CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-753

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	21-753
Submission Number	000
Submission Code	3S
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Reviewer Name	Joseph M. Porres
Review Completion Date	1/19/05
Established Name	Adapalene 0.3% gel
(Proposed) Trade Name	Differin XP 0.3% gel
Therapeutic Class	topical anti-acne
Applicant	Galderma
Priority Designation	S
Formulation	topical gel
Dosing Regimen	nightly
Indication	acne
Intended Population	12 years old and older

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that adapalene gel, 0.3%, not be approved for the topical treatment of acne vulgaris in subjects 12 years of age and older.

This recommendation is based on the failure to demonstrate significantly superior efficacy for adapalene gel, 0.3%, over the 0.1% formulation being marketed –Differin Gel, 0.1%- and used as a comparator, when analysis is performed as pre-specified in the protocol. The results for the per protocol population, where treatment compliance is better and often greater efficacy is anticipated, paralleled those for the ITT population, but they were not better. This recommendation is supported by the failure to demonstrate significantly superior efficacy of adapalene gel, 0.3%, over the 0.1% formulation in the Phase 2 dose-comparison study and in the Phase 3 European study, and by the failure to consistently demonstrate superiority of the comparator 0.1% formulation over vehicle.

Although adapalene gel, 0.3%, showed some increased efficacy over the 0.1% formulation, the 0.3% formulation was also consistently more likely than the 0.1% formulation to cause the following symptoms: erythema, dryness, desquamation, scaling, stinging/burning, and pruritus, and these tended to be generally of greater severity, particularly early during the treatment. These symptoms tended to be mild to moderate overall and decreased with continued treatment, some taking longer than others to normalize. The rate of AEs for each formulation paralleled the results for the symptoms related to tolerance. In addition, adapalene, a known teratogen, was detected in the plasma of 15 of the 16 patients studied, reaching the level of 36.1 ng.h/mL (2 ng/mL) in one subject. It would be difficult to support the approval of a drug formulation that shows no increased efficacy over an existing formulation while producing detectable plasma levels and producing more local irritation than the approved comparator.

Adapalene gel, 0.3%, was superior to vehicle in the pivotal trial. The only other vehicle controlled study was the Phase 2 dose comparison study, where the 0.3% formulation appeared more efficacious than vehicle but the study differed significantly from the pivotal trial in formulation and design. The Sponsor could support an application for approval based on the superiority over vehicle but an additional vehicle-control study demonstrating efficacy would be needed; this study should include investigators, sites and subjects different from those in earlier studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting would be sufficient risk management activities for this drug product.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other Phase 4 studies are requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Sponsor has submitted a 505(b)(1) application for the approval of adapalene gel, 0.3%, a topical, retinoid-like product, for the treatment of acne vulgaris in patients 12 years old and older, using the currently approved Differin gel 0.1% as the reference listed drug (RLD).

The applicant has conducted one Phase 3, safety and efficacy study (RD.06.SRE.18081) to demonstrate superiority to Differin, Gel, 1%, and to vehicle.

The applicant has also conducted other safety and efficacy studies, as follows:

- RD.03.SRE.2673, a European Phase 3 study comparing the 0.3% formulation against a EU formulation of adapalene gel 0.1%, different from the comparator used in the US Phase 3 trial, and without a vehicle arm. Safety was not assessed in the same way as the US pivotal trial.
- RD.SRE.18060, a Phase 2 dose comparison study, in which efficacy was assessed in a different way from the Phase 3 trial.
- RD.06.SRE1.18062, a long term Phase 3 open trial to assess safety and which was interrupted early on. Efficacy was assessed without comparators.

Topical safety studies conducted by the applicant, and which will be reviewed here, include:

- RD.03.SRE.2644, a cumulative irritancy study
- RD.03.SRE.2645, a photoallergy study
- RD.03.SRE.2646, a phototoxicity study
- RD.03.SRE.2017, a topical sensitization study

Each of these 7 studies is described in the Appendix.

The Sponsor has also conducted several pharmacokinetic studies, one being considered pivotal (RD.03.SRE.2690)

The applicant has conducted other topical safety studies, and exploratory studies on indications other than acne. These do not conform to the usual topical safety studies and do not provide additional useful information in relation to the current application and will not be reviewed here.

The Sponsor states that a total of 1,505 subjects have been exposed to adapalene, 0.3% products. Of these, 1,441 subjects were exposed to adapalene gel, 0.3%.

1.3.2 Efficacy

In the Phase 2 trial (RD.06.SRE.18060) adapalene gel, 0.3%, was superior to the 0.1% formulation only for non-inflammatory lesions and it failed to prove superiority to vehicle for inflammatory lesions. Based on the increased efficacy of the 0.3% formulation in this study, the Sponsor chose to proceed with a Phase 3 pivotal study hoping to demonstrate superior efficacy for the higher strength formulation.

In the Phase 3 pivotal trial (RD.06.SRE.18081), a total of 653 subjects were randomized (258 to adapalene gel, 0.3%, 261 to adapalene gel, 0.1%, and 134 to vehicle). There were no statistically significant differences in the ITT population groups with respect to demographic and baseline characteristics. The trial was multi-centered, randomized, double-blind, adequate and well-controlled.

Co-primary efficacy endpoints included success rate - based on the Investigator's Static Global Assessment dichotomized to success and failure - and percent reduction in lesion counts (total, inflammatory and non-inflammatory). Adapalene gel, 0.3%, needed to win on at least two of the three.

The primary analysis for lesion counts was based on the pre-specified correlated repeated measurements at week 8 and week12. Generalized Estimating Equation (GEE) methodology was used as the primary analysis. The analysis group was pre-specified in the statistical analysis plan to be the ITT (LOCF) population. For cases where no post-baseline values were available, baseline values were to be carried forward to all post-baseline visits. For the three total lesion counts (total, inflammatory, and non-inflammatory), the LOCF estimation was to be applied to the individual item (open comedone, close comedone, papules, pustules, nodules/cysts) prior to the totals. The primary efficacy results were sensitive to an outlier (subject #1696), as identified by the sponsor. Due to this outlier, the requirement of normality in the primary GEE analyses was slightly violated. For this reason, GEE analyses results based on the rank data were also considered in assessing the efficacy of adapalene gel, 0.3%.

Overall the 0.3% formulation was more efficacious than the 0.1% formulation but the difference was small. In no case was the success rate for any endpoint higher than 23% after 12 weeks of treatment. The highest average reduction in number of lesions did not exceed 45%. Only 20.5% of patients reached success in the IGA at the end of the study.

In the pivotal trial, adapalene gel, 0.3%, demonstrated superiority over the 0.1% formulation ($p=0.028$) and over vehicle ($p=0.010$) for the Investigator Global Assessment. In the assessment of lesion counts, adapalene gel, 0.3%, failed to demonstrate superiority to the 0.1% formulation for total lesions ($p=0.072$), for inflammatory lesions ($p=0.064$), and for non-inflammatory lesions ($p=0.120$), but demonstrated superiority over vehicle ($p=0.001$ for total, $p=0..002$ for inflammatory,

p=0.001 for non-inflammatory). The approved 0.1% comparator formulation demonstrated superiority over vehicle for total (p=0.06) and for non-inflammatory lesions (p=0.06) but not for inflammatory lesions (p=0.110) or for IGA (p=0.420).

Analyses of efficacy data at week-8 and at week-12 fail to support efficacy. The longer duration of treatment failed to improve on efficacy over the 8-week treatment.
See the Biostatistics Review for further details.

Reviewer comment: Adapalene gel, 0.3% did not demonstrate statistical significance over adapalene gel, 0.1%. However, the 0.3% formulation showed some increased efficacy over the 0.1% formulation and it did demonstrate statistical significance over vehicle in the one pivotal trial. The overall efficacy of both adapalene gel formulations is limited. These products are rarely used in the treatment of acne as sole agents, but rather combined with other topical or systemic agents. They are unlikely to be used during daytime because of interaction with light, or more than once daily because of likely increased local irritation; therefore, no increased efficacy should be anticipated from a possible increase in frequency of application.

1.3.3 Safety

The applicant reports 1505 subjects have been exposed to adapalene 0.3% products. Of these, 1,441 were exposed to adapalene gel, 0.3%: 330 healthy subjects in the Phase 1 clinical pharmacology studies, and 1,111 subjects with *acne vulgaris* in the Phase 1 pharmacokinetic, Phase 2, and Phase 3 studies.

In a pharmacokinetic study (**RD.03.SRE.2690**), quantifiable amounts (lower limit of quantification = 0.10 ng/mL) of adapalene in the plasma samples were found in 15 of 16 subjects following the last dose, and it reached 36.1 ng.h/mL in one subject. The Biopharmaceutics Review underlines the fact that these patients might not have been tested under "maximal use conditions" since they only applied 2 g per application, which would correspond to about 5-6 % BDS. The mean $AUC_{(0\text{-}24h)}$ over a 24-hour dosing interval on Day-10 was 8.94 ± 8.99 ng.h/mL. The mean C_{max} on Day-10 was 0.553 ± 0.466 ng/mL. In earlier studies with the 0.1% gel formulation, adapalene levels were <0.35 ng/mL. The terminal apparent half-life ranged from 13 to 16 hours, thereby indicating that a pharmacokinetic steady-state was reached before Day-10. Adapalene was rapidly cleared from plasma and was not detected 72 hours after the last application except for subject 8, on whom 0.1283 ng/mL was detected at the last measurement at 72 hours. In the Phase 2 study **(RD.06.SRE.18060),** adapalene concentrations were below the limit of detection (LOD = 0.15 ng/mL) in 209 samples. In three samples, adapalene traces were found below the 0.25 ng/mL limit of method of quantification. Average daily usage of adapalene gel, 03%, was 0.856 g/day (range 0.11-2.11 g/d).
Reviewer comment: The detection of small amounts of adapalene in some patients raises the concern for potential teratogenicity with higher exposure. [redacted]

Of the 354 subjects in the Phase 1 studies, (330 healthy subjects and 24 subjects with *acne vulgaris*) 65 subjects had 83 mild and non-persistent adverse events. Eight subjects had 11 adverse events related to treatment, mostly local irritation, and three of these subjects discontinued from the study.

The applicant states there was no evidence of sensitization, photosensitization, or phototoxicity from adapalene gel, 0.3%. In the irritancy study, adapalene gel, 0.3%, was similar to adapalene gel, 0.1%, and both were slightly more irritating than Vehicle and White Petrolatum.

The applicant states that the pivotal Phase 3 study (**RD.06.SRE.18081**) was the only well-controlled study in which signs and symptoms of skin irritation (erythema, scaling, dryness, and stinging/burning) were prospectively defined. They were evaluated from Baseline on a 4-point scale ranging from none to severe, but they were reported only if a worsening from baseline was found. In the study, erythema, scaliness, and dryness, were more common for adapalene gel, 0.3%, than for the 0.1% formulation, and least for the vehicle, symptoms being generally mild, developing early in the treatment and decreasing with continued treatment. At the final visit, erythema worse than at baseline was present in 12.3% and 13.2%, scaling in 13.5% and 11.6%, and dryness in 18.2% and 16.4%, in the 0.3 and 0.1% formulations respectively.

The more frequent AEs were dermatological. Those considered treatment-related were more frequent in the adapalene gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). Only 4 subjects (all in the 0.3% group) had non-dermatological, treatment- related AEs: facial edema, pain, keratoconjunctivitis, and eye pain. Other non-cutaneous AEs were infrequent and mild.
Reviewer comment: The applicant does not provide information whether the keratoconjunctivitis and eye pain were the result of medication getting into the eye during treatment but it would be reasonable to expect such was the case.

There were no mean changes in any hematology, blood chemistries, and urinalysis laboratory results that suggested a systemic effect of study drug. There were no trends in individual laboratory abnormalities that indicated an effect of study drug. Five subjects (3 in the 0.3% group and 2 in the 0.1% group) had laboratory abnormalities that were considered unrelated to treatment and none required treatment.

No deaths have been reported during the development program for adapalene gel, 0.3%. No serious treatment-related AEs has been reported during these studies.

The long term safety of adapalene gel, 0.3%, was studied in the open labeled study **SRE.18082,** which enrolled 551 subjects (303 subjects received adapalene gel, 0.3%, for six months or more; 166 subjects were treated for 12 months). In this study the mean daily usage was lower than in the Phase 2 and in the Phase 3 US trials. These subjects showed a similar pattern of local tolerability and adverse events as those treated in the 12-week controlled studies. Specifically, most adverse events recorded in this trial occurred in the first 12 weeks of treatment and decreased in incidence in the 2nd to 4th quarter of the study.

Reviewer comment: There are two potential problems in the manner in which the Sponsor chose to report adverse events, neither of which were pre-specified in the protocol:

- The symptoms related to local tolerance have been tabulated using the not commonly employed "worse than baseline" concept, which may yield lower totals of AEs than if all AEs had been reported without relation to baseline.
- An Adverse Event Form was to be completed only if the severity of the expected signs and symptoms was such that an interruption of the Subject's participation in the study was requested by either the subject or the Investigator's. It is therefore likely that a number of AEs may not have been reported if the investigator or the subject considered the AE did not require treatment cessation.

Adapalene gel, 0.3%, appears slightly more irritating than the approved adapalene gel, 0.1%, and produces detectable plasma levels.. The type of adverse events reported is consistent with the adverse events expected for a topical retinoid.

1.3.4 Dosing Regimen and Administration

The Sponsor recommends treatment with adapalene gel, 0.3%, to be once daily at night.

Reviewer comment: As is the case with most topical retinoids for the treatment of acne, the efficacy of this product is limited and the product is likely to be used together with other topical or systemic agents rather than as "solo" therapy. Treatment at night is appropriate because of the theoretical concern of drug inactivation/increased irritation when retinoids are used topically with sun exposure. Treatment more than once daily could be anticipated to be too irritating to be practical and is not currently recommended for any approved topical retinoids.

1.3.5 Drug-Drug Interactions

The studies included with the NDA do not address drug-drug interactions.

1.3.6 Special Populations

The proposed labeling for adapalene gel, 0.3%, is for subjects age 12 years old and older. It is classified as Pregnancy Category C. Caution is recommended if it is to be used by nursing mothers Safety and efficacy have not been established for subjects younger than 12 years old or older than 65 years old.

Reviewer comment: The recommendation for patients 12 years of age and older appear appropriate since they reflect the pivotal trial population. [redacted]

[redacted]

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Adapalene is a napthoic acid derivative with retinoid-like activity which has demonstrated efficacy in the treatment of acne vulgaris. The Applicant's proposed indication is for the once nightly, topical treatment of acne vulgaris in patients 12 years old and older.

2.2 Currently Available Treatment for Indications

There are currently multiple approved topical and systemic drug products available for the treatment of acne, including oral and topical antibiotics, oral and topical retinoids, and topical benzoyl peroxide, salicylic acid, azelaic acid, and sulfur products. Often several of these products are used in combination for the treatment of acne, depending on the severity, type and extent of acne, the availability of treatments, and the prescribing physician's preference. It is common to rotate several treatments throughout time if the type of acne evolves or if a treatment modality appears to have lost efficacy.

2.3 Availability of Proposed Active Ingredient in the United States

Adapalene is approved for the topical treatment of acne and has been marketed by Galderma as a 0.1% solution (NDA 20-338) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA20-748) since 5/26/2000. This application is for a new dosage form, 0.3% gel, and the proposed trade name is Differin ® XP ™ Gel.

2.4 Important Issues With Pharmacologically Related Products

Like the retinoids it resembles, adapalene is somewhat irritating to the skin, particularly in the early phase of treatment, depending on the amount of medication applied. Retinoids are customarily applied at night because of possible inactivation and increased irritation if the treated area is exposed to sun light. Retinoids are known teratogens.

2.5 Pre-submission Regulatory Activity

An End-of-Phase 2 meeting took place on 12/3/01 and these are the Clinical minutes from the meeting:

Sponsor's question #1: Based on the results of the Phase 2 study, the Sponsor proposes to proceed to Phase 3 trials with the 0.3% concentration of adapalene to support an indication for *once daily treatment of* [ ] *acne vulgaris*. Does the Agency concur?

Agency's response: The Agency agrees that the data presented in Phase 1 and 2 studies support initiation of Phase 3 studies.

Sponsor's question #2: Concurrence is sought that the two planned safety and efficacy studies and the one long term safety study in subjects with mild to moderately severe acne vulgaris will be sufficient to support the filing of an NDA for this indication.

Agency's response: The Agency recommends that a single three arm study comparing the efficacy and safety of 0.1% and 0.3% adapalene gels with possibly a small vehicle arm be conducted. This would be sufficient for an approvability determination provided the study is adequately powered to detect a significant difference between the two formulations.

Regarding the long-term safety, the Sponsor was encouraged to refer to the ICH E1a guidance document, especially, as levels may be detectable with the higher concentration formulation.

Sponsor's question #3: Concurrence is sought that the proposed endpoints are appropriate to demonstrate the superior treatment effect of adapalene gel, 0.3% compared to its corresponding vehicle.

Sponsor's question #4: The Sponsor considers that the Investigator Global Assessment described is a static overall evaluation of acne based on morphologically defined categories and that it is one of the primary efficacy parameters in the pivotal Phase 3 clinical studies.
Sponsor's question #5: A superior treatment effect is defined as significant efficacy in two of the three lesion count end points plus the success rate by Investigator Global Assessment. Does the Agency concur?

Agency's response: Questions #3, #4, and #5 are interrelated and so are answered together. The Agency concurs that the lesion counts (non-inflammatory, inflammatory, and total counts) and the Investigator's Global Assessment are the primary efficacy parameters.
Superiority of the 0.3% product over the 0.1% should be shown in the mean percent reduction of two of the three lesion counts. For the Investigator's Global Evaluation, the Agency will base its analysis on the percentage of patients that are rated as Clear or Almost Clear at endpoint. T herefore, the Sponsor proposition for using the Leed's scoring system should be reconsidered.

The Investigator's Global Evaluation should consist of no more than five or six categories, with the top ratings designated as Clear and Almost Clear, and should be a static overall evaluation. The category of Almost Clear should be described as having no significant discernible lesions present. Using the Leed's scoring, it appears that only the lowest grade is a win.

Sponsor's question #6: The Sponsor proposes to recruit subjects 12 years and older in age in the adapalene gel, 0.3%, Phase 3 studies. adapalene gel, 0.3%, will not be studied in pediatric subjects below the age of 12 years. The Sponsor will submit a waiver of pediatric studies for subjects below the age of 12 years in the New Drug Application.

Agency's response: It is appropriate for the Sponsor to submit a request for a waiver of pediatric studies.

Additional clinical comments:
1. The inclusion criteria in regard to lesion counts should be 20-100 non-inflammatory lesions, 20-50 inflammatory lesions, and no active nodules or cysts.
2. The washout period for topical medications on the facial area should be four weeks.
3. Grading of the severity of cutaneous signs and symptoms should be done at each return visit; this should include erythema, dryness/scaling, and burning/stinging.

The first medical review for submission 000 for a Phase 2 study, Protocol RD.06.SPR.18060, was completed on 4/3/01. Its objectives were:

a. To determine the treatment differences between adapalene gel, 0.3%, and the gel vehicle, and to assess the magnitude of treatment differences between the 0.3% and 0.1% gel formulations.
b. To determine the relative topical and systemic safety of adapalene gel, 0.3%, adapalene gel, 0.1%, and the gel vehicle.

A Special Protocol (SPR.18081) was submitted (#010) on 12/26/01) and reviewed on 1/11/02, a Phase 3 trial to provide evidence of the superiority of adapalene gel 0.3% over adapalene gel 0.1% and the corresponding vehicle in subjects with acne vulgaris. The Agency supplied to the Sponsor the following comments: "It is felt that the categories of Clear and Almost Clear in the Investigator's Global Assessment, as described, do not reflect a condition that is clear, or one that is almost clear. A grade of Clear should describe a condition in which there are no active lesions, with only perhaps some residual erythema. The description of Almost Clear might be the presence of a few scattered comedones and a few (less than 5) small papules. The study should also be double blind."

Amendment 014 was submitted on 3/8/02 and it included protocol modifications as recommended by the Agency.

The Sponsor is requesting a waiver of pediatric studies in patients younger than 12 years old, and states that the clinical studies have included patients 12-16 years old, for whom there were no appreciable differences in safety or efficacy compared to patients 16 years old and older. The Sponsor further states that since acne vulgaris usually develops after the onset of puberty, it would be impractical to study patients below the age of 12 years old.
Reviewer comment: The request for a waiver from pediatric studies in patients younger than 12 years old appears appropriate and it should be granted if the product were to be approved.

The following table summarizes the related submissions sponsored by the applicant:

RELATED SUBMISSIONS SPONSORED BY GALDERMA LABS	
IND 31,997	Adapalene topical solution
IND 33,540	Adapalene topical gel
IND 38,508	Adapalene topical cream
NDA 20-338 Approved 5/31/96	Differin (adapalene) solution 0.1%
NDA 20-380 Approved 5/31/96	Differin (adapalene) gel 0.1%
NDA 20-748 Approved 5/26/2000	Differin (adapalene) cream 0.1%

2.6 Other Relevant Background Information

Adapalene gel, 0.3%, has not been registered, marketed or withdrawn from clinical investigation in any country. Adapalene Solution, 0.1%, is registered in over 20 countries and marketed in 6. adapalene gel, 0.1%, is registered in over 70 countries and marketed in over 60. Adapalene Cream, 0.1% is registered in 40 countries and marketed in over 20.

3. Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

The following is the formulation for adapalene gel, 0.3%:

Formulation of adapalene gel, 0.3%	
Adapalene	[redacted]
Carbomer 940	
Edetate disodium	
Methylparaben	
Poloxamer 124	
Propylene glycol	
Sodium hydroxide	
[redacted] Hydrochloric acid	
Purified water	

See the Chemistry Review for other CMC details.

3.2 Animal Pharmacology/Toxicology

Adapalene did not exhibit mutagenic or genotoxic effects *in vivo* (mouse micronucleus test) and *in vitro* (Ames test, Chinese hamster ovary cell assay, and mouse lymphoma TK assay) studies. In the rat oral carcinogenicity study, the high-dose males (1.5mg/kg/day) exhibited a significant ($p<0.05$) incidence of benign pheochromocytoma of the adrenals, malignant pheochromocytoma, and pancreatic islet cell tumors. In addition, the incidence of pheochromocytoma in man is very low (0.005 to 0.09%). A high incidence of carcinomas and adenomas of thyroid was also observed in the drug treated females. In the oral rat and rabbit studies (5, 25, and 60mg/kg/day), significant teratologic changes (skeletal and visceral malformations) were recorded at 25mg/kg/day and higher dose levels. Adapalene is secreted in the milk of rats. It is known to cross the placenta

See the Pharmacology/Toxicology Review for details.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is based on data submitted to the NDA. The sponsor's submitted raw data was available on the EDR. The directory link is \\CDSESUB1\N21753\N_000\2004-03-31. The remainder of the data was submitted in paper form. There were additional data and analyses results submitted to the agency based on subsequent requests to aid the review and these were reviewed.

4.2 Tables of Clinical Studies

The following table summarizes the studies submitted by the Sponsor, and indicates which studies were reviewed here and to what purpose:

Table 1 – Studies with adapalene gel, 0.3%

Study Number	Population (subjects)	Study Type	No. of Subjects	Duration of Treatment	Included in review of
Studies with adapalene gel, 0.3% in *Acne Vulgaris*					
RD.03.SRE.2649	Acne	Phase 1 pk	8	10 days	Safety
RD.03.SRE.2690	Acne	Phase 1 pk	16	10 days	Safety
RD.03.SRE.2644 *	Healthy	Phase 1 contact sensitization	215		Safety
RD.03.SRE.2645 *	Healthy	Phase 1 photosensitization	30		Safety
1.CG.03.SRE.2646 *	Healthy	Phase 1 phototoxicity	25		Safety
1.CG.03.SRE.2017	Healthy	Phase 1 cumulative irritation	25	21 days	Safety
RD.06.SRE.18060	Acne	Phase 2 safety and efficacy	70	12 weeks	Safety
RD.06.SRE.18081	Acne	Phase 3 safety and efficacy	258		Safety and efficacy
RD.03.SRE.2673 **	Acne	Phase 3 safety and efficacy	208		Safety
RD.06.SRE.18082	Acne	Phase 3 safety and efficacy	551		Safety
Total exposure to Adapalene 0.3% gel in studies for acne vulgaris			1111		

Table 1 – Studies with adapalene gel, 0.3%

Study Number	Population (subjects)	Study Type	No. of Subjects	Duration of Treatment	Included in review of
Total exposure to Adapalene 0.3% products			**1505**		

Reviewer comment:

** this formulation differs from TBM formulation only in the way pH is adjusted.*

***the comparator was a EU gel, 0.1 % formulation*

4.3 Review Strategy

The Sponsor conducted a Phase 3 US study (RD.06.SRE.18081) to demonstrate the superiority of the 0.3% formulation over the comparator 0.1% formulation. The EU study (RD.03.SRE.2673) compared the proposed 0.3% formulation to a European gel, 0.1%, formulation and did not include a vehicle arm. It differed from the US study in several important ways: it used different inclusion criteria; it assessed efficacy on the basis of lesion counts, and for the Investigator Global Assessment it used a 12 grade scale that markedly differed from that used in the US Phase 3 trial. It was not designed to assess topical safety in the same way as the US trial.

The Phase 2 dose-comparison study (RD.SRE.18060) used different inclusion criteria and acne grading system than those used in the pivotal trial.

Some of the studies submitted by the applicant are not reviewed here because they were conducted with an adapalene formulation, or for an indication, other than the object of the application, or because they were conducted with protocols that included parameters (inclusion criteria, assessment scales or comparators) that differed from those in the pivotal trial.

The Applicant did not rely on literature reports to support this application because the study formulation is new and not marketed anywhere, and there are no published reports with this formulation.

4.4 Data Quality and Integrity

A review of the data from the pivotal Phase 3 US trial has not revealed anomalous findings or sites. No DSI investigations have been considered necessary or have been conducted for this NDA.

4.5 Compliance with Good Clinical Practices

The Sponsor stated that all four studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP Step 5 dated January 1996) and in compliance with local regulatory requirements. Additionally, the Sponsor affirmed that informed consent was obtained from all patients in each of the four clinical studies prior to any study procedures being performed.

4.6 Financial Disclosures

The Applicant has identified all the investigators who have performed studies for this application, and has certified that no financial arrangements have been made with any of these investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in CFR 54.2(a). The applicant further states that each listed investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21CFR 54.2(b), and that none disclose any such interests. The sponsor also certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 43.2(f). Form 3454 has been submitted.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

Dose-response was not studied. The applicant is seeking approval via a 505(b)(2) application and selected the dose

See Biopharmaceutics Review for further clinical pharmacology details.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Acne vulgaris is a chronic disease involving the pilosebaceous unit. Clinically, it presents both non-inflammatory (closed comedones and open comedones) and inflammatory (papules and pustules) lesions. Nodules and cysts can be present in severe acne. Acne usually first occurs around puberty, in female and male subjects, and is primarily a skin disease of adolescents and young adults. Predilection sites are the face, chest and back.

6.1.1 Methods

The clinical efficacy data submitted in support of the acne indication in this application derives from one Phase 3 trial (RD.06.SRE.18081). Please see Section 4.1 for the list of studies, and the Appendix for details of the study.

6.1.2 General Discussion of Endpoints

The endpoints in this application include those commonly found in applications for acne vulgaris, namely the mean percent reduction in lesion counts: total, inflammatory , and non-inflammatory, and the percentage of patients reaching "clear" or "almost clear" in the static Investigator Global Assessment (IGA) at the end of the study. To declare "success, statistically significant efficacy needed to be demonstrated in the IGA as well as in at least two of the three types of lesion counts. In this case, it was necessary to demonstrate superiority of the 0.3% gel formulation over the 0.1% formulation.

In this application repeated measures at weeks 8 and 12 were used, rather than the previously more commonly used week-12 timepoint.

6.1.3 Study Design

The pivotal Phase 3 study (**RD.06.SRE.18081**) was an active- and vehicle-controlled, double-blind, randomized, multi-center, parallel-group comparison study conducted in the U.S. and Canada. Male and female subjects with acne vulgaris, 12 years of age or older, with 20 to 50 inflammatory and 20 to 100 non-inflammatory lesions and no nodules or cysts were eligible to enroll. Subjects were randomized to apply adapalene gel, 0.3%; adapalene gel, 0.1%; or vehicle, once daily in the evening to the face and, if appropriate, to the chest and/or back for up to 12 weeks, the usual duration of acne studies.

The GEE methodology used for the primary analyses is a semi-parametric approach where normality of the distribution is required. Since the distribution for percent changes was markedly skewed to the right, the ranked percent changes in lesion counts were used. All tests were two-sided, each at the 0.050 significance level. No adjustment for multiplicity was required. Additionally CMH

analyses were performed at single time-points as supporting analyses. Both the GEE and CMH analyses were performed in the ITT population, defined as all randomized patients who were dispensed medication (the last observation carried forward including Baseline when post-Baseline data were not available). An analysis in the PP population was intended to be confirmatory. The Sponsor states the study was powered to show superiority of adapalene gel, 0.3 %, over adapalene gel, 0.1%, based on the co-primary efficacy criteria.

The following table summarizes the study populations:

Table 2: Analyzed Subjects

Disposition	Adapalene Gel, 0 .3%	Adapalene Gel, 0.1%	Vehicle	Total
ITT	258	261	134	653
PP	207	223	113	543
Safety	258	261	134	653

Sponsor's Table

6.1.4 Efficacy Findings

The three treatment groups, adapalene gel, 0.3%, adapalene gel, 0.1% and Vehicle, were shown to be comparable with respect to the demographic variables of gender, race and age.

The study population for the assessment of efficacy assessment was the ITT population, The significance of the success rates and percent reductions seen in the adapalene gel, 0.3%, and adapalene gel, 0.1%, groups as compared to the Gel Vehicle group, is summarized in the following table:

Table 3. Significance for Primary Efficacy Criteria from GEE Analyses (RD.06.SRE.18081)

GEE Analysis (Week 8 and 12) ITT	IGA Success	Ranked Percent Change in Lesion Counts		
		Total	Inflammatory	Non-inflammatory
Adapalene Gel, 0.3% vs. adapalene gel, 0.1%				
	0.028	**0.072**	**0.064**	**0.120**
Adapalene Gel, 0.3% vs. Gel Vehicle				
	0.010	**<0.001**	**0.002**	**<0.001**
Adapalene Gel, 0.1% vs. Gel Vehicle				
	0.420	**0.006**	**0.110**	**0.006**

Source: Biostatistics Review Table 10

Success (IGA) rate : The primary GEE analyses showed adapalene gel, 0.3%, was significantly superior to adapalene gel, 0.1% (p = 0.028), and to Vehicle (p = 0.010).

Total lesion counts: In the GEE analyses on the ranked percent changes, adapalene gel, 0.3% did not reach significance over adapalene gel, 0.1% ($p = 0.072$), but was significantly superior to Vehicle ($p < 0.001$).

Inflammatory lesion counts: In the GEE analyses on the ranked percent changes, adapalene gel, 0.3%, was not significantly superior to adapalene gel, 0.1% ($p = 0.064$), but was significantly superior to Vehicle ($p = 0.002$).

Non-inflammatory lesion counts,: In the GEE analyses on the ranked percent changes, the difference between adapalene gel, 0.3% and adapalene gel, 0.1%, did not reach statistical significance ($p = 0.120$). Adapalene gel, 0.3% was shown significantly superior to Vehicle ($p = 0.006$).

In this trial, the 0.1% formulation was superior to vehicle only for total lesion counts (p=0.006) and for non inflammatory lesions (p=006).

The results for the per protocol population paralleled those for the ITT population, but they were not better, as shown in the following table:

Table 4. Primary Efficacy Criteria from GE analysis in PP population (RD.06.SRE.18081)

	IGA Success	Ranked Percent Change in Lesion Counts		
		Total	Inflammatory	Non-inflammatory
Adapalene Gel, 0.3% vs. adapalene gel, 0.1%				
	0.022	**0.226**	**0.070**	**0.556**
Adapalene Gel, 0.3% vs. Gel Vehicle				
	0.010	**0.003**	**0.003**	**0.031**

Source: Biostatistics Review Table 11

Reviewer comment: For the PP population, where treatment is expected to have been used more stringently, similar results were obtained as for the ITT group.

Efficacy Results by demographic groups:

The following table shows the efficacy results for the IGA for various demographic groups:

Table 5 – Success (IGA) Rate by Demographic Group ITT LOCF (RD.06.SRE.18081)

IGA Success Rate	N	Adapalene Gel, 0.3%	N	Adapalene Gel, 0.1%	N	Vehicle	P-value 0.3%-0.1%	P-value 0.3%-Veh
All Subjects	258	20.5%	261	15.7%	134	9.0%		
Gender								
Male	129	17.1%	132	11.4%	62	6.5%	0.188	0.046
Female	129	24.0%	129	20.2%	72	11.1%	0.454	0.027
Race								
Caucasian	194	22.2%	186	16.1%	91	9.9%	0.136	0.013
Non-Caucasian	64	15.6%	75	14.7%	43	7.0%	0.875	0.181
Black	26	15.4%	23	13.0%	18	5.6%		
Asian	6	50%	12	25.0%	4	0%		
Hispanic	27	11.1%	35	14.3%	18	5.6%		
Other	5	0%	5	0%	3	33.3%		
Age Group								
12-17 years	162	16.7%	178	15.7%	79	6.3%	0.815	0.027
18-64 years	96	27.1%	83	15.7%	55	12.7%	0.066	0.041

Source: Biostatistics Review, Tables 16-21

Reviewer comment: the subgroups showing greatest efficacy in the IGA were females, Caucasians, and patients over 18 years old. Similar results were observed for lesion counts.

Following the Agency's request on October 13, 2004, the sponsor carried out two additional sensitivity analyses. In the sensitivity analysis-I, the missing values were imputed by using completer's mean percent change and success rate at week 8 and week 12. In the GEE analyses at multiple time points, adapalene gel, 0.3% was superior to adapalene gel, 0.1%, for IGA success rates (p=0.017), and for inflammatory lesion counts (p=0.03), but not for total lesion counts (p=0.105) or for non-inflammatory lesion counts (p=0.344). However, adapalene 0.1% failed to demonstrate superiority to Vehicle for the IGA (p=0.258). In the analyses using the Rank data, adapalene gel, 0.3% demonstrated superiority over adapalene gel, 0.1% in all three lesion counts.

This data is summarized in the following table:

Table 6.: Sensitivity Analyses. I: Imputed missing data by using Completer's mean percent change and success rate at week 8 and Week 12 in the ITT population

GEE Analyses of multiple timepoints	Mean Difference Estimates (week 8 and 12)		P-Values		
	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.1% vs. Vehicle
IGA (Success)*	1.62	2.20	0.017	0.001	0.258
Total Lesion Count					
Percent change	-3.91	-11.87	0.105	<0.001	0.002
Rank	-36.75	-88.60	0.006	<0.001	0.001
Inflammatory Count					
Percent change	-4.86	-11.34	0.031	<0.001	0.030
Rank	-35.65	-67.34	0.006	<0.001	0.042
Non-Inflammatory Count					
Percent change	-3.14	-13.18	0.344	0.002	0.004
Rank	-28.28	-83.66	0.036	<0.001	0.001

* Sponsor's Analyses; For IGA(success), estimate is the odds ratio. Biostatistics Table 12

In the sensitivity analysis-II, the missing values were imputed by using completer's mean percent change and IGA success rate with similar baseline data at week 8 and week 12. In the GEE analyses, adapalene gel, 0.3%, was significantly superior to adapalene gel, 0.1%, for the IGA success rates (p=0.021) and for inflammatory lesion counts (p=0.03) but not for non-inflammatory lesion (p=0.33) or for total lesion counts (p=0.11). However, adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.229). In the analyses using the Rank data, adapalene gel, 0.3% demonstrated superiority over adapalene gel, 0.1% in all three lesion counts. However, for Inflammatory lesion counts, adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.05). This data is summarized in the following table:

Table 7: Sensitivity Analyses. II: Imputed missing data by using Completer's mean percent change and success rate with similar baseline counts and IGA score at week 8 and Week 12 (ITT population)

GEE Analyses of multiple timepoints	Mean Difference Estimates (week 8 and 12)		P-Values		
	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.1% vs. Vehicle
IGA (Success)*	1.590	2.210	0.021	0.001	0.229
Total Lesion Count					
Percent change	-3.820	-11.790	0.113	<0.001	0.002
Rank	-35.430	-86.690	0.008	<0.001	0.001
Inflammatory Count					
Percent change	-4.870	-11.370	0.030	<0.001	0.031
Rank	-35.080	-66.240	0.007	<0.001	0.046
Non-Inflammatory Count					
Percent change	-3.260	-13.000	0.327	0.002	0.006
Rank	-29.330	-82.240	0.030	<0.001	0.001

*Sponsor's Analyses; For IGA(success), estimate is the odds ratio. Biostatistics Table 13.

6.1.5 Clinical Microbiology: Not applicable.

6.1.6 Efficacy Conclusions

Using the pre-specified analyses, the 0.3% formulation fails to demonstrate superiority over the 0.1% formulation for the ITT formulation on IGA and two lesion counts. These results are paralleled for the PP group. Although the 0.3% formulation was slightly more efficacious than the 0.1% formulation, it was also more irritating. In conclusion, there does not appear to be a significant advantage to the 0.3% formulation to support its approval.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of adapalene gel, 0.3%, will focus on safety in topical safety studies, systemic safety (systemic absorption and laboratory tests), and adverse events in Phase 2 and Phase 3 studies. In the US Phase 3 trial, investigators and subjects were to report all AEs, including local tolerability (erythema, scaling, dryness, stinging/burning, each rated on a scale ranging from 0 [absence] to 3 [severe]). Routine laboratory data (hematology, blood chemistry, urinalysis) was gathered at specified centers.
Reviewer comment: However the Sponsor states that "An Adverse Event Form was to be completed only if the severity of the expected signs and symptoms was such that an interruption of the Subject's participation in the study, at his/her request or at the Investigator's, occurred."(Clinical study report No. RD.06.SRE.18081, section 9.5.5.3, page 55). This approach may have led to under reporting AEs in general.

7.1.1 Deaths

There were no deaths in any of the controlled studies. A total of five subjects experienced serious adverse events (SAEs) in the three controlled studies (**RD.06.SRE.18081**, **RD.06.SRE.18060**, and **RD.03.SRE.2673**); none were related to the study drug.

7.1.2 Other Serious Adverse Events

The following table summarizes the AEs of the study drug, the 0.1% gel formulation and vehicle by severity and relation to treatment:

Table 8–Adverse Events by Severity and Relation to Study Drug (RD.06.SRE.18081, RD.06.SRE.18060, RD.03.SRE.2673)			
	Adapalene Gel, 0.3% N (%)	**Adapalene Gel, 0.1% N (%)**	**Gel Vehicle N (%)**
Subjects with Any Adverse Events	220 (41.0%)	191 (35.3%)	72 (34.6%)
Subjects with Mild Adverse Events	144 (26.9%)	135 (25.0%)	51 (24.5%)
Related	92 (17.2%)	67 (12.4%)	8 (3.8%)
Unrelated	67 (12.5%)	80 (14.8%)	45 (21.6%)
Subjects with Moderate Adverse Events	102 (19.0%)	75 (13.9%)	28 (13.5%)
Related	58 (10.8%)	32 (5.9%)	3 (1.4%)
Unrelated	52 (9.7%)	48 (8.9%)	27 (13.0%)
Subjects with Severe Adverse Events	8 (1.5%)	8 (1.5%)	2 (1.0%)
Related	5 (0.9%)	3 (0.6%)	0 (0.0%)
Unrelated	3 (0.6%)	5 (0.9%)	2 (1.0%)

Related = Possibly, probably, or definitely related
Unrelated = Unlikely or definitely unrelated
Source: **Combined**: ISS 7.2, ISS 14

Reviewer comment: The number of subjects who developed treatment related severe adverse AE's was very small. Treatment related mild and moderate localized reactions were more frequent for the 0.3% formulation than for the 0.1% formulation, and least frequent for vehicle.

7.1.3 Dropouts and Other Significant Adverse Events

There were 354 subjects enrolled in the eight Phase 1 studies with adapalene gel, 0.3%. Fourteen subjects discontinued prematurely: five discontinued due to adverse event (three were considered related to study drug and none were serious), nine subjects requested to be discontinued, and one subject was discontinued due to a protocol violation, as shown in the following table:

Table 9 – Summary of Discontinuations in Phase 1 Studies	
	Adapalene Gel, 0.3%
Discontinued	14
Adverse Event	5
Subject's Request	9
Protocol Violation	1
Lost to Follow-up	0
Other	0
Pregnancy	0

There were 1836 subjects enrolled in the four Phase 2 and 3 studies (**RD.06.SRE.18060, RD.06.SRE.18081, RD.03.SRE.2673,** and **RD.06.SRE.18082**). More than 85% of the subjects in the controlled studies (combined data) completed the 12 weeks of treatment; approximately 30% of the subjects in the long-term, open-label study completed 12 months of treatment. The most frequent reasons for discontinuation in the 12-week controlled studies (combined) in the adapalene gel, 0.3%, group were subject's request (6.7%), adverse event (4.9%), and lost to follow-up (3.4%). The most frequent reasons for discontinuation were comparable for the adapalene gel, 0.1%, group, 3.5%, 1.8%, and 4.3%, respectively, and for the Vehicle Group, 6.7%, 0.5%, and 5.3%, respectively.

In the long-term Phase 3 study (**RD.06.SRE.18082**), the most frequent reasons for discontinuation were site closing (22.9%), sponsor's decision (16.9%), lost to follow-up (12.7%), and subject's request (11.8%). Very few subjects (2.7%) in the long-term study discontinued due to adverse event, as shown in the following table:

Table 10 – Summary of Discontinuations in Phase 2 and 3 Studies

Discontinuation Status	Combined Controlled Clinical Studies - 12 Wks.			Open-label - 12 Mo.
	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Vehicle	Adapalene Gel, 0.3%
N:	536	541	208	551
Completed Study	450 (84.0%)	485 (89.6%)	182 (87.5%)	167 (30.3%)
Discontinued	86 (16.0%)	56 (10.4%)	26 (12.5%)	384 (69.7%)
Condition Clear	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.5%)
Adverse Event	26 (4.9%)	10 (1.8%)	1 (0.5%)	15 (2.7%)
Pregnancy	2 (0.4%)	1 (0.2%)	0 (0.0%)	4 (0.7%)
Protocol Violation	2 (0.4%)	3 (0.6%)	0 (0.0%)	2 (0.4%)
Subject's Request	36 (6.7%)	19 (3.5%)	14 (6.7%)	65 (11.8%)
Lost to Follow-up	18 (3.4%)	23 (4.3%)	11 (5.3%)	70 (12.7%)
Sponsor's Decision*	0 (0.0%)	0 (0.0%)	0 (0.0%)	93 (16.9%)
Site Closing*	0 (0.0%)	0 (0.0%)	0 (0.0%)	126 (22.9%)
Other	2 (0.4%)	0 (0.0%)	0 (0.0%)	4 (0.7%)

Source: **Combined**: ISS 2.1

* The Sponsor states that subjects enrolled in open-label, 12-month safety study after June 1, 2002 were discontinued because the study had overenrolled subjects. On July 11, 2002, [redacted] denied access to monitors to 5 sites until August 12, 2002, then the Sponsor decided to close those sites.

A total of 8 subjects were discontinued from the Phase 3 study due to AEs: 5 (1.9%) in the adapalene gel, 0.3%, group, 2 (0.8%) in the adapalene gel, 0.1%, group, and 1 (0.7%) in the vehicle group. Adverse events leading to discontinuation included spherocytosis, primary irritant dermatitis of the face, facial burning, flaking and burning on the face, and angioedema (upper lip, considered definitely unrelated to study drug, and resolved in 4 days) in the adapalene gel, 0.3% group; impetigo of the chin and burning sensation (face) in the adapalene gel, 0.1% group; and worsening

of facial acne in the vehicle group. Only one AE leading to discontinuation was considered definitely related to study medication (facial burning); this event occurred in subject #1326 in the adapalene gel, 0.3% treatment group.

AEs were categorized using COSTART terms. The Applicant's use of this terminology appears appropriate.

7.1.4 Other Search Strategies

In topical safety studies, there was no evidence of sensitization, photosensitization, or phototoxicity from adapalene gel, 0.3%. Adapalene gel, 0.3%, was similar to adapalene gel, 0.1%, and both were slightly more irritating than Vehicle and White Petrolatum.

7.1.5 Common Adverse Events

The pivotal Phase 3 study (**RD.06.SRE.18081**) was the only well-controlled study in which signs and symptoms of skin irritation (erythema, scaling, dryness, and stinging/burning) were prospectively defined and evaluated at Baseline and at each post-Baseline visit, using a scale ranging from none to severe (0 to 3).

The following table shows the AEs reported in more than 1% of study subjects in the Phase 2 and 3 studies:

Table 11 – Most Frequently Reported (≥1%) Drug Related Adverse Events
(RD.06.SRE.18081, RD.06.SRE.18060, and RD.03.SRE.2673)

	RD.06.SRE.18081			RD.06.SRE.18060			RD.03.SRE.2673	
Treatment Group	**Adapalene Gel, 0.3% N (%)**	**Adapalene Gel, 0.1% N (%)**	**Gel Vehicle N (%)**	**Adapalene Gel, 0.3% N (%)**	**Adapalene Gel, 0.1% N (%)**	**Gel Vehicle N (%)**	**Adapalene Gel, 0.3% N (%)**	**Adapalene Gel, 0.1% N (%)**
N=	**258**	**261**	**134**	**70**	**70**	**74**	**208**	**210**
Total Number of Related[1] AEs	82	52	6	50	44	5	71	45
Total No. (%) of Subjects with Related[1] AES	57 (22.1%)	31 (11.9%)	6 (4.5%)	28 (40.0%)	26 (37.1%)	5 (6.8%)	63 (30.3%)	37 (17.6%)
Skin and Appendages	55 (21.3%)	31 (11.9%)	6 (4.5%)	28 (40.0%)	26 (37.1%)	5 (6.8%)	63 (30.3%)	36 (17.1%)
Skin dry	36 (14.0%)	17 (6.5%)	2 (1.5%)	16 (22.9%)	13 (18.6%)	2 (2.7%)	7 (3.4%)	4 (1.9%)
Erythema	2 (0.8%)	3 (1.1%)	0 (0.0%)	8 (11.4%)	3 (4.3%)	0 (0.0%)	3 (1.4%)	2 (1.0%)
Discomfort skin	15 (5.8%)	12 (4.6%)	0 (0.0%)	8 (11.4%)	7 (10.0%)	0 (0.0%)	1 (0.5%)	4 (1.9%)
Desquamation	4 (1.6%)	2 (0.8%)	0 (0.0%)	6 (8.6%)	5 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pruritus	5 (1.9%)	4 (1.5%)	0 (0.0%)	2 (2.9%)	1 (1.4%)	1 (1.4%)	1 (0.5%)	1 (0.5%)
Irritant derm.	2 (0.8%)	2 (0.8%)	0 (0.0%)	2 (2.9%)	6 (8.6%)	0 (0.0%)	46 (22.1%)	25 (11.9%)
Sunburn	3 (1.2%)	3 (1.1%)	2 (1.5%)	1 (1.4%)	2 (2.9%)	1 (1.4%)	0 (0.0%)	2 (1.0%)
Contact derm.	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)

Table 11 – Most Frequently Reported (≥1%) Drug Related Adverse Events
(RD.06.SRE.18081, RD.06.SRE.18060, and RD.03.SRE.2673)

	RD.06.SRE.18081			RD.06.SRE.18060			RD.03.SRE.2673	
Treatment Group	Adapalene Gel, 0.3% N (%)	Adapalene Gel, 0.1% N (%)	Gel Vehicle N (%)	Adapalene Gel, 0.3% N (%)	Adapalene Gel, 0.1% N (%)	Gel Vehicle N (%)	Adapalene Gel, 0.3% N (%)	Adapalene Gel, 0.1% N (%)
N=	258	261	134	70	70	74	208	210
Dermatitis	1 (0.4%)	2 (0.8%)	1 (0.7%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urticaria	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eczema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	1 (0.5%)
Excoriation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
Atopic derm.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)

Related = Possibly, probably, or definitely related. Source: **18081**: SAF 8.1, **18060**: ISS 10.1, **2673**: ISS 10.1

Treatment related AEs that occurred in greater than 1% of the subjects who used adapalene gel, 0.3%, in the US pivotal Phase 3 study (**RD.06.SRE.18081**) included dry skin (14.0%), skin discomfort (5.8%), pruritus (1.9%), desquamation (1.6%), and sunburn (1.2%). In the Phase 2 study (**RD.06.SRE.18060**) there was a higher proportion of subjects who reported these events with adapalene gel, 0.3%: 22.9%, 11.4%, 2.9%, 8.6%, and 1.4%, respectively. In addition, 11.4% of the subjects reported erythema. In the European Phase 3 study (**RD.03.SRE.2673**) the proportion of subjects who reported these events was lower: 3.4%, 0.5%, 0.0%, 0.0%, and 0.0%, respectively. However, 22.1% of the subjects in the European study reported irritant dermatitis compared to 0.0% of the subjects in the US pivotal study, and to 2.9% of the subjects in the Phase 2 study. The Sponsor states that the higher proportion of subjects with irritant dermatitis in the European study might be explained by the fact that local tolerability was not evaluated in the same manner. The U.S. studies report a higher proportion of adverse events representative of skin irritation (dry skin, erythema, discomfort skin, desquamation, pruritus), whereas the EU study reported a higher proportion of irritant dermatitis, i.e. a specific disease entity that includes a variety of signs and symptoms such as dry skin, erythema, discomfort skin, desquamation and pruritus which were actually reported as such in the U.S. studies. The proportion of adverse events representative of skin irritation was lower for adapalene gel, 0.1%, group and even lower for the Vehicle. As expected with a topical medication, the majority of the treatment related adverse events were for the skin and appendages.

Treatment related AEs from the combined controlled clinical studies that occurred in greater than 1% of subjects who used adapalene gel, 0.3%, included dry skin (11.0%), irritant dermatitis (9.3%), skin discomfort (4.5%), erythema (2.4%), desquamation (1.9%), and pruritus (1.5%). Similar results were obtained for adapalene gel, 0.1%, except for dry skin, which occurred in 6.3% of subjects.

7.1.6 Less common adverse events

The following table summarizes the scores of local irritation (worse than baseline) observed in the pivotal trial:

Text Table 12 – Highest Severity Scores of Local Cutaneous Irritation[1]
(Worse Than Baseline) (RD.06.SRE.18081)

	Adapalene Gel, 0.3% (N=253) N (%)	Adapalene Gel, 0.1% (N=257) N (%)	Gel Vehicle (N=133) N (%)
Erythema			
Mild	66 (26.1%)	76 (29. 6%)	28 (21.1%)
Moderate	33 (13.0%)	27 (10.5%)	6 (4.5%)
Severe	1 (0.4%)	2 (0.8%)	0 (0.0%)
Scaling			
Mild	110 (43.5%)	89 (34.6%)	21 (15.8%)
Moderate	47 (18.6%)	35 (13.6%)	6 (4.5%)
Severe	3 (1.2%)	4 (1.6%)	0 (0.0%)
Dryness			
Mild	113 (44.7%)	94 (36.6%)	30 (22.6%)
Moderate	43 (17.0%)	25 (9.7%)	3 (2.3%)
Severe	2 (0.8%)	7 (2.7%)	0 (0.0%)
Stinging/Burning			
Mild	72 (28.5%)	60 (23.3%)	7 (5.3%)
Moderate	36 (14.2%)	15 (5.8%)	0 (0.0%)
Severe	9 (3.6%)	10 (3.9%)	0 (0.0%)

Source: Report Section 14; **18081.**
Note: Subjects are included if their score during treatment was worse than their Baseline score; each of these subjects is included in the category that reflects the highest severity score recorded during the post-Baseline period.
[1] Local Cutaneous Irritation was reported as Local Cutaneous Tolerance; these terms are used interchangeably.

Reviewer comment: The type of AEs reported match what is expected from this type of product. For each category, the frequency was slightly higher for the 0.3 % formulation.

7.1.7 Laboratory values.

Laboratory evaluations (blood chemistry, hematology, and urinalysis) were conducted in three of the Phase 2 and Phase 3 studies (**RD.06.SRE.18060**, **RD.06.SRE.18081**-11 sites, and **RD.06.18082**). In the first two studies (**RD.06.SRE.18060**, **RD.06.SRE.18081**), samples were taken at Screening and at 12 weeks or last visit. In the long-term study (**RD.06.SRE.18082**), samples were taken at Screening, Month 6 and Month 12 or at the last visit.

In the pivotal Phase 3 study, five subjects had laboratory abnormalities: In the adapalene gel, 0.3%, group, three subjects (#1092, #1886, and #1656) had elevated creatine kinase (CK) values, and one of them (#1656) also had elevated liver enzymes; in the adapalene gel, 0.1%, group, two subjects had elevated CK values (#1093 and #1681), and one of them (#1681) also had a low white blood cell count. All of these were considered by the investigator as unlikely to be related or definitely unrelated to study drug.

In the long-term, open-label study, laboratory adverse events were reported for 14 subjects: increased liver enzymes (n = 7), abnormal cholesterol and triglycerides (n = 3), proteinuria (n = 2) and low glucose and abnormal urinalysis (n = 2). All were mild (n = 11) or moderate (n = 3) and

none resulted in discontinuation from the study. One subject (#290) experienced elevated Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Gamma-Glutamyl Transferase (GGT) values considered by the investigator as possibly related to study drug. However, the subject received concomitant medication that could have caused the increases. There were no trends in individual laboratory abnormalities that indicated an effect of study drug.

Reviewer comment: In summary, there were no patterns of clinically important laboratory changes indicative of a toxic effect following up to 12 months of treatment with adapalene gel, 0.3%. No trends or patterns in laboratory parameters were observed that were indicative of toxicity in the short-term controlled studies or the long-term study.

7.1.8 Vital Signs. No vital sign monitoring took place during these studies.

7.1.9 Electrocardiograms (ECGs). Not applicable.

7.1.10 Immunogenicity . Not applicable.

7.1.11 Human Carcinogenicity. No tumors were reported in any of the studies.

7.1.12 Special Safety Studies

The Phase 1 topical safety studies included sensitization, irritation, phototoxicity, and photosensitization, as follows:

Table 13 Topical safety studies

			No. of Subjects Exposed		
Study No.	**Population (subjects)**	**Study Type**	**Adapalene Gel, 0.3%**	**Adapalene Gel, 0.1%**	**Gel Vehicle**
Exposure in Healthy Subjects					
1.CG.03.SRE.2644	Healthy	Phase 1 Pharmacology – irritation/sensitization, intra-individual	215	215[1]	215
1.CG.03.SRE.2645	Healthy	Phase 1 Pharmacology – photosensitization, intra-individual	30	30[1]	30
1.CG.03.SRE.2646	Healthy	Phase 1 Pharmacology – phototoxicity, intra-individual	25	25[1]	25
1.CG.03.SRE.2017	Healthy	Phase 1 Pharmacology – 21-day cumulative irritancy, intra-individual	25	0	25
		Total Exposure in Healthy Subjects	**295**	**270**	**295**

1 Investigational formulation
2 U.S. marketed formulation
3 European marketed formulation
4 Includes 4 sites from Canada

These studies are described in the Appendix.

The applicant states there was no evidence of sensitization, photosensitization, or phototoxicity from adapalene gel, 0.3%. In the irritancy study, adapalene gel, 0.3% was similar to adapalene gel, 0.1%, and both were slightly more irritating than Vehicle and White Petrolatum.

In a pharmacokinetic study **(RD.03.SRE.2690)**, quantifiable amounts (lower limit of quantification = 0.10 ng/mL) of adapalene in the plasma samples were found in 15 of 16 subjects following the last dose. The mean $AUC_{(0\text{-}24h)}$ over a 24-hour dosing interval on Day-10 was 8.94 ± 8.99 ng.h/mL. The mean C_{max} on Day-10 was 0.553 ± 0.466 ng/mL. The terminal apparent half-life ranged from 13 to 16 hours, thereby indicating that a pharmacokinetic steady-state was reached before Day-10. Adapalene was rapidly cleared from plasma and was not detected 72 hours after the last application except for subject 8, on whom 0.1283 ng/mL was detected at the last measurement at 72 hours. In the Phase 2 study **(RD.06.SRE.18060),** adapalene concentrations were below the limit of detection (LOD = 0.15 ng/mL) in 209 samples. In three samples, adapalene traces were found below the 0.25 ng/mL limit of method of quantification.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of drug abuse were reported in any of the studies. Topical adapalene does not have a known abuse potential, does not produce withdrawal phenomenon, and does not belong to a class of compounds associated with these effects.

7.1.14 Human Reproduction and Pregnancy Data

In the controlled and open-label clinical studies women of childbearing potential were tested for pregnancy. Eight subjects had positive tests during the study: seven subjects discontinued the study due to pregnancy and one subject who had a positive pregnancy test at Screening retested negative at Baseline and completed the study.

In the EU Phase 3 study, two subjects on adapalene gel, 0.3% tested positive on days 43 and 36, respectively, and terminated from the study early. One subject on adapalene gel, 0.1% tested positive on day 72 and voluntarily terminated early from the study. The following are the abbreviated histories of these subjects:

Subject #356, age 19 at study entry, became pregnant after receiving adapalene gel, 0.3%, for approximately five weeks and discontinued from the study due to pregnancy. This subject had a voluntary abortion two months later.

Subject # 394, age 22 at study entry, became pregnant after receiving adapalene gel, 0.3%, for approximately six weeks and discontinued from the study due to pregnancy. A female baby was born by caesarean. No malformation or neonatal illness was observed after birth.

Subject # 508, age 25 at study entry, became pregnant after receiving adapalene gel, 0.1%, for approximately nine weeks and discontinued from the study due to pregnancy. A silent miscarriage occurred approximately four week later.

In the long-term study, four subjects who received adapalene gel, 0.3%, tested positive on days 204, 181, 118, and 61, respectively, and terminated early.

Subject #144, age 25 at study entry, had two previous caesarian sections, and became pregnant after receiving adapalene gel, 0.3%, for approximately six months, and discontinued from the study due to pregnancy. The pregnancy ultrasound was reported normal. A female baby was born five weeks prematurely by normal delivery. The newborn remained in the intensive care unit for two weeks until gaining a normal health state.

Subject #165, age 25 at study entry, became pregnant after receiving adapalene gel, 0.3%, for approximately six months, and discontinued from the study due to pregnancy. The pregnancy ultrasound was reported normal. A female baby was born four weeks prematurely by normal delivery. The newborn remained in the intensive care unit for one week until gaining a normal health state.

Subject #288, age 32 at study entry, became pregnant after receiving adapalene gel, 0.3% for approximately four months and discontinued from the study due to pregnancy. Pregnancy ultrasounds were reported normal. A term healthy, male baby was born by normal delivery.

Subject #296, age 21 at study entry, became pregnant after receiving adapalene gel, 0.3% for approximately two months and discontinued from the study due to pregnancy. This subject was lost to follow-up and the pregnancy outcome was not reported.

In studies **RD.06.SRE.18060** and **RD.06.SRE.18081** no subjects tested positive for pregnancy.

7.1.15 Assessment of Effect on Growth. Not applicable

7.1.16 Overdose Experience. Not applicable

7.1.17 Postmarketing Experience. Adapalene 0.3 % gel is not marketed anywhere; therefore there are no postmarketing events reported.

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.

In the short-term (12-week), controlled Phase 2 (**RD.06.SRE.18060**) and Phase 3 (**RD.06.SRE.18081** and **RD.03.SRE.2673**) studies, 536 subjects with *acne vulgaris* received adapalene gel, 0.3%, 541 subjects received adapalene gel, 0.1%, and 208 subjects received Vehicle.

An additional 551 subjects received adapalene gel, 0.3%, in the long-term, open-label safety study **(RD.06.SRE.18082)**.

In the three, 12-week, Phase 2 and 3 studies (**RD.06.SRE.18060**, **RD.06.SRE.18081**, and **RD.03.SRE.2673**), the mean daily exposure to adapalene products was approximately 0.6 to 0.9 g/day; this is less than half of the amount, 2 g/day, of study medication applied in the pharmacokinetic studies for 10 days (**1.CG.03.SRE.2649** and **RD.03.SRE.2690**). The Sponsor states that the mean daily usage in the European Phase 3 study (**RD.03.SRE.2673**) was lower than in the U.S. studies because subjects in the European study treated the face only, whereas in the U.S. studies, subjects were also allowed to treat the involved areas on the chest and back.
See Table 4.2 in section 4.2 for a listing of the studies and numbers of patients in each study.

7.2.1.2 Demographics

The following tables summarize the demographic data by gender, age and race:

Table 14 – Summary of Gender

	Adapalene Gel, 0.3%		Adapalene Gel, 0.1%		Gel Vehicle		Total	
	N	%	N	%	N	%	N	%
RD.06.SRE.18060								
Male	38	54.3%	43	61.4%	45	60.8%	126	58.9%
Female	32	45.7%	27	38.6%	29	39.2%	88	41.1%
RD.06.SRE.18081								
Male	129	50.0%	132	50.6%	62	46.3%	323	49.5%
Female	129	50.0%	129	49.4%	72	53.7%	330	50.5%
RD.03.SRE.2673								
Male	87	41.8%	80	38.1%	NA	NA	167	40.0%
Female	121	58.3%	130	61.9%	NA	NA	251	60.0%
RD.06.SRE.18082								
Male	276	50.1%	NA	NA	NA	NA	276	50.1%
Female	275	49.9%	NA	NA	NA	NA	275	49.9%

Source: **18060**: ISS 5; **18081**: SUB 5.1; **2673**: ISS 5; **18082**: SUB 4

Table 15 – Summary of Race								
	Adapalene Gel, 0.3%		Adapalene Gel, 0.1%		Gel Vehicle		Total	
	N	%	N	%	N		N	%
RD.06.SRE.18060								
Caucasian	48	68.6%	46	65.7%	53	71.6%	147	68.7%
Black	7	10.0%	8	11.4%	8	10.8%	23	10.7%
Asian	0	0.0%	1	1.4%	0	0.0%	1	0.5%
Hispanic	15	21.4%	14	20.0%	12	16.2%	41	19.2%
Other	0	0.0%	1	1.4%	1	1.4%	2	0.9%
RD.06.SRE.18081								
Caucasian	194	75.2%	186	71.3%	91	67.9%	471	72.1%
Black	26	10.1%	23	8.8%	18	13.4%	67	10.3%
Asian	6	2.3%	12	4.6%	4	3.0%	22	3.4%
Hispanic	27	10.5%	35	13.4%	18	13.4%	80	12.3%
Other	5	1.9%	5	1.9%	3	2.2%	13	2.0%
RD.03.SRE.2673								
Caucasian	182	87.5%	195	92.9%	NA	NA	377	90.2%
Black	10	4.8%	9	4.3%	NA	NA	19	4.5%
Asian	2	1.0%	3	1.4%	NA	NA	5	1.2%
Other	14	6.7%	3	1.4%	NA	NA	17	4.1%
RD.06.SRE.18082								
Caucasian	399	72.4%	NA	NA	NA	NA	399	72.4%
Black	69	12.5%	NA	NA	NA	NA	69	12.5%
Asian	3	0.5%	NA	NA	NA	NA	3	0.5%
Hispanic	69	12.5%	NA	NA	NA	NA	69	12.5%
Other	11	2.0%	NA	NA	NA	NA	11	2.0%
Source: **18060**: ISS 5; **18081**: SUB 5.1; **2673**: ISS 5; **18082**: SUB 4								

Table 16 – Summary of Age				
	Adapalene Gel, 0.3%	**Adapalene Gel, 0.1%**	**Gel Vehicle**	**Total**
RD.06.SRE.18060				
N	70	70	74	214
Mean [Age (Year)]	17.8	16.5	17.6	17.3
Min-Max	12-40	12-45	12-35	12-45
Age 12 – 17 [n (%)]	47 (67.1%)	55 (78.6%)	45 (60.8%)	147 (68.7%)
RD.06.SRE.18081				
N	258	261	134	653
Mean [Age (Year)]	18.4	17.8	18.6	18.2
Min-Max	12-41	12-52	12-39	12-52
Age 12 – 17 [n (%)]	162 (62.8%)	178 (68.2%)	79 (59.0%)	419 (64.2%)
RD.03.SRE.2673				
N	208	210	NA	418
Mean [Age (Year)]	19.1*	19.1*	NA	19.1*
Min-Max	12-39	12-39	NA	12-39
Age 12 – 17 [n (%)]	89 (42.8%)	97 (46.2%)	NA	186 (44.5%)
RD.06.SRE.18082				
N	551	NA	NA	551
Mean [Age (Year)]	18.9	NA	NA	18.9
Min-Max	11-52	NA	NA	11-52
Age 11 – 17 [n (%)]	333 (60.5%)	NA	NA	333 (60.5%)

* The value for mean age here is slightly lower than in the study report (19.6) due to a difference in calculation method.
Source: **18060**: ISS 5; **18081**: SUB 5.1; **2673**: ISS 5; **18082**: SUB 4

7.2.1.3 Extent of exposure (dose/duration)

A total of 1,505 subjects have been exposed to adapalene gel, 0.3% (330 healthy subjects in the Phase 1 clinical pharmacology studies, 1,111 subjects with *acne vulgaris* in the Phase 1 pharmacokinetic, Phase 2, and Phase 3 studies, and 64 subjects from studies in other indications). In studies conducted in acne patients, adapalene was administered once daily. The following table summarizes the exposure to adapalene:

Table 17 – Summary of Subject Exposure to adapalene gel 0.3%

Study No.	Healthy Subjects	*Acne Vulgaris*	Other Indications
Phase 1 Studies			
RD.03.SRE.19027	20		
RD.03.SRE.2649		8	
RD.03.SRE.2690		16	
RD.03.SRE.2644	215		
RD.03.SRE.2645	30		
1.CG.03.SRE.2646	25		
1.CG.03.SRE.2017	25		
RDT.07.SRE.27001.P7T1	15		
Phase 2 Study			
RD.06.SRE.18060		70	
Phase 3 Studies			
RD.06.SRE.18081		258	
RD.03.SRE.2673		208	
RD.06.SRE.18082		551	
Total each population:	**330**	**1111**	[ ]
Total exposure:	**1505 subjects**		

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No studies other than those submitted to the NDA were used in the review of safety.

7.2.2.2 Postmarketing experience

The Sponsor's drug product is not approved in any country at the time of writing of this review. There has been no postmarketing experience with it.

7.2.3 Adequacy of Overall Clinical Experience

One thousand one hundred eleven subjects were exposed to adapalene gel, 0.3% for up to 12 weeks in the Phase 3 trials, and for up to one year in the open label long term safety study. The mean treatment duration for the Phase 2 and Phase 3 trials was 75 days. The median age of the subjects was 18, and the pediatric age group older than 12 years was adequately represented. The racial

makeup of the trials paralleled the racial mix of the US population. The dose, once daily application, was determined by the reference listed drug, Differin gel, 0.1%. The duration of the pivotal trial, 12 weeks, is standard for acne trials. The mean daily exposure to adapalene products was approximately 0.6 to 0.9 g/day, except for the pharmacokinetic studies, where it was 2 g/day for 10 days.

The design of the pivotal study, with both comparator and vehicle arms, is acceptable to assess safety and efficacy.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See the Pharmacology/ Toxicology Review for details.

7.2.5 Adequacy of Routine Clinical Testing

Routine laboratory tests for chemistry, hematology, and urinalysis were conducted in three of the Phase 2 and Phase 3 studies (**RD.06.SRE.18060**, **RD.06.SRE.18081**, and **RD.06.18082**). In the first two studies (**RD.06.SRE.18060**, **RD.06.SRE.18081**), samples were taken at Screening and at 12 weeks or last visit. In the long-term study (**RD.06.SRE.18082**), samples were taken at Screening, Month 6 and Month 12 or at the last visit. The extent of clinical laboratory testing was considered appropriate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No metabolic, clearance or interaction studies were conducted for this application.

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

The Sponsor has conducted adequate topical safety studies to assess for cutaneous irritancy, allergenicity, phototoxicity and photosensitization. The Sponsor actively solicited for complaints of scaling, dryness, erythema, burning, and itching, and assessed the development of adverse events during the studies.

7.2.8 Assessment of Quality and Completeness of Data

No deficiencies have been detected in the quality and completeness of the data.

7.2.9 Additional Submissions, Including Safety Update

The Sponsor states that no additional studies have been conducted beyond those reported in the application.

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

The treatment –related AEs reported in this application are those expected for this type of drug product.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Efficacy data from the different studies were not pooled because the design of the studies was different. Safety was studied to a significant degree of completeness only in the US Phase 3 trial.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

AEs were more common among patients who were exposed to the 0.3% gel formulation than for the 0.1% formulation in the studies were both were compared directly.

7.4.2.2 Explorations for time dependency for adverse findings

In those patients who withdrew from the studies, the timing of the AEs was consistent with a relation to study drug.

7.4.2.3 Explorations for drug-demographic interactions.

Adverse event did not seem to vary as a function of age, gender, or race.

7.4.2.4 Explorations for drug-disease interactions

The efficacy data collected allowed for capture of disease exacerbation duration treatment but failed to reveal any significant findings.

7.4.2.5 Explorations for drug-drug interactions: No drug-drug interactions were identified.

7.4.3 Causality Determination

The study drug elicited application site reactions such as burning, dryness, pruritus, and erythema, and these were more common than for the vehicle group. Most of these reactions developed early, were not severe and resolved with continued treatment.

8. Additional Clinical Issues

8.1 Dosing Regimen and Administration

The Sponsor recommends the drug product be dosed once daily, at night, and this dosage is consistent for this type of drug product.

8.2 Drug-Drug Interactions

Not applicable.

8.3 Special Populations

Adapalene gel, 0.3%, has not been studied in patients younger than 12 years old and this is appropriate because acne is not common in that population. Women of childbearing potential were required to avoid pregnancy during the studies.

8.4 Pediatrics

The Applicant requests a waiver from the requirement to conduct studies in children younger than 12 years old because acne rarely develops below that age and it would be impractical to recruit patients below the age of 12 years old.

Reviewer comment: it seems reasonable to grant the waiver from the requirement to conduct studies in patients younger than 12 years old.

8.5 Advisory Committee Meeting

No advisory committee meetings have taken place regarding this application.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

No risk management plan has been submitted or suggested.

8.8 Other Relevant Materials

No labeling comprehension studies have been suggested or conducted. There have been consultations with the Division of Drug Marketing, Advertising, and Communication (DDMAC) but not with the Office of Drug Safety .

9. Overall Assessment

9.1 Conclusions

The applicant has provided a series of analysis to support approval of the application. However, the analysis conducted by the Agency, following the pre-specified analysis plan on the ITT population fails to show superiority of the study drug to the comparator for the pre-specified endpoints. The differences between the two types of analysis are as follows: the Sponsor excluded an outlier and 45 patients who had missing values for visits at week-8 and week-12. A review of the data for the outlier fails to justify the exclusion, which is otherwise taken into account when an analysis of the ranked data is conducted, as pre-specified. The exclusion of the 45 patients is inconsistent with the pre-specified application of LOCF.

The efficacy data from the Phase 2 dose-comparison study and from the Phase 3 EU study also fail to demonstrate superiority of the study drug to the comparator.

9.2 Recommendation on Regulatory Action

This reviewer recommends adapalene gel, 0.3% not be approved because it fails to provide increased efficacy over the comparator while its safety profile is slightly worse than that of the comparator.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are being recommended.

9.3.1 Risk Management Activity

No risk management programs are being recommended.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are being required.

9.3.3 Other Phase 4 Requests

No Phase 4 commitments are being recommended.

9.4 Labeling Review

A review of Proposed Labeling will not be necessary if the application is not approved.

9.5 Comments to Applicant

The Applicant should be informed this application is considered non-approvable because it failed to demonstrate superiority to the comparator when analysis is performed per protocol while at the same time producing detectable plasma levels of a known teratogen and producing increased local irritation than the comparator.

10. Appendices

10.1 Review of Individual Study Reports

10.1.1 **1.CG.03.SRE2017** – Phase 1– 21-Day Reiterative Skin Irritation Test of 0.3% adapalene gel Formulation and its Vehicle. This single blind, randomized, controlled, intra-individual study was conducted from July 26th 1993 to August 16th 1993 by Dr. [ ] [ ] using 25 healthy adult volunteers (11 males and 14 non-pregnant females, aged from 20 to 51 years). After informed consent and enrollment, 50 microliters of each formula (Adapalene 0.3 % gel or vehicle) were applied, under occlusive patch, to designated sites on the back of each volunteer using a [ ] Chamber. An empty patch was used as a negative control. Applications were renewed daily (except weekends) for three weeks, and sites were scored on the same occasions. This protocol was not reviewed by the Agency.

The following grading system was used to evaluate each test zone at each scoring period :

0.....No erythema,
0.5.....Equivocal erythema,
1.....Slight erythema, with or without edema,
2.....Moderate erythema, edema with or without papules,
3.....Severe erythema, edema with or without papules,
4.....Severe erythema, edema with vesicles or blisters.

The Mean Cumulative Irritancy Index (MCII) was computed for each treatment schedule, as the mean of the sum of the daily irritancy scores divided by the number of subjects.

The Mean Cumulative Irritancy Index (0 to 4) for each test material was as follow :

Adapalene 0.1% gel	-	0.23
Adapalene 0.3% gel	-	0.24
Adapalene vehicle gel	-	0.11
White Petrolatum	-	0.11

Adapalene 0.1% gel and adapalene 0.3% gel were very similar in respect of irritancy; both of these being slightly more irritanting than adapalene vehicle gel and white petrolatum. The Investigator reported no evidence of sensitization.

10.1.3 **RD.03.SRE2645** – Phase 1– Evaluation of the Photoallergy Potential of Adapalene 0.1% Gel and Adapalene 0.3% Gel Versus Their Vehicle and White Petrolatum Following Repeated Applications to the Skin of Healthy Subjects. The study was conducted from 10/04/00 to 19/05/00 by [redacted] M.D. in [redacted], on 30 (28 evaluable, 18 to 65 years old. This protocol was not reviewed by the Agency.

The MED (Minimal Erythemal Dose) of UVA/UVB was determined for each subject within Day 1 and Day 2 visits.

During the Induction phase, Test products were applied under occlusive conditions during 24 hours, twice weekly (e.g. Monday and Thursday) for 3 weeks (one site remained untreated). Twenty four hours after product application the subjects returned to the investigational center for product removal and irradiation (e.g. Tuesday and Friday). Using a total spectrum of UV light, subjects were irradiated with two MEDs during the first week, and three MEDs during the second and the third week.

The Challenge phase followed a 2-week rest. Two sets of the 4 products were applied under occlusion for 24 hours on naive sites of the back, and there were two untreated but occluded sites. One set was irradiated with 0.5 MED full spectrum UV light followed by 4 J/cm² UVA light, and the other served as control.

Skin reactions (erythema score ± other local reactions) were scored before irradiation (after product removal), and then 48 and 72 hours after the end of irradiation, using the same scale as for study 1.CG.03.SRE2017

The following table summarizes the distribution of the erythema scores:

Table 19. Erythema scores in Photosensitation study 1.CG.03.SRE2017

		Adapalene 0.1% gel	Adapalene 0.3% gel	Adapalene Vehicle gel	White petrolatum	Untreated
Induction Phase:	Scores 0	29	31	30	29	31
Challenge Phase:	0.5	97	92	92	100	105
Number of subjects with	1	149	151	155	152	144
photoallergic response during	2	41	42	39	35	36
the challenge phase	3	0	0	0	0	0

Under the conditions of this study adapalene 0.1% gel and adapalene 0.3% gel compared to their vehicle and to petrolatum using a standard photoallergenicity testing methodology in healthy human subjects did not show any potential for photosensitization.

10.1.4 **1.CG.03.SRE2646** – Phase 1– Evaluation of Phototoxicity Potential of Adapalene 0.3% Gel and Adapalene 0.1% Gel Versus Their Vehicle and White Petrolatum after a Single Application to the Skin of Healthy Subjects. This single center study, randomized, controlled, single blind (Investigator/Evaluator masked), intra-individual comparison study was conducted between 27/03/2000 and 02/04/2000 by [redacted] M.D. in [redacted] In it, 25, 18 to 65 years old, healthy subjects were enrolled (7 males and 18 females). This protocol was not reviewed by the Agency.

At Day 1, 50µl of the test products were applied for 24 hours to two sets of 5 patch sites (one site remained untreated) under occlusion. The MED (Minimal Erythemal Dose) was determined for each subject between Day 1 and Day 2. At Day 2, after removal of the patches, one set of sites was irradiated with 20 J/cm^2 of UVA, followed by exposure to 0.8 MED of UVA/UVB light.
All patch sites were evaluated 60 min after irradiation (Day 2), and then 24h (Day 3) , 48h (Day 4) and 72h (Day 5) after the irradiation procedure.

The mean MED observed on the 25 subjects was 164 ± 40 MED/min.sec.

Reactions were scored 60 min after irradiation, and then 24, 48 and 72 hours following the same scale as for study .CG.03.SRE2017.

The means of clinical scores observed for each product at the different reading times are summarized in the Table below:

Table 20. Mean clinical scores (mean+sd)

	Day 2		Day 3		Day 4		Day 5	
	Left I*	Right NI**	Left I	Right NI	Left I	Right NI	Left I	Right NI
Adapalene 0.1% Gel	**0.90**	**0.36**	**0.74**	**0.04**	**0.21**	**0.00**	**0.06**	**0.00**
	±0.20	±0.37	±0.25	±0.14	±0.33	±0.00	±0.17	±0.00
Adapalene 0.3% Gel	**0.84**	**0.36**	**0.68**	**0.04**	**0.17**	**0.00**	**0.04**	**0.00**
	±0.28	±0.31	±0.28	±0.14	±0.32	±0.00	±0.14	±0.00
Vehicle	**0.80**	**0.30**	**0.66**	**0.02**	**0.15**	**0.00**	**0.06**	**0.00**
	±0.25	±0.35	±0.28	±0.10	±0.31	±0.00	±0.17	±0.00
Petrolatum	**0.72**	**0.20**	**0.68**	**0.04**	**0.17**	**0.00**	**0.06**	**0.00**
	±0.33	±0.29	±0.32	±0.20	±0.32	±0.00	±0.17	±0.00
Untreated	**0.76**	**0.28**	**0.64**	**0.02**	**0.15**	**0.00**	**0.08**	**0.00**
	±0.25	±0.33	±0.27	±0.10	±0.31	±0.00	±0.19	±0.00

*: Left I: irradiated left side; **: Right NI: non irradiated right side

At Day 2 all sites presented low scores of erythema (up to grade 1), thought due to occlusion. At Day 3, irradiated sites still had erythema. At Day 4 and Day 5, almost all the observed scored were 0. No phototoxic reaction was observed.

10.1.5 **RD.06.SRE.18060** – Phase 2 - The Safety and Efficacy of adapalene gel, 0.3% (70 subjects) was compared to its Vehicle (74 subjects) and adapalene gel, 0.1% (70 subjects) in the Treatment of Acne Vulgaris. This protocol was reviewed by the Agency on 4/3/01.

The design of this Phase 2 dose-finding study was generally similar to that of the pivotal Phase 3 study (**RD.06.SRE.18081**) described later in the review. However, in the Phase 2 study, the inclusion criteria differed from the pivotal study: There was no specified upper limit for the number of inflammatory and non-inflammatory lesions and subjects with a maximum of two nodules were permitted. Subjects were required to have their acne graded as 4-8 in the 12-grade Leeds Revised Acne Grading System, the scale used to assess the primary efficacy endpoint. The protocol did not pre-specify a success/failure dichotomization of the scale. The two active treatments (Adapalene Gel, 0.1% and 0.3%) were similar but not identical to the currently marketed 0.1% gel formulation (the marketed product utilizes poloxamer 182 while the active treatments in this study utilize poloxamer 124) .

Two hundred fourteen subjects were enrolled and dosed at least once and were evaluable for safety.

A clear dose-response relationship for the three treatments was observed for percent lesion changes in total, inflammatory and non-inflammatory lesion counts at Week 12

In this study, the 0.3% formulation was superior to the 0.1% formulation only for non-inflammatory lesions, but not for inflammatory, for total lesion counts, or for the IGA. The 0.3% formulation was superior to vehicle for all endpoints. The 0.1% formulation was superior to vehicle for inflammatory lesions, total lesion counts and for IGA. The safety findings in this trial parallel those reported for the US Phase 3 trial.. the 0.1% formulation was not superior to vehicle, and
Reviewer comment: Because of the differences in protocol design, this review will look at this study only as to whether it could be merely supportive of efficacy.

10.1.6 **SRE.18082** –Phase 3. An Open Label Long Term Safety Study of adapalene gel, 0.3% in Subjects with Acne Vulgaris. This protocol was not reviewed by the Agency.

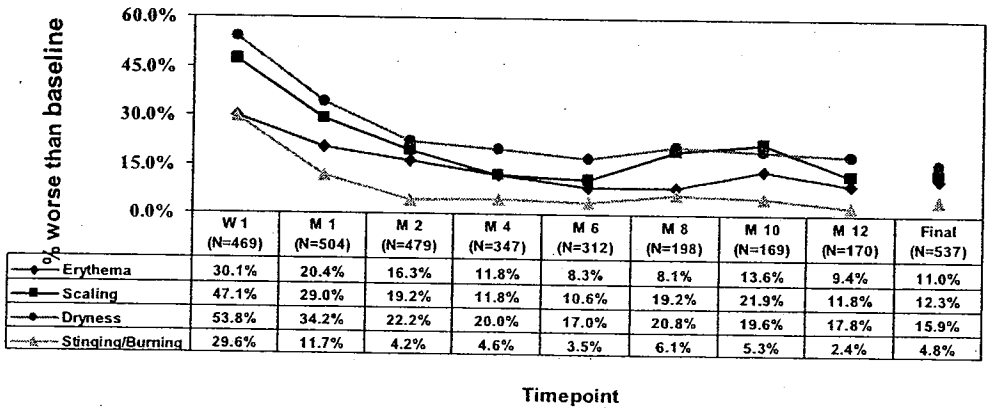
This was an open-label, long-term (up to 12 months) safety study of adapalene gel, 0.3% applied topically in the treatment of *acne vulgaris*. Five hundred fifty-one subjects (276 male and 275 female) in 20 centers were enrolled and evaluable for safety. However, efficacy was also recorded in the study for lesion counts. The applicant reports that efficacy continue to improve with continued treatment up to 12 months.

Approximately 30% of the subjects in the long-term, open-label study completed 12 months of treatment. In the long-term Phase 3 study (**RD.06.SRE.18082**), the most frequent reasons for

discontinuation were site closing (22.9%), sponsor's decision (16.9%), lost to follow-up (12.7%), and subject's request (11.8%). Very few subjects (2.7%) in the long-term study discontinued due to adverse event. (See **Text Table 3900** earlier in the review.)

The following **figure** summarizes the development of erythema, scaling, dryness and stinging/burning in the study

Figure 1 – Time Course of Local Cutaneous Irritation for adapalene gel, 0.3% in the 12 month study (Worse Than Baseline; Observed Data & Final Score) (RD.06.SRE.18082)



	W 1 (N=469)	M 1 (N=504)	M 2 (N=479)	M 4 (N=347)	M 6 (N=312)	M 8 (N=198)	M 10 (N=169)	M 12 (N=170)	Final (N=537)
Erythema	30.1%	20.4%	16.3%	11.8%	8.3%	8.1%	13.6%	9.4%	11.0%
Scaling	47.1%	29.0%	19.2%	11.8%	10.6%	19.2%	21.9%	11.8%	12.3%
Dryness	53.8%	34.2%	22.2%	20.0%	17.0%	20.8%	19.6%	17.8%	15.9%
Stinging/Burning	29.6%	11.7%	4.2%	4.6%	3.5%	6.1%	5.3%	2.4%	4.8%

Source: **18082**: SAF 2.1, SAF 2.2, SAF 2.3, SAF 2.4
Note: Slight data point variations (± 0.1%) in the figure are due to rounding rule effect.
Final: Last observation during post-Baseline period.
N = Number of subjects in the study with data available at Baseline and the specified timepoint (based on erythema)

The following table summarizes the highest irritation scores recorded in the study:

Text Table 21 – Highest Severity Score of Local Cutaneous Irritation[1] (Worse than Baseline) (RD.06.SRE.18082)

Worst (Highest score)*	Erythema	Scaling	Dryness	Stinging/Burning
N	537	537	536	537
Mild	170 (31.7%)	239 (44.5%)	277 (51.7%)	155 (28.9%)
Moderate	71 (13.2%)	84 (15.6%)	79 (14.7%)	41 (7.6%)
Severe	3 (0.6%)	3 (0.6%)	6 (1.1%)	10 (1.9%)

* Proportion of subjects with scores worse than Baseline during the post-Baseline period
[1] Local Cutaneous Irritation was reported as Local Cutaneous Tolerance; these terms are used interchangeably.
N = Number of subjects in study with data available at Baseline and at least one post-Baseline visit.
Source: **18082**: SAF 2.1, SAF 2.2, SAF 2.3, SAF 2.4

Table 18. Mean Cumulative Irritancy Index . 1.CG.03.SRE2017

PRODUCT	MCII	IRRITATION CLASSIFICATION
Adapalene gel 0.3 %	0.48	slightly irritant
Adapalene gel vehicle	0.29	slightly irritant
Untreated patch	0.51	slightly irritant

Under these conditions, both Adapalene 0.3 % gel and its vehicle were classed as "slightly irritant" No severe irritation was observed at any time in any subject.

10.1.2 **RD.03.SRE2644** – Phase 1. Evaluation of the Cumulative Irritation and Cutaneous Contact Sensitization Potential of Adapalene 0.1% Gel and Adapalene 0.3% Gel Versus Their Vehicle and White Petrolatum Following Repeated Application to the Skin of Healthy Subjects. This study was performed in by [redacted] from 08 May 2000 – 01 July 2000, in the UK, as a Single centre, controlled, randomized, single blind) study . This protocol was not reviewed by the Agency.

During the Induction phase, four test products (adapalene 0.1% gel, adapalene 0.3% gel, vehicle, and white petrolatum) were applied under occlusive conditions for 48 hours , on the upper back three times a week (e.g. Monday, Wednesday, Friday), for 3 weeks. Each time 15 to 30 minutes after removal of the patches, skin reactions were assessed (erythema score ± other local reactions). A 2 weeks Rest phase was followed by a Challenge phase, during which the products were applied only once on 4 naïve sites, on the lower back for 48 hours. Skin reactions were scored at 30 minutes, and at 48 and 72 hours after removal of the patches. after removal of the patches. Two hundred and fifteen male and female subjects, 18 to 65 years old were enrolled and patched, and two hundred and three completed the study.

Erythema was graded as for study 1.CG.03.SRE2017. Re-challenges were assessed using the following scale:

0	No dermatitis.
0.5	Erythema does not cover the test area, equivocal reaction.
1	Erythema that covers the test area.
2	Erythema and induration that cover the test area.
3	Erythema, induration, and vesicles covering the test area.
4	Erythema, induration, vesicles, and bullae covering the test area.
IR	Irritative Reaction.

Three subjects (16, 30, an 196) were because of urticarial reactions that develop after 1-7 applications but which were negative after re-challenge.

The Mean Cumulative Irritancy Index (MCII) calculated for each product were:

Reviewer comment: This study supports the safety of adapalene gel, 0.3% but is not adequate to assess efficacy because it was an open study. Over half of the subjects experienced mild dryness, 28% experienced mild stinging. By the 10th month dryness was still 20%.

Text Table 22 – Summary of Adverse Events by Severity and Relationship to Study Drug (RD.06.SRE.18082)

	Adapalene Gel, 0.3% (N = 551) N (%)
Subjects with Any Adverse Events	244 (44.3%)
Subjects with Mild Adverse Events	165 (29.9%)
Related	75 (13.6%)
Unrelated	110 (20.0%)
Subjects with Moderate Adverse Events	126 (22.9%)
Related	60 (10.9%)
Unrelated	88 (16.0%)
Subjects with Severe Adverse Events	10 (1.8%)
Related	0 (0.0%)
Unrelated	10 (1.8%)

Related adverse events that occurred in greater than 1% of subjects who used adapalene gel, 0.3% included dry skin (10.5%), skin discomfort (8.3%), desquamation (3.3%), sunburn (3.1%), erythema (2.5%), pruritus (1.8%), and irritant dermatitis (1.6%). The proportion of subjects with these drug related adverse events was highest in the first quarter and decreased greatly by the second quarter and remained low throughout the duration of the study. Six subjects (1.1%) had serious adverse events; none of these events was drug related. No subjects died in the long-term study

The following table summarizes the AEs leading to discontinuation of treatment and compares to the data for the Phase 3 US trial:

Table 23 – Comparison of Adverse Events (RD.06.SRE.18081 *vs.* RD.06.SRE.18082)

Number (%) of Subjects with Adverse Event	Adapalene Gel, 0.3%	
Study **Study Duration** **Interval**	**RD.06.SRE.18081** **12-week Treatment**	**RD.06.SRE.18082** **12-month Treatment** **Base - 12 Months**
	N = 258	**N = 551**
Total Number of Adverse Events	167	505
Total Number of Subjects With at Least One Adverse Event	104 (40.3%)	244 (44.3%)
Dermatologic	69 (26.7%)	142 (25.8%)
Non-Dermatologic	51 (19.8%)	155 (28.1%)
Subjects With Related[1] Adverse Events	57 (22.1%)	119 (21.6%)
Dermatologic	55 (21.3%)	117 (21.2%)
Non-Dermatologic	4 (1.6%)	4 (0.7%)
Subjects with Serious Adverse Event(s)	1 (0.4%)	6 (1.1%)
Dermatologic	0 (0.0%)	0 (0.0%)
Non-Dermatologic	1 (0.4%)	6 (1.1%)
Subject Discontinuations Due to Adverse Event	5 (1.9%)	15 (2.7%)
All	4 (1.6%)	15 (2.7%)
Dermatologic	1 (0.4%)	1 (0.2%)
Non-Dermatologic	3 (1.2%)	13 (2.4%)
Related to Treatment	3 (1.2%)	13 (2.4%)
Dermatologic	0 (0.0%)	1 (0.2%)
Non-Dermatologic		
Subjects Who Died	0 (0.0%)	0 (0.0%)

[1] Related = possibly, probably or definitely related
N+ = Number at risk, the number of subjects at the beginning of each period.
Source: **18081**: SAF 4, SAF 5, SAF 7.1, SAF 7.2, **18082**: SAF 4, SAF 5, SAF 7.1, SAF 7.2

Reviewer comment: The overall rate of AEs related to treatment ad those leading to discontinue treatment was similar for both trials

10.1.7. **RD.03.SRE.2673-** Phase 3. A Long Term Safety and Efficacy Study of adapalene gel, 0.3% in Subjects with Acne Vulgaris.

This European study was a multicenter (34 centers), 12 weeks, randomized, investigator-masked, parallel comparison of the safety and efficacy between adapalene gel, 0.3% and adapalene gel, 0.1% when applied topically in the treatment of *acne vulgaris*. Four hundred-eighteen subjects were enrolled in the study (208 (87 males, 121 females) to adapalene gel, 0.3%, 210 (80 males, 130 females) to adapalene gel, 0.1%) , dosed at least once, and evaluable for safety. The inclusion criteria differed slightly from the US pivotal study, The primary efficacy endpoint was percent change in total lesion counts. The assessment of Global Severity Grade, was a secondary endpoint and was based on the 12-grade Leeds revised acne scale, which differs from the scale used in the US pivotal trial. No vehicle arm was included in the study. Safety was assessed by recording adverse

events at each visit. The adapalene gel, 0.1% formulation used in the study differed from that used in the US study.

At Endpoint, no significant differences were observed between the formulations for counts for inflammatory, non-inflammatory, total lesion counts, or in global severity, both for the ITT and the Per-Protocol populations. However, efficacy was slightly higher for the 0.3% formulation for all endpoints.

Reviewer comment: No comparisons were made to the pivotal study due to the substantial differences in study design: lack of a vehicle arm, different inclusion criteria and different Endpoint analyses.

10.1.8 **RD.06.SRE.18081** – Phase 3.– The Safety and Efficacy of adapalene gel, 0.3% as Compared to adapalene gel, 0.1% and adapalene gel Vehicle in the Treatment of Acne Vulgaris. This protocol was reviewed by the Agency .

This study was a multi-center, active and vehicle controlled, double-blind, parallel-group comparison between adapalene gel, 0.3%, adapalene gel, 0.1%, and vehicle (randomized 2:2:1) in subjects with acne vulgaris. Study drug was applied once daily in the evening. Blood and urine samples were collected at Screening and Week 12 (or at the time of discontinuation) at specified sites for blood chemistries, hematology, and urinalysis.

The study planned to enroll 630 subjects and randomized: 653 subjects (258 adapalene gel, 0.3%, 261 adapalene gel, 0.1% and 134 vehicle gel), and it was conducted during 28 March 02- 21 August 02.

The following is the lists of participating investigators:

Investigator #	Name/Address/Tel./Fax	Subject Identifier Series [d]
429 [a]		1121-1125, 1261-1265, 1646-1655, 1806-1810
438 [b]		1026-1030, 1371-1381
2006 [b]		1706-1715, 1811-1815
2020 [a]		1056-1060, 1231-1241
2023 [b]		1626-1639
2028 [a]		1091-1095, 1266-1275, 1701-1705, 1886-1887
2036 [b]		1331-1346

Investigator #	Name/Address/Tel./Fax	Subject Identifier Series [d]
2051 [a]		1571-1573
2052 [b]		1061-1070, 1131-1155, 1316-1330
2065 [b]		1086-1090, 1276-1287
2092 [b]		1016 – 1025, 1731-1739
2094 [b]		1036-1045, 1561-1568
2095 [b]		1111-1115, 1421-1454
2102 [a]		1071-1075, 1656-1665, 1881-1883
2103 [b]		1046-1055, 1596-1605, 1771-1776
2114 [b]		1096-1105, 1176-1200, 1581-1585
2129 [a]		1006-1015, 1826-1830
2131 [b]		1076-1080, 1511-1525, 1156-1175, 1741-1750
2137 [a]		1552-1556
2157 [b]		1211-1225, 1686-1695, 1751-1764
2160 [a]		1081-1085, 1246-1255, 1291-1315
2166 [b]		1256-1260, 1616-1625, 1831-1845, 1901-1904
2179 [b]		1001-1005, 1696-1698

Investigator #	Name/Address/Tel./Fax	Subject Identifier Series [d]
2180 [a]		1226-1230, 1786-1795, 1871-1875
2195 [a]		1491-1500, 1716-1720, 1821-1825
2196 [b]		1106-1110, 1386
2197 [a]		1031-1035, 1681-1685
2198 [b]		1126-1130, 1456-1465
2199 [b]		1116-1120, 1801-1805, 1891-1895
2201		NA (none enrolled)
2218 [b]		1206-1210, 1666-1668
2219		1526-1534
2220		1606-1614

[a] Lab sites
[b] Photo sites
[c] Dates reflect First Subject In and Last Subject Out
[d] Study drug kits dispensed to subjects at each site

Source: Appendix 16.1.1

Inclusion criteria:

- males and females, aged 12 years and older, with facial acne.
- a minimum of 20 but not more than 50 inflammatory lesions, with no nodules or cysts.
- a minimum of 20 but not more than 100 non-inflammatory lesions.
- if a female of childbearing potential, must have a negative urine pregnancy test at the beginning of the study, and avoid pregnancy.
- willingness and ability to sign consent form (or guardian if younger than 18 years old), be photographed, and follow study procedures.

Exclusion criteria:

- clinically important abnormal physical findings (other than acne) which might, in the opinion of the investigator, interfere with the objectives of the study, including laboratory

findings at the specific centers.

- acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), or severe acne requiring more than topical treatment.
- underlying diseases or other dermatological conditions that require the use of interfering topical or systemic therapy,such as atopic dermatitis, perioral dermatitis, or rosacea.
- Oral Vitamin A up to the recommended daily dose of 400-5000 IU is acceptable. Aspirin for prophylactic use, 325 mg, is not considered to be an anti-inflammatory dose.
- known sensitivities to any of the study preparations
- beard or other facial hair which might interfere with study assessments.
- failure to undergo the specified washout periods for the following topical preparations, or a requirement for the concurrent use of any of the following topical medications on the face:

	Washout period	Products
Topicals	1 day	Alpha hydroxy acid products, astringents, preparations with alcohol
	4 weeks	Corticosteroids, antibiotics, other anti- inflammatory drugs, other acne treatments, retinoids
Systemic	4 weeks	Corticosteroids, anti-inflammatory drugs, antibiotics (excluding plain penicillin)
	6 months	Other acne treatments, including Accutane and Ortho Tri-Cyclen

STUDY FLOW CHART	**Scheduled Visits** [i]						
Procedures **Visit** **Week**	Screening[a]	Baseline[a]	**1**	**2**	**4**	**8**	**Final**[b] **12**
Informed Consent	X						
Demographics/Medical and Rx Hx Incl/Excl Criteria	X	X					
Blood and Urine Sampling[a] Pregnancy Testing[d]	X						X
Assessment : Investigator's Global, lesion counts[e]		X	X	X	X	X	X
Oiliness (face), Photographs (face)[f]		X	X	X	X	X	X
Treatment Dispensed		X			X	X	
Treatment Returned					X	X	X
Concomitant Therapy[c], Local Tolerability[g]		X[h]	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Subject's Assessment of Acne, Exit Form							X

[a]Screening and baseline visit should have occurred on separate days (within seven days of each other only if washout was not required) to allow time for laboratory values to be assessed for normalcy at specified centers. These visits should have been combined at centers not involved in obtaining blood and urine samples other than for pregnancy testing.
[b]Should have been conducted earlier if Subject discontinued prior to Week 12, and recorded on the Early Termination pages of the CRF.
[c]Therapy that continued after baseline should have been recorded on the Concomitant Medication page of the CRF.

[d]At Screening and the final visit, pregnancy testing was mandatory for all females of childbearing potential. Investigators decided whether or not to conduct pregnancy testing on female subjects during the course of the study.
[e]Inflammatory lesion counts and non-inflammatory lesion counts.
[f]Photographs should have been taken at specified centers according to instructions from [redacted] for documentation purposes and possible presentations only and not used for evaluations. (See Appendix 16.1.1).
[g]The Investigator should have recorded and graded the severity of the signs and recorded the Subject's assessment of symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) on the local tolerability assessment of each visit.
[h]Local tolerability should have been evaluated at baseline prior to the first application of study medication at the site.
[i]To assist subject compliance, a study window of plus or minus 3 days was allowed for baseline, Week 1, and Week 2. A study window of plus or minus 5-7 days was allowed for Week 4, and Week 8 and Week 12.

Treatment regimen: Applications are to be made once daily to the face for 12 weeks. The trunk may be treated, as indicated, but only the face will be evaluated for efficacy. The subjects may use a moisturizer for symptomatic relief of skin dryness or irritation; otherwise, no other topical treatment is to be permitted.

Test Materials: adapalene gel, 0.3%, adapalene gel, 0.1%, and vehicle gel were dispensed according to the randomization code. Subjects were to treat the face and trunk, as applicable, once daily, with adapalene gel, 0.3%, adapalene gel, 0.1%, or vehicle gel for 12 weeks.

The following test materials were used in the study:

Test Material Identification			
Test product:	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Vehicle Gel
Lot/Batch Number	RIGW-4	RIA	RIC
Formulation Number	BOH-1	BOG-1	P-BOG-1
Expiration Date	September 2003	September 2003	September 2003
Manufacturer	DPT Laboratories, LTD. 318 McGullough, San Antonio, TX		

Source: Appendix 16.1.1

Study material were packaged in 45 grams and were to be stored at 20-25°C (68-77°F).

Efficacy parameters: Assessments at baseline and weeks 1, 2, 4, 8, and 12, for the following:

a. Lesion counts for non-inflammatory, inflammatory, and total lesions.
b. Investigator's Global Assessment, using the following scale.

Investigator's Global Assessment			
	Grade		Description
SUCCESS	0	Clear	Residual hyperpigmentation and erythema may be present
	1	Almost Clear	A few scattered comedones and a few (less than five) small papules.
	2	Mild	Easily recognizable; less than half the face involved. Many comedones and many papules and pustules.
FAILURE	3	Moderate	More than half of the face is involved. Numerous comedones, papules and pustules.
	4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules and few nodules and cysts.
	5	Very Severe	Highly inflammatory acne covering the face; with nodules and cysts present

The patient's assessment of acne was done at the end of treatment, using the following scale:

0	Clear
1	Marked Improvement
2	Moderate Improvement
3	Minimal Improvement
4	No Change
5	Worse

Primary efficacy criteria: The percent lesion reduction, and the success rate based on the Investigator's Global Assessment, defined as the percentage of patients who are rated as Clear or Almost Clear.

Secondary efficacy criteria: The patient's assessment of acne, and the response rate, defined as the percentage of patients who achieved at least 50% lesion reduction.

Safety evaluation. At baseline and each return visit, erythema, scaling, dryness, and stinging/burning, graded as follows:

Erythema: abnormal redness of the skin.

None	0	No erythema
Mild	1	Slight pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness

Scaling: abnormal shedding of the stratum corneum.

None	0	No scaling
Mild	1	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production

Dryness: brittle and/or tight sensation

None	0	No dryness
Mild	1	Slight but definite roughness
Moderate	2	Moderate roughness
Severe	3	Marked roughness

Stinging/Burning: prickling pain sensation immediately after (within 5 minutes of) dosing.

None	0	No stinging/burning
Mild	1	Slight warm, tingling/stinging sensation; not really bothersome
Moderate	2	Definite warm, tingling/stinging sensation that is somewhat bothersome
Severe	3	Hot, tingling/stinging sensation that has caused definite discomfort

Adverse events will be recorded, with the date of onset, severity, relationship to the test product, and the outcome.

Laboratory evaluations will be done at about half of the centers. These will include Hgb, Ht, RBC, WBC, MCV, MCH, MCHC, platelets, protein, albumin, globulin, A/G ratio, total bilirubin, SGPT, SGOT, alkaline phosphate, GGT, lactic dehydrogenase, BUN, creatinine, uric acid, cholesterol, triglycerides, and glucose, and complete urinalysis.

Adapalene Gel (0.3% and 0.1%) and vehicle gel are slightly different in appearance. However, study blinding was maintained by having a third party, other than the Investigator/Evaluator, dispense the medication. An investigator could break the blind in an emergency and would have to inform the Sponsor in writing. Written approval from Galderma Data Management and Galderma Biostatistics was required for unblinding the study.

Method of Treatment Assignment: A randomization list was generated, prior to the start of the study, by Galderma R&D, and attached to the packaging labeling. The randomization number, the same as the subject number, was assigned to qualified subjects sequentially. No number should have been omitted. The study drug kits were dispensed in chronological order at baseline.

Dose Selection in Study: The Sponsor states that a clear concentration-dependent effect was observed with adapalene gel, 0.3%, adapalene gel, 0.1% and corresponding vehicle gel in a Phase 2 study in acne vulgaris. Local tolerability and safety of adapalene gel, 0.3% was comparable to adapalene gel, 0.1%. This pivotal Phase 3 study was designed to provide evidence in support of the hypothesis that the 0.3% formulation would have a superior therapeutic effect over the 0.1% formulation.

Application: All subjects were instructed to apply study medication once a day, in the evening for 12 weeks, and the first dose of study medication was to be applied under study personnel supervision. The study drugs were required to be returned at each applicable visit to the Investigators. At the end of the study, all used an unused study drugs were returned to the Sponsor.

Primary Efficacy Measurement:

Lesion Counts: Each type of facial lesion (excluding the nose) was counted separately and recorded on the appropriate Case Report Form. The following are the definitions of the lesions that were counted:

Non-inflammatory Lesions
-Open Comedone: A mass of sebaceous material that is impacted behind an open follicular orifice (blackhead).

-Closed Comedone: A mass of sebaceous material that is impacted behind a closed follicular orifice (whitehead).

Inflammatory Lesions
-Papules: A small, solid elevation less than one centimeter in diameter.
-Pustules: A small, circumscribed elevation of the skin which contains yellow-white exudate.
-Nodules/Cysts: (not present at baseline; may have developed post-baseline) A circumscribed, elevated, lesion generally more than 1.0 cm in diameter.

Investigator's Global Assessment of Acne Severity: It was evaluated at each visit, using the described scale. This clinical instrument was dichotomized as success or failure, as shown on the preceding scale.

An AE was defined as any unfavorable and unintended sign *(e.g., including a clinically relevant abnormal laboratory finding)*, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An Adverse Event Form was to be completed only if the severity of the expected signs and symptoms was such that an interruption of the subject's participation in the study, at his/her request or at the Investigator's discretion, had occurred.
Reviewer comment: Adverse events should have been recorded as they developed, rather than only if they required interruption of treatment. Recording AEs in this manner may have led to under-recording of AEs

At specified centers, blood and urine samples were obtained at Screening (the results were available at the baseline visit) and the Final Study Visit, to perform chemistries (protein, albumin, globulin, A/G ratio, bilirubin (total), alanine transaminase (ALT), serum glutamic pyruvic transaminase (SGPT), aspartate transaminase (AST), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphate, GGT, lactic dehydrogenase, urea nitrogen, creatinine, uric acid, cholesterol (total), triglycerides, and glucose), and hematology testing (hematocrit, hemoglobin, red cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white cell count, and platelet count). A routine urinalysis was also performed.

Statistical and Analytical Plans

Variables to be Analyzed:

The primary efficacy variables were:

- Percent lesion reduction from baseline (inflammatory, non-inflammatory, and total)
- Success rate, the percentage of subjects with "Clear" or "Almost Clear" on the Investigator's Global Assessment.

The secondary efficacy variables were:

- Response rate – the percentage of subjects who achieved at least 50% reduction in lesion counts (inflammatory, non-inflammatory, and total)
- Lesion reduction in inflammatory, non-inflammatory, and total lesion counts
- Subject's assessment of acne.

The safety variables were:

- Local tolerability (erythema, scaling, dryness, stinging/burning)
- Adverse events
- Routine laboratory data (hematology, blood chemistry, urinalysis) at specified centers

Other variables included facial oiliness in all subjects and photographs at each visit at specified centers.

Data Transformations: No data transformations were planned.

Populations Analyzed, Evaluability and Limitation/Evaluation of Bias: The statistical analysis was performed based on the following subject populations:

- The intent-to treat (ITT) population

The intent-to-treat population was primary for assessing efficacy. The intent-to-treat population was defined as all subjects who were randomized and dispensed medication.

- Per-Protocol (PP) population

The Per-Protocol (PP) population was the ITT subjects who met all major protocol criteria.

SAFETY POPULATION

The safety population was defined as the ITT population who have applied the study medication at least once.

Statistical Analyses and Sample Size Determination: The primary hypotheses were to show superiority of adapalene gel, 0.3% over adapalene gel, 0.1% using the data (ITT) at multiple timepoints (Week 8 and Week 12) on (1) two of the three percent lesion changes and (2) success

rate. All tests were two-sided, each at the 0.050 significance level. Comparisons of adapalene gel, 0.3% versus vehicle were performed to validate the superiority of adapalene gel, 0.3% over vehicle.

The Generalized Estimating Equation (GEE) methodology was used as the primary analysis for the correlated repeated measurements at Week 8 and Week 12. For success rates, the logit link function was used to model the marginal expectation. For percent changes on lesion counts, the identity link function was used. The option for the unstructured working correlation matrix was used. The efficacy results were confirmed by using alternative specifications for the correlation matrix. The SAS GENMOD procedure was used for the GEE method.

The dependent variables in the models were either success rate or the percent change on lesion counts. The independent variables included treatments (0.3% vs. vehicle, 0.1% vs. vehicle), center (k -1 terms), time8_12 (data at Weeks 8, 12), treatment* center. The comparison between 0.3% and 0.1% on the success rate and percent changes on lesion count for the data at multiple timepoints (Week 8 and Week 12) were performed using the CONTRAST statement. The primary analyses were performed based on the ITT. The analyses were repeated based on the PP population to confirm the results.

Secondary Efficacy Analyses

All efficacy data derived from Investigator's Global Assessment (IGA) of Acne Severity and response rate were analyzed by the CMH test controlling for center to validate results obtained by the GEE in the ITT and PP populations.

For each population (ITT and PP), (a) the LOCF data at baseline and each visit, and (b) the observed data at each visit including LOCF endpoint, were summarized and analyzed. In (a), the LOCF principle was applied to all subsequent visits. In (b), "endpoint" was the last available data. If no post-baseline data were available, the baseline value was carried forward.

Counts for the three lesion types were summarized including raw counts, change from baseline, and percent change from baseline.

Facial Oiliness was summarized as categorical variable by visit.

Subgroup analyses were performed for the primary efficacy variables for the following subgroups of subjects: center, gender, race, and age. These data were summarized for the observed data plus endpoint in the ITT population, using the CMH test.

Sample Size Determination: To demonstrate a significant effect of adapalene gel, 0.3% over adapalene gel, 0.1%, the hypotheses was to test superiority of 0.3% over 0.1% using the data at multiple timepoints (Week 8 and Week 12) on (1) two of the three percent lesion reduction (inflammatory, non-inflammatory, and total) and (2) success rate (the percentage of subjects with "Clear" or "Almost Clear" on the Investigator's Global Assessment).
In calculating the sample size, the minimum 10% of treatment difference in percent lesion reduction and success rate between adapalene gel, 0.3% and adapalene gel, 0.1% was considered statistically and clinically relevant. Using 0.29 to 0.32 as the ratio of treatment difference to variability in

percent lesion reduction observed in the Phase 2 dose-finding study,[6] 252 subjects for the 0.3% or 0.1% treatment group were required to detect 10% difference to variability in percent lesion reduction and success rate with at least 80% of power at the 0.05 alpha level. Using the allocation ratio of 2:2:1 for the 0.3%, 0.1%, and vehicle treatment arms, the total sample size was planned for 630 enrolled subjects, with 252 subjects in each of the adapalene gel, 0.3% and 0.1% treatment arms, and 126 for the vehicle gel treatment arm.

See Biostatistics Review for further details.

Protocol Amendments: There were two amendments to the Protocol:

- Protocol Amendment 01, 19 April 2002, specified changes in the protocol regarding:
  - — Added double barrier method to the list of acceptable birth control methods in the Inclusion Criteria in Section 3.3 of the protocol.
  - — Removed incorrect information from Verification of Blinding in Section 5.4.1 of the protocol to clarify the difference between active and vehicle.
- Protocol Amendment 02, 1 October 2002, specified changes in the protocol regarding:
  - — Clarified the maximum number of subjects that could have been enrolled at any one site while not jeopardizing the statistical balance in favor of the larger enrolling sites.

Statistical Analysis Plan Modifications:
The following modifications were made to the documented statistical analysis plan; the document was signed on 18 October 2002, prior to unblinding:

- One site (Dr. [redacted] #2092) used the draft Investigator's Global Assessment (IGA) score prior to finalization, instead of the final IGA scores. These subjects were excluded from analysis and from the pooling procedure.

- The Generalized Estimating Equation (GEE) Methodology
  Only the primary efficacy parameters, success rate and percent change from baseline in lesion counts, were analyzed by GEE methodology. Response rates were analyzed by the CMH test.

Study subjects
The following table summarizes the disposition of randomized subjects:

Table 24- Disposition of Analyzed Subjects

Disposition	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Vehicle	Total
ITT	258	261	134	653
PP	207	223	113	543
Safety	258	261	134	653

The following table summarizes the demographic characteristics of the ITT population:

Table 25- Demographic and Baseline Characteristics – ITT Population

Demographic Parameter	Adapalene Gel, 0.3% (N=258)		Adapalene Gel 0.1% (N=261)		Vehicle Gel (N=134)		Total (N=653)		P-value[1]
	n	(%)	n	(%)	N	(%)	n	(%)	
Gender									
Male	129	(50.0)	132	(50.6)	62	(46.3)	323	(49.5)	0.703
Female	129	(50.0)	129	(49.4)	72	(53.7)	330	(50.5)	
Race									
Caucasian	194	(75.2)	186	(71.3)	91	(67.9)	471	(72.1)	0.422
Black	26	(10.1)	23	(8.8)	18	(13.4)	67	(10.3)	
Asian	6	(2.3)	12	(4.6)	4	(3.0)	22	(3.4)	
Hispanic	27	(10.5)	35	(13.4)	18	(13.4)	80	(12.3)	
Other	5	(1.9)	5	(1.9)	3	(2.2)	13	(2.0)	
Skin Type									
Oily	145	(56.2)	152	(58.2)	76	(56.7)	373	(57.1)	0.365
Normal	82	(31.8)	72	(27.6)	39	(29.1)	193	(29.6)	
Dry	20	(7.8)	14	(5.4)	11	(8.2)	45	(6.9)	
Normal + Dry	1	(0.4)	1	(0.4)	0	(0.0)	2	(0.3)	
Oily + Normal	6	(2.3)	11	(4.2)	2	(1.5)	19	(2.9)	
Oily + Dry	3	(1.2)	11	(4.2)	6	(4.5)	20	(3.1)	
Oily + Normal + Dry	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.2)	
Age (years)									
Mean	18.4		17.8		18.6		18.2		0.409
S.D.	6.19		5.97		6.39		6.14		
Median	16.0		16.0		16.0		16.0		
Min, Max	12, 41		12, 52		12, 39		12, 52		
12 – 17 [n (%)]	162 (62.8)		178 (68.2)		79 (59.0)		419 (64.2)		0.134
18 – 64 [n (%)]	96 (37.2)		83 (31.8)		55 (41.0)		234 (35.8)		

Sponsor's Table

[1]: P-values for categorical variables were based on the CMH general association statistic, adjusted for center; P-values for continuous variables were based on two-way ANOVA model with terms for treatment and center

Reviewer comment: There were no significant differences among the treatment groups in demographic and baseline characteristics in the ITT population.

The following table summarizes the number of subjects who completed or discontinued the study:

Table 26- Subjects Completed/Discontinued the Study: ITT Population

Disposition	Adapalene 0.3% (N=258)		Adapalene 0.1% (N=261)		Vehicle (N=134)		Total (N=653)	
	N	(%)	n	(%)	n	(%)	n	(%)
Completed Study	227	(88.0)	240	(92.0)	120	(89.6)	587	(89.9)
Discontinued	31	(12.0)	21	(8.0)	14	(10.4)	66	(10.1)
Adverse Event	5	(1.9)	2	(0.8)	1	(0.7)	8	(1.2)
Subject Request	16	(6.2)	6	(2.3)	8	(6.0)	30	(4.6)
Protocol Violation	2	(0.8)	1	(0.4)	0	(0.0)	3	(0.5)
Lost to Follow-up	8	(3.1)	12	(4.6)	5	(3.7)	25	(3.8)

Reviewer comment: There were relatively more subjects discontinued in Adapalene 0.3% arm compared to the adapalene gel, 0.1% and vehicle; and majority of the discontinued (16/31) were based on subject request.

The most common reason for subjects to request that they be discontinued from the study were logistical reasons (e.g., relocation; 1.8% of total population). There were 3 subjects (Subject #1662 and #2094 in the adapalene gel, 0.3%, treatment group and subject #2157 in the adapalene gel, 0.1%, treatment group) that requested early withdrawal due to irritation. However, the investigator did not consider the irritation as the primary reason for discontinuation. The following table summarizes the reasons for discontinuation due to subject request:

Table 27 - SUMMARY OF DISCONTINUATIONS DUE TO SUBJECT REQUEST (ITT)

Disposition	Adapalene Gel, 0.3% (N=258)		Adapalene Gel, 0.1% (N=261)		Vehicle Gel (N=134)		Total (N=653)	
	n	(%)	n	(%)	n	(%)	n	(%)
Logistical Reasons	5	(1.9)	2	(0.8)	5	(3.7)	12	(1.8)
Compliance Visits	2	(0.8)	1	(0.4)	0	(0.0)	3	(0.5)
Compliance Meds	5	(1.9)	2	(0.8)	1	(0.7)	8	(1.2)
Lack of Effect	2	(0.8)	0	(0.0)	2	(1.5)	4	(0.6)
Irritation	2	(0.8)	1	(0.4)	0	(0.0)	3	(0.5)

ITT - intent-to-treat Source: Section 14, Table SUB 2.4; Section 16, Listing SAFL 3

Protocol deviations, which led to exclusion from the Per-Protocol population, are summarized in the following table:

Table 28 - Subjects Excluded From Per-Protocol Population

Major Protocol Violation	Adapalene Gel, 0.3% (N=258)		Adapalene Gel, 0.1% (N=261)		Vehicle Gel (N=134)		Total (N=653)	
	n	(%)	(n)	(%)	n	(%)	n	(%)
Administrative Error	9	(3.5)	7	(2.7)	5	(3.7)	21	(3.2)
Entrance Criteria Violation	10	(3.9)	7	(2.7)	5	(3.7)	22	(3.4)
Insufficient Treatment	19	(7.4)	10	(3.8)	6	(4.5)	35	(5.4)
No Post-baseline Data	5	(1.9)	4	(1.5)	1	(0.7)	10	(1.5)
Non-Compliance	5	(1.9)	5	(1.9)	2	(1.5)	12	(1.8)
Prohibited Medication	3	(1.2)	5	(1.9)	2	(1.5)	10	(1.5)
Total	51	(19.8)	38	(14.6)	21	(15.7)	110	(16.8)

Source: Section 14, Table SUB 3.1

Reviewer comment: There were relatively more subjects excluded from the PP group in Adapalene 0.3% arm compared to the adapalene gel, 0.1% and vehicle; and the majority was for insufficient treatment.

A summary of randomization deviations is presented in the following table:

Table 29 - Summary of Randomization Deviations

Investigator No/Name	Deviation in Randomization
438/Whiting	Out of Sequence; Subject number 1374, 1375, 1376 assigned before 1373.
2094/Loven	Out of sequence; Subject number 1564, 1565, 1566 assigned before Subject number 1561, 1562, 1563.
2095/Kempers	Out of sequence; Subject number 1423, 1424 assigned before 1422.
2103/Fowler	Out of sequence; Subject number 1601 to 1605 assigned before Subject number 1596 to 1600.
2137/Farber	Number skipped; Subject number 1551, 1554. Medication kit was dispensed to a screening failure at screening visit by mistake (Subject number 1551). Randomization number was assigned to a screening failure by mistake (subject 1554).
2180/Lynde	Out of sequence; Subject number 1872, 1873, 1874 assigned before 1871.
2195/Barber	Number skipped; Subject number 1496, 1497, 1499 not assigned.
	Out of sequence for subject number 1491 to 1495, 1498, 1500, 1716 to 1720, 1821 to 1825

Source: Appendix 16.1.7

The following table summarizes the numbers of patients and their duration of treatment:

Table 30 : Summary of Treatment Duration: ITT population

Number of days	Adapalene Gel 0.3%	Adapalene Gel 0.1%	Vehicle
1-7	7 (2.7%)	5 (1.9%)	0 (0.0%)
8-14	5 (1.9%)	4 (1.5%)	3 (2.2%)
15-21	1 (0.4%)	4 (1.5%)	2 (1.5%)
22-28	5 (1.9%)	1 (0.4%)	1 (0.8%)
29-35	6 (2.3%)	2 (0.8%)	1 (0.8%)
36-42	2 (0.8%)	0 (0.0%)	0 (0.0%)
43-49	2 (0.8%)	0 (0.0%)	0 (0.0%)
50-56	2 (0.8%)	2 (0.8%)	5 (3.7%)
57-63	1(0.0%)	3 (1.2%)	0 (0.8%)
64-70	0(0.0%)	3(1.2%)	0(0.0%)
71-76	1(0.4%)	7 (2.7%)	3 (2.2%)
77-84	145(56.2%)	149(57.1%)	74 (55.2%)
85-91	64(24.8%)	69(26.4%)	34 (25.4%)
>91	17(6.6%)	12(4.6%)	10(7.5%)

Source: Biostatistics Table 4

Reviewer comment: Based on the above table, 535/653(82%) of the patients received treatment in the 77-84 days window of treatment duration. Among these patients, 209/535(39.0%) were in the Adapalene 0.3% arm, 218/535(41.0%) in the Adapalene 0.1% arm, and 108/535(20.0%) in the vehicle arm. The protocol specified treatment for 12 weeks (plus or minus 5-7 days to assist with subject compliance). The proportion of subjects within the 77-84 days window is similar across the three treatment arms.

There were a total of 39 subjects treated beyond 91 days and these were protocol violators: 17(6.6%) in the Adapalene 0.3% arm, 12(4.6%) in the Adaplene 0.1% arm, and 10(7.5%) in the vehicle arm.

Of the 653 subjects in the ITT population, 624 had baseline lesion counts that met the inclusion criteria, 538 subjects had Week 8 data collected between Day 49 and Day 6,3 and 520 subjects had Week 12 data collected between Day 77 and Day 91. There were 26 subjects whose lesion counts were outside the pre-specified inclusion criteria (<20 and >50 for Inflammatory, <20 and >100 for non-inflammatory) and these should have been excluded from analysis but were not. Sensitivity analyses were performed after excluding these cases to assess their impact on the efficacy results, as shown in Table 10.1.r

EFFICACY EVALUATION

The overall efficacy was very limited. The percent of patients reaching success for the IGA never reached 25% after 12 weeks of treatment. The percent reduction of lesions never reached 45% for any lesion count.

Statistical analyses of success (IGA) rates and the three percent lesion reductions (total, inflammatory, and non-inflammatory) was made using the generalized estimating equation (GEE) methodology on data collected at multiple timepoints (Week 8 and Week 12) in the ITT population with LOCF. The Sponsor identified an outlier (subject #1696) whose data impacted the normality assumption in the primary GEE analyses and influenced the primary efficacy results. For this reason, GEE analyses results based on the rank data were also considered in assessing the efficacy of Adapalene 0.3%, in addition to ITT analyses (LOCF method) and other sensitivity analyses.

In the ITT population using LOCF, Adapalene 0.3% failed to demonstrate superiority over Adapalene 0.1% in all three lesion counts (based on percent change from baseline and rank analysis). However, in both the sensitivity analyses using the completer's mean percent change and success rate for imputation at week 8 and week 12, Adapalene 0.3% demonstrated superiority over Adapalene 0.1% only based on the rank data, as shown on the next table:

Table 31 - ITT Population (LOCF): Repeated Measures Analysis (GEE) of Week 8 and Week 12

	Mean Difference Estimates (week 8,12)*			P-Values		
	0.3% vs. 0.1%	0.3% vs. Veh	0.1% vs. Veh	0.3% vs. 0.1%	0.3% vs. Veh	0.1% vs. Veh
Total						
Absolute change	-1.24	-8.26	-7.03	0.480	<0.001	<0.001
% change	-2.55	-10.08	-7.54	0.326	0.001	0.010
Rank	-23.33	-63.34	-39.82	0.072	<0.001	0.006
Inflammatory						
Absolute change	-0.78	-2.96	-2.18	0.301	0.003	0.030
% change	-3.42	-9.62	-6.20	0.164	0.003	0.050
Rank	-23.61	-47.59	-23.98	0.064	0.002	0.110
Non-Inflammatory						
Absolute change	-0.50	-5.37	-4.88	0.717	<0.001	<0.001
% change	-2.04	-11.47	-9.44	0.560	0.007	0.010
Rank	-20.24	-60.36	-40.12	0.120	<0.001	0.006
IGA Success	.61	2.03	1.26	0.028	0.010	0.420

(results as reported by the Biostatistics Reviewer)

The Cochran-Mantel-Haenszel (CMH) test at single timepoints was performed as a secondary analysis to validate the results.
Reviewer comment: Efficacy analysis for the ITT group, as pre-specified in the protocol, demonstrates superiority of the 0.3% formulation over the 0.1% formulation only for the IGA.

The following table summarizes the efficacy results for the Per-Protocol group:

Table 32 - PP Population: GEE Analysis using multiple time points (Weeks 8 and 12)

	0.3% vs. 0.1%			, 0.3% vs.Vehicle		
Endpoint	**Estimates**	**95% CI**	**P-value**	**Estimates**	**95% CI**	**P-value**
IGA	1.72	(1.09, 2.72)	0.022	2.53	(1.38, 4.64)	0.001
Mean difference: % Changes in Total Lesion Counts	-3.54	(-9.27, 2.18)	0.226	-10.31	(-17.04, -3.58)	0.003
Mean difference: % Changes in Inflammatory Lesion Counts	-4.51	(-9.36, 0.34)	0.070	-9.89	(-16.35, -3.43)	0.003
Mean difference: % Changes in Non-inflammatory Lesion Counts	-2.45	(-10.58, 5.69)	0.556	-10.58	(-20.04, -1.11)	0.031

Reviewer comment: In the more stringent Per-Protocol population the 0.3% formulation demonstrated superiority over the 0.1% formulation only for the IGA, a result consistent with that for the ITT group.

The Sponsor has conducted other analysis where the effect of removing several patients from analyses was studied. The exclusions were:
- An outlier (subject #1696) with extreme values in percent change from baseline in non-inflammatory lesions: 325% at Week 8 and 490% at Week 12. Several FDA sensitivity analyses were performed to examine the influence of the outlier, which was found to only slightly affect the GEE primary analysis. on the leverage suggesting that this observation did impact the model parameters.
Reviewer comment: Based on evaluating other subjects enrolled by the investigator (#2179) who enrolled the" outlier", there was nothing unusual noticed in his assessment which would classify it as an outlier. Subject #1696 was evaluated like any other subject in the data with the exception that the baseline non-inflammatory counts were low, inflating the percent reduction from baseline. The exclusion of this subject from analysis does not appear justified since rank analysis was expected to counter the effect of this patient on the efficacy results.

- Forty five subjects with missing values at week 8 and week 12. The sponsor argues that based on the protocol, these subjects were assumed missing completely at random. Based on the end of phase 2 meeting minutes dated December 3, 2001, the sponsor had agreed to the definition of the IIT population as all subjects randomized and dispensed study medication, LOCF.
Reviewer comment: The removal of these 45 patients from analysis does not appear to be justified, based on the pre-specified analysis plan.

- The sponsor reported that one site (n=19 subjects) belonged to Dr. [redacted] used the draft Investigators Global Assessment (IGA) score prior to finalization, instead of the final IGA score.

Reviewer comment: Analysis performed by the Agency indicates that excluding subjects from this center from efficacy analysis for IGA does not appear to alter the final efficacy results.

An analysis of efficacy was made at single time points.

At week 8, adapalene gel, 0.3%, demonstrated superiority to adapalene gel, 0.1% (p=0.04) only for the IGA, but failed to show superiority over the vehicle (p=0.29). The cure rates for adapalene gel, 0.1%, were lower than for the vehicle. adapalene gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene 0.1% for all three lesion counts, and was superior over vehicle only for non-inflammatory lesion counts, as shown in the following table:

Table 33 - ITT (LOCF): Univariate Analysis of Percent change in Total, Inflammatory, Non- Inflammatory and IGA Success rates for Week 8

	P-Values		
	0.3% vs. 0.1%	**0.3% vs. Vehicle**	**0.1% vs. Vehicle**
Total	0.320	0.070	0.290
Inflammatory	0.240	0.630	0.700
Non-Inflammatory	0.570	0.030	0.090
IGA Success	0.037	0.290	0.500

At week 12, the IGA success rate for adapalene gel, 0.3% was not significantly different compared to adapalene gel 0.1% (p=0.07). Adapalene gel 0.3% demonstrated superiority over Adapalene 0.1%, for total and non-inflammatory lesions, as shown in the following table:

Table 34 - ITT (LOCF): Univariate analysis of percent change in Total, Inflammatory, Non-Inflammatory and IGA Success rates at Week 12

	P-Values		
	0.3% vs. 0.1%	**0.3% vs. Vehicle**	**0.1% vs. Vehicle**
Total Lesions	0.02	<0.001	0.006
Inflammatory	0.38	<0.001	0.007
Non-inflammatory	0.01	<0.001	0.005
IGA Success	0.16	0.002	0.100

Reviewer comment: The additional analysis at week-8 and at week-12 confirmed the failure to demonstrate superiority of the 0.3% formulation over the 0.1% formulation.
Depending on the type of analysis performed, the Sponsor was able to demonstrate significance for one or another endpoint but the results were inconsistent in as much as the endpoint reaching significance varied depending on the type of analysis performed. It is the opinion of this reviewer that such inconsistent results do not significantly contribute to the demonstration of superiority of the 0.3% formulation over the 0.1% formulation. The support of such analysis as performed by the Sponsor is even less robust when considering that in a number of these analysis, the 0.1% formulation would not demonstrate superiority over vehicle.

The following table summarizes the analysis excluding patients with lesion counts outside the inclusion criteria and those with treatment longer than 91 days:

Table 35: Observed Data and ITT(LOCF): Repeated Measures Analysis (GEE) of Week 8 and Week 12 (Subjects with baseline inflammatory (20 50 counts), non inflammatory (20 100 counts), efficacy assessment of week 8 (49 63 days), week 12 (77 91 days)

GEE Analyses of multiple time points	Mean Difference Estimates		P-Values	
	0.3% vs. 0.1%	0.3% vs. Vehicle	0.3% vs. 0.1%	0.3% vs. Vehicle
Total				
% change	-3.56	-12.37	0.297	0.004
Rank	-27.29	-63.75	0.025	<0.001
LOCF	-1.87	-10.54	0.476	0.002
LOCF-Rank	-19.00	-61.12	0.134	<0.001
Inflammatory				
% change	-5.57	-13.62	0.050	0.002
Rank	-28.44	-47.56	0.013	0.002
LOCF	-2.88	-10.25	0.246	0.003
LOCF-Rank	-20.38	-48.09	0.100	0.002
Non-Inflammatory				
% change	-1.22	-11.61	0.800	0.035
Rank	-19.27	-62.05	0.121	<0.001
LOCF	-1.24	-11.87	0.726	0.011
LOCF-Rank	-16.41	-57.61	0.192	<0.001
IGA Success *	1.62	2.52	0.051	0.004
LOCF	1.63	1.87	0.026	0.022

Sponsor's analysis. IGA(success) of the observed data; estimate is the odds ratio Biostatistics Table 11.

Based on the GEE analyses of the multiple time points (weeks 8 and 12), Adapalene 0.3% failed to demonstrate superiority over Adapalene 0.1% for Total lesion counts and for non-inflammatory counts. IGA success rate and the percent change in inflammatory lesion counts achieved only border-line significance. The analyses of the ITT using LOCF and the rank data (LOCF), failed to provide evidence of superiority of Adapalene 0.3% over Adapalene 0.1% in all three lesion counts.

An analysis performed excluding the subjects in Dr. [redacted]'s site is summarized in the following table:

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Table 36: Summary of IGA Success Rate: Observed Data (excluding Dr. [redacted]'s site; n=19 subjects):								
Success	**0.3%**		**0.1%**		**Vehicle**		**P-value 0.3%-0.1%**	**P-value 0.3%-Veh**
Week8	30/222	(13.5%)	19/236	(8.1%)	12/118	(10.2%)	0.042	0.290
Week12	48/220	(21.8%)	39/231	(16.9%)	11/117	(9.4%)	0.157	0.003
ITT	48/250	(19.2%)	40/254	(15.7%)	11/130	(8.5%)	0.307	0.004

Biostatistics Table 6.

Reviewer comment: An analysis based on the exclusion of Dr. [redacted]'s subjects paralleled the results for the Observed subjects. At week 8, Adapalene 0.3% demonstrated superiority to Adapalene 0.1% (p=0.04) for the IGA , but failed to show superiority over the vehicle (p=0.29). However, at week 12, Adapalene 0.3% demonstrated superiority over the vehicle(p=0.003) but not over Adapalene 0.1% (p=0.16.

See the Biostatistics Review for comments on the alternative analyses conducted by the Sponsor.

SAFETY EVALUATION

Extent of Exposure

A summary of treatment duration by treatment group is presented in Table 78545. Mean treatment duration ranged from 77.8 days in the adapalene gel, 0.3% group to 80.0 days in the vehicle group. The majority of subjects received study treatment for 57 to 91 days: 81.8% in the adapalene gel, 0.3% group, 88.5% in the adapalene gel, 0.1% group, and 83.6% in the vehicle group.

The mean total amount of medication used was 70.10 grams in the adapalene gel, 0.3% group, 74.09 grams in the adapalene gel, 0.1% group, and 82.99 grams in the vehicle gel group. The mean daily medication usage was 0.904 grams/day, 0.936 grams/day, and 0.998 grams/day in the adapalene gel, 0.3%, adapalene gel, 0.1%, and vehicle gel groups, respectively.

Local Tolerability

Local tolerability summaries of erythema, scaling, dryness, and stinging/burning over time are presented below.

The following Table summarizes the number of subjects whose erythema worsened from baseline:

Table 37- HIGHEST ERYTHEMA SEVERITY SCORE (WORSE THAN BASELINE)

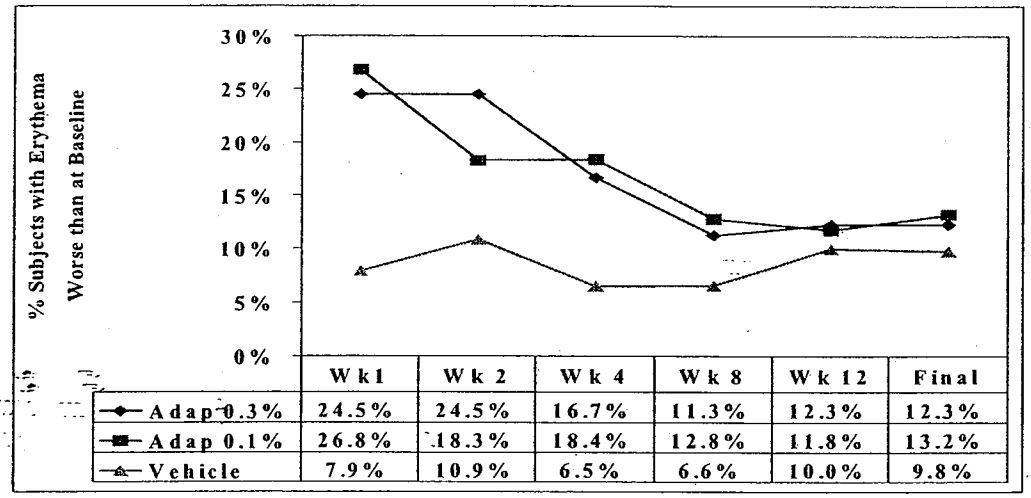
Erythema	0.3% (N=253)		0.1% (N=257)		Vehicle (N=133)	
	n	(%)	(n)	(%)	n	(%)
Mild	66	(26.1)	76	(29.6)	28	(21.1)
Moderate	33	(13.0)	27	(10.5)	6	(4.5)
Severe	1	(0.4)	2	(0.8)	0	(0.0)

Source: Section 14, Table SAF 2.1
Note: Subjects are included if their erythema score during treatment was worse than their baseline erythema score; each of these subjects is included in the category that reflects the highest severity score that was recorded during the post-baseline period.

The majority developed erythema of mild severity. In the 0.3% formulation, there were fewer with mild erythema than for the 0.1% formulation.
Reviewer comment: The protocol did not specify that local tolerability experiences would be reported to express those that worsened from baseline. This manner of reporting is not usual and there is a concern that it may actually lead to underreporting of the total number of events. It seems that, compared to the 0.1% formulation, there are fewer subjects with mild erythema in 0.3% group, but possibly at the expense of having a greater number with the more intense "moderate" erythema.

The time course for erythema is summarized in the following Figure:

Figure 2 : Local Tolerability: Time Course of Erythema Incidence (Worse Than Baseline)



	Wk1	Wk 2	Wk 4	Wk 8	Wk 12	Final
Adap 0.3%	24.5%	24.5%	16.7%	11.3%	12.3%	12.3%
Adap 0.1%	26.8%	18.3%	18.4%	12.8%	11.8%	13.2%
Vehicle	7.9%	10.9%	6.5%	6.6%	10.0%	9.8%

Source: Section 14, Table SAF 2.1

Reviewer comment: The percentage of subjects with erythema worse than at baseline in the two Adapalene treatment groups was highest at Week 1, and decreased over time during treatment. This decrease in erythema over time was not present in the vehicle group. At the final visit, the

precentages of subjects with erythema worse than baseline were comparable across treatment groups.

Local Tolerability – Scaling
The following table summarizes the subjects whose scaling worsened from baseline:

Table 38 - HIGHEST SCALING SEVERITY SCORE (WORSE THAN BASELINE)

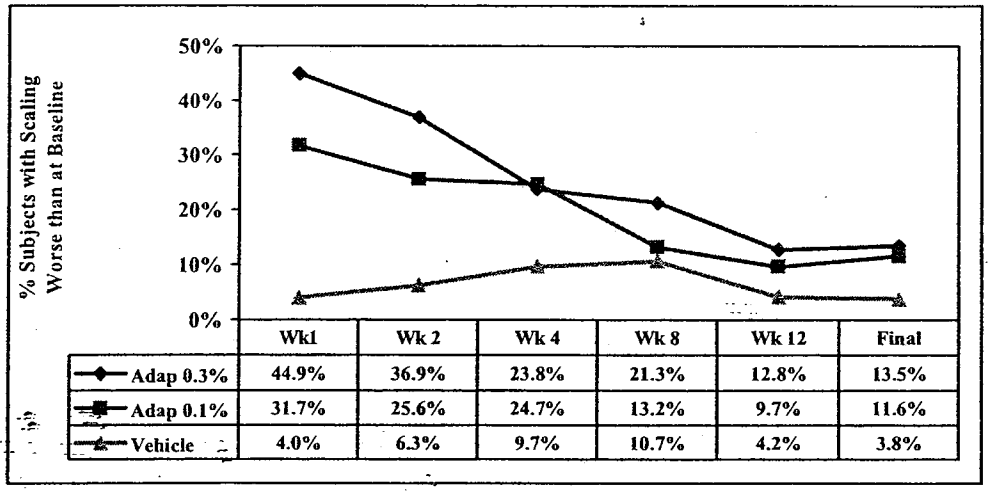
Scaling	0.3% (N=253)		0.1% (N=257)		Vehicle (N=133)	
	n	(%)	(n)	(%)	n	(%)
Mild	110	(43.5)	89	(34.6)	21	(15.8)
Moderate	47	(18.6)	35	(13.6)	6	(4.5)
Severe	3	(1.2)	4	(1.6)	0	(0.0)

Source: Section 14, Table SAF 2.2

Reviewer comment: Subjects in the adapalene gel, 0.3%, developed scaling of mild or moderate severity more often than for the 0.1% formulation.

The time course for scaling is summarized in the following figure:

Figure 3 - Local Tolerability: Time Course of Scaling Incidence (Worse Than Baseline)



	Wk1	Wk 2	Wk 4	Wk 8	Wk 12	Final
Adap 0.3%	44.9%	36.9%	23.8%	21.3%	12.8%	13.5%
Adap 0.1%	31.7%	25.6%	24.7%	13.2%	9.7%	11.6%
Vehicle	4.0%	6.3%	9.7%	10.7%	4.2%	3.8%

Source: Section 14, Table SAF 2.2

Reviewer comment: The percentage of subjects with scaling worse than at baseline was highest at Week 1, and decreased over time. This decrease in scaling over time was not present in the vehicle group.

Local Tolerability – Dryness
The number of subjects who developed dryness is summarized in the following table:

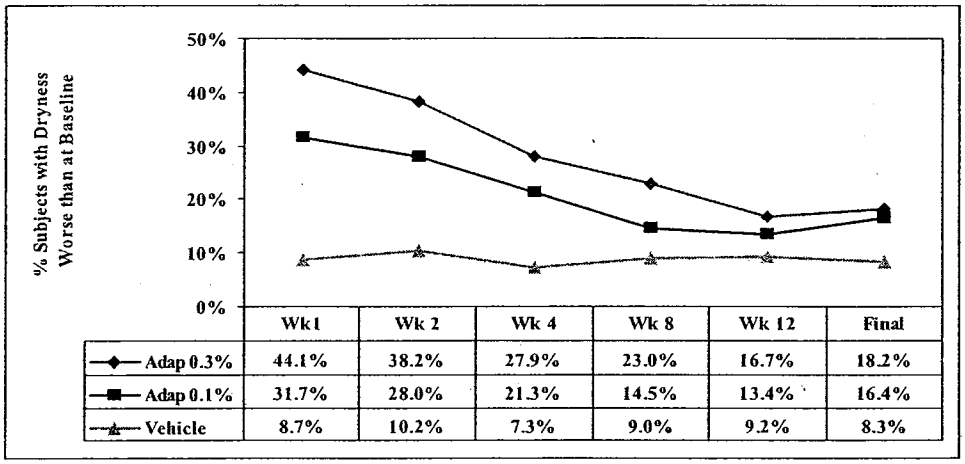
Table 39 - HIGHEST DRYNESS SEVERITY SCORE (WORSE THAN BASELINE)

Dryness	0.3% (N=253)		0.1% (N=257)		Vehicle (N=133)	
	N	(%)	(n)	(%)	n	(%)
Mild	113	(44.7)	94	(36.6)	30	(22.6)
Moderate	43	(17.0)	25	(9.7)	3	(2.3)
Severe	2	(0.8)	7	(2.7)	0	(0.0)
Source: Section 14, Table SAF 2.3						

Reviewer comment: Subjects on the 0.3% formulation were more likely to develop mild and moderate dryness than those in the 0.1% formulation.

The time course for dryness is summarized in the following figure:

Figure 4 - Local Tolerability: Time Course of Dryness Incidence (Worse Than Baseline)



	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Final
Adap 0.3%	44.1%	38.2%	27.9%	23.0%	16.7%	18.2%
Adap 0.1%	31.7%	28.0%	21.3%	14.5%	13.4%	16.4%
Vehicle	8.7%	10.2%	7.3%	9.0%	9.2%	8.3%

Source: Section 14, Table SAF 2.3

Reviewer comment: Greater numbers of subjects developed dryness in the 0.3% formulation and these took longer to normalize.

Local Tolerability – Stinging/Burning

The number of subjects whose stinging/burning worsened from baseline is summarized in the following table:

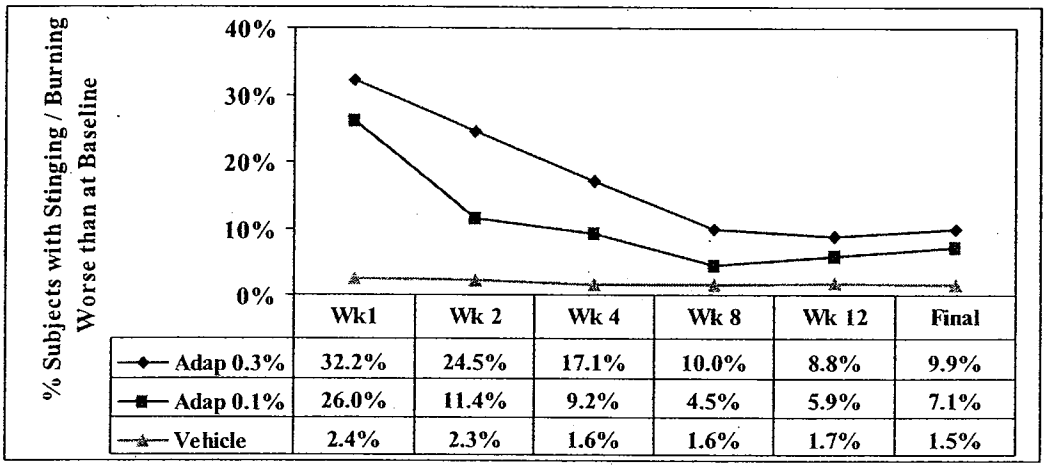
Table 40 - HIGHEST STINGING/BURNING SEVERITY SCORE (WORSE THAN BASELINE)

Stinging/Burning	0.3% (N=253)		0.1% (N=257)		Vehicle (N=133)	
	N	(%)	(n)	(%)	n	(%)
Mild	72	(28.5)	60	(23.3)	7	(5.3)
Moderate	36	(14.2)	15	(5.8)	0	(0.0)
Severe	9	(3.6)	10	(3.9)	0	(0.0)
Source: Section 14, Table SAF 2.4						

Reviewer comment: Greater numbers of subjects on the 0.3% formulation developed mild and moderate stinging/burning in the 0.3% formulation.

The time course for stinging/burning is summarized in the following figure:

Figure 5 - Local Tolerability: Time Course of Stinging/Burning Incidence (Worse Than Baseline)



	Wk1	Wk 2	Wk 4	Wk 8	Wk 12	Final
Adap 0.3%	32.2%	24.5%	17.1%	10.0%	8.8%	9.9%
Adap 0.1%	26.0%	11.4%	9.2%	4.5%	5.9%	7.1%
Vehicle	2.4%	2.3%	1.6%	1.6%	1.7%	1.5%

Source: Section 14, Table SAF 2.4

Reviewer comment: throughout the first 8 weeks the number of subjects with stinging/burning was consistently higher for the 0.3% group.

Adverse events: An Adverse Event Form was to be completed only if the severity of the expected signs and symptoms was such that an interruption of the Subject's participation in the study, at his/her request or the Investigator's, occurred. A summary of the incidence of AEs is presented in the following table:

TABLE 41 - OVERALL SUMMARY OF ADVERSE EVENTS

		0.3% (N=258)	0.1% (N=261)	Vehicle (N=134)
Subjects who had any AE	*n (%)*	104 (40.3)	88 (33.7)	42 (31.3)
Dermatologic	*n (%)*	69 (26.7)	42 (16.1)	12 (9.0)
Non-dermatologic	*n (%)*	51 (19.8)	58 (22.2)	35 (26.1)
Subjects with AE related to study drug	*n (%)*	57 (22.1)	31 (11.9)	6 (4.5)
Dermatologic	*n (%)*	55 (21.3)	31 (11.9)	6 (4.5)
Non-dermatologic	*n (%)*	4 (1.6)	0 (0.0)	0 (0.0)
Subjects with SAE	*n (%)*	1 (0.4)	2 (0.8)	0 (0.0)
Dermatologic	*n (%)*	0 (0.0)	0 (0.0)	0 (0.0)
Non-dermatologic	*n (%)*	1 (0.4)	2 (0.8)	0 (0.0)
Subjects with AE leading to discontinuation	*n (%)*	5 (1.9)	2 (0.8)	1 (0.7)
Dermatologic	*n (%)*	4 (1.6)	2 (0.8)	1 (0.7)
Non-dermatologic	*n (%)*	1 (0.4)	0 (0.0)	0 (0.0)

Source: Section 14.3, Table SAF 4

The majority dermatological AEs were treatment-related and were more frequently in the adapalene gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). Only 4 subjects (all in the adapalene gel, 0.3% group) had non-dermatological AEs that were considered related to study treatment: facial edema, pain, keratoconjunctivitis, and eye pain.

Three subjects had SAEs but none were considered treatment-related to study: spherocytosis, accidental displacement of mediport, and paralytic migraine.

The following table shows the AEs reported in at least 1% of subjects:

TABLE 42 - MOST FREQUENTLY REPORTED (≥1%) ADVERSE EVENTS

		0.3% (N=258)	0.1% (N=261)	Vehicle (N=134)
Total No. of Subjects with Any AE	*n (%)*	104 (40.3)	88 (33.7)	42 (31.3)
Skin and Appendages	*n (%)*	69 (26.7)	42 (16.1)	12 (9.0)
Skin dry	*n (%)*	36 (14.0)	18 (6.9)	2 (1.5)
Discomfort - skin	*n (%)*	15 (5.8)	12 (4.6)	0 (0.0)
Sunburn	*n (%)*	8 (3.1)	8 (3.1)	5 (3.7)
Pruritus	*n (%)*	6 (2.3)	4 (1.5)	0 (0.0)
Desquamation	*n (%)*	5 (1.9)	2 (0.8)	0 (0.0)
Erythema	*n (%)*	3 (1.2)	4 (1.5)	1 (0.7)
Dermatitis – contact	*n (%)*	1 (0.4)	3 (1.1)	0 (0.0)
Body as a Whole	*n (%)*	33 (12.8)	38 (14.6)	24 (17.9)
Flu syndrome	*n (%)*	15 (5.8)	22 (8.4)	10 (7.5)
Headache	*n (%)*	6 (2.3)	7 (2.7)	5 (3.7)
Injury – accidental	*n (%)*	6 (2.3)	7 (2.7)	5 (3.7)
Lab test abnormal	*n (%)*	3 (1.2)	2 (0.8)	0 (0.0)
Infection	*n (%)*	0 (0.0)	0 (0.0)	2 (1.5)
Digestive System	*n (%)*	9 (3.5)	8 (3.1)	3 (2.2)
Nausea	*n (%)*	3 (1.2)	3 (1.1)	0 (0.0)
Respiratory System	*n (%)*	9 (3.5)	13 (5.0)	10 (7.5)
Pharyngitis	*n (%)*	4 (1.6)	4 (1.5)	3 (2.2)
Rhinitis	*n (%)*	2 (0.8)	3 (1.1)	4 (3.0)
Sinusitis	*n (%)*	0 (0.0)	3 (1.1)	3 (2.2)
Special Senses	*n (%)*	3 (1.2)	1 (0.4)	1 (0.7)

Source: Section 14, Table SAF 5

Reviewer comment: An Adverse Event Form was to be completed only if the severity of the expected signs and symptoms was such that an interruption of the Subject's participation in the study, at his/her request or the Investigator's, occurred. It is therefore likely that a number of AEs may not have been reported if the investigator considered the AE did not require treatment cessation. Dermatological AEs were more frequently reported in the adapalene gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). The majority of dermatological AEs were considered related to study drug treatment. Four subjects (all in the adapalene gel, 0.3% group) had non-dermatological AEs that were considered related to study treatment; these events were facial edema, pain, keratoconjunctivitis, and eye pain. There were no notable differences in the overall frequency of AEs between the different demographic groups.

AEs That Led to Discontinuation:

Dermatological AEs that led to discontinuation were reported in 4 (1.6%), 2 (0.8%), and 1 (0.7%) subjects in the adapalene gel, 0.3%, adapalene gel, 0.1%, and vehicle gel groups, respectively. The majority of AEs were transient, and mild or moderate in severity, occurring predominantly in the early weeks of treatment, and generally did not limit further treatment with adapalene gel.

The percentage of subjects with drug-related AEs increased with gel concentration: 22.1%, 11.9%, and 4.5% in the adapalene gel, 0.3%, adapalene gel, 0.1%, and vehicle gel groups, respectively.

Only one AE leading to discontinuation was considered definitely related to study medication (facial burning); this event occurred in subject #1326 in the adapalene gel, 0.3% treatment group.

Clinical Laboratory Evaluation:

There were no mean changes in any laboratory parameter that suggested a systemic effect of study drug. There were no trends in individual laboratory abnormalities that indicated an effect of study drug. Five subjects (3 in the adapalene gel, 0.3% group and 2 in the adapalene gel, 0.1% group) had laboratory abnormalities that were reported as AEs. In the adapalene gel, 0.3% group, 3 subjects (#1092, #1886, and #1656) had elevated creatine kinase (CK) values, and 1 of these subjects (#1656) also had elevated liver enzymes. In the adapalene gel, 0.1% group, 2 subjects had elevated CK values (#1093 and #1681), and 1 of these subjects (#1681) also had a low white blood cell count. All of these events were considered by the Investigator as unlikely to be related or definitely unrelated to study drug. None of the events required treatment.

Reviewer comment. Safety Conclusions: As expected with a topical retinoid, concentration-dependent increases were noted in the incidence of scaling, dryness, pruritus, and stinging/burning. Most of the signs and symptoms of skin irritation were mild or moderate in severity, and tended to occur early and decrease over time, but they tended to be more intense with adapalene gel, 0.3% than with adapalene gel, 0.1%, and tended to take a little longer to normalize. Only one AE leading to discontinuation (facial burning in subject #1326 in the adapalene gel, 0.3% group) was considered definitely related to study medication.

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/s/

Joseph Porres
1/19/05 01:50:17 PM
MEDICAL OFFICER

Markham Luke
1/21/05 04:18:39 PM
MEDICAL OFFICER
See Clinical Team Leader Secondary Review.

Jonathan Wilkin
1/31/05 12:01:16 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-753

NDA: 21-753
Serial Number: 000

Correspondence Date: May 22, 2006
CDER Stamp Date: May 23, 2006
Review Date: November 30, 2006

Sponsor: Galderma Laboratories, LP
14501 North Freeway
Fort Worth, Texas 76177

Drug: Differin (adapalene) Gel 0.3%

Pharmacologic Category: Topical anti-acne synthetic retinoid

Proposed Indication: Acne vulgaris

Dosage Form and Route of Administration: Topical gel

Regulatory Summary:
Differin (adapalene), 0.1%, a synthetic retinoid, is approved as a once daily topical treatment of acne vulgaris in patients 12 years of age and older, as a 0.1% solution (NDA 20-338, since discontinued) and gel (NDA 20-380) since 5/31/1996, and as a 0.1% cream (NDA 20-748) since 5/26/2000. A New Drug Application (NDA) was submitted April 1, 2004 for adapalene gel, 0.3%.

The Division's action on February 1, 2005 was a non-approvable letter listing two deficiencies:

1. The pivotal study failed to demonstrate statistical superiority of the 0.3% adapalene gel over Differin (adapalene) Gel, 0.1%. Therefore, there is insufficient information to support the increased risk of the higher concentration.

2. The higher concentration of adapalene gel, 0.3%, resulted in greater systemic exposure, and consequent teratogenic risk, than with the currently approved Differin Gel, 0.1%.

The sponsor was requested to provide the following information to address the deficiencies:

1. Adequate evidence that the higher concentration of adapalene gel offers benefit over the currently available concentration of adapalene gel when used in the treatment of acne vulgaris (i.e., a comparative clinical study).

2. A risk management program (e.g., adequate labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetic study."

Following teleconference on April 13, 2005, and a guidance meeting on October 12, 2005, concurrence was reached on the first issue regarding statistical superiority, despite reservations from the Biostatistics team about the robustness of the data and the GEE analysis. The Division noted that "the efficacy benefit of the 0.3% product appears to be minimally greater than that of the 0.1%, but with a notable increase in potential teratogenic risk. Approval of such a product is dependent on a demonstration that the benefit outweighs the risk which may not be evident for Differin 0.3%".

The remaining non-approval issue is whether the adapalene 0.3 % product has a potential considerable teratogenic risk [redacted]

Topical adapalene 0.1% products currently have a pregnancy category C labeling status. This category C states that animal reproduction studies have shown an adverse effect, or animal reproduction studies have not been conducted, and the benefits from use of the drug in pregnant women may be acceptable despite its potential risks.

The sponsor, in a letter dated May 11, 2006, requested supervisory oversight from the Office level on the Division's prior conclusion that the 0.3% product [redacted]

The original approval of the 0.1% topical formulations included assessment of systemic exposure using an assay less sensitive than that used for the assessment of the 0.3% formulation (LOQ of 0.35 ng/mL versus LOQ of 0.1 ng/mL, respectively).

The Biopharmaceutics comments from the April 13, 2005 teleconference summarize the pharmacokinetic assessments:

3. When 2g of adapalene gel was applied to acne patients, 0.3% gel resulted in higher systemic exposure than the 0.1% gel (historical data) even when the difference in the sensitivity of the analytical methods used was considered.
4. 2g (that covers 6% body surface area) may not represent the maximal usage conditions, i.e., patients could use more than 2 g in the clinical setting. If a more than 2 g of adapalene gel (0.3%) dose is used, the exposure of adapalene could be higher than what was obtained in the current PK study.
5. If a larger than 2g dose is expected to be used in patients (for patients with >6% BSA), additional PK studies that enroll patients with larger body surface areas may be necessary to link safety to adapalene exposure.

The Biopharm reviewer recommended that:

The Sponsor could conduct a study to compare the systemic exposure of 0.1% and 0.3% gel under the "maximal usage conditions" (i.e., with a dose that would cover as large a body surface area as possible of the diseased skin), using the sensitive analytical method (LOQ ≤ 0.1 ng/mL). The results from this study would not only provide information to guide the safety assessment of 0.3% adapalene gel relative to the approved 0.1% gel product, but also provide valuable dose/exposure-response relationship information for adapalene gel via the topical route.

A direct comparison of the two concentrations was not performed by the sponsor using the more sensitive assay, therefore, the data reported from submitted studies indicate that the 0.1% formulations have no systemic absorption, and the 0.3% formulation has a C_{max} of 0.55 ± 0.47 ng/mL and $AUC_{0\text{-}24hr}$ 8.4 ± 8.5 ng*h/mL.

A separate issue from that 4/13/05 T-con as well as the 10/12/05 meeting was the result from the PK study RD.03.SRE.2690 that showed that female subjects had higher adapalene exposures than male subjects. In this PK study, mean C_{max} and AUC (0-24) for females were ~100% and 150% higher than those for males, respectively. This additional issue for increased teratogenicity does not seem to have been addressed by the sponsor in subsequent communications.

Current Submission: Worldwide Pharmacovigilance Monitoring of Adapalene Formulations—Monitoring for Pregnancy Data

The current submission is a report that summarizes worldwide pregnancy exposures to all adapalene exposures from spontaneous reports and clinical trials. Consultations with the Division of Drug Risk Evaluation in the Office of Surveillance and Epidemiology and the Pediatric and Maternal Health Staff were requested to assess the risk from adapalene and for recommendations for labeling if the 0.3% gel formulation is approved.

The sponsor states that since the launch of adapalene 0.1% in September, 1995, approximately [redacted] patients have been exposed to adapalene, of which 64% were female patients. 156 pregnancies have been reported through March, 2006. Though adapalene 0.3% is not yet marketed in any country, 6 patients reported pregnancies while exposed to the 0.3% formulation. One additional patient received several formulations (0.05%, 0.2%, and 0.3% during an adapalene clinical trial.

Of these 163 pregnancies, 55 were lost to follow up, 11 were ongoing at the time of the report, and 97 (59%) had a known outcome. 68 of the 97 had a "normal" outcome (details were not provided); 10 cases ended with spontaneous abortion, 10 cases with elective abortion, and congenital abnormalities in 6 cases. One case was a premature baby's death (gestational age not reported), one case was a fetal death following placental abruption, and one case ended with an ectopic pregnancy.

Data for the proposed 0.3% adapalene gel product included 7 pregnancies, of which 6 had a known outcome. 4 healthy babies and 2 elective abortions were reported in this group.

Six cases of congenital abnormalities were included in this submission, of which five were previously known to the Agency. All of these cases were associated with the adapalene 0.1% formulations. Three of the five cases were considered potential cases of retinoid-specific, adapalene associated teratogenicity. The sixth new case occurred in a young woman who used both adapalene 0.1% and topical clindamycin during the first two weeks of her pregnancy. This case described multiple organ system anomalies, including Dandy Walker malformation and scimitar syndrome which were not consistent with the overall picture of retinoid abnormalities.

DDRE previously analyzed AERS post-marketing reports of pregnancy exposure with adapalene 0.1% in May, 2004. From the AERS data alone, they concluded that a compelling safety signal for retinoid specific birth defects was not identified.

In their May 11, 2006 letter to Dr. Julie Beitz, ODE 3 Director, which accompanies the review of adapalene exposed pregnancies outlined above, the sponsor outlines 4 bullet points (*in italics below*) to explain their position that category C pregnancy labeling is more appropriate, but does not provide any other substance or documentation to the deficiency #2 except for detailed information on pregnancies in women exposed to adapalene:

- *The existing database for 0.1 % adapalene does not show any evidence of a qualitatively higher rate of birth defects compared to normal population rates.*

It appears that rates of congenital malformations, miscarriage, and elective abortion are not statistically different from the expected rate in the general population. The rate of congenital malformations, 6.6 %, while not statistically significant, is slightly higher than the expected rate in the general population which ranges from 3 % - 4 %.

Whether the population size is large enough for the entire adapalene population to find an infrequent association is questionable and the seven pregnancies for the higher 0.3 % population is certainly not large enough to draw any conclusions about the lack of teratogenic effect. Additionally, AERS has well acknowledged limitations due to underreporting and lack of clinical detail in its reports.

- *There are no qualitative findings for retinoid-specific patterns of birth defects associated with adapalene use. Importantly, the apparent increase in systemic exposure of adapalene with the 0.3 % compared with the 0.1 % strength is very small and only measurable as a result of the recent development of highly sensitive methods.*

The sponsor states that the congenital malformations reported in 6 cases are not typical for retinoid malformations described in the literature. However, the lack of any association with this small number of reports is not proof of a negative association.