CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

MEDICAL REVIEW

CLINICAL REVIEW

Medical Officer's Review of NDA 21-535
Original

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DDDDP HFD-540

NDA #21-535

Submission date: 9/25/02
CDER Stamp date: 9/27/02
Assignment date: 10/08/02
Review began: 10/15/02
Review completed: 6/9/03

Sponsor:	Galderma Laboratories, L.P. 14501 North Freeway Fort Worth, TX 76177 USA
Generic name:	Clobetasol Propionate
Trade name:	Clobex
Chemical name:	Clobetasol Propionate
Pharmacologic Category:	Anti-inflammatory
Indication:	Moderate to Severe Plaque Psoriasis
Dosage Form(s):	Lotion
Route (s) of Administration:	Topical
Related Reviews:	Statistical Review dated: 5/7/03 Biopharmaceutics Review dated: draft 6/2/03

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Clinical Review for NDA 21-535

Executive Summary

I. Recommendations

A. Recommendation on Approvability

It is recommended, from a clinical perspective, that the NDA for clobetasol propionate lotion should be a "non-approvable". Review of the data presented in the application is such that it is not in the interest of the public health to approve another clobetasol propionate drug product such as clobetasol propionate lotion that is not only less efficacious than currently marketed clobetasol propionate products but more importantly has a poorer safety profile.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The sponsor may wish to consider the following:

1. Alteration of the drug product's vehicle such that less systemic absorption of the active chemical moiety, clobetasol propionate, takes place. Confirmation of such would require a new HPA axis suppression study. The criteria for HPA axis suppression should be agreed upon in advance with the Division such that all patients who exhibit HPA axis suppression can be followed for time to recovery.

2. [redacted]

3. [redacted]

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This NDA was submitted in support of clobetasol propionate lotion, 0.05% for the indication of corticosteroid responsive dermatoses. To achieve this indication, the sponsor has submitted two pivotal US trials, one in psoriasis and one in atopic dermatitis. There is also one supportive European trial in psoriasis. The chemical moiety, clobetasol propionate, is a super potent corticosteroid that has been approved in other topical formulations. For this reason, the sponsor chose the 505(b)(2) route of application. This is a route in which the new drug product, in this case, clobetasol propionate lotion, attempts to establish a bridge of bioequivalence and safety to a reference listed drug product. In the case of topical drug products, clinical trials can be designed to establish this bridge. The sponsor chose Temovate E Emollient Cream

(clobetasol propionate), 0.05% as the reference listed drug (RLD) product in each of its pivotal trials. Temovate E Emollient Cream, 0.05% was also chosen as it is the only super potent Class I topical clobetasol propionate corticosteroid which allows for treatment of 5-10% body surface area (BSA) up to 4 weeks in psoriasis. All others are limited to 2 weeks of consecutive use. The chemical moiety has the potential, although topical, of causing systemic adverse effects, namely, suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, 3 phase 2 safety studies to address this potential were undertaken, 1 in psoriasis and 2 in atopic dermatitis. The second HPA axis study in atopic dermatitis was to address the issue of safety in the adolescent population, ages 12-17. These studies comprise the bulk of the bridge for the establishment of the finding of safety to the reference listed drug product, Temovate E Emollient Cream. Since the natural history of atopic dermatitis and psoriasis is the same in the adult and pediatric population, findings of efficacy will be extrapolated down to the pediatric population, ages 12 and older, if CP lotion establishes adequate safety in the adolescent population.

The number of patients enrolled in the two pivotal US trials were 421 patients, which included 397 adults and 24 adolescents. There were 222 adults enrolled in the European study. In the HPA axis studies a total of 84 subjects were enrolled, of which 37 were adolescents. The total number of patients exposed to the study drug, clobetasol propionate lotion, was 309.

B. Efficacy

There were three phase 3 trials that were reviewed in support of efficacy of clobetasol propionate (CP) lotion, 2 U.S. pivotal and 1 European supportive. Trial CR.U9707.R02 (9707), a U.S. pivotal trial, and trial RD.06.SRE.2651(2651), the European trial, are done in patients with moderate to severe plaque psoriasis. Trial RDS.06.SPR.18001.R02 (18001), a U.S. pivotal trial is done in patients with moderate to severe atopic dermatitis. Each trial has 3 arms, CP Lotion, CP lotion vehicle, and Temovate E Cream.

The primary efficacy variable for the trials is the Investigator's Global Severity Assessment Scale. Secondary variables for the psoriasis trials are erythema, plaque elevation, and scaling and for the atopic dermatitis trials, the secondary variables are erythema, induration/papulation, oozing/crusting, and pruritus. The efficacy endpoint is at the end of 4 weeks of treatment for psoriasis and at the end of 2 weeks of treatment for atopic dermatitis.

The definition of success is, according to the Division's previous practice for a 505 (b)(2) application, clobetasol propionate lotion has to be superior to its vehicle and has to be non-inferior to the reference listed drug product. A 10% margin of non-inferiority has been allowed. Success for the primary variable is defined as a score of 0 or 0.5 on the Global Severity Scale at end of treatment. Secondary variables are viewed as successful with a score of 0 at end of treatment, which correlated well with the mean change from baseline to endpoint for each of these variables.

Analysis of pivotal study 9707, chronic plaque psoriasis, demonstrates that clobetasol propionate lotion is statistically superior to its lotion vehicle in the primary efficacy measure of success in global severity ($p<0.001$). This is true for both the ITT (intent-to-treat) and PP (per protocol) analysis. The secondary efficacy parameters support the primary efficacy analysis as clobetasol propionate is statistically superior to vehicle in erythema ($p=0.0124$), plaque elevation (<0.001), and scaling ($p<0.001$). However, although non-inferiority to Temovate E Emollient Cream is established for the secondary efficacy variables of individual signs of psoriasis, non -

inferiority is not established in the primary efficacy variable of Global Severity, as the margin of non-inferiority is greater than 10% for both the ITT and PP analysis (18.9% and 22.4%, respectively).

Analysis of pivotal study 18001, atopic dermatitis, demonstrates that CP lotion is statistically superior to its vehicle in the primary efficacy measure of success in global severity ($p=0.001$). The results were similar for the per protocol population ($p=0.003$). The secondary efficacy parameters support the primary efficacy analysis as clobetasol propionate is statistically superior to vehicle in erythema ($p<0.001$), papulation ($p<0.001$), oozing/crusting ($p=0.0083$), and pruritus ($p<0.001$). However, non-inferiority to the RLD is not established, as the non-inferiority margin of clobetasol propionate lotion as compared to Temovate E Emollient Cream is 12.0% and 12.9% for both the ITT and PP populations, respectively. This is supported by the secondary efficacy variables, as CP lotion failed to establish the non-inferiority margin in 3 of the 4 signs and symptom (erythema, oozing/crusting, and pruritus). The range of non-inferiority for these signs and symptom is 11.84% to 15.30%.

Analysis of supportive study 2651, chronic plaque psoriasis, demonstrates the efficacy of clobetasol propionate lotion over its vehicle. Efficacy of clobetasol propionate over vehicle was statistically significant in both the primary efficacy variable ($p<0.001$) and in the secondary efficacy variables ($p<0.001$). Clobetasol propionate lotion does not establish non-inferiority to another of the clobetasol propionate drug products, Dermoval (clobetasol propionate) Cream. The limit of the one-sided 97.5% confidence interval for all efficacy variables, both primary and secondary, are smaller than -10%.

C. Safety

Five additional studies are analyzed to establish safety of clobetasol propionate lotion in the context of a 505(b)(2) application, two vasoconstrictor studies and 3 phase 2 trials. The two vasoconstrictor studies, CG.03.SRE.2117 and CG.03.SRE.2570, are to establish the relative potency of clobetasol propionate lotion; the 3 phase 2 trials, CR.U9708, 1.GUS.04.SPR.18009, and RD.06.SPR.18061, are to establish the systemic safety profile of clobetasol propionate lotion by evaluating its potential to suppress the HPA axis; and both the pivotal phase 3 trials and phase 2 trials evaluate the cutaneous safety profile of CP lotion.

Evaluation of the vasoconstrictor studies demonstrate that clobetasol propionate lotion is a super potent Class I steroid, comparable to that of other super potent Class I steroids, namely, Temovate E Emollient Cream and Temovate E Cream.

The three phase 2 studies compare clobetasol propionate lotion to Temovate E Emollient Cream. Cortrosyn® stimulation was used in the studies to evaluate the HPA axis. Criteria used to determine suppression of the HPA axis are those delineated in the Cotrosyn® label. In the adult studies, one in psoriasis and one in atopic dermatitis, the adrenal gland was stimulated on multiple occasions, rather than at baseline and end of treatment, as in the adolescent atopic dermatitis study.

The systemic safety profile of CP Lotion is much worse than that of Temovate E Emollient Cream, suggesting greater systemic bioavailability. Clobetasol propionate lotion caused HPA axis suppression at some point during treatment of psoriasis in 80% of patients as compared to 33% in patients treated with Temovate E. Furthermore, at the end of the study 40% of patients had HPA axis suppression compared to 0% treated with Temovate E. This study

further demonstrates that the potential for HPA axis suppression by clobetasol propionate lotion may be underestimated as the adrenal glands of the patients were constantly being stimulated (almost q week during the study) and suppression still occurred at the endpoint (4 weeks) for patients on CP Lotion but not in patients on Temovate E Cream. The greater ability of CP lotion to cause HPA axis suppression is substantiated in the atopic dermatitis studies, of which the adolescent study is demonstrative. In this study 64.3% of patients experienced HPA axis suppression on CP lotion compared to 20% of those who used Temovate E.

Two related parameters were examined in evaluating the systemic safety profile of clobetasol propionate lotion as compared to Temovate E Emollient Cream, the time to recovery of the HPA axis and the amount of drug product used. The time to recovery from HPA axis suppression was not clear for all the patients who had follow-up. A greater number did not recover in the time tested who were treated with clobetasol propionate lotion as compared to Temovate E Emollient Cream. This imposes another safety concern. The overuse of the lotion is two-pronged. In the adult psoriasis trial, for example, overuse of drug product was comparable between CP Lotion and Temovate E, with 8 and 7 patients using more than 50 grams per week, respectively. However, more patients using CP lotion experienced HPA axis suppression (5-63%) compared to Temovate E (2-29%). In the adolescent study, all of the patients who went over the limit (≥123grams/2weeks) experienced HPA axis suppression. None of the patients in this same age group used more than the recommended amount of Temovate E Emollient Cream. Again, this underscores a concern for abuse of this drug product because of the nature of the formulation.

The cutaneous safety profiles of clobetasol propionate lotion and Temovate E Emollient Cream show no significant difference.

D. Dosing

The sponsor proposes the following dosing for clobetasol propionate lotion, "...2 consecutive weeks for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, [redacted] The total dosage should not exceed 50 g [redacted] per week...."

The data from the trials, as discussed above, demonstrates that these endpoints for use of this drug is a safety concern. Furthermore, labeling for Temovate E Emollient cream has an upper limit of 5-10% of the BSA allowed to be treated for 4 weeks in psoriasis patients.

E. Special Populations

Clobetasol propionate lotion failed to demonstrate a safety profile that is not worse than that of Temovate E Emollient Cream in the adolescent population. It caused more HPA suppression than did Temovate E Cream. It also failed to demonstrate safety and efficacy compared to the RLD in the adult population. Thus, in failing to establish a bridge of safety and efficacy to Temovate E Emollient Cream, efficacy in this population cannot be extrapolated from the adult data in the pivotal trials.

There are not any specific concerns or differences found in the treatment of patients based on older adults (geriatrics) or based on ethnicity.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The drug is clobetasol propionate lotion, 0.05%, and it is an anti-inflammatory, topical corticosteroid with a proposed indication for corticosteroid responsive dermatoses. The sponsor is proposing a labeled use for 2 weeks of treatment for corticosteroid responsive dermatoses and

B. State of Armamentarium for Indication(s)

There are several formulations of clobetasol propionate for the indication of corticosteroid responsive dermatoses. These include Temovate Cream, 0.05%, Temovate Gel, 0.05%, Temovate Ointment, 0.05%, Temovate Scalp Application, 0.05%, and Temovate E Emollient Cream, 0.05%.

C. Important Milestones in Product Development

PreIND Meeting - November 20, 1997

- FDA recommended that testing for HPA axis suppression be performed on dermatidic skin and be done at the beginning and end of treatment.
- Pivotal studies should be 2 separate studies: one for psoriasis and another for atopic dermatitis for a labeling of "corticosteroid-responsive dermatoses". The HPA axis study would not constitute a pivotal study.
- For primary efficacy, individual disease signs would be scored for the target lesion. For global assessment, the final status of the patient should be noted, not just percent improvement. A "win" would be constituted by clearing or near clearing (approx. 90% clearing).

End-of-Phase 2 Meeting - September 20, 1999

- Guidance at this meeting was that for a 505(b)(2) application as the sponsor indicated that this was the route of approval being considered.
- The following studies were recommended:
    - Comparative vasoconstrictor study
    - Topical safety studies with the to-be-marketed formulation
    - HPA axis suppression study to be conducted prior to initiation of phase 3 clinical trials. It should have the following features:
        - Cortrosyn stimulation testing is suggested at baseline and at the end of study.

- A minimum of 20% BSA should be treated in patients with the disease being studied.
- Representative numbers of pediatric patients should be studied (i.e. 12-17 year old age group) if the RLD recommends treatment of this population.
- The HPA-axis stimulation testing should include a comparator arm. Assessment should include local safety, systemic safety, HPA axis suppression.
- If safety has been demonstrated in HPA-axis suppression testing in the pediatric and safety and efficacy have been demonstrated in phase 3 adult studies, the Division would infer efficacy in the pediatric group studied.
- A minimum of 12 evaluable patients per treatment group would be acceptable.
- Any patient with signs of adrenal suppression should be followed until resolution of suppression is established.

- Two three-am clinical trials assessing efficacy and safety with use of the Sponsor's drug product vs. a reference listed drug should be conducted, one study in plaque-type psoriasis and one in atopic dermatitis.

IND 54,230/SN:012/Reviewer's Comments - faxed to sponsor 5/3/2000

- The Global Severity (all lesions) scoring scale lists values for Very Mild and Mild as 0.5 and 1, respectively. The morphologic distinction between Very Mild and Mild are subtle and may be difficult to assess clinically. Half point scoring scale values are not recommended.
- The Global Assessment Scale should incorporate morphologic clinical descriptions. These descriptions should convey a picture of the patient along a global scale that would depict a disease state ranging from Clear to Severely involved. The levels of the global assessment scale should be discrete and static. Each level of the scale should be adequately described such that variability between investigators is minimized. The global scale should be dichotomized to "success" and "failure".

Reviewer's Comment: *The sponsor did not take the advice to use whole ordinal numbers for severity scoring. However, the morphologic descriptors were such that the first two scores, that of 0 and 0.5, corresponded to the Division's policy that in disease states such as these, patients should have a score of clear or almost clear to be considered a success.*

Pre-NDA Meeting - October 2, 2001

- The sponsor was advised to use all 3 Cortrosyn labeled criteria to evaluate corticosteroid induced adrenal suppression. Failure to meet one criterion would indicate adrenal suppression.

D. Other Relevant Information

Clobetasol propionate lotion is not registered in any foreign country at this time nor has the drug product been withdrawn from marketing in any foreign country for any reason. This New Drug Application is the first filing for CP Lotion in the world.

E. Important Issues with Pharmacologically Related Agents

The clobetasol propionate topical drug products are in the super potent class of topical corticosteroids. The main concern with these drug products is their potential for suppression of the HPA axis. To reduce this possibility, all of the drugs in this class with the exception of Temovate E Emollient Cream, 0.05%, is limited to 2 weeks consecutive use at not more than 50 grams a week. Temovate E Emollient Cream, 0.05% is allowed to be used for 4 weeks in chronic plaque psoriasis when the body surface area of treatment is limited to 5-10%.

There is not a lotion formulation in this class. Clobetasol propionate lotion, the subject of this NDA, is hoping to be the first, and to attain labeling similar to Temovate E Emollient Cream, 0.05%.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Chemistry

Clobetasol propionate lotion (the finished product) is a white topical corticosteroid preparation containing clobetasol propionate USP at a concentration of 0.05% (0.5 mg/g). The vehicle lotion consists of a fluid emulsion (lotion) containing hydroxypropylmethyl cellulose USP, polyoxyethylene glycol 300 isostearate, mineral oil USP, propylene glycol USP, Carbomer [redacted] sodium hydroxyde NF and purified water USP. The drug product will be packaged in four different fill size presentations in white plastic squeeze containers with white plastic closures. Three of the packages are commercial with fill volume of 1, 2, 4 fl. oz while the fourth is professional samples with a 0.5 fl. oz fill volume.

All clinical studies, including the biopharmacology studies were performed with the to-be-marketed formulation, 661.337. The ingredients of formulation number 661.337 are listed in table 1.

Table 1
Formulation 661.337

Ingredients	Percent (w/w)	Per gram	Per 200 kg	Per 1300 kg
Clobetasol propionate, USP	0.05	0.5 mg	0.100 kg	0.650 kg
Hydroxypropylmethyl cellulose, USP				
Polyoxyethylene glycol 300 isostereate *				
Carbomer				
Mineral Oil, USP				
Propylene Glycol, USP				
Sodium hydroxyde, NF				
Purified water, USP				

Source: Sponsor's NDA submission, Volume 1.1, Item 3, page 47
*Non compendial excipient

Reviewer's Comment: *It should be noted in this formulation that there is a large amount of propylene glycol, ——— of the drug product. Propylene glycol is an absorption enhancer and as will be seen in the body of the review, this large amount may be responsible for the efficacy and safety findings of this drug product as compared to the RLD.*

Dermoval (cobetasol propionate) Cream is the RLD for the European trial, RD.06.SRE.2651. It could not be established in communications with the sponsor that there is an identical drug product to Dermoval Cream marketed in the United States. Thus, for this reason, and because it is not the RLD used in the other 2 phase 3 trials, this trial is viewed as a supportive trial in this NDA application.

III. Human Pharmacokinetics and Pharmacodynamics

The sponsor conducted two vasoconstrictor studies to establish the potency of clobetasol propionate lotion. These studies were reports numbers CG.03.SRE.2117 and CG.03.SRE.2570 which compared clobetasol propionate lotion with Temovate (clobetasol propionate) Cream, 0.05%, Temovate (clobetasol propionate) E Emollient Cream, 0.05%, and Diprolene (betamethasone dipropionate) Cream, 0.05%. The reader is referred to the clinical pharmacology and biopharmaceutics review of Dr. Chandra S. Chaurasia. His conclusion regarding these studies is as follows:

" Clobetasol Propionate Lotion 0.05% is comparable to two known formulations containing the same active ingredient at the same concentrations (Temovate Cream and Temovate E Emollient Cream) in its ability to cause vasoconstriction. Both Temovate cream and emollient cream are Class I super potent steroids. Clobetasol lotion does produce more vasoconstriction than Diprolene cream, a Class I low potency steroid. Thus, the potency of Clobetasol propionate lotion 0.05% is expected to be comparable to Temovate Cream and Temovate E Emollient Cream."

Three HPA axis suppression trials were conducted in subjects with either psoriasis or atopic dermatitis as a surrogate marker for in vivo bioavailability of clobetasol propionate in this particular formulation, lotion vehicle.

Reviewer's Comment: The HPA axis suppression trials were reviewed independently by both Dr. Chaurasia and the author of this review. Dr. Chaurasia's conclusion regarding the safety aspects of this drug product are supportive of my conclusions.

IV. Description of Clinical Data and Sources

A. Overall Data

Data sources for this review included the Sponsor's submission, volumes 1.1 and volumes 1.18 -1.42, the biostatistical review of Dr. Shiowjen Lee, the clinical pharmacology and biopharmaceutics review of Dr. Chandra S. Chaurasia, and the Cortrosyn label. Dr. Lee's review was critical to the analysis of the efficacy data as the data had to be recalculated using success criteria that is standard for the Division, which differed from the success criteria proposed by the sponsor and reflected in the submission's analysis. The Cortrosyn label was consulted for the criteria of a normal adrenal response to Cortrosyn stimulation.

B. Tables Listing the Clinical Trials

Psoriasis Studies

Study Number	CR.U9708	1.CR.U9707.R02	RD.06.SPR.2651
Phase/Design	2/open-label	3/double-blind, parallel group comparison	3/double-blind, parallel group comparison
Location	US – multicenter	US- multicenter	Europe – multicenter
Objective	HPA Axis Safety	Safety and Efficacy	Safety and Efficacy
Formulations	-CP Lotion -Temovate E Emollient Cream	-CP Lotion -Temovate E Emollient Cream -Lotion Vehicle	-CP Lotion -Temovate Cream* -Lotion Vehicle
Enrollment	24 adults	192 adults	222 adults
Enrollment Date	3/18/1998 - 6/17/1998	2/1/2000- 6/19/2000	12/09/2000 - 9/01/2001
Randomization ratio	1:1	3:3:1	3:3:1
Dose	-3.6g/application, ≤50 g/wk 10-20% BSA	≤50 g/wk ≥15% BSA	≤50 g/wk ≥10% BSA
Number of Doses per Study Time Frame	4 wks, twice daily	4 wks, twice daily	4 wks, twice daily
Number of Visits	6	5	4
Measurement Timepoints	Screening, Baseline, wk 1, 2, 3, 4	Baseline, wk 1, 2, 4, and wk 8 follow-up	Baseline, wk 1, 2, 4

*This Temovate used in Europe is actually a clobetasol propionate called Dermoval and it could not be documented that it is identical to any marketed product in the US, thus this study is a supportive and not pivotal study in the evaluation for efficacy.

Clinical Review Section

Atopic Dermatitis Studies

Study Number	1.GUS.04.SPR.18009	RD.06.SPR.18061	1.GUS.04.SPR.18001.R02
Phase/Design	2/open label	2/open label	3/double-blind, parallel group comparison
Location	US/multicenter	US/multicenter	US/multicenter
Objective	HPA axis Safety in subjects aged 12 or older	HPA axis safety in adolescents (ages 12-17)	Safety and Efficacy in subjects aged 12 or older
Formulations	-CP Lotion -Temovate E Emollient Cream	-CP Lotion -Temovate E Emollient Cream -Temovate Cream	-CP Lotion -Temovate E Emollient Cream -Lotion Vehicle
Enrollment	23 adults 1 adolescent	36 adolescents	204 adults 24 adolescents
Enrollment Date	3/17/1998 - 6/17/1998	8/31/2000 - 7/25/2001	3/28/2000 - 1/17/2001
Randomization ratio	1:1	1:1:1	3:3:1
Dose	Twice daily application ~3.6 g/application ≤50 g/wk 10-20% BSA	Twice daily application ~3.6g /application ≤50 g/wk ≥20% BSA	Twice daily application ≤50 g/wk ≥20% BSA
Number of Doses per Study Time Frame	Twice daily for 2 wks	Twice daily for 2 wks	Twice daily for 2 wks
Number of Visits	4	6	4
Measurement Time points	Screening, Baseline, wks 1 and 2	Screening Baseline, wks 1, 2, and wk 4 and 6 wk follow-up	Baseline, wks 1, 2, and wk 4 follow-up

C. Postmarketing Experience

This is a new formulation of clobetasol propionate and is not approved in any country.

V. Clinical Review Methods

A. How the Review was Conducted

The phase 3 pivotal trials were reviewed with the same amount of detail for both efficacy and safety. Cutaneous safety was the main focus of the safety aspects of these trials. All three of the phase 2 trials to evaluate systemic safety of clobetasol propionate lotion were reviewed with the same attention to detail as safety of the drug product is a driving parameter for approval. The phase 1 dermal safety trials were reviewed with less scrutiny than the other 6 trials of the study and is mentioned in the integrated summary of safety conclusion.

B. Overview of Materials Consulted in Review

Materials used for this review are as listed under section IV. A - Overall Data sources.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

There were two potential issues with investigators in this NDA. Dr. [redacted] is being investigated by OCI for a failure to have a valid medical license to practice in the state of Florida in study 18001 and there were two other investigators, Dr. Bruce Miller and Dr. Debra Breneman who enrolled patients in both pivotal studies, 18001 and 9707.

DSI was asked to audit Dr. [redacted] site but because of the OCI case, the records for that site were not available. Therefore, a sensitivity analysis was performed by the statistician to determine what effect, if any, Dr. [redacted] site had on the outcome of the trial. The analysis of study 18001 without Dr. [redacted] site was exactly the same as that based on the whole data set. Therefore, exclusion of this site did not alter the efficacy conclusion based on the whole data set (see the statistical review for details, table 7).

Sensitivity analysis was also done for the two sites where the principal investigators, Dr. Miller and Dr. Breneman, enrolled patients in both trials, although each trial was for a different disease process, psoriasis and atopic dermatitis. In the psoriasis trial, 9707, these 2 sites had higher success rates for both the clobetasol propionate lotion and Temovate E Emollient Cream arms as compared to the other sites. However, excluding the sites did not alter the efficacy conclusion. In the atopic dermatitis trial, the success rate for clobetasol propionate lotion at these two sites was also higher than the other sites. When these sites were excluded, this did affect the efficacy results for clobetasol propionate lotion, showing CP lotion to be more inferior to Temovate E Emollient Cream. However, this also did not change the overall efficacy conclusion.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials did seem to be conducted with accepted ethical standards and the sponsor states such in the NDA submission.

E. Evaluation of Financial Disclosure

The sponsor states that during the course of development, financial disclosure forms were collected from each investigator who participated in a "covered clinical study" as defined in 21 CFR Part 54.2 (e). The sponsor further states that studies CR.U9708 and 1.GUS.04.SPR.18009 were not concerned since they were completed prior to the implementation of CRF Part 54. One investigator, Dr. [redacted] met the requirement for disclosable financial arrangements. Dr [redacted] was a principal investigator at [redacted] in study 18001. Dr. [redacted] and his sub-investigators indicated that they had received "significant payments of other sorts" as a result of a grant for health economics, outcomes, and health services research.

The sponsor does not feel that bias was introduced by Dr. [redacted] center as there were 14 centers in the United States in this study and this center enrolled 14 subjects out of 229. The primary efficacy analysis were performed based on success rates. The CMH test for Row Mean Difference controlling for center was used to test treatment effect. Overall no association of treatment effect with the center was detected.

Reviewer's Comment: After reviewing the line listings in volume 1.31, pages 5320-5331, I would concur with the sponsor that the results from Dr. — center do not suggest a bias favoring clobetasol propionate lotion.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Clobetasol propionate lotion demonstrated efficacy in the two pivotal clinical trials when compared to its vehicle. The studies were conducted in patients with psoriasis and atopic dermatitis and thus would support an indication for the treatment of corticosteroid responsive dermatoses. The sponsor, however, overestimated the proportion of patients who achieved treatment success by dichotomizing the primary efficacy variable at a point below which this reviewer would consider a successful outcome. The sponsor considered a success (and thus put it in draft labeling) patients who achieved a score of none, very mild, or mild on the Global Severity scale as a success in both studies. The Division considers success as those patients who achieve a score of none or very mild, corresponding to patients whose disease is clear or almost clear after treatment. The differences are detailed in table 2.

Table 2
Treatment Success - Pivotal Trials

Trial	Treatment Success			
	Sponsor's Analysis[1]		Reviewer's Analysis[1]	
	Clobetasol Lotion	Vehicle	Clobetasol Lotion	Vehicle
9707- Psoriasis	60/82 (73.2%)	2/29 (6.9%)	30/82 (36.6%)	0/29
18001 - Atopic Dermatitis	70/96 (72.9%)	12 (36.4%)	41/96(42.7%)	4/33 (12.1%)
Source: sponsor's NDA Submission - Volume 1.26, page 3317, Volume 1.30, page 5236, and draft labeling Volume 1.1, Item 2, page 8 and 9.				

The sponsor had one other hurdle to achieve with this application as the application was submitted via a 505 (b)(2) route. Therefore, clobetasol propionate needed to show non-inferiority to a reference listed drug product in order to establish a bridge of bioequivalence/bioavailability and to rely on safety findings of that reference listed drug product. The chosen reference listed drug product is Temovate E Emollient Cream. In the two pivotal clinical trials, clobetasol proprionate lotion **failed** to establish itself as non-inferior to the RLD, Temovate E Emollient Cream (clobetasol propionate cream), 0.05%, by having a margin of inferiority that was greater than 10%. Therefore, the 1st part of the needed bridge (the efficacy part) to establish bioequivalence/bioavailablity to Temovate E was not accomplished.

B. General Approach to Review of the Efficacy of the Drug

There were two pivotal trials that make up the basis for the evaluation of efficacy of this drug product, clobetasol propionate lotion, CR.U9707.R02 (9707) and RDS.06.SPR.18001.R02 (18001). One phase 3 European study, RD.06.SPR.2651 (2651) was a supportive trial, although

it did not use the same comparator product.

. Table 3 lists the phase 3 trials studied in detail.

Table 3
Overview of Phase 3 Trials

Study	Site of Centers (month/year)	Types of Patients	Treatment Arms, n	Comments on Treatments
Pivotal Trials				
9707	US (2/00 - 6/00)	Patients aged 18 and above with moderate to severe psoriasis	Clobex Lotion: 82 Temovate Emollient Cream: 81 Lotion Vehicle: 29	Treatment was twice daily for 4 weeks
18001	US (3/00 - 1/01)	Patients aged 12 and above with moderate to severe atopic dermatitis	Clobex Lotion: 96 Temovate Emollient Cream:100 Lotion Vehicle: 33	Treatment was twice daily for 2 weeks
Supportive Trial				
2651	Europe (9/00-1/01)	Patients aged 18 and above with moderate to severe psoriasis	Clobex Lotion: 94 Dermoval Cream: 95 Lotion Vehicle: 33	Treatment was twice daily for 4 weeks
Format adapted from Dr. Lee's statistical review, page 1				

C. Detailed Review of Trials by Indication

Trial #1 – CR.U9707.R02

Title: "The Safety and Efficacy of Clobetasol 17-Propionate Lotion, 0.05% as compared to its Vehicle and Temovate E Emollient Cream in the treatment of Moderate to Severe Plaque-Type Psoriasis"

Investigators

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Objective/Rationale

The objectives of the study are to evaluate clobetasol propionate lotion for safety and superior efficacy to its vehicle lotion in adult patients with moderate to severe psoriasis. Furthermore, it also aims to show non-inferiority to another clobetasol propionate product, Temovate E Emollient Cream, 0.05%.

Overall Study Design

This study was to be conducted as a multicenter, randomized, double-blind, parallel group, investigator-masked, active and vehicle controlled comparison in patients with moderate to severe psoriasis. The clobetasol propionate lotion and its vehicle were double-blinded. The clobetasol lotion and Temovate E Cream were investigator masked as the formulations of the two substances are different. Qualified patients, who met specific inclusion criteria, were randomized in a 3:3:1 ratio to receive either clobetasol propionate lotion, 0.05%, Temovate E Emollient Cream, 0.05%, or clobetasol propionate lotion vehicle, respectively. This was to minimize the number of patients receiving vehicle lotion. Patients were to apply the medication to the affected areas twice daily for 4 weeks, not to exceed 50 grams/week application of medication. A 4-week follow-up period was to assess duration of response and any late occurring safety issues.

Evaluations of patients occurred at baseline, weeks 1, 2, 4, and 8.

Protocol

Inclusion Criteria

Male or female subject of any race, 18 years of age or older
All female subjects (except women who had a hysterectomy, bilateral ovariectomy, tubal ligation and postmenopausal) were to have a negative urine pregnancy test (UPT) at the beginning of the study. (Postmenopausal was defined as no menstruation for at least 2 years).
Subjects were to be diagnosed with stable moderate to severe plaque-type psoriasis, as defined as a total of at least 6 points out of a maximum 12 points for the symptoms of erythema, plaque elevation, and scaling for the target lesion. The target lesion selected for evaluation and treatment was to have been at least 3 to 4 cm in diameter and must not have been on the face, axillae, or groin (product application should be avoided on these areas for safety reasons) or the scalp, hands, or feet (evaluation is difficult on these areas).
Subjects were to have at least a 15% body surface involvement using the "rule of nines"
Subjects were to be willing and capable of cooperating to the extent and degree required by the protocol.

Subjects were to sign and understand the informed consent form prior to receiving study treatment.

Exclusion Criteria

Pregnant and/or nursing females or females planning a pregnancy.
Subjects with concomitant medical or dermatologic disorders, which might have precluded accurate evaluation of the psoriasis.
Subjects who did not undergo the following washout periods, including, but not limited to, the following topical treatments that have a known beneficial effect on psoriasis:

Corticosteroids	4 weeks
Other anti-inflammatories	4 weeks
Anthralin	4 weeks
UV light therapy, including sunbathing	4 weeks
Retinoids	4 weeks
Vitamin D analogues	4 weeks

Subjects who did not undergo the following washout periods, including, but not limited to, the following systemic medications:

Corticosteroids or ACTH analogue	6 weeks
Lithium	2 weeks
Antineoplastic agents	6 weeks
Beta-blockers	2 weeks
Iodides	2 weeks
ACE inhibitors	2 weeks
Indomethacin and other anti-inflammatories	2 weeks
PUVA therapy	6 weeks
Methotrexate	16 weeks
Acitretin, etretinate, isotretinoin	16 weeks
Cyclosporin, interferon, tacrolimus	16 weeks

However, if the subject had been under the following treatments: indomethacin, ibuprofen, lithium, beta blockers, ACE inhibitors only, for more than 6 months without any worsening of the psoriasis, he/she was eligible for the study. Moreover, if the subject was under prophylactic dosage of aspirin (up to 325 mg/day), he/she was allowed to enter the study.
Subjects who used concomitant therapies during the course of the study that could have interfered with the interpretation of the study results at the investigator's discretion (see also Criteria 3 and 4).
Subjects whose psoriasis appeared to have been spontaneously improving without treatment (eg, acute psoriasis of guttata form).
Subjects who had known sensitivities to any ingredients of the study preparations (see Attachment 11.3 of the protocol).

Subjects who had participated in a clinical drug or device research study within the last 30 days of enrollment.

Withdrawal Criteria

Reasons for withdrawal may have included but were not limited to the following:

Psoriasis flare that needed an interfering therapy
Pregnancy
Either at the investigator's request, for safety reasons (e.g. severe adverse reactions or unauthorized concomitant therapy) or at the subject's request
When the requirements of the protocol were not respected
When a concomitant therapy liable to interfere with the results of the study was reported or required by the subject (the investigator was to report all such information on the case report form and was to decide, in accordance with Galderma, whether the subject was to be withdrawn)
If the condition cleared or almost cleared before the end of the study

Procedures and Observations

Each subject was to receive both verbal and written instructions as to the proper dosing and study medication application techniques. Topical application of the test materials, either clobetasol propionate lotion, its lotion vehicle, or Temovate E cream, 0.05%, were to be made to the designated target lesion, as well as to other affected areas, twice daily for 4 weeks. The test material was to be applied as a thin coating; the total weekly dosage of the test material was not to exceed 50g/week. The first application of the test material was to be made under the supervision of the investigator's designee. Table 4 is a flow chart of the assessments to be made throughout the trial.

Table 4
Efficacy and Safety Evaluations

Parameter	Baseline	Week 1	Week 2	Week 4	Week 8
Disease Evaluation	X	X	X	X	X
Efficacy Variables					
Erythema	X	X	X	X	X
Plaque Elevation	X	X	X	X	X
Scaling	X	X	X	X	X
Pruritus	X	X	X	X	X
Global Assessment of Severity	X	X	X	X	X
Global Improvement		X	X	X	X
Body Surface Area Assessment	X	X	X	X	X
Safety Variables					
Telangiectasis	X	X	X	X	X
Skin Atrophy	X	X	X	X	X
Adverse Events		X	X	X	X
Psoriasis Disability Index	X			X	
Source: Sponsor's NDA submission: Volume 1.26, page 3296					

Reviewer's Comment: *The sponsor has listed multiple variables to be assessed in the above table. However, as will be delineated below under endpoints, the ones that the Division considered significant and that were discussed in the EOP2 meeting are the ones that will be used to evaluate the efficacy of clobetasol propionate lotion, 0.05%.*

Efficacy Endpoints

The primary efficacy variable was the Investigator's Global Assessment Severity Scale, which is a static scale with morphologic descriptors. Success was defined by the sponsor as a patient having a classification of none, very mild, or mild corresponding to a numerical score of 0, 0.5, or 1. This success was to reach statistical significance against its vehicle or show non-inferiority to the active comparator, Temovate E Cream, 0.05%. The Global Assessment Scale is found in table 5.

Table 5
Investigator's Global Severity Assessment Scale
Study CR.U9707

Severity	Score	Morphologic Description
None	0	No clinical signs or symptoms detected
Very Mild	0.5	Only very slight signs or symptoms detected (e.g. very fine scaling or slight erythema)
Mild	1	Slight signs or symptoms detected (e.g., mild erythema and scaling, eventually associated to some barely detectable plaque elevation
Moderate	2	Moderate, clearly detectable signs or symptoms (e.g. definite redness with obvious scaling on a plaque often elevated above skin level)
Severe	3	Severe signs or symptoms detected (e.g. intense redness, profuse shedding, and definite plaque thickness most often all present)
Very Severe	4	Very severe signs or symptoms detected (e.g. Maximum erythema with heavy scale production on highly elevated plaque; in some acute phases, pustules seen
Source: Sponsor's NDA submission: Volume 1.26; page 3298		

Reviewer's Comment: *The Division has always considered a success on the Investigator's Global Assessment Scale that which falls in the categories of clear or almost clear. The sponsor chose to use the words "None" or "Very Mild", instead of those usually used. In spite of that, it is apparent that the morphologic descriptors of the top two categories fit the definition of success as considered by the Division. As will be seen when the efficacy results are discussed, more than half of the patients who entered the study had moderate psoriasis (~60%), and one would expect that success would be reflected in a clinically meaningful outcome. Given that this is a super potent corticosteroid, no less would be expected of it than other drug products that have been approved for the same indication. In this review, the criteria evaluated for success follow the guidelines of the Division and correspond to scores of 0 or 0.5 on this Investigator's Global Assessment Scale.*

The major secondary efficacy variables the sponsor delineated in the protocol were erythema, plaque elevation, scaling, and the dermatologic sum score. The ones considered

supportive of the primary efficacy variable by the Division are detailed below (Source: Sponsor's submission volume 26, pages 3297-3798).

Erythema (as evaluated for the target lesion): abnormal redness of the skin.

None	0	No detectable erythema; skin of normal color
Mild	1	Slight pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness
Very Severe	4	Very severe dark erythema

Plaque Elevation (as evaluated for the target lesion): abnormal thickness of the psoriasis lesion.

None	0	Normal skin thickness; no elevation of skin
Mild	1	Barely perceptible elevation (by touching) of the Psoriasis plaques
Moderate	2	Obvious elevation above the normal skin level; moderate thickening
Severe	3	Definite thick elevation above normal skin level
Very Severe	4	Very thick plaque elevation

Scaling (as evaluated for the target lesion): abnormal shedding of the stratum. corneum.

None	0	No shedding
Mild	1	Barely perceptible shedding, noticeable only on Light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production
Very Severe	4	Very thick scales possibly fissured

Results

The total number of patients enrolled was 192 subjects. The subjects were randomized and treated at 15 centers in the United States. Table 6 shows the subject disposition.

Table 6
Disposition of Study Subjects
Study 9707

Subjects	Clobetasol Lotion	Temovate E® Cream	Vehicle Lotion
Randomized	82	81	29
Used Study Medication	82 (100%)	81 (100%)	29 (100%)
Completed Study	77 (93.9%)	77 (95.1%)	21 (72.4%)
Completed each visit			
Baseline	82 (100%)	81 (100%)	29 (100%)
Week 1	81 (98.8%)	78 (96.3%)	27 (93.1%)
Week 2	82 (100%)	78 (96.3%)	27 (93.1%)
Week 4	77 (93.9%)	78 (96.3%)	24 (82.8%)
Week 8 (follow-up)	81 (98.8%)	78 (96.3%)	24 (82.8%)
Discontinued	5 (6.1%)	4 (4.9%)	8 (27.6%)
Source: Sponsor's NDA submission - Volume 1.26, page 3309			

Of the 5 clobetasol lotion discontinuations, 3 were due to lack of efficacy and 2 to protocol violations. Of the 4 Temovate E® Cream discontinuations, 2 were due to subject request, 1 due to adverse events, and 1 subject was lost to follow-up. Six of the 8 vehicle lotion discontinuations were by subject request, 1 subject discontinued due to lack of efficacy and 1 was lost to follow-up.

Patient demographics are outlined in Table 7.

***Reviewer's Comment:** . In the review, the analysis will focus on the intent-to-treat (ITT) population. The per protocol (PP) population showed similar results, unless otherwise noted. The reader is referred to the statistical review for details on the PP population.*

Table 7
Demographic Characteristics of Study Subjects - ITT Population
Study 9707

		Clobetasol Lotion (N=82)	Temovate E® Cream (N=81)	Vehicle Lotion (N=29)	P-value
Age (years)	Mean Range	48.72 (19-72)	49.09 (21-77)	47.21 (26-78)	0.795
Gender					
Male	N (%)	58 (70.7)	52 (64.2)	16 (55.2)	0.286
Female	N (%)	24 (29.3)	29 (35.8)	13 (44.8	
Race					
White	N(%)	69 (84.1)	66 (81.5)	24 (82.8)	0.286
Black	N(%)	2 (2.4)	1 (1.2)	2 (6.9)	
Hispanic	N (%)	11 (13.4)	14 (17.3)	3 (10.3)	
Skin Phototype (T.B. Fitzpatrick)					
I	N(%)	3 (3.7)	1 (1.2)	4 (13.8)	0.103
II	N(%)	23 (28.0)	27 (33.3)	6 920.7)	
III	N(%)	28 (34.1)	30 (37.0)	10 (34.5)	
IV	N(%)	15 (18.3)	20 (24.7)	5 (17.2)	
V	N(%)	11 (13.4)	2 (2.5)	3 (10.3)	
VI	N (%)	2 (2.4)	1 (1.2)	1 (3.4)	

Source: Sponsor's NDA submission - Volume 1.26- page 3312

Baseline severity of disease was similar across all arms. All subjects had moderate to very severe disease at baseline with at least 15% of the body surface area (BSA) involved. The mean percentage BSA affected at baseline was 28.0%, 27.0%, and 26.3% for clobetasol propionate lotion, Temovate E Emollient Cream, and lotion vehicle, respectively.

Efficacy Endpoint Outcomes

Reviewer's Comment: *The success criteria for the primary efficacy endpoint, as discussed earlier, has been re-defined as a score of 0 or 0.5 at week 4 on the Investigator's Global Assessment Severity Scale in the evaluation of plaque psoriasis. The following analysis in table 8 shows the results.*

Table 8
Number of Patients with Success in Global Severity
Study 9707

Population Type	Clobetasol Lotion n/n (%)	Temovate E Cream n/n (%)	Vehicle n/n (%)	Clobetasol Lotion vs. Vehicle[1] (p-value)	Clobetasol Lotion vs. Temovate E	
					Difference (Clobetasol Lotion – Temovate E)	Limit of 97.5% CI (Asymp.)[1]
ITT	30/82 (36.6%)	33/81 (40.7%)	0/29	< 0.001	–4.2%	–18.9%
PP	27/76 (35.5%)	32/75 (42.7%)	0/26	< 0.001	–7.1%	–22.4%

Source: Sponsor's NDA submission - Volume 1.26, page 3317
[1]From statistical review - page 10

The results of the secondary efficacy variables are delineated in table 9.

Table 9
Number (%) of Patients with Score of 0 at Endpoint in Clinical Signs - Psoriasis
ITT Population - Study 9707

Signs	Clobetasol Lotion (N=82)	Temovate E Cream (N=81)	Vehicle (N=29)	Clobetasol Lotion vs. Vehicle (p-value)[1]	Clobetasol Lotion vs. Temovate E	
					Difference (Clobetasol Lotion – Temovate E)	Limit of 97.5% CI (Asymp.)[1]
Erythema —	13 (15.9%)	11 (13.6%)	0	0.0124	2.3%	–8.91%
Plaque elevation	45 (54.9%)	33 (40.7%)	0	< 0.001	14.1%	–1.20%
Scaling	48 (58.5%)	41 (50.6%)	2 (6.9%)	< 0.001	7.9%	–7.33%

Source: Sponsor's NDA submission, Volume 1.26 page 3320
[1]From statistical review - page 9

Reviewer's Comment: *Efficacy results show that clobetasol lotion is statistically superior to its vehicle in the primary efficacy measure of success in global severity ($p<0.001$). This is true for both the ITT and PP analysis. The secondary efficacy parameters support the primary efficacy analysis as clobetasol propionate is statistically superior to vehicle in erythema ($p=0.0124$), plaque elevation (<0.001), and scaling ($p<0.001$).*

The sponsor has submitted a 505 (b)(2) application using Temovate E Cream as the reference listed drug (RLD) product. Clobetasol lotion in this context should be non-inferior to this RLD. The margin of non-inferiority that the Division has used for similar NDA applications has been a non-inferiority margin of 10%. As can be seen from table 8, clobetasol lotion has a non-inferior margin that is smaller than -10% of Temovate E in the primary efficacy variable.

Although the non-inferiority margin is established in the secondary signs, these are only supportive of the global severity scale which assesses the entire disease state.

Trial #2 – RDS.06.SPR.18001.R02

Title: "The Safety and Efficacy of Clobetasol 17-Propionate Lotion, 0.05% as compared to its Vehicle and Temovate E Emollient Cream in the treatment of Moderate to Severe Atopic Dermatitis: A Randomized, Active- and Vehicle-Controlled, Investigator-masked Parallel Comparison"

Investigators

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8.	[redacted]	
9.	[redacted]	
10.	[redacted]	
11.	[redacted]	
12.	[redacted]	
13.	[redacted]	
14.	[redacted]	

Objective/Rationale

The objectives of the study are to evaluate clobetasol propionate lotion for safety and superior efficacy to its vehicle lotion in adult patients with moderate to severe atopic dermatitis. Furthermore, it also aims to show non-inferiority to another clobetasol propionate product, Temovate E Emollient Cream, 0.05%.

Overall Study Design

This study was to be conducted as a multicenter, randomized, double-blind, investigator-masked, parallel group, active and vehicle controlled comparison in patients with moderate to severe psoriasis. The clobetasol propionate lotion and its vehicle were double-blinded. The clobetasol lotion and Temovate E Cream were investigator masked as the formulations of the two substances are different. Qualified patients, who met specific inclusion criteria, were randomized in a 3:3:1 ratio to receive either clobetasol propionate lotion, 0.05%, Temovate E Emollient Cream,0.05%, or clobetasol propionate lotion, respectively. This was to minimize the number of patients receiving vehicle lotion. Patients were to apply the medication to the affected

areas twice daily for 2 weeks, not to exceed 50 grams/week application of medication. A 2-week follow-up period was to assess duration of response and any late occurring safety issues.

Evaluations of patients occurred at baseline, weeks 1, 2, 4, and 6.

Protocol

Inclusion Criteria

Male or female subjects, 12 years of age or older

All female subjects (except pre-menses adolescents, women who had undergone a hysterectomy, bilateral ovariectomy, tubal ligation and postmenopausal) were to have a negative urine pregnancy test (UPT) at the beginning of the study. (Postmenopausal was defined as no menstruation for at least 2 years).

Subjects with a confirmed diagnosis of AD meeting the following criteria:

Must have had three or more of these basic features:

- ⇒ Pruritus
- ⇒ Typical morphology and distribution: flexural lichenification or linearity in adults with a variety of skin lesions
- ⇒ Chronic or chronically-relapsing dermatitis
- ⇒ Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Subjects with AD involvement of at least 20% of total body surface area, using the "Rule of Nines".

Subjects with an AD history of at least six months.

Subjects with a total Baseline DSS of at least six in the target area to be evaluated. The target area selected for evaluation and treatment must have been at least 25 cm^2 in size, and must not have been on the facial area, axillae, groin, scalp, hands or feet.

Subjects willing and capable of cooperating to the extent and degree required by the protocol.

Subjects (and parent or guardian in case of a minor) must have signed and understood the Informed Consent form prior to receiving study treatment.

Exclusion Criteria

Pregnant and/or nursing females or females planning a pregnancy.

Subjects who had not undergone the following washout period(s) including but not limited to the following **topical** treatments that have a known beneficial effect on AD:

• Corticosteroids	4 weeks
• Other medications used in AD	4 weeks
• Ultraviolet (UV) light therapy including sunbathing	4 weeks

Subjects who had not undergone the following washout period(s) including but not limited to the following **systemic** medications:

• Corticosteroids or adrenocorticotropic hormone (ACTH) analogue	6 weeks
• Anti-histamines	2 weeks
• Theophylline derivatives	2 weeks
• Other medications used in AD	6 weeks
• Psoralen ultraviolet light (PUVA) therapy	6 weeks
• Cyclosporin, interferon, tacrolimus	16 weeks

Subjects utilizing concomitant therapies during the course of the study that could have interfered with the interpretation of study results at the discretion of the investigator.

Subjects with concomitant medical or dermatological disorder(s) that might have precluded accurate evaluation of the AD (e.g., cutaneous infection, psoriasis, or acne in the areas of AD involvement).

Subjects with known sensitivities to any ingredients of the study preparations.

Subjects who had participated in an investigational drug or device research study within the last 30 days.

Withdrawal Criteria

Premature Terminations

These were determined as follows:

- An AD flare which needed an interfering therapy.
- Pregnancy.
- Either at the investigator's request, for safety reasons (e.g., severe adverse reactions, worsening of the study condition, or unauthorized concomitant therapy), or at the subject's request.
- When the requirements of the protocol were not respected.
- When a concomitant therapy liable to interfere with the results of the study was reported, or required, by the subject (the investigator reported all such information on the CRF and decided whether the subject was to be withdrawn).
- If condition cleared or almost cleared before the end of study.
- When a subject was lost to follow-up, the investigators tried twice to reach the subject by telephone and sent a follow-up letter before considering that the subject was lost-to-follow-up.

These actions were reported on the CRF, and a copy of the follow-up letter was maintained in the investigator's file.

Procedures and Observations

Each subject received both verbal and written instructions regarding the proper dosing and study medication application techniques. All subjects were instructed to dose twice a day, morning and evening, with the test material. Subjects were to have washed with a mild cleanser, patted the area dry, and allowed several minutes before application of the test material. No time interval between dosing and meals or any other activity was specified.

After the 2-week treatment period (or less if the condition cleared before Week 2), the subject was instructed to avoid using any medication for atopic dermatitis during the 2-week follow-up period.

Table 10 outlines the visits and evaluations for this trial.

Table 10
Study Flow Chart
Study 18001.R02

Procedures	Screening/ Baseline[1] (visit 1)	Week 1 (visit 2)	Week 2 End of treatment[9] (visit 3)	Week 4[8] End of study (visit 4)
Informed Consent	X			
Demographics	X			
Medical History	X			
Inclusion/Exclusion Criteria	X			
Physical Examination[2]	X		X	X
Pregnancy Test (Urine)	X		X	
Target Area Identification[3]	X			
Body Surface Area Assessment	X	X	X	X
Clinical Disease Evaluation	X	X	X	X
Skin Safety Evaluation	X	X	X	X
Photography of the Target Lesion[4]	X		X	X
BID Dosing[3,5]	X	X	X	
Medication Dispensed	X			
Medication Weighed[7]	X	X	X	
Medication Collected			X	
Concomitant Therapy	X	X	X	X
Evaluate Compliance		X	X	
Adverse Events		X	X	X
Final Report Form			X	X[6]

1 Screening visit and Baseline visit may have occurred on the same day. If visits occurred on two separate days, the Screening visit must have been within seven days of Baseline visit.
2 Review of basic systems.
3 Applications made to a designated target lesion as well as other affected areas.
4 Photographs were taken as documentation and for scientific purpose in selected sites (see Appendix 16.1.1, Attachment 11.4).
5 Drug amounts not to exceed 50 g per week. First application was made under the supervision of the study personnel.
6 The treatment period could be shortened, if all treated atopic dermatitis areas were judged by the investigator as "clear" or "almost clear" prior to Week 2. The subject was allowed to enter the follow-up phase earlier.
7 Medication was weighed prior to distribution and at each study visit.
8 Week 4 procedures were conducted earlier if subject terminated early.
9 If condition cleared before Week 2, subjects entered the 2-week follow-up period before Week 2.

Source: Sponsor's NDA submission - Volume 1.30, page 5195

Efficacy Endpoints

The sponsor listed several variables as efficacy endpoints. These included global severity, dermatological sum score, erythema, excoriation, induration/papulation, lichenification,

oozing/crusting, dryness/scaling, pruritus, global improvement, and body surface area assessment.

Reviewer's Comment: *The Division considers the primary efficacy variable to be that of the Global Assessment Severity Scale dichotomized to success vs. failure. The sponsor wants a score of 0, 0.5. or 1 to be a success. The Division has equated success with those patients whose morphological description of disease equates to that of clear or almost clear. Accordingly, on the Global Assessment Severity Scale provided by the protocol, that would equate to a score of 0 or 0.5. Furthermore, approximately 65% of patients who entered this trial were scored a 2 (moderate) at baseline and an improvement of 1 score on the assessment scale is not considered a clinically meaningful success for a drug product such as this one.*

The scale for the primary efficacy variable is outlined in table 11.

Table 11
Investigator's Global Severity Assessment Scale
Study 18001.R02

Severity	Score	Morphologic Description
None	0	No clinical signs or symptoms detected
Very Mild	0.5	Only very slight signs or symptoms detected (e.g. often only dry skin with equivocal shedding and mild erythema)
Mild	1	Slight signs or symptoms detected (e.g., some papules and few excoriations on slightly red, somewhat indurated skin).
Moderate	2	Moderate, clearly detectable signs or symptoms (e.g., papules and excoriations as a sign of scratching were present; rare hemorrhagic crusts or oozing; skin can be of normal thickness or indurated; itching was often temporarily bothersome).
Severe	3	Severe signs or symptoms detected (e.g., important papulation and vesiculation associated with marked oozing and crusting; many erosions on edematous red skin; considerable itching; sleep disturbing).
Very Severe	4	Very severe signs or symptoms detected (e.g., many papules and large often deep erosions with hemorrhagic crusts; vesicles with considerable weeping and severe sleep disturbing; itching in a more chronic stage, thick lichenifications and prurigo-like erosions were seen).
Source: Sponsor's NDA submission: Volume 1.30; page 5207		

Secondary efficacy variables that the Division considers important in the evaluation of treatment of acute atopic dermatitis include erythema, induration/papulation, oozing/crusting, and pruritus. These were the signs and symptom analyzed in the review and considered supportive of the primary efficacy variable. The scales for these efficacy variables are delineated below.

Erythema (as evaluated for the target lesion)

Erythema		**Abnormal redness of the skin.**
None	0	No detectable erythema. Skin of normal color.
Mild	1	Slight pinkness present.
Moderate	2	Definite redness, easily recognized.
Severe	3	Intense redness.
Very severe	4	Very severe dark erythema.

Induration/Papulation (as evaluated for the target lesion)

Induration/Papulation		**A hardening or firmness of the tissue at and around the site of the lesions.**
None	0	No induration/papulation.
Mild	1	Slight tenseness of skin. Absent to minimal papulation.
Moderate	2	Moderate thickening of skin with edematous feel. Moderate papules.
Severe	3	Firm resistance to distortion; non-distensible. Marked papulation, urtication or diffuse non-pitting edema.
Very severe	4	Firm resistance to distortion; non-distensible. Very important papulation.

Oozing/Crusting (as evaluated for the target lesion)

Oozing/Crusting		**The continuing process of exudation of fluid from the lesions / formation of scab-like material on the surface of lesions resulting from dried serum.**
None	0	No oozing/crusting.
Mild	1	Faint sign of oozing and/or weeping; slight crusting on a few (25% or less) of the lesions.
Moderate	2	Definite oozing, but not extensive (a few lesions/areas); definite crusting on several (approximately 26-50%) of the lesions.
Severe	3	Marked oozing/weeping; heavy crusting on the majority (51% or more) of the lesions.
Very severe	4	Very important and extensive oozing/weeping; heavy crusting on all (more than 70%) of the lesions.

Pruritus (as evaluated on all treated areas)

The investigator scored the subjective assessment of pruritus after discussing the symptom with the subject and listening to the subject's description of the sensation. The subject was

not given the opportunity to simply select the score nor to consider the target area only when describing pruritus. This variable was meant to describe the pruritus associated with atopic dermatitis and not as a side effect of the study medication. Therefore, the subject was questioned about general itching and not about itching related to the application of the medication.

Pruritus		**An itching sensation.**
None	0	No itching.
Mild	1	Slight itching, not really bothersome.
Moderate	2	Definite itching that is somewhat bothersome; without loss of sleep.
Severe	3	Intense itching that has caused pronounced discomfort; night rest interrupted. Excoriations of the skin from scratching may be present.
Very severe	4	Very intense itching that has caused pronounced discomfort during daily activities; night sleep is disturbed. Many excoriations of the skin from scratching.

Results

A total of 229 subjects were enrolled at 14 centers in the United States. Enrollment was to stop when 224 subjects had been entered into the study, however, an additional five subjects were enrolled prior to all the investigators being informed that enrollment was terminated. There were 23 (10%) subjects discontinued from the study: nine (9.4%) subjects receiving clobetasol propionate lotion, seven (7.0%) subjects receiving Temovate E® Emollient Cream, and seven (21.2%) subjects receiving lotion vehicle. Subject request and loss to follow-up were the major reasons for discontinuation in each treatment group. In the lotion vehicle group, one subject discontinued due to an adverse event (worsening of atopic dermatitis), and one was discontinued due to a protocol violation (over used study medication). The disposition of subjects is summarized in Table 12.

Table 12
Disposition of Study Subjects
Study 18001.R02 - ITT Population

Subjects	Clobetasol Lotion (N=96)	Temovate E® Emollient Cream (N=100)	Lotion Vehicle (N=33)
Completed study	87 (90.6%)	93 (93.0%)	26 (78.8%)
Completed each visit [1]			
Week 1	93 (96.9%)	96 (96.0%)	29 (87.9%)
Week 2	87 (90.6%)	96 (96.0%)	27 (81.8%)
Week 4 (follow-up)	88 (91.7%)	93 (93.0%)	27 (81.8%)
Discontinued	9 (9.4%)	7 (7.0%)	7 (21.2%)
Adverse event	0 (0%)	0 (0%)	1 (3.0%)
Subject's request	2 (2.1%)	3 (3.0%)	3 (9.1%)
Protocol Violation	0 (0%)	0 (0%)	1 (3.0%)
Lost to Follow-up	5 (5.2%)	4 (4.0%)	1 (3.0%)
Other	2 (2.1%)	0 (0%)	1 (3.0%)

Source: Sponsor's NDA submission - Volume 1.30, page 5226

The baseline demographics are presented in table 13. There were 24 adolescent subjects enrolled (12-17 years old, inclusive): 12 subjects in the clobetasol propionate lotion group, nine subjects in the Temovate E® Emollient Group, and three subjects in the lotion vehicle group.

Table 13
Demographic Characteristics
ITT Population - Study 18001.R02

		Clobetasol Lotion (N = 96)	Temovate E® Emollient Cream (N = 100)	Lotion Vehicle (N = 33)	p-value*
Age	Mean±SD Range	39.3 ± 19.0 12-84	42.4 ± 17.8 12-83	40.7 ± 19.4 12-86	0.344
Gender					
Male	n (%)	39 (40.6%)	45 (45.0%)	15 (45.5%)	0.824
Female	n (%)	57 (59.4%)	55 (55.0%)	18 (54.5%)	
Race					
White	n (%)	69 (71.9%)	67 (67.0%)	23 (69.7%)	
Black	n (%)	12 (12.5%)	27 (27.0%)	8 (24.2%)	
Yellow	n (%)	6 (6.3%)	1 (1.0%)	0 (0%)	0.087
Hispanic	n (%)	6 (6.3%)	4 (4.0%)	2 (6.1%)	
Other	n (%)	3 (3.1%)	1 (1.0%)	0 (0%)	
Skin Phototype					
I	n (%)	4 (4.2%)	8 (8.0%)	4 (12.1%)	
II	n (%)	28 (29.2%)	19 (19.0%)	8 (24.2%)	
III	n (%)	33 (34.4%)	32 (32.0%)	8 (24.2%)	0.351
IV	n (%)	14 (14.6%)	14 (14.0%)	4 (12.1%)	
V	n (%)	7 (7.3%)	6 (6.0%)	4 (12.1%)	
VI	n (%)	10 (10.4%)	21 (21.0%)	5 (15.2%)	

Sponsor's NDA submission, Volume 1.30

As stated earlier, approximately 65% of patients were scored as 2, moderate disease at baseline. However, of the patients that were graded as severe or very severe the arms were not equal. There was a higher proportion of those patients in the lotion vehicle arm (42.4%) when compared to CP Lotion (25.0%) and Temovate E Emollient Cream (35.0%) arms. The mean percentage of BSA involvement at baseline was similar for each treatment group being 40.1%, 38.6%, and 43.7% for clobetasol propionate lotion, Temovate E Emollient Cream, and lotion vehicle, respectively.

Reviewer's Comment: *According to Dr. Lee, the biostatistician, because the sponsor used simple randomization, there may be an appearance of imbalance for a few parameters. However, in the case of the distribution of disease severity score between Clobetasol propionate lotion and vehicle the difference is not statistically significant (p=0.1137).*

Efficacy Endpoint Outcomes

Reviewer's Comment: *The success criteria for the primary efficacy endpoint, as discussed earlier, has been re-defined as a score of 0 or 0.5 at week 4 on the Investigator's Global Assessment Severity Scale in the evaluation of atopic dermatitis. The following analysis in table 14 shows the results based on this criterion for success.*

Table 14
Number of Patients with Success in Global Severity
Study 18001.R02

Population Type	Clobetasol Lotion n/n (%)	Temovate E Cream n/n (%)	Vehicle n/n (%)	Clobetasol Lotion vs. Vehicle (p-value)[1]	Clobetasol Lotion vs. Temovate E	
					Difference (Clobetasol Lotion – Temovate E)	Limit of 97.5% CI (Asymp.)[1]
ITT	41/96 (42.7%)	41/100 (41.0%)	4/33 (12.1%)	0.001	1.7%	–12.0%
PP	40/90 (44.4%)	41/95 (43.2%)	4/28 (14.3%)	0.003	1.3%	–12.9%

Source: Sponsor's NDA submission - Volume 1.30, page 5236
[1]From statistical review - page 10

The results for the secondary efficacy analysis is shown in table 15.

Table 15
Number (%) of Patients with Score of 0
At Endpoint in Clinical Signs - Atopic Dermatitis
ITT Population - Study 18001.R02

Signs and Symptom	Clobetasol Lotion (N=96)	Temovate E Cream (N=100)	Vehicle (N=33)	Clobetasol Lotion vs. Vehicle (p-value)[1]	Clobetasol Lotion vs. Temovate E	
					Difference (Clobex – Temovate E)	Limit of 97.5% CI (Asymp.)[1]
Erythema	34 (35.4%)	34 (34.0%)	2 (6.1%)	< 0.001	1.4%	–11.84%
Papulation	50 (52.1%)	48 (48.0%)	5 (15.2%)	< 0.001	4.1%	–9.85%
Oozing/Crusting	82 (85.4%)	88 (88.0%)	21 (63.6%)	0.0083	–2.6%	–12.50%
Pruritus	56 (58.3%)	60 (60.0%)	5 (15.2%)	< 0.001	–1.7%	–15.30%

Source: Sponsor's NDA submission - Volume 1.30, pages 5238-5239.
[1]Statistical review - page 12

Reviewer's Comment: *Efficacy results show that clobetasol lotion is statistically superior to its vehicle in the primary efficacy measure of success in global severity (p=0.001). The results were similar for the per protocol population (p=0.003). The secondary efficacy parameters support the primary efficacy analysis as clobetasol propionate is statistically superior to vehicle in erythema (p<0.001), papulation (p<0.001), oozing/crusting (p=0.0083), and pruritus (p<0.001).*