CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-835

MEDICAL REVIEW

Clinical Team Leader Memorandum
NDA 21-835 CLOBEX™ (clobetasol propionate) Spray, 0.05%

NDA:	**21-835**
Drug:	**CLOBEX™ (clobetasol propionate) Spray, 0.05%**
Indication:	**treatment of moderate to severe plaque psoriasis in patients 18 years of age and older**
Dose:	**BID for up to 4 weeks**
Applicant:	**Dow Pharmaceutical Sciences**
Submission received:	**December 27, 2004**
Clinical review completed:	**October 11, 2005**
Date of memorandum:	**October 24, 2005**

The applicant has requested approval of CLOBEX™ (clobetasol propionate) Spray, 0.05%, for the indication of treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. CLOBEX™ Spray represents a new formulation (spray) for a moiety that is marketed in lotion and shampoo formulations by this applicant, and in ointment, cream, emollient cream, lotion, solution, gel, and foam formulations by other applicants. In support of this application, the sponsor conducted two Phase 2 HPA axis suppression (safety) studies and two Phase 3 pivotal efficacy and safety trials.

In each of two identical Phase 3 trials, the applicant enrolled 120 subjects (240 total), who were randomized 1:1 to receive treatment with either CLOBEX™ Spray (120 total) or vehicle (120 total). Subjects were eligible for enrollment if they had ≥2% body surface area of psoriatic involvement and a score of 3(moderate) or 4 (severe/very severe) on the Overall Disease Severity Scale (ODS), a static global severity scale that incorporated investigator assessment of erythema, scaling and plaque elevation. The primary timepoints were Week 2 and Week 4, with demonstration of success at Week 2 a prerequisite for consideration of Week 4 data. The primary endpoint at Week 2 was the proportion of patients who scored a 2 or less (Clear/Almost Clear/Mild) on the ODS, which was less stringent than the primary endpoint at Week 4, the proportion of patients who scored a 1 or less (Clear/Almost Clear) on the ODS.

The study results, from Dr. Kathleen Fritsch's review, follow:

	Study 8			Study 10		
	Clobetasol N=60	Vehicle N=60	p-value	Clobetasol N=60	Vehicle N=60	p-value
Week 2 ODS						
0 (Clear)	1 (2%)	0 (0%)		0 (0%)	0 (0%)	
1 (Almost Clear)	32 (53%)	1 (2%)		28 (47%)	0 (0%)	
2 (Mild)	19 (32%)	16 (27%)		24 (40%)	16 (27%)	
3 (Moderate)	7 (12%)	38 (63%)		7 (12%)	36 (60%)	
4 (Severe)	1 (2%)	5 (8%)		1 (2%)	8 (13%)	
Clear/Almost Clear/ Mild[1]	52 (87%)	17 (28%)	<0.0001	52 (87%)	16 (27%)	<0.0001
Clear/Almost Clear	33 (55%)	1 (2%)	<0.0001	28 (47%)	0 (0%)	<0.0001
Week 4 ODS						
0 (Clear)	15 (25%)	0 (0%)		18 (30%)	0 (0%)	
1 (Almost Clear)	32 (53%)	2 (3%)		31 (52%)	1 (2%)	
2 (Mild)	6 (10%)	17 (28%)		6 (10%)	11 (18%)	
3 (Moderate)	6 (10%)	37 (62%)		4 (7%)	38 (63%)	
4 (Severe/Very Severe)	1 (2%)	4 (7%)		1 (2%)	10 (17%)	
Clear/Almost Clear[2]	47 (78%)	2 (3%)	<0.0001	49 (82%)	1 (2%)	<0.0001

[1]Week 2 primary endpoint
[2]Week 4 primary endpoint
Source: Statistical Review for NDA 21-835, Dr. Kathleen Fritsch, p.11.

CLOBEX™ Spray was statistically superior to its vehicle in both of the pivotal studies. Success was achieved at both primary timepoints, Week 2 and Week 4. A greater percentage of subjects achieved a score of 1 or less at Week 4 than at Week 2.

Systemic safety was assessed in two HPA axis suppression studies. In the first, thirteen patients were treated for four weeks; suppression was seen in 15.4% of subjects (2/13). In the second, patients were treated for two or four weeks; suppression was seen in 19% of subjects (4/21) treated for two weeks, and in 20% of subjects (3/15) treated for four weeks. HPA axis suppression is seen in 15 to 20% of subjects treated with CLOBEX™ Spray treated for two to four weeks. In all cases, suppression reversed off-therapy.

Local safety was assessed by provocative dermal safety studies, active assessment for telangiectasia, atrophy, burning/stinging, and folliculitis, and reported adverse events. By active solicitation, burning/stinging was reported on any week by up to 29% of subjects in the CLOBEX™ arm and up to 32% of subjects in the vehicle arm (subjects were queried at weekly visits). Application site burning was reported as an adverse event by a total of 40% of subjects receiving CLOBEX™ Spray and 47% of subjects receiving vehicle. In the cumulative irritation study, a modest irritation signal was seen for both

CLOBEX™ Spray (irritation score 456/2088) and vehicle (irritation score 403/2088), but both were less irritating that the positive control, sodium lauryl sulfate (irritation score 1607/2088). This signal is not unexpected for a drug product containing alcohol. Telangiectasia, atrophy and folliculitis were not seen in the pivotal trials, however these are recognized sequelae of treatment with topical steroids, particularly ultrapotent topical steroids such as clobetasol propionate, and can be expected to be reported as adverse events in the postmarketing period. Similarly, although a signal for contact allergy was not identified in the provocative battery of dermal safety studies, both clobetasol propionate and isopropyl myristate are known sensitizers (albeit uncommon), and occasional reports of contact dermatitis may be seen with wider use following approval. All of these local adverse effects are described in the product labeling.

The indication of moderate to severe plaque psoriasis represents a chronic, non-life-threatening condition, hence ICH E1A Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions, is applicable. However, because the initial marketed clobetasol propionate product, Temovate (clobetasol propionate) Cream, 0.05%, was approved almost twenty years ago (December 27, 1985), and multiple formulations have been marketed since that time, a great deal of post-marketing safety data is available. It is not expected that a 6 or 12 month safety study of long-term intermittent use of CLOBEX™ Spray would yield new information for labeling, as the risks for HPA axis suppression, atrophy and telangiectasia are already described. Therefore no long term safety study was requested of the applicant prior to approval, nor is one recommended as a condition of approval.

The applicant requested a waiver for pediatric studies based on insufficient numbers of pediatric patients with moderate to severe plaque psoriasis. This is reasonable. The applicant was encouraged to but did not perform HPA axis studies in the adolescent age-group. Because the applicant has pursued the narrower indication of psoriasis, rather than corticosteroid responsive dermatoses, I do not think it is necessary to request a Phase 4 commitment for pediatric HPA axis suppression studies. All of the other clobetasol proprionate formulations other than CLOBEX™ Lotion and CLOBEX™ Shampoo are approved for use in ages 12 to 17 and for the broader indication of corticosteroid-responsive dermatoses, which would include atopic dermatitis, a condition more common than psoriasis in the adolescent population. Because multiple clobetasol propionate formulations are already marketed for use in this population, it does not seem necessary to request a Phase 4 HPA axis suppression study in adolescents or to extrapolate efficacy to adolescents in the advent of demonstration of an acceptable level of systemic safety.

In summary, the applicant has established the safety and efficacy of CLOBEX™ (clobetasol propionate) Spray, 0.05% for the treatment of moderate to severe psoriasis, and I agree with the recommendations of the primary review team that the applicant's NDA 21-835 be approved for marketing, with a non-clinical Phase 4 commitment to study dermal carcinogenicity and photocarcinogenicity as recommended by Dr. Jill Merrill.

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/s/

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10/24/2005 06:31:56 PM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-835
Submission Code	000
Letter Date	December 22, 2004
Stamp Date	December 27, 2004
PDUFA Goal Date	October 27, 2005
Reviewer Name	Denise Cook, M.D.
Review Completion Date	
Established Name	Clobetasol Propionate
(Proposed) Trade Name	Clobex Spray
Therapeutic Class	Anti-inflammatory
Applicant	Dow Pharmaceutical Sciences
Priority Designation	S
Formulation	Spray
Dosing Regimen	Twice a day for 4 weeks
Indication	Moderate to Severe Psoriasis
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended, from a clinical perspective, that NDA 21-835 for Clobex (clobetasol propionate) Spray, 0.05% be an approval for the treatment of moderate to severe psoriasis. Efficacy was demonstrated after both 2 weeks and 4 weeks of treatment, although treatment success was higher at 4 weeks. Analysis of safety of Clobex Spray did not reveal any major new safety concerns for a topical clobetasol propionate drug product.

1.2 Recommendation on Postmarketing Actions

The sponsor will need to develop a Patient Information Brochure, as this is a class one topical corticosteroid capable of inducing systemic and cutaneous side effects if not used appropriately.

1.2.1 Risk Management Activity

There are no plans for risk management in the post-market.

1.2.2 Required Phase 4 Commitments

There are not any phase 4 commitments needed from a clinical perspective.

1.2.3 Other Phase 4 Requests

There are not any other phase 4 requests from clinical.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This NDA was submitted in support of Clobex (clobetasol propionate) Spray, 0.05% for the proposed indication of treatment of moderate to severe chronic plaque psoriasis. To support the indication, the sponsor submitted two pivotal, multicentered phase 3 trials for efficacy and safety and 2 phase 2 open-label trials to evaluate systemic safety in this topically applied corticosteroid.

Clobex Spray, 0.05% was studied in adult patients greater than or equal to 18 years of age. A total of 640 subjects were evaluated in the clinical program. Of these subjects, 496 were

exposed to CLOBEX™ (clobetasol propionate) Spray, 0.05% (292 healthy subjects and 204 patients with psoriasis). The two phase 3 pivotal trials enrolled 240 patients randomized in a 1:1 ratio into either a Clobex Spray arm or a placebo arm. The phase 2 systemic safety studies enrolled 57 subjects who had either a 2 or 4 week course of treatment. In the systemic safety studies patients had at least 20% of their body surface area affected by psoriasis.

1.3.2 Efficacy

There were two phase 3 trials that were reviewed in support of efficacy of Clobex Spray, 0.05% in the treatment of moderate to severe chronic plaque psoriasis. Both trials, T101-01008 and T101-01010 were multicentered double-blind, placebo controlled trials located in the United States. The trials were identical in design with each trial having 2 arms, active drug and placebo, with a 1:1 randomization.

The primary efficacy variable for the trials was the Overall Disease Assessment (ODA) score based on a severity scale of 0-4. All patients who entered the trials had to have at least moderate disease (3 on the ODA scale). Secondary efficacy variables in the assessment of psoriasis were erythema, plaque elevation, and scale. Erythema, plaque elevation, and scale are essential elements to evaluate in the severity of psoriasis, as these are the primary signs of the disease. The ODA scale incorporates each of these signs. Pruritus was also evaluated as a secondary efficacy variable in the pivotal trials. The efficacy endpoint was assessed as a nested approach. If success was achieved at the end of 2 weeks, then efficacy would also be assessed at the end of 4 weeks. Patients were treated topically twice a day with Clobex Spray to all psoriasis lesions excluding those in intertriginous areas and the face.

Success for the pivotal trials is based on dichotomization of the primary efficacy endpoint, the Overall Disease Assessment score. A statistically significant proportion of patients had to achieve a score of 2 or less on the Overall Disease Severity score scale at week 2 and a statistically significant proportion of patients had to achieve a score of 1 or less on the Overall Disease Severity Score scale at week 4 (end of treatment). The efficacy evaluation in the trials was based on disease severity in a static fashion, not as a comparison to baseline. Secondary efficacy variables were also evaluated based on a static scale and were to be supportive of the primary efficacy variable.

Analysis of studies -01008 and -01010 demonstrated that Clobex Spray, 0.05% was statistically significantly superior in treating moderate to severe psoriasis than its placebo ($p<0.001$). More than three-fourths of the patients treated in the trials demonstrated efficacy when treated with Clobex Spray for either 2 or 4 weeks. In pivotal trial, T010-01008, 87% of patients on Clobex Spray were categorized as a success at week 2 compared to 28% in the vehicle arm and 78% were a success at week 4 in the Clobex Spray arm compared to 3% in the vehicle arm. In the second pivotal trial, T101-01010, 87% of the patients on Clobex Spray had a successful treatment outcome compared to 27% at week 2 and 82% of patients had a successful outcome at week 4 who were treated with Clobex Spray compared to 2% of patients on vehicle.

A significant proportion of patients also benefited from an additional two weeks of treatment. In study -01008, the aggregate number of subjects on Clobex Spray, 0.05% that were Clear or Almost Clear increased by 42% from 33/60 subjects at week 2 to 47/60 subjects at week 4. In study -01010, the aggregate number of subjects on Clobex Spray that were Clear or Almost Clear increased by 75% from 28/60 subjects at week 2 to 49/60 subjects at week 4.

The secondary efficacy variables of erythema, plaque elevation, scale, and pruritus were all supportive of the primary efficacy variable. Each parameter achieved statistical significance at both week 2 and week 4 ($p<0.001$).

Subjects were followed for 4 weeks post treatment for persistence of efficacy or evidence of rebound flare. The data show that Clobex Spray, 0.05% has a sustained effect and low relapse rate. The analysis demonstrated that for 4 weeks post treatment 51% of patients continued to be clear or almost clear of disease compared to 6% of those who were on placebo. No patients in placebo were clear 4 weeks after ceasing treatment. The incidence of rebound flare was low (1/120, 0.8%) and this was mild. There were also no instances of transformation to life-threatening forms of psoriasis in the follow-up period.

1.3.3 Safety

The safety of topical Clobex Spray, 0.05% was examined in 2 phase 3 trials, 2 phase 2 trials, and 5 phase 1 studies, 4 of which were cutaneous safety studies. It should be noted that although the cutaneous safety studies are labeled phase 1 studies, they were done with the to-be-marketed formulation. Thus, these studies are often done simultaneously with phase 3 pivotal trials. The double-blind placebo-controlled trials consisted of 4 weeks of treatment with Clobex Spray twice daily, as did the phase 1 bilateral efficacy and safety study. The phase 2 studies which evaluated systemic safety, primarily the effect of Clobex Spray, 0.05% on the HPA axis, had cohorts that were treated for both 2 weeks and 4 weeks.

A total of 640 subjects were evaluated in the clinical program. Of these subjects, 496 were exposed to CLOBEX^{TM} (clobetasol propionate) Spray, 0.05% (292 healthy subjects and 204 patients with psoriasis). In the phase 3 efficacy trials, 110 out of 120 (92%) subjects completed the trials and in phase 2 systemic safety trials, 49 out of 57 (86%) subjects completed the trials.

There were two adverse events that were associated with Clobex Spray, 0.05%, those that were primarily associated with topical application of the drug product and systemic effects on the HPA axis. The most common adverse event found with the use of Clobex (clobetasol propionate spray), 0.05% was that of application site burning. This occurred equally as much in the vehicle spray arm, with 40% experiencing this adverse event on Clobex Spray and 47% experiencing it on vehicle. This suggests that the adverse event is due to the vehicle and not to the chemical moiety. Although this is a significant incident for an adverse event, the majority of these were mild in severity and very few dropouts were because of this event. Of the 240 patients in the pivotal trials, 8 (3.3%) discontinued because of burning/stinging. Only 2/120 (1.6%) dropped in the Clobex (clobetasol propionate) Spray, 0.05% arm, suggesting that the chemical moiety may have some mitigating effect on this adverse event contributed by the vehicle. It is likely, however, that some patients will not be able to tolerate the drug because of this adverse event. Interestingly, during the trial and for 4 weeks post treatment, there was not any cutaneous evidence in the Clobex treated individuals of cutaneous atrophy.

As expected for a class I topical corticosteroid such as clobetasol propionate, this formulation also negatively influences the HPA axis. After 2 weeks of treatment with Clobex Spray, 0.05%, 15.8% of subjects suppressed. After 4 weeks of treatment with Clobex Spray, 0.05%, suppression varied from 14.3% in one study to 20% in a second study. When one looks at the

results of all three cohorts across both studies, there is a slight increase in risk for HPA axis suppression when Clobex Spray is used for 4 weeks. However, this small difference (1.4%) is acceptable given the efficacy results that demonstrate many more patients can benefit from an additional two weeks of treatment. Further, this effect on the HPA axis was reversible. It is also encouraging that many patients maintained a remission for at least 4 weeks post treatment and given the natural history of the disease may not require reinstitution of such a potent steroid when relapse again occurs. There were not any clinical signs of adrenal insufficiency in any of the patients in the open-label trials.

Phase 1 dermal safety studies corroborated what was found in the clinical trials. Clobex Spray, 0.05% and its vehicle is somewhat irritating but not as irritating as the positive control, sodium lauryl sulfate, 0.05%. There was no evidence of sensitization from using this drug product in the phase 1 dermal safety studies.

1.3.4 Dosing Regimen and Administration

The dosing regimen chosen for this product is in line with most topical corticosteroids, in that it is to be applied twice a day for two weeks. Patients should be re-evaluated after 2 weeks of therapy and if needed, an additional 2 weeks of treatment can be administered. Patients also are not to exceed the use of 50 grams/week.

1.3.5 Drug-Drug Interactions

There are not any specific drug-drug interactions that were investigated in the conduct of this NDA.

1.3.6 Special Populations

The majority of the subjects in the trials were Caucasian and male. In the pivotal trials, 90% of the subjects were Caucasian and 58% were male. This is not unusual as Caucasians make up the majority of patients who have psoriasis in the general population. Those patients aged 65 years or younger accounted for 91% of the patients in the pivotal trials. When subgroup analyses were performed on these groups, the efficacy response to treatment with Clobex Spray, 0.05% was the same for non-whites as it was for whites, for those $\geq$ 65 years of age as it was for those < 65 years of age, and for females as it was for males.

Pediatric evaluations, those less than 18 years of age, were not done in this NDA. The sponsor was informed, however, that the labeling for pediatrics for Clobex Spray, 0.05% would be the same as for Clobex Lotion, 0.05% in the absence of new data. Thus, Clobex Spray, 0.05% will not be recommended for use in those < 18 years of age because of the numerically higher rates of HPA axis suppression that was found in the studies in this age group with Clobex Lotion.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.11 Description of the Product

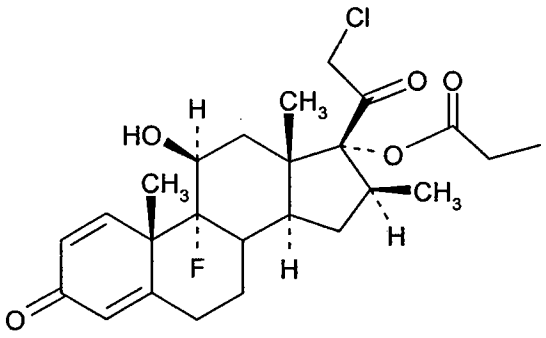
CLOBEX™ (clobetasol propionate) Spray, 0.05% contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Clobetasol propionate is 21-chloro-9-fluoro-11b,17-dihydroxy-16b-methylpregna-1,4-diene-3,20-dione17-propionate, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.97 (CAS Registry Number 25122-46-7).

2.12 Established Name and Proposed Trade Name

The established name of the product is clobetasol propionate spray. The proposed trade name is CLOBEX™ Spray, 0.05%.

2.13 Chemical Class

The following is the chemical structure:



Clobetasol propionate is a white to almost white crystalline powder that is practically insoluble in water. Each gram of CLOBEX™ (clobetasol propionate) Spray, 0.05% contains 0.5 mg of clobetasol propionate, in a vehicle base composed of Alcohol, Isopropyl Myristate, Sodium Lauryl Sulfate, and Undecylenic Acid.

2.14 Pharmacological Class

Like other topical corticosteroids CLOBEX™ (clobetasol propionate) Spray, 0.05% has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are

thought to act by induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

2.15 Indication, Dosing Regimen, Age Groups

CLOBEX™ (clobetasol propionate) Spray, 0.05% is a super-high potent corticosteroid formulation indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age or older (see PRECAUTIONS). Treatment should be limited to 4 consecutive weeks. The total dosage should not exceed 50 g (50 mL or 1.75 fl. oz.) per week.

Patients should be instructed to use CLOBEX™ (clobetasol propionate) Spray, 0.05% for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

Use in patients younger than 18 years of age is not recommended.

Reviewer's Comment: *The above section is taken from the draft labeling of the sponsor. The indication and usage section, section 2.15, is that as it is proposed by the sponsor. Changes may occur depending on the outcome of the review.*

2.2 Currently Available Treatment for Indication

There are many drug products on the market for the treatment of moderate to severe chronic plaque psoriasis. These therapies include topical therapies, phototherapy and photochemotherapy, and systemic therapies. However, there does not exist any perfect treatment for psoriasis. Treatments to date do not induce a permanent remission and most often must be given in cyclical or continuous fashion in an effort to circumvent unwanted adverse events in a disease that has to be treated over an individual's lifetime.

Since clobetasol propionate spray, the subject of this NDA, is a topical therapy, this section will five a brief overview on available topical therapy for moderate to severe psoriasis, including appropriate efficacy data, if available, and safety information.

Topical Corticosteroids

Topical corticosteroids have been the mainstay of treatment of psoriasis since their introduction in 1952. They are often first-line treatment for mild to moderate psoriasis as well as in sites such as the flexures and genitalia. The development of high potency and super potent topical steroids have opened the door for successful treatment of severe psoriasis, as well. The high potency topical steroids include the fluocinonide family (cream, ointment, gel) as well as

betamethasone dipropionate cream. The super potent topical steroids include the clobetasol propionate family (cream, ointment, gel, foam, lotion) as well as diflorasone diacetate ointment and betamethasone dipropionate ointment.

The efficacy of these drug products is well established in the treatment of chronic plaque psoriasis. A recent study of clobetasol propionate lotion in the treatment of moderate to severe psoriasis demonstrated efficacy after 4 weeks of twice daily treatment in 36.6% of patients compared to 0% in placebo. Treatment success was achieved in patients who obtained a score of clear or almost clear on the Investigator's Global Assessment Scale, the same scale used to determine success in the oral tazarotene trials.

Side effects associated with the use of topical corticosteroids include skin atrophy, burning and stinging, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This may occur after two weeks of use with certain topical corticosteroids.

Topical Vitamin D_3 Analogues

The prototype of this group of drug products is calcipotriene, approved in the United States. It comes in 3 formulations, cream, ointment, and scalp solution. The former two are approved for plaque psoriasis and the scalp solution is approved for moderately severe psoriasis of the scalp. In clinical trials, patients with at least marked improvement after 8 weeks of twice daily therapy was 50% and 49.6% for the cream and ointment formulations, respectively. Thirty-one percent of patients after 8 weeks of twice daily treatment with scalp solution were clear or almost clear.

Side effects are cutaneous and include burning, stinging, itching, skin irritation, and tingling of the skin.

Topical Retinoids

Topical tazarotene gel is approved in two strengths, 0.05% and 0.1%, for the treatment of stable plaque psoriasis of up to 20% BSA involvement. In clinical trials, patients with at least moderate psoriasis were treated for 12 weeks once daily. The percentage of patient with at least a 75% improvement from baseline was 28% and 18% for the 0.05% concentration in two placebo controlled studies and 38% and 25% for the 0.1% formulation in two placebo controlled studies. The vehicle effect was 12% and 10%.

The most frequent adverse reactions were limited to the skin. These included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain.

Tazarotene gel is a pregnancy category X drug product and as such is contraindicated in women who are or may become pregnant. A negative pregnancy test should be obtained 2 weeks prior to initiation of therapy and therapy should be initiated during a normal menses. Women of childbearing potential should use adequate birth control.

Phototherapy

Phototherapy is usually reserved for moderate to severe psoriasis. Phototherapy involves treatment with UVB alone. Broadband UVB phototherapy has been an effective approach to

treatment of moderate to severe psoriasis. In recent years, a shift to narrow band UVB (311-313 nm) has become the most optimal irradiation available today.

Treatment with UVB is time consuming, requiring 2-3 visits/week for treatment for several months and the possibility of experiencing an acute sunburn reaction.

2.3 Availability of Proposed Active Ingredient in the United States

Clobetasol propionate was first approved for the treatment of psoriasis in the United States in the 1980's. Clobetasol propionate is currently available in the U.S. in topical ointment, cream, emollient cream, gel, solution, shampoo, and foam formulations. These products are super potent topical steroids, which although are very efficacious in the treatment of corticosteroid responsive dermatoses, can cause reversible HPA axis suppression within 2 weeks of use. Therefore, treatment is limited to 2 weeks for all of the clobetasol propionate products with the exception of Temovate Emollient Cream, 0.05%, with no more than 50 grams of medication to be used in a week. Temovate Emollient Cream can be applied to 5% to 10% of BSA for up to 4 consecutive weeks as long as additional benefits of using the drug product beyond 2 weeks is weighed against the risk of HPA axis suppression.

Cutaneous side effects include atrophy of the skin and appearance of telangiectasia. These effects may also occur within 2 weeks with this super potent class of topical corticosteroids, although the usual is after prolonged use.

Two formulations, the lotion and shampoo, are limited to patients 18 years of age and older. The other formulations can be used in patients 13 years of age and older.

2.4 Important Issues with Pharmacologically Related Products

The most important safety issue with the super potent class of topical corticosteroids is their ability to cause HPA axis suppression. When used appropriately, according to labeling, it appears that in most instances the HPA axis suppression is short term and reversible.

2.5 Presubmission Regulatory Activity

PreIND Meeting – 12/19/2000

- Sponsor at this point considering a 505 (b)(2) route
- Advised they would need a reference listed drug (RLD) product
- Advised that systemic safety via HPA axis suppression studies would need to be performed to help determine the efficacy endpoint and if doing as a 505 (b)(2), would have to compare to the RLD

End-of-Phase 2 Meeting – 3/18/02

- Sponsor decided to pursue a 505 (b)(1) route and submit 2 well-designed placebo controlled trials
- Sponsor advised to take a nested approach with the drug product, looking at efficacy at the 2 week time point and if a success at that time point, the 4 week time point would be evaluated.
- The sponsor is expected to have systemic safety data performed for the 2 week and 4 week time point
- The primary efficacy time point is the Overall Disease Severity for psoriasis dichotomized a priori in the protocol to success vs. failure for both efficacy time points.

Pre-NDA Meeting - 10/5/04

- Sponsor plans to submit 2 placebo controlled trials to support a 505 (b)(1) application
- Line listings should be provided for all patients who participated in the HPA axis suppression studies
- Provide plans for pediatric development of Clobex Spray. If no plans, appropriate sections of the label concerning pediatric patients will come from the Clobex Lotion label.
- The 120-day safety update should be submitted along with a review of all available safety data from all Clobex products.

2.6 Other Relevant Background Information

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

Reviewer's Comment: *The following is a summary of the animal toxicology data as taken from Dr. Jill Merrill's review. For more details, the reader is referred to that review.*

The sponsor conducted a 90 day dermal toxicity study of 0.05% clobetasol propionate spray in micro-pigs. Local effects in the skin included irritation, breakdown of connective tissue, hyperkeratosis, increase in basophilic material and epidermal inflammation. The systemic effects were typical of corticosteroids, such as thymic and adrenal atrophy, which were observed grossly and microscopically. Systemic effects of the clobetasol propionate were observed even though the toxicokinetic measurements seldomly detected quantifiable levels of drug. This phenomenon is also observed in human studies of potent corticosteroids. A NOEL was not identified in this study. Adrenal atrophy, white blood cell changes and skin effects were noted even at the low dose of 150 mg/kg (3900 mg/m^2). This dose was equal to approximately 1.6 mg/cm^2 at the site of application.

A dosage level of less than 12.5 µg/kg/day was considered to be the NOEL for maternal toxicity and a dosage level of 12.5 µg/kg/day was considered the NOAEL for viability and growth in the offspring after subcutaneous administration to rats on gestation day 7 through lactation day 25. According to CPSC-FSHA guidelines, clobetasol propionate (0.05%) was considered to be an ocular irritant in both rinsed and nonrinsed eyes when tested in rabbits. However, it was classed as nonirritating to rabbit skin. Clobetasol propionate was not sensitizer when tested in the guinea pig maximization test.

Dr. Merrill does state, "Clobetasol propionate, like other corticosteroids, is teratogenic in multiple species when administered at sufficient doses and at the vulnerable gestational periods. Topical application of clobetasol propionate appears to be less likely to result in teratogenic effects probably due to lower exposure to clobetasol propionate by the topical route than by systemic exposure."

No other non-clinical studies have been recommended at this time, but the sponsor has committed to phase 4 animal carcinogenicity studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Data used in the review of this drug product for the indication of the treatment of moderate to severe psoriasis in patients 18 years of age or older came entirely from the sponsor's NDA submission. This also includes the 120-day safety update submitted to the NDA on 4/25/05.

4.2 Tables of Clinical Studies

Phase 3 Pivotal Trials

Study ID	Number of Study Centers Locations	Study start Enrollment status, date Total enrollment/ Enrollment goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	#Subjects by arm entered/ completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
101-1008	6 USA	September 2002 Study completed April 2003 120 subjects enrolled/108-	Multiple center, randomized double blind vehicle controlled, parallel group,	Clobex spray, 0.05%; topically applied to psoriatic plaques bid for up to 4 weeks	Clobex Spray, 0.05%; treatment group 60/55	4 weeks	Clobex Spray, 0.05% 38M/22F 46.72 (21.0 – 76.0) years	Plaque psoriasis 1. Subject with at least 2% BSA involvement (excluding scalp, face, groin, axillae, and other intertriginous	Dichotomized Overall severity score. The scale of 0 (clear) to 4 (severe/very severe) was used. Success was defined

		120	compara-tive study.	Clobex Spray Vehicle, topically applied to psoriatic plaques bid for up to 4 weeks	Clobex Spray Vehicle, 0.05% treatment group 60/52		Clobex Spray Vehicle, 0.05% 34M/26F (49.3 (24.0 – 73.0) years	areas. 2. Subject had an Overall Disease Severity score of at least 3 (moderate, on a 0-4 scale) on the area of plaque psoriasis to be treated	as a grade of 2 or less on the 0-4 scale at Week 2 or earlier and defined as a grade of 1 or less on the 0-4 point scale at the end of treatment (Week 4 or later).

Adapted from table 2.7.3.1.1 of eCTD, page 2 of the Summary of Clinical Efficacy

Study ID	Number of Study Centers Locations	Study start Enrollment status, date Total enrollment/ Enrollment goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	#Subjects by arm entered/ completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
101-	6 USA	September 2002 Study completed April 2003 120 subjects enrolled/108-120	Multiple center, randomized double blind vehicle controlled, parallel group, compara-tive study.	Clobex spray, 0.05%; topically applied to psoriatic plaques bid for up to 4 weeks Clobex Spray Vehicle, topically applied to psoriatic plaques bid for up to 4 weeks	Clobex Spray, 0.05%; treatment group 60/55 Clobex Spray Vehicle, 0.05% treatment group 60/47	4 weeks	Clobex Spray, 0.05% 31M/29F 46.17 (18.0 – 81.0) years Clobex Spray Vehicle, 0.05% 37M/23F (45.9 (18.0 – 77.0) years	Plaque psoriasis 1. Subject with at least 2% BSA involvement (excluding scalp, face, groin, axillae, and other intertriginous areas. 2. Subject had an Overall Disease Severity score of at least 3 (moderate, on a 0-4 scale) on the area of plaque psoriasis to be treated	Dichotomized Overall severity score. The scale of 0 (clear) to 4 (severe/very severe) was used. Success was defined as a grade of 2 or less on the 0-4 scale at Week 2 or earlier and defined as a grade of 1 or less on the 0-4 point scale at the end of treatment (Week 4 or later).

Adapted from table 2.7.3.1.1 of eCTD, page 3 of the Summary of Clinical Efficacy

Phase 2 Safety Trials

Study ID	Number of Study Centers Locations	Study start Enrollment status, date Total enrollment/ Enrollment goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	#Subjects by arm entered/ completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Axis	2 USA	September 2001	Dual-center Open-label	BID topical application	16/14	4 weeks	11M/5F	Psoriasis 1. Stable plaque	Cosyntropin Stimulation

7101-)1009		Study completed March 2002 16 subjects enrolled/16	non-compara-tive study of laboratory-based HPA Axis suppression	of Clobex Spray, 0.05% to all psoriasis plaques, ~ 7 grams a day for 4 weeks			37.75 (20.0 – 55.0) years	psoriasis with minimum body surface are of 20% 2. Overall disease severity score of at least 5 (midpoint between Moderate and Severe)	Test at week 4/end of treatment for safety; Overall Disease Severity and Signs and Symptoms for Psoriasis for Efficacy
IPA \xis)02-)204-)3	4 USA	December 2003 Study completed April 2004 41 subjects enrolled/40	Multicenter open-label non-compara-tive study of laboratory based HPA Axis suppression	BID topical application of Clobex Spray, 0.05% to all psoriasis plaques, ~ 7 grams a day for 2 or 4 weeks	2 week group 21/17 4 week group 20/16	2 or 4 weeks	11M/8/F 49.06 (24.6-66.0) years 15M/2F 44.31 (22.4-61.3) years	Psoriasis 1. Stable plaque psoriasis with minimum body surface area of 20% 2. Overall disease severity score of at least 3 (moderate)	Cosyntropin Stimulation Test at week 2 or 4/end of treatment for safety; Overall Disease Severity and Signs and Symptoms for Psoriasis for Efficacy

\dapted from table 2.7.3.1.1 of eCTD, page 4 of the Summary of Clinical Efficacy

4.3 Review Strategy

In this review, pivotal clinical trials were reviewed in detail. These would include the two phase 3 pivotal trials for efficacy, the 2 HPA axis suppression studies, which are surrogate trials for systemic safety, and the 4 dermal safety studies.

4.4 Data Quality and Integrity

Investigators and study staff were trained during initiation visits prior to enrollment of their first subject.

The data required by the protocol were recorded in the appropriate Case Report Forms (CRFs). Data in the CRFs were validated and verified against original source documentation including, but not limited to patient and hospital records. All subject data were available to the study monitor, who performed a 100% source document review (comparison of the data recorded in the CRFs with those in the source documents). The CRFs, files and all other records are maintained at the study sites.

Data were entered using EntryPoint90/Plus, a data entry software program, and verified by a different person. All discrepancies were reviewed and any resulting queries were resolved with the study sites and amended on the clinical database prior to breaking the treatment blind.

Reviewer's Comment: *The Division requested one DSI inspection of a site, Dr. Karl Beutner's site in Davis, California because of the high efficacy rate of 100% with treatment by the drug*

product reported at this site (see statistical review for an analysis by center). After the audit, DSI did not find any violation of protocol that would influence the results of the study.

4.5 Compliance with Good Clinical Practices

The trials were conducted in accordance with the Helsinki Declaration and in accordance with the CRF. All trials were conducted under an IRB.

In pivotal trial, -01010, 8 subjects who completed the study were considered discontinuations due to protocol violations. One subject was inappropriately enrolled due to incomplete washout of topical medications (last visit was on Day 72). The other 7 patients were enrolled at site 2 and were improperly scheduled for their final visits in week 5 rather than week 8. These patients were counted as discontinuations in the sponsor's report due to this procedural error.

4.6 Financial Disclosures

The sponsor has submitted FDA from 3454 and states that there are no financial conflicts with the clinical investigators that participated in the trials.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

CLOBEX™ (clobetasol propionate) Spray, 0.05% is a super-high potent corticosteroid formulation indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age or older.

6.1.1 Methods

The two pivotal phase 3 trials, T101-01008 and T101-01010 were reviewed in detail to support the proposed indication of the sponsor. As stated in section 4.1, these are identical trials. They are double-blind, placebo controlled, parallel-group, and multicentered trials.

6.1.2 General Discussion of Endpoints

The efficacy endpoint for the two pivotal trials is the "Overall Disease Severity" score. This is a scale that describes the severity of psoriasis from "0" which is clear to "4" which is severe/very severe as indicted in the following table.

Table
Overall Disease Severity

Grade	Score	Description
Clear	0	Scaling: no evidence of scaling Erythema: no evidence of erythema (except possible residual discoloration Plaque elevation: no evidence of plaque elevation above normal skin level
Almost clear	1	Scaling: limited amount of very fine scales partially covers some of the plaques Erythema: very few of the plaques are light red Plaque elevation: very slight elevation above normal skin level, easier felt than seen
Mild	2	Scaling: mainly fine scales, some plaques are partially covered Erythema: some plaques are light red Plaque Elevation: slight but definite elevation above the normal skin level, typically with edges that are indistinct or sloped, on some of the plaques
Moderate	3	Scaling: somewhat coarser scales; most plaques are partially covered Erythema: most plaques are red Plaque Elevation: moderate elevation with rounded or sloped edges on most of the plaques
Severe/Very Severe	4	Scaling: coarse, thick scales; virtually all or all plaques are covered; rough surface Erythema: virtually all or all plaques are bright to dusky red Plaque elevation : marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques
Source: eCTD NDA 21-835, Efficacy Summary, pages 8-9		

Success for the pivotal trials is based on dichotomization of this efficacy endpoint. A statistically significant proportion of patients had to achieve a score of 2 or less on the Overall Disease Severity score scale by week 2 and a statistically significant proportion of patients had to achieve a score of 1 or less on the Overall Disease Severity Score scale by week 4 (end of treatment).

Secondary efficacy endpoints included pruritus and the signs of psoriasis: scaling, erythema, and plaque elevation. Each of these parameters has a severity scale and was dichotomized to success vs. failure, with 0 or 1 being a success. The following tables show the severity scale for each of the secondary efficacy variables.

Table
Signs of Psoriasis – Scaling

Grade	Score	Description
Clear	0	No evidence of scaling
Almost clear	1	Limited amount of very fine scales partially covers some the plaques
Mild	2	Mainly fine scales; some plaques are partially covered
Moderate	3	Somewhat coarser scales; most plaques are partially covered
Severe/Very Severe	4	Coarse, thck scales; virtually all or all plaques are covered; rough surface
Source: eCTD NDA 21-835, Efficacy Summary, page 9		

Table
Signs of Psoriasis – Erythema

Grade	Score	Description
Clear	0	No evidence of erythema (except possible residual discoloration)
Almost clear	1	Very few of the plaques are light red
Mild	2	Some plaques are light red
Moderate	3	Most plaques are red
Severe/Very Severe	4	Virtually all or all plaques are bright to dusky red
Source: eCTD NDA 21-835, Efficacy Summary, page 9		

Table
Signs of Psoriasis – Plaque Elevation

Grade	Score	Description
Clear	0	No evidence of plaque elevation above the normal skin level
Almost clear	1	Very slight elevation above skin level, easier felt than seen
Mild	2	Slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques
Moderate	3	Moderate elevation with rounded or sloped edges on most of the plaques
Severe/Very Severe	4	Marked to very marked elevation, with hard to very hard sharop edges on virtually all or all of the plaques
Source: eCTD NDA 21-835, Efficacy Summary, page 10		

Table
Symptom of Psoriasis – Pruritus

Grade	Score	Description
Clear	0	No evidence of pruritus
Almost clear	1	Pruritus is infrequently noticeable and never disrupts daily activity
Mild	2	Pruritus is noticeable but does not disrupt daily activity
Moderate	3	Urge to scratch occasionally disrupts daily activity
Severe/Very Severe	4	Marked to extreme urge to scratch routinely disrupts daily activity and may disrupt sleep
Source: eCTD NDA 21-835, Efficacy Summary, page 10		

6.1.3 Study Design

The sponsor conducted two multi-center, randomized, double-blind, vehicle-controlled, parallel comparison studies in patients with moderate to severe psoriasis. These studies, conducted entirely in the United States, enrolled a total of 240 subjects with stable plaque psoriasis covering at least 2% body surface area excluding the face, scalp, groin, axillae, and other intertriginous areas. Application of the study medication was made by the subject to affected plaques twice daily for up to 4 weeks. Subjects were evaluated for efficacy (overall disease severity, pruritus and signs of psoriasis: scaling, erythema and plaque elevation) and safety (adverse events and adverse events associated with the use of topical corticosteroids: telangiectasia, skin atrophy, burning/stinging and folliculitis) at Baseline and at Weeks 1, 2, 4 and 8 (or early termination). The Week 8 visit was a follow-up visit 4 weeks after the end of treatment.

6.1.4 Efficacy Findings

The following table summarizes the efficacy results from the two pivotal trials for the primary endpoint, Overall Disease Severity score:

Table
Results of Pivotal Efficacy Studies

Study	Treatment Arm	#Enrolled/ Completed	Primary Efficacy Endpoint	ITT/MITT Results	P value
T010-01008	Clobex (clobetasol propionate) spray, 0.05% Clobex (clobetasol propionate) Spray Vehicle	60/55 60/52	Dichotomized Overall Disease Severity score. The scale of 0 (clear) to 4 (severe/very severe) was used. Success was defined as a grade of 2 or less on the 0-4 point scale at Week 2 or earlier and defined as a grade of 1 or less on the 0-4 point scale at the end of treatment (week 4).	87% success at Week 2 78% success at Week 4 28% success at Week 2 3% success at Week 4	<0.001 Clobex Spray vs. vehicle at week 2 <0.001 Clobex Spray vs. vehicle at week 4
T101-01010	Clobex (clobetasol propionate) spray, 0.05% Clobex (clobetasol propionate) Spray Vehicle	60/55 60/47	Dichotomized Overall Disease Severity score. The scale of 0 (clear) to 4 (severe/very severe) was used. Success was defined as a grade of 2 or less on the 0-4 point scale at Week 2 or earlier and defined as a grade of 1 or less on the 0-4 point scale at the end of	87% success at Week 2 82% success at Week 4 27% success at Week 2 2% success at Week 4	<0.001 Clobex Spray vs. vehicle at week 2 <0.001 Clobex Spray vs. vehicle at week 4

			treatment (week 4).		
Adapted from Sponsor's NDA, eCTD, Section 2.7.3, Summary of Clinical Efficacy, page 6					

As can be seen from the table, Clobex™ Spray, 0.05% was statistically superior to its vehicle at both 2 weeks of treatment and at 4 weeks of treatment, $p<0.001$. In pivotal trial, T010-01008, 87% of patients on Clobex Spray were categorized as a success at week 2 compared to 28% in the vehicle arm and 78% were a success at week 4 in the Clobex Spray arm compared to 3% in the vehicle arm. In the second pivotal trial, T101-01010, 87% of the patients on Clobex Spray had a successful treatment outcome compared to 27% at week 2 and 82% of patients had a successful outcome at week 4 who were treated with Clobex Spray compared to 2% of patients on vehicle.

In study -01008, the aggregate number of subjects on Clobex Spray, 0.05% that were Clear or Almost Clear increased by 42% from 33/60 subjects at week 2 to 47/60 subjects at week 4. In this group, at week 2, the Overall Disease Severity Scores of subjects rated as Clear or Almost Clear were 2% (1/60) and 53% (32/60) respectively in comparison to Week 4 where the ratings were 25% (15/60) (Clear) and 53%(32/60) (Almost Clear). The additional two weeks of therapy resulted in 14 more subjects clearing their disease totally compared to the solitary patient in that group at week 2.

In study -01010, the aggregate number of subjects on Clobex Spray that were Clear or Almost Clear increased by 75% from 28/60 subjects at week 2 to 49/60 subjects at week 4. In this group, at Week 2, the Overall Disease Severity Scores of subjects rated as Clear or Almost Clear were 0% (0/60) and 47% (28/60) respectively in comparison to week 4 where the ratings were 30% (18/60) (clear) and 52% (31/60) (almost Clear). The additional two weeks of therapy resulted in 18 subjects clearing their disease totally compared to no subjects clear in that group at week 2.

The secondary efficacy parameters were reflective of the success observed with the primary efficacy parameter. Success was defined as a score of 0 (clear) or 1 (almost clear) on the severity scale for each sign or symptom of psoriasis. Improvement in all of the secondary efficacy variables: scaling, erythema, plaque elevation, and pruritus showed statistical significance at both efficacy time points of 2 weeks and 4 weeks ($p<0.001$). Tables x and x show the rates of success for the secondary efficacy variables of scaling, erythema, plaque elevation, and pruritus for studies -01008 and -01010, respectively.

Table
Secondary Efficacy Variables
Success Rate – Study T101-01008

	Clobex Spray, 0.05%	Vehicle Spray	P value
Number of Subjects	60	60	
SCALING			
Success Rate* Week 2			
Success	60%	10%	
Failure	40%	90%	<0.001
Success Rate* Week 4			

Success	82%	13%	
Failure	18%	87%	<0.001
ERYTHEMA			
Success Rate* Week 2			
Success	48%	2%	
Failure	52%	98%	<0.001
Success Rate* Week 4			
Success	73%	3%	
Failure	27%	97%	<0.001
PLAQUE ELEVATION			
Success Rate* Week 2			
Success	67%	5%	
Failure	33%	95%	<0.001
Success Rate* Week 4			
Success	80%	7%	
Failure	20%	93%	<0.001
PRURITUS			
Success Rate* Week 2			
Success	80%	30%	
Failure	20%	70%	<0.001
Success Rate* Week 4			
Success	85%	35%	
Failure	15%	65%	<0.001

*Defined as those subjects who obtained a score of 0 (clear) or 1 (almost clear) on the respective severity scales
Adapted from Sponsor's NDA – eCTD Clinical Summary of Efficacy, Section 2.73, pages 26-29

Table
Secondary Efficacy Variables
Success Rate – Study T101-01010

	Clobex Spray, 0.05%	Vehicle Spray	P value
Number of Subjects	60	60	
SCALING			
Success Rate* Week 2			
Success	57%	10%	
Failure	43%	90%	<0.001
Success Rate* Week 4			
Success	82%	7%	
Failure	18%	93%	<0.001
ERYTHEMA			

Success Rate* Week 2 Success Failure Success Rate* Week 4 Success Failure	 45% 55% 83% 17%	 7% 93% 5% 95%	 <0.001 <0.001
PLAQUE ELEVATION Success Rate* Week 2 Success Failure Success Rate* Week 4 Success Failure	 53% 47% 85% 15%	 5% 95% 10% 90%	 <0.001 <0.001
PRURITUS Success Rate* Week 2 Success Failure Success Rate* Week 4 Success Failure	 77% 23% 85% 15%	 40% 60% 32% 68%	 <0.001 <0.001
*Defined as those subjects who obtained a score of 0 (clear) or 1 (almost clear) on the respective severity scales Adapted from Sponsor's NDA – eCTD Clinical Summary of Efficacy, Section 2.73, pages 26-29			

Subgroup Analyses

The ITT population was analyzed to investigate possible differences in response to treatment with respect to gender (males vs. females), ethnicity (race, given as "white" or "non-white"), and age (<65 and ≥65 years). The analysis was performed looking at the primary efficacy variable, "Overall Disease Severity". Table shows the analysis for gender.

Table
Subgroup Analysis for Gender
Pivotal Studies Combined – ITT Population

Variable	Clobetasol Propionate Spray, 0.05% (N=120)	Vehicle Spray (N= 120)
Week 2		
Male Subjects		
Success[1]	59 (86%)	17 (24%)
Failure	10 (14%)	54 (76%)
Female Subjects		
Success[2]	45 (88%)	16 (33%)
Failure	6 (12%)	33 (67%)
P-Value[3]	0.930	0.514

Week 4		
Male Subjects		
Success[1]	55 (80%)	1 (1%)
Failure	14 (20%)	70 (99%)
Female Subjects		
Success[2]	41 (80%)	2 (4%)
Failure	10 (20%)	47 (96%)
P-Value[3]	0.713	0.232

1 Success is defined as a grade of 2 or less on the 0-4 point Overall Disease Severity Scale.
2 Success is defined as a grade of 1 or less on the 0-4 point Overall Disease Severity Scale.
3 P-values obtained from a Cochran-Mantel-Haenszel test, stratified by grouped study sites.
Adapted from the Sponsor's NDA, eCTD Clinical Summary of Efficacy, table 2.7.3.3.3.1, page 57

As can be seen from the table, the percentage of males and females that had a success in the treatment of their psoriasis was not statistically significantly different. Table shows the analysis for ethnicity in the two pivotal efficacy trials.

Table
Subgroup Analysis for Race
Pivotal Studies Combined – ITT Population

Variable	Clobetasol Propionate Spray, 0.05% (N=120)	Vehicle Spray (N= 120)
Week 2		
White Subjects		
Success[1]	92 (86%)	30 (28%)
Failure	15 (14%)	79 (72%)
Non-White Subjects		
Success[2]	12 (92%)	3 (27%)
Failure	1 (8%)	8 (73%)
P-Value[3]	0.739	0.431
Week 4		
White Subjects		
Success[1]	84 (79%)	3 (3%)
Failure	23 (21%)	106 (97%)
Non-White Subjects		
Success[2]	12 (92%)	0 (0%)
Failure	1 (8%)	11 (100%)
P-Value[3]		

1 Success is defined as a grade of 2 or less on the 0-4 point Overall Disease Severity Scale.
2 Success is defined as a grade of 1 or less on the 0-4 point Overall Disease Severity Scale.
3 P-values obtained from a Cochran-Mantel-Haenszel test, stratified by grouped study sites.
Adapted from the Sponsor's NDA, eCTD Clinical Summary of Efficacy, table 2.7.3.3.3.3, page 59

There was no significant difference between the response rate of Whites vs. Non-Whites in the pivotal trials. Table shows the analysis for age. Again, there was no clinically significant or statistically significant difference in response for age.

Table
Subgroup Analysis for Age

Pivotal Studies Combined – ITT Population

Variable	Clobetasol Propionate Spray, 0.05% (N=120)	Vehicle Spray (N= 120)
Week 2		
Age <65 Years		
Success[1]	95 (86%)	28 (26%)
Failure	16 (14%)	80 (74%)
Age ≥65 Years		
Success[2]	9 (100%)	5 (42%)
Failure	0 (0%)	7 (58%)
P-Value[3]	0.206	0.145
Week 4		
Age <65 Years		
Success[1]	89 (80%)	2 (2%)
Failure	22 (20%)	106 (98%)
Age ≥65 Years		
Success[2]	7 (78%)	1 (8%)
Failure	2 (22%)	11 (92%)
P-Value[3]	0.819	0.367

1 Success is defined as a grade of 2 or less on the 0-4 point Overall Disease Severity Scale.
2 Success is defined as a grade of 1 or less on the 0-4 point Overall Disease Severity Scale.
3 P-values obtained from a Cochran-Mantel-Haenszel test, stratified by grouped study sites.
Adapted from the Sponsor's NDA, eCTD Clinical Summary of Efficacy, table 2.7.3.3.3.5, page 61

Relapse and Rebound Flare

Patients were followed for 4 weeks post treatment for persistence of efficacy or evidence of relapse. Table shows the results of both pivotal studies combined at week 8 for Overall Disease Severity for studies T101-01008 and T101-01010.

Table
Analysis of Efficacy at Week 8
(Four Weeks Post Treatment – Pivotal Studies Combined)

	Clobetasol Propionate Spray, 0.05% (N=120)	Vehicle Spray (N= 120)
Overall Disease Severity		
0 (Clear)	11 (10%)	0 (0%)
1 (Almost Clear)	48 (42%)	6 (6%)
2 (Mild)	26 (23%)	25 (23%)
3 (Moderate)	25 (22%)	54 (50%)
4 (Severe/Very Severe)	5 (4%)	22 (21%)
Missing	5	13
Success Rates		
Success	59 (51%)	6 (6%)
Failure	56 (49%)	101 (94%)

Adapted from Sponsor's NDA – eCTD Clinical Summary of Efficacy, Section 2.7.3.5, table 2.7.3.5.1, page 67

As expected, the analysis shows recurrence of psoriasis as evidenced by a decline in success rates for overall disease severity in the ITT Clobex Spray group observed at week 8 (51%) when compared with those at week 4 (80% success).

There was one subject in study 01008 that could be classified as a rebound flare after stopping study medication. Subject 74 had a severity score of 3 at baseline and throughout study treatment. At week eight, the patient's severity score was 4.

Reviewer's Comment: *The data show that Clobex Spray has a sustained effect and low relapse rate. The percentage of patients with a rebound flare was 1/120 (0.8%). This was mild rebound, at the most, as the patient did not improve but was maintained on Clobex Spray and then became worse without any medication. In this reviewer's opinion, the risk for rebound flare with this medication is minuscule. There were not any instances of transformation to life-threatening forms of psoriasis in the follow-up period.*

6.1.5 Clinical Microbiology

This section is not applicable for this topical corticosteroid product.

6.1.6 Efficacy Conclusions

The two pivotal trials in this NDA demonstrated that CLOBEX™ (clobetasol propionate) Spray, 0.05% is efficacious in the treatment of moderate to severe plaque psoriasis. The data demonstrate a clinically significant improvement at 2 weeks for the majority of patients in both trials with 87% of patients in both trials improving from moderate to severe to mild psoriasis. Further, with an additional 2 weeks of treatment, more than three-quarters of the patients, 78% in trial -01008 and 82% in trial -01010, attained clearing or almost clearing of their disease. There was no clinically significant difference in the response rate for gender, race, or age.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in the trials for Clobex Spray, 0.05%.

7.1.2 Other Serious Adverse Events

There were 2 serious adverse events reported in the pivotal trials, both in trial -01008. In the Clobex Spray group, an adverse event of endometriosis and in the vehicle arm, an adverse event of volvulus of the bowel. I would agree with the sponsor that endometriosis is not a side effect of topical corticosteroids. Both events resolved without consequential sequelae.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 10/120 (6.3%) subjects in the phase 3 pivotal trials discontinued because of adverse events. In study -01008 five subjects discontinued because of adverse events, two treated with Clobex Spray and 3 treated with vehicle spray. One subject in the Clobex Spray arm discontinued after three days of treatment due to moderate stinging after each treatment application; one discontinued on Day 51 due to a flare of guttate psoriasis on untreated areas. Two subjects in the Clobex Spray vehicle arm discontinued after 15 and 51 days, respectively because of treatment related burning/stinging. One of these subjects also experienced pain and soreness in the treated areas with edema of the lower legs. The third vehicle treated patient was discontinued after 25 days due to infected eczema.

In study -01010 five subjects discontinued participation from the study due to one or more adverse events. These included mild burning in one subject treated with Clobex Spray and moderate to severe burning/stinging (4 subjects), moderate skin atrophy(1 subject), severe itching (1 subject), and worsening of psoriasis (1 subject) in four Clobex Vehicle Spray subjects.

Reviewer's Comment: *The adverse events of burning and stinging is probably treatment related and as noted in the "Common Adverse Events" section, it appears that this adverse event is due to the vehicle. The incidence of a flare of psoriasis in untreated areas (1/120; 0.8%) is very low and no conclusion can be drawn from this one event.*

7.1.3.1 Overall profile of dropouts

Disposition of Dropouts for Phase 3 Studies Combined

	Clobetasol Propionate 0.05% Spray	Vehicle Spray	Total
Number of Subjects	120	120	240
Subjects completed the study			
Yes	110	99	209
No	10	21	31
Reason for Discontinuation			
Subject's Decision to Withdraw	0	1	1
Lost to Follow-up	2	1	3
Subject's Best Interest	0	0	0
Never Treated with Study Medication	0	0	0
Adverse Event	3	7	10
Non-Compliance	0	1	1

Pregnancy	0	0	0
Ineligible	0	1	1
Treatment Failure	1	6	7
Other*+	4	4	8

*One Subject moved out of town
+ 3 subjects prematurely attended Visit 5
Source: Sponsor's Submission eCTD, Module 5, table 1.2, page 54 (study -01008), Module 5, table 1.2, page 52 (study -01010),

Disposition of Dropouts for Phase 2 Studies Combined

	2 weeks	4 weeks	Total
Number of Subjects	21	36	57
Subjects completed the study			
Yes	19	30	49
No	2	6	8
Reason for Discontinuation			
Abnormal Baseline Serum cortisol Level and/or Abnormal Baseline HPA-System Function	2	2	4
Out-of-Range and Clinically Significant Baseline Laboratory Result	0	1	1
Subject's Decision to Withdraw	0	1	1
Lost to Follow-up	0	0	0
Subject's Best Interest	0	0	0
Never Treated with Study Medication	0	0	0
Adverse Event	0	1	1
Non-Compliance	0	1	1
Pregnancy	0	0	0
Ineligible	0	0	0
Treatment Failure	0	0	0
Other	0	0	0

Source: Sponsor's Submission eCTD, Module 5, table 1.2, page 42 (study D02-0204-03), Module 5, table 1, page 34 (study -01009),

7.1.3.2 Adverse events associated with dropouts

See section 7.1.3. In addition to those adverse events discussed in that section, in study -01009, a phase 2 HPA axis suppression study, one patient experienced chest pain during the cosyntropin injection. The injection was stopped and the patient taken to the emergency room where he was discharged several hours later. The site was unable to obtain the discharge summary and the patient was subsequently lost to follow-up after three unsuccessful attempts at contact by phone and certified mail failed.

Reviewer's Comment: *The exact etiology of the subject's chest pain cannot be ascertained for certain without the discharge summary. However, one can assume that it was not a myocardial infarction, as the patient was discharged from the hospital ER within several hours.*

7.1.3.3 Other significant adverse events

There were not any other significant adverse events.

7.1.4 Other Search Strategies

There are some common adverse events that may be expected when using a topical steroid, especially a super potent one such as clobetasol propionate. Those side effects include telangiectasia, skin atrophy, burning/stinging, and folliculitis. To this end, the sponsor had investigators specifically examine and query patients for these effects. The investigators in these trials also looked for clinical signs/symptoms of adrenal suppression for we know that clobetasol propionate can cause laboratory evidence of adrenal suppression. The table below illustrates that for the major adverse events that might be expected, telangiectasia, skin atrophy, and folliculitis, it is significant that these effects did not occur, even at 4 weeks post treatment. This is not to say that with repeated courses over time, these events may not occur, as they are usually late occurring events. As mentioned elsewhere in the review, the burning/stinging appears to be due to the vehicle spray and not the chemical moiety.

Summary of Queried Adverse Events Associated with Topical Application of Corticosteroids

Clobex Spray	**Baseline**	**Week 1**	**Week 2**	**Week 4**	**Week 8**
Telangiectasia					
N	120	117	117	118	115
Absent	120 (100%)	117 (100%)	117 (100%)	118 (100%)	115 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin Atrophy					
N	120	117	117	118	115
Absent	120 (100%)	117 (100%)	117 (100%)	118 (100%)	115 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Burning/Stinging					
N	120	117	117	118	115
Absent	100 (83%)	83% (71%)	88 (75%)	93 (79%)	111 (97%)
Present	20 (17%)	34 (29%)	29 (25%)	25 (21%)	4 (3%)
Folliculitis					
N	120	117	117	118	115
Absent	120 (100%)	117 (100%)	117 (100%)	118 (100%)	115 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clinical Signs/Symptoms of Adrenal Suppression					
N	120	117	117	118	115
Absent	120 (100%)	117 (100%)	117 (100%)	118 (100%)	115 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vehicle Spray *Telangiectasia*					
N	120	118	118	112	107
Absent	120 (100%)	118 (100%)	118 (100%)	112 (100%)	107 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin Atrophy					

N	120	118	118	112	107
Absent	120 (100%)	118 (100%)	117 (99%)	112 (100%)	107 (100%)
Present	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Burning/Stinging					
N	120	118	118	112	107
Absent	96 (80%)	81 (69%)	83 (70%)	76 (68%)	102 (95%)
Present	24 (20%)	37 (31%)	35 (30%)	36 (32%)	5 (5%)
Folliculitis					
N	120	118	118	112	107
Absent	120 (100%)	118 (100%)	118 (100%)	112 (100%)	107 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Clinical Signs/Symptoms of Adrenal Suppression					
N	120	118	118	112	107
Absent	120 (100%)	118 (100%)	118 (100%)	112 (100%)	107 (100%)
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Source: Sponsor's eCTD NDA submission, Module 2, table 2.7.4.2.1.5, page 37					

7.1.5 Common Adverse Events

The most common adverse event found with the use of Clobex (clobetasol propionate spray), 0.05% was that of application site burning. This occurred equally as much in the vehicle spray arm, with 40% experiencing this adverse event on Clobex Spray and 47% experiencing it on vehicle. This suggests that the adverse event is due to the vehicle and not to the chemical moiety. Although this is a significant incident for an adverse event, the majority of these were mild in severity and very few dropouts were because of this event. Of the 240 patients in the pivotal trials, 8 (3.3%) discontinued because of burning/stinging. Only 2/120 (1.6%) dropped in the Clobex (clobetasol propionate) Spray, 0.05% arm, suggesting that the chemical moiety may have some mitigating effect on this adverse event contributed by the vehicle. It is likely, however, that some patients will not be able to tolerate the drug because of this adverse event.

The second most common adverse events reported were associated with the class Infections and Infestations which were reported in 17 subjects (14%) in the CLOBEX™ (clobetasol propionate) Spray,0.05% group and in 12 subjects (10%) in the CLOBEX™ (clobetasol propionate) Spray Vehicle group. The majority of events in this class were related to upper respiratory tract infections (URI) and nasopharyngitis. In the CLOBEX™ (clobetasol propionate) Spray, 0.05% group, 10 subjects (8%) reported upper respiratory tract infections and 6 subjects (5%) reported nasopharyngitis. In the CLOBEX™ (clobetasol propionate) Spray Vehicle group the incidence of upper respiratory tract infections and nasopharyngitis within this class were 2 subjects (2%) and 3 subjects (3%), respectively.

See section 7.5.1.3 for the common adverse event table that most likely should be included in labeling for this drug product.

7.1.5.1 Eliciting adverse events data in the development program

In the phase 3 clinical trials, the sponsor reports that the investigator instructed the subject to report any adverse events that occurred during the study. At each visit, the investigator asked the subject, in a non-directive fashion, about any change in the subject's overall condition since the

previous visit. The investigator decided whether the particular problem was study medication related or not and recorded his/her decision accordingly, using the definitions included with the Non-Serious Adverse Events CRF. There was no attempt to adjust the percentage of subjects with first occurrences of an adverse event on the basis of treatment exposure to calculate a true incidence rate, e.g. number of adverse events per subject-month of treatment.
Pruritus was evaluated from the subject's report at each study visit and reported as an adverse event if additional supportive therapy was required. In addition, at each visit the investigator specifically queried the subject about adverse events associated with topical application of corticosteroids (Telangiectasia, Skin atrophy, Burning/stinging, and Folliculitis).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used the MedDRA system of classification for adverse events that occurred in the study.

7.1.5.3 Incidence of common adverse events

The incidence of common adverse events that occurred at a rate of 1% or greater in either the drug product (Clobetasol propionate arm) or the vehicle arm is listed below in section 7.1.5.4. The following table will highlight those common adverse events that occurred at a greater than 1% incidence in the clobetasol arm as compared to vehicle and/or most likely related to study drug and /or vehicle.

Variable	Clobetasol Propionate 0.05% Spray (N=120)	Vehicle Spray (N=120)	P-Value*
System Organ Class			
General disorders and administration site conditions	50 (42%)	56 (47%)	0.516
Application site atrophy	0 (0%)	1 (1%)	1.000
Application site burning	48 (40%)	56 (47%)	0.362
Application site dryness	2 (2%)	0 (0%)	0.498
Application site irritation	1 (1%)	0 (0%)	1.000
Application site pain	1 (1%)	2 (2%)	1.000
Application site pigmentation changes	1 (1%)	0 (0%)	1.000
Application site pruritus	4 (3%)	3 (3%)	1.000
Infections and infestations	17 (14%)	12 (10%)	0.429
Influenza	0 (0%)	2 (2%)	0.498
Nasopharyngitis	6 (5%)	3 (3%)	0.499
Pharyngitis streptococcal	1 (1%)	0 (0%)	1.000
Upper respiratory tract infection	10 (8%)	2 (2%)	0.034
Skin and subcutaneous tissue disorders	4 (3%)	2 (2%)	0.684
Eczema asteatotic	2 (2%)	0 (0%)	0.498

a Fisher's Exact test was used to compare the proportion of subjects in each treatment group who reported adverse events and to compare system organ classes and preferred terms reported by at least 1% of subjects in either group. Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class (Version 7.0). At each level of summarization (system organ

class or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Source: Sponsor's eCTD

7.1.5.4 Common adverse event tables

Treatment Effect P-Values for Adverse Events Occurring at a Frequency of ≥ 1% of Subjects in at Least One Group (Pivotal Studies T101-01008 and T101-10101 Combined)

Variable	Clobetasol Propionate 0.05% Spray (N=120)	Vehicle Spray (N=120)	P-Value*
Number of Subjects Reporting Events	68 (57%)	70 (58%)	0.896
System Organ Class			
Ear and labyringth disorders	0 (0%)	1 (1%)	1.000
Ear Pain	0	1 (1%)	1.000
Eye Disorders	2 (2%)	2 (2%)	1.000
Eye disorder	1 (1%)	0 (0%)	1.000
Eye movement disorder	1 (1%)	0 (%)	1.000
Eye pruritus	0 (%)	1 (1%)	1.000
Retinal degeneration	0 (0%)	1 (1%)	1.000
Gastrointestinal disorders	3 (3%)	3 (3%)	1.000
Abdominal pain upper	0 (0%)	1 (1%)	1.000
Diarrhea	1 (1%)	1(1%)	1.000
Gastritis	0 (0%)	1 (1%)	1.000
Melana	1 (1%)	0 (0%)	1.000
Nausea	0 (0%)	1 (1%)	1.000
Toothache	1 (1%)	0 (0%)	1.000
Volvulus of bowel	0 (0%)	1 (1%)	1.000
General disorders and administration site conditions	50 (42%)	56 (47%)	0.516
Application site atrophy	0 (0%)	1 (1%)	1.000
Application site burning	48 (40%)	56 (47%)	0.362
Application site dryness	2 (2%)	0 (0%)	0.498
Application site irritation	1 (1%)	0 (0%)	1.000
Application site pain	1 (1%)	2 (2%)	1.000
Application site pigmentation changes	1 (1%)	0 (0%)	1.000
Application site pruritus	4 (3%)	3 (3%)	1.000
Edema peripheral	0 (0%)	1 (1%)	1.000
Rigors	0 (0%)	1 (1%)	1.000
Sensation of pressure	0 (0%)	1 (1%)	1.000
Infections and infestations	17 (14%)	12 (10%)	0.429
Candidiasis	0 (0%)	1 (1%)	1.000
Eczema infected	0 (0%)	1 (1%)	1.000
Gastrointeritis	1 (1%)	0 (0%)	1.000
Herpes simplex	0 (0%)	1 (1%)	1.000
Hordeolum	0 (0%)	1 (1%)	1.000

Influenza	0 (0%)	2 (2%)	0.498
Nasopharyngitis	6 (5%)	3 (3%)	0.499
Pharyngitis streptococcal	1 (1%)	0 (0%)	1.000
Sinusitis	1 (1%)	1 (1%)	1.000
Tooth abscess	0 (0%)	1 (1%)	1.000
Upper respiratory tract infection	10 (8%)	2 (2%)	0.034
Injury, poisoning and procedural complications	4 (3%)	3 (3%)	1.000
Back injury	1 (1%)	0 (0%)	1.000
Excoriation	1 (1%)	0 (0%)	1.000
Injury	0 (0%)	1 (1%)	1.000
Joint dislocation	0 (0%)	1 (1%)	1.000
Laceration	1 (1%)	0(0%)	1.000
Post procedural pain	1 (1%)	1 (1%)	1.000
Investigations	1 (1%)	0 (0%)	1.000
Albumin urine present	1 (1%)	0 (0%)	1.000
Musculoskeletal and connective tissue disorders	11 (9%)	9 (8%)	0.816
Arthralgia	1 (1%)	0 (0%)	1.000
Arthritis	1 (1%)	0 (0%)	1.000
Back pain	4 (3%)	2 (2%)	0.684
Myalgia	2 (2%)	3 (3%)	1.000
Osteoarthritis	0 (0%)	1 (1%)	1.000
Osteoporosis	1 (1%)	0 (0%)	1.000
Pain in extremity	1 (1%)	2 (2%)	1.000
Rotator cuff syndrome	1 (1%)	0 (0%)	1.000
Tenosynovitis stenosans	0 (0%)	1 (1%)	1.000
Nervous System Disorders	4 (3%)	3 (3%)	1.000
Headache	4 (3%)	3 (3%)	1.000
Psychiatric disorders	1 (1%)	0 (0%)	1.000
Insomnia	1 (1%)	0 (0%)	1.000
Reproductive system and breast disorders	1 (1%)	0 (0%)	1.000
Endometriosis	1 (1%)	0 (0%)	1.000
Respiratory, thoracic and mediastinal disorders	0 (0%)	3 (3%)	0.247
Pharyngolaryngeal pain	0 (0%)	3 (3%)	0.247
Skin and subcutaneous tissue disorders	4 (3%)	2 (2%)	0.684
Eczema asteatotic	2 (2%)	0 (0%)	0.498
Psoriasis aggrevated	2 (2%)	2 (2%)	1.000
Surgical and medical procedures	1 (1%)	0 (0%)	1.000
Dental operation	1 (1%)	0 (0%)	1.000

a Fisher's Exact test was used to compare the proportion of subjects in each treatment group who reported adverse events and to compare system organ classes and preferred terms reported by at least 1% of subjects in either group. Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class (Version 7.0). At each level of summarization (system organ class or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Source: sponsor's eCTD submission, Module 2, table 2.7.4.2.1.1, pages 25-27

7.1.5.5 Identifying common and drug-related adverse events

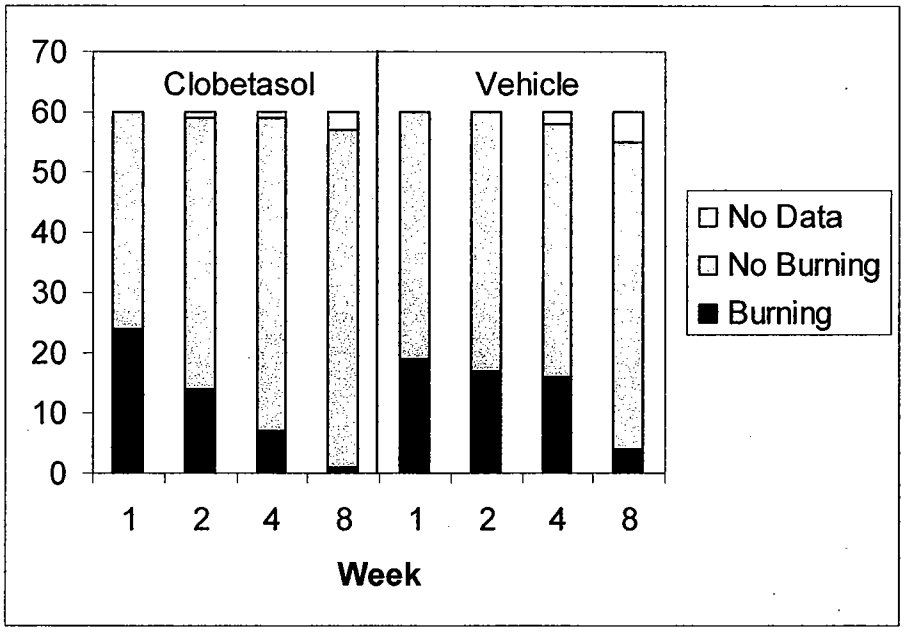
The most common adverse event in the studies, application site burning, which occurred in 40% of patients on study drug, is drug-related. As this also occurred in 47% of patients on vehicle, also, it is clear that the adverse event is related to the vehicle and not the chemical moiety. Other

common adverse events that appear to be related to topical application of Clobex Spray are application site pruritus (3%), application site dryness (2%), and eczema asteatotic (2%). Other common adverse events, upper respiratory tract infections (8%) and nasopharyngitis (5%), cannot be so clearly linked to the drug product.

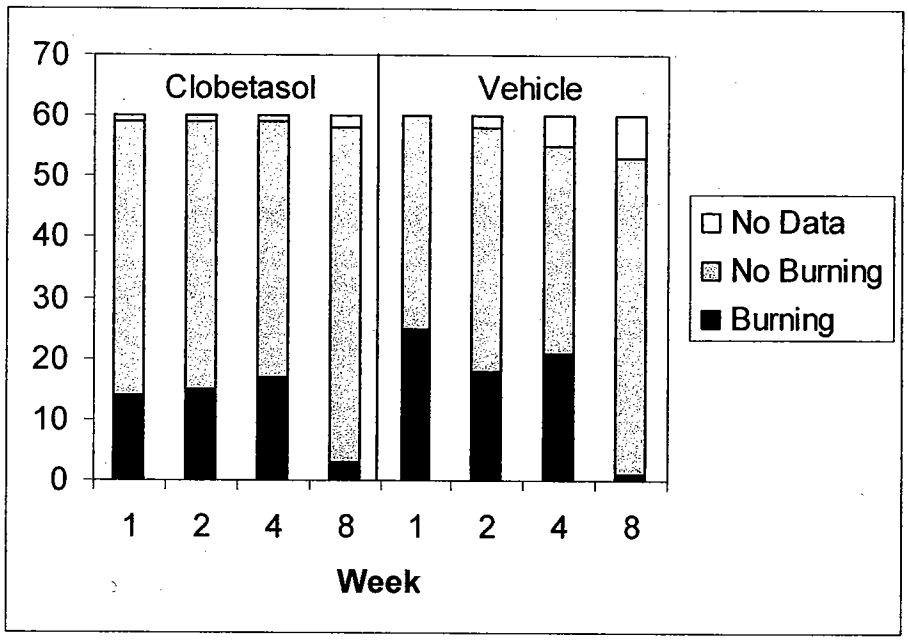
7.1.5.6 Additional analyses and explorations

The most common adverse event that occurred in the pivotal trials was that of application site burning. As can be seen from the charts below, in study -01008, this adverse event dissipated over time, although it appeared to be constant in study -01010 (from Statistical Review by Dr. Kathleen Fritsch, page 18). The dropouts in the trials for this adverse event was lower in the Clobex Spray, 0.05% arm, 2/120 (1.7%) than in the Clobex Vehicle arm, 6/120 (5%). This is, no doubt, due to the anti-inflammatory properties of the chemical moiety, clobetasol propionate, found in the drug product arm. In study -01010, the chart shows lesser complaints by week 8 in the Clobex vehicle arm than in the Clobex Spray arm. However, this may be due to the fact that 4 patients dropped out earlier in the study due to this complaint.

Adverse Event – Burning/Stinging Over Time
Pivotal Trial – T101-01008



Adverse Event – Burning/Stinging Over Time
Pivotal Trial – T101-01010



7.1.6 Less Common Adverse Events

There were not any adverse events that could be classified as rare events of significant concern.

7.1.7 Laboratory Findings

Routine laboratory monitoring was performed in the open-label HPA axis suppression studies, studies T101-01009 and D02-0204-03. These included routine chemistries, CBC, and urinalysis. There were no abnormalities of significance that could be attributed to Clobex Spray. Specifically, there were not any abnormalities in serum glucose that could be considered a direct effect of the drug product. Most serum glucoses remained in the normal range. For those that began with elevated glucoses, the changes in serum glucose throughout the study were not significant.

7.1.7.1 Overview of laboratory testing in the development program

The following table is a summary of the number of patients exposed to drug product who had laboratory testing.

Laboratory Test	**Number of Exposed Patients at Baseline**	Number of Exposed Patients with Follow-up
Chemistries*	54	52
Hematology*	55	51
U/A*	56	52
Serum Cortisol*	57	49
ACTH[a]	16	15

Serum Pregnancy[1]	59	58

*Open- label Phase 2 HPA axis suppression studies combined
[a]Study T101-01009 – Open- label HPA axis suppression
[1]Phase 2 and Phase 3 trials

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

Given that there is a wealth of data on the chemical moiety, clobetasol propionate spray, in all of its approved forms; laboratory data was not collected in the controlled studies but in the open-label studies. As expected, there were no significant safety signals detected.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7

7.1.7.4 Additional analyses and explorations

As there were not any significant laboratory abnormalities attributable to the drug product, there were no additional analyses or explorations.

7.1.7.5 Special assessments

As there were not any significant laboratory abnormalities attributable to the drug product, there were no additional analyses or explorations.

7.1.8 Vital Signs

Vital signs were not done in these studies.

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were not done in these studies.

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

Vital signs were not done in these studies.

7.1.8.3 Standard analyses and explorations of vital signs data

Vital signs were not done in these studies.

7.1.8.4 Additional analyses and explorations

There were not additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

This section is not applicable to this drug product. EKGs were not performed. There is not any evidence that topically applied corticosteroids effect the heart rhythm.

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

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

Not applicable. See comment section 7.1.9

7.1.9.3 Standard analyses and explorations of ECG data

EKGs were not performed.

7.1.9.4 Additional analyses and explorations

See comment section 7.1.9

7.1.10 Immunogenicity

See section 7.1.12, "Special Safety Studies" for topical dermal studies performed.

7.1.11 Human Carcinogenicity

There were no formal analyses to explore human carcinogenicity.

7.1.12 Special Safety Studies

Special safety studies were done in this NDA. These included two phase 2 HPA axis suppression studies, which are done to ascertain the systemic effect of topical corticosteroids, and 4 phase 1 dermal safety studies, done under exaggerated conditions in an effort to ascertain topical adverse effects of the drug product. These effects include contact irritancy, contact allergy, contact photoirritancy, and contact photoallergy.

Phase 2 HPA Axis Suppression Studies

Study T101-01009

Study T101-01009 was a 4-week study with 14 evaluable subjects that had moderate to severe plaque psoriasis with at least 20% BSA involvement. Subjects applied colobetasol propionate spray, 0.05% to all psoriasis plaques twice daily for 28 days or until the investigator verified the subject's psoriasis had cleared. Study medication was not applied to the face, scalp, groin, axillae and other intertriginous areas. The study was designed to determined the adrenal suppression potential of the study medication when the subject applied s maximum of 7 grams daily (3.5 grams twice daily) for a total of approximately 50 grams per week.

Subjects received the cosyntropin stimulation test prior to treatment and at the end of treatment. Patients received 0.25 mg of cosyntropin intravenously over a two-minute period. The sponsor's definition of an abnormal response to cosyntropin stimulation is as follows: (1) a pre-stimulation plasma cortisol level less than or equal to 5 micrograms/100 mL, or (2) an increase in the 30-minute post-stimulation plasma cortisol level by less than 7 micrograms/100 mL above pre-stimulation level, or (3) the 30-minute post-stimulation plasma cortisol level less than or equal to 18 micrograms/100 mL AND was less than double the pre-stimulation plasma cortisol level.

Reviewer's Comment: *The Agency considers an abnormal response to cosyntropin stimulation, and thus an indication of HPA axis suppression, a serum cortisol value that is ≤ 18 µg/dL. Below is a table that denotes the subjects with an abnormal response to cosyntropin stimulation according to the sponsor and to this reviewer. Given our criteria, only 2/14 (14.3%) of patients experienced HPA axis suppression and these 2 patients recovered when retested 7-8 days post treatment.*

Summary Statistics for Cosyntropin Stimulation Test in Subjects with Abnormal Response Study T101-01009

	Visit 2		Visit 5		Visit 6		Days out from Visit 5
Subject	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	
Sponsor's Analysis							
1/ [redacted]	7.1	20.0	7.4	14.5	13.7	21.0	7 days
5/ [redacted]	12.4	20.9	14.3	19.8	16.5	24.3	7 days
9/ [redacted]	11.0	26.0	2.0	6.6	16.0	24.0	8 days
11 [redacted] *	32.0	39.0	34.0	38.0	33.0	36.0	10 days
Reviewer's Analysis							
1 [redacted]	7.1	20.0	7.4	14.5	13.7	21.0	7 days
9 [redacted]	11.0	26.0	2.0	6.6	16.0	24.0	8 days

* Sponosr still considered this patient suppressed and a repeat CST test was performed 8 days later and the patient had a pre value of 24 ug/dL and a post value of 31 ug/dL
Source: Adapted from Sponsor's eCTD – Module 2, table 2.7.2.2.2, pages 15-16

Study D02-0204-03

This study had two cohorts of patients. There were 19 evaluable patients from the 2-week cohort and 16 evaluable patients from the 4-week cohort. All subjects had moderate to severe plaque psoriasis with at least 20% BSA involvement. Subjects applied colobetasol propionate spray, 0.05% to all psoriasis plaques twice daily for 14 or 28 days or until the investigator verified the subject's psoriasis had cleared. Study medication was not applied to the face, scalp, groin, axillae and other intertriginous areas. The study was designed to determine the adrenal suppression potential of the study medication when the subject applied s maximum of 7 grams daily (3.5 grams twice daily) for a total of approximately 50 grams per week.

Subjects received the cosyntropin stimulation test prior to treatment and at the end of treatment. Patients received 0.25 mg of cosyntropin intravenously over a two-minute period. The sponsor's definition of an abnormal response to cosyntropin stimulation is as follows: (1) a pre-stimulation plasma cortisol level less than or equal to 5 micrograms/100 mL, or (2) an increase in the 30-minute post-stimulation plasma cortisol level by less than 7 micrograms/100 mL above pre-stimulation level, or (3) the 30-minute post-stimulation plasma cortisol level less than or equal to 18 micrograms/100 mL AND was less than double the pre-stimulation plasma cortisol level.

Reviewer's Comment: *Again, as in study -01009, the Agency considers an abnormal response to cosyntropin stimulation, and thus an indication of HPA axis suppression, a serum cortisol value that is ≤ 18 µg/dL. Below is a table that denotes the subjects with an abnormal response to cosyntropin stimulation according to the sponsor and to this reviewer. Given our criteria, in the 2 week cohort, 3/19 (15.8%) of patients experienced HPA axis suppression and in the 4-week cohort 3/15(20%) of patients experienced HPA axis suppression. This reviewer reduced the number of evaluable patients in the 4-week cohort to 15, as 2 patients cleared at the end of 2 weeks. One of those 2 patients suppressed and was excluded from the number of patients who suppressed after 4 weeks of treatment. All patients did recover when re-stimulated at a later date. Below is a table of the results of patients with an abnormal response to cosyntropin stimulation, according to both the sponsor and this reviewer.*

Summary Statistics for Cosyntropin Stimulation Test in Subjects with Abnormal Response Study D02-0204-03 – 2-week Cohort

	Visit 1		Visit 3		Follow-up		Days out from Visit 3
Subject	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	
Sponsor's Analysis							
13	9.5	31.9	7.0	18.0	11.7	40.3	16*
14	18.1	37.4	0.7	24.7	19.5	37.0	9
30	10.3	22.9	0.9	8.2	9.1	21.1	7
41[a]	7.1	20.8	0.3	3.3	14.1	20.7	7
Reviewer's Analysis							
13	9.5	31.9	7.0	18.0	11.7	40.3	16*
30	10.3	22.9	0.9	8.2	9.1	21.1	7
41[a]	7.1	20.8	0.3	3.3	14.1	20.7	7

*Patient was not flagged as abnormal at first, therefore there was a lag time before the patient was retested.

[a]Patient was retested under the sponsor's criteria, and 9 days later pre value was 10.5 µg/dL and post value was 21.8 µg/dL
Source: Adapted from Sponsor's eCTD – Module 2, table 2.7.2.2.5, pages 22-23

Summary Statistics for Cosyntropin Stimulation Test in Subjects with Abnormal Response Study D02-0204-03 – 4-week Cohort

	Visit 1		Visit 4		Follow-up		Days out from Visit 3
Subject	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	Pre µg/dL	Post µg/dL	
Sponsor's Analysis							
4	15.8	28.7	0.6	4.7	11.7	20.7	7
7	15.2	22.9	11.7	16.4*	19.2	25.6	7
27	22.2	41.6	3.3	14.2	12.1	22.8	6
29	15.8	24.6	9.1	16.7	10.1	24.6	7
Reviewer's Analysis							
4	15.8	28.7	0.6	4.7	11.7	20.7	7
27	22.2	41.6	3.3	14.2	12.1	22.8	6
29	15.8	24.6	9.1	16.7	10.1	24.6	7

*Patient cleared after 2 weeks of treatment. Treatment discontinued and patient had cosyntropin stimulation
Source: Adapted from Sponsor's eCTD – Module 2, table 2.7.2.2.6, pages 24-25

Reviewer's Comment: *After 2 weeks of treatment with Clobex Spray, 0.05%, 15.8% of subjects suppressed. After 4 weeks of treatment with Clobex Spray, 0.05%, suppression varied from 14.3% in one study to 20% in a second study. When one looks at the results of all three cohorts across both studies, there is a slight increase in risk for HPA axis suppression when Clobex Spray is used for 4 weeks. However, this small difference (1.4%) is acceptable. There were not any clinical signs of adrenal insufficiency in any of the patients in the open-label trials.*

Phase 1 Dermal Safety Studies

Study T101-01004 – 21-Day Cumulative Irritation Test of Clobetasol Propionate Spray, 0.05%

This was a single-center, within subject, randomized, positive and vehicle controlled, evaluator blind trial to test the cumulative irritancy potential of Clobex Spray, 0.05% in healthy volunteers. The test products included Clobex Spray, 0.05%, its vehicle spray, and a positive control, sodium lauryl sulfate, 0.5%. The study testing began on June 11, 2001 and ended July 2, 2001.

Thirty healthy males and females participated in the study, all of whom were at least 18 years of age. Females were ineligible if they were pregnant or nursing. Females enrolled in this study were required to be post-menopausal, surgically sterile or using an effective form of birth control. A negative urine pregnancy test was required for all fertile females to be enrolled into the study.

Each subject received a total of 18 applications of test material under occlusive patches with 0.2 ml or 0.2 g of study medication over a 3 week period. Patches were placed on the backs

of subjects and left in place for 24 hours. The patches were then removed and after 5 minutes but before 16 minutes, the sites were graded for irritation. This process was repeated 6 times a week for 21 days. If severe (Grade 4) was observed at any site, no further applications were made to that site, and the maximum score was assigned to that site for the duration of the study.

The following grading system was used:

0 = No sign of erythema
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc. were noted as comments.

Results

Twenty-nine subjects completed the study. One subject dropped because of missed visits. The irritation scores are summarized as the following:

Product A: Clobetasol Propionate Spray, 0.05% - During the course of the study there were numerous grade 1's, 2's, and 3's. The irritation score for this product was 456/2088. As tested, this product was somewhat irritating.

Product B: Sodium Lauryl Sulfate, 0.05% (positive control) – During the course of the study there were a few grade 1's, several grade 2's, and by the sixth grading most of the scores were grade 4's. By the fourteenth grading, all scores were grade 4's. The irritation score was 1607/2088. As tested this product was extremely irritating.

Product C: Clobetasol Propionate Spray Vehicle - During the course of the study there were numerous grade 1's and 2's and several grade 3's. The irritation score was 403/2088. As tested this product was somewhat irritating.

Reviewer's Comment: *After reviewing the summary sheet of scores, it is agreed that Clobetasol Spray, 0.05% and its vehicle spray are somewhat irritating. The vehicle is probably responsible for the irritation found in the drug product, as there are many other clobetasol propionate products on the market that are not irritating. The one adverse event during the study was a serious adverse event not related to study drug, a fall resulting in a broken leg.*

Study T101-01005 – Repeated Insult Patch Test of Clobetasol Propionate Spray, 0.05%

This was a single-center, within subject, randomized, evaluator blind trial to determine the safety in terms of contact allergy potential of the intended to-be-marketed formulation of Clobex Spray, 0.05% in healthy volunteers.

The test products included Clobex Spray, 0.05% and its vehicle spray. The study testing began on July 23, 2001 and ended August 31, 2001.

Two hundred twenty-six (226) healthy males and females participated in the study, all of whom were at least 18 years of age. Females were ineligible if they were pregnant or nursing. Females enrolled in this study were required to be post-menopausal, surgically sterile or using an effective form of birth control. A negative urine pregnancy test was required for all fertile females to be enrolled into the study.

Each subject received a total of 10 applications of test material under occlusive patches over a six week period. Patches were placed on the backs of subjects and left in place for 48 hours. The patches were then removed. At least 5 minutes and no longer than 15 minutes after removal, the sites were graded for irritation.

During the 3 week induction period, 0.2 ml of the test material was applied to the occlusive patch and secured to the patient on Monday, Wednesday, and Friday. After a two-week rest period, one challenge application of the study medications was made.

The following grading system was used:

0 = No sign of irritation
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering
/ = Patch moved to new site due to excessive reactions. Residual reaction on old site recorded below slash. New reaction recorded above slash.
X = Product has been dropped due to excessive reaction.

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc. were noted as comments. Special notations were made of any reactions evaluated as being related to the patches or tape.

Results

Two hundred and three (203) subjects completed the study. Twenty-three subjects were dropped prior to completing the study and there were 8 adverse events reported during the study. The following reasons were responsible for the dropped subjects: missed visits (17), subject request (3), concomitant medications (1), and incarceration (1). Adverse events were reviewed on the CRFs and none could be attributed to study medication. The sensitization results are summarized as follows:

Product A: Clobetasol Propionate Spray, 0.05%: During the course of the induction there were numerous grade 1's and grade 2's. At the challenge there were numerous grade 1's. Subject #39 had a 0 at the first reading and a grade 2 at the final reading. Subject #56 had a grade 2 that fell to 0. As tested this product was somewhat irritating and not a sensitizer.

Product B: Clobetasol Propionate Spray Vehicle: During the course of the induction there were numerous grade 1's and 2's. One subject had a grade 3 that fell to a grade 1. Subjects #29, #56, #96, #108, & #147 had grade 4's. At the challenge there were many grade 1's. Subject #126 & #129 had grade 2's that fell to grade 1's. Subject #198 had a grade 2 that fell to

0. Subject #214 had a grade 1 that changed to a 2 at the final grading. Subject #164 had grade 2 at both final gradings. As tested this product was somewhat irritating and not a sensitizer.

Reviewer's Comment: *After reviewing the summary score sheets, it is agreed that clobetasol propionate spray is not a sensitizer.*

Study T101-01006 – Phototoxicity Test of Clobetasol Propionate Spray, 0.05%

This is a single-center within subject, vehicle controlled, evaluator blind trial in healthy subjects. The purpose of the trial is to determine the safety in terms of phototoxicity potential of the to-be-marketed formulation of clobetasol propionate spray, 0.05%. The test products were clobetasol propionate spray, 0.05% and its vehicle. The study began on September 11, 2001 and ended on September 13, 2001.

A panel of 30 healthy males and females were enrolled in the study who were at least 18 years of age. Females were ineligible if they were pregnant or nursing. Females enrolled in this study were required to be post-menopausal, surgically sterile or using an effective form of birth control. A negative urine pregnancy test was required for all fertile females to be enrolled into the study.

Within seven days prior to the start of the study, each subject's Minimum Erythema Dose (MED) was determined and recorded. The time of UVA light exposure was equal to 10 times the MED equivalent. Following irradiation with UVA, the filter was removed from the light source and the irradiated sites further exposed to 0.5 MED of UVA/UVB light.

Five test sites were taped stripped to the "glistening layer" and study medication at a concentration of $2ml/cm^2$ were applied to all test sites except one, which was the control. The subjects were asked to refrain from showers, not to go swimming, not to engage in vigorous exercise that would result in excessive sweating, and not to expose the test sites to sunlight for the duration of the study.

Evaluations were made by a technician experienced and trained in the reading of skin patch tests on a five point scale. Questionable reactions were referred to the investigator for evaluation. The rater evaluated skin reactions on each test site at: 5-15 minutes, 3 hours, 24 hours, and 48 hours after irradiation.

The following grading system was used:

0 = No sign of irritation
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering
/ = Patch moved to new site due to excessive reactions. Residual reaction on old site recorded below slash. New reaction recorded above slash.
X = Product has been dropped due to excessive reaction.

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc. were noted as comments. Special notations were made of any reactions evaluated as being related to the patches or tape.

Results

Thirty subjects were enrolled and there were no dropouts in the study. There were no adverse events reported in the study. The results for each product are summarized below.

Product A: Clobetasol Propionate Spray, 0.05% - During the study for the irradiated sites there was one grade 1 for subject #17 at the 48 hour post irradiation grading. All other grades were 0/s. For the non-irradiated sites all grades were 0/s. As tested this product was not phototoxic.

Product B: Clobetasol Propionate Spray Vehicle – During the study for the irradiated sites there was one grade 1 for subject #24 at the 48 hour post irradiation grading. All other grades were 0's. For the non-irradiated sites all grades were 0's. As tested this product was not phototoxic.

Irradiated Control – The irradiated control site was all 0's for all gradings.

Reviewer's Comment: *I would agree with the investigator that neither Clobex Spray nor its vehicle have any phototoxic potential.*

Study T101-01007 – Photocontact Allergy Test of Clobetasol Propionate Spray, 0.05%

This is a single-center, within subject, vehicle controlled, evaluator blind trial in healthy subjects to determine the safety and photocontact allergy potential of clobetasol propionate spray, 0.05% and its vehicle spray. This study was to determine the safety and photocontact allergy potential of clobetasol propionate spray and its vehicle spray. The study was conducted from August 21, 2001 to September 21, 2001.

Thirty males and females were enrolled into the study who were at least 18 years of age. Females were ineligible if they were pregnant or nursing. Females enrolled in this study were required to be post-menopausal, surgically sterile or using an effective form of birth control. A negative urine pregnancy test was required for all fertile females to be enrolled into the study.

Within seven days prior to the start of the study, each subject's Minimum Erythema Dose (MED) was determined and recorded. Two test sites were marked for each study medication on untanned areas of the back. Patches with 0.2ml of study medication were applied at visits 2, 4, 6, 8, 10, 12, and 14. At visits 3, 5, 7, 9, 11, and 13 one of each of the pair of induction phase test sites treated with each study medication was exposed to two times the MED equivalent with a combination UVA/UVB radiation.

At visit 14, two challenge phase test sites were identified on previous untreated, UV unexposed and untanned skin. At visit 15, one of each of the pair of challenge phase test sites treated with each study medication and a previously untreated, UV unexposed test site (control site) was exposed to ten times the MED equivalent with UVA radiation. Following the UVA exposure the filter was removed from the solar stimulator and the test sites further exposed to 0.5 times the MED equivalent with a combination of UVA/UVB radiation.

Patches were removed after 24 hours and evaluated. If severe irritation (Grade 4) was observed at any site, the patch site was moved or dropped. The following grading system was used:

0 = No sign of irritation
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering
/ = Patch moved to new site due to excessive reactions. Residual reaction on old site recorded below slash. New reaction recorded above slash.
X = Product has been dropped due to excessive reaction.

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc. were noted as comments. Special notations were made of any reactions evaluated as being related to the patches or tape.

Results

Thirty subjects were enrolled in the study and completed it. There was one adverse event but it was not related to the study medication. The results for each product are summarized below:

Product A: Clobetasol Propionate Spray, 0.05% - During the induction on the irradiated sites there were numerous grade 1's and 2's. At the challenge three subjects had grade 1's that fell to 0's at the final grading.

During the induction on the non-irradiated sites there were numerous 1's and a few grade 2's. At the challenge two subjects had grade 1's that fell to 0's and two subjects had grade 1's at the final grading. As tested, this product did not cause photo allergy.

Product B: clobetasol Propionate Spray Vehicle – During the induction on the irradiated sites there were numerous grade 1's and 2's. At the challenge four subjects had grade 1's at the final grading, three subjects had grade 1's that fell to 0's and two subjects had grade 2's that fell to 0's or 1's.

During the induction on the non-irradiated sites there were numerous 1's and a few grade 2's. At the challenge three subjects had grade 1's that fell to 0's, three subjects had grade 1's at the final grading, and two subjects had grade 2's that fell to 1's or 0's. As tested this product did not cause photo allergy.

Irradiated Control – During the induction there were numerous grade 1's and grade 2's. At the challenge phase all grades were 0's.

Reviewer's Comment: *I agree with the investigator that neither Clobex Spray nor its vehicle cause photo allergy.*

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Upon discontinuation of Clobex Spray, 0.05%, there is a very small risk of rebound flare, as one patient out of 120 (0.8%) exhibited rebound flare. There were no instances, however, of transformation to life-threatening forms of psoriasis.

7.1.14 Human Reproduction and Pregnancy Data

In the phase 3 study, T101-01008, subject 136, a 23-year-old female in the CLOBEX (clobetasol propionate) Spray, 0.05% group had a positive pregnancy test result at the end- of-treatment visit. This subject was not dropped from the study because she had completed the treatment phase so she continued and completed the safety follow-up period. At the end of the study, this patient had no complications.

At gestational week 38, a normal, healthy girl weighing 6.625 pounds was born. There were no other pregnancies reported in any of the other phase 1, 2 or 3 trials.

7.1.15 Assessment of Effect on Growth

There were no formal analyses attempted for the effect of Clobex Spray, 0.05% on growth, as the majority of the patients in the study were adults beyond the growing years.

7.1.16 Overdose Experience

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

7.1.17 Postmarketing Experience

This drug product is not approved in any other jurisdiction.

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

A total of 640 subjects were evaluated in the clinical program. Of these subjects, 496 were exposed to Clobex Spray, 0.05% (292 healthy subjects and 204 patients with psoriasis). The safety data are from two HPA axis suppression studies in patients with psoriasis, two adequate and well-controlled phase 3 clinical efficacy studies of bid

application of Clobex Spray, 0.05% in patients with psoriasis up to 4 weeks, one phase 1 bilateral safety and efficacy study in patients with psoriasis, and four phase 1 dermal safety studies in healthy subjects. See section 4.1 and 4.2.

7.2.1.2 Demographics

All subjects enrolled in the studies that were dispensed and applied study medication at least once, were included in the analysis of safety and considered the safety population. Tables a and b shows the demographic and baseline (pre-treatment) characteristics for the safety populations of the five studies.

Table a
Demographic Profile of Patients Exposed to Clobex Spray, 0.05%
Phase 2 and 3 Trials

	Combined T101-01008 and T101-01010 (Phase 3 Studies)		**T101-01009 (Phase 2 HPA study)**	**D02-0204-03 (Phase 2 HPA study)**	
	Clobex	Vehicle		Clobex 2 weeks	Clobex 4 weeks
Number of Subjects	120	120	16	21	20
Age (years)					
Mean (SD)	46.4 (12.94)	47.60 (13.27)	37.75 (10.30)	50.99 (13.39)	45.00 (11.35)
Range	18.0-81.0	18.0-77.0	20.0-55.0	24.6-76.7	22.4-61.3
Sex					
Male	69 (58%)	71 (59%)	11 (60%)	13 (62%)	18 (90%)
Female	51 (43%)	49 (41%)	5 (31%)	8 (38%)	2 (10%)
Race					
White	107 (89%)	109 (91%)	13 (81%)	16 (76%)	16 (80%)
Black	5 (4%)	2 (2%)	0 (0%)	1 (5%)	0 (0%)
Asian/Pacific Islander	2 (2%)	1 (1%)	2 (13%)	0 (0%)	1 (5%)
Hispanic/Latino	5 (4%)	6 (5%)	1 (6%)	3 (14%)	2 (10%)
American/Alaskan Native	1 (1%)	1 (1%)	0 (0%)	1 (5%)	1 (5%)
Other	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)

Source: Sponsor's NDA submission – Table 2.7.4.1.3.1, eCTD Summary of Safety, page 19

Table b
Demographic Profile of Patients Exposed to Clobetasol Propionate Spray, 0.05%
Phase 1 Trials

	0215-C1.P-01-01 (Phase 1 Safety and Efficacy)	**T101-01004 21-day Cumulative Irritancy**	**T101-01005 Dermal Safety-RIPT[1]**	**T101-01006 Dermal Safety Phototoxicity**	**T101-01007 Dermal Safety-Photoallergy**
	Clobex 4 weeks	Clobex; Lauryl Sulfate, Vehicle	Clobex, Vehicle	Clobex, Vehicle	Clobex, Vehicle

		3 weeks	6 weeks	4 days	5 weeks
Number of Subjects	27	30	226	30	30
Age (years)					
Mean (SD)	51.59 (12.76)	50.17	49.40	46.9	49.53
Range	21.0-75.0	(19.0 – 78.0)	(18.0 – 83.0)	(29.0 – 74.0)	(19.0 – 72.0)
Sex					
Male	18 (67%)	10 (33%)	54 (24%)	8 (27%)	7 (23%)
Female	9 (33%)	20 (67%)	172 (76%)	22 (73%)	23 (77%)
Race					
White	23 (85%)	19 (63%)	104 (46.0%)	29 (97%)	29 (97%)
Black	1 (4%)	11 (37%)	119 (52.7%)	1 (3%)	1 (3%)
Asian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hispanic/Latino	2 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
American/Alaskan	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)
Native		0 (0%)	2 (0.9%)	0 (0%)	0 (0%)
Other	1 (4%)				

[1]RIPT – Repeat Insult Patch Test
Source: Sponsor's NDA submission – Table 2.7.4.1.3.1, eCTD Summary of Safety, pages 5-7

As can be seen in the tables, the majority of the patients in the studies were Caucasian, male, and in their forties.

7.2.1.3 Extent of exposure (dose/duration)

For the phase 3 studies, patients applied study medication twice a day to all psoriatic plaques identified at Visit 1 for four weeks or until the investigator verified their psoriasis had cleared. If a subject cleared at Visit 2 (day 8), the expected number of applications of study medication was 14. If a subject cleared at Visit 3 (Day 15), the expected number of applications was 28. If a subject continued dosing to the end of the treatment phase, Visit 4 (day 28), the expected number of applications of study medication was 56.

In the pivotal studies, 111/120 (92.5%) patients were ≥ 90% compliant with study medication application and 119/120 (99%) patients used the medication for greater than 3 weeks. More than 96% of the subjects received at least 29 applications of study medication. The mean number of applications was 54.49 (SD 8.59) for the CLOBEX™ (clobetasol propionate) Spray, 0.05% group and 54.66 (SD = 8.48) for the CLOBEX™ (clobetasol propionate) Spray Vehicle group. The mean treatment duration was 27.84 days (SD 4.25) for the CLOBEX™ (clobetasol propionate) Spray, 0.05% group and 27.76 days (SD =4.23) for the CLOBEX™ (clobetasol propionate) Spray Vehicle group. The mean %BSA at baseline was 8.25% (SD 7.09) for the CLOBEX™ (clobetasol propionate) Spray, 0.05% group and 8.35% (SD = 8.34) for the CLOBEX™ (clobetasol propionate) Spray Vehicle group. The mean %BSA at the end of treatment decreased significantly for the CLOBEX™ (clobetasol propionate) Spray, 0.05% group to 4.48% (SD = 5.59) while it increased slightly for the CLOBEX™ (clobetasol propionate) Spray Vehicle group to 8.67% (SD=8.77).

The extent of exposure to study medication for the phase 2 studies, T101-01009 and D02-2024-03, was adequate. For study TI01-01009, subjects on average applied 50.25 applications of study medication across 26.38 days. Treatment duration ranged from 3 to 30 days and

applications ranged from 5 to 60 applications. For study D02-0204-03, intent-to-treat (ITT) safety subjects in the 2-week treatment group, on average, applied 26.48 applications of study medication with a range of 12 to 30 applications across 13.24 days using 79.33 grams of study medication. Treatment durations ranged from 12 to 15 days and gram use ranged from 30.7 grams to 111.3 grams. Subjects in the 4-week ITT treatment group applied an average of 48.32 applications of study medication over an average of 24.21 days using 151.21 grams of study medication. In this study a Modified Intent to Treat (MITT) population was used which excluded subjects who dropped or were excluded from the study due to abnormal serum cortisol levels at Visit 2, abnormal HPA-system function, or out-of- range clinically significant baseline laboratory test results. Subjects in the MITT 2-week treatment group applied an average of 27.79 applications of study medication across an average of 13.89 days using 81.88 grams of study medication. Subjects in the MITT 4-week treatment group applied 52.94 applications of study medication over an average of 26.53 days using 166.15 grams of study medication.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

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

7.2.2.1 Other studies

See section 7.2.2

7.2.2.2 Postmarketing experience

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

7.2.2.3 Literature

No literature sources were reviewed to support this application.

7.2.3 Adequacy of Overall Clinical Experience

A total of 204 patients were exposed to clobetasol propionate spray in the clinical trials who had moderate to severe psoriasis. Given that there is a wealth of safety data from decades of use of clobetasol propionate in various formulations, it was felt that these numbers would be adequate to ascertain any safety issues that may be unique to the vehicle in this new formulation. There were enough patients in the trial to do subset analysis on various demographic groups.

The doses and duration of exposure was adequate to assess the safety for intended use and the design of the studies was adequate to answer critical safety questions. The critical questions revolved around if any added safety concerns could be ascertained as it related to systemic absorption and cutaneous effects because of the different vehicle.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical animal studies were adequate, except that the sponsor has to do carcinogenicity studies. These can be done in phase 4.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See biopharmaceutics review.

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

7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review was complete and the quality was good.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update submitted to the NDA covers safety updates for the drug product that is the subject of this NDA, clobetasol propionate spray, along with a safety update for other clobetasol propionate drug products by Galderma International. This is a consolidated 5 year report and includes the data collected by Galdermal International from worldwide sources during the period starting on June 29, 1999 and ending on June 28, 2004. In different market areas, the company has various formulations of clobetasol propionate. These include Clobex lotion, Clobex shampoo, Clob-X cream, Clob-X gel, Clob-X ointment, and Clob-X scalp lotion.

The estimated number of patients exposed to Clobe/Clob-X during the review period is 227,484 patients. No new safety findings concerning clobetasol propionate lotion or shampoo has been published during the review period. Until June 28, 2004, no serius and unlisted case was collected with clobetasol propionate topical formulations. There was no report of drug interaction, overdose, or drug abuse/misuse during the reference period. There was no report of use during pregnancy or lactation during the reference period. No specific issues were identified in special patient groups. There were no cases of adverse event suggest a specific link to a long-term treatment effect.

There were no additional adverse events to report for the trials in this NDA concerning Clobex Spray, 0.05%.

Reviewer's Comment: *Upon review of the case reports submitted to the safety update, it is agreed that no new safety findings concerning clobetasol propionate lotion or shampoo has been published.*

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

Application site burning
This occurred in 40% of patients using Clobex spray. For some patients this adverse event dissipated over time. However, it lead to only a few drop outs in the pivotal trials (see sections 7.1.3, 7.1.5.4, and 7.1.5.6).

Application site pruritus
This occurred in 3% of patients using Clobex spray. See sections 7.1.5.3, 7.1.5.4, and 7.1.5.5.

Application site dryness
This occurred in 2% of patients using Clobex spray. See sections 7.1.5.3, 7.1.5.4, and 7.1.5.5.

Application site irritation
This occurred in 1% of patients using Clobex spray. See sections 7.1.5.3, 7.1.5.4, and 7.1.5.5.

Application site pigmentation changes
This occurred in 1% of patients using Clobex spray. See sections 7.1.5.3, 7.1.5.4, and 7.1.5.5.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

See section 7.4.1.1

7.4.1.1 Pooled data vs. individual study data

The adverse event profile was similar in the individual study reports for the pivotal trials as in the combined data. In study -01008, 31/60 subjects (52%) in the Clobex Spray arm reported a total of 58 adverse events and 29/60 subjects (48%) in the Clobex Spray Vehicle arm reported a total of 47 adverse events. In study -10101, 37/60 subjects (62%) in the Clobex Spray arm reported a total of 61 adverse events and 41/60 subjects (68%) in the Clobex Spray Vehicle group reported a total of 68 adverse events. In the pooled data for the two studies, a total of 68/120 subjects (57%) in the Clobex Spray arm reported a total of 119 adverse events and 70 subjects (58%) in the Clobex Spray Vehicle arm reported a total of 115 adverse events.

The majority of the adverse events were mild to moderate in severity. Of these, the majority were of mild intensity. Application site burning accounted for 33% of mild events and 6% of moderate events in the Clobex Spray arm. Application site burning accounted for 38% of mild events and 5% of moderate events in the Clobex Spray vehicle arm. In the Clobex Spray, 0.05% arm, there were only 2 events that were severe, one (1%) each of application site burning and application site pruritus. In the vehicle spray arm, there were 8 events that were severe, 5/115 (4%) of application site burning, 2 (2%) of application site pruritus, and 1 (1%) headache.

7.4.1.2 Combining data

Pooling of the data was done across the two pivotal trials simply by combining the total number of patients exposed to the drug product. The number of patients who experienced the adverse event was the numerator and the total number of patients exposed in the intent-to-treat population was the denominator. The intent-to-treat population included all patients who were dispensed study drug. The same was done for the vehicle arm in the pivotal trials.

7.4.2 Explorations for Predictive Factors

See section 7.1.5.6.

7.4.2.1 Explorations for dose dependency for adverse findings

Patients were followed for 4 weeks post treatment in the pivotal trials to assess for signs of cutaneous atrophy. This can be dependent on dose (potency) of a topical corticosteroid. No atrophy occurred in these trials in patients who used the drug product.

7.4.2.2 Explorations for time dependency for adverse findings

Patients were followed for 4 weeks post treatment in the pivotal trials to assess for signs of cutaneous atrophy. This can be dependent on duration of use of a topical corticosteroid. No atrophy occurred in these trials in patients who used the drug product.

7.4.2.3 Explorations for drug-demographic interactions

For the combined Phase 3 studies, a summary analysis for the possible influence of gender, race (white vs. non-white) and age (<65 years vs. ≥65 years) on adverse events reports was performed, and the results are shown in the table below.

The percentage of male subjects reporting adverse events in each treatment group was approximately equal, with a slightly higher frequency in the CLOBEX™ (clobetasol propionate) Spray Vehicle group. The percentage of female subjects reporting adverse events in each treatment group was also approximately equal, with slightly higher frequency in the CLOBEX™ (clobetasol propionate) Spray, 0.05% group. As a result, the percentage of subjects reporting

adverse events in the CLOBEX™ (clobetasol propionate) Spray, 0.05% group was slightly higher for females than males.

The percentage of subjects reporting adverse events in each treatment group was approximately equal for whites [57% in the CLOBEX™ (clobetasol propionate) Spray, 0.05% group versus 59% in the CLOBEX™ (clobetasol propionate) Spray Vehicle group] and non-whites [54% in the CLOBEX™ (clobetasol propionate) Spray, 0.05% group versus 55% in the CLOBEX™ (clobetasol propionate) Spray Vehicle group]. The percentage of subjects reporting adverse events in each treatment group was approximately equal for those younger than 65 years; whereas, in those ≥65 years there were a slightly higher percentage of subjects reporting adverse events in the CLOBEX™ (clobetasol propionate) Spray, 0.05% group. However, it should be noted that the number of patients ≥65 years of age was relatively small (21) compared to subjects <65 years of age (219).

Summary of Subjects with Adverse Events for the Subgroup Gender, Race and Age Phase 3 Studies T101-01008 and T101-01010 Combined

	Clobetasol Propionate 0.05% Spray (N=120) n (%)	Vehicle Spray (N=120) n (%)
Gender: Male		
Number of Subjects	69	71
Number of Events Reported	50	59
Number of Subjects Reporting One or More Events	35 (51%)	41 (58%)
Gender: Female		
Number of Subjects	51	49
Number of Events Reported	69	56
Number of Subjects Reporting One or More Events	33 (65%)	29 (59%)
Race: White	N (%)	N (%)
Number of Subjects	107	109
Number of Events Reported	108	102
Number of Subjects Reporting One or More Events	61 (57%)	64 (59%)
Race: Non-White		
Number of Subjects	13	11
Number of Events Reported	11	13

Number of Subjects Reporting One or More Events	7 (54%)	6 (55%)
Age < 65 Years		
Number of Subjects	111	108
Number of Events Reported	107	107
Number of Subjects Reporting One or More Events	62 (67%)	64 (59%)
Age ≥ 65 Years		
Number of Subjects	9	12
Number of Events Reported	12	8
Number of Subjects Reporting One or More Events	6 (67%)	6 (50%)

Source: Sponsor's eCTD submission, module 2, table 2.7.4.5.1.1, page 71

7.4.2.4 Explorations for drug-disease interactions

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

7.4.2.5 Explorations for drug-drug interactions

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

7.4.3 Causality Determination

Given that this is a topical drug product, it is clear that the common adverse events, which were application site types of reactions, are due to the drug product.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen and administration does not pose any safety concerns that are serious in nature. Surprisingly, for a class one topical corticosteroid, no objective evidence for cutaneous atrophy was found up to 4 weeks post treatment. This is not an uncommon adverse event for potent topical steroids but it was not found in this drug product, at least for this duration of time.

8.2 Drug-Drug Interactions

No formal drug- drug interactions studies were performed. Usually systemic levels of topically applied corticosteroids are not reliably detected at the limits of quantitation.

8.3 Special Populations

There are not any outstanding issues with any special populations. See section 7.4.2.3.

8.4 Pediatrics

The sponsor has requested a full waiver of the requirement to treat pediatric patients with Clobex (clobetasol propionate) Spray, 0.05%. This is based on the fact that according to the sponsor Clobex Spray does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and that Clobex Spray is not likely to be used in a substantial number of patients.

The sponsor offers the following data from the IMS National Disease and Therapeutic Index (NDTI) to support that the number of pediatric patients with moderate to severe psoriasis:

Physician Visits Made by Patients Aged 10-19 Years for the Diagnosis of Psoriasis

	Number of visits for Psoriasis
2002 (full year)	
2003 (full year)	
2004 (year-to-date to July)	
2004 (full year estimated)	

There were not any numbers available for only those patients with moderate to severe psoriasis or for the age group 12-17 alone. Therefore, the figures above include all severities of psoriasis and some young adults.

Reviewer's Comment: *The sponsor's analysis is accepted and a waiver will be granted on the condition that the labeling for Clobex spray will be the same as for Clobex lotion as it pertains to pediatric patients. Clobex lotion is restricted to patients 18 years of age and older because of HPA axis suppression in a significant number of patients ages 12-17. This can be updated if the sponsor provides any new data in this population.*

8.5 Advisory Committee Meeting

There was not an advisory committee meeting concerning this drug product.

8.6 Literature Review

No additional literature review was performed.

8.7 Postmarketing Risk Management Plan

The adverse event profile will be discussed in labeling.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

Clobex (clobetasol propionate) Spray, 0.05% is efficacious in the treatment of moderate to severe plaque psoriasis. The data from the pivotal trials demonstrate a clinically significant improvement at 2 weeks for the majority of patients in both trials with 87% of patients in both trials improving from moderate to severe to mild psoriasis. Further, with an additional 2 weeks of treatment, more than three-quarters of the patients, 78% in trial -01008 and 82% in trial -01010, attained clearing or almost clearing of their disease. Statistical significance was achieved for all the primary endpoints at a $p < 0.001$. There was no clinically significant difference in the response rate for gender, race, or age.

There were not any serious adverse events related to the drug in the studies. The most common adverse events were related to topical application of the drug product, primarily application site burning/stinging. However, the majority of the patients continued and finished the trials. Rebound occurred in 1/120 (0.8%) of patients and this was a mild rebound flare. This would not be totally unexpected with a class one topical corticosteroid. Importantly, however, there were not any instances of transformation to more life-threatening forms of psoriasis. Thus, it is concluded that Clobex Spray, 0.05% is also safe to use in the treatment of moderate to severe psoriasis.

9.2 Recommendation on Regulatory Action

Clobex Spray, 0.05%, from a clinical perspective, should be approved for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older for up to 4 weeks.

9.3 Recommendation on Postmarketing Actions

No post marketing activity required.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The sponsor should include in the labeling:

- Details regarding the data in pediatric patients concerning HPA axis suppression with the use of Clobex Lotion in the Pediatric Use section
- An incidence table of commonly occurring adverse events from the trials

The sponsor should also develop a Patient Package Insert for Clobex Spray, 0.05% because of its novel application and also because of its risk as a class I topical corticosteroid.

See appendix for a line-by-line labeling review.

9.5 Comments to Applicant

The sponsor needs to develop a patient package insert for Clobex Spray, 0.05% prior to approval to be launched with the drug product. It can be similar to the one developed for Clobex Lotion, 0.05%.

10 APPENDICES

10.1 Review of Individual Study Reports

Reviewer's Comment: *The phase 3 pivotal trials were identical; therefore the summary of the protocol described below is for both studies, unless otherwise noted.*

Trials T101-01008 & T101-01010 – "A Randomized, Double-Blind, Vehicle Controlled, Parallel Group Study of the Safety and Efficacy of Clobetasol Propionate 0.05% Spray versus its Vehicle Spray in the Treatment of Plaque Psoriasis"

Investigators for -01008

Michael T. Jarratt, M.D.	01/Austin, TX
Scott d. Clark, M.D.	02/Longmont, CO
Ronald C. Savin, M.D.	03/New Haven, CT 06511
Leonard J. Swinyer, M.D.	04/Salt Lake City, UT
Charles F. Safley, Jr., M.D.	05/Memphis, TN
Robert T. Brodell, M.D.	06/Warren, OH

Investigators for – 01010

J. Michael Maloney, M.D.	01/Denver, CO
Janet L. Roberts, M.D.	02/Portland, OR
Daniel M. Stewart, D. O.	03/Clinton Township, MI
Robert W. Loss, M.D.	04/Rochester, NY
Alicia D. Bucko, D. O.	05/Albuqueque, NM
Karl R. Beutner, M.D., Ph.D.	06/Davis, CA

Study Objective

This study was designed to evaluate the efficacy and safety of the to-be- marketed formulation of Clobetasol Propionate 0.05% Spray and its Vehicle Spray in the treatment of subjects with plaque psoriasis. This study is one of two well-controlled pivotal studies to support submission of a New Drug Application for this formulation of clobetasol propionate spray, 0.05%.

Study Design/Plan

This was a multiple center, randomized, double blind, vehicle controlled, parallel group study of the efficacy and safety of the intended market formulation of clobetasol propionate 0.05% spray versus its vehicle spray in subjects with plaque psoriasis. It was planned between 108 and 124

outpatient volunteers, at least 18 years old, of either sex who had stable plaque psoriasis of at least moderate overall severity (grade 3 on a 0-4 scale) on a potential treatment area, appropriate for topical therapy, covering at least 2% body surface area (excluding the face, scalp, groin, axillae and other intertriginous areas) that met the inclusion/exclusion criteria were enrolled in this study at multiple U.S. study sites. There were two treatment groups: clobetasol propionate 0.05% spray and vehicle spray. Subjects were assigned treatment at Visit 1 via a randomization schedule stratified by investigational site. Subjects were randomized to clobetasol propionate 0.05% spray or vehicle spray in a 1:1 ratio with a randomization block size of four subjects. Subjects applied the assigned study medication twice daily to all active psoriasis plaques except on the face, scalp, groin, axillae and other intertriginous areas for four weeks or until the investigator determined their psoriasis has cleared. The treatment phase was followed by a four week no treatment follow-up phase. Clinical evaluations of plaque psoriasis and monitoring for adverse events were performed throughout the study.

Inclusion Criteria

1. Subject completed an appropriately administered informed consent process which included signing the Institutional Review Board approved informed consent form.
2. Subject was at least 18 years old of either sex.
3. Subject was willing and able to apply the assigned study medication as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
4. Subject had a clinical diagnosis of stable plaque psoriasis.
5. Subject had an area of plaque psoriasis, appropriate for topical treatment, covering at least 2% body surface area (BSA)[1] (excluding face, scalp, groin, axillae and other intertriginous areas).
6. Subject had an Overall Disease Severity score of at least 3 (on a 0 to 4 scale) on the area of plaque psoriasis that was treated.
7. Subject was willing and able to avoid prolonged exposure of the treatment area to ultraviolet radiation (natural and artificial) for the duration of the study.
8. Subject was in good general health and free of any disease state or physical condition that could have impaired evaluation of plaque psoriasis or which, in the investigator's opinion, exposed the subject to an unacceptable risk by study participation.
9. Women of childbearing potential[2] had a negative urine pregnancy test[3] and agreed to use an effective, non-prohibited form of birth control for the duration of the study (stabilized on oral contraceptives for at least three months, implant, injection, IUD, condom and spermicidal or diaphragm and spermicidal).

1 1% BSA is approximately equal to the surface of the subject.s hand with fingers together. For the BSA determination residual discoloration (pigmentation and/or erythema) should not be included.
2 Women of Child Bearing Potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >12 consecutive months; or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level >35mLU/mL]. Even women who are using oral, implanted or, injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.
3 Urine pregnancy tests must have a minimum sensitivity of 25-mIU ß-HCG/mL of urine and must be performed within 72 hours prior to the start of study medication.

Exclusion Criteria

1. Subject had spontaneously improving or rapidly deteriorating plaque psoriasis.
2. Subject had guttate, pustular, erythrodermic, or other non-plaque form of psoriasis.
3. Subject had used any psoriasis vaccine or had participated in an investigational study of any psoriasis vaccine.
4. Subject used systemic immunomodulatory therapy known to affect psoriasis that **DOES** typically decrease immune cell populations (e.g.: alefacept) within the 36 weeks prior to the study.
5. Subject used systemic immunomodulatory therapy known to affect psoriasis that **DOES NOT** typically decrease immune cell populations (e.g.: etanercept) within 12 weeks prior to the study.
6. Subject used photo-therapy (including laser), photo-chemotherapy or systemic psoriasis therapy (such as systemic corticosteroids, methotrexate, retinoids or cyclosporine) within four weeks prior to the study.
7. Subject had prolonged exposure to natural or artificial sources of ultraviolet radiation within four weeks prior to the study or was intending to have such exposure during the study, thought by the investigator likely to modify the subject's psoriasis.
8. Subject used topical anti-psoriatic therapy (including topical retinoids) on the areas to be treated within two weeks prior to the study.
9. Subject used emollients/moisturizers on areas to be treated within two days prior to the study.
10. Subject was currently using lithium or plaquenil.
11. Subject was currently using a beta-blocking medication (e.g. propranolol) with a dose that has not been stabilized.
12. Subject had a history of sensitivity to any of the ingredients in the study medications.
13. Subject was pregnant or a nursing mother.
14. Subject was currently participating in, or had in the 30 days prior to the study participated in an investigational study.

Removal of Subjects From Therapy or Assessment

A subject was withdrawn from the study prior to completion for any of the following reasons:

Whenever the subject/care giver decided it was in their best interest to withdraw.
Whenever investigator decided it was in the subject.s best interest to be withdrawn.
Severe adverse events.
Intercurrent illness which may, in the investigator.s opinion, have significantly affected assessment of clinical status.
Noncompliant.
Pregnant.

If a subject prematurely withdrew during the treatment phase, the appropriate Visit 4 procedures and CRFs were completed. If a subject prematurely withdrew during the notreatment follow up phase, the Visit 5 procedures and CRFs were completed.

If the investigator instructed a subject to stop treatment because his or her psoriasis cleared prior to Visit 4, the Visit 4 procedures and case report forms were completed and the subject was scheduled for Visit 5 in four weeks.
If a subject withdrew from the study due to an adverse event, when possible, the subject was followed until the adverse event resolved.

Treatments Administered

The study staff assigned subject numbers in ascending order beginning with the lowest available subject number. Subjects were assigned treatment at Visit 1 via a randomization schedule stratified by investigational site. Subjects were randomized to clobetasol propionate 0.05% spray or vehicle spray in a 1:1 ratio with a randomization block size of four subjects.

The study medication was packaged in 60 mL white high-density polyethylene (HDPE) bottles with screw top caps. Each bottle contained 50 grams of study medication. A metered dose, non-aerosol spray mechanism that delivers approximately 0.14 mL (approximately 0.116 grams) of study medication per pump was provided for each bottle. The subject removed the screw top cap and installed the spray mechanism prior to using each study medication container. The application instructions were designed so that the skin surface concentration of the study medication on the psoriasis plaques was approximately 1mg/cm2.

Subjects applied the study medication twice daily to all active psoriasis plaques except on the face, scalp, groin, axillae and other intertriginous areas for the 28-day treatment period or until the investigator determined the subject's psoriasis had cleared. Subjects were instructed to allow at least 8 hours between applications, not to wash the treated area for at least four hours following a study medication application, not apply more than 50 grams of study medication (contents of one container) per week, and not apply the study medication within four hours prior to any study visit.

Efficacy Assessments

For the efficacy assessments, the same investigator completed the evaluations for a given subject throughout the study. If this became impossible, a sub-investigator with overlapping experience with the subject and the study completed the evaluations.

Overall Disease Severity

The Overall Disease Severity score was an evaluation of the overall severity of a subject's psoriasis, and took into consideration the three individual characteristics of psoriasis (plaque elevation, scaling and erythema). The investigator did NOT refer to any other assessments to assist with this evaluation. This evaluation WAS NOT a comparison with the Overall Disease Severity at any other visit or a mathematical calculation based on the Signs of Psoriasis scores. At every study visit all active psoriasis plaques were evaluated except on the face, scalp, groin, axillae and other intertriginous areas using the following scale (at Visit 1 this evaluation occurred PRIOR to the first study medication application):

0 - Clear
Scaling: no evidence of scaling
Erythema: no evidence of erythema (except possible residual discoloration
Plaque elevation: no evidence of plaque elevation above normal skin level
1 - Almost clear
Scaling: limited amount of very fine scales partially covers some of the plaques
Erythema: very few of the plaques are light red
Plaque elevation: very slight elevation above normal skin level, easier felt than seen.
2 - Mild
Scaling: mainly fine scales; some plaques are partially covered
Erythema: some plaques are light red
Plaque Elevation: slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques
3 - Moderate
Scaling: somewhat coarser scales; most plaques are partially covered
Erythema: most plaques are red
Plaque Elevation: moderate elevation with rounded or sloped edges on most of the plaques
4 - Severe/Very Severe
Scaling: coarse, thick scales; virtually all or all plaques are covered; rough surface
Erythema: virtually all or all plaques are bright to dusky red
Plaque elevation: marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques

Reviewer's Comment: *This efficacy variable was considered the primary efficacy variable by both the sponsor and the Division.*

Signs of Psoriasis

This evaluation was an assessment of the average severity of each of three key characteristics of plaque psoriasis. The investigator did NOT refer to any other evaluations to assist with this assessment. At every study visit the investigator evaluated all active psoriasis plaques except on the face, scalp, groin, axillae and other intertriginous areas for each subject and reported the one integer score that described the average severity for each sign of psoriasis using the following scales (at Visit 1 these evaluations occurred PRIOR to the first study medication application):

Scaling:
0 - Clear: no evidence of scaling
1 - Almost clear: limited amount of very fine scales partially covers some of the plaques
2 - Mild: mainly fine scales predominate; some plaques are partially covered
3 - Moderate: somewhat coarser scales predominate; most plaques are partially covered
4 - Severe/Very Severe: coarse, thick tenacious scales predominate; virtually or all plaques are covered; rough surface.
Erythema:

0 - Clear: no evidence of erythema (except possible residual discoloration)
1 - Almost clear: very few of the plaques are light red
2 - Mild: some plaques are light red
3 - Moderate: most plaques are red
4 - Severe/Very Severe: virtually all or all plaques are bright red to dusky dark red.

Plaque Elevation:

0 - Clear: no evidence of plaque elevation above normal skin level
1 - Almost clear: very slight elevation above normal skin level, easier felt than seen
2 - Mild: slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques
3 - Moderate: moderate elevation with rounded or sloped edges on most of the plaques
4 - Severe/Very Severe: marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques.

Safety Assessments

- Adverse Events Associated With Topical Application of Corticosteroids: At every study visit, the investigator or designee observed and directly queried the subject about the following adverse events associated with topical application of corticosteroids on the treated areas: telangiectasia, skin atrophy, burning/stinging, and folliculitis.

- HPA Axis Suppression: Given the 4-week duration of therapy, clinical signs and symptoms of HPA axis suppression were not anticipated. However, at every study visit, the investigator or designee observed and directly queried the subject about clinical signs and symptoms of adrenal suppression.

- Pregnancy Test: A urine pregnancy test was performed on all women of childbearing potential at Visit 1 and 4 or when the subject prematurely withdrew from the treatment phase of the study. The investigator reported the urine pregnancy test results on the case report forms, in the subject's medical records and in independent records maintained at the study site.

- Adverse Events: Any adverse event that was not designated as serious was recorded on the Non-Serious Adverse Events Case Report Form. Adverse events were followed to resolution or stabilization, and reported as serious adverse events if they became serious. The investigator decided whether the particular adverse event was study medication related or not and recorded his/her decision accordingly, using the terms included with the Serious and Non-Serious Adverse Events CRFs.

For both serious and non-serious adverse events, the investigator evaluated the intensity and relationship to study medication of each adverse event reported during the study according to the following scales:

Severity:

1 - Mild

2 - Moderate
3 - Severe
4 - Very Severe

Relationship to Study Medication:

1 - Certain
2 - Probable
3 - Possible
4 - Unrelated
5 – Unassessable

Statistical Methods

Two data sets will be constructed for the efficacy analysis: 1) All subjects randomized into the study who are dispensed drug (intent-to-treat subjects); 2) All subjects randomized into the study who are dispensed drug and are without significant protocol violations (evaluable subjects). The primary data set will be the intent-to-treat data set. Efficacy analyses will be undertaken for both data sets, while safety analyses will only be undertaken for the intent-to-treat data set.

The primary response measure is the success rate in Overall Disease Severity, defined as a grade of 2 or less on the 0-4 scale at Week 2 or earlier and defined as a grade of 1 or less on the 0-4 scale at the end of treatment (Week 4) or later. All other response measures and evaluation periods are considered secondary. All statistical tests are two-tailed with an alpha level of 0.05. All response measures will be analyzed at each evaluation.

Subjects who have been dispensed drug and prematurely withdraw from the study will have their last observation carried forward to Week 4. The success rate in Overall Disease Severity (the primary endpoint), will be assessed using a Cochran Mantel-Haenszel test (controlling for investigators) to test the null hypothesis of no treatment difference in proportions. The primary evaluation periods are Week 2 and Week 4. A nested approach will be used in which Week 4 will be evaluated if and only if Week 2 is statistically significant. Treatment differences in the Signs of Psoriasis (scaling, erythema, and plaque elevation) and pruritus, measured on a 5-point ordinal scale, will be evaluated by a Wilcoxon rank-sum test (controlling for investigators).

Differences between treatment groups in the proportion of subjects reporting at least one adverse event will be assessed by a Cochran Mantel-Haenszel test (controlling for investigators) or a Fisher's Exact Test to test the null hypothesis of no treatment difference in proportions. Individual tabling of telangiectasia, skin atrophy, burning/stinging and folliculitis will be provided.

Baseline treatment-group differences in sex and race (dichotomized into white/non-white) will be evaluated by the Cochran Mantel-Haenszel test, while group differences in age, % BSA, Overall Disease Severity and Signs of Psoriasis will be assessed by Wilcoxon rank-sum tests.

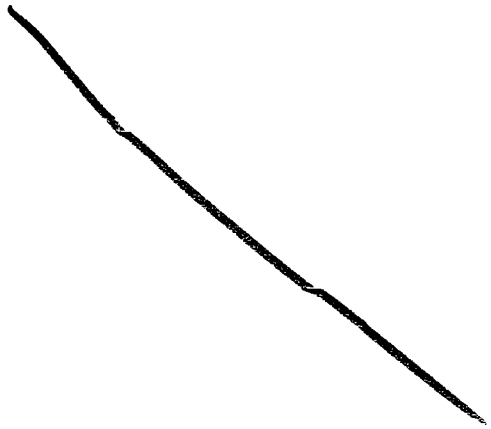
Subgroup Analysis

Subgroup analyses will be undertaken for the effects of race (dichotomized into white/non-white), age, gender, baseline % BSA and baseline Overall Disease Severity using Overall Disease Severity at study week 4 as the dependent variable. Qualitative variables (race and gender) will be evaluated using a two-way analysis of variance (ANOVA) with race and gender, treatment and their interaction as effects in the model, with the rank of week 4 Overall Disease Severity as the dependent variable.

Quantitative variables (age, %BSA and baseline Overall Disease Severity) will be assessed by regressing the rank Week 4 Overall Disease Severity on age, BSA or baseline Overall Disease Severity. Additionally, treatment will be included as an effect in the model. The interaction of treatment and age, BSA or baseline Overall Disease Severity will be included in the model to test the homogeneity of slope assumption. If this effect is not statistically significant, it will be dropped from the model and the analysis re-run.

10.2 Line-by-Line Labeling Review

Reviewer's Comment: *The following is the proposed label by the sponsor. Changes are noted by strikeouts and additions are in red.*



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