CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-502

MEDICAL REVIEW(S)

ADDENDUM TO CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-502
Priority or Standard	Standard
Submit Date(s)	February 27, 2009
Received Date(s)	March 2, 2009
PDUFA Goal Date	January 2, 2010
Reviewer Name(s)	Amy Woitach, D.O.
Review Completion Date	March 2, 2010
Established Name	Adapalene Lotion, 0.1%
(Proposed) Trade Name	Differin Lotion, 0.1%
Therapeutic Class	Naphthoic acid/ Retinoid
Applicant	Galderma Laboratories LP
Formulation(s)	Topical lotion
Dosing Regimen	Once daily
Indication(s)	Acne vulgaris
Intended Population(s)	12 years and older

Galderma submitted an original NDA on March 2, 2009 for Differin (adapalene) Lotion 0.1% for the treatment of acne vulgaris. The clinical review was closed on November 12, 2009. Inspections of manufacturing facilities were pending at the time of the close of the review. Labeling negotiations were also ongoing.

Inspections of Manufacturing Facilities:
On December 18, 2009 the Office of Compliance issued an overall recommendation of "*withhold*" based on the inspection of the (b) (4) back-up facility. Inspectors determined the facility was not ready for inspection. The sponsor was notified of the recommendation to withhold the approval by teleconference on December 22, 2009. On December 23, 2009 the sponsor submitted an amendment to remove the facility from the application. The amendment is considered a major amendment and extends the review clock by 3 months with a new PDUFA date of April 2, 2009. Based on the amendment, the Office of Compliance has issued a recommendation of "*acceptable*" on January 14, 2010.

Labeling Negotiations:
A labeling amendment was submitted on October 22, 2009, to provide the Agency with colored mock ups of the container/closure systems. In addition to draft carton and container labels for 2 ounce and 4 ounce trade sizes with pumps, (b) (4) . The sponsor confirmed that clinical trials were conducted with the pump configuration. A teleconference between the Agency and the sponsor was held on November 23, 2009 in which the FDA stated that:

> (b) (4) *The Agency will continue its review and action based only on the product described for use with the pump, because this was the drug product design used in the pivotal Phase 3 studies.* (b) (4)

(b) (4)

The Agency initiated a second teleconference in which the sponsor confirmed that clinical trials were conducted with the pump inserted into the bottle prior to dispensing to subjects. (b) (4) The Agency requested that the sponsor submit color mock ups of carton and container labels and provide instructions to the pharmacist; Galderma submitted this information in amendment on December 1, 2009.

DMEPA reviewer Lori Cantin provided draft comments to the Division stating that labeling is not likely to prevent the dispensing of the (b) (4) configuration.

Reviewer comment: This reviewer recommends approving the assembled configuration, with the pump inserted into the bottle, so that the configuration and dosing is consistent with that used in the phase 3 trials. (b) (4)

The Agency initiated a teleconference on January 28, 2010 to inform the applicant that the (b) (4)

With the Office of Compliance issuing an overall recommendation of "*acceptable"* and the resolution of labeling issues the CMC reviewer is recommending approval of this NDA.

Reviewer comment: This reviewer concurs and recommends approval of the NDA.

Labeling negotiations are complete. The revised carton and container labeling was deemed acceptable. The agreed upon label is appended to this review.

10 Page of Draft Labeling as been withheld in full after this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY S WOITACH
03/03/2010

DAVID L KETTL
03/03/2010
Concur with approval recommendation as CMC issues have been resolved.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-502
Priority or Standard	Standard
Submit Date(s)	February 27, 2009
Received Date(s)	March 2, 2009
PDUFA Goal Date	January 2, 2010
Reviewer Name(s)	Amy Woitach, D.O.
Review Completion Date	November 10, 2009
Established Name	Adapalene Lotion, 0.1%
(Proposed) Trade Name	Differin Lotion, 0.1%
Therapeutic Class	Naphthoic acid/ Retinoid
Applicant	Galderma Laboratories LP
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Intended Population(s)	12 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

An approval recommendation is being made for the use of Differin Lotion, 0.1% indicated for the topical treatment of acne vulgaris in patients 12 years and older. An outstanding issue for approvability at the date of this review is a pending recommendation of acceptable from the Office of Compliance regarding facility inspection.

1.2 Risk Benefit Assessment

The active ingredient, adapalene has been previously approved in gel, cream, and solution formulations for marketing in the United States. For this new formulation, the applicant conducted two well-controlled pivotal trials in support of efficacy; the studies were of appropriate design and demonstrated adequate evidence of effectiveness. A total of 1382 subjects have been exposed to Differin Lotion in this development program. The designs of the pivotal studies were generally adequate to assess safety. Topical safety was adequately studied in the development program and included an assessment for local tolerability and dermal safety studies to evaluate contact sensitization and irritation. Safety for phototoxicity and photoallergenicity relied on data from previous studies conducted for other Differin products with the same precautionary labeling proposed for Differin Lotion. No other risk management is recommended by this reviewer other than the revised information in product labeling.

1.3 Recommendations for Postmarket Risk Management Activities

None recommended. A REMS is not necessary for this application.

1.4 Recommendations for Postmarket Studies/Clinical Trials

The level of safety for this product appears comparable to other marketed Differin products approved for acne vulgaris in patients 12 years and older. However, information regarding systemic exposure in 12-17 year olds is not known for any of the adapalene-containing products. Although the majority of the samples in adult PK (pharmacokinetics) studies for adapalene products were below the limit of quantitation, and it is unlikely that the adolescent population will be different from the adult population regarding absorption, the PK data should mirror the population for which this product is approved. Therefore, this reviewer recommends a post-marketing commitment to evaluate systemic exposure in the 12-17 year old population.

The protocol for such a study should be submitted by June 2010
The protocol should be initiated by November 2010
The study results should be submitted to the FDA by June 2011

2 Introduction and Regulatory Background

2.1 Product Information

Adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid) is a naphthoic acid derivative with retinoid-like and anti-inflammatory properties. It is a receptor-selective retinoid analogue binding preferentially to retinoic acid receptor beta (RAR-β), and retinoic acid receptor gamma (RAR-γ), the latter predominantly expressed in the epidermis. Topical adapalene is purported to normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation.

2.2 Tables of Currently Available Treatments for Proposed Indications

There currently are multiple prescription and over-the-counter topical and systemic drug products available for the treatment of acne. Often several of these products are used in combination, depending on the severity, type and extent of acne, the availability of treatments, and the prescribing physician's preference.

Table 1: Available Drug Treatments for Acne Vulgaris

Treatment Class	Drug Products
Topical	
Benzoyl peroxide	Various products
Salicylic acid	Various products
Azelaic acid	20% Cream, 15% gel
Sulfa products	Sulfacetamide, Sulfacetamide/Sulfur
Antibiotics	Clindamycin, Erythromycin
Retinoids	Adapalene, Tazarotene, Tretinoin
Systemic	
Antibiotics	Erythromycin, Doxycycline, Tetracycline, Minocycline
Retinoids	Isotretinoin
Oral Contraceptives	Various products

2.3 Availability of Proposed Active Ingredient in the United States

Adapalene is approved for the topical treatment of acne vulgaris in patients 12 years of age and older and has been marketed by Galderma as:

0.1% solution (NDA 20-338), approved 5/31/1996, now discontinued
0.1% gel (NDA 20-380), approved 5/31/1996

0.1% cream (NDA 20-748) approved 5/26/2000
0.3% gel (NDA 21-753), approved 6/19/2007
Adapalene 0.1%/Benzoyl Peroxide 2.5 % (Epiduo) Gel (NDA 22-320), approved 12/8/2008

This application is for a new dosage form, 0.1% lotion, and the proposed trade name is Differin Lotion 0.1%.

2.4 Important Safety Issues With Consideration to Related Drugs

Adapalene, though structurally distinct from retinoic acid is considered a "retinoid" since it acts at retinoic acid receptors. Retinoids are irritants and known teratogens. Use of these products may also make for heightened sun sensitivity because topical retinoids may decrease the number of layers in the stratum corneum.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program was conducted under IND 76,057. The applicant met with the Agency for a pre-IND meeting (3/2/07) and an End of Phase 2 meeting (8/7/07). A scheduled pre-NDA was cancelled by the sponsor. The drug development scheme submitted in this application largely agrees with the Agency's advice that was conveyed to the applicant at prior meetings. There were no major unresolved disagreements regarding endpoints, number of trials or protocol design.

Pre-IND meeting March 2, 2007

1. The Agency concurred that the lesion counts (non-inflammatory, inflammatory, and total counts) and the Investigator's Global Assessment are the primary efficacy endpoints to evaluate acne.
The Agency recommended the use of absolute changes in lesion counts as the preferred the primary analysis to use with percent changes for lesion counts submitted as a secondary efficacy variable.

For the Investigator's Global Evaluation, the Agency agreed with a two point reduction at week 12 as specified *a priori.* The Agency also recommended that the IGA be on a 5-point scale, with the 'severe'category from the proposed scale condensed, i.e. IGA score of 4 = severe.

Reviewer comment: The applicant adequately incorporated the Agency's recommendations in the design of the phase 3 protocols.

2. The sponsor was requesting a waiver for long term studies. The Agency made no agreement and requested data from the pharmacokinetic exposure and shorter term efficacy studies for review so that a determination of the need for long term studies can be made. The sponsor was

informed that they must be established that the proposed lotion product in similar enough to existing adapalene products to rely on established safety information.

Reviewer comment: The sponsor made the same request at the EOP2 meeting and no agreement was made prior to submission of this application. The PK data was submitted as part of this application, has been reviewed by Biopharmacology (4.4.3 Pharmacokinetics) and demonstrates low systemic absorption. Cross-study comparisons were made with other Differin Gel, 0.3% and are supportive of the sponsor's conclusion that Differin Lotion demonstrates low systemic exposure. Other adapalene formulations have conducted long term studies. Epiduo studied 452 subjects (299 of those were 12-17 years of age) and Differin gel, 0.3 % studied 551 subjects treated for 1 year as part of their respective drug development plans. This reviewer recommends that given the existing data for this application and that of other adapalene formulations, no long term studies be required.

3. The sponsor requested a waiver of photoirritation/photoallergy studies based on the negative findings in previous phototoxicity/photoallergenicity studies with various adapalene formulations, and the absence of absorption of visible light and UV light above 290 nm by the vehicle of the Differin Lotion 0.1%. The Agency responded "this may be acceptable as long as labeling similar to currently approved Differin (adapalene) products is agreed to with the Agency".

Reviewer comment: The sponsor has not submitted photoirritation and/or photoallergy studies to this application and requests a waiver for conducting these studies. The applicant has proposed adequate warnings in the precaution and information to the patient sections of the label. See 7.4.5 Special Safety Studies/Clinical Trials. This reviewer recommends waiving these studies and concurs that the labeling is adequate to communicate these risks.

4. The sponsor was asked to clarify the function of PPG-12/SMDI copolymer in the formulation because a skin conditioning agent is not considered to be an excipient by the Agency.

Reviewer comment: Considering a component of the drug product as a skin conditioning agent has the potential to lead to clinical claims. In the application, the sponsor has complied and characterized the function of *PPG-12/SMDI copolymer as a* (b) (4) *agent. However, another excipient's characterization (medium chain triglycerides as an emollient) also raises concerned for potential clinical labeling claims. This was addressed via an information request to the applicant (4.1 Chemistry Manufacturing and Controls). The applicant's response was deemed satisfactory by the CMC review team.*

5. The sponsor was relying on treatment effect result from Differin Gel for sample size justification for the Phase 3 trial for Differin Lotion. Since the treatment effects of adapalene lotion may differ from that of adapalene gel and the efficacy results for adapalene gel was relatively small, the Division recommended the sponsor to conduct a Phase 2 trial to get estimates of the treatment effects and use them to power their Phase 3 trials or two Phase 3 trials for replication of study findings.

Reviewer comment: The sponsor has submitted two phase 3 trials in support of the application. This reviewer concurs with the conclusion of the Biostatistics reviewer that the statistical basis for efficacy has been established.

End of Phase 2 Meeting August 7, 2007

Study design and statistical analysis plans for a single phase 3 protocol were not agreed upon. Various scenarios were discussed at the meeting and the sponsor was to present their study plan in a future protocol with sufficient time for review by the Agency prior to conduct.

> "We support a mutual understanding of endpoints and statistical plan prior to the initiation of clinical trials conducted to demonstrate safety and efficacy. During the meeting it was agreed that the sponsor will submit a more finalized protocol and statistical plan for review and the Agency will review and provide comments."

Reviewer comment: The phase 3 protocols were revised and submitted for review. They were reviewed by Dr. Clara Kim (Biostatistics) and Dr. David Kettl (Clinical), however, not under a special protocol assessment. Both reviewers generally agreed with the revised protocols.

Pre-NDA Meeting February 24, 2009

A Pre-NDA Meeting was scheduled. However, the sponsor elected to cancel the meeting, prior to receipt of Agency draft comments, on 01/19/2009. The reason stated for canceling the meeting was, "The sponsor had successful results from their Phase 3 clinical studies".

2.6 Other Relevant Background Information

The applicant has requested three (3) years of exclusivity from the date of approval of NDA 22-502. Two clinical studies were conducted to demonstrate the safety and effectiveness of Differin 0.1% Lotion in once-daily applications for the treatment of acne vulgaris in patients 12 years and older. The applicant, Galderma Research and Development states that they sponsored all clinical investigations conducted under IND 76,057 and requests listing of 3-year exclusivity in the "Orange Book" from the date of approval for Differin 0.1% Lotion.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No study site investigations by the Division of Scientific Integrity were performed.

[redacted] of site # [redacted] (study [redacted]) in [redacted] was identified as having a conflict of interest as a shareholder of [redacted] the developer of adapalene Lotion. Based upon this finding, a DSI inspection was recommended. However, the Division of Scientific Investigations (DSI) recommended against inspection since the site had been subject to a recent inspection (June 2008) with no issued identified.

A second site recommended for inspection included Dr. Michael Jarratt of site #26 (study 18113) in Austin, TX. This site was recommended as it had a relatively large sample size and demonstrated a relatively large treatment effect. Again DSI recommended against inspection as Dr. Jarratt was currently the subject of inspection for NDA 22-483 (imiquimod 3.75% cream for the treatment of actinic keratosis). The results of that inspection showed deviations from regulations, but DSI determined that the data generated by Dr. Jarratt's site appear acceptable in support of NDA 22-483.

3.2 Compliance with Good Clinical Practices

The studies were conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure was complete. One investigator, [redacted], (site [redacted]) is the [redacted], a division of [redacted], and is a shareholder in [redacted]. [redacted] site enrolled [redacted] subjects in trial [redacted], which was not critical for demonstration of efficacy. This apparent conflict did not seem to affect any conclusions related to safety or efficacy.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Rajiv Agarwal, Chemist, concluded in his review:

> This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. There are two outstanding issues that must be resolved prior to an APPROVAL recommendation from CMC.
>
> - The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is pending. Until the Office of Compliance issues an ACCEPTABLE recommendation, this NDA is not recommended for APPROVAL from a CMC standpoint.

- Required information is provided on the carton and container closure labels. However, the information is not in the recommended format and must be presented as recommended.

Once the labeling issues are resolved and the Office of Compliance issues an ACCEPTABLE recommendation, the NDA would be recommended for APPROVAL from a CMC standpoint.

Reviewer comment: Carton and labeling changes were received on October 28, 2009 and deemed acceptable. Facility inspection final reports are expected 11/30/09, after the closure of this review.

It was identified during the review that the applicant had characterized medium chain triglycerides as an emollient. An information request was sent to the sponsor stating:

Clarify the description and function of the medium chain triglycerides in the formulation. If claims for (b) (4) are being made, you will need to adequately support such a claim with clinical data. Alternatively, a different description/function based on physicochemical properties of this excipient should be amended in the application with justification.

Reviewer comment: The applicant responded by characterizing the excipient as an (b) (4) which is acceptable to the Agency.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

As the active substance, adapalene, is well characterized pharmacologically, no specific nonclinical pharmacology, carcinogenicity, mutagenicity or impairment of fertility studies were performed with the to-be-marketed product. The applicant relied on previous studies conducted for the development of the other adapalene formulations.

Differin Lotion, 0.1% was evaluated in repeat-dose toxicity studies and two local tolerance studies. In these studies, systemic toxicity was not observed and moderate irritation was observed. The pharmacology/ toxicology reviewer, Dr. Kumar Daivender Mainigi, concludes the non-clinical safety of Differin (adapalene) Lotion 0.1% is well established and recommends approval with labeling modifications as negotiated with the sponsor.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

According to the proposed label, adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

4.4.2 Pharmacodynamics

Pharmacodynamics is unknown. No additional studies were requested for this application.

4.4.3 Pharmacokinetics

A 30-day clinical PK study (18108) was conducted in 14 patients with severe acne who were treated with Differin Lotion, 0.1%, 2 g Lotion/day to 1000 cm² of acne involving the face, chest and upper back. The results showed that all plasma concentrations from 12 of the 14 subjects studied were less than 0.1 ng/mL (the limit of quantification), and all plasma concentrations from the other two subjects were less than 0.131 ng/mL. See Dr. Seongeun Julia Cho's Clinical Pharmacology review of the study.

The applicant provided a cross-study comparison of plasma exposure of adapalene lotion 0.1 % with the previously reported adapalene gel, 0.3% as support for requesting waivers for conducting long-term safety and QT/QTc studies.

Dr. Cho concluded: *This PK comparison provides supportive evidence for the safety of the currently proposed formulation.*

Again, while recognizing that a cross-study analysis comparing two formulations (Lotion vs. Gel) or dose strengths (0.1 % vs. 0.3 %) does not provide an absolute determination of PK properties of the proposed product, it is this reviewer's opinion that the information provided in this NDA supports the applicant's conclusion that the systemic exposure following adapalene lotion 0.1 % is low. Therefore, waiver requests for long-term safety and QT/QTc studies seem to be reasonable from the clinical pharmacology standpoint.

Reviewer comment: This reviewer concurs that a QT/QTc waiver seems reasonable based on low systemic exposure and no post-marketing or literature reports of arrhythmias or EKG changes with the use of other adapalene formulations.

The information submitted for the PK trial conducted for Differin lotion, as well as the previously conducted referenced studies for other adapalene formulations, which are approved for ages 12 and older, only included subjects as young as 18 years of age. No pharmacokinetic data is available for any adapalene product for adolescents. Although this information is important for the safety of the drug, it is unlikely to be different from that of adults and the other

adapalene formulations have been used safely in adolescents. Therefore, lack of PK data in 12-17 year olds is not an approval issue, but should be evaluated as a post-marketing commitment.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Clinical Trials

Study No./Description	Treatment Dose/Duration	No. Subjects/ Patient Population
RD.06.SPR.18108 A pharmacokinetic study to determine the systemic exposure to Adapalene during dermal application of Adapalene Lotion 0.1% for 30 days in subjects with acne vulgaris	Adapalene Lotion, 0.1%; 2 g once daily/30 days	14 acne vulgaris subjects (7 males and 7 females) 18-35 years old
RD 06. SPR 18110 A Single Center Evaluation of the Cumulative Irritation of Adapalene Lotion, 0.1% and Adapalene Vehicle Lotion Following Repeated Topical Application to Healthy Subjects	Adapalene Lotion, 0.1%, White Petrolatum, Adapalene Vehicle Lotion, and 0.2% SLS; 0.2 mL, 0.2 g for 5 days/wk for 15 applications over 21 days	50 healthy M&F subjects aged 18 to 65 years, of which 44 completed the study.
RD 06. SPR 18111 A Single Center Evaluation of the Contact Sensitization of Adapalene Lotion (0.1%) and Placebo for Adapalene Lotion (0.1%) Following Repeated Topical Applications to Healthy Subjects	Induction phase: White Petrolatum, Placebo for Adapalene Lotion, 0.1% and Adapalene Lotion, 0.1% (0.2 mL, 0.2 g); occlusive patches on left side of back 3 days/wk for 3 consecutive weeks for a total of nine applications. Challenge phase: 7-18 days after last induction application, occlusive patches of the Placebo for Adapalene Lotion, 0.1% and Adapalene Lotion, 0.1% were applied to the right side of backs for ~48 hrs.	203 evaluable healthy M&F subjects, 18-65 years of age
RD.06.SPR.18113 A Multi-center, Randomized, Double-Blind, parallel-group study to demonstrate the Efficacy and Safety of Adapalene Lotion, 0.1% compared with vehicle lotion in subjects with Acne Vulgaris	Application of Adapalene Lotion, 0.1% or Lotion vehicle once daily to face and trunk as applicable for 12 weeks.	1075 M&F subjects 12-50 years old with acne vulgaris (533 adapalene Lotion, 0.1%; 542 Lotion vehicle)
RD.06.SPR.18114 A Multi-center, Randomized, Double-Blind, parallel-group study to demonstrate the Efficacy and Safety of Adapalene Lotion, 0.1% compared with vehicle lotion in subjects with Acne Vulgaris	Application of Adapalene Lotion, 0.1% or Lotion vehicle once daily to face and trunk as applicable for 12 weeks.	1066 M&F subjects 12-64 years old with acne vulgaris (535 adapalene Lotion, 0.1%; 533 Lotion vehicle)

Trial ID	Design	Dosing/ Duration	Severity	Number of Sites	Number of Subjects Enrolled	Subject Age	Primary Endpoint/ Objective
113	Randomized, double-blind, vehicle controlled	Once daily for 12 weeks	Subjects had, excluding the nose, ≥20, ≤50, papules and pustules on the face and ≥30, ≤100, non-inflammatory on the face. Subjects also had an IGA of 3 (moderate) or 4 (severe).	39	1075 533 adapalene 542 vehicle	12-50 years old	Two co-primary efficacy endpoints: Two-point reduction from baseline to week 12 in IGA score and the absolute change from baseline to week 12 in inflammatory, non-inflammatory, and total lesion counts (demonstrating a reduction of 2 of the 3 lesion counts).
114	Randomized, double-blind, vehicle controlled	Once daily for 12 weeks	Subjects had, excluding the nose, ≥20, ≤50, papules and pustules on the face and ≥30, ≤100, non-inflammatory on the face. Subjects also had an IGA of 3 (moderate) or 4 (severe).	36	1066 535 adapalene 533 vehicle	12-64 years old	Two co-primary efficacy endpoints: Two-point reduction from baseline to week 12 in IGA score and the absolute change from baseline to week 12 in inflammatory, non-inflammatory, and total lesion counts (demonstrating a reduction of 2 of the 3 lesion counts).
108	PK study	2 g once daily/30 days	Subjects had minimum of 20 inflammatory lesions on the face (excluding the nose) and 30 non-inflammatory lesions on the face (excluding the nose). Subjects also had an IGA of 4 (severe).	1	14	18-35 years old	Assess the systemic exposure to adapalene during topical application of adapalene Lotion, 0.1%
110	Dermal irritation	0.2 g for 5 days/wk for 15 applications over 21 days	Healthy subjects	1	50 44 completed	18-65 years old	Dermal safety
111	Dermal sensitization	Induction: 3 days/wk for 3 weeks (total of 9 applications) Challenge: after 7-18d, occlusive patches applied for 48 hrs.	Healthy subjects	1	203	18-65 years old	Dermal safety

5.2 Review Strategy

The five trials listed in the table above were submitted in support of this application. Two phase 3 trials were reviewed for efficacy. The following studies were reviewed with regard to safety:

- Two dermal safety studies in healthy subjects (18110, 18111).
- One pharmacokinetic study in subjects with acne vulgaris (18108).

- Two identically designed phase 3 studies (18113, 18114) which were integrated for safety analysis.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Study: 18113
Title: A Multi-center, Randomized, Double-Blind, Parallel-Group Study to Demonstrate the Efficacy and Safety of adapalene Lotion, 0.1% Compared with Vehicle Lotion in Subjects with Acne Vulgaris

Objective: To demonstrate the superiority in efficacy and assess safety of adapalene lotion, 0.1% versus adapalene vehicle lotion in the treatment of acne vulgaris for up to 12 weeks.
Study Design: A multi-center, randomized, double-blind, parallel group study with 12 weeks of treatment of acne vulgaris. Subjects were evaluated at Screening, Baseline, and Weeks 1, 2, 4, 8 and 12. Physical exam, vital signs, and pregnancy testing for all females were conducted at screening and at week 12 or early termination. The evaluator of a subject should remain the same during the study.
Study Sites: 39 study centers located in the U.S. and Canada.

Country	Site #	Principal Investigator	Site Name/City
Canada	10	Lorne Albrecht, MD	Guildford Dermatology Specialists Surrey, British Columbia
United States	11	Elizabeth Arthur, MD	500 Helendale Road, Suite 100 Rochester, NY
United States	12	Alicia Barba, MD	International Dermatology Research, Inc. Miami, FL
Canada	13	Kirk Barber, MD	Kirk Barber Research Calgary, Alberta
United States	14	Michael Bond, MD	Advanced Dermatology Clermont, FL
United States	15	Alicia Bucko, DO	Academic Dermatology Albuquerque, NM
United States	16	Scott Clark, MD	Longmont Clinic Longmont, CO
United States	17	Raymond Cornelison, MD	OU Health Sciences Center Oklahoma City,
United States	18	Scott Dinehart, MD	Medical Towers Building I Little Rock, AR
United States	19	James Dinulos, MD	Dartmouth-Hitchcock Medical Center Lebanon, NH
United States	20	George Fisher, MD	Unifour Medical Research Associates Hickory, NC
United States	21	Scott Glazer, MD	600 W. Lake Cook Rd., #110 Buffalo Grove, IL
United States	22	Marcia Glenn, MD	Dermatology and Laser Center, Inc Marina Del Rey, CA
United States	23	Robert Haber, MD	Haber Dermatology & Cosmetic Research South Euclid, OH

Country	Site #	Principal Investigator	Site Name/City
United States	24	Iltefat Hamzavi, MD	Hamzavi Dermatology Fort Gratiot, MI
United States	25	Holly Harris, MD	South Bend Clinic South Bend, IN
United States	26	Michael Jarratt, MD	DermResearch, Inc. Austin, TX
Canada	27	Ian Landells, MD	Nexus Clinical Research St. Johns, Newfoundland
United States	28	Mark Lee, MD	Progressive Clinical Research San Antonio, TX
United States	29	Craig Leonardi, MD	Central Dermatology, PC St. Louis, MO
United States	30	Anne Loebl, MD	Augusta Centre for Dermatology and Skin Renewal, LLC August, GA
Canada	32	Charles Lynde, MD	Lynderm Research, Inc. Markham, Ontario
United States	33	Robert Matheson, MD	Oregon Medical Center, PC Portland, OR
United States	34	Serena Mraz, MD	Solano Clinical Research Vallejo, CA
Canada	35	Kim Papp, MD	K. Papp Clinical Research, Inc. Waterloo, Ontario
United States	36	David Pariser, MD	Virginia Clinical Research, Inc. Norfolk, VA
United States	37	Elyse Rafal, MD	Derm Research Center of New York Stony Brook, NY
United States	38	Stacy Smith, MD	Therapeutics Clinical Research San Diego, CA
United States	39	Dow Stough, MD	Burke Pharmaceutical Research Hot Springs, AR
United States	40	James Swinehart, MD	Colorado Medical Research Center Denver, CO
Canada	41	John Toole, MD	Dermadvance Research Winnipeg, Manitoba
United States	42	Stephen Tyring, MD	Center For Clinical Studies Houston, TX 77058
Canada	43	Norman Wasel, MD	Stratica Medical Edmonton, Alberta
United States	44	Hector Wiltz, MD	FXM Research Miami, FL
United States	45	David Wilson, MD	Education and Research Foundation, Lynchburg, VA

Country	Site #	Principal Investigator	Site Name/City
United States	46	Angela Moore, MD	Arlington Center for Dermatology Arlington, TX
Canada	47	Ronald Vender, MD	Dermatrials Research Hamilton, Ontario
United States	48	Patricia Westmoreland, MD	Palmetto Clinical Trial Services, LLL Simpsonville, SC
United States	49	Zoe Draelos, MD	Zoe Draelos, MD High Point, NC

Number of Subjects: 1075 (533 in the adapalene lotion treatment group, 542 in the vehicle group)
Study Period: November 7, 2007 to November 6, 2008
Diagnosis and Main Criteria for Inclusion:
1. Male and female subjects 12 years of age or older.
2. A clinical diagnosis of acne vulgaris with facial involvement.
3. A minimum of 20 but not more than 50 papules and pustules in total on the face (excluding the nose).
4. A minimum of 30 but not more than 100 noninflammatory lesions (open comedones and closed comedones) on the face (excluding the nose).
5. A score of 3 (Moderate) or 4 (Severe) on the Investigator's Global Assessment Scale.
6. All females (including pre-menstrual subjects) with a negative urine pregnancy test (UPT) at Baseline.

Exclusion Criteria:
1. More than one acne nodule on the face.
2. Any acne cyst on the face.
3. Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), or severe acne requiring systemic treatment.
4. Underlying diseases or other dermatologic conditions that require the use of interfering topical or systemic therapy such as, but not limited to, atopic dermatitis, perioral dermatitis or rosacea.
5. Beard or facial hair which might interfere with study assessments.
6. Use of tanning booths or other light devices within 2 weeks prior to or planned used during the study.
7. Use of oral contraceptives solely for control of acne
8. Known sensitivities to the study preparations.
9. Clinically significant abnormal findings or condition (other than acne), which might, in the opinion of the Investigator, interfere with study evaluations or pose a risk to subject safety during the study.
10. Subjects who are pregnant, nursing, or planning a pregnancy.
11. Participation in another investigational drug or device research study within 30 days of Screening visit and during the study.
12. Use of prohibited medications past the wash-out period or planned use during the study. All medications and treatments requiring a washout period are prohibited during the study. Also

prohibited, but not requiring washout periods are alpha hydroxy acid products, medicated shaving creams, astringents, and preparations with alcohol.

Specified washout period(s) up to Baseline for TOPICAL treatments on the face:

1 Week:	Phototherapy devices for acne (e.g., ClearLight™) and adhesive cleansing strips (e.g., Pond®, Biore®)
	Cosmetic procedures (i.e., facials, peeling, comedone extraction)
2 Weeks:	Anti-inflammatory drugs, salicylic acid (e.g., Clearasil®, Clean & Clear®)
	Corticosteroids, antibiotics, antibacterials (including Benzoyl Peroxide containing products [e.g., benzamycin]), retinoids
	Other topical acne treatments (including photodynamic therapy or laser or medicated soaps)

Specified washout period(s) up to Baseline for SYSTEMIC medications:

2 Weeks:	Anti-inflammatory drugs (used for more than two weeks)
4 Weeks:	Oral antibiotics (except plain penicillin)

The following medications must have had the specified length of stable usage and must not have been expected to change during the course of the study:

2 Months:	Inhaled/Nasal steroids
6 Months:	Hormonal contraceptives and therapies. Hormonal contraceptives solely for control of acne are prohibited.

Duration of Treatment: Once daily in the evening for duration of 12 weeks

Criteria for Evaluation:

Two Co-Primary Endpoints were assessed:

1. Success Rate was defined as the percentage of subjects who achieved at least a two-point reduction at Week 12 in the IGA score from baseline, Last Observation Carried Forward (LOCF), Intent to Treat population (ITT).

2. Change in lesion counts:
- Absolute change from baseline to Week 12 (LOCF, ITT) in inflammatory lesion counts;
- Absolute change from baseline to Week 12 (LOCF, ITT) in noninflammatory lesion counts;

- Absolute change from baseline to Week 12 (LOCF, ITT) in total lesion counts

The trial would be claimed positive regarding efficacy of adapalene lotion for the indication of acne vulgaris if (1) Success Rate and (2) at least two out of the three absolute changes in lesion counts were significant versus vehicle, each at the two-sided 0.05 level for the week 12 (LOCF) data. Multiplicity in part (2) was handled by using a stepwise approach to the test sequence: the change in total lesion counts were required to show significance at the 0.05 level to allow making further inferences on the remaining two lesion types. If this was the case, significance at the 0.05 level on one or both of these two lesion types were required to claim success.

Secondary Efficacy Criteria:

- Percent change in Inflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT).
- Percent change in Noninflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT).
- Percent change in Total Lesion Counts from Baseline to Week 12 (LOCF, ITT).

Tertiary Efficacy Criteria:

- Change in IGA (full scale) at Week 12 (LOCF, ITT).
- Subject's Assessment of Acne at Week 12/Early Termination Visit.

Only facial lesions (excluding the nose) were studied for efficacy. Proposed labeling claims for the product will only be based on the primary and secondary criteria and not the tertiary endpoints.

Safety Evaluation: Safety assessments were conducted for all subjects at baseline and each subsequent visit and included:

1. Adverse Events (AEs).
2. Local Tolerability Assessment of Erythema, Scaling, Dryness and Stinging/Burning; each evaluated on a scale ranging from "0"(None) to "3" (Severe).

No laboratory tests were done for these studies. Skin reactions which are possibly related to contact allergy were to be confirmed with challenge patch testing.

Statistical Methods:
The primary efficacy analyses:
Success rates (Dichotomized IGA) were analyzed by the Cochran-Mantel-Haenszel test stratified by analysis center, using general association. A subject was considered a success if IGA is at least 2 grades lower than the Baseline assessment.

Absolute change in inflammatory, non-inflammatory, and total lesion counts at week 12 (LOCF) in the ITT population were analyzed using the two-way analysis of covariance (ANCOVA) with

factors of treatment and analysis center and baseline lesion count as a covariate. The analyses were performed based on the rank transformed data if the normality assumption is not met. The results of both analyses will be presented, however the rank-transformed analyses was considered primary.

Secondary efficacy analyses:
The percent change in inflammatory, non-inflammatory, and total lesion counts at Week 12 (LOCF) were analyzed using the Cochran-Mantel-Haneszel test with row mean difference statistic using RIDIT score, stratified by analysis center.

Subset analyses were conducted for the ITT population for the subgroups defined by Baseline IGA score, gender, age group (<18, 18-64, 65 and above), race (Caucasian and non-Caucasian) and hormonal contraception use.

Protocol Amendments: none

Clinical Study: 18114
Both studies (18113 and 18114) were designed to be identical and were conducted simultaneously at different sites with different investigators and subjects.
Title: A Multi-Center, Randomized, Double-Blind, Parallel Group Study to Demonstrate the Efficacy and Safety of adapalene lotion,
0.1% Compared with vehicle lotion in Subjects with Acne Vulgaris
Objective: To demonstrate the superiority in efficacy and assess safety of adapalene Lotion, 0.1% versus adapalene Vehicle Lotion in the treatment of acne vulgaris for up to 12 weeks.
Study Design: A multi-center, randomized, double-blind, parallel group study with 12 weeks of treatment of acne vulgaris. Subjects will be evaluated at Screening, Baseline, and Weeks 1, 2, 4, 8 and 12. Physical exam, vital signs, and pregnancy testing for all females were conducted at screening and at week 12 or early termination.
Study Sites: 36 study centers located in the U.S. and Canada.

Country	Site #	Principal Investigator	Site Name/City
United States	50	Suzanne Bruce, M.D.	Suzanne Bruce & Associates, PA The Center for Skin Research Houston, TX
Canada	51	Wayne Carey, M.D.	Siena Medical Research Montreal, Quebec
United States	52	Fran Cook-Bolden, M.D.	20 East 66th St. Suite 1A New York, NY
United States	53	Lesly Davidson, M.D.	Palmetto Medical Research Mount Pleasant, SC
United States	54	Lawrence Eichenfield, M.D.	University of California, San Diego San Diego, CA
United States	55	Lester Fahrner, M.D.	Christie Clinic, PC Champaign, IL
United States	56	Joseph Fowler, M.D.	Dermatology Specialists Louisville, KY
United States	57	Paul Gillum, M.D.	Central Sooner Research Norman, OK
United States	58	Michael Gold, M.D.	Tennessee Clinical Research Center Nashville, TN
United States	59	David Greenstein, M.D.	East Coast Clinical Research, Inc. Haverhill, MA
United States	60	Gary Heller, D.O.	Dermatology Research North Pinellas Park, FL
United States	61	David Horowitz, M.D.	Dermatology Research Associates Nashville, TN
United States	62	Terry Jones, M.D.	J&S Studies, Inc. College Station, TX
United States	63	Steven Kempers, M.D.	Minnesota Clinical Study Center Fridley, MN
Canada	64	Rod Kunynetz, M.D.	Ultranova Skincare Barrie, Ontario

Country	Site #	Principal Investigator	Site Name/City
United States	65	Cindy Lamerson, M.D.	650 Sierra Rose Drive, #A Reno, NV
United States	66	John Tu, M.D.	Dermatology Associates of Rochester Rochester, NY
United States	67	Aida Lugo-Somolinos, M.D.	University of North Carolina at Chapel Hill Chapel Hill, NC
United States	68	Michael Maloney, M.D.	Cherry Creek Dermatology Research Inc. Denver, CO
United States	69	Adnan Nasir, M.D.	Wake Research Associates, LLC Raleigh, NC
United States	70	John Proffitt, M.D.	Compliant Clinical Research Olathe, KS
United States	71	Phoebe Rich, M.D.	Northwest Cutaneous Research Specialists Portland, OR
United States	72	Toivo Rist, M.D.	Dermatology Associates Knoxville, TN
Canada	73	Les Rosoph, M.D.	North Bay Dermatology Centre North Bay, Ontario
United States	74	Joel Schlessinger, M.D.	Skin Specialists, PC Omaha, NE
United States	75	Pranav Sheth, M.D.	University Dermatology Consultants Cincinnati, OH
United States	76	James Solomon, M.D.	Advanced Dermatology Ormond Beach, FL
United States	77	Linda Stein Gold, M.D.	Henry Ford Medical Center New Center One, Detroit, MI
United States	78	Daniel Stewart, D.O.	Midwest Cutaneous Research, NE Clinton Township, MI
United States	79	Leonard Swinyer, M.D.	Dermatology Research Center Salt Lake City, UT
Canada	80	Richard Thomas, M.D.	Derm Research @888 Inc. Vancouver, British Columbia
United States	81	William Werschler, M.D.	Premier Clinical Research Spokane, WA
United States	82	Darryl Wong, M.D.	Dermatology Specialists, Inc. Vista, CA
Canada	83	Derek Woolner, M.D.	Dermatology Associates Calgary, Alberta
United States	84	Stephen Schleicher, M.D.	Derm Dx Centers for Dermatology Hazelton, PA
United States	85	George Murakawa, M.D.	Somerset Skin Care Center Troy, MI

Number of Subjects: 1066 (535 in the adapalene Lotion treatment group, 531 in the vehicle group)
Study Period: November 6, 2007 to November 14, 2008
Diagnosis and Main Criteria for Inclusion: Same as study 18113 (see above).
Exclusion Criteria: Same as study 18113 (see above).
Duration of Treatment: Once daily in the evening for duration of 12 weeks as in study 18113.

Criteria for Evaluation: Co-Primary Endpoints of success in the IGA and change in lesion counts as above in study 18113. Secondary and tertiary efficacy criteria as in study 18113 (see above).

Safety Evaluation: Same as study 18113.
Statistical Methods: Same as study 18113.

Protocol Amendments: none

Important differences between studies
The studies were designed to be identical and were conducted simultaneously at different sites with different investigators and subjects.

6 Review of Efficacy

Efficacy Summary

Differin Lotion, 0.1% demonstrated superiority over its vehicle in pivotal phase 3 studies 18113 and 18114. Subjects ≥ 12 years of age with moderate to severe acne vulgaris were treated once daily with adapalene lotion, 0.1% or adapalene vehicle lotion for up to 12 weeks.

Determination was made upon the agreed upon co-primary endpoints.

- Success Rate as defined as the percentage of subjects who achieve at least a two-point reduction at Week 12 in the IGA from Baseline, Last Observation Carried Forward (LOCF), Intent to Treat population (ITT).
- Change from Baseline in two out of three lesion counts:
  Absolute change from baseline to Week 12 (LOCF, ITT) in inflammatory lesion counts;
  Absolute change from baseline to Week 12 (LOCF, ITT) in non-inflammatory lesion counts;
  Absolute change from baseline to Week 12 (LOCF, ITT) in total lesion counts.

In both studies, Differin was statistically superior to its vehicle for the percent of IGA successes and the change in all lesion counts for the protocol defined primary analysis as well as several supportive and sensitivity analyses.

The observed treatment effects for the dichotomized IGA were 9.0% ($p < 0:001$) and 8.0% ($p = 0:001$) for studies 18113 and 18114, respectively. The treatment effects for the mean absolute change in total lesions were 11.2 and 9.0 lesions; in inflammatory lesions were 4.1 and 2.5 lesions; in non-inflammatory lesions were 7.1 and 6.5 lesions in studies 18113 and 18114, respectively.

6.1 Indication

The indication sought by the applicant is for topical application in the treatment of acne vulgaris in patients 12 years of age and older.

6.1.1 Methods

The efficacy evaluation of adapalene 0.1%/ lotion is based on detailed review of 2 pivotal, identically designed, randomized, double-blind, 12-week, multicenter, vehicle-controlled studies 18113 and 18114. See 5.3 Discussion of Individual Studies/Clinical Trials for details on the individual protocols.

6.1.2 Demographics

Study 18113: The mean age of subjects was 19.5 in the active arm and 18.9 in the vehicle arm. More than 60% of subjects were identified as Caucasian and 53% of subjects were female. The most prevalent skin phototype was Type III which accounted for approximately 35% of subjects.

Study 18114: The mean age of subjects was 19.1 in the active arm and 19.2 in the vehicle arm. Approximately 70% of subjects were identified as Caucasian and 54% of subjects were female. The most prevalent skin phototype was Type III which accounted for approximately 34% of subjects.

Table 3: Demographics of Subjects in Studies 18113 and 18114

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Age Category : 18 to 64 years	39% (206)	37% (199)	37% (197)	37% (195)
Sex : Male	47% (250)	46% (252)	44% (235)	49% (259)
Race : Asian	4% (22)	3% (18)	3% (14)	2% (13)
Black	12% (63)	12% (63)	18% (98)	16% (84)
Caucasian	60% (321)	62% (334)	70% (376)	70% (373)
Hispanic	21% (111)	20% (108)	6% (33)	7% (39)
Other	3% (16)	4% (19)	3% (14)	4% (22)
Skin Phototype : I	5% (25)	5% (29)	5% (29)	3% (18)
II	21% (113)	21% (114)	18% (94)	16% (85)
III	35% (187)	35% (188)	33% (176)	35% (185)
IV	20% (106)	22% (120)	21% (111)	22% (117)
V	12% (66)	11% (57)	10% (55)	11% (61)
VI	7% (36)	6% (34)	13% (69)	12% (65)

Numbers after percents are frequencies.
Source: Agency Biostatistical Review

Reviewer comment: Treatment groups were comparable with respect to gender, age, race distribution, and skin phototype within each study. Acne is predominately a disease of adolescents and young adults and the study population is generally representative of the intended use population. While the Division recently changed its recommendation for the lower age boundary for acne drug development down to 9 years of age, meeting discussions with this applicant preceded that change. This reviewer supports the efficacy conclusion down to 12 years of age and recommends labeling down to 12 years of age which mirrors that of related adapalene products.

Entry criteria were based on both lesion counts and an Investigator's Global Assessment (IGA) scale.

Baseline disease severity for study 18113:
The mean total lesion count was 75.1 for both the active treatment arm and the vehicle arm. The mean inflammatory lesion count was 27.3 for both the Differin arm and the vehicle arm. The mean non-inflammatory lesion count was 47.7 for the active arm and 47.8 for the vehicle arm. The majority of subjects had an IGA score of 3 (moderate) with fewer subjects with baseline scores of 4 (severe).

Baseline disease severity for study 18114:
The mean total lesion count was 73.5 for the active treatment arm and 74.6 for the vehicle arm. The mean inflammatory lesion count was 28.0 for the Differin arm and the 28.5 for the vehicle arm. The mean non-inflammatory lesion count was 45.5 for the active arm and 46.1 for the vehicle arm. The majority of subjects had an IGA score of 3 (moderate) with fewer subjects with baseline scores of 4 (severe).

Table 4: Baseline Distribution of IGA score and Lesion Counts in Studies 18113 and 18114

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
IGA : Moderate	91% (487)	92% (501)	96% (511)	94% (501)
Severe	9% (46)	8% (41)	4% (24)	6% (30)
Total Lesions	60 70 86	60 69 84	59.0 68.0 82.0	60.0 70.0 84.5
Inflammatory Lesions	22 25 30	22 25 31	22 25 32	22 25 33
Non-inflammatory Lesions	35.00 42.00 56.00	35.00 42.0055.75	34 39 51	34 40 52

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables.
Numbers after percents are frequencies.

Source: Agency Biostatisitical Review

Reviewer comment: The treatment arms are similar for baseline distribution IGA scores and lesion counts in both pivotal studies. The majority of subjects (> 90%) enrolled with a baseline IGA score of 3 (Moderate).

6.1.3 Subject Disposition

In the Phase 3 studies a total of 273 out of 2141 subjects (12.8%) discontinued from the trial. The dropout rate was slightly higher in the vehicle arm than the Differin treatment arm for each study. The reason for dropout was similar in each treatment arm; most of the subjects discontinued the study due to reasons of either Lost to Follow-Up or Subject's Request. The table below summarizes subject disposition.

Table 5: Subject Completion/ Discontinuation in Studies 18113 and 18114

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Completed the Trial	471 (88.4)	460 (84.9)	475 (88.8)	462 (87.0)
Discontinued	62 (11.6)	82 (15.1)	60 (11.2)	69 (13.0)
Adverse Event	6 (1.1)	2 (0.4)	4 (0.7)	1 (0.2)
Lack of Efficacy	3 (0.6)	7 (1.3)	4 (0.7)	8 (1.5)
Lost to Follow-Up	24 (4.5)	29 (5.4)	23 (4.3)	23 (4.3)
Other	2 (0.4)	4 (0.7)	0 (0.0)	0 (0.0)
Pregnancy	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)
Protocol Violation	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.2)
Subject's Request	25 (4.7)	36 (6.6)	28 (5.2)	34 (6.4)

Source: Agency's Biostatistical Review

Reviewer comment: The number of subjects that discontinued for an adverse event was greater in the Differin treatment arm than in the vehicle arm (see safety review in 7.3.3 Dropouts and/or Discontinuations *for analysis) for both studies 18113 and 18114).*

6.1.4 Analysis of Primary Endpoint(s)

Co-primary endpoints assessed at week 12 in the phase 3 studies 18113 and 18114 were:

- Success Rate as defined as the percentage of subjects who achieve at least a two-point reduction in the IGA score from baseline, Last Observation Carried Forward (LOCF), Intent to Treat population (ITT).

- Absolute change in lesion counts (total, inflammatory, and non-inflammatory) from baseline (LOCF, ITT)

The following IGA Scale was used in both studies:

Table 6: IGA Scale for phase 3 studies 18113 and 18114

0	Clear	Normal, clear skin with no evidence of acne vulgaris.
1	Almost Clear	Rare non-inflammatory lesions present, with rare non inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red).
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules/cysts may or may not be present.

Reviewer comment: The endpoints were discussed with the division and were consistent with the recommendations of the Division. The use of both a global scale and lesion counts allow for a balanced approach toward the evaluation of acne severity as recommended by the draft Guidance for Industry Acne Vulgaris: Developing Drugs for Treatment. The dichotomized IGA scale used is consistent with scales used for approval of other Differin products. For the majority of subjects enrolled in the trial, whose baseline score was Grade 3, a 2 point reduction or greater would achieve a clinically meaningful result of clear or almost clear. However, the assessment of facial acne lesion counts did not include areas of the nose, which is not recommended in the draft guidance. Therefore, although acne vulgaris of the nose is a prevalent clinical presentation it has only been assessed in the global scale, but not in the lesion counts in the development of Differin Lotion, 0.1%.

Efficacy results of one of the co-primary endpoints, the dichotomized IGA scale are shown in the table below. Success is defined as a two grade improvement from Baseline to Week 12.

Table 7: Efficacy Results based on Investigator Global Assessment (ITT-LOCF)

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
IGA Success (%)	140 (26.3)	94 (17.3)	129 (24.1)	87 (16.4)
p-value†	-	< 0.001	-	0.001

† P-value is based on CMH stratified on "analysis center".
Source: Agency biostatistical review

Reviewer comment: IGA success rates for each treatment arm were similar in the two Phase 3 trials. Differin Lotion, 0.1% demonstrated superiority to its vehicle.

Efficacy results of one of the co-primary endpoints, lesion counts are shown in the tables below. The statistical analysis for lesion counts was pre-specified in the protocol and was to be performed step-wise with testing of the total lesion counts followed by inflammatory and non-inflammatory lesions. Each type of lesion (inflammatory and non-inflammatory) was counted separately and counts were taken from the forehead, left and right cheeks and chin above the jaw line (excluding the nose). Total lesions are the sum of inflammatory and non-inflammatory lesions.

In both studies Differin Lotion, 0.1% was superior to vehicle on the basis of the absolute change in total lesion counts. The treatment effects for the mean absolute change were 11.2 and 9.0 lesions in Studies 18113 and 18114, respectively.

Table 8: Efficacy Results based on Change in Total Lesion Counts (ITT-LOCF)

	Study 18113		**Study 18114**	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Mean Change	37.9	26.7	32.4	23.4
Mean Percent Change	51.5	37.1	44.6	32.8
p-value†	-	< 0.001	-	< 0.001
p-value‡	-	< 0.001	-	< 0.001

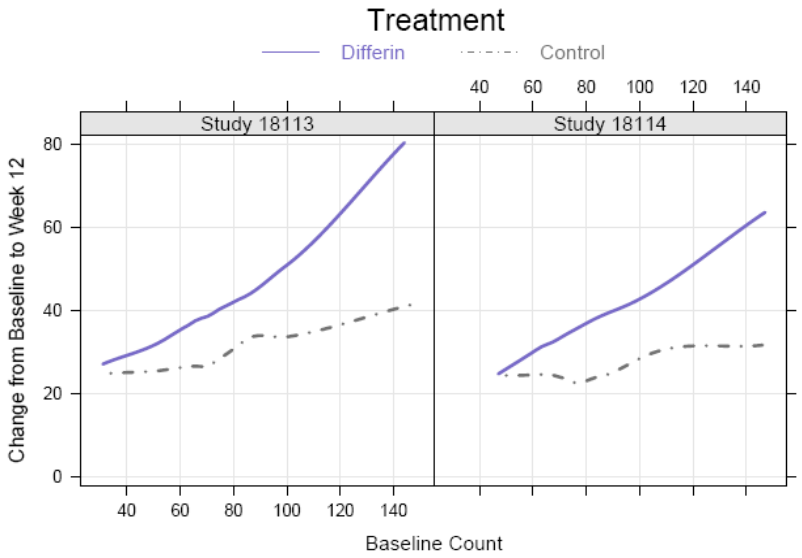
† P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and "analysis center" as main effects.

‡ P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Agency biostatistical review

In both studies, a graphical summary of results across the range of the baseline total lesion counts shows a treatment effect which was largest for higher lesion counts.

Figure 1: Total Lesion Counts (ITT-LOCF)



Source: Agency biostatistical review

In both studies, Differin Lotion, 0.1% was superior to vehicle for the absolute change in inflammatory lesions. The treatment effects for the mean absolute change were 4.1 and 2.5 lesions in Studies 18113 and 18114, respectively.

Table 9: Efficacy Results based on Change in Inflammatory Lesion Counts (ITT-LOCF)

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Mean Change	14.7	10.6	12.7	10.2
Mean Percent Change	54.9	40.3	46.0	36.9
p-value†	-	< 0.001	-	< 0.001
p-value‡	-	< 0.001	-	< 0.001

† P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and "analysis center" as main effects.

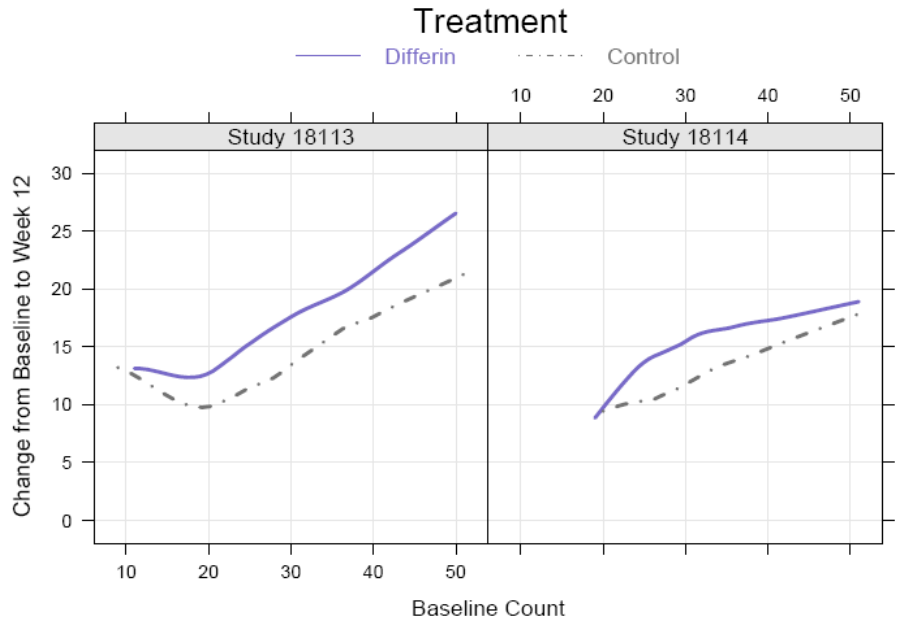
‡ P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Agency biostatistical review

A graphical summary of results across the range of the baseline inflammatory lesion count is depicted below. Note that in Study 18113 four subjects had baseline inflammatory lesion counts less than 20 (protocol violation) which impacts the curve of line. Discounting these four subjects, the treatment effect is constant across the range.

In Study 18114, there is a trend showing a treatment effect in favor of Differin Lotion, 0.1%. However, the slopes of the lines are not parallel suggesting differences in treatment effects across the range of the baseline inflammatory lesion counts as lesion counts increase.

Figure 2: Inflammatory Lesion Counts (ITT-LOCF)



Source: Agency biostatistical review

In both studies, Differin Lotion, 0.1% was superior to vehicle for the absolute change in non-inflammatory lesions. The treatment effects for the mean absolute change were 7.1 and 6.5 lesions in Studies 18113 and 18114, respectively. The two studies showed more consistent results for non-inflammatory lesions than for inflammatory lesions.

Table 10: Efficacy Results based on Change in Non-Inflammatory Lesion Counts (ITT-LOCF)

	Study 18113		**Study 18114**	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Mean Change	23.2	16.1	19.6	13.1
Mean Percent Change	49.6	35.7	43.1	30.2
p-value†	-	< 0.001	-	< 0.001
p-value‡	-	< 0.001	-	< 0.001

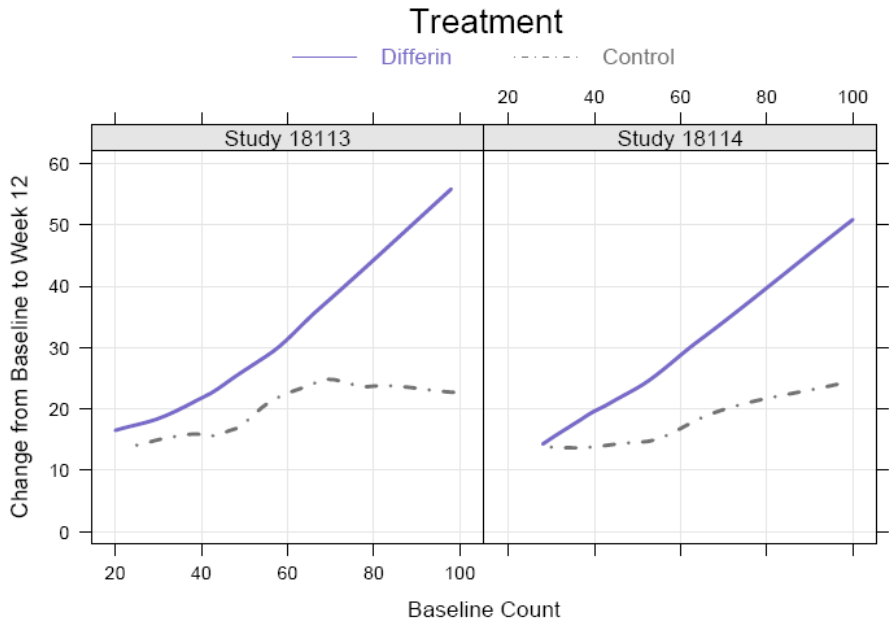
† P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and "analysis center" as main effects.

‡ P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Agency biostatistical review

A graphical summary of results across the range of the baseline non-inflammatory lesion count is depicted below. Note that in Study 18113 three subjects had baseline non-inflammatory lesion counts less than 30 (protocol violation) which impacts the curve of line. Discounting these three subjects, there is a clear treatment effect across the range. In Study 18114, there is also a clear treatment effect across the range although the difference is small for baseline non-inflammatory lesion counts around 30.

Figure 3: Non-Inflammatory Lesion Counts (ITT-LOCF)



Source: Agency biostatistical review

Sensitivity analyses using two alternate imputation approaches for IGA scores were performed:

- impute all missing week 12 data as failures
- impute all missing week 12 data as successes

Table 11: Missing Data Sensitivity Analysis of IGA Scores

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Missing Imputed as Failures				
IGA Success (%)	136 (25.5)	93 (17.2)	126 (23.6)	85 (16.0)
p-value†	-	< 0.001	-	0.0013
Missing Imputed as Successes				
IGA Success (%)	198 (37.1)	170 (31.4)	183 (34.2)	152 (28.6)
p-value†	-	0.0355	-	0.0447

† P-value is based on CMH stratified on "analysis center".

Reviewer comment: Efficacy conclusions based on the sensitivity analyses were similar to those of the primary analysis for IGA scores.

Sensitivity analyses of changes in lesion counts were performed. Missing values at Week 12 were imputed by the median change for the respective treatment group from the subjects with complete data. A second sensitivity analysis of lesion counts included only subjects with both Baseline and Week 12 lesion counts (i.e., subjects with missing Week 12 lesion counts will be excluded from the analysis).

Table 12: Missing Data Sensitivity Analysis of Change in Lesion Counts

	Study 18113		Study 18114	
Imputed using the Median Week 12 Data				
	Differin™ Lotion ($N = 533$)	Vehicle Lotion ($N = 542$)	Differin™ Lotion ($N = 535$)	Vehicle Lotion ($N = 531$)
Total Lesion Count				
Mean Change	41.4	29.7	34.5	25.3
p-value†	-	< 0.001	-	< 0.001
Inflammatory Lesion Count				
Mean Change	16.1	11.8	13.9	11.2
p-value†	-	< 0.001	-	< 0.001
Non-Inflammatory Lesion Count				
Mean Change	25.1	17.9	20.7	14.2
p-value†	-	< 0.001	-	< 0.001
Only Subjects with Baseline and Week 12 Data				
	Differin™ Lotion ($N = 472$)	Vehicle Lotion ($N = 465$)	Differin™ Lotion ($N = 478$)	Vehicle Lotion ($N = 464$)
Total Lesion Count				
Mean Change	41.2	28.7	35.2	25.2
p-value†	-	< 0.001	-	< 0.001
Inflammatory Lesion Count				
Mean Change	16.1	11.5	14.1	11.1
p-value†	-	< 0.001	-	< 0.001
Non-Inflammatory Lesion Count				
Mean Change	25.1	17.1	21.1	14.1
p-value†	-	< 0.001	-	< 0.001

† P-value is based on using an ANCOVA model with main effects only on the unranked data.

Source: Agency Biostatistical Review

Reviewer comment: Efficacy conclusions for the sensitivity analyses for lesion counts were similar to those of the primary analysis.

The final assessment of efficacy is that Differin Lotion, 0.1% has a statistically significant treatment effect that is of marginal clinical significance for mild acne and inflammatory acne. Figure 1 *demonstrates that the treatment effect is smallest for subjects with fewer numbers of lesions and* Table 9 *shows the absolute change in the mean of inflammatory lesions was a modest reduction of 4.1 and 2.5 lesions in studies 18113 and 18114, respectively. However, these results are consistent with the efficacy profile of other Differin products and this information is provided in the label. The clinical study section describes the mean absolute change and percent change for each type of lesion (inflammatory and non-inflammatory) and the entry criteria based on lesion counts and IGA scale for the studies is described. The label states the majority of subjects enrolled were of moderate severity. It is this reviewer's opinion that the information in the label adequately informs prescribing in regard to the population likely to benefit from treatment.*

6.1.5 Analysis of Secondary Endpoints(s)

Percent changes of the lesion counts are the only secondary endpoints intended for labeling claims. These endpoints included:

- Percent change in Total Lesion Counts from Baseline to Week 12 (LOCF, ITT).
- Percent change in Inflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT).
- Percent change in Non-inflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT).

The treatment effects for the mean percent change in total lesions were 14.4 and 11.8 lesions in Studies 18113 and 18114, respectively (see Table 8).

The treatment effects for the mean percent change in inflammatory lesions were 14.6 and 9.1 lesions in Studies 18113 and 18114, respectively (see Table 9).

The treatment effects for the mean percent change in non-inflammatory lesions were 13.9 and 12.9 lesions in Studies 18113 and 18114, respectively (see Table 10).

6.1.6 Other Endpoints

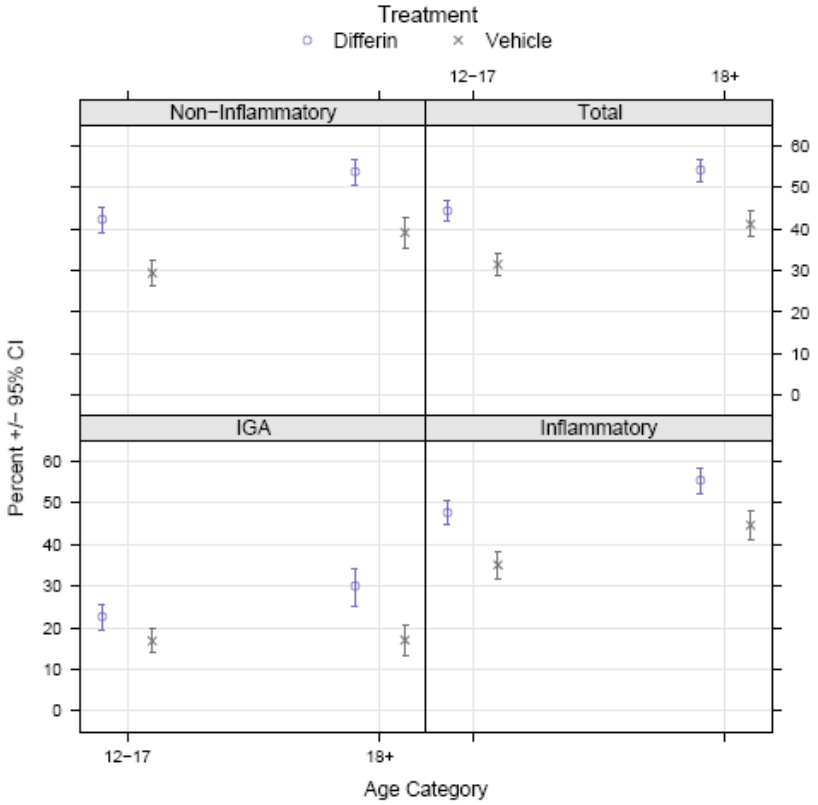
The sponsor studied tertiary efficacy parameters such as the change from Baseline to Week 12 in IGA (full scale) and the outcome of the Subject Assessment of Acne at Week 12. These will not be included in labeling and will not be reviewed.

6.1.7 Subpopulations

The age of subjects was dichotomized into two categories: 12 to 17 years old and 18 years and older. Differin Lotion, 0.1% had greater efficacy as compared to vehicle for both age groups for

each of the co-primary endpoints. Subjects 18 years of age and older tended to have slightly higher response rates than subjects 12 to 17 years old

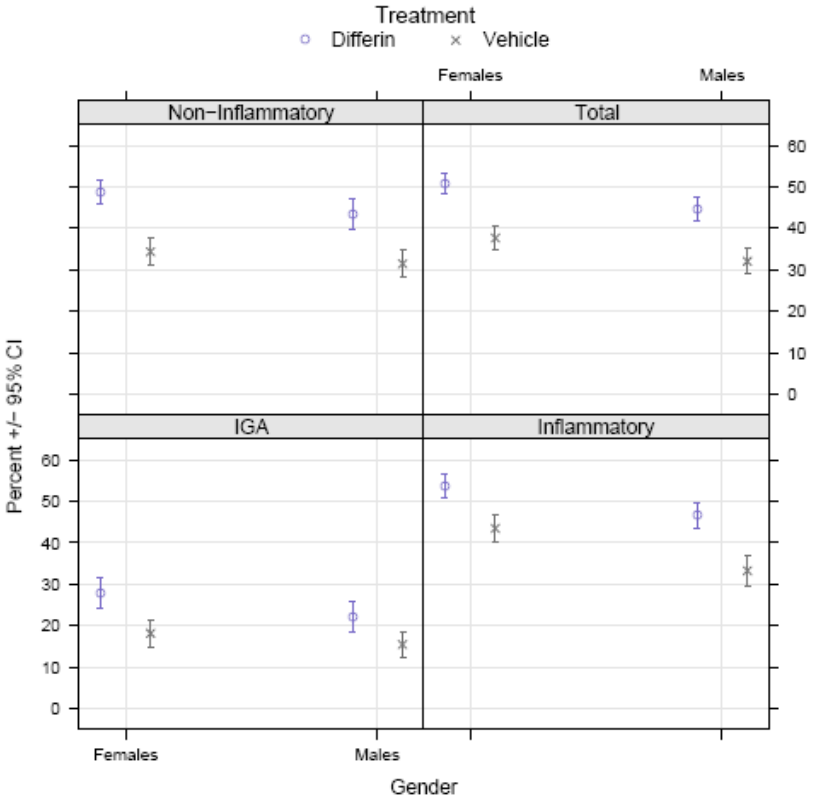
Figure 4: Efficacy Results Analyzed by Age



Source: Agency Biostatistical Review

Differin Lotion, 0.1% had greater efficacy as compared to vehicle for both genders for each of the co-primary endpoints. In general, efficacy results are similar for males and females. However, for all endpoints, females tended to have higher means than males.

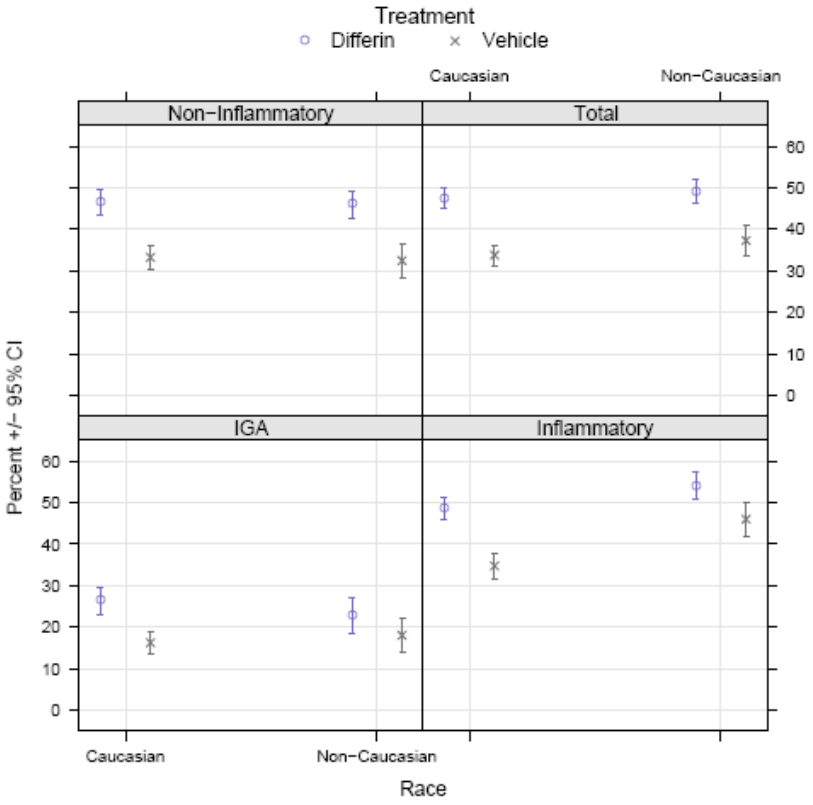
Figure 5: Efficacy Results Analyzed by Gender



Source: Agency Biostatistical Review

Race was dichotomized into two categories: Caucasian and Non-Caucasian due to the limited number of subjects enrolled with race categorized as either Asian, Black, Hispanic, or Other. Differin Lotion, 0.1% had greater efficacy as compared to vehicle for both race categories for each of the co-primary endpoints. Overall the efficacy results were quite consistent across subgroups.

Figure 6: Efficacy Results Analyzed by Race



Source: Agency Biostatistical Review

Reviewer comment: The results of the subgroup analyses by and age group (12 to 17 years of age and 18 to 64 years of age)gender (male and female),and race (Caucasian and non-Caucasian), support the conclusion established for the overall population, that the efficacy profile of Differin Lotion 0.1% is superior to vehicle lotion across all subgroups. In general, older subjects (18 – 64 years of age), female subjects, and Caucasian subjects were more likely to have IGA successes and greater lesion count reductions than were the opposing subjects within the same subset categorizations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Once daily dosing was the only dosing regimen evaluated for efficacy in phase 3 studies. No phase 2 studies were conducted. Dosing for this formulation's development studies were similar to those of existing approved adapalene formulations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy was assessed at Week 12. Persistence of Efficacy and/or Tolerance was not part of the development program.

6.1.10 Additional Efficacy Issues/Analyses

(b) (6) of site (b) (6) was identified as having a conflict of interest as a shareholder of (b) (6), developer of adapalene lotion (see 3.1 Submission Quality and Integrity). Based upon this finding, a DSI inspection was recommended. However, DSI recommended against inspection since the site had been subject to a recent inspection with no issued identified. Therefore, the Agency Biostatistical reviewer conducted analysis excluding this site to determine if it had influenced efficacy findings.

The center (b) (6) enrolled a total of (b) (6) subjects, (b) (6) randomized to each treatment arm. The site was removed in an Agency's biostatistics sensitivity analysis of the (b) (6) endpoint using the ITT population of Study (b) (6) with the missing data imputed using LOCF. The original treatment effect was (b) (6) Deleting the data of center (b) (6) resulted in an estimated treatment effect of (b) (6)

Reviewer comment: Based on the Agency's sensitivity analysis, there is no evidence that center (b) (6) *influenced the efficacy results of Study* (b) (6). *This reviewer concludes that this conflict of interest had no bearing on efficacy conclusions.*

7 Review of Safety

Safety Summary

Five clinical studies (three Phase 1 and two Phase 3) were conducted to evaluate the safety of Differin Lotion, 0.1%. These studies exposed an adequate number, 1382 subjects, to Differin Lotion 0.1%.

The two Phase 3 studies (18113 and 18114) were designed to be identical and were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated in the development program and included an assessment for local tolerability and dermal safety studies to evaluate contact sensitization and irritation. Safety data for phototoxicity and photoallergenicity relied on previous studies conducted for other Differin products which demonstrate photosensitivity and are labeled as such. The proposed label for Differin Lotion, 0.1% contains the same precautions.

No deaths occurred in the clinical development program. Five serious adverse events (SAEs) were reported in study 18113 and no SAEs were reported in study 18114. Three of the serious adverse events (depression, multiple drug overdose, cerebral hemorrhage) occurred in 2 subjects being treated with Differin, did not result in discontinuation from the study and are not likely

related to the study drug. Significant AEs considered related to the study medication were not reported for organ systems other than skin and subcutaneous tissue.

Most of the signs and symptoms of local tolerability were mild or moderate in severity with the peak of severity at week 1 and a gradual reduction during the 12 weeks of treatment. The four month safety update report did not reveal new information that would effect labeling.

Adapalene is a widely marketed acne product and its adverse event profile is reasonably well understood. The common side effects of skin irritation, dryness, erythema, burning and scaling and are expected. The reported AEs and local tolerability for Differin Lotion, 0.1% are comparable to other approved Differin products. These safety concerns can be adequately conveyed by labeling.

Recommendations for labeling:

Combined Study 1 and Study 2	Maximum Severity During Treatment (N = 1057)			Week 12 Treatment Severity (N = 950)		
Local Cutaneous Irritation (skin irritation)	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	(b) (4)					
Scaling						
Dryness						
Stinging/burning						

7.1 Methods

The safety review of Differin Lotion, 0.1%, will focus on safety data from topical safety studies, systemic safety (systemic absorption) studies, and adverse events in Phase 1 and Phase 3 studies. In both Phase 3 trials, investigators and subjects were to report all AEs and an assessment for local tolerability was included (erythema, scaling, dryness, stinging/burning, each rated on a scale ranging from 0 [none] to 3 [severe]). Laboratory data with the exception of pregnancy testing (at Baseline and Week 12) was not collected. Physical exams including measurement of vital signs were conducted at Baseline and Week 12. Deaths, serious adverse events, discontinuations due to adverse events, and clinically important adverse events were considered from all clinical studies.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In total five clinical trials with Differin Lotion, 0.1% were presented by the sponsor in support of this application:

Protocol No. (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites (Location)	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
RD.06.SPR.18108 (1)	To assess the systemic exposure to adapalene in subjects with acne during once daily dermal treatment for 30 days with 2 g of Adapalene Lotion, 0.1% on the face, upper part of chest, and upper part of back (maximized usage conditions)	Single-center, open-label, 30-day, PK study	Males and females, 18-35 years of age with severe acne vulgaris (a score of 4 on the IGA), and a minimum of 20 inflammatory (papules and pustules) lesions and 30 non-inflammatory lesions (open comedones and closed comedones) on the face (excluding the nose) (14/14)	1 (US)	Adapalene Lotion, 0.1% = 14	Once daily / 30 days	17 May 2007 – 21 July 2007
RD.06.SPR.18110 (1)	To determine the dermal irritation of Adapalene Lotion, 0.1%, relative to Lotion Vehicle, and both a positive and a negative control	Single-center, test site randomized, 21-day, cumulative irritation study	Healthy males and females, 18-65 years of age (35/50)*	1 (US)	Adapalene Lotion, 0.1% = 50 Lotion Vehicle = 50 Sodium Lauryl Sulfate = 50 White Petrolatum = 50	Occlusive patches worn for 24 hours post-application / 21 days	12 July 2007 – 4 August 2007

* The target was 35 evaluable subject; 50 subjects actually were enrolled and 44 successfully completed the study.

Protocol No. (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites (Location)	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
RD.06.SPR.18111 (1)	To determine the contact sensitization potential of Adapalene Lotion, 0.1% relative to Lotion Vehicle and a negative control by repetitive applications to the skin	Single-center, test site randomized, contact sensitization study	Healthy males and females, 18-65 years of age (200/250)[b]	1 (US)	Adapalene Lotion, 0.1% = 250 Lotion Vehicle = 250 White Petrolatum = 250	Occlusive patches worn 48 or 72 hours (Induction), and 48 hours (Challenge) / 3 weeks (Induction), 48 hours (Challenge)	23 July 2007 – 8 September 2007
RD.06.SPR.18113 (3)	To demonstrate the superiority in efficacy and assess safety of Adapalene Lotion, 0.1% versus Adapalene Vehicle Lotion in the treatment of acne vulgaris for up to 12 weeks	Multi-center, randomized, double-blind, parallel group, vehicle controlled, safety and efficacy study	Males and females 12 years of age or older with acne including facial involvement, and IGA score of 3 (moderate) or 4 (severe), a minimum of 20 but not more than 50 papules and pustules in total on the face (excluding the nose), and a minimum of 30 but not more than 100 non-inflammatory lesions (open comedones and closed comedones) on the face (excluding the nose). (1,066/1,075)	39 (31 US, 8 Canada)	Adapalene Lotion, 0.1% = 533 Lotion Vehicle = 542	Once daily / 12 weeks	7 Nov 2007 – 6 Nov 2008

[b] The target was 200 evaluable subject: 250 subjects actually were enrolled and 203 successfully completed the study.

Protocol No. (Study Phase)	Objective	Study Design	Subject Population (Plan/Actual)	# Sites (Location)	Treatment Group(s) = # Subjects	Dosing Regimen/ Treatment Duration	Study Period
RD.06.SPR.18114 (3)	To demonstrate the superiority in efficacy and assess safety of Adapalene Lotion, 0.1% versus Adapalene Vehicle Lotion in the treatment of acne vulgaris for up to 12 weeks	Multi-center, randomized, double-blind, parallel group, vehicle controlled, safety and efficacy study	Males and females 12 years of age or older with acne including facial involvement, and IGA score of 3 (moderate) or 4 (severe), a minimum of 20 but not more than 50 papules and pustules in total on the face (excluding the nose), and a minimum of 30 but not more than 100 non-inflammatory lesions (open comedones and closed comedones) on the face (excluding the nose). (1,066/1,066)	36 (31 US, 5 Canada)	Adapalene Lotion, 0.1% = 535 Lotion Vehicle = 531	Once daily / 12 weeks	6 Nov 2007 – 14 Nov 2008
Total Number of Subjects Randomized in the Clinical Development Plan and Evaluated for Safety (Regardless of Treatment) = 2,455 **Total Number of Subjects Exposed to Adapalene Lotion, 0.1% = 1,382** **Total Number of Subjects with Acne Exposed to Adapalene Lotion, 0.1% = 1,082**							

7.1.2 Categorization of Adverse Events

MedDRA preferred terms were used for classification of AEs. Phase 1 PK study 18108 used MedDRA version 10.1 and in both Phase 3 studies 18113 and 18114 used MedDRA version 10.0. Terms are appropriated to evaluate for safety signals.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The combining of results across the Phase 3 studies is considered appropriate since the trials had identical inclusion/exclusion criteria and study designs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Three topical dosage forms of adapalene at a concentration of 0.1% (cream, gel, and solution) and one gel formulation at the higher concentration of 0.3% have been approved in many countries, including the US, for the treatment of acne. The applicant reports that over 4500 subjects with acne have been evaluated for efficacy and/or safety in clinical and post-marketing investigations of adapalene 0.1% formulations.

The clinical program for the development of the current Differin Lotion, 0.1% formulation included three Phase 1 (one PK, one contact sensitization, and one cumulative irritation) trials and two Phase 3 trials. Combined these trials included 2455 subjects, 1382 of whom were exposed to Differin Lotion, 0.1%. Within the clinical trials, 1082 of the enrolled subjects had acne and were treated with Differin Lotion. 1068 of these subjects were treated once daily for 12 weeks in phase 3 trials. The average daily use of Differin Lotion, 0.1% in these trials was 0.6 g in study 18113 and 0.5 g in study 18114.

Reviewer comment: Clinical trials exposed an adequate number of subjects to assess safety for 12 weeks of use in patients 12 and older with acne vulgaris. Topical safety was adequately evaluated in the development program and included an assessment for local tolerability and dermal safety studies to evaluate contact sensitization and irritation. Although the phase 3 trials included a large number of subjects aged 12-17 years, systemic exposure was not evaluated in these subjects in the PK study.

7.2.2 Explorations for Dose Response

Only one dosing frequency (one application daily in the evening) and one concentration (0.01%) was evaluated in the phase 3 trials. Adjustment of the dose by a reduction in frequency of application to every other day was permitted per protocol for the symptomatic relief of skin dryness or irritation.

7.2.3 Special Animal and/or In Vitro Testing

As the active substance, adapalene, is well characterized pharmacologically. No specific nonclinical pharmacology, carcinogenicity, mutagenicity or impairment of fertility studies were performed with the to-be-marketed product.

Differin Lotion, 0.1% was evaluated in repeat-dose toxicity studies and two local tolerance studies. In these studies, systemic toxicity was not observed and moderate irritation was observed. Refer to the pharmacology/ toxicology review by Dr. Kumar Daivender Mainigi for details.

Reviewer comment: Irritation is an expected adverse event related to adapalene products and has been specifically assessed in the clinical trials for Differin Lotion 0.1%.

7.2.4 Routine Clinical Testing

Routine clinical testing was deemed adequate to assess short-term safety and efficacy.

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant did not perform metabolic, clearance or interaction workup for this application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adapalene is a widely marketed acne product and its adverse event profile is reasonably well understood. The common side effects for this product include skin irritation, dryness, erythema, burning/ stinging and scaling. Topical safety was adequately evaluated in the development program and included an assessment for local tolerability and dermal safety studies to evaluate contact sensitization and irritation. Safety data for phototoxicity and photoallergenicity relied on previous studies conducted for other Differin products which demonstrate photosensitivity.

Adapalene is a pregnancy category C drug. Teratogenic effects were observed in animals at doses greater than 100 times the maximum recommended human dose. There are no well-controlled trials in pregnant women and pregnant subjects were excluded in the trials for Differin Lotion,0.1% as well. However, 2 subjects in the Differin Lotion,0.1% treatment group became pregnant during the course of the trials and the outcomes for both of these pregnancies were sufficiently determined. (see 7.6.2 Human Reproduction and Pregnancy Data)

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in any of the five studies conducted as part of the development plan for Differin Lotion, 0.1%.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) in either phase 1 study 18108 or 18111. Also, no SAEs were reported in phase 3 study 18114. Both study 18110 (cumulative irritation) and 18114 (phase 3) reported SAEs which are shown in the table below.

Table 13: Serious Adverse Events in Studies 18110 and 18113

Subject	Event	Onset Date	Resolution Date	Treatment (Relationship)[a]
Study RD.06.SPR.18110				
26	Broken bones and shattered wrist	(b) (6)		Patch Application (Unrelated)
Study RD.06.SPR.18113				
17-002	Suicide Attempt	(b) (6)		Lotion Vehicle (Unrelated)
19-030	Multiple drug overdose			Adapalene Lotion, 0.1% (Unrelated)
	Depression			Adapalene Lotion, 0.1% (Unrelated)
24-004	Cerebral hemorrhage			Adapalene Lotion, 0.1% (Unrelated)
28-001	Ovarian cyst			Lotion Vehicle (Unrelated)

Source: Table 5.1.7-1
(a) relationship to study drug characterized by the sponsor

One subject in study 18110 suffered a serious AE that occurred as a result of a motorcycle accident and included broken bones and a shattered wrist. The event was unrelated to treatment, but resulted in study discontinuation.

Five SAEs in study 18113 were reported. Two subjects in the Differin Lotion, 0.1% treatment group reported three SAEs and two subjects in the lotion vehicle treatment group reported two SAEs. Specifically, within the Differin Lotion treatment group, the SAEs included multiple drug overdose and depression (both reported by subject 19-30) and a cerebral hemorrhage (reported by subject 24-04). Narratives of the SAEs in the treatment arm are below:

> Subject 19-30 is a 22-year-old female with a medical history of asthma, anemia, chronic cryptic tonsillitis, anal fissure and major depression, generalized anxiety, panic attacks,

bulimia nervosa. She had a history of sexual abuse two years ago (with a court trial around the time of the study) and her father died in (b) (6) from alcohol poisoning. She reported a depressed mood for the past two months with trouble getting asleep and problems of concentration. Concomitant treatments included Pulmicort (budesonide), albuterol and Cymbalta (duloxetine). The study treatment was introduced on 28-APR-2008. The intentional ingestion of multiple drugs occurred on (b) (6). She ingested acetaminophen, lorazepam, dramamine (dimenhydrate), Benadryl (diphenhydramine), ethyl alcohol and inhaled cannabis. The patient denied suicide attempt and stated that she wanted to sleep for a long time. She was diagnosed with depression and multiple medication overdose and admitted to an inpatient psychiatric unit. Study treatment was continued.

Reviewer comment: CDC WISQARS (web-based injury statistics query and reporting system) database provides these statistics regarding suicide in the U.S. based on 2006 data:

- Overall rate was 10.9 suicide deaths per 100,000 people.
    - Children ages 10 to 14 — 1.3 per 100,000
    - Adolescents ages 15 to 19 — 8.2 per 100,000
    - Young adults ages 20 to 24 — 12.5 per 100,000
- An estimated 12 to 25 attempted suicides occur per every suicide death.
- Suicide was the third leading cause of death for young people ages 15 to 24.

The National Institute of Mental Health reports several risk factors for suicide based on research:

- Depression and other mental disorders, or a substance-abuse disorder (often in combination with other mental disorders). More than 90 percent of people who die by suicide have these risk factors.
- Family violence, including physical or sexual abuse
- Family history of mental disorder or substance abuse
- Family history of suicide

In this reviewer's opinion, details of this case are consistent with an attempted suicide and the relationship to the study drug is unlikely based on the following: the subject is in the age category at highest risk for suicide, based on medical history provided, this subjects has multiple risk factors for suicide, and both the vehicle arm and the treatment arm have one subject each attempting suicide. Although there has been consideration given to a relationship between vitamin A/ retinoids and depression/ suicide based on AEs reported for isotretinoin and symptoms of hypervitaminosis A, Differin Lotion, 0.1% demonstrates low systemic absorption and thus low potential if a link is demonstrated. Therefore, no additional labeling or REMS is needed based on this one AE. If post-marketing reporting demonstrates additional cases of depression or suicidality, a reevaluation of labeling may be needed.

> Subject 24-04 is a16-year-old male with a medical history of myringotomy tubes, spiral fracture of the right leg, tonsillectomy, right wrist fracture, right arm fracture, bipolar disorder, substance abuse, tobacco use, otitis media, and asthma. The study treatment was introduced on 12-DEC-2007. On (b) (6), he developed headache, dizziness and visual changes and drowsiness. He was tachycardic, hypertensive and was diagnosed with a right frontal lobe intraxial petechial hemorrhage status post drug ingestion. His urine was positive to marijuana and phencyclidine. Study treatment was continued unchanged. The patient recovered on (b) (6). The event was considered by the investigator as unrelated to the study treatment.

Reviewer comment: This reviewer agrees with the investigator that the SAE is unrelated to the study treatment.

7.3.3 Dropouts and/or Discontinuations

In study 18108, seventeen (17) subjects were screened. Of these, fourteen (14) subjects received treatment with Differin Lotion, 0.1%, and thirteen (13) subjects completed the study. One (1) subject requested to be withdrawn form the study because he was going out of town.

In study 18110, fifty (50) subjects were enrolled and forty-four (44) completed the study. Six (6) subjects were discontinued from the study. One (1) experienced tape reactions at the test sites, four (4) discontinued for noncompliance, and one (1) was discontinued for a serious adverse event.

In study 18111, 250 subjects were enrolled in the study, of which 203 completed the study. Forty-seven (47) subjects were discontinued from the study. Two (2) had violations of inclusion criteria (possible cancer and HIV positive blood test), four (4) experienced tape reactions at the test sites, thirty-two (32) discontinued for noncompliance, and nine (9) were lost to follow up.

In the Phase 3 studies a total of 273 out of 2141 subjects (12.8%) discontinued from the trial. The dropout rate was slightly higher in the vehicle arm than the Differin Lotion, 0.1% treatment arm for each study. The reason for dropout was similar in each treatment arm; most of the subjects discontinued the study due to reasons of either Lost to Follow-Up or Subject's Request. The number of subjects that discontinued for and adverse event was greater in the Differin Lotion, 0.1% treatment arm. (see Table 14 and Table 15)

Table 14: Subject Completion/ Discontinuation in Phase 3 Studies 18113 and 18114

	Study 18113		Study 18114	
	Differin™ Lotion	Vehicle Lotion	Differin™ Lotion	Vehicle Lotion
	($N = 533$)	($N = 542$)	($N = 535$)	($N = 531$)
Completed the Trial	471 (88.4)	460 (84.9)	475 (88.8)	462 (87.0)
Discontinued	62 (11.6)	82 (15.1)	60 (11.2)	69 (13.0)
Adverse Event	6 (1.1)	2 (0.4)	4 (0.7)	1 (0.2)
Lack of Efficacy	3 (0.6)	7 (1.3)	4 (0.7)	8 (1.5)
Lost to Follow-Up	24 (4.5)	29 (5.4)	23 (4.3)	23 (4.3)
Other	2 (0.4)	4 (0.7)	0 (0.0)	0 (0.0)
Pregnancy	2 (0.4)	2 (0.4)	0 (0.0)	2 (0.4)
Protocol Violation	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.2)
Subject's Request	25 (4.7)	36 (6.6)	28 (5.2)	34 (6.4)

Source: Agency biostatistical review

Adverse Events associated with dropouts

Phase 1 open-label studies:
In study 18110, one subject discontinued for an adverse event. The subject reported broken bones and shattered wrist related to a motorcycle accident.

Phase 3 studies:
In study 18113, six subjects within the Differin Lotion, 0.1% treatment group discontinued because of AEs including acne (two subjects), skin irritation (two subjects), irritant contact dermatitis on the face (one subject), and periocular skin burning sensation, skin discomfort, and skin swelling (all three events were reported by one subject). Within the lotion vehicle treatment group, one subject discontinued because of possible allergic contact dermatitis and one subject because of skin irritation.

In study 18114, four subjects within the Differin Lotion, 0.1% treatment group discontinued because of AEs including acne (two subjects), skin discomfort (one subject), and oral herpes (one subject). Within the lotion vehicle treatment group, one subject discontinued because of acne.

Table 15: Discontinuations due to Adverse Events

	Adapalene Lotion, 0.1% (N=1068)	Lotion Vehicle (N=1073)
Number of Subjects Discontinued the Study Due to Adverse Events	10 (0.9%)	3 (0.3%)
Adverse Event[a]		
Infections and infestations	1 (0.1%)	0 (0.0%)
Oral herpes	1 (0.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders	9 (0.8%)	3 (0.3%)
Acne	4 (0.4%)	1 (0.1%)
Dermatitis contact	1 (0.1%)	1 (0.1%)
Skin burning sensation	1 (0.1%)	0 (0.0%)
Skin discomfort	2 (0.2%)	0 (0.0%)
Skin irritation	2 (0.2%)	1 (0.1%)
Skin swelling	1 (0.1%)	0 (0.0%)

Source: Sponsor's Table 12-13

Reviewer comment: There were more discontinuations due to local reactions in the Differin Lotion, 0.1% treatment group as compared to its vehicle. Stinging/ burning and irritation are expected AEs for adapalene products. This has been further evaluated in the local tolerability assessment for Differin Lotion, 0.1%. Labeling is recommended to address these expected AEs.

7.3.4 Significant Adverse Events

Of the 2,141 subjects included in the safety population in the two Phase 3 studies combined, 354/1068 subjects in the Differin Lotion, 0.1% treatment group reported 494 AEs; fewer subjects reported fewer AEs in the lotion vehicle treatment group. Specifically, in this group, 300/1073 subjects reported 428 AEs. The following table summarizes the AEs of the study drug and vehicle by severity and relation to treatment:

Table 16: AEs by severity and Relation to Study Drug in Studies 18113 and 18114

	Adapalene Lotion, 0.1% (N=1068)	Lotion Vehicle (N=1073)
Number of Events Reported	494	428
Number of Subjects Who Reported One or More Events	354 (33.1%)	300 (28.0%)
Number of Related Events	118	49
Number of Serious Events Reported	3	2
Number of Subjects Who Reported at Least One Serious Event	2 (0.2%)	2 (0.2%)
Severity[a]		
Mild	264 (24.7%)	198 (18.5%)
Moderate	83 (7.8%)	95 (8.9%)
Severe	7 (0.7%)	7 (0.7%)
Relationship to Study Medication[b]		
Not Related	245 (22.9%)	251 (23.4%)
Related	109 (10.2%)	49 (4.6%)

[a] Subjects are counted once under the greatest reported severity.
[b] Subjects are counted once under the highest reported attribute.

Source: Sponsor's Table 12-14

Only events in the system organ classes of skin and subcutaneous tissue disorders (both treatment groups) and eye disorders (lotion vehicle treatment group only) were considered treatment-related by the investigators. Of the 7 events categorized by investigators as "severe", two were considered related. These were skin burning sensation and skin discomfort reported by two subjects.

Reviewer comment: This reviewer agrees that 2 out of 7 severe AEs were likely to be related to the study drug and that the number of subjects who developed treatment related severe AEs was very small.

Adverse events leading to dose adjustment:
Temporary adjustments to the treatment regimen were permitted as outlined in each of the protocols for the pivotal studies (18113 and 18114). If subjects experienced excessive dryness or irritation then the Investigator could consider use of a moisturizer. If the dryness or irritation continued then an altered dosing regimen to every other day could then be considered. If the once daily dosage regimen was altered (i.e., to treat local irritation) an attempt was to be made by the Investigator to return the subject to once daily treatment within two weeks of the interruption.

Reviewer comment: This information would be useful in the clinical trial section of the label and in the patient counseling information

7.3.5 Submission Specific Primary Safety Concerns

There were no additional submission specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The pivotal Phase 3 studies 18113 and 18114 were the only well-controlled studies 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) (see 7.4.5 Special Safety Studies/Clinical Trials). These signs and symptoms were reported as AEs only if their severities interrupted a subject's participation in the study, resulted in a subject's discontinuation from the study, or required a subject to use concomitant prescription or over-the-counter therapy during the study.

Treatment related AEs from the combined controlled clinical studies that occurred in greater than 1% of subjects who used Differin Lotion, 0.1% included dry skin (7.7%) and skin irritation (1.5%). Skin discomfort/ burning (0.9%) occurred more frequently in the treatment arm. Pruritus (0.7%) and sunburn (0.6%) were similar in both treatment groups. The following table shows adverse events occurring at rates of ≥1% or more (> 1 subject) in either study arm in the phase 3 studies.

Table 17: AEs with rate ≥1% in studies 18113 and 18114, ITT population

	Differin ($N = 1068$)	Vehicle ($N = 1073$)
Infections and infestations		
Nasopharyngitis	49 (4.6)	47 (4.4)
Upper respiratory tract infection	34 (3.2)	39 (3.6)
Influenza	13 (1.2)	20 (1.9)
Bronchitis	11 (1.0)	4 (0.4)
Pharyngitis streptococcal	9 (0.8)	8 (0.7)
Sinusitis	9 (0.8)	8 (0.7)
Gastroenteritis viral	5 (0.5)	9 (0.8)
Pharyngitis	4 (0.4)	9 (0.8)
Nervous system disorders		
Headache	25 (2.3)	18 (1.7)
Reproductive system and breast disorders		
Dysmenorrhoea	4 (0.4)	9 (0.8)
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	12 (1.1)	13 (1.2)
Nasal congestion	9 (0.8)	4 (0.4)
Sinus congestion	6 (0.6)	10 (0.9)
Skin and subcutaneous tissue disorders		
Dry skin	82 (7.7)	32 (3.0)
Skin irritation	16 (1.5)	8 (0.7)
Pruritus	7 (0.7)	8 (0.7)
Sunburn	6 (0.6)	5 (0.5)

Source: Agency biostatistical review

Reviewer comment: The reported incident rates for each preferred term were similar between Differin Lotion, 0.1% and vehicle except for dry skin which was reported in a higher percentage of subjects treated with Differin Lotion, 0.1%. Local cutaneous adverse events are as expected for topical retinoids and are comparable to the rates for the other Differin products.

The Agency's statistical analysis of adverse events differed by one subject in the applicant's table 12-15 for dry skin. The label should reflect the Agency's analysis of 82 subjects (7.7%). In

this reviewer's opinion preferred terms "Skin burning" and "Skin discomfort" should be combined and reported in the label as follows:

Dry skin	82 (7.7%)	32 (3.0%)
Skin irritation	16 (1.5%)	8 (0.7%)
Skin burning/ skin discomfort	10 (0.9%)	0 (0.0%)
Sunburn	6 (0.6%)	6 (0.6%)

7.4.2 Laboratory Findings

Hematology and Blood Chemistry testing was performed in 13 subjects as part of the PK study (18108). No clinically significant values or trend related to treatment was demonstrated.

No clinical laboratory assessments were conducted in the cumulative irritation, contact sensitization or phase 3 trials.

7.4.3 Vital Signs

In the PK study 18108, vital signs were assessed at the screening and end of treatment. No clinically significant values or trend related to treatment was demonstrated. There were no vital signs collected as part of either study 18110 or 18111.

In the Phase 3 studies, vital signs were collected at Baseline and Week 12 (or last study visit) for all randomized subjects. There were no patterns of clinically important changes indicative of a toxic effect following 12 weeks of treatment with Differin Lotion, 0.1%.

7.4.4 Electrocardiograms (ECGs)

No electrocardiogram data was collected during any phase of drug development. The applicant is requesting a waiver for clinical QT/QTc evaluations and has submitted the following rationale:

(1) Differin Lotion 0.1 % is the same or a lower strength of adapalene compared to marketed products,
(2) Differin Lotion 0.1% leads to similar or lower systemic exposure compared to marketed products,
(3) there is no signal of cardiotoxicity observed from Pharmacovigilance Database, clinical and preclinical studies, and the literature of marketed products.

Reviewer comment: Both this reviewer and the Biopharmacology reviewer, Dr. Cho, agree that information provided in this NDA supports the applicant's conclusion that the systemic exposure following Differin Lotion 0.1 % is low. This in addition to the long history of marketed use of the active ingredient without a signal of cardiotoxicity, as well as supportive pre-clinical data adequately addresses the requirements established in ICH Guidance E14. This reviewer concurs

that no additional cardiac studies are needed to support approval or as part of a post marketing study.

7.4.5 Special Safety Studies/Clinical Trials

Local Tolerability Assessment:
In both phase 3 studies 18113 and 18114, local tolerability was actively assessed at each visit by evaluating signs and symptoms of dryness, erythema, scaling, and stinging. Reactions were scored as follows: 0 = none, 1 = mild, 2 = moderate 3 = severe. Local reactions were shown to peak at week 1 and lessen over the course of the 12 week trial. Therefore, both maximum severity and end of treatment severity were analyzed. A summary of the results for each of the tolerability assessments from the Agency's analysis is shown in the table below.

Table 18: Local Tolerability Assessments for Studies 18113 and 18114

Combined Study 1 and Study 2	Maximum Severity During Treatment (*N* = 1057)			Week 12 Treatment Severity (*N* = 950)		
Local Cutaneous Irritation (skin irritation)	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	38.7%	10.3%	0.3%	18.8%	2.6%	0.0%
Scaling	32.2%	7.1%	0.1%	7.5%	1.1%	0.0%
Dryness	46.0%	8.4%	0.3%	10.2%	2.3%	0.0%
Stinging/burning	24.2%	7.2%	0.9%	4.8%	1.1%	0.1%

Source: Agency Biostatistical Analysis

For all local skin reactions the mean profile of Differin Lotion, 0.1% is above that of its vehicle. The applicant submitted analysis which differed significantly from the Agency's analysis. The applicant determined local cutaneous irritation as worse than baseline.

Table 19: Local Tolerability Assessments Worse than Baseline for Studies 18113 and 18114

	Adapalene Lotion, 0.1%			Lotion Vehicle		
Local Cutaneous Irritation[a]	Mild	Mod	Severe	Mild	Mod	Severe
Erythema	21.8%	8.0%	0.2%	15.3%	5.3%	0.0%
Scaling	25.3%	6.5%	0.1%	14.1%	2.7%	0.0%
Dryness	36.1%	7.3%	0.3%	16.9%	3.0%	0.1%
Stinging/burning	22.1%	7.0%	0.9%	6.1%	2.7%	0.0%

[a] Worse than Baseline

Reviewer comment: It appears that the applicant's analytical approach may have been used for Epiduo and Differin 0.3% gel based on labels which report a maximum severity worse than baseline. However, this approach discounts subjects from the analysis, affecting the sample size,

which results in a more favorable outcome. It is this reviewer's opinion that labeling would be more clinically informative to include the Agency's analysis in the label, especially for assessment of tolerability after 12 weeks of use regardless of baseline cutaneous irritation.

Dermal Safety Studies:
Dermal safety of Differin Lotion 0.1%was evaluated in studies 18110 (a provocative cumulative irritancy trial) and 18111 (a contact sensitization trial). Both studies were submitted to IND 76,057 and reviewed by Dr. David Kettl on September 22, 2008. Details of the protocol are described in that review.

Study 18110: A Single Center Evaluation of the Cumulative Irritation of Adapalene Lotion, 0.1% and Adapalene Vehicle Lotion Following Repeated Topical Application to Healthy Subjects

This was a single-center, test site randomized, clinical trial designed to evaluate the relative cumulative irritation potential of two different test articles when compared to a negative and positive control following 15 daily applications (Monday through Friday) to the skin of normal, healthy adult volunteers. Each test site was evaluated by a clinical evaluator for signs of irritation, pruritus, burning/stinging and tape reaction.

Number of Subjects: 50 enrolled, 44 completed; aged 18-65 years, mean age of 44.2 years; 72% were female and 28% were male; 56% were Caucasian, 26% African American, 14% Hispanic and 4% Other.

Subject Disposition:
Fifty (50) subjects were enrolled in the study, of which 44 completed the study. Six (6) subjects were discontinued from the study for the following reasons:

- One (1) test subject [Subject No. 13] was discontinued due to tape reaction (tape dermatitis) at the test sites.
- Four (4) test subjects [Subject Nos.: 14, 45, 48 and 50] were discontinued due to noncompliance (excessive missed visits or unwillingness to follow procedures outlined in the protocol).
- One (1) test subject [Subject No. 26] was discontinued due to a serious adverse event.

Efficacy assessments were not performed in this study.

Adverse events:
One serious adverse event occurred during the course of the study, and involved a severe motorcycle accident causing multiple fractures and necessitating hospital admission. This was assessed as unrelated to study treatment.

Four non-serious adverse events were reported: a test site reaction from white petrolatum, low back pain, head cold, and wrist surgery for an injury that occurred prior to the start of the study. Only the first was judged as related to the study test materials.

Irritancy of each test article was evaluated by assessment of the application sites. Observed and perceived responses, e.g., erythema, tape reaction, pruritus and burning/stinging) were graded according to the protocol-specified grading scales.

Individual Cumulative Irritation Index (CII) results were averaged across subjects to obtain a Mean Cumulative Irritancy Index (MCII) for each product. Worst scores for each subject were tabulated. The responses are summarized in the following tables:

Table 20: Total Clinical Irritation Scores

		Total Clinical Scores			
Sponsor's Test Article Codes	RCTS' Test Article Codes	Cumulative Irritation	Pruritus	Burning/Stinging	Tape Reaction
Adapalene Vehicle Lotion	2264.1171	344	243	56	675
Adapalene Lotion, 0.1%	2264.1172	539	263	67	693
0.2% Sodium Lauryl Sulfate*	2264.1173	2645	509	126	460
White Petrolatum	2264.1174	351	204	44	675

*Tested as a 0.2% aqueous dilution (w/v in deionized water)

Table 21: Mean Cumulative Irritancy Index (MCII)

Sponsor's Test Article Codes	RCTS' Test Article Codes	MCII (SD)**
Adapalene Vehicle Lotion	2264.1171	0.37 (0.35)
Adapalene Lotion, 0.1%	2264.1172	0.58 (0.47)
0.2% Sodium Lauryl Sulfate*	2264.1173	2.86 (0.54)
White Petrolatum	2264.1174	0.38 (0.44)

*Tested as a 0.2% aqueous dilution (w/v in deionized water)
SD = Standard Deviation

Under the conditions of the study, adapalene vehicle lotion and adapalene lotion, 0.1% had mean calculated cumulative irritancy indices of 0.37 and 0.58, respectively. The positive control (Sodium Lauryl Sulfate) and the negative control (white petrolatum) had mean calculated cumulative irritancy indices of 2.86 and 0.38, respectively. The mean cumulative irritancy index scores of adapalene vehicle lotion, adapalene lotion, 0.1% and the negative control are indicative of test articles with a mild irritation profile.

The conclusion from Dr. Kettl's review: *"This reviewer concurs with the assessment of the investigator that the irritancy index scores indicate a mild irritation profile for adapalene lotion 0.1%. The scores for the positive and negative controls are typical for these types of studies and are consistent with the results of the test products."*

Study 18111: A Single Center Evaluation of the Contact Sensitization of Adapalene Lotion (0.1%) and Placebo for Adapalene Lotion (0.1%) Following Repeated Topical Applications to Healthy Subjects

This was a Human Repeat Insult Patch Test (HRIPT) to determine the contact sensitization potential of [adapalene lotion (0.1%) and vehicle by repetitive applications to the skin of approximately two hundred (200) normal, healthy adult volunteers.

This was a single-center, double blinded, test site randomized, clinical trial and was divided into two phases: Induction and Challenge. During the induction phase of the study, each subject had three application sites on their backs, between the left scapula and the spinal midline, designated for product/patch application. Patch test sites were randomized to eliminate test site bias. Occlusive patches of the test articles [white petrolatum, Placebo for adapalene lotion (0.1%) and adapalene lotion (0.1%)] were applied to the same test sites every Monday, Wednesday and Friday for three (3) consecutive weeks for a total of nine applications. Patches applied on Mondays and Wednesdays were worn for approximately 48 hours and patches applied on Fridays were worn for approximately 72 hours.

Test sites were evaluated 5-15 minutes after patch removal. After the removal of the last Induction patch, subjects underwent a rest period, which lasted approximately 7-18 days, where no patches were applied.

Seven to eighteen days after the last induction patch application subjects returned to the testing facility for the challenge phase at which time occlusive patches of the vehicle and adapalene lotion (0.1%) were applied to the right side of their backs, at previously unpatched virgin sites, between the right scapula and spinal midline (Note: White Petrolatum was not evaluated during the challenge phase). Patch test sites were randomized to eliminate test site bias.

The patches remained in contact with the skin for approximately 48 hours after which they were removed. Test site evaluations were made 15-30 minutes after challenge patch removal and again approximately 24 hours after challenge patch removal, and were also evaluated at 96 hours after patch removal if test site reactivity warranted additional visits.

At each study visit test site evaluations were performed by a blinded evaluator for 1) signs of irritation 2) pruritus 3) burning/stinging and 4) tape reaction.

Efficacy assessments were not made in this study.

The irritancy/contact sensitization potentials were evaluated by assessment of the application sites. Observed and perceived responses (e.g., erythema, tape reaction, pruritus and burning/stinging) were graded according to the protocol-specified grading scales.

Two hundred and fifty (250) subjects were enrolled in the study, of which 203 completed the study. Forty-seven (47) subjects were discontinued from the study. 2 had violations of inclusion

criteria (possible cancer and HIV positive blood test), 4 experienced tape reactions at the test sites, 32 discontinued for noncompliance, and 9 were lost to follow up.

No deaths, serious adverse events, pregnancies or other unexpected events were reported during this study. 21 adverse events were reported, all non-serious events that were unrelated to the study product except for irritation at the application site which is discussed below.

The mean cumulative irritancy index was similar for all three test products:

Table 22: Mean Cumulative Irritancy Index

Sponsor's Test Article Codes	RCTS' Test Article Codes	MCII (SD)**
Placebo for Adapalene Lotion (0.1%)	2265.1155	0.24 (0.21)
Adapalene Lotion (0.1%)	2265.1158	0.31 (0.24)
White Petrolatum	2265.1159	0.24 (0.19)

SD = Standard Deviation

Scores between 0 and 1 are categorized as mildly irritating.
The primary measure of the induction of contact sensitization was determined through assessments of the application sites during the challenge phase of the study. The conclusion of the sponsor was that the reactivity observed for both adapalene lotion 0.1% and its vehicle were not considered evidence of induced contact sensitization.

250 subjects enrolled (203 completed). Five subjects had initial skin reactions at the 96 hour evaluation of the challenge phase, but upon re-challenge, no visible erythema or edema was present.

The conclusion from Dr. Kettl's review: "*This reviewer concurs with the assessment of the investigator that the irritancy index scores indicate a mild irritation profile for adapalene lotion 0.1%, and no evidence that either adapalene lotion 0.1% nor its vehicle demonstrated evidence of induced contact sensitization.*"

Reviewer comment: Consistent with the phase 3 studies, the provocative cumulative irritation study (18110) demonstrates that Differin Lotion, 0.1% causes cutaneous irritation and should be labeled as such.

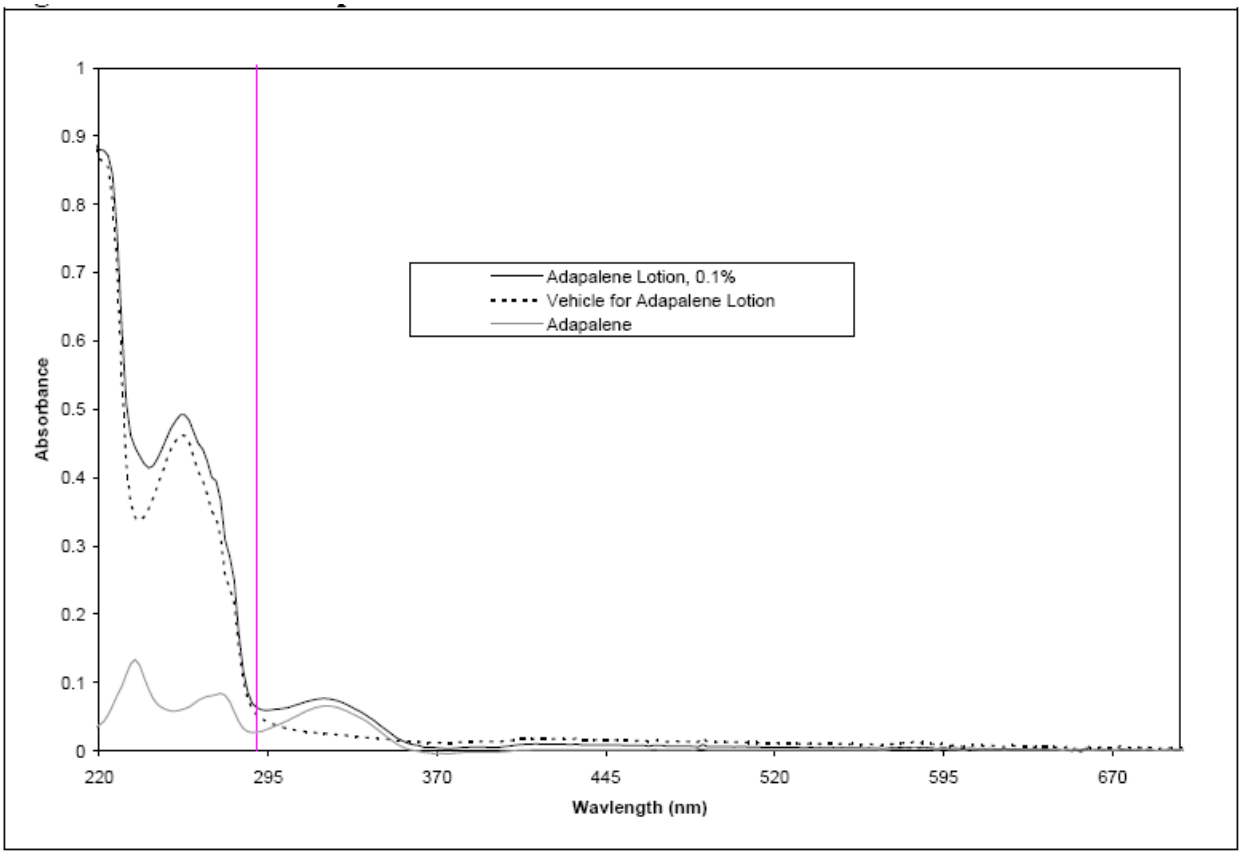
No Phototoxicity or Photoallergy studies were conducted. The applicant is requesting a waiver based on the negative findings in previous phototoxicity/photoallergenicity studies with various adapalene formulations, and the absence of absorption of visible light and UV light above 290nm by the vehicle of the lotion.

The applicant discussed the possibility of a waiver at the preIND meeting of February 26, 2007. The Agency's response was:

> "This may be acceptable as long as labeling similar to currently approved Differin (adapalene) products is agreed to with the Agency."

The applicant submitted UV-Vis spectra comparing adapalene Lotion with its vehicle and adapalene alone. Absorbance above 290 nm was seen for Differin Lotion, 0.1%. However, the applicant proposes the UV absorbance is due to the adapalene moiety which has been evaluated in phototoxicity/ photoallergenicity studies during the development of other, currently approved, Differin products.

Figure 7: UV-Vis Spectrum of Adapalene, Adapalene Lotion, 0.1% and its Vehicle



Based on analysis of the above UV spectra, the Agency sent the following Information Request:

> *Submit your waiver request with accompanying rationale for phototoxicity and photoallergenicity studies along with the UV absorption spectrum of your final to-be marketed drug formulation and other approved topical adapalene products for comparison.*

The applicant's position is that no additional phototoxicity or photoallergy studies should be required because the absorbance of Differin Lotion, 0.1% was similar to the other adapalene-containing products currently on the market. A comparison of the spectra of the Differin products demonstrates very similar absorbance in the region above 290 nm (same size and shape) indicating that longer wavelengths of light interact with all of the products in the same manner. Furthermore, the vehicle for Differin Lotion, 0.1% displayed no absorbance above 290 nm, demonstrating that the lotion contains no new chromophores that absorb light between 290 and 700 nm. The UV-spectra for the other Differin products for comparison are below.

Figure 8: Overlaid Scaled Spectra of 0.1% Adapalene Products

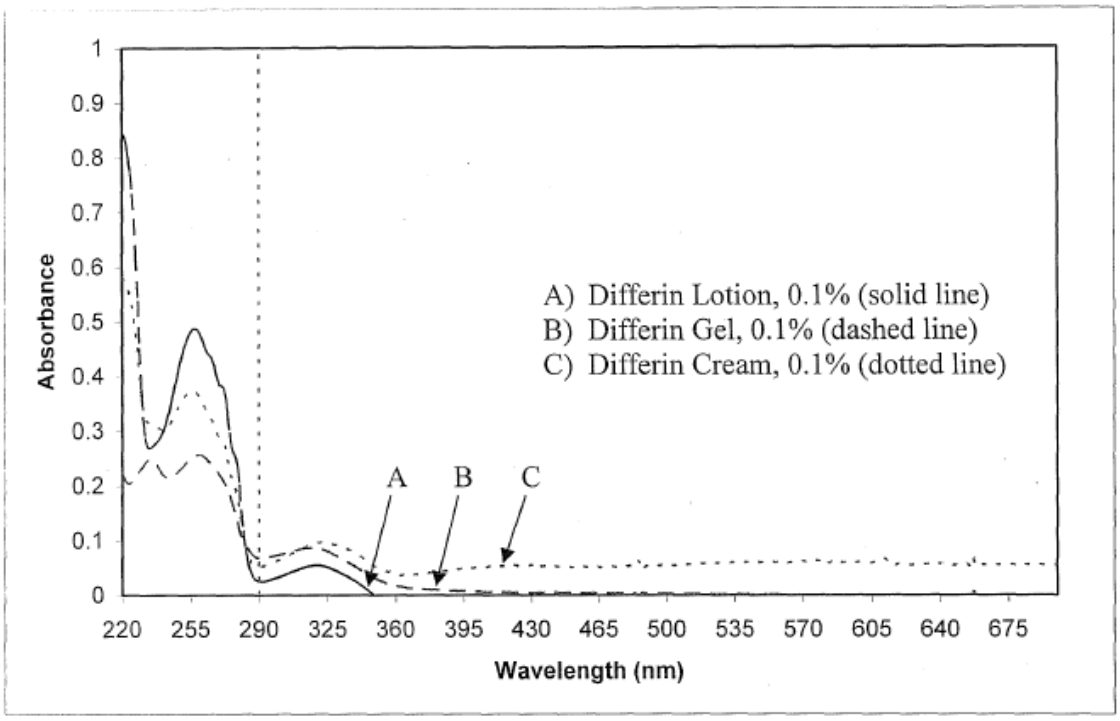
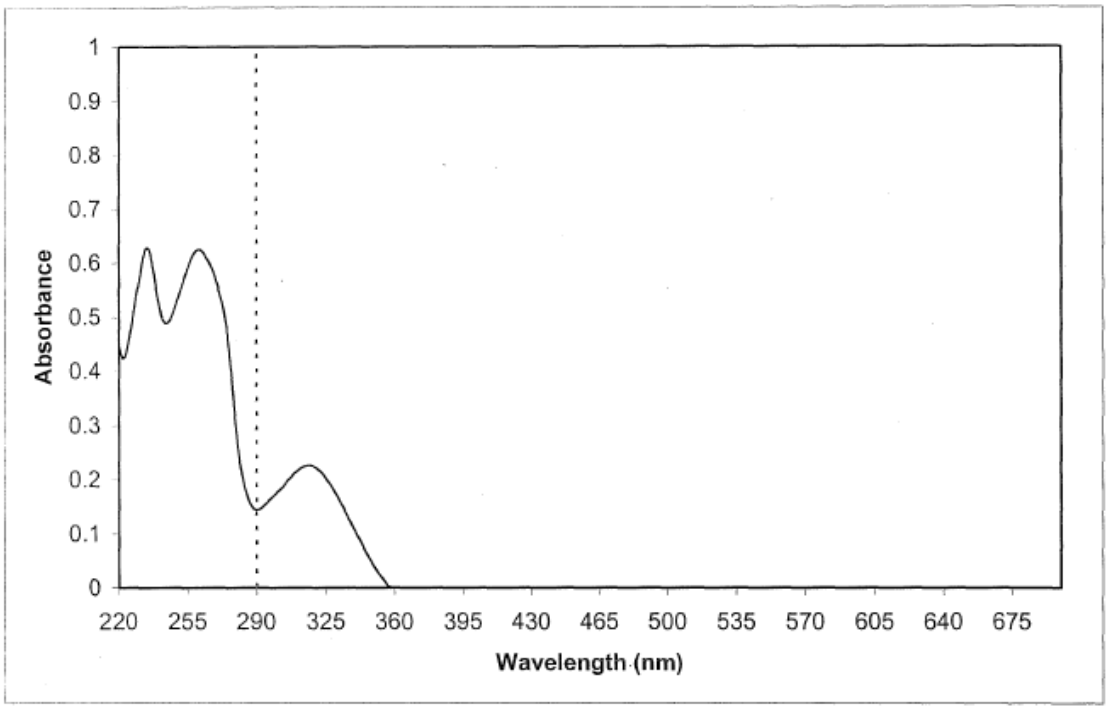


Figure 9: UV-Vis Spectrum of Differin Gel, 0.3%



Reviewer comment: The applicant's rationale seems reasonable. Additionally, the proposed label provides adequate precautions regarding sun exposure that are identical to precautions in the labels of the other Differin products. It is this reviewer's opinion that conducting phototoxicity and photoallergy studies with Differin Lotion , 0.1% would provide no additional information to inform labeling of this product and thus have little regulatory utility. However, granting a waiver to conduct the studies does not imply that the product does not have the potential for causing phototoxicity and/or photoallergic reactions, only that the applicant accepts the proposed labeling to warn related to these issues.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

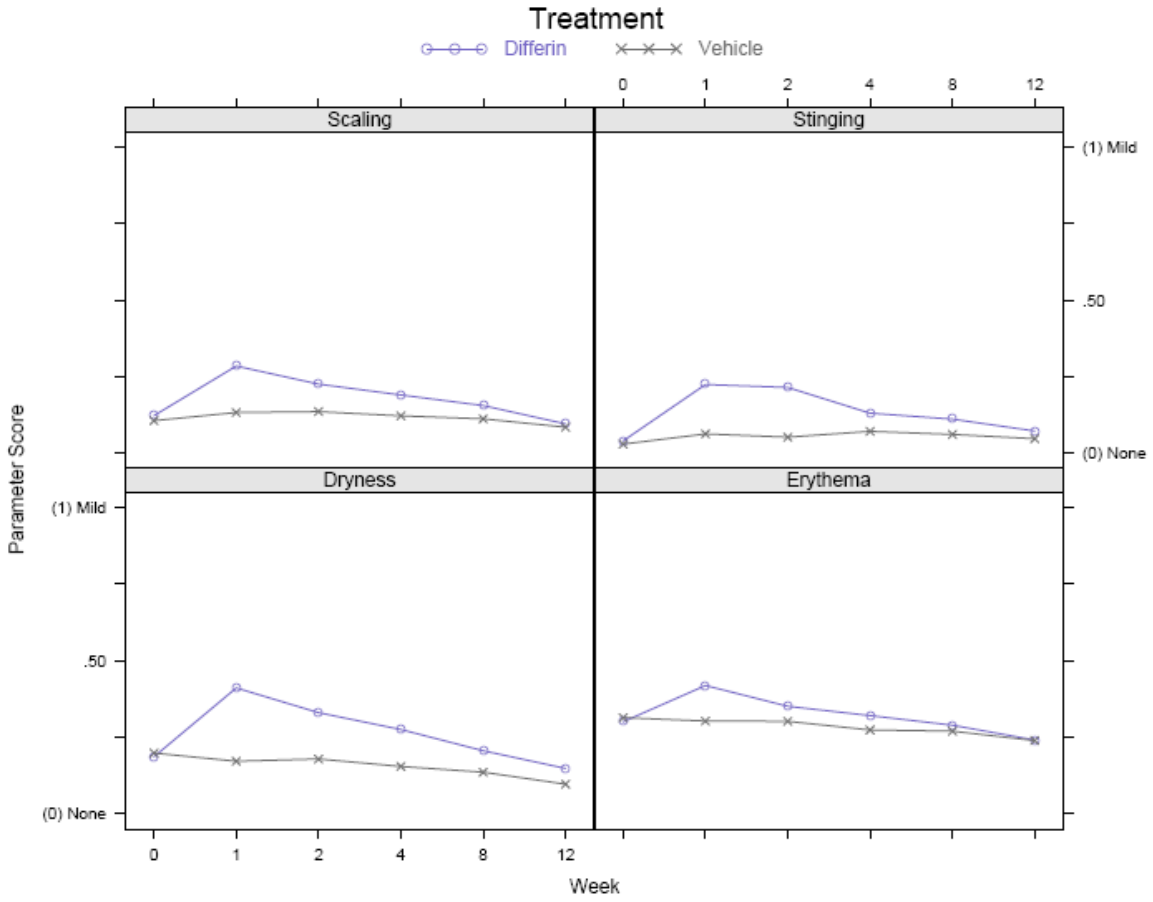
7.5.1 Dose Dependency for Adverse Events

Only one concentration of this formulation, 0.1%, was studied.

7.5.2 Time Dependency for Adverse Events

Local tolerability was prospectively evaluated at baseline and each post-baseline visit (see 7.4.5 Special Safety Studies/Clinical Trials). Analysis of the data depicting the mean profile over time for each local skin reaction grouped by treatment arm demonstrates that the peak of the mean for each local reaction is at Week 1 with a gradual reduction thereafter during the twelve weeks of treatment.

Figure 10: Local Tolerability Assessment Over 12 weeks in Studies 18113 and 18114



Source: Agency Biostatistical Review

Reviewer comment: Precedent products Epiduo and Differin gel 0.3% contain this information in the label. Agency analysis supports the applicant's proposed labeling claim that cutaneous irritation peaks at week 1 and returns to baseline after 12 weeks.

7.5.3 Drug-Demographic Interactions

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

7.5.4 Drug-Disease Interactions

There was no evaluation of drug-disease interactions in the clinical development plan.

7.5.5 Drug-Drug Interactions

There was no evaluation of drug-drug interactions in the clinical development plan.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No tumors were reported in any of the clinical studies.

7.6.2 Human Reproduction and Pregnancy Data

The protocol for each of the clinical studies excluded the participation of pregnant females; nevertheless, in the Phase 3 studies, six subjects, two of whom were in the Differin Lotion, 0.1% treatment group, became pregnant during the course of the trials. Outcomes for both of these subjects are known: Subject 11-02 delivered a healthy baby and Subject 34-50 voluntarily terminated the pregnancy. Narratives of these cases are below:

> Subject 11-02 is a 30 year-old female in study 18113. She had a medical history of depression, anxiety and chronic tendinitis. Concomitant treatment was ibuprofen. The study drug was introduced on 19-DEC-2007. On 21-DEC-2007, the patient became pregnant. Study drug was stopped on 01-JAN-2008. She had an uncomplicated pregnancy and on (b) (6) weeks, delivered a healthy female baby weighing 3225 g with a height of 53.34 cm. Apgar score was 8 after 1 minute and 8 after 5 minutes. Pediatrician examination of the infant was normal.
>
> Subject 34-50 is 16-year-old female in study18113. She had a medical history of hypertension and six previous pregnancies resulting in 2 miscarriages, three elective abortions and one normal child living. Concomitant treatment included lisinopril and hydrochlorothiazide. The study drug was introduced on 05-JUN-2008. Last menstruations occurred on 30-MAY-2008. The study drug was stopped on 29-JUN-2008. On (b) (6) an elective abortion was performed.

Reviewer comment: This reviewer recommends the addition of pregnancy outcome data to the pregnancy precaution section.

7.6.3 Pediatrics and Assessment of Effects on Growth

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: Acne has been shown to begin in the prepubertal period in children as young as 8-9 years old, when the adrenal glands mature and secrete increasing amounts of adrenal androgens, leading to increased production of sebum. However, the three retinoid products, adapalene, tazarotene and tretinoin are approved for prescription use in acne vulgaris in patients ≥12 years. The exceptions are the topical tretinoin product, Atralin (tretinoin 0.05% topical gel) which is approved 7/26/07 for the treatment of acne vulgaris in patients down to 10 years of age and Epiduo (adapalene 0.1%/ benzoyl peroxide 2.5%), approved 12/8/08, which has a post-marketing commitment to study subjects 9 to 11 years of age with acne vulgaris.

Although acne does appear in patients under age 12, albeit less so than in those over 12 years of age, it seems reasonable to grant the waiver from the requirement to conduct studies in patients younger than 12 years old. It is only recently, based on emerging prevalence data, that the Division has requested enrollment of younger children down to age 9 in trials for acne vulgaris. These trials for Differin Lotion, 0.1% were designed and completed prior to this change. Additionally, for the last 7/8 (Epiduo is the exception) products approved since the enactment of PREA, the pediatric study requirements have been waived for patients < 12 years of age.

Keeping the labeled age indication uniform for the Differin product line also seems reasonable to this reviewer. If Differin Lotion, 0.1% is approved for a younger patient population, it is likely the other Differin products, not studied in this patient population, would gain a marketing advantage in a younger patients based on name recognition and cross product confusion.

The Pediatric Review Committee met on November 4, 2009 to review the Differin (adapalene) Lotion, 0.1% partial waiver/appropriately labeled application. The committee agreed with the Division to grant a partial waiver in 0-11 year olds and that the product is appropriately labeled.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions

The applicant submitted a 120-day safety update on June 29, 2009. Differin Lotion is not marketed anywhere and there have been no new studies conducted.

Regarding the other Differin products, 51 post-marketing spontaneous cases were reported from January 26, 2009 to April 30, 2009. The most frequently reported spontaneous Adverse Events (AEs) were “drug ineffective” (14 AEs), “dry skin” (12 AEs), “erythema” (11 AEs), “skin

burning sensation" (9 AEs) and "skin exfoliation" (7 AEs), "skin irritation" (6 AEs), "pain of skin" (6 AEs) and "worsening of acne" (5 cases).

Additionally three cases of photosensitivity reactions have been reported. European authorities had requested a review of nine cases that had already been reported. This review did not lead to any label change due to the fact that all these cases were poorly documented and that in most of the cases, the patients were concomitantly treated with a tetracycline.

Reviewer comment: Based on this information, this reviewer questioned if concomitant use of adapalene with tetracycline or other phototoxic acne treatments could potentiate phototoxicity, requiring additional labeling precautions.

The Division of Dermatology and Dental Products (DDDP) requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Event Reporting System (AERS) database for post-marketing reports of adapalene in association with phototoxicity when used concomitantly with tetracycline or doxycycline.

Dr. Tracy Salaam conducted the search of the AERS database which retrieved one case. The case is unclear regarding whether adapalene and doxycycline were used at the same time or if these treatments were still being used at the time sun sensitivity was reported. The case is also confounded by the use of other medications that are also labeled for an association with photosensitivity (isotretinoin, doxycycline, tetracycline, and tretinoin). Refer to Dr. Salaam's review for additional details of the AERS search.

Reviewer comment: No labeling changes are warranted for this potential drug-drug interaction.

8 Postmarket Experience

The applicant has provided the following information regarding postmarketing experience for Differin products. Differin Lotion is not currently marketed.

The estimated number of patients exposed to Differin formulations during the September 1995 through 28 September, 2007 review period is more than (b) (4) patients. Up toSeptember 28, 2007, 2110 serious and non serious adverse events have been spontaneously reported during post-marketing surveillance. These cases do not include case reports linked to pregnancies and miscarriages. The safety information is consistent with the known safety profile of adapalene and there were no unexpected safety signals. The most frequently reported AEs by Preferred Term included erythema, skin exfoliation, skin irritation and burning, pruritus, dry skin, eczema and irritant contact dermatitis.

Regarding pregnancies, up to July 2, 2008, 189 cases of pregnancy exposed to adapalene have been collected. The rates of congenital malformations, miscarriage and elective abortion were not statistically different to the expected rate in the general population.

Reviewer comment: This reviewer agrees that no new safety signals are seen in the post-marketing reports other than the possible potentiating effect on phototoxicity which has been reviewed by DPV1 as described in 7.7 Additional Submissions.

9 Appendices

9.1 Literature Review/References

No literature was reviewed for this NDA.

9.2 Labeling Recommendations

11 Page of Draft Labeling as been withheld in full after this page as B4 (CCI/TS)

GALDERMA is a registered trademark. (Part Number)

9.3 Advisory Committee Meeting

Not applicable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

AMY S WOITACH
11/10/2009

DAVID L KETTL
11/12/2009
Concur with approval recommendation pending final CMC facility inspection report and acceptance of PK trial PMC and final labeling.

DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA 22-502

Differin (Adapalene)Lotion 0.1% Galderma IND: 76057

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	Electronic CTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	YES			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	YES			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	YES			
5. Are all documents submitted in English, or are English translations provided when necessary?	YES			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	YES			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	YES			Draft PLR label in word and SPL format.
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	YES			Overview and summaries present
9. Has the applicant submitted the integrated summary of safety (ISS)?	YES			Module 5.3.5.3
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	YES			Module 5.3.5.3
11. Has the applicant submitted a benefit-risk analysis for the product?	YES			Module 2.5.6
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(1)			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		NO		No dose ranging studies were conducted. Same dose as Differin solution, gel, and cream
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 18113 Subjects enrolled: 1075 Indication: acne vulgaris in subjects 12-50 years old	YES			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

Pivotal Study #2 18114 Subjects enrolled: 1066 Indication: acne vulgaris in subjects 12-64 years old				
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	YES			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	YES			At EOP2 meeting the Agency agrees that absolute change in lesion counts should be used together with success for the IGA as co-primary evaluations.
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			N/A	US and Canadian sites 13: 32 US/7 Ca. 14: 31 US/5 Ca.
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	YES			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?			N/A	
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?		NO		Previously submitted/approved NDAs for Differin are referenced
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	YES			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			N/A	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	YES			Module 1.9.1 Waiver < 12 years of age
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			N/A	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			N/A	
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	YES			
27. Has the applicant submitted datasets in the format agreed to	YES			

previously by the Division?				
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	YES			
29. Are all datasets to support the critical safety analyses available and complete?	YES			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	YES			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	YES			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			N/A	None were requested, no additional CRFs submitted
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	YES			1 investigator, (b) (6) is a shareholder in DPS
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	YES			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	YES			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Submit your waiver request with accompanying rationale for phototoxicity and photoallergenicity studies along with the UV absorption spectrum of your final to-be-marketed drug formulation and other approved topical adapalene products for comparison.

Amy Woitach, D.O. April 14, 2009

Reviewing Medical Officer

David Kettl, M.D.

Clinical Team Leader

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/s/

Amy S Woitach
4/27/2009 09:12:02 AM
MEDICAL OFFICER

David Kettl
4/27/2009 09:15:45 AM
MEDICAL OFFICER