorption in the UVA/UVB/VIS spectrum, a waiver of the phototox/photoallergy studies is requested and should be granted (letter date December 12, 2004).

1) Special Safety Studies (See Biopharm review for complete details of the vasoconstrictor studies.) Four supporting vasoconstriction assay (VCA) studies were conducted to assess the potency of ██████ (fluocinonide) Cream, 0.1%. The vasoconstrictor assay is the most widely used surrogate test to assess the potency of topical corticosteroids. When applied to the skin, topical corticosteroids produce a localized skin-blanching response, 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.

(fluocinonide) Cream, 0.1% was classified as a Class 1 (potent) topical corticosteroid by the Applicant based on results from the following VCA studies: Study MED-00-018, a multi-point study comparing various formulations in 12 healthy adults, Study MED-01-022, blinded single point study comparing different dose levels in 36 healthy adults, Study MED-02-004, blinded single point study comparing different dose levels of active 36 healthy adults, and Study MED-02-005, blinded single point study comparing different dose levels 36 healthy adults.

No SAE was reported in any of the supportive/VCA studies.

- 2) Sensitizing Potential Study (Study MED 02-015, a provocative sensitization and irritancy in 226 subjects)

Study title:

“A Randomized, Controlled Study to Evaluate the Sensitizing Potential of A New Formulation of Fluocinonide Cream in Healthy Volunteers, Using A Repeat Insult Patch Test Design”.

Study Dates June 10, 2002 to August 21, 2002

This was a multicenter, double-blind, controlled, within-subject comparison, repeat insult patch test study conducted in 203 subjects. On treatment days, the investigational product (Fluocinonide 0.1% Cream) and a negative control (white petrolatum) were applied under occlusive conditions to sites on the infrascapular region of the back 3 times weekly for 3 weeks (9 applications total) during the induction phase. Following a 10-14 day rest period, a single challenge application was performed. Study personnel who were involved in the preparation/application and removal of the treatments did not perform the evaluation of responses.

Efficacy was not evaluated in this study.

Safety Evaluations: Cumulative irritancy and dermal sensitization irritancy potential were evaluated by the assessment of the application sites during the induction and challenge phases of the study and, if needed, the rechallenge phase. Observed responses (e.g., erythema, edema, and vesiculation) were graded according to a protocol-specified grading scale. Safety was further evaluated by the assessment of any adverse events reported during the study.

Statistical Methods: Cumulative irritancy during induction was quantified by means of the mean and total cumulative irritancy scores received during the induction phase (9 readings). These parameters were tested pairwise for product differences using analysis of variance (subject, product). Determination of dermal sensitization potential was based on specific scoring criteria derived from observations in the challenge phase of the study, and confirmed by rechallenge, if required. For subjects undergoing rechallenge, a narrative description of each reaction in the challenge and rechallenge phases were provided together with the opinion of the investigator as to whether such reactions were felt to be indicative of contact sensitization.

Subject Disposition

A total of 226 subjects were enrolled, 216 treated and 203 subjects completed the study. Twenty-three (23) subjects discontinued one non-study related AE, 2 found to be ineligible, 1 protocol violation, 7 voluntarily withdrew consent, and 12 lost to follow-up.

Study Results:

Two-hundred and three (203) subjects completed all aspects of the study and were included in the sensitization analysis. Most of the responses observed during induction and challenge were minimal. Two subjects had definite erythema without edema at 0.5 hours and 24 hours (in the case of 1 subject) following challenge patch application. These responses were reduced to minimal at the next observation and no response was observed for any subject at 120 hours following challenge patch application. No subject showed a reaction indicative of sensitization. Twelve subjects had 12 treatment-emergent adverse events. One adverse event (mild poison ivy) resulted in discontinuation of the subject from the study. None of the adverse events was considered related to study product.

Conclusions: There was no evidence of sensitization potential following repeated applications of Fluocinonide 0.1% Cream in this subject population and under the conditions used in this study.

3) Study MED 02-016 (irritancy study in 39 subjects).

Title: "A 21-Day Randomized, Controlled Study to Evaluate the Irritation Potential of a New Formulation of Fluocinonide Cream in Healthy Volunteers Using a Cumulative Irritant Patch Test Design"

Study dates: May 1, 2002 to May 22, 2002.

The objective of the study was to determine the irritation potential of a new formulation of fluocinonide cream on normal skin.

Study Design:

This was a single-center, double-blind, controlled, within-subject comparison, 21-day cumulative irritation study. On treatment days, the investigational product (Fluocinonide 0.1% Cream), comparator product (Psorcon Ointment, diflorasone diacetate ointment), and positive (0.2% SLS) and negative (white petrolatum) controls were applied under occlusive conditions to sites on the infrascapular region of the back for 24 hours (72 hours over weekends). Local tolerability was assessed visually at the time of removal of each patch using an ordinal scoring system. Total study duration was approximately 3 weeks. Target enrollment was 30 completed subjects evaluable for analysis. Actual enrollment was 39 subjects; 32 subjects completed all aspects of the study.

Study Population: Healthy subjects aged 18 years of age or older, and fulfilling the inclusion/exclusion criteria were eligible for participation in the study.

Fluocinonide 0.1% Cream, 0.2 g or an amount sufficient to cover the patch, applied topically under occlusive patch conditions, once daily on 5 consecutive days a week for 3 weeks. Comparator product were Psorcon Ointment (diflorasone diacetate) and commercially available white petrolatum served as the negative control. Commercially available sodium lauryl sulfate, was prepared as a 0.2% aqueous solution by ██████████ for topical administration and served as a positive control for irritancy.

Dosage and frequency:

Comparator product and controls, 0.2 mL/g or an amount sufficient to cover the patch, were applied under occlusive patch conditions once daily on 5 consecutive days a week for 3 weeks

Evaluation of Cumulative Irritancy: Cumulative irritancy was evaluated by assessment of the application sites. Observed responses (i.e., erythema, edema, and vesiculation) were graded according to a protocol-specified grading scale.

Safety Evaluations: Safety was evaluated by the assessment of any adverse events reported during the study.

Statistical Methods: Determination of cumulative irritancy was based on specific scoring criteria derived from observations and was quantified for each subject/product by the mean and total cumulative irritancy score. These parameters were tested pairwise for product differences using analysis of variance (subject, product).

Cumulative Irritancy Results:

Individual irritancy scores are preferable to mean cumulative score; however, individual line listings were not provided. According to the Applicant, the investigative product, Fluocinonide 0.1% Cream, the comparator product, Psorcon Ointment, and the petrolatum negative control showed no evidence of significant irritation. The mean cumulative irritation scores for these study products were 0.00, 0.01, and 0.02, respectively. The positive control, 0.2% SLS was classified as moderately irritating with a mean cumulative irritation score of 2.13, which was statistically significantly higher than the scores of the other study products.

Table 16 (Applicant's Text Table 8-1)
Text Table 8-1 Mean Cumulative Irritation Scores

Product Tested	Mean Score (SD)	Total Score	Irritancy Classification
Fluocinonide 0.1% Cream	0.00 (0.02)	1	No significant irritation
Psorcon Ointment	0.01 (0.06)	3	No significant irritation
Petrolatum	0.02 (0.14)	5	No significant irritation
SLS 0.2%	2.13 (0.69)*	447	Moderately irritating

Source data: Table 3.2

* Statistically significantly different (p<0.001) from Fluocinonide 0.1% Cream, Psorcon Ointment, and petrolatum.

No subjects had patches with Fluocinonide 0.1% Cream, Psorcon Ointment, or the petrolatum negative control discontinued due to irritation, whereas 31 subjects (94%) had positive control patches discontinued due to limiting irritation.

Safety Results:

Five subjects had 5 treatment-emergent adverse events. One of the AEs (mild dermatitis) was assessed by the investigator as possibly related to study product, and resulted in discontinuation of the subject from the study; however, the study product was not identified and all four substances had been applied. The remaining AEs were considered unlikely to be related or unrelated to study product. One of the AEs (pneumonia) was considered serious and resulted in subject discontinuation.

Conclusions: In this subject population and under the conditions used in this study, there was no evidence of irritancy potential for Fluocinonide 0.1% Cream.

4) Adrenal Suppression Safety Studies

Two adrenal suppression safety studies in adults were conducted: Study MP-0201-01, an adrenal suppression study in 37 adult patients with plaque-type psoriasis randomized to bid dosing with (fluocinonide) Cream, 0.1%, and Lidex (fluocinonide) Cream, 0.05% and adrenal suppression assessed in a subset of atopic dermatitis patients in Study MP-0201-06. These studies results are located in Section 7.1.5.6 Additional analyses and explorations.

One adrenal suppression Study MP-0201-07 is an *ongoing* in pediatric patients studied in sequential cohorts with use of (fluocinonide) Cream, 0.1% with qd and bid dosing. Projected date of study completion is January 2005.

Withdrawal Phenomena and/or Abuse Potential

In Studies MP-0201-05 and MP-0201-06, an evaluation of the extent of rebound was based on the comparison of symptom scores and Physician's Global Assessment scores between treatments at Week 4, 2 weeks after the cessation of treatment. Although the Applicant assessed considered overall lesion severity 2 weeks after treatment as rebound, this assessment was a measure of durability of treatment effect. Typically rebound is a phenomenon associated with treatment of psoriasis patients who after a response, in a short period of time, relapse to worse than baseline or transform to life-threatening forms of psoriasis. Overall, review of symptoms and AE reports showed no evidence in any of the clinical studies of a rebound phenomenon associated with the use of fluocinonide 0.1% cream.

Human Reproduction and Pregnancy Data

These data are based on class labeling for corticosteroids.

Assessment of Effect on Growth

No growth assessment studies have been performed; however, the Applicant is encouraged to explore growth suppression studies . ~~_____~~

Overdose Experience

Two subjects (335 and 286 in Study MP-0201-06) received higher than the protocol recommended dosage of Fluocinonide 0.1% Cream. No TEAEs were reported for either subject. Adverse effects of excessive amounts or improper use has been documented. As a class, topical corticosteroids are known to cause cutaneous (e.g., striae, atrophy, acne, purpura, etc.) and systemic side effects (HPA axis suppression, etc.).

In general, topical corticosteroids can be absorbed through normal intact skin and absorption can be influenced by various factors (e.g., vehicle, use of occlusion, percent body surface area of application site of application, diseased skin, etc.). Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids: they are bound to plasma proteins to varying degrees, metabolized primarily in the liver, and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into bile.

The extent of adrenal suppression of the hypothalamic-pituitary-adrenal (HPA) axis by a steroid is generally related to the steroid potency, dose administered, body surface area (BSA), and skin barrier function. Manifestations of Cushing's syndrome, hyperglycemia and glucosuria can also be produced in some subjects by systemic absorption of topical corticosteroids. Patients receiving super-potent corticosteroids are advised not to use them for more than 2 weeks at a time, and to treat only small areas at any one time. Since the risk of corticosteroid-induced HPA axis suppression is believed to be increased in children, pediatric use of these products have been restricted.

Postmarketing Experience

Although Lidex® Cream 0.05% (NDA 16-908) has been marketed since 1971, the periodic update only covered the period from 2000 through the present (March 2004). During this period, a total of 11 adverse events were reported for any topical fluocinonide formulation; all events occurred within the United States and Canada. Of the events, none were considered severe.

Safety Information for the Currently Marketed Products

Results of a literature search were provided for currently marketed fluocinonide products.

Clinical Review
{Brenda E. Vaughan, M.D.}
{NDA 21-758}
{[REDACTED] (fluocinonide) Cream, 0.1%, }

Adequacy of Patient Exposure and Safety Assessments

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

7.1.1.8 Study type and design/patient enumeration

7.1.1.9 Demographics

A more diverse atopic dermatitis patient population should be studied since the majority of patients were Caucasian. Age subgroup analysis should be categorized over or under age 65.

7.1.1.10 Extent of exposure (dose/duration)

In the pooled Phase 2 and Phase 3 studies, the overall treatment exposure was approximately 15 days, with a range from 3 to 22 days. Subjects in the *qd* treatment arms used a mean of 34.3g (Fluocinonide 0.1% Cream) and 33.3g (vehicle) of study treatment, for an average of 15 applications. Subjects in the *bid* treatment arms used a mean of 48.8g (Fluocinonide 0.1% Cream) and 46.7g (vehicle) of study treatment, for an average of 29 applications.

8 ADDITIONAL CLINICAL ISSUES

Dosing Regimen and Administration

Drug-Drug Interactions

Special Populations

[REDACTED] Cream label carries the Pregnancy Category C drug classification as other drugs in this class. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, [REDACTED]™ Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pediatrics

Advisory Committee Meeting

Pediatric subcommittee recommended simultaneous cosyntropin testing of all pediatric cohorts; however, the Applicant and Division concurred that sequential cosyntropin testing with a stopping rule was warranted since [REDACTED] is a super-potent topical corticosteroid and adrenal suppression was expected.

Literature Review

The Applicant provided 37 references that included safety and efficacy with use of topical steroids and vasoconstrictor assay. As a class of drugs, topical corticosteroids have been well characterized and no additional literature review was made.

Postmarketing Risk Management Plan

No post marketing management plan has been submitted.

Other Relevant Materials

9 OVERALL ASSESSMENT

Conclusions

The Applicant is seeking approval of ██████ (fluocinonide) Cream, 0.1%, a topical corticosteroid, for relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in adults. Corticosteroid-responsive dermatoses include a broad range of inflammatory and pruritic skin disorders of which the most common are psoriasis and atopic dermatitis. Psoriasis and atopic dermatitis are the disease entities studied in this application as representative of corticosteroid responsive dermatoses.

Since atopic dermatitis is primarily a pediatric disorder and no pediatric patients were studied, the application is only approved for use in adults in treatment of plaque-type psoriasis. Based on Pediatric Research Equity Act (PREA), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Safety studies with use of fluocinonide 0.1% cream in pediatric patients with atopic dermatitis to assess the potential of adrenal suppression are on going at the time of this review and only preliminary data are available.

In the ITT population, statistical superiority was demonstrated for active over vehicle in both studies (MP-0201-05 and MP-0201-06) for both disease entities (psoriasis and atopic dermatitis) for both once daily (qd) and twice daily (bid) treatment regimens in adults; however, bid dosing frequency was statistically superior ($p < 0.001$) to qd dosing ($p = 0.43$) in patients with plaque psoriasis. In atopic dermatitis patients, ██████ versus vehicle was significant ($p < 0.001$) for both qd and bid dosing regimen. Seven centers were common between two studies; however, according to the Statistical review, elimination of the common investigators from both studies did not impact study results.

Although, statistical superiority was demonstrated for use of a corticosteroid classified as “super potent” over vehicle in treatment of psoriasis, the efficacy margin is small with only 18% and 33% of patients achieving a global assessment of clear or almost clear. Additionally, although the numbers studied in the adrenal suppression study is small (18 and 19 subjects; ██████ and Lidex® study arms, respectively) adrenal suppression was numerically greater in the ██████ study arm compared to Lidex®; three compared to one, respectively without noticeable increased

efficacy. _____

Twice daily dosing in Study MP-0201-05, did not appear to be associated with increased incidence of AEs. Only twice daily dosing was assessed in patients with psoriasis in Study MP-0201-01; therefore, comparative effect on adrenal function with once dosing in psoriasis patients is not available. It should be noted that in the subset of atopic dermatitis patients assessed for adrenal function that no suppression was noted in the twice daily dosing study arm compared to two subjects with abnormal cosyntrophin stimulation results in the once daily study arm. It is difficult to make definitive conclusions about the risk of adrenal suppression based on % BSA and total grams used due to small sample size.

Recommendation on Regulatory Action

An *Approval* recommendation is being made for use of _____ (fluocinonide) Cream, 0.1% applied twice daily (*bid*) for treatment of plaque-type psoriasis affecting up to 10% body surface area (BSA) in patients ≥ 18 years of age.

Recommendation on Postmarketing Actions

Required Phase 4 Commitments

9.4 Labeling Review

Please refer to the approval letter for the official label as the line by line labeling review located in the Appendices that follows is subject to modification.

9.5 Comments to Applicant

7 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Medical- 1

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Brenda Vaughan
12/16/04 06:57:40 PM
MEDICAL OFFICER

Markham Luke
12/20/04 03:29:02 PM
MEDICAL OFFICER

NEXT REVIEW

Jonathan Wilkin
2/10/05 07:27:09 PM
MEDICAL OFFICER
See also TL Summary signed 2/10/05