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RESEARCH**

APPLICATION NUMBER:
22-013

MEDICAL REVIEW

Team Leader Memo for NDA 22-013
Olux-E (clobetasol propionate) Foam, 0.05%

Letter date: 3/14/06

CDER Stamp date: 3/16/06

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Applicant: Dow Pharmaceuticals.

Indication sought: treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older.

The applicant has requested approval for Olux-E (clobetasol propionate) Foam, 0.05% for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older. In support of this indication, the applicant has submitted results from a two pivotal safety and efficacy trials and five supportive safety and pharmacokinetic/pharmacodynamic (PK/PD) trials.

Regulatory Background

The applicant pursued approval of their product under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, with Temovate (clobetasol propionate) Ointment, 0.05% as the reference listed drug (RLD). Temovate Ointment (NDA 19-323) was approved on December 27, 1985, for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. To construct a clinical bridge to the Agency's findings of safety for the RLD, the sponsor conducted a three arm trial to demonstrate that Olux-E Foam was not superior in efficacy to the RLD and did not manifest a worse local safety profile, and a comparative bioavailability study to demonstrate that the systemic exposure for subjects treated with Olux-E did not exceed that for those treated with the RLD.

Efficacy

The applicant submitted data from two adequate and well-controlled trials, one in atopic dermatitis and one in psoriasis, to demonstrate the safety and efficacy of their product used twice daily for two weeks for the treatment corticosteroid responsive dermatoses in patients 12 years of age and older. The reader is referred to Dr. Kathleen Fritsch's biostatistical review and Dr. Patricia Brown's clinical review for a thorough discussion of the trials and results. Both reviewers found that the applicant convincingly demonstrated that the applicant's product, Olux-E Foam, is superior to vehicle for the treatment of corticosteroid responsive dermatoses.

Safety

The reader is referred to the clinical review by Dr. Patricia Brown for a full discussion of the safety database. The safety population included 572 subjects with atopic dermatitis or psoriasis who were treated with Olux-E Foam. There were no deaths or serious adverse events attributed to study drug. Treatment related adverse events occurred in 7% of subjects treated with Olux-E Foam, 9% of subjects treated with Vehicle Foam, and 2% of subjects treated with the RLD. The most common treatment-related adverse events occurred at the application site (application site reaction and application site atrophy).

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Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

Special safety studies included repeat insult patch test studies to assess cumulative irritation and sensitization potential, respectively, of Olux-E Vehicle Foam, a hypothalamic-pituitary-adrenal (HPA) axis suppression study of Olux-E Foam, and a comparative systemic bioavailability study of Olux-E Foam and Temovate Ointment.

The provocative repeat insult patch test studies, which used Vehicle Foam rather than Olux-E Foam to reduce the likelihood of false-negative results due to the potent anti-inflammatory effect of clobetasol propionate, did not identify significant irritation or sensitization signals.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with use of Olux-E Foam was studied in 52 pediatric and adult subjects with atopic dermatitis, with enrollment proceeding in sequential cohorts from adults to adolescents to progressively younger pediatric subjects. In subjects 12 years of age and older, the rate HPA axis suppression was 16.2% (6 of 37). In subjects 6 to 12 years of age, 7 of 15 subjects (47%) manifested HPA axis suppression. Because this rate exceeded the prespecified threshold of 20%, enrollment did not continue to subjects younger than 6 years of age, and subjects younger than 12 years of age were not enrolled in the pivotal studies.

A comparative bioavailability study in subjects with psoriasis was conducted to assess the relative bioavailability of Olux-E Foam and Temovate Ointment. In that study, subjects treated with Olux-E Foam received less systemic exposure to clobetasol propionate than subjects treated with Temovate Ointment, as demonstrated by mean C_{max} and AUC values. The relative bioavailability of Olux-E Foam, as calculated by the applicant, is 35.7% that of Temovate Ointment. The clinical pharmacology review by Dr. Suliman Al-Fayoumi provides a comprehensive review of the comparative bioavailability and HPA axis suppression studies, as well as the cutaneous vasoconstrictor assay study.

Chemistry

The reader is referred to the review by Dr. Rao Puttagunta for full discussion of Chemistry issues.

The applicant markets another product, Olux Foam (NDA 21-142, approved on May 26, 2000), which contains the same active ingredient at the same concentration in the same dosage form for a very similar indication. However, the two products are not identical. In the DESCRIPTION section of the Olux labeling, the dosage form is described as a thermolabile foam. In the draft labeling of Olux-E Foam, the dosage form is described as an emulsion aerosol foam. Although both products are dispensed as an aerosol foam, Olux melts at body temperature to form an ethanolic solution on the skin, whereas Olux-E mechanically dissipates into an emulsion on the skin and is not thermolabile at body temperature. Although comparative safety and efficacy studies were not performed (and are not required for approval), it is anticipated that the differences in the composition of the excipients between the two products as well as the differences breakdown characteristics (solution versus emulsion) may translate into differences in safety, efficacy, and prescriber and patient acceptability profiles. There is precedent in the

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Agency for approval of more than one product containing the same active ingredient at the same dose in the same dosage form for the same indication (e.g., Temovate cream and Temovate E cream, Diprolene cream and Diprolene AF cream, Lidex cream and Lidex-E cream, Advil capsules and Advil Gel-caps). This reviewer is not opposed to the approval of a second foam dosage form of clobetasol propionate, 0.05%, for this applicant, as it may offer real benefit to prescribers and patients in terms of specific product characteristics.

Trade Name

The trade name for this product is Olux-E Foam. Because it is possible that a patient may be prescribed Olux-E Foam and Olux Foam concurrently (for example, for use on the body and scalp, respectively), the use of a common trade name with a modifier for the second product is preferable to two unrelated, unique trade names. Additionally, this is consistent with Agency precedent (see above). DDMAC and DMETS have reviewed this trade name and found it acceptable.

Pharmacology Toxicology

The reader is referred to the reviews by Drs. Carmen Booker and Paul Brown. The sponsor has agreed to conduct dermal carcinogenicity and photocarcinogenicity studies as Phase 4 commitments.

Conclusion

In two adequate and well-controlled clinical trials, in combination with supportive safety, pharmacokinetic and pharmacodynamic, and non-clinical studies, the sponsor has constructed a biobridge to the RLD and has demonstrated the safety and efficacy of Olux-E Foam applied twice daily for up to two weeks in the treatment of corticosteroid-responsive dermatoses in patients twelve years of age and older. I concur with the recommendations of the multi-disciplinary review team for approval of NDA 22-013.

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/s/

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1/11/2007 09:44:28 PM
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1/12/2007 08:55:27 AM
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Concur with review.

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CLINICAL REVIEW

Application Type NDA 505(b)(2)
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Reviewer Name Patricia Brown, MD
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Established Name Clobetasol propionate
(Proposed) Trade Name PrimoluxTM
Therapeutic Class Anti-inflammatory
Applicant Connetics Corporation

Priority Designation S

Formulation Foam
Dosing Regimen Twice a day for 2 weeks
Indication Corticosteroid responsive
dermatoses
Intended Population Adults and children ages 12 and
older

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Patricia C. Brown, MD
NDA 22-013
Primolux Foam, 0.05% (clobetasol propionate)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Olux E (clobetasol propionate) foam 0.05% be approved for topical administration for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years or older.

1.2 Recommendation on Post-Marketing Actions

1.2.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling, and spontaneous adverse event reporting are adequate risk management activities for this drug at this time.

1.2.2 Required Phase 4 Commitments

The sponsor has committed to conduct dermal carcinogenicity and photo-carcinogenicity studies during Phase 4. Please Pharmacology/Toxicology review by Dr. Carmen D. Booker.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Olux E (clobetasol propionate) foam 0.05%, hereinafter referred to as EF Clobetasol foam, is a topical product intended for twice daily application for up to two weeks (100g/two weeks) for the treatment of corticosteroid responsive dermatoses in patients 12 years of age and older. The sponsor has submitted a 505(b)(2) application with Temovate® (clobetasol propionate) Ointment, 0.05% (NDA 19-323) as the Reference Listed Drug (RLD). EF Clobetasol Foam was developed as a new dosage form of the reference listed drug. To support approval by this pathway, EF Clobetasol foam 0.05% has been studied in comparison with Temovate® Ointment

in a three-arm psoriasis trial and a bioavailability study to permit reference to the Agency's finding of short-term and long-term clinical safety. Objectives include demonstrating that EF Clobetasol foam 0.05% does not show superior efficacy compared to the RLD and does not exhibit a safety profile that is inferior to the RLD. In addition EF Clobetasol foam 0.05% should not show a greater systemic bioavailability than the RLD.

To support the indication, the sponsor has submitted two pivotal, multi-center phase 3 trials for efficacy and safety including CPE.C.301 (two arms, active and vehicle, subjects with atopic dermatitis) and CPE.C.302 (three arms; active, vehicle, and RLD). These two studies enrolled a total of 874 subjects age 12 and older with 504 being randomized to EF Clobetasol foam 0.05%, the latter including 251 with atopic dermatitis and 253 with psoriasis.

The remainder of the clinical development program included 5 studies. Three of these were phase 1 studies; CPE.C.101 (skin blanching-relative potency), DES.C.103 (repeat insult patch test-allergic contact sensitization), and DES.C.104 (cumulative irritation). Phase 2 included two studies, CPE.C.201 (HPA axis effect-open label safety-atopic dermatitis) having 52 subjects enrolled and exposed to EF Clobetasol foam 0.05%, and CPE.C.202 (comparative bioavailability against RLD-psoriasis) having 32 subjects enrolled 16 of whom were exposed to EF Clobetasol foam 0.05%. The safety database includes the 572 subjects exposed to EF Clobetasol foam 0.05% in phases 2 and 3. EF Clobetasol foam 0.05% is not marketed in any country at this time.

1.3.2 Efficacy

The applicant has submitted data from two randomized, well controlled clinical trials to demonstrate the efficacy and safety of EF Clobetasol foam used twice daily for two weeks for the treatment of corticosteroid responsive dermatoses in patients twelve years of age and older.

Trial CPE.C.301 involved 377 subjects with moderate to severe atopic dermatitis, 251 randomized to EF Clobetasol foam and 126 to Vehicle foam. In this trial EF Clobetasol foam showed statistically significant efficacy when compared with Vehicle foam. Treatment success was measured at Week 2 using the primary endpoint defined as follows: ISGA score of 0 or 1, a minimum improvement in the IGSA score of 2 grades from baseline to week 2, and a score of 0 or 1 for both erythema and induration/papulation. Treatment effects were generally consistent across subgroups; gender, age and race. Results with secondary endpoints were supportive.

Trial CPE.C.302 involved 497 subjects with mild to moderate plaque-type psoriasis, 253 randomized to EF Clobetasol foam, 123 Vehicle foam, and 121 to Temovate® Ointment. This trial included the Temovate® Ointment arm in order to allow a bridge, in combination with the results of the comparative bioavailability study CPE.C.202, to the Agency's findings of safety for Temovate® Ointment. In this trial EF Clobetasol foam showed statistically significant efficacy when compared with Vehicle foam. Although not a prespecified efficacy comparison, EF Clobetasol foam was inferior to Temovate® Ointment. Treatment success was measured at Week 2 using the primary endpoint defined as follows: 1) a score of clear (0) or almost clear (1) on the ISGA with 2) at least a reduction of 2 grades from baseline, 3) a score of 0 or 1 for erythema, 4) a score of 0 or 1 for scaling, and 5) a score of 0 for plaque thickness. The

evaluation of erythema, scaling, and plaque thickness was performed on a target lesion identified at baseline. Treatment effects were generally consistent across the subgroups of gender and age. Treatment efficacy was lower in non-Caucasians in all three treatment arms and no non-Caucasians achieved treatment success on EF Clobetasol foam or Vehicle foam; however the number of subjects involved was small. Results for secondary endpoints were supportive.

1.3.3 Safety

To evaluate safety, the sponsor conducted two Phase 3 trials, CPE.C.301(atopic dermatitis) & 302 (psoriasis), as well as 2 Phase 1 studies, DES.C.103 & 104, and one Phase 2 study, CPE.C.201 (atopic dermatitis). All of these studies were conducted with the final to-be-marketed formulation.

A total of 942 patients were enrolled in the phase 2 and 3 studies. Of these 572 were exposed to EF Clobetasol foam 0.05% and 249 to Vehicle foam. Median duration of exposure was 15 days. The 4 month safety update report was reviewed and did not contain new safety information.

No deaths were reported in any of the EF Clobetasol foam 0.05% studies. Serious adverse events identified included one event of streptococcal pneumonia in the Phase 3 study, CPE.C.301-atopic dermatitis, and one event of syncope in the Phase 3 study, CPE.C.302-psoriasis. These occurred in the EF Clobetasol foam arm in both studies; however they were not attributed to study drug use.

Six patients discontinued study drug due to adverse events: 2/572 in the EF Clobetasol foam treatment group and 4/249 in the Vehicle foam group. In the EF Clobetasol foam group the adverse experiences that led to study withdrawal were, urticaria at study drug applications areas (probably related to study drug) and atopic dermatitis on hands (possibly related to study drug.) In the Vehicle foam group, the adverse experiences that resulted in study withdrawal were, allergic reaction to the study drug (probably related to the study drug), irritant contact dermatitis (definitely related to study drug), generalized increased pruritus (possibly related to study drug), and infected atopic dermatitis (reported as probably not related to study drug).

Overall, roughly the same percentage of subjects 17% (99/572) exposed to EF Clobetasol foam as those 16% (41/249) exposed to Vehicle foam experienced adverse events. Of those exposed to the reference-listed drug, Temovate® Ointment, 8% (11/137) experienced adverse events. For the foam products, a slightly higher percentage 9% (22/249) of subjects exposed to Vehicle foam were considered to have treatment related adverse events as compared with subjects exposed to EF Clobetasol foam, 7% (42/572). For the reference-listed drug 2% (1/137) of exposed subjects had adverse experiences that were considered treatment related.

The most common adverse event reported across study arms was application site reaction, occurring in 1.6% of subjects (9/572) on study drug as compared with 2.8% (7/249) on vehicle foam and 1.5% (2/137) on Temovate ointment. When this adverse events is examined it is found to include .05% (3/572) subjects on EF Clobetasol foam and 1.2% (3/249) subjects on Vehicle

foam who reported stinging after application of study medication. This subgroup of application site reaction appears related to components of the Vehicle foam.

The second most common adverse event across study arms was application site atrophy, occurring in 1.9% of subjects (11/572) on study drug as compared with .08% (2/249) on Vehicle foam and 0% on Temovate® Ointment. This appears to be related to the chemical moiety. The next most common adverse events were application site burning and application site pruritus which were reported by .08% (5/572) and .02% (1/572) respectively of subjects exposed to EF Clobetasol foam and by 1.2% (3/249) and 2.8% (7/249) respectively of subjects exposed to Vehicle foam. These appear to be related to components of the Vehicle foam.

As compared with Temovate® Ointment, EF Clobetasol foam does show a higher rate of application site atrophy through reported adverse events and through local safety assessments. Application site pruritus and burning were also greater in the Vehicle foam group and the EF Clobetasol foam group than in the Temovate® Ointment group. However, Temovate® Ointment was associated with almost twice the rate of worsening of pigmentation as EF Clobetasol foam. It should also be noted that these events involve relatively small percentages of patients and are local and self limited. These events are addressed in EF Clobetasol foam labeling.

Systemic safety was evaluated with the Phase 2 study, CPE.C.201, wherein the potential for HPA axis suppression was studied in 52 pediatric and adult patients with mild to moderate atopic dermatitis. A significant number of patients, 7 out of 15 (47%), in the youngest cohort, ages 6 to 11, showed suppression. No younger cohorts were studied. The proportion of subjects 12 years of age and older demonstrating HPA axis suppression was 16.2% (6 out of 37). The laboratory suppression reversed in all subjects, returning to normal by 4 weeks after last treatment.

Cutaneous safety was evaluated with the two Phase 1 studies, DES.C.103 & 104. In both studies, DES.C.103 & 104, EF Clobetasol Vehicle foam was found to be somewhat irritating but not as irritating as the positive control, sodium laurel sulfate, 0.1%. In study DES.C.103, one subject out of 206 who completed challenge phase of the trial showed possible sensitization to Vehicle foam. Wider use of the EF Clobetasol foam product in the post-marketing phase may result in rare occurrences of true allergic contact dermatitis from the known sensitizing substances in the formulation.

The sponsor has requested a waiver for clinical photo-safety studies (phototoxicity and photoallergenicity). The amount of absorption detected in the drug product and drug substance (respectively 0.085 and 0.003 AU) at 290 nm wavelength is minimal, therefore photo-safety studies are not necessary.

1.3.4 Dosing Regimen and Administration

The dosing regimen for EF Clobetasol foam is twice daily (morning and evening) topical application to the skin. This is the dosing regimen that was studied in the Phase 2 and Phase 3 clinical trials. In clinical trials subjects were instructed to apply the foam in an amount sufficient

to cover affected areas and to avoid application to the face, scalp, and intertriginous areas. Subjects were also instructed not to exceed using 50 grams of the drug product per week; however drug product was issued in 100 gram cans. The two week treatment period is similar to that for many other clobetasol propionate products.

1.3.5 Drug-Drug Interactions

Studies of drug-drug interactions were not conducted in the clinical development program for this product.

1.3.6 Special Populations

In the Phase 3 trials, EF-Clobetasol foam was studied in patients age 12 and older. EF Clobetasol foam was tested for safety and efficacy across subgroups including age, race, and gender. Generally treatment success rates were consistent across age, race, and gender. However, in study CPE.C.302 (psoriasis) EF Clobetasol foam did not show superiority to vehicle foam in non-Caucasians.

Patients aged 65 and older numbered 58, too small a number to permit separate analysis of efficacy and safety. However, in a grouping consisting of 111 patients aged 65 and older and consisting of 58 on EF Clobetasol foam, 39 on Vehicle foam, and 14 on Temovate® Ointment, the adverse event rate was 14% (compared with 17% for patients on EF Clobetasol foam in all age groups combined). The data available do not indicate a need for dose adjustment in patients over age 65.

Pregnant and breast-feeding women were excluded from these studies. This is appropriate based on information from animal studies indicating clobetasol propionate is teratogenic at doses similar those used topically in humans. The pregnancy category assigned is C.

Pediatrics:

The indication of corticosteroid responsive dermatoses includes atopic dermatitis and psoriasis. Atopic dermatitis is principally a disease of children. EF Clobetasol foam, 0.05% is a new dosage form, therefore a pediatric assessment is required by the Pediatric Research Equity Act (PREA). In accordance with 21 CFR 314.55(c)(3)(iii), the applicant has submitted a request that the FDA waive the requirement to submit the pediatric assessment for pediatric age groups under 12 years of age. This is based on evidence from study CPE.C.201 (HPA axis suppression study) indicating that the drug product would be unsafe in all pediatric age groups. In this trial, 47% of subjects ages 6 to 11 demonstrated HPA axis suppression. This suppression was reversible. A partial pediatric waiver will be granted to the sponsor.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor, Connetics Corporation, has submitted a 505(b)(2) application for TRADENAME Emulsion Formulation Clobetasol Propionate Foam, 0.05% (EF Clobetasol Foam). This product was developed as a change in the dosage form of the reference listed drug Temovate® Ointment, 0.05%. EF Clobetasol foam contains the active ingredient clobetasol propionate, USP, which is a synthetic corticosteroid for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. The active ingredient, clobetasol propionate, is present at a concentration of 0.5 mg per gram in an emulsion aerosol foam vehicle of cetyl alcohol, anhydrous citric acid, cyclomethicone, isopropyl myristate, light mineral oil, polyoxyl 20 cetostearyl ether, potassium citrate monohydrate, propylene glycol, purified water, sorbitan monolaurate, white petrolatum, and phenoxyethanol as a preservative, pressurized with a hydrocarbon (propane/butane) propellant.

The sponsor seeks the proposed indication, topical treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The foam is to be applied twice daily in patients 12 years of age and older. Treatment beyond 2 consecutive weeks is not recommended, and labeling proposed by the sponsor states that the total dosage should not exceed 50 g/week.

The established name for the chemical moiety is clobetasol propionate. For the drug product, the sponsor proposed the trade name, Primolux™ Foam, 0.05%, but this was not found to be acceptable. The sponsor has proposed two additional names, _____ and _____. Consultation with the Division of Medication Errors and Technical Support (DMETS) and the Division of Marketing, Advertising, and Communications (DDMAC) regarding the suitability of these names is ongoing at the time of completion of this review.

The Division, DMETS, and DDMAC are concerned that confusion could arise from the presence on the market of two different trade names (Olux® and the current product) for the same drug substance, at the same concentration, in the same dosage form, and for essentially the same indication. Please see section 8.8 of this review for further discussion.

2.2 Currently Available Treatment for Indications

Atopic Dermatitis:

For the treatment of atopic dermatitis, particularly of the moderate to severe variety, topical corticosteroids of various strengths are often the first line of therapy. This category of drug is effective in controlling acute and chronic skin inflammation. Less potent corticosteroids such as hydrocortisone or desonide are appropriate for areas such as the face and intertriginous areas (groin, axillae, and inframammary folds) that are at higher risk for corticosteroid induced atrophy. Mid-potency (e.g. 0.1% triamcinolone acetonide) and higher (e.g. fluocinonide or

desoximetasone) preparations are appropriate for the rest of the body. Super-high potency preparations such as halobetasol propionate and clobetasol propionate are generally limited to two to four weeks of treatment, with use not to exceed 50 grams a week. Topical corticosteroids are also subject to the risk of tachyphylaxis.

More recently developed are the calcineurin inhibitors (pimecrolimus and tacrolimus) which are approved as second-line therapy for atopic dermatitis. Although the exact mechanism of these agents in atopic dermatitis is not known, they are known to inhibit the activation of a number of key effector cells, including T cells and mast cells. Pimecrolimus is approved for mild to moderate disease and is available as a 1% cream. Tacrolimus is approved for moderate to severe disease and is available as .03% and .1% ointments. For these agents, a major side effect is burning at the site of application. These agents also carry a boxed warning about the possibility of increased rates of malignancy with use. Additional less commonly employed treatments for atopic dermatitis include various phototherapy regimens, systemic corticosteroids, and oral cyclosporine (off-label) among others.

Psoriasis:

For psoriasis, a variety of approved treatments are available. Among topical therapies, topical corticosteroids have been commonly used since the 1950's and are considered first-line therapy for mild to moderate psoriasis. Corticosteroids come in various strengths and in various vehicles, including ointments, creams, lotions, gels, foams and sprays. Super-high potency corticosteroids include halobetasol propionate, augmented betamethasone dipropionate, and clobetasol propionate. For many of these products use is limited to two to four weeks with maximum usage limited to 50 grams a week. Side effects can include epidermal atrophy (usually reversible), dermal atrophy with the development of striae, more commonly in intertriginous areas, and HPA axis suppression. Burning and itching may also occur at sites of application. Topical corticosteroids can induce contact dermatitis.

Among topical therapies, the topical vitamin D3 analogues have more recently become an accepted first-line form of treatment for psoriasis, as monotherapy for mild to moderate psoriasis and as combination therapy for severe psoriasis. In the U.S. calcipotriene, approved in 1993, is the prototype. Vitamin D3 inhibits epidermal proliferation in hyperproliferative epidermis and induces normal differentiation by enhancing cornified envelope formation and activating transglutaminase. Evidence from *in vitro* studies suggests that calcipotriene is roughly the equivalent to the natural vitamin in its effects on proliferation and differentiation of a variety of cell types. Calcipotriene is available as ointment, cream, and solution. The most frequently reported adverse reactions for calcipotriene are burning, itching, and skin irritation. Calcipotriene should not be used by patients with hypercalcemia or evidence of vitamin D toxicity. Calcipotriene is a pregnancy category C drug product.

Approved in 1997 is topical tazarotene, a retinoid prodrug. The mechanism of tazarotene action in psoriasis is not defined. In human keratinocyte culture it inhibits cornified envelope formation. Tazarotene also induces expression of gene which may be a growth suppressor in human keratinocytes and which may inhibit epidermal hyperproliferation in treated plaques. Tazarotene is available in strengths of .05% and .1% as both a gel and cream. The gel is

indicated for the topical treatment of stable plaque psoriasis up to 20 % body surface involvement. The cream is indicated for the topical treatment of plaque psoriasis. In clinical trials, the most frequently reported side effects for the gel included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain. The most frequently reported side effects for the cream were pruritus, erythema, and burning. Tazarotene is a category X drug product and contraindicated for use in pregnant women. According to labeling, a negative pregnancy test should be obtained two weeks prior to starting therapy and therapy should begin during a normal menstrual period. Women of childbearing potential should also employ adequate birth control while using tazarotene.

Other therapies for psoriasis include phototherapy with ultraviolet B (UVB) and more recently narrowband UVB. Another form of phototherapy employs the use of ultraviolet A (UVA) following topical or oral psoralen. Systemic therapies for psoriasis also include methotrexate, cyclosporine, systemic retinoids, fumarates, mycophenolate mofetil, hydroxyurea, and 6-thioguanine among others. These are generally reserved for patients with moderate or, more often, severe disease.

2.3 Availability of Proposed Active Ingredient in the United States

Clobetasol propionate has been marketed in the United States since 1985. It is currently available in the .05% strength as a cream, emollient cream, lotion, ointment, solution, gel, hydroethanolic foam, shampoo, and spray. Many of these formulations are available as generic products. These products are classified as super potent topical steroids. Since reversible HPA axis suppression can occur with as little as two weeks of use, treatment is limited to 2 or 4 weeks. Temovate® .05% Cream and Ointment as well as Olux® Foam .05% are limited to two weeks of use. Clobex Spray .05%, Lotion .05%, and Shampoo .05% may be used for up to 4 weeks. For all these trade name products, patients are instructed to use no more than 50 grams a week. Branded formulations limited to ages 18 and older are the spray, lotion, and shampoo. The remaining branded formulations may be used by patients 12 years of age and older. Temovate® Ointment 0.05% is the reference listed drug for this NDA.

Safety concerns for these products include the local reactions of atrophy, striae, telangiectasia, and pigmentation change. These reactions generally occur after longer term use but can occur with as little as two weeks of use. Clobetasol propionate is also a known sensitizer with rates of sensitization ranging between .4% and .8% of patients with suspected contact dermatitis who were tested.^{1,2}

¹ Riettschel RL and Fowler JF; Fisher's Contact Dermatitis, 4th Ed. ©1995, Williams & Wilkins, Baltimore, p. 1028.

² Boffa MJ, Wilkinson SM, and Beck MH. Screening for corticosteroid hypersensitivity. Contact Dermatitis 1995; 33(3);149-51.

2.4 Important Issues with Pharmacologically Related Products

Clobetasol propionate topical steroid products are generally classified as super potent. The significant safety issue for this class is the potential ability of the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. If used according to the label the risk of HPA axis suppression is reduced. If suppression occurs, usually HPA axis function will recover upon discontinuation of the topical steroid product. Due to a larger body surface area to body mass, children are at higher risk for HPA axis suppression.

2.5 Pre-submission Regulatory Activity – IND 67,818

The sponsor requested a number of regulatory meetings and submitted a number of protocols for review and Agency comment. The following include the highlights of comments made during these regulatory interactions.

Guidance Meeting 11/24/2003

The sponsor attended a regulatory guidance meeting and Agency comments included the following:

- a) The Sponsor should "...include HPA suppression study(s) in target population under maximal use conditions along with the vasoconstriction study to establish the bioavailability of the proposed ethanol-free clobetasol foam."
- b) "For the indication of corticosteroid-responsive dermatoses (not restricted to scalp) it is recommended that a demonstration of efficacy and safety in both atopic dermatitis and psoriasis be provided." To pursue the indication of corticosteroid-responsive dermatoses, "... it is imperative that the Sponsor study the safety and efficacy of their product in the pediatric atopic dermatitis population..."
- c) "If the two clobetasol propionate foam formulations demonstrate similar efficacy, the safer product alone should be marketed. The Sponsor is asked to address the public health need served by the simultaneous marketing of two clobetasol propionate foam products, and the information that would be included in labeling to assist clinicians in selecting the appropriate product for their patients."

The sponsor has performed studies as requested in comments a) and b) above. Please see sections 5.2 and 6.1.3 of this review. It appears that the sponsor has responded to comment c) by stating that hydroethnaolic (Olux®) formulation might be useful for scalp application while the ethanol-free formulation (EF Clobetasol foam) might be useful for application to "the eroded skin of atopic dermatitis." The Division, DMETS, and DDMAC are concerned that confusion could arise from the presence on the market of two different trade names (Olux® and the current product) for the same drug substance, at the same concentration, in the same dosage form, and for essentially the same indication. At the time of completion of this review, negotiations are ongoing with the sponsor regarding the trade name.

IND Submission 04/16/2004:

The sponsor submitted an Investigative New Drug protocol and the following Agency comments were made regarding study CPE.C.201 - Hypothalamic Pituitary Adrenal Axis (HPA) suppression study:

- a) "Performance of cosyntropin stimulation test (CST) more frequently than every 4 weeks may result in higher stimulated cortisol levels after each successive cosyntropin injection and may invalidate data from later timepoints. The CST at week 2 should be eliminated, unless the duration of treatment is limited to 2 weeks (in which case the CST should be performed at the conclusion of treatment rather than at week 4)."
- b) "The Sponsor should identify a threshold for the proportion of HPA axis suppression in a cohort which would represent a significant safety signal, and above which the progression to the next cohort would not be warranted."

The sponsor has responded to these comments. However, the study performed was only of two weeks duration and the baseline CST was performed at an interval of -7 to -3 days. Therefore, the interval between the two CST tests was between 2 ½ and 3 weeks instead of 4 weeks. Please see sections 5.2 and 10.1.4 of this review and the Clinical Pharmacology Review.

End-of-Phase 2 meeting on 11/29/2004:

The sponsor attended an end-of-Phase 2 meeting and Agency comments included the following:

- a) "The anticipated regulatory pathway for approval will be via a 505 (b) (2) application."
- b) The Sponsor was requested to extend enrollment to pediatric subjects in both the atopic dermatitis trial and the psoriasis trial, pending completion of the HPA axis suppression study. "Demonstration of safety in psoriasis will not rest as heavily on data from pediatric subjects as will be the case for atopic dermatitis."
- c) Comments on Protocol CPE.C.301 (atopic dermatitis)
 - "Approval will largely rest upon adequate demonstration of safety in the pediatric population."
 - The primary endpoint as specified is acceptable.
"The primary endpoint is the proportion of subjects who have the following at week 2 (or end of treatment):"
 - ISGA score of clear or almost clear (0 or 1, respectively). and
 - Score of 0 or 1 for both erythema and induration/papulation, and
 - Minimum improvement in the ISGA score of 2 grades from baseline to week 2 (or end of treatment)."
 - "Preferred secondary endpoints would be the parameters of erythema, induration/papulation and lichenification dichotomized to success and failure..."
 - "Please actively assess for skin atrophy, striae, telangiectasia and pigmentation."
- d) Comments on Protocol CPE.C.302
 - "The proposed primary endpoint is the proportion of subjects who have the following at Week 2 (or end of treatment):"
 - An ISGA score of clear or almost clear (0 or 1, respectively), and
 - A score of 0 or 1 for erythema and scaling, and

- A score of 0 for induration”

To make the proposed primary endpoint acceptable, the Agency requested that the following parameter be added: “Minimum improvement in the ISGA score of 2 grades from baseline to week 2 (or end of treatment).”

- “Preferred secondary endpoints would be the parameters of erythema, scaling, and induration dichotomized to success and failure,…”
- “Please actively assess for skin atrophy, striae, telangiectasia, and pigmentation.”
- “Should the sponsor choose to pursue the indication of corticosteroid-responsive dermatoses, a three-arm psoriasis trial (sponsor’s product, sponsor’s vehicle, listed product) in subjects 12 years of age and older and a two-arm atopic dermatitis trial (sponsor’s product vs. vehicle) weighted toward the younger ages could together provide the requisite biobridge and efficacy and safety data.”

The sponsor has addressed the above comments regarding the design of studies CPE.C.301 and 302. Please see sections 10.1.1 and 10.1.2 of this review.

SPA Submitted on 12/7/2004 (Protocol CPE.C.301 atopic dermatitis):

The sponsor submitted a protocol for Special Protocol Assessment and Agency comments include the following:

- a) “Since the indication is primarily pediatric, this application would not be fileable without a safety database adequate to inform all pediatric age groups.”
- b) “Please enroll subjects with moderate to severe disease intensity on the ISGA, as atopic dermatitis of mild severity is not appropriate for treatment with a highly potent steroid such as clobetasol propionate.”
- c) “The Subject’s Global Assessment addresses only erythema, so it would be more accurately entitled Subject’s Assessment of Erythema. This parameter will not have regulatory utility.”
- d) “Please provide category descriptors for the assessment scales for the cutaneous signs of potential sequelae of topical corticosteroid use (atrophy, striae, telangiectasia, pigmentation changes).”

The sponsor has addressed comments a), b), and d). Please see sections 7.2.1.2, 10.1.1, and 10.1.2 of this review. The Subject’s Global Assessment in the Final Study Report CPE.C.301 addressed only erythema. Please see section 10.1.1 of this review.

SPA Submitted on 12/7/2004 (Protocol CPE.C.302 psoriasis):

The sponsor submitted a protocol for Special Protocol Assessment and Agency comments include the following:

- a) “The category descriptor for Almost Clear (1) in the ISGA is permissive rather than definitive. ‘No more than...’ would be preferred to ‘There may be...’ Ideally, the descriptors will clearly describe distinct categories.”
- b) “Please provide information on the reliability and reproducibility of investigator assessments of differences in plaque elevation of 0.5mm increments. Alternatively, provide verbal descriptions for the grades of plaque elevation in both the ISGA and plaque thickness scale for the target lesion.”

- c) "Please provide category descriptors for the assessment scales for the cutaneous signs of potential sequelae of topical corticosteroid use (atrophy, striae, telangiectasia, pigmentation changes)."
- d) The secondary endpoint, proportion of subjects with a pruritus score of 0 at week 2, may not have regulatory utility.

The sponsor has addressed the comments a), b) and c). Please see section 10.1.2 of this review.

SPA Meeting on 03/02/2005:

The sponsor attended a Special Protocol Assessment meeting and Agency comments included the following:

- a) The sponsor agreed to do a relative bioavailability study, in at least 15 evaluable subjects, comparing the test product with the reference product under maximal use conditions.
- b) "The sponsor stated that they intend to establish a clinical bridge to Temovate E cream and rely on the Agency's finding of safety for the RLD in order to meet the safety data needs described in ICH E1A as well as non-clinical data needs. The Agency responded that establishment of such a bridge would rest on demonstration that the sponsor's product was not superior to the RLD for efficacy (in a three-arm psoriasis trial), did not have a worse safety profile than the RLD, and did not demonstrate greater systemic bioavailability as demonstrated in a comparative HPA axis suppression study or very robust PK study."

The sponsor has performed a relative bioavailability study. To build their clinical bridge, the sponsor has performed the relative bioavailability study as well as safety and efficacy studies. Instead of Temovate® E cream the RLD used was Temovate® Ointment. Please see sections 5.1 and 10.1.2 of this review and the Clinical Pharmacology Review.

Pre-NDA Meeting on 12/14/2005:

The sponsor attended a Pre-NDA (New Drug Application) meeting and Agency comments included the following:

- a) Nonclinical carcinogenicity and photo-carcinogenicity studies with EF Clobetasol Foam will be conducted as post-marketing commitments and a timeline for the conduct of both post-marketing commitments will be included in the NDA.
- b) "The adequacy of the clinical bridge will be a review issue. The sponsor needs to provide sufficient evidence of the safety of their product, as addressed in the ICH E1A Guideline, in their NDA submission, whether through a clinical bridge, clinical studies, or other means."
- c) If the sponsor does not intend the propylene glycol to function as a penetration enhancer, this should be stated in the NDA submission. No safety or efficacy claims will be possible for such an excipient.

The sponsor has addressed the above comments. In reference to comment a) please see section 3.2 of this review and the Pharmacology/Toxicology Review and Evaluation. In reference to comment b) please see section 10.1.2 of this review. In reference to comment c), propylene glycol is described as a solvent in the listing of components of EF Clobetasol Foam (See this review section 3.1 (CMC) and sponsor's NDA submission, module 3, section 3.2.P.1, p.1.). The

cyclomethicone were the other excipients selected for the Phase I phase because of their ability to

The previously approved foam product, Olux® (clobetasol propionate), is described as having a hydroethanolic foam vehicle that is a single-phase, clear aerosol base containing greater than 50% alcohol and water. When this is dispensed from the pressurized can it is thermolabile and dissipates at a specific temperature. By comparison, EF Clobetasol foam has an aerosol base that is an ethanol-free oil-in-water emulsion and contains excipients that are expected to be occlusive and moisturizing. EF Clobetasol foam is dispensed from a pressurized can as foam and after dispensing the foam dissipates independent of temperature. The sponsor proposes that the hydroethanolic formulation might be useful for scalp application while the ethanol-free formulation might be useful for application to "the eroded skin of atopic dermatitis."

The composition of the-to-be marketed formulation is shown in Table 1. This formulation is the same formulation used in all the clinical trials and registration stability batches. The composition of the EF Clobetasol vehicle is the same except for the absence of clobetasol propionate.

Table 1: Quantitative Composition of EF Clobetasol Foam

Component	Reference to Quality Standard	Function	%w/w1
Clobetasol propionate	USP	Active ingredient	0.05
Propylene Glycol	USP		
Phenoxyethanol	NF		
White Petrolatum	USP		
Light Mineral Oil	NF		
Isopropyl Myristate	NF		
Sorbitan Monolaurate	NF		
Cetyl Alcohol	NF		
Cyclomethicone	NF		
Purified Water	USP		
Anhydrous Citric Acid	USP		
Potassium Citrate (Monohydrate)	USP		
Polyoxyl 20 Cetostearyl Ether	NF		

1 Per can concentrations

Source: Sponsor's NDA submission, module 3, section 3.2.P.1, p. 1.

Pregnancy: *Teratogenic Effects*: Pregnancy Category C.

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 to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of TRADENAME Foam based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 0.003 and 0.01 mg /kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of TRADENAME Foam based on body surface area comparisons. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. TRADENAME Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data used in the review of the EF Clobetasol Foam drug product came entirely from the sponsor's NDA submission. This also includes the 120 day safety update received on July 17, 2006.

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4.2 Tables of Clinical Studies

Table 2: Clinical Studies for EF Clobetasol Foam

Study Identifier Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CPE.C.101 Vaso-constriction Phase 1	Compare the relative vasoconstrictor potency of EF Clobetasol Foam, 0.05% to: 1) Vehicle Foam 2) Temovate-E Cream, 0.05%, and 3) Cutivate Ointment 0.005%	Randomized, evaluator-blinded, active comparators; topical application	EF Clobetasol Foam, Vehicle Foam Temovate-E Cream, and Cutivate Ointment; 10 mg; applied topically to 1 cm ² on forearm	36	Healthy Subjects	Single dose, 16 hr duration
DES.C.103 Skin Sensitization (RIPT) Phase 1	Determine the allergic contact sensitization potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and EF Clobetasol Vehicle Foam	Single-center, evaluator-blinded; occlusive patches. Positive and negative controls.	Desonide Foam, Desonide Vehicle Foam, EF Clobetasol Vehicle Foam; sodium lauryl sulfate, 0.1% (positive control), and distilled water (negative control).	240	Healthy Subjects	Three times a week for 3 weeks then one challenge dose. Re-challenge if needed.

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Table 2(Cont'd): Clinical Studies for EF Clobetasol Foam

Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
DES.C.104 Skin Irritation Phase 1	Evaluate the cutaneous irritation potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and EF Clobetasol Vehicle Foam	Single-center, evaluator-blinded. Positive and negative controls.	Desonide Foam, Desonide Vehicle Foam, EF Clobetasol Propionate Vehicle Foam; sodium lauryl sulfate, 0.1% (positive control), and distilled water (negative control); daily; topical application	40	Healthy volunteers	Daily for 3 weeks
CPE.C.201 HPA Axis Phase 2	Safety of EF Clobetasol Foam, 0.05% including its effect on the hypothalamic pituitary adrenal (HPA) axis	Open-label, non-controlled.	EF Clobetasol Foam twice daily; topical application	52	Patients with atopic dermatitis	2 weeks
CPE.C.202 Comparative Bioavailability Phase 2	Bioavailability of EF Clobetasol Foam, 0.05% and Temovate Ointment, 0.05%	Randomized, Open-Label,	EF Clobetasol Foam or Temovate Ointment; twice daily for 2 weeks; topical application	32	Patients with mild to moderate psoriasis	2 weeks

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Table 2(Cont'd): Clinical Studies for EF Clobetasol Foam

Study Identifier Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CPE.C.301 Phase 3 Atopic Dermatitis	Safety and Efficacy	Randomized, double-blind, vehicle controlled	EF Clobetasol Foam or Vehicle Foam; twice daily for 2 weeks; topical application	377	Patients with moderate to severe atopic dermatitis	2 weeks
CPE.C.302 Phase 3 Psoriasis	Safety and Efficacy	Randomized, double-blind, vehicle controlled, Temovate Ointment as RLD	EF Clobetasol Foam, Vehicle Foam or Temovate Ointment; twice daily for 2 weeks; topical application	497	Patients with mild to moderate plaque-type psoriasis	2 weeks

RIPT = Repeat Insult patch Test

RLD = Reference Listed drug

Source: Sponsor's NDA submission, Module 2, section 2.7.6, pp. 2-4.

4.3 Review Strategy

The pivotal Phase 3 trials CPE.C.301 (atopic dermatitis) and CPE.C.302 were reviewed in detail with regard to safety and efficacy. The Phase 2 study CPE.C.201, an investigation of HPA axis suppression, was also reviewed in detail. All of the preceding studies are included in the integrated safety database, as well as CPE.C.202 which examines comparative bioavailability. These Phase 2 and 3 studies also comprise the bulk of the drug exposure. The Phase 1 trials DES.C.103 (RIPT Skin Sensitization) and DES.C.104 (Skin irritation) were reviewed in reference to local irritancy and allergenicity.

The safety database as designated by the sponsor does not include the Phase 1 studies. These studies are less significant for the safety database since the amount of drug used is minimal, use is in healthy volunteers (not patients with diseased skin), and use is under occlusion for the skin sensitization and irritation studies (DES.C.103 & 104).

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4.4 Data Quality and Integrity

A review of pivotal trial data by the biostatistician and this reviewer did not reveal significantly anomalous findings or sites. Therefore the Division of Scientific Integrity (DSI) was not consulted to audit the applicant's data or study sites.

4.5 Compliance with Good Clinical Practices

The sponsor states that all seven of the clinical studies conducted for this NDA were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) and in compliance with local regulatory requirements (CFR). All trials were conducted under an IRB. Informed consent was obtained from all patients participating in the studies.

In the pivotal trial CPE.C.301, site 107 was unable to contact and maintain scheduled visits for seven subjects because of the effects of Hurricane Katrina. At this study site, no data was retrieved for five subjects and partial data was obtained for two subjects

4.6 Financial Disclosures

The sponsor has provided Form FDA 3454 covering 127 clinical investigators. The sponsor certifies that these investigators did not have financial arrangements with the sponsor that would compromise the integrity of the data submitted for NDA review. For one investigator who participated in study CPE.C.302 (Phase 3 Study of EF Clobetasol foam vs. Vehicle foam and Temovate® Ointment in Subjects with Mild to Moderate Plaque-Type Psoriasis) the sponsor has provided FDA Form 3455 with financial disclosure information because the named investigator has more than \$50,000 in equity or other financial interest in Connetics Corporation. The sponsor states that procedures used to minimize this investigator's bias were those employed for all investigators. Study CPE.C.302 was investigator-blinded to all treatment assignments. The study nurse/coordinator and subject were aware of the use of foam versus ointment but were blinded to the use of EF Clobetasol foam versus Foam Vehicle. None of the study sites broke the blind during the study. (Source: Sponsor's NDA submission, module 1, section 1.3.4)

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5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Relative bioavailability was evaluated in study CPE.C.202, an open label, randomized, parallel group study of 32 adult patients (19M, 13 F, age 24-72 years) with mild to moderate psoriasis. EF Clobetasol foam 0.05% was compared against Temovate® (clobetasol propionate) ointment 0.05% over a course of two weeks with approximately 3.5g twice daily topical doses (maximal use). Pertinent results of this study are shown in Table 3.

Table 3: Pharmacokinetic Parameters of EF Clobetasol Foam and Temovate Ointment (Day 8)

Parameter	EF Clobetasol Foam (N)	Temovate Ointment (N)	t-Value ^a
C _{max} (pg/mL)	59.0 ± 36.2 (15)	188.1 ± 274.2 (16)	0.081
AUC ₍₀₋₁₂₎ (pg h/mL)	562.0 ± 336.0 (15)	1572.9 ± 2436.8 (16)	0.122

^a Significance level set at 0.05

Source: Sponsor's NDA submission, module 5, Study Report CPE.C.202, p. 35.

Note that the mean C_{max} and AUC₍₀₋₁₂₎ values were 3.2- and 2.8-fold lower for EF Clobetasol foam as compared to Temovate® Ointment, however the *t*-values obtained from a non-paired Student's *t*-Test do not achieve statistical significance. It should also be noted that for subjects in the EF Clobetasol foam arm, the mean amount of drug used over the treatment period was higher (94g) than that for subjects in the Temovate® ointment arm (77g).

This study demonstrates that EF Clobetasol foam does not have a greater systemic bioavailability than the Reference Listed Drug, Temovate® ointment. The clinical pharmacology reviewer has calculated that the relative bioavailability of clobetasol propionate in the EF Clobetasol foam formulation is 35.7% when compared with the Temovate® Ointment formulation. Please see Clinical Pharmacology review NDA 22-013.

5.2 Pharmacodynamics

The vasoconstrictive potency of EF Clobetasol foam was evaluated in study CPE.C.101, a 36 patient, randomized, evaluator and subject blinded, single application study. This study was designed to bracket the expected relative potency of EF Clobetasol foam by comparison with a corticosteroid of similar potency (Clobetasol Emollient Cream 0.05%) and one of lower potency (Fluticasone Propionate Ointment 0.005%). Pertinent results of this study are shown in Table 4.

Table 4: Mean Vasoconstrictor Scores

Mean Vasoconstriction Score	Test Articles
0.1389	Vehicle Foam
1.4440	EF Clobetasol Foam
1.7500	Fluticasone Ointment
2.0278	Clobetasol Emollient Cream

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.101, p. 21.

The differences between EF Clobetasol foam, Vehicle foam and Clobetasol Emollient Cream were statistically significant. The difference between EF Clobetasol foam and Fluticasone Ointment was not statistically significant.

The clinical pharmacology reviewer has concluded that the results of this study do not support the sponsor's contention that EF Clobetasol foam, 0.05% is a super high potency corticosteroid formulation. Please see Clinical Pharmacology Review by Dr. Suliman I. Al-Fayoumi, NDA 22-013.

The potential for HPA axis suppression in 52 pediatric and adult patients with mild to severe atopic dermatitis was evaluated in study CPE.C.201. This study was multi-center, open-label and evaluated the effects of EF Clobetasol foam following twice daily application to a minimum of 30% treatable BSA for up to two weeks and not to exceed 50g/week. Pertinent results of this study are shown in Table 5.

Table 5: Incidence of (Reversible) HPA Axis Suppression by Cohort

	Cohort 1	Cohort 2	Cohort 3	Total
Week 2/End of Treatment				
Suppression	5/21 (24%)	0/15 (0%)	7/15 (47%)	12/51 (24%)
Conditional Visit				
Reversible Suppression	5/5 (100%)	NA	7/7 (100%)	12/12 (100%)

Note: Suppression is defined as a post-injection serum cortisol level less than or equal to 18 µg/dL. Reversible suppression is defined as a post-injection serum cortisol level greater than 18 µg/dL at the Conditional Visit after the cortisol level was less than or equal to 18 µg/dL at the Week 2/End of Treatment Visit.

Cohort 1 = age ≥ 18 years, Cohort 2 = age ≥ 12 years but < 18, Cohort 3 = age ≥ 6 years but < 12

Source: Sponsor's NDA submission, module 5, Study Report CPE.C.201, p 41.

A significant number of subjects (47%) in Cohort 3 (age ≥ 6 years but < 12) showed suppression. This caused termination of the study after this cohort without further study in two planned younger cohorts.

An element in the study design may add to uncertainty in the interpretation of the results. Cosyntropin was administered to patients over an interval of roughly 2 ½ to 3 weeks, instead of a

recommended interval of no less than 4 weeks. The clinical pharmacology reviewer has stated, "... the flawed study design casts doubt into the validity of the study findings. As such, no valid conclusions may be drawn from the study." Despite this, the reviewer has stated that from the view point of the Office of Clinical Pharmacology, NDA 22-013 is acceptable. Furthermore, although the interval of cosyntropin administration was somewhat short, suppression (substantial in the 6 to 11 year old age cohort) was seen in the study. The study though not ideal is interpretable. Please see Clinical Pharmacology Review. Please also see discussion in this review under section 7.1.12.

5.3 Exposure-Response Relationships

Dose-response was not formally studied in this application. Since the sponsor is pursuing approval via the 505(b)2 route, the dose was selected (0.05%) to correspond with the reference listed drug, Temovate® Ointment, 0.05%.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for emulsion formulation clobetasol propionate foam, 0.05% is relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

6.1.1 Methods

The efficacy evaluation will focus upon a detailed review of pivotal trials CPE.C.301 (study 301) and CPE.C.302 (study 302). Study 301 is designed to evaluate the safety and efficacy of Emulsion Formulation Clobetasol Propionate Foam, 0.05% (EF Clobetasol Foam) in the treatment of moderate to severe atopic dermatitis and to demonstrate that EF Clobetasol foam is superior to its vehicle.

Study 302 is designed to evaluate the safety and efficacy of EF Clobetasol Foam by demonstrating that EF Clobetasol Foam is superior to its vehicle in the treatment of mild to moderate plaque-type psoriasis. Additionally, Temovate® (clobetasol propionate) Ointment is employed as a reference listed drug in order to allow reference to the safety database of Temovate Ointment by showing non-superior efficacy and comparable safety of EF Clobetasol Foam compared to Temovate Ointment.

6.1.2 General Discussion of Endpoints

For study CPE.C.301 (atopic dermatitis), the primary efficacy endpoint was defined as treatment success at week 2. Treatment success was defined as the proportion of subjects having at Week

2: 1) An Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) AND 2) A score of 0 or 1 for both erythema and induration/papulation AND 3) A minimum improvement in the ISGA score of 2 grades from Baseline to week 2. This was agreed upon with the applicant at the end of Phase 2 meeting 11/29/2004. The requirement that there be at least a two grade improvement in ISGA from baseline to week 2 ensures that what is considered to be a success is clinically meaningful. The use of a scale such as the ISGA, with incorporated scales for signs of atopic dermatitis, as a key component of the primary efficacy endpoint has been previously accepted by the FDA.

For study CPE.C.302 (psoriasis), the primary efficacy endpoint was defined as treatment success at week 2. Treatment success was defined as the proportion of subjects having at Week 2: 1) An ISGA score of clear (0) or almost clear (1) with at least a reduction of 2 grades from baseline AND 2) a score of 0 or 1 for erythema AND 3) a score of 0 or 1 for scaling AND 4) a score of 0 for plaque thickness. This general form was agreed upon with the applicant in response to the Special Protocol Assessment dated January 19, 2005. With respect to the ISGA, an Agency comment to the sponsor (Jan 19, 2005) was made in reference to the plaque thickness scale. On March 10, 2005 the sponsor responded with a revised plaque thickness scale. However, the scales for scaling and erythema were also changed inadvertently. The sponsor corrected the ISGA scale April 25, 2005, after 46 subjects had been enrolled. Please see FDA biostatistician's review for further discussion. The requirement that there be at least a two grade improvement in ISGA from baseline to week 2 ensures that what is considered to be a success is clinically meaningful. The use of a scale such as the ISGA, with incorporated scales for signs of psoriasis, as a key component of the primary efficacy endpoint has been previously accepted by the FDA.

6.1.3 Study Design

Pivotal Study: Protocol Number CPE.C.301

Title: "A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Ethanol-Free Clobetasol Propionate Foam, 0.05% in the Treatment of Moderate to Severe Atopic Dermatitis"

Study CPE.C.301 was conducted as a multicenter, randomized, double-blind, trial of EF Clobetasol foam against Vehicle foam. Subjects aged 12 and older with moderate to severe atopic dermatitis were enrolled in a 2:1 ratio to EF Clobetasol foam and Vehicle foam. The study enrolled 377 subjects (251 EF Clobetasol foam, 126 Vehicle foam) at 20 investigational sites in the United States. Subjects applied study drug twice daily for two weeks to cover all areas affected by atopic dermatitis (excluding face, scalp and intertriginous areas). Study visits were Baseline, Week 1, Week 2, and two weeks post-treatment (Week 4). The severity of atopic dermatitis was assessed using Investigator's Static Global Assessment (ISGA), erythema, induration/papulation, oozing/crusting and body surface area (BSA) involvement. Also evaluated was the sign of lichenification and the symptom of pruritus.

Pivotal Study: CPE.C.302

Title: “A Multicenter, Randomized, Double-Blinded Study of the Safety and Efficacy of Ethanol-Free Clobetasol Propionate Foam, 0.05%, versus Vehicle Foam and Temovate® (clobetasol propionate) Ointment, 0.05%, (Investigator-Blinded) in the Treatment of Mild to Moderate Plaque-Type Psoriasis”

Study CPE.C.302 was conducted as a 21 (only 20 enrolled subjects) center, randomized, trial comparing EF Clobetasol Foam to vehicle foam (double-blind) and to Temovate® Ointment (investigator-blinded). Subjects were 12 years of age and older and had mild to moderate plaque-type psoriasis. Qualified subjects (497) were randomized into one of three parallel treatment groups in a 2:1:1 ratio (EF Clobetasol Foam-253: Temovate Ointment-121: Vehicle Foam-123). Subjects applied study drug twice daily for two weeks to cover all lesions (excluding face, scalp, and intertriginous areas). Study visits were Baseline, Week 1, Week 2, and two weeks post-treatment (Week 4). The severity of psoriasis was evaluated was assessed using Investigator’s Static Global Assessment (ISGA), erythema, scaling, plaque thickness, and BSA involvement. Also evaluated was the symptom of pruritus.

6.1.4 Efficacy Findings

Efficacy Endpoint Outcomes: Study CPE.C.301

Success Rate

Primary Efficacy Endpoint

EF Clobetasol foam was superior to vehicle foam as measured by subjects achieving treatment success at week 2. This finding held true for both the ITT and Per Protocol populations.

Table 6: Subjects with Treatment Success at Week 2 (Study 301)

	Clobetasol Foam	Vehicle Foam
<i>ITT</i>	N=251	N=126
Treatment Success ¹	131 (52%)	18 (14%)
P-value		<0.0001
<i>PP</i>	N=230	N=108
Treatment Success ¹	125 (54%)	18 (17%)
P-value		<0.0001

¹ ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, and induration/papulation = 0 or 1

Note: Success is defined as the proportion of subjects who have the following at Week 2: An ISGA score of 0 or 1, a score of 0 or 1 for both erythema and induration/papulation, and a minimum improvement in the ISGA score of 2 grades from Baseline to Week 2.

Treatment success was analyzed with a Cochran-Mantel-Haenszel test on pooled center.

Source: Kathleen Fritsch, Biostatistician, FDA, statistical Review and Evaluation, NDA 22-013, Table 9.

Both the FDA and the sponsor analysis are in agreement regarding the results of the primary efficacy endpoint.

As previously agreed upon, this study uses a composite endpoint consisting of four components at Week 2; an ISGA score of 0 or 1, a minimum improvement in the IGSA score of 2 grades from baseline to week 2, and a score of 0 or 1 for both erythema and induration/papulation. To be noted the ISGA itself includes erythema, induration/papulation, and oozing/crusting.

Subgroup Analyses:

Subgroup analyses were performed on subjects in the ITT population and included; gender, race, age cohort and baseline ISGA score. The results of subgroup analysis for gender, age cohort, and race are shown in Table 7. As shown, treatment effects are generally consistent across these subgroups.

Table 7: Treatment Success at Week 2 by Subgroup

		Clobetasol Foam	Vehicle Foam
Gender	Male	37/80 (46%)	5/53 (9%)
	Female	94/168 (56%)	13/71 (18%)
Race	Caucasian	76/148 (51%)	13/74 (18%)
	Afr.-Amer.	37/69 (54%)	3/31 (10%)
	Other†	18/31 (58%)	2/19 (11%)
Age	12 <- 18	38/69 (55%)	3/32 (9%)
	18 <- 65	85/157 (54%)	13/79 (16%)
	≥ 65	8/22 (36%)	2/12 (17%)

†For purposes of analysis, Hispanic and Asian subjects were combined with the "Other" race category.

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 24.

Subjects with severe disease at baseline showed less treatment success than those with moderate disease as defined by ISGA. This is most likely a result of the requirement that the ISGA score be 0 or 1 for success in the composite primary efficacy endpoint. To meet this requirement, subjects with baseline severe disease (ISGA 4) would have to improve by 3 grades as opposed to only two grades for those of baseline moderate severity (ISGA 3).

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Table 8: Treatment Success at Week 2 by Baseline Severity

	EF Clobetasol Foam	Vehicle Foam
Overall Success		
n (% success)	131/251 (52%)	18/126 (14%)
Moderate (ISGA = 3)		
n (% success)	122/217 (56%)	18/111 (16%)
Severe (ISGA = 4)		
n (% success)	9/31 (29%)	0/13 (0%)

Data for 3 subjects in EF Clobetasol Foam group and 2 subjects in Vehicle Foam group were not available due to effects of hurricane Katrina.

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, adapted from Table 27, p.63.

Secondary Efficacy Analysis:

The four secondary endpoints included the proportion of subjects who had the following at Week 2: (1) a score of 0 for pruritus, (2) a score of 0 for lichenification, (3) a score of 0 or 1 for erythema, and (4) a score of 0 or 1 for induration/papulation. A reduction of at least two grades at week 2 was required for success with these endpoints. As shown in Table 9, EF Clobetasol Foam was superior to vehicle foam for all four secondary endpoints.

Table 9: Success¹ on Secondary Efficacy Endpoints

	Clobetasol Foam N= 251	Vehicle Foam N= 126	p-value
Pruritus = 0	104 (41%)	10 (8%)	<0.0001
Lichenification = 0	56 (22%)	5 (4%)	<0.0001
Erythema = 0 or 1	134 (53%)	19 (15%)	<0.0001
Induration/Papulation = 0 or 1	141 (56%)	14 (11%)	<0.0001

¹ All definitions of success required at least 2 grades reduction from baseline.

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 13.

Efficacy Endpoint Outcomes: Study CPE.C.302

Success Rate

Primary Efficacy Endpoint

EF Clobetasol foam was superior to vehicle foam as measured by the proportion of subjects achieving treatment success at Week 2. This finding held true for both the ITT and Per Protocol populations. In the ITT population, at Week 2, the proportion of subjects achieving treatment success was 16% for EF Clobetasol foam versus 4% for vehicle foam. Although not a planned

efficacy comparison, note that EF Clobetasol foam was inferior to Temovate® Ointment, 16% versus 31% (p= .0007).

Table 10: Treatment Success for Psoriasis at Week 2

	Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
<i>ITT</i>	N=253	N=123	N=121
Treatment Success ¹	41 (16%)	5 (4%)	38 (31%)
P-value (vs. Clob. Foam)		0.0005	(0.0007) ²
<i>PP</i>	N=234	N=112	N=111
Treatment Success ¹	39 (17%)	5 (4%)	34 (31%)
P-value (vs. Clob. Foam)		0.0011	(0.0031) ²

¹ ISGA = 0 or 1 with 2 grades reduction, erythema = 0 or 1, scaling = 0 or 1, and plaque thickness = 0

² Clobetasol foam versus Temovate Ointment was not a planned efficacy comparison

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 10.

Treatment success was defined as proportion of subjects achieving all of the following at Week 2: 1) a score of clear (0) or almost clear (1) on the ISGA with 2) at least a reduction of 2 grades from baseline, 3) a score of 0 or 1 for erythema, 4) a score of 0 or 1 for scaling, and 5) a score of 0 for plaque thickness. The evaluation of erythema, scaling, and plaque thickness was performed on a target lesion identified at baseline. Of note, the IGSA included evaluation of erythema, scaling, and plaque thickness.

Both the FDA and the sponsor analysis are in agreement regarding the results of the primary efficacy endpoint.

Subgroup Analysis:

Subgroup analyses were performed on subjects in the ITT population and included; gender, race, age, and baseline disease severity. The results of subgroup analysis for gender, age, and race are shown in Table 11.

Table 11: Treatment Success at Week 2 by Subgroup

	Clobetasol Foam	Vehicle Foam	TEMOVATE Ointment
Gender Male	21/127 (17%)	4/71 (6%)	23/76 (30%)
Female	20/126 (16%)	1/52 (2%)	15/45 (33%)
Race Caucasian	41/221 (19%)	5/111 (5%)	35/105 (33%)
Other†	0/32 (0%)	0/12 (0%)	3/16 (19%)
Age 12 < 18	2/8 (25%)	0/1 (0%)	--
18 < 65	37/216 (17%)	3/95 (3%)	31/108 (29%)
≥ 65	2/29 (7%)	2/27 (7%)	7/13 (54%)

† For purposes of analysis, the sponsor has combined African-American, Hispanic, and Asian subjects with the "Other" race category.

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 25.

Response to treatment was similar for both male and female subjects. The great majority of study subjects were Caucasian and in the 18 to 64 year old age group. The small numbers of subjects outside of these categories make conclusions more tentative. Treatment response did vary by race, with the proportion of subjects who achieved treatment success with EF Clobetasol foam being 19% (Caucasian) versus 0% (Other). The success rate for "Other" (or non-Caucasian) versus Caucasian was also lower in the Temovate arm, 19% versus 33%.

Treatment success for those treated with EF Clobetasol foam or foam vehicle was independent of baseline ISGA for subjects judged to have mild or moderate disease. For those treated with Temovate ointment, moderate disease (ISGA = 3) versus mild disease (ISGA = 2) at baseline was associated with greater treatment success at Week 2.

Table 12: Treatment Success at Week 2 by Baseline Severity (Study 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Overall success			
n (% success)	41/253 (16%)	5 /123(4%)	38/121 (31%)
Mild (ISGA = 2)			
n (% success)	15/93 (16%)	2/37 (5%)	7/34 (21%)
Moderate (ISGA = 3)			
n (% success)	24 /155(15%)	3/85 (4%)	30/84 (36%)
Marked / Severe (ISGA = 4/5)			
n (% success)	2/5 (40%)	0/1 (0%)	1/3 (33%)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.302, adapted from Table 28, p. 66.

Secondary Efficacy Analysis:

The four secondary endpoints included the proportion of subjects who had the following at Week 2: 1) a score of 0 or 1 for erythema, 2) a score of 0 or 1 for scaling, or 3) a score of 0 for plaque thickness, or 4) a score of 0 for pruritus. Note that a reduction of at least two grades from baseline is not required for success on these endpoints.

Table 13: Success on Secondary Efficacy Endpoints

	Clobetasol Foam N= 253	Vehicle Foam N= 123	TEMOVATE Ointment N=121	p-value ¹	p-value ²
Pruritus = 0	106 (42%)	23 (19%)	71 (59%)	<0.0001	0.0022
Erythema = 0	39 (16%)	3 (2%)	24 (20%)	0.0002	0.2284
Erythema = 0 or 1	135 (53%)	25 (20%)	83 (69%)	<0.0001	0.0042
Scaling = 0 or 1	180 (71%)	34 (28%)	107 (88%)	<0.0001	0.0002
Plaque Thickness = 0	78 (31%)	6 (5%)	59 (49%)	<0.0001	0.0006

¹ P-value for clobetasol foam versus vehicle foam

² P-value for clobetasol foam versus TEMOVATE Ointment

Source: Kathleen Fritsch, Biostatistician, FDA, Statistical Review and Evaluation, NDA 22-013, Table 14, with minor modifications.

As shown in Table XX, EF Clobetasol foam was superior to vehicle foam for all secondary endpoints, including erythema whether success defined as a score of 0 or as a score of 0 or 1. Note also that EF Clobetasol foam is inferior to Temovate® ointment for all four secondary endpoints when erythema success is defined as a score of 0 or 1. With erythema, when success is defined as a score of 0, EF Clobetasol foam is not statistically inferior to Temovate® Ointment.

6.1.5 Clinical Microbiology

The Sponsor did not perform any clinical microbiology studies.

6.1.6 Efficacy Conclusions

Pivotal Phase 3 trial CPE.C.301 was multi-center, randomized, vehicle-controlled against topical study drug, and double-blind. This trial was of adequate design and sufficiently powered to study the safety and efficacy of EF Clobetasol foam at a dose of twice daily for two weeks in subjects 12 years of age and older with moderate to severe atopic dermatitis.

EF Clobetasol Foam was superior to Vehicle foam (52% versus 14%, $p < 0.0001$) as measured by subjects achieving treatment success at Week 2 with the composite primary endpoint as follows; an ISGA score of 0 or 1, a minimum improvement in the IGSA score of 2 grades from baseline to week 2, and a score of 0 or 1 for both erythema and induration/papulation. Treatment effects were generally consistent across subgroups analyzed for gender, age cohort, and race.

EF Clobetasol Foam was superior to Vehicle foam ($p < 0.0001$) on all four secondary endpoints at Week 2. These endpoints included; a score of 0 for pruritus, a score of 0 for lichenification, a score of 0 or 1 for erythema, and a score of 0 or 1 for induration/papulation. A reduction of at least two grades at week 2 was required for success with these endpoints.

Protocol changes included changing the inclusion criteria for pruritus, dropping the requirement that the subject's assessment of pruritus score be 2 or greater. Another protocol change modified the criteria for success on the secondary endpoints to require a reduction of at least two grades. Analyses performed by the FDA biostatistician showed that these changes did not materially affect the results of study CPE.C.301.

Pivotal Phase 3 trial CPE.C.302 was a multi-center, randomized, trial comparing EF Clobetasol Foam to Vehicle foam (double-blind) and to Temovate® Ointment (investigator-blinded). This trial was of adequate design and sufficiently powered to study the safety and efficacy of EF Clobetasol foam at a dose of twice daily for two weeks in subjects 12 years and older with mild to moderate plaque-type psoriasis.

EF Clobetasol foam was superior to Vehicle foam (16% versus 4%, $p < 0.0005$) as measured by subjects achieving treatment success at Week 2 using the primary composite endpoint as follows; a score of clear (0) or almost clear (1) on the ISGA with at least a reduction of 2 grades from baseline, a score of 0 or 1 for erythema, a score of 0 or 1 for scaling, and a score of 0 for plaque thickness. The evaluation of erythema, scaling, and plaque thickness was performed on a target lesion identified at baseline. Although not prespecified as an efficacy comparison in the protocol, EF Clobetasol foam was also inferior to Temovate Ointment (16% versus 31%, $p=0.0007$). Response to treatment was similar for both male and female subjects. The great majority of study subjects were Caucasian and in the 18 to 64 year old age group. Treatment success did vary by race (19% (41/221) Caucasian, 0% (0/32) Other); however the number of subjects involved in the "Other" category was fairly small.

EF Clobetasol Foam was superior to Vehicle foam for all secondary endpoints at Week 2 ($p < 0.0001$). These endpoint included; a score of 0 or 1 for erythema, a score of 0 or 1 for scaling, or a score of 0 for plaque thickness, or a score of 0 for pruritus. A reduction of at least two grades from baseline was not required for success on these endpoints. EF Clobetasol foam is also inferior to Temovate® Ointment for all four secondary endpoints when erythema success is defined as a score of 0 or 1. With erythema, when success is defined as a score of 0, EF Clobetasol foam is not statistically inferior to Temovate® Ointment.

A protocol change occurred during the study that involved the psoriasis scale that was used to enroll the first 46 patients. Typographical errors were present that involved the scaling and erythema components of the scale. The sponsor provided corrected scales to the investigational sites. Data analyses by sponsor and FDA biostatistician, including exclusion of the 46 subjects enrolled under the incorrect scale, indicate that this protocol change did not materially affect the results of study CPE.C.302.

In both studies CPE.C.301 and CPE.C.302, approximately 20% of subjects in the EF Clobetasol foam and Vehicle foam arms used more than 100 grams of study drug during the treatment period. In study CPE.C.302 subjects in the foam product study arms used approximately twice as much study drug as those subjects in the Temovate® Ointment arm.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of EF Clobetasol Foam will focus on adverse events, systemic safety (laboratory evaluation, HPA axis studies) and local safety (cutaneous signs and symptoms at application sites in Phase 2 and Phase 3 studies). Additionally, Phase 1 studies of cutaneous irritancy and allergenicity (repeat insult patch test study) will be reviewed. Adverse events in the comparator arm, Temovate® Ointment, have not been included unless necessary for comparison.

The integrated safety data base consisted of patients from studies CPE.C201 (HPA axis suppression study, atopic dermatitis), CPE.C.202 (Bioavailability study, psoriasis), CPE.C.301 (safety and efficacy study, 2 arm, atopic dermatitis), and CPE.C.302 (safety and efficacy study, 3 arm & reference listed drug, psoriasis).

7.1.1 Deaths

No deaths were reported in any of the EF Clobetasol Foam studies.

7.1.2 Other Serious Adverse Events

Serious adverse events included one event of streptococcal pneumonia in the Phase 3 atopic dermatitis study (CPE.C.301) and one event of syncope in the Phase 3 psoriasis study (CPE.C.302). Both of these events were reported by the Investigator as not related to study drug.

Table 14: Incidence of All Serious Adverse Experiences Classified by MedDRA System Organ Class and Preferred Term Safety Population (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302)

SYSTEM ORGAN CLASS Preferred Term	-EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total
Number of Subjects	572	249	137	958
Subjects with a(n) Serious adverse experience	2 (< 1%)	0 (0%)	0 (0%)	2 (< 1%)
INFECTIONS AND INFESTATIONS	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
Pneumonia streptococcal	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
NERVOUS SYSTEM DISORDERS	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
Syncope	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)

Note: Subjects reporting a particular adverse experience more than once are counted only once for that adverse experience. Adverse experiences reported during post treatment follow-up period are included.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, p. 24.

After review of the narratives of the two serious events, it does appear that these events are unrelated to study drug use. Please also see safety subsections, sections 10.1.1 and 10.1.2 of this review, for these narratives.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

**Table 15: Reason for Study Drug Discontinuation
 Safety Population (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302)**

	.EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total
Number of Subjects	572	249	137	958
Subjects who Completed Study	552 (97%)	224 (90%)	133 (97%)	909 (95%)
Subjects who Discontinued	20 (3%)	25 (10%)	4 (3%)	49 (5%)
Reasons for Discontinuation				
Adverse Experience	2 (< 1%)	4 (2%)	0 (0%)	6 (1%)
Subject Non-Compliance	4 (1%)	1 (< 1%)	2 (1%)	7 (1%)
Disease Progression	1 (< 1%)	7 (3%)	0 (0%)	8 (1%)
Subject Request to Withdraw	4 (1%)	6 (2%)	1 (1%)	11 (1%)
Subject Died	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other Reason*	9 (2%)	7 (3%)	1 (1%)	17 (2%)

* Eight subjects had no termination information and hence, were deemed lost to follow-up due to hurricane Katrina.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, p. 25.

A total of 5% (49/958) subjects in the safety population discontinued participation early. Of those who discontinued early the following were reported; 1% (6/958) AEs, 1% (7/958) subject non-compliance, 1% (8/958) disease progression, 1% (11/958) subject request to withdraw, and 2% (17/958) other reason. Included in the other reason category were eight subjects who had no termination information and were determined to be lost to follow-up due to hurricane Katrina.

7.1.3.2 Adverse events associated with dropouts

The portion of the safety population who discontinued early, reported as due to AEs, included 1% or 6/958 subjects.

In the .EF Clobetasol foam group, less than 1% (2/572) of study terminations occurred because of an AE. In the .EF Clobetasol foam group the adverse experiences that led to study withdrawal were, urticaria at study drug applications areas (reported as probably related to study drug) and atopic dermatitis on hands (reported as possibly related to study drug.)

The case report form (CRF) for the episode of urticaria at drug application sites (subject 301-110-1474, atopic dermatitis study) was reviewed. Study drug therapy started 8/29/06 and simultaneously with the urticaria there was onset of wheezing and rhinitis on 9/02/06. Prior to this episode, the patient was on liothyronine sodium for hypothyroidism and oxycodone, as needed, for pain from herniated disc in the neck. The patient was prescribed telithromycin (Ketek) and fexofenadine hydrochloride (Allegra). The wheezing and rhinitis resolved 9/03/06 and the urticaria at drug application sites resolved 9/08/06. This reviewer agrees with the sponsor's assessment that the episode of urticaria at study drug application sites was probably related to study drug use.

The CRF for the case of atopic dermatitis of hands (subject 302-211-3553, psoriasis study) was reviewed. Study drug therapy started 5/23/06. Atopic dermatitis was noted on both hands, not a study drug application site, 5/27/06. No concomitant medications are listed prior to this episode. As a result of this episode, the subject was prescribed oral prednisone (6/02 to 6/19) and hydroxyzine (5/29 to 6/08). The patient was also prescribed hydrocodone and gabapentin (5/29 to 6/8) for "pain from atopic dermatitis." Although the hands in this case were not a study drug application site, the patient may have been exposed on the hands to study drug in the course of application to psoriasis on other parts of the body. Subjects were instructed to, "...gently massage the medication into affected areas until the study drug is absorbed" (page 13, Protocol Amendment 2, CPE.C.302). It appears possible that study drug, most likely components of the vehicle, was related to the episode of atopic dermatitis of the hands.

In the Vehicle Foam group, AEs caused 2% (4/249) of the terminations. The adverse experiences that resulted in study withdrawal were, allergic reaction to the study drug (reported as probably related to the study drug), irritant contact dermatitis (reported as definitely related to study drug), generalized increased pruritus (reported as possibly related to study drug), and infected atopic dermatitis (reported as probably not related to study drug).

Review of the CRFs for the cases of allergic reaction (subject 302-211-3540) and irritant contact dermatitis (subject 301-102-1052), revealed that they happened fairly quickly after starting study drug. The criteria for distinguishing irritant versus allergic reaction are not given. Subject 301-103-1113 was reported as having increased generalized pruritus. This occurred by 2 days after the Baseline visit and on a query form it is confirmed that generalized increased pruritus is related to atopic dermatitis. This could represent a pruritic response to Vehicle foam.

Review of the CRF for the case of infected atopic dermatitis (subject 301-117-1835) reveals an entry of moderate itching lasting 30 minutes after study medication application, on the Baseline visit. Two days later bacterial infection of atopic dermatitis is listed as well as worsening of asthma. On the CRF the relationship of the itching to study drug is reported as probably related and the action taken as permanent withdrawal of study drug. However, in the final study report no mention of the itching is made, only the bacterial infection considered probably not related to study drug.

In the Temovate Ointment group, there were no terminations (0/137) caused by AEs.

7.1.3.3 Other significant adverse events

No additional information is provided in this submission regarding adverse events that led to dose reduction or significant additional concomitant therapy without discontinuation of treatment.

7.1.4 Other Search Strategies

Common adverse events that may occur with use of a super-potent topical steroid such as clobetasol propionate include skin atrophy, striae, telangiectasia, and pigmentation changes. In both pivotal Phase 3 studies the sponsor queried these signs.

To be noted, the Baseline incidence of the cutaneous sign of atrophy is higher in the EF Clobetasol foam and Vehicle foam groups than in the Temovate Ointment groups. This is explained on the basis that subjects with atopic dermatitis had a higher Baseline incidence of atrophy than subjects with psoriasis. In study CPE.C.301, at Baseline 29 (12%) of the subjects in the EF Clobetasol foam arm and 17 (13%) of subjects in the Vehicle foam arm were rated as having mild atrophy at Baseline. Whereas, in study CPE.C.302, 6 (2%), 3 (2%), and 2 (2%) of the subjects in the EF Clobetasol foam, Vehicle foam, and Temovate® Ointment arms, respectively, were rated as having mild atrophy at Baseline.

Table 16: Change in Atrophy from Baseline Phase 3 Studies (CPE.C.301 and CPE.C.302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects*	504	249	121
Baseline			
Missing	3 (1%)	2 (1%)	0 (0%)
None	464 (92%)	226 (91%)	119 (98%)
Mild	35 (7%)	20 (8%)	2 (2%)
Moderate	2 (< 1%)	0 (0%)	0 (0%)
Severe	0 (0%)	1 (< 1%)	0 (0%)
Week 2			
Missing	13 (3%)	18 (7%)	1 (1%)
1-Grade Improvement	6 (1%)	4 (2%)	1 (1%)
No Change	475 (94%)	225 (90%)	119 (98%)
1-Grade Worsening	10 (2%)	2 (1%)	0 (0%)

* Number of subjects only includes Phase 3 studies.

Source: Sponsor's NDA submission, Module 2, Summary of Clinical Safety, p. 81.

At Week 2, the incidence of worsening of atrophy was low in all treatment groups. There was a mildly higher incidence of 1-grade worsening of atrophy in the EF-Clobetasol Foam group. This mildly higher incidence of 1-grade worsening of atrophy in the EF Clobetasol Foam group may represent statistical variation or possibly be a signal of a slightly higher risk of atrophy with the use of this product as compared with Vehicle foam or Temovate® Ointment.

Table 17: Change in Striae from Baseline Phase 3 Studies (CPE.C.301 and CPE.C.302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects*	504	249	121
Baseline	17 (3%)	9 (4%)	0 (0%)
Week 2	15 (3%)	6 (2%)	0 (0%)

* Number of subjects only includes Phase 3 studies.

Source: Sponsor's NDA submission, Module 2, Summary of Clinical Safety, p. 82.

Striae were evaluated as either being present or absent. These results indicate that, after 2 weeks of treatment, the number of subjects having striae did not increase in any treatment arm.

Table 18: Change in Telangiectasia from Baseline Phase 3 Studies (CPE.C.301 and CPE.C.302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects*	504	249	121
Baseline			
Missing	3 (1%)	2 (1%)	0 (0%)
None	487 (97%)	234 (94%)	120 (99%)
Mild	12 (2%)	12 (5%)	1 (1%)
Moderate	2 (< 1%)	1 (< 1%)	0 (0%)
Week 2			
Missing	13 (3%)	18 (7%)	1 (1%)
1-Grade Improvement	4 (1%)	2 (1%)	0 (0%)
No Change	485 (96%)	228 (92%)	118 (98%)
1-Grade Worsening	1 (< 1%)	1 (< 1%)	2 (2%)
2-Grade Worsening	1 (< 1%)	0 (0%)	0 (0%)

* Number of subjects only includes Phase 3 studies.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, p. 83.

Evaluation of telangiectasia at Week 2 revealed no significant trend either toward worsening or improvement.

Table 19: Change in Pigmentation from Baseline Phase 3 Studies (CPE.C.301 and CPE.C.302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects*	504	249	121
Baseline			
Missing	3 (1%)	2 (1%)	0 (0%)
None	398 (79%)	204 (82%)	117 (97%)
Mild	61 (12%)	21 (8%)	2 (2%)
Moderate	41 (8%)	21 (8%)	1 (1%)
Severe	1 (<1%)	1 (<1%)	1 (1%)
Week 2			
Missing	14 (3%)	18 (7%)	1 (1%)
3-Grade Improvement	0 (0%)	0 (0%)	0 (0%)
2-Grade Improvement	4 (1%)	1 (<1%)	1 (1%)
1-Grade Improvement	22 (4%)	7 (3%)	1 (1%)
No Change	445 (88%)	219 (88%)	108 (89%)
1-Grade Worsening	17 (3%)	3 (1%)	8 (7%)
2-Grade Worsening	2 (<1%)	1 (<1%)	2 (2%)

*Number of subjects only includes Phase 3 studies.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, p. 84.

Evaluation of change in pigmentation at Week 2 revealed that there was a higher incidence of 1 or 2 grade worsening in subjects receiving Temovate Ointment (8%, 10/121 subjects) when compared to subjects receiving EF Clobetasol Foam (4%, 19/504 subjects) or Vehicle Foam (2%, 4/249 subjects).

7.1.5 Common Adverse Events

7.15.1 Eliciting adverse events data in the development program

The integrated safety data base consisted of patients from studies CPE.C.201 (HPA axis suppression study, atopic dermatitis), CPE.C.202 (Bioavailability study, psoriasis), CPE.C.301 (safety and efficacy study, 2 arm, atopic dermatitis), and CPE.C.302 (safety and efficacy study, 3 arm, psoriasis).

In the Phase 3 trials, CPE.C.301 and CPE.C.302, the safety of EF Clobetasol Foam was evaluated by assessments of vital signs, adverse events, as well as change from Baseline in the

severity of skin atrophy, telangiectasia, pigmentation changes, and the presence or absence of striae at treatment sites.

More specifically, a complete examination of the skin was performed by the Investigator at each study visit. Treated areas were assessed and scored (same scoring method for both studies) for changes in atrophy, striae, telangiectasia, and pigmentation. Worsening of any of these signs was reported as an adverse event. Vital signs (systolic/diastolic blood pressure and pulse) and temperature were to be measured at the Baseline and the Week 2 visit. The Investigator was to monitor the occurrence of adverse experiences during the course of the study and adverse experiences were recorded from the first application of study medication until the last study visit. Subjects were instructed to report any physical changes or new symptoms they noticed during the course of the study.

In the Phase 2 trial, CPE.C.201, the primary safety evaluation for the study was the cosyntropin stimulation test. Additionally, in this trial and in the other Phase 2 trial CPE.C.202, the investigator was to monitor the occurrence of adverse experiences during the course of the study. All adverse experiences occurring after the first dose of study drug were to be recorded. Subjects were instructed to report any physical changes or new symptoms they noticed during the course of the study.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor classified adverse events by MedDRA System Organ Class (SOC) and Preferred term. The sponsor's categorization of AEs and use of preferred terms appears reasonable. The data listing reference is AE.SAS7BDAT. Analysis of instances of use of the Preferred term "application site reaction" did reveal subcomponents consisting of "application site stinging" and of "application site telangiectasia." Please see section 7.1.5.5 of this review.

7.1.5.3 Incidence of common adverse events

The incidence of all adverse events by MedDRA System Organ Class and Preferred Term is given for the safety population (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302) is given in table 20.

Please see Table 20 next page.

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Table 20: Incidence of Adverse Experiences Classified by MedDRA System Organ Class and Preferred Term, Safety Population (Preferred Terms Omitted if < 1%)

SYSTEM ORGAN CLASS Preferred Term	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total	p-value ^a
Number of Subjects	572	249	137	958	
Subjects with a(n) adverse experience	99 (17%)	41 (16%)	11 (8%)	151 (16%)	0.7681 0.0071
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (< 1%)	0 (0%)	0 (0%)	2 (< 1%)	
CARDIAC DISORDERS	2 (< 1%)	1 (< 1%)	0 (0%)	3 (< 1%)	
EAR AND LABYRINTH DISORDERS	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)	
EYE DISORDERS	2 (< 1%)	1 (< 1%)	0 (0%)	3 (< 1%)	
GASTROINTESTINAL DISORDERS	10 (2%)	1 (< 1%)	1 (1%)	12 (1%)	
Nausea	3 (1%)	0 (0%)	0 (0%)	3 (< 1%)	
Vomiting	3 (1%)	0 (0%)	0 (0%)	3 (< 1%)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					0.3660
	34 (6%)	19 (8%)	2 (1%)	55 (6%)	0.0318
Application site atrophy	11 (2%)	2 (1%)	0 (0%)	13 (1%)	
Application site burning	5 (1%)	3 (1%)	0 (0%)	8 (1%)	
Application site dryness	2 (< 1%)	0 (0%)	0 (0%)	2 (< 1%)	
Application site eczema	0 (0%)	2 (1%)	0 (0%)	2 (< 1%)	
Application site pruritus	1 (< 1%)	7 (3%)	0 (0%)	8 (1%)	
Application site reaction	9 (2%)	5 (2%)	2 (1%)	16 (2%)	
IMMUNE SYSTEM DISORDERS	2 (< 1%)	1 (< 1%)	0 (0%)	3 (< 1%)	
					0.1743
INFECTIONS AND INFESTATIONS	28 (5%)	7 (3%)	3 (2%)	38 (4%)	0.1642
Application site folliculitis	3 (1%)	0 (0%)	0 (0%)	3 (< 1%)	
Nasopharyngitis	2 (< 1%)	1 (< 1%)	1 (1%)	4 (< 1%)	
Tinea versicolour	1 (< 1%)	0 (0%)	1 (1%)	2 (< 1%)	
Upper respiratory tract infection	7 (1%)	1 (< 1%)	1 (1%)	9 (1%)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (2%)	4 (2%)	0 (0%)	15 (2%)	
INVESTIGATIONS	2 (< 1%)	1 (< 1%)	0 (0%)	3 (< 1%)	
METABOLISM AND NUTRITION DISORDERS	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)	

SYSTEM ORGAN CLASS Preferred Term	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total	p-value ^a
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (1%)	4 (2%)	2 (1%)	9 (1%)	
Exostosis	0 (0%)	0 (0%)	2 (1%)	2 (< 1%)	
Intervertebral disc displacement	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)	
Myalgia	0 (0%)	2 (1%)	0 (0%)	2 (< 1%)	
NERVOUS SYSTEM DISORDERS	11 (2%)	2 (1%)	3 (2%)	16 (2%)	
Headache	8 (1%)	2 (1%)	2 (1%)	12 (1%)	
Neuralgia	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)	
PSYCHIATRIC DISORDERS	2 (< 1%)	0 (0%)	0 (0%)	2 (< 1%)	
RENAL AND URINARY DISORDERS	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (< 1%)	2 (1%)	0 (0%)	3 (< 1%)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (1%)	2 (1%)	0 (0%)	10 (1%)	
Pharyngolaryngeal pain	3 (1%)	0 (0%)	0 (0%)	3 (< 1%)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (1%)	3 (1%)	3 (2%)	11 (1%)	
Dermatitis	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)	
Pityriasis rosea	1 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)	
Post inflammatory pigmentation change	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)	
Urticaria generalized	0 (0%)	0 (0%)	1 (1%)	1 (< 1%)	
VASCULAR DISORDERS	1 (< 1%)	2 (1%)	0 (0%)	3 (< 1%)	

^a P-values are based on comparing EF Clobetasol Foam versus Vehicle Foam (top) and Temovate Ointment (bottom), respectively, based on the Chi-Square ($\alpha = 0.10$) and are calculated when incidence is at least five percent in any on treatment group.

Note: Subjects reporting a particular adverse experience more than once are counted only once for that adverse experience. Adverse experiences reported during post treatment follow-up period are included.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, adapted from Table Q, pp. 57-64.

The sponsor compared adverse events based on a two-sided chi-square test ($\alpha=0.10$) when the significance was at least 5% in any one treatment group. As can be seen, the difference in rate of adverse experiences between the EF Clobetasol group (99/572, 17%) and the vehicle group (41/249, 16%) was negligible. However, the EF Clobetasol foam group (99/572, 17%) as compared to the Temovate Ointment® (11/137, 8%) group did show twice the rate of adverse experiences. With these sample sizes this is a notable difference compared with what could be expected by chance. Since this comparison was not prespecified, making conclusions about statistical significance is problematic.

When examined by sub-grouping by System Organ Class, the largest observed difference between EF Clobetasol foam and Temovate® was in General Disorders and Administration Site Conditions. Within this category the three preferred terms exhibiting the principal difference between the EF Clobetasol Foam group and the Temovate Group were application site atrophy (11 or 2% vs. 0), application site burning (5 or 1% vs. 0), and application site reaction (9 or 2% vs. 2 or 1%). This SOC had the highest number of reported adverse experiences, 55/958 or 6% of subjects overall.

The System Organ Class with the next highest number of reported adverse events was the Infections and Infestations SOC with 38/958 or 4% of subjects overall. In this SOC, there were generally no large differences in the incidence of AEs between any of the treatment groups. To be noted, there was a higher incidence of events in the EF-Clobetasol foam subjects, 5% (28/572) compared to subjects receiving Vehicle foam, 3% (7/249) or Temovate Ointment, 2% (3/137). Within this SOC the preferred terms having the greatest number of reported adverse events are upper respiratory tract infection (9/958) and nasopharyngitis (4/958). These were generally not considered to be treatment related. If these preferred terms are excluded, the incidence of events in the EF Clobetasol foam subjects becomes 3% (19/572), more comparable to Vehicle foam 2% (5/249) and Temovate Ointment 1% (1/137).

Events considered, by investigators, related to treatment are listed in table 21.

Table 21: Incidence of Treatment-Related Adverse Experiences Classified by MedDRA System Organ Class and Preferred Term, Safety Population

SYSTEM ORGAN CLASS Preferred Term	EF-Clobetasol Foam	Vehicle. Foam	Temovate Ointment	Total
Number of Subjects	572	249	137	958
Subjects with a Treatment-Related adverse experience	42 (7%)	22 (9%)	3 (2%)	67 (7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (6%)	19 (8%)	2 (1%)	53 (6%)
Application site atrophy	11 (2%)	2 (1%)	0 (0%)	13 (1%)
Application site burning	5 (1%)	3 (1%)	0 (0%)	8 (1%)
Application site dermatitis	1 (< 1%)	1 (< 1%)	0 (0%)	2 (0%)
Application site dryness	2 (< 1%)	0 (0%)	0 (0%)	2 (<1%)
Application site eczema	0 (0%)	2 (1%)	0 (0%)	2 (<1%)
Application site erythema	0 (0%)	1 (< 1%)	0 (0%)	1 (<1%)
Application site hypersensitivity	1 (< 1%)	0 (0%)	0 (0%)	1 (<1%)
Application site pain	1 (< 1%)	0 (0%)	0 (0%)	1 (<1%)
Application site pigmentation changes	2 (< 1%)	0 (0%)	0 (0%)	2 (<1%)
Application site pruritus	1 (< 1%)	7 (3%)	0 (0%)	8 (1%)

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Application site reaction	9 (2%)	5 (2%)	2 (1%)	16 (2%)
Application site urticaria	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
IMMUNE SYSTEM DISORDERS	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Hypersensitivity	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
INFECTIONS AND INFESTATIONS	7 (1%)	1 (<1%)	0 (0%)	8 (1%)
Application site folliculitis	3 (1%)	0 (0%)	0 (0%)	3 (<1%)
Application site infection	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Folliculitis	2 (<1%)	0 (0%)	0 (0%)	2 (<1%)
Rhinitis	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Upper respiratory tract infection	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
NERVOUS SYSTEM DISORDERS	2 (<1%)	0 (0%)	0 (0%)	2 (<1%)
Headache	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Paraesthesia	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Wheezing	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1%)	1 (0%)	1 (1%)	5 (1%)
Dermatitis atopic	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Pityriasis rosea	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Post inflammatory pigmentation change	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Skin burning sensation	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Telangiectasia	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)

Note: Subjects reporting a particular adverse experience more than once are counted only once for that adverse experience. Adverse experiences reported during post treatment follow-up period are included. Treatment related experiences are defined as definitely, probably, or possibly related to the study drug.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, adapted from Table H on pp. 20-21.

Treatment related adverse events were reported in seven percent (67/958) of subjects in the safety population. Treatment related adverse events were reported in 7% (42/572) of subjects receiving EF Clobetasol Foam, 9% (22/249) of subjects receiving Vehicle Foam, and 2% (3/137) of the subjects receiving Temovate Ointment.

7.1.5.4 Common adverse event tables

Table 22 summarizes adverse events that occurred at a rate of 1% or greater of subjects in at least one group (safety population; CPE.C.201, CPE.C.202, CPE.C.301, and CPE.C.302).

Table 22: Incidence of AEs Occurring in $\geq 1\%$ of subjects (active and vehicle arms) in the safety population

Preferred Term	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	572	249	137
Subjects with an adverse experience	99 (17%)	41 (16%)	11 (8%)
Application site reaction	9 (2%)	5 (2%)	2 (1%)
Application site atrophy	11 (2%)	2 (1%)	0 (0%)
Headache	8 (1%)	2 (1%)	2 (1%)
Upper respiratory tract infection	7 (1%)	1 (< 1%)	1 (1%)
Application site burning	5 (1%)	3 (1%)	0 (0%)
Application site pruritus	1 (< 1%)	7 (3%)	0 (0%)
Nasopharyngitis	2 (< 1%)	1 (< 1%)	1 (1%)
Application site folliculitis	3 (1%)	0 (0%)	0 (0%)
Nausea	3 (1%)	0 (0%)	0 (0%)
Pharyngolaryngeal pain	3 (1%)	0 (0%)	0 (0%)
Vomiting	3 (1%)	0 (0%)	0 (0%)
Application site eczema	0 (0%)	2 (1%)	0 (0%)
Asthma	0 (0%)	2 (1%)	0 (0%)
Hypertension	0 (0%)	2 (1%)	0 (0%)
Myalgia	0 (0%)	2 (1%)	0 (0%)

Source: Sponsor's NDA submission, Module 2, Summary of Clinical Safety, adapted from Table S on p. 73.

7.1.5.5 Identifying common and drug-related adverse events

The most common adverse event across study arms was "application site reaction" occurring in 1.6% (9/572) of patients on study drug as compared with 2.8% (5/249) of patients on vehicle foam and 1.5% (2/137) of patients on Temovate ointment. When the adverse event descriptions coded as "application site reaction" are examined study by study, application site stinging is noted more frequently in study 301 than 302. In study 301, application site stinging is noted in 3/251 (1.2%) on EF Clobetasol foam and 2/126 (1.6%) on Vehicle foam.

Table 23: Adverse Event Descriptions Study 301 Coded as Application Site Reaction

Subject	"Reaction"	Study Drug	Related	Age
102-1053	Stinging (10 min. post application)	EF Clobetasol Foam	Definite	23
102-1066	Application site reaction	EF Clobetasol Foam	Definite	12
117-1829	Stinging after study drug application for 30 min.	Vehicle Foam	Probable	27
117-1830	Stinging on neck area after study drug application < 1 min. (Severe)	EF Clobetasol Foam	Probable	15
117-1833	Stinging on areas of study med application	EF Clobetasol Foam	Probable	13
117-1834	Mild stinging on areas of study medication application	Vehicle Foam	Probable	28
118-1881	Striae at study drug application site	EF Clobetasol foam	Possible	33

Table 24: Adverse Event Descriptions Study 302 Coded as Application Site Reaction

Subject	"Reaction"	Study Drug	Related	Age
212-3575	Stinging of psoriasis after study drug application lasting about 10 min	Vehicle Foam	Probably	52
213-3630	Telangiectasia=application site=target lesion location	EF Clobetasol Foam	Possible	79
213-3656	Telangiectasia(Target lesion location)	Vehicle Foam	Possible	60
214-3683	Telangiectasia-application site	Temovate Ointment	Possible	46
214-3685	Telangiectasia-application site	Vehicle Foam	Probable	34
214-3692	Telangiectasia-application site	EF Clobetasol Foam	Possible	39
214-3706	Telangiectasia-application site	Temovate ointment	Possible	56
215-3743	Telangiectasia-in study drug application site	EF Clobetasol foam	Possible	40
216-3788	Telangiectasia-application site	EF-Clobetasol foam	Possible	54

Source (for Tables 23&24): Sponsor's NDA submission, Data Listings, AE.SAS7BDAT and KEYVAR.

Examining study 302, of nine instances of the adverse reaction coded as "application site reaction", eight of the descriptions are of telangiectasia. These are evenly distributed across study arms, 4/253 (1.6%) EF Clobetasol foam, 2/123 (1.6%) Vehicle foam, and 2/121 (1.6%) Temovate® Ointment.

It appears likely that the episodes of stinging reported in study 301 are related to components of study drug vehicle. Note also the occurrence of an instance of stinging of psoriasis after Vehicle foam application in study 302. The telangiectasia reported in study 302 does not appear to be related to the study drug or its vehicle.

Likely Drug Related

The second most common adverse across study arms was application site atrophy which occurred in 1.9% of (11/572) subjects on study drug as compared with .08% (2/249) on vehicle foam and 0% on Temovate ointment. This very likely is drug related. The fourth most common adverse event was application site burning which occurred in .08% (5/572) subjects on study drug as compared with 1.2% (3/249) on vehicle foam and 0% on Temovate ointment. This may be related to components of the foam. Also tied for fourth most common adverse event was

application site pruritus, occurring in .02% (1/572) of subjects on study drug, 2.8% (7/249) of subjects on vehicle foam, and 0% of those on Temovate ointment. This appears to be related to elements of the vehicle foam.

Likely not Drug Related

The third most common adverse events was upper respiratory tract infection, occurring in 1% (7/572) of patients on study drug, < 1% (1/249) patients on vehicle foam, and 1% (1/137) of patients on Temovate ointment. This most likely is a random event.

7.1.5.6 Additional analyses and explorations

Data for additional analyses was not submitted.

7.1.6 Less Common Adverse Events

There were no adverse events that could be classified as rare events of significant concern.

7.7.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Phase 2

Clinical laboratory monitoring was performed in study CPE.C.201 and consisted of testing serum cortisol levels to evaluate the effect of EF Clobetasol Foam on the HPA axis and testing glucose levels to evaluate for steroid induced diabetes. Clinically meaningful changes in serum glucose levels were not seen in study subjects. Urine pregnancy tests were performed on all subjects of child bearing potential prior to each cosyntropin stimulation test. The results of these tests were all negative.

Levels of clobetasol propionate were measured in study CPE.C.202, a comparative bioavailability study. EF Clobetasol Foam had a mean C_{max} of 59.0 pg/mL after twice daily application. After application of Temovate Ointment, clobetasol propionate plasma concentrations were higher but more variable having a mean C_{max} of 188.1 pg/mL. Urine pregnancy tests were given to subjects of child-bearing potential on Day 1 and on Day 15. The results of these tests were all negative.

Phase 3

In studies CPE.C.301 and CPE.C.302, subjects of childbearing potential were given urine pregnancy tests at Baseline and at Week 2. The results of these tests were all negative in both studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory assessments were not performed that can be used for drug-control comparisons.

7.1.7.3 Standard analyses and explorations of laboratory data

None were performed. Except for urine pregnancy testing, laboratory testing was not performed as part of the Phase 3 development program.

7.1.7.4 Additional analyses and explorations

None were performed.

7.1.7.5 Special assessments

No special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs consisting of systolic and diastolic blood pressure and pulse as well as temperature were measured at Baseline and Week 2 visits for studies CPE.C.201, CPE.C.301, and CPE.C.302. In general, no clinically significant differences in the vital sign measurements between any of the treatment groups were reported for any of these studies.

Vital signs were not performed in studies DES.C.103 (repeat insult patch test study) or DES.C.104 (cumulative irritation study). Vital signs were obtained only at baseline for study CPE.C.202 (bioavailability).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

In study CPE.C.201 (HPA axis suppression study) vital signs were performed at screening, baseline, week 2 (end of treatment) and conditional visits. Since all subjects in this study were applying EF Clobetasol Foam, no control group for comparison of effect on vital signs is available.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 25: Mean Blood Pressure and Vital Signs Study CPE.C.301

	EF Clobetasol Foam		Vehicle Foam	
	Baseline	Week 2/End of Treatment	Baseline	Week 2/End of Treatment
Systolic Blood Pressure (mmHg)				
N	248	245	124	121
Mean (std)	120.3 (15.5)	119.9 (15.6)	122.1 (17.4)	121.0 (14.4)
Diastolic Blood Pressure (mmHg)				
N	248	245	124	121
Mean (std)	74.9 (10.2)	73.5 (10.0)	76.0 (11.5)	74.3 (9.8)
Pulse (bpm)				
N	248	245	124	121
Mean (std)	75.1 (10.7)	75.1 (11.0)	75.0 (10.7)	75.9 (11.2)
Temp (°C)	N = 248	N = 245	N = 124	N = 119
Mean (std)	36.6 (0.4)	36.6 (0.4)	36.6 (0.4)	36.7 (0.4)

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, adapted from Tables 63, 64, 65, and 66, pp.113-115.

In Study CPE.C.301, there were no clinically significant differences between treatment arms or changes from baseline to end of treatment.

Table 26: Mean Blood Pressure and Vital Signs Study CPE.C.302

	EF Clobetasol Foam		Vehicle Foam	
	Baseline	Week 2/End of Treatment	Baseline	Week 2/End of Treatment
Systolic Blood Pressure (mmHg)				
N	253	251	123	120
Mean (std)	125.4 (13.5)	124.5 (13.3)	127.4 (15.0)	126.6 (15.6)
Diastolic Blood Pressure (mmHg)				
N	253	251	123	120
Mean (std)	74.9 (10.2)	73.5 (10.0)	77.5 (10.0)	76.3 (9.4)
Pulse (bpm)				
N	253	251	123	120
Mean (std)	73.3 (9.1)	73.5 (8.1)	72.1 (9.3)	72.8 (8.8)
Temp (°C)	N = 253	N = 251	N = 123	N = 120
Mean (std)	36.6 (0.4)	36.6 (0.4)	36.6 (0.4)	36.6 (0.4)

Source: Sponsor's NDA submission, module 5, Final study Report CPE.C.302, adapted from Tables 60, 61, 62, and 63, pp. 111-113.

In Study CPE.C.302, there were no clinically significant differences between treatment arms or changes from baseline to end of treatment.

7.1.8.4 Additional analyses and explorations

None were performed

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were not performed during any of the studies of EF Clobetasol Foam. According to the pharmacology/toxicology review, the literature and previous clinical experience with Temovate® Ointment and Olux® Foam suggest that there are no safety pharmacology concerns associated with clobetasol propionate.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable because ECGs were not performed.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable because ECGs were not performed.

7.1.9.4 Additional analyses and explorations

Not applicable because ECGs were not performed.

7.1.10 Immunogenicity

This is not applicable since the drug is not a therapeutic protein. Please see section 7.1.12, "Special Safety Studies" for topical dermal studies performed.

7.1.11 Human Carcinogenicity

No malignancies were reported during any of the clinical studies performed for this NDA. One 44 year old female subject (218-3885) in study CPE.C.302, and randomized to EF Clobetasol foam, was reported to have a precancerous lesion from a breast biopsy. This was considered probably not related to study medication.

7.1.12 Special Safety Studies

Special safety studies were performed in this NDA. These included two Phase 1 dermal safety studies and a Phase 2 HPA Axis suppression study.

Phase 1 Dermal Safety Studies

Study DES.C.103: "A Repeat Insult Patch Test Study to Determine the Potential of Desonide Foam, 0.05%, Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam to Induce Allergic Contact Sensitization"

Study DES.C.104: "A Cumulative Irritation Study of Desonide Foam, 0.05%, Desonide Vehicle Foam, and Ethanol Free Clobetasol Propionate Vehicle Foam"

In both studies, DES.C.103 & 104, EF Clobetasol Vehicle foam was found to be somewhat irritating but not as irritating as the positive control, sodium laurel sulfate, 0.1%. In study DES.C.103, one subject out of 206 who completed challenge phase of the trial showed possible sensitization to EF Clobetasol vehicle. Wider use of the EF Clobetasol Foam product in the post-marketing phase may result in rare occurrences of true allergic contact dermatitis from the known sensitizing substances in the formulation. For review of the individual study reports please see Appendices, section 10.1.3.

Phase 2 HPA Suppression Study, CPE.C.201: An Open-Label Study to Evaluate the Safety of Ethanol Free Clobetasol Propionate Foam, 0.05%, including its effect on the Hypothalamic Pituitary Adrenal (HPA) Axis"

Systemic safety was evaluated with the Phase 2 study, CPE.C.201, wherein the potential for HPA axis suppression was studied in 52 pediatric and adult patients with mild to moderate atopic dermatitis. A significant number of patients, 7 out of 15 (47%), in the youngest cohort, ages 6 to 11, showed suppression. No younger cohorts were studied since the prespecified proportion of subjects (20%) showing suppression in cohort 3 was exceeded. The proportion of subjects 12 years of age and older demonstrating HPA axis suppression was 16.2% (6 out of 37). The laboratory suppression reversed in all subjects, returning to normal by 4 weeks after last treatment. For review of the individual study report please see Appendices, section 10.1.4.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal and rebound were not listed among the adverse events reported in the EF Clobetasol Foam studies, CPE.C.201, CPE.C.202, CPE.C.301, and CPE.C.302. In study CPE.C.301, three cases of worsening of atopic dermatitis at study drug application site were noted, however all had received foam vehicle.

7.1.14 Human Reproduction and Pregnancy Data

For the studies included in the integrated safety database; CPE.C.201 & 202, CPE.C. 301 & 302, all pregnancy results were negative. For study DES.C.103, one subject had a positive end of study urine pregnancy test. Despite efforts to contact the subject regarding the pregnancy, no follow-up information was received.

In study CPE.C.101 (skin blanching study), urine pregnancy tests were performed on all female subjects of childbearing potential prior to study drug application. All test results were negative. In study DES.C.104 (cumulative irritation study), urine pregnancy tests were administered to all female subjects of child bearing potential on Day 1 and Day 22. All pregnancy test results were negative.

7.1.15 Assessment of Effect on Growth

There were no formal analyses of the effect of EF Clobetasol Foam on growth.

7.1.16 Overdose Experience

There were no formal analyses of overuse experience with this topical drug product.

7.1.17 Post-marketing Experience

The drug product, EF Clobetasol Foam, has not been marketed in any country at the time of writing this review. (mod. 2, p. 50.)

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1.1 Study type and design/patient enumeration

The clinical development program for EF Clobetasol Foam included seven clinical studies. Bioavailability studies included CPE.C.101 (skin blanching-relative potency) and CPE.C.201 (HPA axis effect-open label safety). Tolerability studies included DES.C.103 (repeat insult patch test-allergic contact sensitization) and DES.C.104 (cumulative irritation). Comparative bioavailability against reference listed drug (Temovate® Ointment, 0.05%) was studied in CPE.C.202. Safety and efficacy were studied in the phase 3 trials, CPE.C.301 (superiority to vehicle) and CPE.C.302 (superiority to vehicle and bridge to reference listed drug). All of these studies were conducted in the United States.

Table 27: Phase I Studies

Study Identifier Type of Study	Objective(s) of the Study	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CPE.C.101 Vasoconstriction Phase 1	Compare the relative vasoconstrictor potency of EF Clobetasol Foam, 0.05% to: 1) Vehicle Foam 2) Temovate-E Cream, 0.05% 3) Cutivate Ointment 0.005%	EF Clobetasol Foam, Vehicle Foam Temovate-E Cream, and Cutivate Ointment; 10 mg; applied topically to 1 cm ² on forearm	36	Healthy Subjects	Single dose, 16 hr duration
DES.C.103 Skin Sensitization (RIPT) Phase 1	Determine the allergic contact sensitization potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and EF Clobetasol Vehicle Foam	Desonide Foam, Desonide Vehicle Foam, EF Clobetasol Vehicle Foam; sodium lauryl sulfate, 0.1% (positive control), and distilled water (negative control).	240	Healthy Subjects	Three times a week for 3 weeks then one challenge dose. Re-challenge if needed.
DES.C.104 Skin Irritation Phase 1	Evaluate the cutaneous irritation potential of Desonide Foam, 0.05% (Desonide Foam), Desonide Vehicle Foam, and EF Clobetasol Vehicle Foam	Desonide Foam, Desonide Vehicle Foam, EF Clobetasol Propionate Vehicle Foam; sodium lauryl sulfate, 0.1% (positive control), and distilled water (negative control)	40	Healthy volunteers	Daily for 3 weeks

Source: Sponsor's NDA submission, Module 2, adapted from section 2.7.6, pp. 2, 3.

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Table 28: Clinical Safety Studies of EF Clobetasol Foam Included in the Clinical Summary of Safety

Study ID	Clinical Study Title	Total Subjects by Treatment Arm	Treatment Duration	Safety Parameters
CPE.C.201	An Open-Label Study to Evaluate the Safety of Ethanol Free Clobetasol Propionate Foam, 0.05%, including its effect on the Hypothalamic Pituitary Adrenal (HPA) Axis	EF Clobetasol Foam: 52	14 days	Effect on HPA axis as determined by response to cosyntropin stimulation tests. Measurement of serum glucose levels. Vital signs, other reported adverse experiences
CPE.C.202	A Randomized, Open-Label Study to Assess the Bioavailability of Ethanol Free Clobetasol Propionate Foam, 0.05%, and Temovate® Ointment, 0.05%, in Patients with Mild to Moderate Plaque-Type Psoriasis	EF Clobetasol Foam: 16 Temovate Ointment: 16	14 days	Adverse experiences, vital signs, investigator clinical assessments of the signs of cutaneous atrophy, striae, telangiectasia, and pigmentation changes at the application site
CPE.C.301	Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Ethanol-Free Clobetasol Propionate Foam, 0.05% in the Treatment of Moderate to Severe Atopic Dermatitis	EF Clobetasol Foam: 251 Vehicle Foam: 126	14 days	Adverse experiences, vital signs, investigator clinical assessments of the signs of cutaneous atrophy, striae, telangiectasia, and pigmentation changes at the application site
CPE.C.302	A Multicenter, Randomized, Double-Blinded Study of the Safety and Efficacy of Ethanol-Free Clobetasol Propionate Foam, 0.05%, versus Vehicle Foam and Temovate® (clobetasol propionate) Ointment, 0.05%, (Investigator-Blinded) in the Treatment of Mild to Moderate Plaque-Type Psoriasis	EF Clobetasol Foam: 253 Vehicle Foam: 123 Temovate Ointment: 121	14 days	Adverse experiences, vital signs, investigator clinical assessments of the signs of cutaneous atrophy, striae, telangiectasia, and pigmentation changes at the application site

Source: Sponsor's NDA submission, module 2, section 2.7.4, p. 56.

The safety database as designated by the sponsor does not include the Phase I studies. These would appear to be less critical for the safety database since the amount of drug used is minimal, use is in healthy volunteers (not patients with diseased skin), and use is under occlusion for the skin sensitization and irritation studies (DES.C.103&104).

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7.2.1.2 Demographics

**Table 29: Demographics of Summary of Clinical Safety Population
 (CPE.C.201, 202, 301, 302)**

		EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total
Number of Subjects		572	249	137	958
Age					
n		569	246	137	952
mean (std)		39.2 (18.6)	43.6 (18.8)	47.1 (13.8)	41.5 (18.3)
median		40.0	44.5	46.0	42.5
min, max		(6.0,83.0)	(12.0,89.0)	(19.0,81.0)	(6.0,89.0)
Age Category					
Missing		3 (1%)	3 (1%)	0 (0%)	6 (1%)
6 < 12 Years		15 (3%)	0 (0%)	0 (0%)	15 (2%)
12 < 18 Years		92 (16%)	33 (13%)	0 (0%)	125 (13%)
18 < 65 Years		404 (71%)	174 (70%)	123 (90%)	701 (73%)
≥ 65 Years		58 (10%)	39 (16%)	14 (10%)	111 (12%)
Gender					
Missing		3 (1%)	2 (1%)	0 (0%)	5 (1%)
Male		240 (42%)	124 (50%)	84 (61%)	448 (47%)
Female		329 (58%)	123 (49%)	53 (39%)	505 (53%)
Race	US Population³				
Missing*		3 (1%)	2 (1%)	0 (0%)	5 (1%)
Caucasian	75.1%	417 (73%)	185 (74%)	120 (88%)	722 (75%)
African-American	12.3%	82 (14%)	31 (12%)	3 (2%)	116 (12%)
Hispanic	12.5%†	39 (7%)	20 (8%)	10 (7%)	69 (7%)
Other		31 (5%)	11 (4%)	4 (3%)	46 (5%)

† In the Census 2000, "Hispanic or Latino" was employed as a category for ethnicity. In the safety summary, "Hispanic" is a category for race.

* Data missing due to effects of Hurricane Katrina.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, p. 15.

The Summary of Clinical Safety included 958 subjects who had received at least one dose of study drug in studies CPE.C.201 & 202 and CPE.C.301 & 302. Subjects were randomized as follows; 527 to EF Clobetasol Foam, 249 to Vehicle Foam, and 137 to Temovate Ointment.

³ Overview of Race and Hispanic Origin, U.S. Census Bureau, Census 2000 Brief, March 2001, p. 3.

The mean age of the Summary of Clinical Safety population was 41.5 (± 18.3) years. The mean age among those receiving Temovate Ointment was higher, 47.1 (± 13.8) years, due to the fact that no patients under age 18 received this treatment. The mean age of those receiving EF Clobetasol Foam was slightly lower, 39.2 (± 18.6), because the HPA axis study, being the only study to enroll subjects less than 12 years of age, did not include treatment with Vehicle Foam or Temovate Ointment.

The overall gender balance was fairly even at 47% (448/958) male and 53% (505/958) female. However, a larger proportion of males than females received Temovate Ointment (61% vs. 39%). For EF Clobetasol Foam the proportion was 42% vs. 58% and for Vehicle Foam 50% vs. 49%.

In general the Summary of Clinical Safety population follows the distribution of the U.S. population, with mild under representation of those of Hispanic origin. A higher proportion of African-Americans received EF Clobetasol Foam (14%) and Vehicle Foam (12%) as compared with Temovate Ointment (2%).

7.2.1.3 Extent of exposure (dose/duration)

Table 30: Study Drug Exposure – Safety Population (CPE.C.201 & 202, CPE.C 301 & 302)

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment
Number of Subjects	572	249	137
Days on Study Drug			
N	569	245	136
mean (std)	14.8 (2.4)	14.4 (2.6)	14.7 (1.3)
median	15.0	15.0	14.0
min, max	(1,36)	(1,22)	(12,21)
Study Drug Usage(g)			
N	561	240	132
mean (std)	68.13 (42.37)	65.54 (42.08)	34.69 (28.37)
median	60.40	54.35	23.65
min, max	(1.6,260.5)	(4.5,200.6)	(1.6,102.4)
Daily Mean Drug Usage(g)	N = 561	N = 240	N = 132
mean (std)	4.65 (2.98)	4.59 (3.19)	2.38 (1.94)
median	4.10	3.80	1.65
min, max	(0.1,18.6)	(0.3,28.7)	(0.1,7.9)

Note: Study drug usage is defined as total container weight dispensed minus total container weight returned. Mean drug usage is defined as the average amount of drug subjects use per study day.

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, p.12.

A total of 572 subjects received at least one dose of EF Clobetasol Foam in the studies comprising the Clinical Summary of Safety. In these studies, the frequency and duration of treatment was twice daily for 2 weeks. It should be noted that the total study drug used and the mean daily dose of study drug was similar for the EF Clobetasol Foam group and the Vehicle Foam group. Subjects using these products applied approximately two times as much study drug as those using Temovate Ointment.

Within study CPE.C.302(psoriasis), having EF Clobetasol Foam, Vehicle Foam, and Temovate Ointment arms, subjects also used about twice as much of the foam products daily as the Temovate Ointment (Final Study Report CPE.C.302, p. 97). The baseline ISGA, % Body Surface Area, erythema, scaling, and plaque thickness were reported as well balanced among the three treatment arms in this study (Final Study Report CPE.C.302, pp. 48-50). One may speculate that, despite receiving similar instructions relating to study drug application (twice daily, the amount of study drug necessary to cover all lesions excluding face, scalp, and intertriginous areas and not to exceed 50g per week), study subjects may have found the foam formulation easier to apply than the ointment formulation.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no secondary clinical data sources used to evaluate safety. All safety evaluations came from the clinical trials submitted to support the approval of the NDA.

7.2.2.2 Post-marketing experience

This drug product has not been approved in any other jurisdiction.

7.2.2.3 Literature

The sponsor has conducted a review of the literature focusing on clobetasol propionate .05% in randomized clinical trials and on the role of this substance in creating adrenal suppression and skin atrophy.

The sponsor has submitted articles with summaries addressing topical clobetasol propionate 0.05%, various formulations, in randomized trials in patients (adults, adolescent, and pediatric) with psoriasis (scalp and non-scalp), eczema/atopic dermatitis, as well as oral lichen planus, bullous pemphigoid and vitiligo.

The sponsor has submitted articles with summaries reporting results of trials assessing adrenal function after use of clobetasol propionate 0.05% (mainly ointment and cream) in various treatment regimens. Also summarized are representative reports describing the effects of overuse of clobetasol propionate, mainly ointment, in adult and pediatric patients.

Summaries are provided of articles relating to clobetasol propionate, various formulations, and production of skin atrophy in healthy volunteers. Articles addressing other side effects (such as contact dermatitis to clobetasol propionate, osteonecrosis of the femoral head, and secondary development of infections) are also summarized with references provided.

The sponsor has provided a summary of a review of the literature regarding the prevalence of atopic dermatitis. References and articles are included.

Comparative safety for atopic dermatitis:

Connetics states that the FDA requested that it (the sponsor) address the comparative safety of EF Clobetasol foam in atopic dermatitis. The sponsor states that no comparative data (relative to Temovate Ointment) was requested or generated in the EF Clobetasol Foam studies for this NDA. In order to address the FDA's request, the sponsor states that they must rely on publicly available literature and on data produced in the EF Clobetasol Foam studies.

The use of data from the EF Clobetasol Foam studies is summarized by the statements that follow. There were no meaningful differences in the incidence or types of AEs observed between subjects with atopic dermatitis and those with psoriasis. The incidence of AEs in psoriasis subjects receiving Temovate Ointment was low. It is expected that the incidence of AEs among atopic dermatitis subjects treated with Temovate Ointment would be low. Therefore the safety profile of EF Clobetasol Foam compared with that of Temovate Ointment in subjects with atopic dermatitis would be expected to be similar to that seen in subjects with psoriasis. In support of the latter statement, the sponsor cites an article by Datz and Yawalkar⁴ reporting on a double-blind trial in 127 patients with localized, chronic, severe atopic dermatitis or lichen simplex chronicus. Treatments included either .05% halobetasol ointment or .05% clobetasol propionate ointment applied up to twice daily for up to 21 days. One subject receiving clobetasol propionate reported skin irritation while subjects receiving halobetasol propionate reported pruritus, numbness and telangiectasia. The sponsor also cites the Medical officer's review of Temovate Ointment (NDA 19-323) as well as current product labeling; the latter indicating that the most frequent adverse events reported were burning sensation, irritation, and itching in 0.5% of treated patients.

In the December 14, 2005 Pre-NDA meeting, the sponsor was asked to address the comparative safety of their product in atopic dermatitis. Since a three-arm atopic dermatitis trial was not requested, the argument that is made is by inference and use of public literature.

⁴Datz B and Yawalkar S. A double-blind, multicenter trial of 0.05% halobetasol propionate ointment and 0.05% clobetasol 17-proionate ointment in the treatment of patients with chronic localized atopic dermatitis or lichen simplex chronicus. J. Am Acad of Dermatology 1991;25(6 Part 2): 1157-60.

7.2.3 Adequacy of Overall Clinical Experience

In the Phase 2 and 3 trials, a total of 572 subjects were exposed to EF Clobetasol Foam 0.05% for a mean of 14.8 days. This included 303 subjects with atopic dermatitis and 269 with psoriasis. The median age was 40 years.

In reference to atopic dermatitis, the sponsor has provided an acceptable review of the literature that indicates that the prevalence of atopic dermatitis in children in all children could range between .6% and 20%. The sponsor also employed the Verispan Physician Drug & Diagnosis Audit database to show that 12 to 17 year olds with moderate to severe atopic dermatitis represent 17.9% of all patients over 12 years with any atopic dermatitis. The study CPE.C.301 enrolled a total of 101 (27%) of subjects 12 to 17 years of age (69 or 27% randomized to EF Clobetasol Foam and 32 or 25% to Vehicle Foam). In the combined safety population (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302) a total of 92 (16%) of the subjects aged 12 to 17 years were treated with EF Clobetasol Foam. An adequate number of pediatric subjects was included in these trials to obtain useful efficacy and safety information. Please also see section 10.1.1 for review of protocol of pivotal trial in subjects with atopic dermatitis.

The racial composition of the trials roughly approximates that of the US population, with mild under representation of those of Hispanic origin.

The dose, twice daily for two weeks and not to exceed 50 g/week was determined by that of the reference listed drug, Temovate® Ointment 0.05%. Since the study drug was supplied in 100 gram cans, the dose as studied was 100 grams/ two weeks. Duration of the pivotal trials, two weeks, was also based on the reference listed drug and is standard for super-high potency steroid trials. For long term safety (ICH-E1A), the sponsor is relying on the Agency's findings for the reference listed drug.

The design of the pivotal trials, with both study drug and study drug vehicle arms and one trial having a third arm to establish a clinical bridge to the RLD, is acceptable to assess safety and efficacy.

The exclusion of subjects under age 12 in the pivotal trials is reasonable based on the findings of high rates of HPA axis suppression in that age group.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

To establish safety, the sponsor is relying on the Agency's previous findings of nonclinical safety for Temovate Ointment, NDA 19-323, and supporting literature. The sponsor also conducted eight nonclinical studies to support the current application. These appear adequate; however, the sponsor has committed to perform a dermal carcinogenicity and a photo-carcinogenicity study as post-marketing commitments.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing, consisting of urine pregnancy screening, was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Biopharmaceutics review. The Sponsor did not perform metabolic, clearance or interaction workup for this 505(b)(2) application and is relying on the Agency's finding for the reference listed product, Temovate Ointment.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor has performed an adequate repeat insult patch test to assess for cutaneous irritancy and allergenicity. An additional cumulative irritation study was performed to assess for cutaneous irritancy. These are standard for topical medications.

The sponsor has requested a waiver for clinical photo-safety studies (phototoxicity and photoallergenicity). The amount of absorption detected in the drug product and drug substance (respectively 0.085 and 0.003 AU) at 290 nm wavelength is minimal.

The sponsor conducted an HPA axis suppression study that revealed a high level of suppression in the cohort ages 6 to 12. Because of this, patients younger than age 12 were not included in the pivotal trials.

In the pivotal trials, treated areas were assessed and scored for changes in atrophy, striae, telangiectasia, and pigmentation.

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety were of an acceptable quality and were acceptably complete.

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update, received by the Agency July 17, 2006, included no new safety information. The sponsor stated that they have not conducted any additional nonclinical or clinical studies with EF Clobetasol Foam other than those reported in the NDA.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events for EF Clobetasol Foam were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Those adverse events considered to be drug related in the safety summary population follow generally in decreasing order of frequency:

- 1) Application site reaction occurred in 1.6% of subjects (9/572) on study drug as compared with 2% (5/249) on vehicle foam and 1.5% (2/137) on Temovate ointment. See section 7.1.5.5.
- 2) Application site atrophy occurred in 1.9% of subjects (11/572) on study drug as compared with .08% (2/249) on vehicle foam and 0% on Temovate ointment. See section 7.1.5.5.
- 3) Application site burning occurred in .08% of subjects (5/572) on study drug as compared with 1.2% (3/249) on vehicle foam and 0% on Temovate ointment. See section 7.1.5.5.
- 4) Application site pruritus occurred in .02% of subjects (1/572) on study drug as compared with 2.8% (7/249) on vehicle foam and 0% of those on Temovate ointment. This appears to be related to the vehicle foam. See section 7.1.5.5.
- 5) Application site folliculitis occurred in .05% of subjects (3/572) on study drug as compared with 0% on Vehicle foam and 0% on Temovate Ointment. See section 7.1.5.3.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Adverse event data from the phase 2 and 3 studies (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302) were pooled together. Test product, dose, mode of administration, and duration of treatment were similar for the four studies. Studies CPE.C.201 and 301 involved subjects with atopic dermatitis. Studies CPE.C.202 and 302 involved subjects with psoriasis. Study CPE.C.201 was open label and had only one treatment arm, EF Clobetasol Foam. Study CPE.202 was open label; however, it was randomized, having two treatment arms EF Clobetasol Foam and Temovate® Ointment. Studies CPE.C.301 and 302 were multicenter, randomized, double-blind, and vehicle controlled. Study CPE.C.302 also had a third treatment arm, Temovate® Ointment.

7.4.1.2 Combining data

The data from the phase 2 and 3 studies (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302) were pooled together without weighting.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable as only one dose (EF Clobetasol Foam 0.05%) was evaluated for this application.

7.4.2.2 Explorations for time dependency for adverse findings

In the EF Clobetasol Foam group, a subject dropped out due to urticaria that was probably drug related. The timing of this AE is consistent with a relation to study drug use.

In the Vehicle Foam group, two subjects dropped out due to the AEs of "allergic reaction to study drug" and "irritant contact dermatitis". The timing of these AEs is consistent with a relation to study drug. An additional two subjects dropped out due to "moderate itching" and "generalized increased pruritus". Again the timing of these AEs is consistent with a relation to study drug.

7.4.2.3 Explorations for drug-demographic interactions

The sponsor did perform sub-group analysis by gender, age and race.

On the basis of gender there were no significant differences in the incidence and type of AEs as compared with the overall population. Between male and female subjects there were some differences in the types of AEs. Of note, events of application site pruritus were reported only in females. Also the majority of the events of application site reaction were reported in females.

In reference to age, the incidence of AEs was analyzed by four age groups: ages 6 to < 12 years; ages 12 to < 18 years; ages 18 to < 65 years; and ages \geq 65 years. Please see Table 31.

Table 31: Adverse Events by Age Group

	EF Clobetasol Foam	Vehicle Foam	Temovate Ointment	Total	Adverse Events
Number of Subjects	572	249	137	958	16% (151/958)
Age Category					
Missing	3 (1%)	3 (1%)	0 (0%)	6 (1%)	
6 < 12 Years	15 (3%)	0 (0%)	0 (0%)	15 (2%)	20% (3/15)
12 < 18 Years	92 (16%)	33 (13%)	0 (0%)	125 (13%)	18% (22/125)
18 < 65 Years	404 (71%)	174 (70%)	123 (90%)	701 (73%)	16% (110/701)
\geq 65 Years	58 (10%)	39 (16%)	14 (10%)	111 (12%)	14% (16/111)

Source: Sponsor's NDA submission, module 2, Summary of Clinical Safety, pp. 15, 36.

In general, the overall incidence of adverse events is similar across age groups. In the group 6 to < 12 years of age, three subjects experienced adverse events, three upper respiratory tract infections and one event of vomiting. Due to the small number of subjects in this group, it is difficult to draw conclusions about safety.

In subjects 12 < 18 years there was a higher incidence of AEs in the Infections and Infestations SOC 10% (12/125) than in the overall population, 4% (38/958). Other than this finding, the safety profile in the age group 12 < 18 years was comparable to the overall study population. In reference to application site atrophy among those treated with EF Clobetasol Foam, 1% (1/92) was reported in patients aged 12 < 18 years versus 2% (10/447) in subjects \geq 18 years.

In reference to race, the incidence of AEs was analyzed by the groups as follows: Caucasians, African-Americans, Hispanics, Asians included with a small number of subjects categorized as Other, respectively. According to the sponsor, Asians were included in the "Other" category because of the small number enrolled. The percentages and numbers of AEs reported for subjects in these groups were as follows: Caucasians group 15% (109/722), African-Americans 22% (26/116), Hispanics 7% (5/69), Other 24% (11/46).

7.4.2.4 Explorations for drug-disease interactions

No formal analyses were performed for drug-disease interactions with this topical drug product.

7.4.2.5 Explorations for drug-drug interactions

No formal analyses were performed for drug-drug interactions with this topical drug product.

7.4.3 Causality Determination

The common adverse events were application site types of reactions and included application site atrophy, burning, pruritus, and folliculitis. Of these, application site atrophy and folliculitis were more common in the EF Clobetasol Foam group and application site burning was more common in the Vehicle Foam group.

The EF Clobetasol Vehicle foam contains propylene glycol which is a known cause of irritant dermatitis. The cumulative irritancy score for EF Clobetasol Foam Vehicle was greater than that of distilled water (negative control). The EF Clobetasol Foam drug product contains known rare sensitizers including phenoxyethanol, isopropyl myristate, and cetyl alcohol. In addition, clobetasol propionate is itself a known sensitizer. In the repeat insult patch test study performed by the sponsor, one subject appeared to show sensitization to the EF Clobetasol Vehicle Foam. This information supports the causality of both Vehicle and drug substance in application site reactions.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen for EF Clobetasol foam is twice daily (morning and evening) topical application to the skin. This is the dosing regimen that was studied in the Phase 2 and Phase 3 clinical trials. In clinical trials subjects were instructed to apply the foam in an amount sufficient to cover affected areas and to avoid application to the face, scalp, and intertriginous areas. Subjects were also instructed not to exceed using 50 grams of the drug product per week; however drug product was issued in 100 gram cans. The two week treatment period is similar to that for most other clobetasol propionate products.

8.2 Drug-Drug Interactions

Studies of drug-drug interactions were not conducted in the clinical development program for this product.

8.3 Special Populations

In the Phase 3 trials, EF Clobetasol foam was studied in patients age 12 and older. EF Clobetasol foam was tested for safety and efficacy across subgroups including age, race, and gender. Generally treatment success rates were consistent across age, race, and gender. However, in study CPE.C.302 (psoriasis) EF Clobetasol foam did not show superiority to vehicle foam in non-Caucasians.

Patients aged 65 and older numbered 58, too small a number to permit separate analysis of efficacy and safety. However, in a grouping consisting of 111 patients aged 65 and older and consisting of 58 on EF Clobetasol foam, 39 on vehicle foam, and 14 on Temovate ointment, the adverse event rate was 14% (compared with 17% for patients on EF Clobetasol foam in all age groups combined). The data available do not indicate a need for dose adjustment in patients over age 65.

Pregnant and breast-feeding women were excluded from these studies. This is appropriate based on information from animal studies indicating clobetasol propionate is teratogenic at doses similar those used topically in humans. The pregnancy category assigned is C.

8.4 Pediatrics

The indication of corticosteroid responsive dermatoses includes atopic dermatitis and psoriasis. Atopic dermatitis is principally a disease of children. EF Clobetasol Foam, 0.05% is a new dosage form, therefore a pediatric assessment is required by the Pediatric Research Equity Act (PREA). In accordance with 21 CFR 314.55(c)(3)(iii), the applicant has submitted a request that the FDA waive the requirement to submit the pediatric assessment for pediatric age groups under

12 years of age. This is based on evidence from study CPE.C.201 (HPA axis suppression study) indicating that the drug product would be unsafe in all pediatric age groups. In this trial, 47% of subjects ages 6 to 11 demonstrated HPA axis suppression. This suppression was reversible. A partial pediatric waiver will be granted to the sponsor.

In reference to atopic dermatitis, the sponsor has provided an acceptable review of the literature that indicates that the prevalence of atopic dermatitis in children in all children could range between .6% and 20%. The sponsor also employed the Verispan Physician Drug & Diagnosis Audit database to show that 12 to 17 year olds with moderate to severe atopic dermatitis represent 17.9% of all patients over 12 years with any atopic dermatitis. The study CPE.C.301 enrolled a total of 101 (27%) of subjects 12 to 17 years of age (69 or 27% randomized to EF Clobetasol Foam and 32 or 25% to Vehicle Foam). In the combined safety population (CPE.C.201, CPE.C.202, CPE.C.301, CPE.C.302) a total of 92 (16%) of the subjects aged 12 to 17 years were treated with EF Clobetasol Foam. An adequate number of pediatric subjects was included in these trials to obtain useful efficacy and safety information.

8.5 Advisory Committee Meeting

No Advisory Committee was convened in response to this application.

8.6 Literature Review

Literature reviewed indicates that clobetasol propionate is a known sensitizer with rates of sensitization ranging between .4% and .8% of patients with suspected contact dermatitis who were tested. See section 7.1.12, special safety studies.

8.7 Post-Marketing Risk Management Plan

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug at this time.

8.8 Other Relevant Materials

The sponsor originally submitted the trade name Primolux™ (clobetasol propionate) Foam 0.05%. Consultation with the Division of Medication Errors and Technical Support (DMETS) revealed no objection to the use of the proprietary name, Primolux™. However, the Division of Marketing, Advertising, and Communications (DDMAC) objects to the proposed name Primolux™ because it overstates the efficacy of the drug product by misleadingly implying that it is superior to other treatment options. The Division of Dermatology and Dental Products concurs with DDMAC's objection. As a consequence, the Agency has requested and the sponsor has submitted two alternative trade names, ~~Primolux~~ and ~~Primolux~~. Consultation with DMETS and DDMAC regarding the suitability of these names is ongoing at the time of completion of this review.

The Division, DMETS, and DDMAC are concerned that confusion could arise from the presence on the market of two different trade names (Olux® and the current product) for the same drug substance, at the same concentration, in the same dosage form, and for essentially the same indication. A single trade name with a modifier is consistent with the precedent set by other products. Safety concerns center on possible overuse of the drug substance by consumers switching back and forth from one trade name product (Olux®) to the other (the current product). This safety issue which is a concern with the presence of two different trade names would be addressed by a single trade name with a modifier.

9 OVERALL ASSESSMENT

9.1 Conclusions

Olux E (clobetasol propionate) foam 0.05% is a topical product intended for twice daily application for up to two weeks (100g/two weeks) for the treatment of corticosteroid responsive dermatoses in patients 12 years of age and older. Olux E (clobetasol propionate) foam 0.05% has an aerosol base that is an ethanol-free oil-in-water emulsion.

The sponsor has demonstrated in two well controlled Phase 3 trials that Olux E (clobetasol propionate) foam 0.05% is safe and efficacious for the treatment of corticosteroid responsive dermatoses in patients 12 years of age and older. In a trial involving subjects with moderate to severe atopic dermatitis, Olux E (clobetasol propionate) foam 0.05% demonstrated statistically significant efficacy when compared with vehicle foam. In a trial involving subjects with mild to moderate plaque-type psoriasis, Olux E (clobetasol propionate) foam 0.05% demonstrated statistically significant efficacy when compared with vehicle foam and was not superior to the reference listed drug, Temovate® Ointment. A central element of the primary efficacy endpoint in both trials was an Investigator's Static Global Assessment, dichotomized to success and failure. A sufficient number of pediatric patients was included, principally in the atopic dermatitis study, to allow for evaluation of efficacy and safety in this age group.

Relative bioavailability was evaluated in a study involving subjects with mild to moderate psoriasis and findings indicate that Olux E (clobetasol propionate) foam 0.05% does not have greater systemic bioavailability than the reference listed drug, Temovate® Ointment.

No deaths occurred during the development program and no serious adverse events were attributed to study drug use. The most common adverse events were application site atrophy and application site reaction, occurring in 1.9% and 1.6% of subjects respectively. The next most common adverse events reported were application site burning and application site pruritus which appear to be related to components of the vehicle. The active assessments for local reactions did not reveal significant safety concerns. The drug product was studied for systemic safety in an HPA axis suppression study in subjects with mild to moderate atopic dermatitis

down to age 6. Significant levels of suppression (47%) were found in the youngest age group, 6 to 11, and lower levels (16.2%) were found in subjects ages 12 and older.

Thus, the sponsor has adequately fulfilled the requirements for approval under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Olux E (clobetasol propionate) foam 0.05% does not show superior efficacy compared to the RLD. Olux E (clobetasol propionate) foam 0.05% does not exhibit an overall safety profile that is inferior to the RLD. Olux E (clobetasol propionate) foam 0.05% does not show a greater systemic bioavailability than the RLD.

9.2 Recommendation on Regulatory Action

This reviewer recommends that Olux E (clobetasol propionate) foam 0.05% be approved for topical administration for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years or older. This recommendation is conditional upon revised labeling and agreement to required Phase 4 commitments.

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

Post-marketing risk management measures will include prescription status, professional labeling, spontaneous adverse event reporting, and submission of annual reports.

9.3.2 Required Phase 4 Commitments

The sponsor has committed to conduct dermal carcinogenicity and photo-carcinogenicity studies during Phase 4.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are needed.

9.4 Labeling Review

Please see appended line-by-line labeling review for details.

For review of the trade name please see section 8.8 of this review.

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9.5 Comments to Applicant

There are no additional comments to be conveyed to the sponsor other than the Phase 4 commitments needed for pharmacology/toxicology and the changes to the proposed label.

Appears This Way
On Original

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Pivotal Study: CPE.C.301

Title: “A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Ethanol-Free Clobetasol Propionate Foam, 0.05% in the Treatment of Moderate to Severe Atopic Dermatitis”

Investigators:

Table 32: Investigators CPE.C.301 (or Study 301)

Site Number	Investigator	Center	Patients Enrolled N = 377
117	Diane Baker, MD	Allergy, Asthma, & Derm Research Ctr. Lake Oswego, OR	8 (2%)
119	Robert Brown, MD	North Florida Dermatology Assoc., PA Jacksonville, FL	3 (1%)
101	Harold Farber, MD	Farber & Associates Philadelphia, PA	18 (5%)
102	David Fiorentino, MD	Stanford University Stanford, CA	15 (4%)
103	Joseph Fowler Jr., MD	Dermatology Specialists Louisville, KY	24 (6%)
104	Alice B. Gottlieb, MD., PhD.	UMDNJ-RWJMS New Brunswick, NJ	19 (5%)
105	Jo Lynn Herzog, MD	Radiant Research Birmingham, AL	14 (4%)
106	Robert T. Matheson	Oregon Medical research Center, P.C. Portland, OR	40 (11%)
107	Larry Millikan, MD	Tulane University Health Sciences Center New Orleans, LA	23 (6%)
116	Eugene Monroe, MD	Advanced Healthcare Milwaukee, WI	21 (6%)
108	Amy Morris	Coastal Clinical Research, Inc. Mobile, AL	36 (10%)
109	Toivo Rist, MD	Dermatology Associates of Knoxville Knoxville, TN	19 (5%)
110	Ronald C. Savin, MD	The Savin Center New Haven, CT	18 (5%)
118	Joel Schlessinger, MD	Skin Specialists Omaha, NE	22 (6%)
120	Harry Sharata, MD	Madison Skin & Research, Inc. Madison, WI	8 (2%)

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113	Dow B. Stough IV, MD	Burke Pharmaceutical Research Hot Springs, AR	11 (3%)
111	Linda Stein Gold, MD	Henry Ford Medical Center Detroit, MI	27 (7%)
112	Stephen Stone, MD	SIU School of Medicine Springfield, IL	2 (1%)
114	Eduardo Tschen, MD	Academic Dermatology Associates Albuquerque, NM	40 (11%)
115	David Whiting, MD	Dallas Associated Dermatologists Dallas, TX	9 (2%)

Source: Sponsor's NDA submission module 5, Final Study Report CPE.C.301, pp. 127, 538, and 539; Also sponsor's NDA 22-013/Amendment 006, p. 2

Objective: The primary objectives of this study were to evaluate the safety and efficacy of Emulsion Formulation Clobetasol Propionate Foam, 0.05% (EF Clobetasol Foam) in the treatment of subjects 12 years of age and older with moderate to severe atopic dermatitis and to demonstrate superior efficacy of EF Clobetasol Foam to its vehicle.

Study Design: This was conducted as a 20 center, randomized, double-blind, vehicle-controlled trial involving subjects 12 years of age and older with moderate to severe atopic dermatitis. Qualified subjects were randomized to one of two parallel treatment groups in a 2:1 ratio (EF Clobetasol Foam: Vehicle Foam). Subjects applied study drug twice daily for two weeks to cover all areas affected by atopic dermatitis (excluding face, scalp and intertriginous areas). Study visits were Baseline, Week 1, Week 2, and two weeks post-treatment (Week 4).

Protocol:

No subjects were enrolled under the original protocol or the first amendment to the protocol. Subjects were not enrolled in the study until the second amendment was implemented. A third amendment to the protocol was submitted 28 June 2005. The third amendment made the following changes to the protocol:

- Subjects younger than 12 years of age were excluded from study participation.
This change was made because the results of the HPA axis study showed high rates of suppression in the ≥ 6 to < 12 year old age cohort, and therefore the study did not enroll younger age cohorts.
- The number of study sites was increased from approximately 15 to approximately 20 study sites.
- Inclusion criterion 3 "a subject's assessment of pruritus score of 2 or greater" was removed.
With this change, subjects could come in with a score of only 0 or 1 for pruritus.
- The success of the secondary endpoints of the study was changed to require a reduction of at least two grades.
Prior to this amendment, a subject could achieve success on the individual criteria of erythema, lichenification, or induration/papulation coming in with a score of 0.

The remainder of the discussion is based on the final version (Amendment 3) of the protocol.

Inclusion Criteria:

1. Subjects must be male or female 12 years of age and older and in good general health.
2. Subjects must have atopic dermatitis as defined by the criteria of Hanifin and Rajka. The atopic dermatitis must be of moderate to severe intensity (score 3 or 4) as determined by the ISGA involving at least 5% treatable BSA (excluding the face, scalp, and intertriginous areas), with a sum of the scores for erythema, induration/papulation and oozing/crusting greater than or equal to 4.
3. The subject must be able and willing to follow all study procedures, attend all scheduled visits, and successfully complete the study.
4. The subject must be able to understand and sign a written informed consent form, which must be obtained prior to treatment. If subjects are under the age of 18, a parent or guardian must sign the informed consent form, and the subject must provide written assent, in accordance with the local IRB guidance and state governance.
5. The subject must be able to understand and sign a Health Information Portability and Accountability Act (HIPAA) authorization form which shall permit the use and disclosure of the subject's individually identifiable health information.

Exclusion Criteria:

1. Known allergy to clobetasol or other topical corticosteroids or to any component of the investigational formulations
2. Clinically infected atopic dermatitis
3. Other serious skin disorder or any chronic condition that is not well controlled
4. Use of topical corticosteroid therapy for atopic dermatitis within the past one week or other topical therapy for atopic dermatitis (e.g., topical antibiotics and immunomodulators [tacrolimus or pimecrolimus]) within the past two weeks
5. Use of topical antihistamines within the past one week
6. Use of systemic medications or phototherapy that affects atopic dermatitis (e.g., corticosteroids, PUVA, UVB, cyclosporine, azathioprine, tacrolimus, methotrexate) within the past four weeks
7. Use of systemic antibiotics for treatment of atopic dermatitis within the past two weeks
8. Use of any investigational therapy within the past four weeks
9. Pregnant women, women who are breast feeding, or women of child bearing potential who are not practicing an acceptable method of birth control (abstinence, birth control pill, patch, implant, barrier with spermicidal jelly, IUD, etc.) as determined by the investigator – An acceptable method of birth control must be used during the entire study.
10. Current drug or alcohol abuse (drug screening not required)
11. Any other condition which, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study

Concomitant Medications/Allowed Therapy:

- 1) The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, acute infections, etc.) is permitted during this study.

- 2) The use of systemic antihistamines is permitted as long as the subject has not changed dose or drug within the past 2 weeks and does not expect to change the dose or discontinue use during the study.
- 3) Use of inhaled/intranasal steroids is permitted prior to and during the conduct of the study if already being used by the subject.
- 4) Only a bland moisturizer such as Eucerin Cream is permitted for use on areas that are not to be treated with study drug (i.e., the face, scalp and intertriginous areas). Eucerin Cream may be used between applications on areas to be treated with the study drug but not within four hours of a study visit.
- 5) It is recommended that bathing during the study period should:
 - be limited to once daily;
 - use tepid (not hot) water;
 - last no longer than 5 minutes;
 - use mild cleansing agents (such as Basis Bar or Dove).

Withdrawal Criteria:

- 1) Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, require discontinuation of drug, or both
- 2) Unacceptable toxicity
- 3) Subject noncompliance
- 4) Subject's request to withdraw

Blinding:

The study CPE.C.301 was designed as a randomized, double-blind, vehicle-controlled trial. Both study drug treatments were packaged in identically appearing containers. The two study drug treatments (active foam and vehicle foam) were also identical in appearance. The subject, the coordinator, and the Investigator did not know which treatment the subject would receive.

Study Procedures:

Subjects were to apply study treatments twice daily (morning and evening) for a maximum of two weeks. Subjects were instructed to apply study drug sufficient to cover all areas affected by atopic dermatitis (excluding the face, scalp, and intertriginous areas), and not to exceed 50 g of study drug per week.

Each study subject was assigned one kit containing either two cans of EF Clobetasol Foam (Batch number UFB-1C or UFC-1C, product size 100g)⁵ or vehicle foam (Batch number UEBA-C, product size 100g)¹. Subjects were dispensed one can at the Baseline visit and the other can at the Week 1 visit. Additional cans/tubes could be requested at or between study visits. Study drug was to be weighed prior to dispensing and when returned by subject.

Subjects were issued 100 gram cans of study drug. It is not clear to this reviewer that subjects could follow instructions to use no more than 50 grams a week since it is not possible to know when the can is halfway depleted.

⁵ Sponsor's NDA submission, NDA 22-013, Amendment 11 (Response to clinical reviewer's request), p. 2.

The study consisted of two weeks of treatment. Visits occurred at Baseline, Week 1, Week 2, and two weeks following the last study drug administration. At the first visit (Baseline, Day 1), written informed consent was obtained; a medical history/review of systems was conducted; vital signs (blood pressure, pulse, temperature), weight, and height were measured; a urine pregnancy test was performed on all females of childbearing potential; subjects were to complete the Dermatology Life Quality Index (DLQI) or the Children's Dermatology Life Quality Index (CDLQI) questionnaire; and clinical photography was performed at two investigational sites.

Efficacy was evaluated at all study visits. This included ISGA (Investigator's Static Global Assessment); subject self-evaluation of pruritus; complete examination of the skin to assess extent of BSA involvement; evaluation of treated areas for erythema, induration/papulation, lichenification, scaling, and oozing/crusting; and Subject's Global Assessment (SGA) of treated areas.

Safety was evaluated at all study visits. Beginning with the Week 1 visit, subjects were questioned about adverse experiences (AEs) and their use of concomitant medications. Treated areas of the skin were assessed for changes in atrophy, striae, telangiectasia, and pigmentation.

At the Week 2 visit, subjects were to complete the DLQI or CDLQI questionnaire, a urine pregnancy test was performed on all females of childbearing potential, and clinical photography was performed at two investigational sites. All subjects were required to complete the Week 2 evaluation independent of their response to treatment prior to Week 2.

Table 33: Schedule of Study Procedures (Study 301)

Parameter	Baseline (Day 1)	Week 1 (Day 8 ± 2 Days)	Week 2 (Day 15 ± 2 Days)	Follow-Up Visit (4 weeks ± 4 Days)
Written informed consent and HIPAA authorization	X			
Medical history/review of systems	X			
Vital signs: temp, BP, pulse	X		X	
Height and weight	X			
Complete skin examination (assessment of BSA)	X	X	X	X
Investigator's Static Global Assessment	X	X	X	X
Evaluation of erythema, induration/papulation, lichenification, scaling, and oozing/crusting	X	X	X	X
Document cutaneous signs of atrophy, striae, telangiectasia, and pigmentation changes at treated sites	X	X	X	X

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Subject's assessment of pruritus	X	X	X	X
Subject's Global Assessment	X	X	X	X
DLQI or CDLQI	X		X	
Adverse experience query		X	X	X
Concomitant medications query	X	X	X	X
Weigh and dispense study medication	X	X		
Collect and weigh study medication		X	X	
Urine pregnancy test	X		X	
Clinical photography (selected sites)	X		X	
Subject's Post-Study Questionnaire			X	

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 23.

Table 34: Investigator's Static Global Assessment (Study 301)

Score	Definition
0	Clear; minor residual discoloration; no erythema or induration/papulation, no oozing/crusting
1	Almost Clear; trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild; faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate; pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe; deep or bright red erythema with severe induration/papulation and with oozing/crusting

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 24.

Table 35: Subject's Assessment of Pruritus (Study 301)

Score	Definition
0	No itching
1	Minimal; very rarely aware of localized itching; only present when relaxing and lasts for very short time
2	Mild; only aware of itching at times; only present when relaxing; not present when focused on other activities
3	Moderate; often aware of itching; annoying; sometimes disturbs sleep and daytime activities
4	Severe; constant itching; distressing; frequent sleep disturbance; interferes with activities

Source: Sponsor's NDA submission, module 5, Final Study Report CPE.C.301, p. 24.