

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-748

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
ADDENDUM TO THE AMENDMENT

JAN 31 2000

NDA/DRUG CLASS: 20-748/3S

NAME OF DRUG: Differin Cream (Adapalene Topical, 0.1%)

APPLICANT: Galderma Laboratories, Inc.

INDICATIONS: Topical Treatment of Acne Vulgaris

TYPE OF REVIEW: Statistical

DOCUMENTS REVIEWED: Study SRE18035, Dated 9/20/99

MEDICAL REVIEWER: Phyllis Huene, M.D./HFD-540

STATISTICAL REVIEWER: Shahla S. Farr, M.S./ HFD-725

I. INTRODUCTION

This is an addendum to the statistical review for NDA 20-748, dated 9/20/99 the Differin (adapalene) cream in treating patients with mild to moderate acne vulgaris. The purpose of this addendum is to address R. Srinivasan, Ph.D., the previous team leader, about "Baseline Value Carried Forward" (BVCF), instead of the "Last Observation Carried Forward" (LOCF) in performing the Intent-to-Treat (ITT) analyses.

II. REVIEW

The results of this review were based on the Week 12, ITT population, where ITT includes all subjects who were randomized to the study and were given the study medication, (active or placebo) regardless of their use of the dispensed drug. For subjects with no week 12 data available, their baseline data was carried forward as the last available observation.

A total of 237 subjects were randomized to participate in this study; One hundred and nineteen in the Differin 0.1% arm and 118 subjects were randomized to the Vehicle group. At the end of week 12, 107 (90%) of the Differin group and 106 (90%) of the vehicle arm had finished the study.

Table I lists the number of drop outs at the end of treatment by treatment arm:

Table I
Drop Outs

	Whole Population N = 237	Differin N = 119	Vehicle N = 118
Drop Outs	24 (10%)	12 (10%)	12 (10%)

The sponsor had used the LOCF method to create their ITT population to perform their analyses. The results of this review was based on BVCF, which are similar to the sponsor's findings. For that reason alone, this reviewer justifies that the method of BVCF is robust and produced acceptable results.

Table II illustrates the results of the primary endpoint variables based on sponsor's and the reviewer's ITT analysis.

Table II
Mean Percent Change ± SD in Lesion Counts
ITT

% Change from Baseline	Differin (n=119)	Vehicle (n=118)	P-Value
Inflammatory			
Sponsor (LOCF)	-32% ± 41%	-16% ± 49%	0.007
FDA (BVCF)	-32% ± 40%	-17% ± 46%	0.008
Non-Inflammatory			
Sponsor (LOCF)	-35% ± 37%	-19% ± 51%	0.005
FDA (BVCF)	-34% ± 35%	-18% ± 50%	0.004
Total Lesion			
Sponsor (LOCF)	-35% ± 32%	-18% ± 43%	0.001
FDA (BVCF)	-34% ± 31%	-18% ± 40%	0.001

As seen in Tables II, no significant differences were observed between the results of the sponsor and results of the FDA reviewer.

III. CONCLUSION:

Based on these findings, it can be concluded that the ITT analyses based on LOCF and BVCF are both reliable outcomes and acceptable for the review of this NDA.

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Archival NDA 20-748

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STATISTICAL REVIEW AND EVALUATION
AMENDMENT

NDA/DRUG CLASS: 20-748/3S

NAME OF DRUG: Differin Cream (Adapalene Topical, 0.1%)

APPLICANT: Galderma Laboratories, Inc.

INDICATIONS: Topical Treatment of Acne Vulgaris

TYPE OF REVIEW: Statistical

DOCUMENTS REVIEWED: Study SRE18035, Dated 9/20/99

MEDICAL REVIEWER: Phyllis Huene, M.D./HFD-540

STATISTICAL REVIEWER: Shahla S. Farr, M.S./HFD-725

I. INTRODUCTION

This amendment to the NDA 20-748 is to assess the safety and efficacy of Differin (adapalene) cream in treating patients with mild to moderate acne vulgaris.

Previously, the sponsor had submitted two pivotal, Phase 3 clinical studies, one of which was a vehicle-controlled, double-blind study, conducted in U.S. and Canada and the other was a reference-controlled, investigator-blind study, conducted in Europe, both for 12 weeks. The reference-controlled study was intended to show non-inferiority of Differin Cream to Retin-A. But, the results of this study were inconclusive. Therefore, the sponsor performed another study to demonstrate the superiority of Differin Cream to its Vehicle and submitted an amendment to the first submission. The review is based on the results of this amendment.

II. REVIEW

The sponsor has performed a single pivotal, Phase 3, vehicle-controlled, double-blind study to demonstrate the superiority of Differin Cream 0.1% to its Vehicle in treatment of mild to moderate acne vulgaris for 12 weeks. Table I lists this pivotal study:

Table I
Summary of Study SRE 18035

# of Centers	Study Design, Duration	Treatment Arm (n)	N	Endpoint
10	Parallel, Multicenter, Randomized, Vehicle-Controlled, Double-Blind (12 weeks)	1) Differin Cream 0.1% qid (119) 2) Differin Vehicle qid (118)	237	1) Reduction in Total Lesion Count 2) Reduction of Non-inflammatory Lesn 3) Reduction of Inflammatory Lesions 4) Global Assessment of Acne Severity

Study SRE 18035:

Objective, Design, Primary Efficacy Variable, Patient Population and Statistical Methods:

The objective of this trial was to assess the efficacy and safety of Differin cream administered topically once a day at bedtime for the treatment of acne vulgaris.

This was a multicenter (10 center), randomized, double-blind, placebo-controlled with two parallel treatment arms: Differin 0.1% cream or the adapalene vehicle administered once a day for 12 weeks.

The minimum number of non-inflammatory and inflammatory lesions required to enter this study was 20 and 10 respectively.

Primary efficacy variables were:

- 1) The mean percent change from baseline in the Total Lesion Count
- 2) The mean percent change from baseline in the Non-inflammatory Lesions (open and closed comedones)
- 3) The mean percent change from baseline in the Inflammatory Lesions (papules, pustules, nodules and cysts), and
- 4) The Global Assessment of Acne Severity; FDA's requirements for global assessment have changed. This parameter was examined in a dichotomized fashion, with two outcome categories, success and failure. At the end of the treatment, the values of 0 and 0.25 (completely clear or almost clear) were pooled in one category as "Success" (cured) and the rest were classified as "Failure" (not cured).

To qualify for study entry, patients were required to be between the ages of 12 to 30 and to have mild or moderate acne vulgaris of the face.

The results of this review are based on the Week 12, Intent-to-Treat (ITT) population, where ITT includes all subjects who were randomized to the study and were given the study medication,

(active or placebo) regardless of their use of the dispensed drug. For subjects with no week 12 data available, their baseline data was carried forward as the last available observation.

The sponsor has performed an analysis of covariance on square root transformed data to analyze the primary efficacy lesion counts at each study visit and endpoint. In this review, an analysis of variance (ANOVA) was performed on the mean percent change from baseline on the primary endpoint variables using the original data, with and without center interaction. Categorical variables (e.g., race, gender, global assessment) were analyzed using a Chi-Square and CMH test. Continuous variables (age, weight, mean percent change in lesions) were analyzed using one-way and two-way analysis of variance (ANOVA).

In order to show efficacy of this formulation, the sponsor should demonstrate statistical superiority of Differin to its vehicle in two out of three of the objective primary endpoint variables (percent reduction of lesion counts), in addition to the global assessment of acne severity, at a two-sided $\alpha=0.05$.

Demographics and Baseline Characteristics:

A total of 237 subjects were randomized to participate in this study; One hundred and nineteen in the Differin 0.1% arm and 118 subjects were randomized to the Vehicle group.

Tables II and III summarize the demographics and baseline characteristics of these subjects respectively.

Table II
Demographics of All Randomized Subjects

	Whole Population (N=237)	Differin (n=119)	Vehicle (n=118)	P-Value
Gender (n):				0.3
Male	125 (53%)	59 (50%)	66 (56%)	
Female	112 (47%)	60 (50%)	52 (44%)	
Race (n):				0.9
White	176 (74%)	89 (75%)	87 (74%)	
Black	14 (6%)	7 (6%)	7 (6%)	
Oriental	4 (2%)	3 (3%)	1 (1%)	
Hispanic	39 (16%)	18 (15%)	21 (18%)	
Other	4 (2%)	2 (2%)	2 (2%)	
Age (Mean ± SD):	17.4 ± 4.3	17.5 ± 4.4	17.3 ± 4.1	0.7

Table III
Baseline Characteristics of All Randomized Subjects
Mean ± SD

	Differin (n=119)	Vehicle (n=118)	P-Value
Inflammatory Lesions	21 ± 9	20 ± 8	0.7
Non-Inflammatory Lesions	45 ± 25	46 ± 23	0.8
Total Lesions	66 ± 30	66 ± 27	1.0

As shown in Tables II and III, no statistical difference was found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.3$).

Clinical Efficacy Analysis and Results:

At the end of week 12, 107 (90%) of the Differin group and 106 (90%) of the vehicle arm had finished the study.

Tables IV, V and VI illustrate the results of the primary endpoint variables at different time points for the ITT population.

Table IV
Mean ± SD in Inflammatory Lesion Counts
ITT

(Without Center Adjustment)

	Differin (n=119)	Vehicle (n=118)	P-Value
Baseline	21 ± 9	20 ± 8	0.7
Week-2	18 ± 11	17 ± 9	0.4
Week-4	17 ± 13	17 ± 11	0.9
Week-8	16 ± 14	15 ± 12	0.7
Week-12	14 ± 11	17 ± 12	0.06
% Change from Baseline	-32% ± 40%	-17% ± 46%	0.008

Table V
Mean ± SD in Non-Inflammatory Lesion Counts
ITT

(Without Center Adjustment)

	Differin (n=119)	Vehicle (n=118)	P-Value
Baseline	45 ± 25	46 ± 23	0.8
Week-2	39 ± 29	41 ± 26	0.6
Week-4	35 ± 28	37 ± 24	0.6
Week-8	32 ± 28	39 ± 29	0.09
Week-12	30 ± 25	37 ± 27	0.03
% Change from Baseline	-34% ± 35%	-18% ± 50%	0.004

Table VI
Mean ± SD in Total Lesion Counts
ITT

(Without Center Adjustment)

	Differin (n=119)	Vehicle (n=118)	P-Value
Baseline	66 ± 30	66 ± 27	1.0
Week-2	58 ± 35	58 ± 30	0.9
Week-4	52 ± 35	55 ± 30	0.6
Week-8	49 ± 38	55 ± 34	0.2
Week-12	44 ± 31	54 ± 35	0.02
% Change from Baseline	-34% ± 31%	-18% ± 40%	0.001

As seen in Tables IV, V and VI, highly statistically significant results were observed when Differin was compared to its vehicle in regards to the mean percent change from baseline in inflammatory, non-inflammatory and total lesion counts ($p \leq 0.008$).

In order to analyze the Global Assessment, the values of 0 and 0.25 (completely clear or almost clear) were pooled in one category as "Success" (cured) and the rest were classified as "Failure" (not cured).

Table VII lists the results of the Investigator's Assessment.

Table VII
Global Assessment
Rate of Cure @ Week 12
(Without Center Adjustment)

	Differin (119)	Vehicle (118)	P-Value
Week-12	11 (9%)	5 (4%)	0.1

No statistically significant difference between Differin and vehicle was found ($p=0.1$).

No center by treatment interactions was observed for any of the primary efficacy variables ($p>0.05$).

Safety Analysis:

Burning, dryness, erythema, pruritus and scaling were compared between the two arms . Table VIII gives the p-values for the secondary endpoint variables.

Table VIII
Secondary Endpoint Variables @ Week 12
 (Without Center Adjustment)

Secondary Endpoint Variables	Differin (n=119)	Vehicle (n=118)	P-Value
Burning Mild Moderate Severe	94% 4% 2%	98% 2% 0%	0.3
Dryness Mild Moderate Severe	79% 20% 2%	86% 14% 0%	0.2
Erythema Mild Moderate Severe	84% 14% 2%	86% 13% 1%	0.8
Pruritus Mild Moderate Severe	88% 10% 2%	94% 6% 0%	0.2
Scaling Mild Moderate Severe	87% 12% 1%	93% 7% 0%	0.2

As shown in table VIII, no statistically significant result was observed between Differin and vehicle in regards to burning, dryness, erythema, pruritus and scaling ($p \leq 0.8$).

Subset Analysis:

Since the whole population in the study was between the ages of 12 to 30 a subgroup analysis based on age was not required.

A total of 125 males had participated in this study, of which 59 were in the Differin arm and 66 in the vehicle group. One hundred and twelve women were enrolled, where 60 were randomized in the Differin arm and 52 in the vehicle group. The subset analysis for gender yielded the following results:

Table IX
Mean \pm SD in Percent Change from Baseline
All Primary Endpoint Variables @ Week 12

Primary Endpoint Variables	Males (N=116)			Females (N=112)		
	Differin (n=59)	Vehicle (n=66)	P-Value	Differin (n=60)	Vehicle (n=52)	P-Value*
Inflammatory Lesions	-28% \pm 38%	-18% \pm 46%	0.2	-36% \pm 40%	-16% \pm 46%	0.01
Non-Inflammatory Lesions	-31% \pm 40%	-20% \pm 48%	0.2	-38% \pm 30%	-16% \pm 51%	0.006
Total Lesions	-31% \pm 32%	-20% \pm 40%	0.08	-37% \pm 29%	-16% \pm 45%	0.003

* These P-Values should be interpreted with caution, since the subgroups might not have enough power for the statistical analyses performed.

As shown in Table IX, the male sub-population did not show statistically significant results in regards to the lesion counts ($p > 0.05$). But, the female sub-population showed statistically significance results in the three primary endpoint variables ($p \leq 0.01$). These results should be interpreted with caution, since the statistical power might have diminished by dividing the whole sample size into two groups.

III. CONCLUSION:

The results of the study SRE 18035 demonstrate statistical superiority of the Differin cream over its vehicle in three of the four primary efficacy endpoints (Inflammatory, non-inflammatory and total lesion count) ($p < 0.05$). The global assessment showed no statistical significance ($p > 0.05$) at the end of the 12 week treatment in the ITT population.

No statistically significant results were found in the safety variables (burning, dryness, erythema, pruritus and scaling in study SRE 18035 ($p \geq 0.2$)).

The results of the subgroup analyses showed that there was a statistically significant difference in regards to all the lesion counts ($p < 0.05$) in the female population. But, the male sub-population did not show any statistically significant results ($p > 0.05$) in these endpoint variables.

Based on the findings of this pivotal study (SRE 18035), the sponsor has provided evidence to demonstrate statistical superiority of Differin Cream 0.1% over Vehicle in the topical treatment of Acne Vulgaris in the dynamic endpoints (inflammatory, non-inflammatory and total lesions) ($p < 0.05$). The results of the analyses of the global assessment of the acne severity did not reach statistical significance ($p > 0.05$).

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11/19/99

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This review contains 9 pages.

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The Statistical reviewer has done LOCF analysis of the ITT Population, carrying forward for patients with missing week 12 values. While this is claimed to be most conservative, the correct procedure is to carry forward any measurement value available at some intermediate time points. With this type of analysis, it is possible that the results might be different or same, depending on the number of available measurement values at the intermediate time points, both in the treatment and vehicle groups.

Despite the team leader's several comments to the reviewer about the need for checking for measurement values at intermediate time points, it is very unclear why the reviewer did not attempt to check for the presence of intermediate measurement values to be carried forward in the LOCF analysis.

I suggest that the reviewer should look into the data set again to make sure there are no measurement values at intermediate time points, before carrying the baseline values forward.

SS
Nov. 25, 1999

CLINICAL/STATISTICAL REVIEW AND EVALUATION

MAR 24 1998

NDA/DRUG CLASS: 20-748/ 3S

NAME OF DRUG: Differin Cream (Adapalene Topical, 0.1%)

APPLICANT: Galderma Laboratories, Inc.

INDICATIONS: Topical Treatment of Acne Vulgaris

TYPE OF REVIEW: Clinical/Statistical

DOCUMENTS REVIEWED: Studies: 9111-CD271C-EV & CR90087,
Dated 11/4/97

MEDICAL REVIEWER: Phyllis Huene, M.D./HFD-540

STATISTICAL REVIEWER: Shahla S. Farr, M.S./ HFD-725

I. INTRODUCTION

The purpose of this submission is to assess the safety and efficacy of Differin (adapalene) cream in treating patients with mild to moderate acne vulgaris.

Adapalene is a new chemical entity originating from a series of naphthoic acids with retinoid-like activity and is intended for the topical treatment of acne vulgaris.

II. REVIEW

The sponsor has submitted two pivotal, phase III clinical studies one of which was a vehicle-controlled, double-blind study, conducted in U.S. and Canada (9111-CD271C-EV) and the other was a reference-controlled, investigator-blind study, conducted in Europe (CR90087), both for 12 weeks. These two trials are the focus of this review. Table I lists the two pivotal studies:

**Table I
Summary of Studies**

Study # (# of Centers)	Study Design, Duration	Treatment Arm (n)	N	Endpoint
9111-CD271C-EV (13)	Parallel, Multicenter, Randomized, Placebo-Controlled, Double-Blind (12 weeks)	1) Differin Cream 0.1% qid (175) 2) Differin Vehicle qid (175)	350	1) Reduction in Total Lesion Count 2) Reduction of Non-inflammatory Lesn 3) Reduction of Inflammatory Lesions 4) Global Assessment of Acne Severity
CR 90087 (9)	Parallel, Multicenter, Randomized, Reference-Controlled, Investigator-Blind (12 Weeks)	1) Differin Cream 0.1% qid (136) 2) Tretinoin Cream 0.05% qid (140)	276	1) Reduction in Total Lesion Count 2) Reduction of Non-inflammatory Lesn 3) Reduction of Inflammatory Lesions 4) Global Assessment of Acne Severity

The two studies were similar in terms of the primary efficacy variables, patient population and statistical methodology.

Primary Efficacy Variable, Patient Population & Statistical Methods:

Primary efficacy variables were the mean percent change from baseline in:

- 1) The Total Lesion Count
- 2) The Non-inflammatory Lesions (open and closed comedones)
- 3) The Inflammatory Lesions (papules, pustules, nodules and cysts)
- 4) The Global Assessment of Acne Severity,

The FDA's requirements for global assessment have changed since these trials had been conducted. Therefore, in addition to investigating the mean percent change in the global assessment, this parameter was examined in a dichotomized fashion, with two outcome categories, success and failure. At the end of the treatment, the values of 0 or 0.25 (completely clear or almost clear) were pooled in one category as "Success" (cured) and the rest were classified "Failure" (not cured).

To evaluate the acne severity, the investigators were provided with a photographic acne grader designed by Galderma and based on the Cunliffe grading system of acne.

To qualify for study entry, patients were required to be between the ages of 12 to 30 and to have mild or moderate acne vulgaris of the face.

The results of this review are based on the Week 12, Intent-to-Treat (ITT) population, where ITT includes all subjects who were randomized to the study and were given the study medication, (active or placebo) regardless of their use of the dispensed drug. For subjects with no week 12 data available, their baseline data was carried forward as the last available observation.

Baseline categorical demographic variables (race and sex) were analyzed using Pearson's chi-square test. Continuous demographic variables (age, weight) were analyzed using one-way analysis of variance (ANOVA).

The sponsor has performed an analysis of covariance on square root transformed data to analyze the primary efficacy lesion counts at each study visit and endpoint. In this review, an analysis of variance was performed on the mean percent change from baseline on the primary endpoint variables on the original data, with and without center interaction. In order to gain approval of this formulation, the sponsor should demonstrate statistical superiority of Differin to its vehicle and therapeutic equivalence of Differin to Tretinoin 0.05% on two out of three of the objective primary endpoint variables (percent reduction of lesion counts), in addition to the global assessment at a two-sided $\alpha=0.05$.

Study 9111-CD271C-EV :

Objective & Design:

The objective of this trial was to assess the efficacy and safety of Differin cream administered topically once a day at bedtime as a treatment for the acne vulgaris.

This was a multicenter (13 center), randomized, double-blind, placebo-controlled with two parallel treatment arms: Differin 0.1% cream or the adapalene vehicle administered on a q.i.d. regimen for a 12-week treatment period. This was a U.S./Canada study.

The minimum number of noninflammatory and inflammatory lesions required to enter this study was 30 and 10 respectively.

Sample Size:

Approximately, 300 patients were to be enrolled in this study. Considering 190 evaluable patients at endpoint, a 10% between-treatment difference in total lesion count reduction could be detected with 80% power and alpha level of 0.05, at a two-sided test.

Demographics & Baseline Characteristics:

A total of 350 subjects were randomized to participate in this study. These subjects were equally divided between the two arms.

Although the minimum number of inflammatory and noninflammatory lesions required to enter this study was 10 and 30 respectively, one subject in the vehicle arm had 9 inflammatory and one patient in the Differin group had 27 non-inflammatory lesions at entry to the study.

Tables II and III summarize the demographics and baseline characteristics of these subjects respectively.

Table II
Demographics of All Randomized Subjects
Study 9111-CD271C-EV

	Whole Population (N=350)	Differin (n=175)	Vehicle (n=175)	P-Value
Gender (n):				0.7
Male	205 (59%)	104 (59%)	101 (58%)	
Female	145 (41%)	71 (41%)	74 (42%)	
Race (n):				0.1
White	285 (81%)	145 (83%)	140 (80%)	
Black	17 (5%)	6 (3%)	11 (6%)	
Oriental	12 (3%)	3 (2%)	9 (5%)	
Other	36 (10%)	21 (12%)	15 (9%)	
Age (Mean ± SD):	18.6 ± 5	18.6 ± 5	18.6 ± 5	0.99
Weight (Mean ± SD):	150.6 ± 34	151.6 ± 33	150 ± 34	0.6
Investigator (n):				
	29 (8%)	14 (8%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	
	23 (7%)	11 (6%)	12 (7%)	
	14 (4%)	8 (5%)	6 (3%)	
	14 (4%)	7 (4%)	7 (4%)	
	30 (9%)	15 (9%)	15 (9%)	
	30 (9%)	15 (9%)	15 (9%)	

Table III
Baseline Characteristics of All Randomized Subjects
Mean ± SD
Study 9111-CD271C-EV

	Differin (n=175)	Vehicle (n=175)	P-Value
Inflammatory Lesions	26 ± 18	26 ± 23	0.8
Non-Inflammatory Lesions	75 ± 50	69 ± 40	0.3
Total Lesions	101 ± 56	95 ± 50	0.3
Global Assessment	1.5 ± 0.6	1.5 ± 0.6	0.98

As it is shown in Tables II and III, no statistical difference was found among the two treatment arms in regards to the demographics and baseline characteristics of the subjects.

Clinical Efficacy Analysis & Results:

At the end of the 12th week, 159 (91%) of the Differin group and 162 (93%) of the vehicle arm had finished the study.

Table IV, illustrates the results of the primary endpoint variables at Week-12 for the ITT population.

Table IV
Mean ± SD in Percent Change from Baseline
All Primary Endpoint Variables @ Week 12
(Without Center Adjustment)
Study 9111-CD271C-EV

Primary Endpoint- Variables	Differin (n=175)	Vehicle (n=175)	P-Value
Inflammatory Lesions	0.14 ± 0.53	0.06 ± 0.6	0.2
Non-Inflammatory Lesions	0.35 ± 0.36	0.15 ± 0.64	0.0006
Total Lesions	0.30 ± 0.33	0.15 ± 0.5	0.0008
Global Assessment	0.21 ± 0.25	0.17 ± 0.25	0.1

This reviewer did an independent analysis of global assessment as a dichotomized variable, (cured vs. not cured). No statistically significant difference between Differin and vehicle was found ($p=0.8$).

Table V
Least Square Means in Percent Change from Baseline
All Primary Endpoint Variables @ Week 12
(With Center Adjustment)
Study 9111-CD271C-EV

	Differin (n=175)	Vehicle (n=175)	P-Value
Inflammatory Lesions	0.15	0.07	0.2
Non-Inflammatory Lesions	0.35	0.15	0.0005
Total Lesions	0.30	0.15	0.0004
Global Assessment	0.22	0.17	0.04

As it is seen in Tables IV and V, highly statistically significant results were observed when Differin was compared to its vehicle in regards to non-inflammatory and total lesions regardless of the center interactions ($p \leq 0.0004$). However, inflammatory lesions did not show a statistically significant result with or without the center adjustment ($p=0.2$).

The results of our analysis of the three lesion count primary endpoint variables were similar to that of the sponsor's.

In addition, global assessment of the lesions did not show statistically significant result when the data was analyzed without the center effect ($p=0.1$). But, after adjustment by center a statistically significant result was observed ($p=0.04$).

Secondary Endpoint Variables:

Burning, dryness, erythema, pruritus and scaling were compared between the two arms. Table VI gives the p-values for the secondary endpoint variables.

Table VI
Secondary Endpoint Variables @ Week 12
 (Without Center Adjustment)
 Study 9111-CD271C-EV

Secondary Endpoint Variables	Differin	Vehicle	P-Value
Burning Mild Moderate Severe	92% 6% ---	96% 3% ---	0.3
Dryness Mild Moderate Severe	81% 15% 2%	91% 7% 1%	0.08
Erythema Mild Moderate Severe	74% 17% 7%	79% 18% 1%	0.1
Pruritus Mild Moderate Severe	91% 7% ---	96% 3% ---	0.2
Scaling Mild Moderate Severe	88% 8% 3%	94% 4% 1%	0.2

As it is shown in table VI, no statistically significant result was observed between Differin and vehicle in regards to burning, dryness, erythema, pruritus and scaling ($p \leq 0.08$). However, after adjustment for center, dryness showed a statistically significant difference between Differin and vehicle arm ($p=0.02$).

Subset Analysis:

Since the whole population in the study was between the ages of 12 to 30 a subgroup analysis based on age was not required.

A total of 205 males had participated in this study, of which 104 were in the Differin arm and 101 in the vehicle group. One hundred and forty five women were enrolled, where 71 were randomized in the Differin arm and 74 in the vehicle group. The subset analysis for gender yielded the following results:

Table VII
Mean ± SD in Percent Change from Baseline
All Primary Endpoint Variables @ Week 12
Study 9111-CD271C-EV

Primary Endpoint Variables	Males (N=205)			Females (N=145)		
	Differin (n=104)	Vehicle (n=101)	P-Value	Differin (n=71)	Vehicle (n=74)	P-Value
Inflammatory Lesions	0.15 ± 0.5	0.04 ± 0.56	0.1	0.11 ± 0.53	0.09 ± 0.65	0.8
Non-Inflammatory Lesions	0.35 ± 0.35	0.12 ± 0.67	0.003	0.35 ± 0.36	0.20 ± 0.58	0.08
Total Lesions	0.30 ± 0.33	0.12 ± 0.48	0.002	0.29 ± 0.32	0.18 ± 0.50	0.1
Global Assessment	0.22 ± 0.24	0.18 ± 0.24	0.3	0.21 ± 0.27	0.15 ± 0.27	0.2

As it is shown in Table VII, the male population had similar trend in the lesion count as the whole population. But, the female sub-population did not show statistically significance results in any of the primary endpoint variables ($p \geq 0.08$). These results should be interpreted with caution, since the statistical power might have diminished by dividing the whole sample size into two groups.

Study CR90087:

Objective & Design:

The objective of this trial was to assess the efficacy and safety of Differin cream administered topically once a day at bedtime as a treatment for acne vulgaris.

This was a multicenter (9 center), randomized, investigator-blind, reference-controlled with two parallel treatment arms: Differin 0.1% cream or the Tretinoin cream, 0.05% administered on a q.i.d. regimen for a 12-week treatment period. This was a European study.

In order to demonstrate therapeutic non-inferiority of Differin to Retin-A, a 95% Confidence Interval (CI) for the difference in the mean percent reduction in lesion counts, (Differin - Retin-A) was constructed. The lower bound of this CI must not be less than 0.1 of the control drug (Retin-A). This CI must also include zero.

The minimum number of noninflammatory and inflammatory lesions required for this study was 20 and 10 respectively.

Sample Size:

Each center was expected to recruit approximately 30 patients, which would have led to a total of 270 patients. In terms of percent reduction of total lesion counts from baseline to week 12, an 8% between-treatment difference could be detected with the enrollment of 240 evaluable patients with 80% power, alpha level of 0.05 at a two-sided test.

Demographics & Baseline Characteristics:

A total of 277 subjects were randomized to participate in this study. Of these, 136 received Differin 0.1% cream and 141 were randomized to the Retin-A 0.05% cream.

Tables VIII and IX summarize the demographics and baseline characteristics of these subjects.

**Table VIII
Demographics of All Randomized Subjects
Study CR90087**

	Whole Population (N=277)	Differin (n=136, 49%)	Retin-A (n=140, 51%)	P-Value
Gender (n):				0.3
Male	132 (48%)	69 (51%)	63 (45%)	
Female	145 (52%)	67 (49%)	77 (55%)	
Race (n):				0.4
White	230 (83%)	113 (83%)	117 (84%)	
Black	1 (0.4%)	1 (1%)	0 (0%)	
Hispanic	43 (16%)	22 (16%)	21 (15%)	
Asian	2 (0.7%)	0 (0%)	2 (1%)	
Age (Mean ± SD):	19 ± 4	19 ± 4	20 ± 4	0.08
	34 (12%)	17 (13%)	17 (12%)	
	30 (11%)	15 (11%)	15 (11%)	
	26 (9%)	12 (9%)	14 (10%)	
	34 (12%)	16 (12%)	18 (13%)	
	27 (10%)	14 (10%)	13 (9%)	
	30 (11%)	14 (10%)	16 (11%)	
	34 (12%)	17 (13%)	17 (12%)	
	30 (11%)	15 (11%)	15 (11%)	
	32 (12%)	16 (12%)	16 (11%)	

As it is shown in Table X, Retin-A was statistically superior to Differin in all lesion counts ($p \leq 0.01$). Global assessment showed a border-line significance ($p = 0.06$).

This reviewer did an independent analysis of global assessment as a dichotomized variable, (cured vs. not cured). No statistically significant difference between Differin and vehicle was found ($p = 0.8$).

Table XI shows the results of the primary endpoint variables after adjusting for the center.

Table XI
Least Square Means in Percent Change from Baseline
All Primary Endpoint Variables @ Week 12
(With Center Adjustment)
Study CR90087

Primary Endpoint Variables	Differin (n=136)	Retin-A (n=140)	P-Value
Inflammatory Lesions	0.36	0.50	0.003
Non-Inflammatory Lesions	0.55	0.64	0.004
Total Lesions	0.50	0.60	0.001
Global Assessment	0.44	0.50	0.07

As it is listed in Table XI, similar results were observed as the findings without the center interaction.

In order to further look in to the non-inferiority of Differin to Retin-A, 95% confidence intervals were constructed around the difference (Differin - Retin-A) in mean percent change of all the primary endpoint variables. Table XII illustrates these findings.

Table XII
Confidence Interval for the Difference in Mean Percent Change
(Differin - Retin-A)
All Primary Endpoint Variables
Study CR90087

Primary Endpoint Variables	95% CI
Inflammatory Lesions	136,140(-0.23, -0.05)36%,50%
Non-Inflammatory Lesions	136,140(-0.17, -0.01)53%,64%
Total Lesions	136,140(-0.17, -0.03)50%,60%
Global Assessment	136,140(-0.14, 0.002)44%,51%

As it is shown in Table XII, mean percent change of the lesions did not show statistical equivalence (none included 0 and the lower bound was smaller than -0.10.). However, the global assessment did cross 0, but the lower bound was beyond -10%. The 95% CI for the global static was (-0.13, 0.07). This confidence interval also, includes 0 but the lower bound is less than -0.10. Therefore, statistical equivalence was not achieved in any of the primary endpoint variables.

Secondary Endpoint Variables:

Skin irritation was the only secondary variable in this study. No statistically significant difference was found between Differin and Retin-A, (p=0.25).

Subset Analysis:

Since the whole population in the study was between the ages of about 13 to 29 a subgroup analysis based on age was not required.

A total of 132 males had participated in this study, of which 69 were in the Differin arm and 63 in the Retin-A group. One hundred and forty four women were enrolled, where 67 were randomized in the Differin arm and 77 in the Retin-A group. The subset analysis for gender yielded the following results:

Table XIII
Mean \pm SD in Percent Change from Baseline
All Primary Endpoint Variables @ Week 12
Study CR90087

Primary Endpoint Variables	Males (N=132)			Females (N=144)		
	Differin (n=69)	Vehicle (n=63)	P-Value	Differin (n=67)	Vehicle (n=77)	P-Value
Inflammatory Lesions	0.33 \pm 0.42	0.45 \pm 0.41	0.1	0.39 \pm 0.40	0.54 \pm 0.34	0.02
Non-Inflammatory Lesions	0.52 \pm 0.33	0.60 \pm 0.30	0.1	0.58 \pm 0.32	0.68 \pm 0.32	0.06
Total Lesions	0.46 \pm 0.32	0.55 \pm 0.28	0.08	0.54 \pm 0.3	0.65 \pm 0.30	0.03
Global Assessment	0.40 \pm 0.33	0.46 \pm 0.29	0.3	0.48 \pm 0.29	0.55 \pm 0.31	0.2

As it is shown in Table XIII, the female population had similar trend in all the primary endpoint variables ($p \geq 0.08$) as the whole population. Whereas, the male sub-group did not show statistically significant results in any of the primary endpoint variables. These results should be interpreted with caution, since the statistical power might have diminished by dividing the whole sample size into two subgroups.

III. CONCLUSION:

The results of the study 9111-CD271C-EV indicates the superiority of the Differin cream to its vehicle in two of the three objective outcomes (non-inflammatory and total lesion count) ($p < 0.001$). In addition, the mean percent change for global assessment showed statistical significance after center adjustment ($p = 0.04$) at the end of the 12 week treatment in the ITT population.

The findings of the second study (CR90087) submitted by the sponsor did not indicate the non-inferiority of the Differin cream to Retin-A in any of the four primary endpoint variables ($p \leq 0.07$).

No statistically significant results were found in the secondary variables (burning, dryness, erythema, pruritus and scaling in study 9111-CD271C-EV, and skin irritation in study CR90087) between the two treatment groups in both studies ($p \geq 0.08$).

The results of the subgroups analyses were mixed. In study 9111-CD271C-EV, males showed a statistical difference in non-inflammatory and total lesion counts ($p < 0.01$) between Differin and the vehicle (similar to the trend for the whole population). However, females did not demonstrate statistically significant results in any of the four primary endpoint parameters

($p > 0.05$). In study CR90087, females showed statistically significant results in inflammatory and total lesion counts ($p \leq 0.03$), between Differin and Retin-A, and a marginal significance in the non-inflammatory lesion count ($p = 0.06$). However, the male sub-population did not show statistically significant differences in any of the four primary endpoint variables ($p > 0.05$). Therefore, no inference can be made based on these results.

According to the reviewing medical officer, the data presented by the sponsor did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

Based on the findings of these pivotal studies, the sponsor has demonstrated superiority of Differin over vehicle in the first study (study 9111-CD271C-EV) but has failed to show non-inferiority of Differin over Retin-A in the second study (study CR90087). Therefore, since the results of these submitted trials are inconclusive, further trials are needed to make any inferences regarding the efficacy of Differin cream.

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