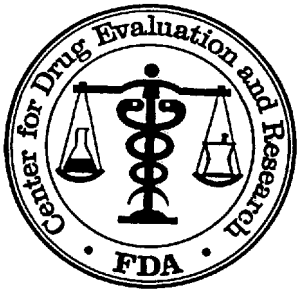
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-502

STATISTICAL REVIEW(S)



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

New Drug Application

Clinical Studies

NDA/Serial Number:	22-502/SN000
Drug Name:	Differin™ (adapalene) Lotion, 0.1%
Indication(s):	Acne vulgaris
Applicant:	Galderma
Dates:	Submitted: 03/02/2009
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Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Mat Soukup, Ph.D.
Concurring Reviewer:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products
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Project Manager:	Kelisha Turner (DDDP)
Keywords:	acne, superiority

Contents

1 Executive Summary

1.1 Conclusions and Recommendations

Differin™ consists of adapalene 0.1% in a topical lotion forumulation for the treatment of acne vulgaris. The clinical program consisted of two Phase 3 studies (Studies 18113 and 18114), Studies 18113 and 18114 were used to assess the safety and efficacy of Differin™ compared to its vehicle with the objective of establishing the superiority of Differin™ to vehicle. The primary efficacy endpoints were:

- Change from Baseline in two out of three lesion counts (total, inflammatory and non-inflammatory) after accounting for multiplicity adjustment.
- Percent of subjects with an IGA success defined as a Week 12 two grade improvement from baseline.

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. In the safety assessment of local skin reactions, on average Differin™ was more irritating than vehicle, especially within the first week of therapy. However, the mean intensity of the local skin reaction score for Differin™ was below a mild rating, and the irritation tended to resolve and reach near baseline levels by week 12.

1.2 Brief Overview of Clinical Studies

In the clinical development of Differin™, two adequate and well-controlled twelve week, randomized, double-blind, and parallel group studies (18113 and 18114) were conducted to assess the safety and efficacy of Differin™ in the treatment of acne vulgaris. The efficacy objective of the two trials was to demonstrate the superiority of Differin™ over its vehicle. Study 18113 enrolled a total of 1075 subjects from 39 centers in the U.S. and Canada. Study 18114 enrolled a total 1066 subjects from 35 centers in the U.S. and Canada.

1.3 Statistical Issues and Findings

Based upon protocol agreed upon statistical methods, both Study 18113 and 18114 established the superiority of Differin™ over its vehicle. Determination was made based upon the agreed upon co-primary endpoints.

- IGA Success rate is 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 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 non-inflammatory lesion counts;
  - Absolute change from baseline to Week 12 (LOCF, ITT) in total lesion counts.

Additional sensitivity and supportive analyses were conducted which were consistent with conclusions reached based upon the primary analysis.

The local tolerability of Differin™ appears to be slightly more irritating than its vehicle with most irritation (dryness, erythema, scaling, and stinging) occurring within the first week of treatment. While the mean level of irritation for Differin™ does appear to be highest at Week 1, the mean is still scored below a mild rating. Irritation tends to resolve by the end of treatment (Week 12) reaching near baseline levels.

2 Introduction

2.1 Product Description

Three topical dosage forms of adapalene at a concentration of 0.1% (cream, gel, and solution) have been approved in the US and many foreign countries for the treatment of acne. In addition to the 0.1% concentrations in the various vehicles, adapalene has been approved in a gel vehicle at a concentration of 0.3% for the treatment of acne[1]. The product used in the clinical studies for the current NDA submission is a lotion formulation of adapalene at a concentration of 0.1%.

2.2 Regulatory History

The following sections provide a summary of communications about issues that were influential in the clinical development and statistical evaluation of Differin™; summaries are based on comments made during the review of the IND (IND number 76,057).

2.2.1 Pre-IND Meeting: 02/26/2007

The following is a summary of the comments that were conveyed to the sponsor during the Pre-IND Meeting held between the Agency and the Sponsor on February 26, 2007.

Clinical Development : The sponsor proposed to conduct a single Phase 3 trial. In response the Division provided the following comments.

- As the sponsor did not conduct a Phase 2 trial and no previous studies had been conducted with the proposed formulation, the Division recommended the sponsor conduct a Phase 2 dose ranging trial prior to initiating Phase 3 trials.
- The estimates of the treatment effects for Adapalene Gel were relatively small. Consequently, a non-inferiority trial design, which preserves a certain proportion of treatment effect to conclude efficacy, would be very large. Therefore, the Division recommends the sponsor to conduct either
  1. one three-arm Phase 2 trial followed by one two-arm Phase 3 trial (depending on the results of the Phase 2 trials); or
  2. two Phase 3 trials for replication of study findings.

Endpoints : The following endpoints are considered to be co-primary endpoints which must reach statistical significance to establish the efficacy of Differin™.

- Absolute change in 2 out of 3 lesion counts (inflammatory, non-inflammatory, and total) at week 12; percent change will be considered as secondary after addressing multiplicity.
- Two grade reduction in the week 12 IGA score from the baseline IGA score which is protocol defined as moderate.

Statistical Analysis Details : The following comments pertained to the statistical analysis of the Phase 3 study.

- The sensitivity analyses to address missing data should be considered supportive to the primary analysis.
- The protocol should address how to handle a significant treatment by center interaction (tested at the $\alpha = 0.10$ level).
- Multiplicity adjustments should be provided for secondary endpoints intended for labeling claims.

2.2.2 End of Phase 2 Meeting: 08/07/2007

The following is a summary of the comments that were conveyed to the sponsor during the End of Phase 2 Meeting held between the Agency and the Sponsor on August 8, 2007.

Clinical Development : The sponsor proposed to conduct a single study - the Division stated this was acceptable though it was recommended that the study be powered using a significance level smaller than $\alpha = 0.05$.

Co-primary Endpoints : Multiplicity adjustments for utilizing 2 out of 3 lesions counts as a co-primary endpoint along with a dichotomized IGA score were discussed. Specifics of the multiplicity adjustment were not agreed upon and the sponsor stated they will submit details in a revised protocol.

2.2.3 Statistical Review of SN006: 09/19/2007

The sponsor submitted two similar Phase 3 protocols in SN006 (stamp date 09/19/2007) with the intention that the completed trials will provide evidence of the safety and efficacy of Differin™ lotion. In the review of the revised protocols the Biostatistics review contained the following comment.

Power Calculations : The Division stated that the trials should be powered for both the absolute change in inflammatory and non-inflammatory lesion counts in addition to powering the studies for the dichotomized IGA score. The sponsor was also informed of the risk of relying on historical data of different formulations to power the Phase 3 trials.

2.2.4 Pre-NDA Meeting: 02/24/2009

A Pre-NDA Meeting was scheduled for 02/24/2009. However, the sponsor elected to cancel the meeting on 01/19/2009. The reason stated for canceling the meeting was, "The sponsor had successful results from their Phase 3 clinical studies."

2.3 Clinical Trial Overview

In the clinical development of Differin™ lotion, 0.1%, two adequate and well-controlled twelve week, randomized, double-blind, parallel group, multi-center studies (SPR.18113 and SPR.18114) were conducted to assess the safety and efficacy of Differin™ in the treatment of acne vulgaris. The primary objective of each study was to compare the efficacy and safety of Differin™ to its vehicle with the efficacy objective to demonstrate the superiority of Differin™ over its vehicle. A brief summary of each Phase 3 trial is provided below (table 1).

2.4 Data Sources

The sponsor submitted both data tabulations as well as analysis data sets. To describe the contents of the data sets a Define.XML file was submitted. The data set structures followed CDISC data standards. The location of the data sets and the Define.XML files are available from the EDR at `//cdsesub1/evsprod/NDA022502/0000/m5/datasets`.

Table 1: **Efficacy and Safety Studies Overview**

Study	Development Objective	Drug Products	Number Subjects	Date†
SPR.18113 (Study 18113)	Phase 3 Superiority	Differin™ Lotion Vehicle Lotion	533 542	11/7/2007 – 11/6/2008
SPR.18114 (Study 18114)	Phase 3 Superiority	Differin™ Lotion Vehicle Lotion	535 531	11/6/2007 – 11/14/2008

† Dates correspond to the start and end of the study.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The evaluation of efficacy is based upon two identically designed Phase 3 trials: Study 18113 and Study 18114. The titles of the studies are "A Multi-Center, Randomized, Double-Blind, Parallel Group Study to Demonstrate the Efficacy and Safety of Adapalene Lotion, 0.1% with Vehicle Lotion in Subjects with Acne Vulgaris."

3.1.1 Study Design

The Phase 3 studies are multi-center, randomized, double-blind, parallel-group, and vehicle controlled studies in subjects with acne vulgaris. Eligibility criteria requires subjects to be male or female, 12 years of age or older, with a minimum of 20 but not more than 50 papules and pustules in total and 30 to 100 non-inflammatory lesions on the face (excluding the nose) and who are evaluated with a score of 3 (Moderate) or 4 (Severe) on the IGA scale; one nodule may be present at inclusion. Even if acne lesions are only evaluated on the face, subjects presenting both facial and truncal acne vulgaris were eligible to participate in the studies.

Subjects were to be randomized in a 1:1 ratio to Differin™ Lotion or Vehicle Lotion. Study 18113 enrolled a total of 1075 subjects (533 randomized to Differin™ lotion and 542 to vehicle lotion) from 39 centers in the U.S. and Canada. Study 18114 enrolled a total of 1066 subjects (535 randomized to Differin™ lotion and 531 to vehicle lotion) from 35 centers in the U.S. and Canada.

Subjects meeting the inclusion/exclusion criteria and not needing any wash-out were randomized at baseline and treated for a period of up to 12 weeks. In case of dry skin, subjects were requested to use a moisturizer throughout the study. Subjects returned to centers for evaluations at Weeks 1, 2, 4, 8 and 12/Early Termination.

3.1.2 Endpoints

Investigators were trained by the sponsor to perform efficacy evaluations for the following assessments which were collected at each visit: Investigator Global Assessment (IGA), inflammatory lesion counts (papules, pustules, nodules and cysts) and non-inflammatory lesion counts (open and closed comedones). Only the face (excluding the nose) of the subject were evaluated for IGA and lesion counts.

Investigators evaluated the subjects acne at each visit performing a static (snap-shot) evaluation of acne severity using the IGA scale. No reference to other previous visits were to be made by the investigator when evaluating the subjects facial acne. A 2-point change from baseline, or greater, will be considered an IGA success. The Investigators Global Assessment is outlined in the following table:

Value	Label	Description
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.

Each type of lesion was counted separately and recorded on the appropriate source document and CRF form. The lesion 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.

3.1.2.1 Co-Primary Efficacy Criteria The following are the protocol defined co-primary criteria for the evaluation of efficacy.

- Success rate is 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 in lesion counts:
  - Absolute change from Baseline to Week 12 (LOCF, ITT) in total 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;

The trial will be claimed positive regarding efficacy of adapalene for the indication of acne vulgaris if (1) Success rate, and (2) at least two out of the three absolute changes in lesion counts are significant versus vehicle, each at the two-sided $\alpha = 0.05$ level for the week 12 (LOCF) data. Multiplicity in part (2) will be handled by using a stepwise approach to the test sequence: the change in total lesion counts will be required to show significance at the $\alpha = 0.05$ level to allow making further inferences on the remaining two lesion types.

3.1.2.2 Secondary Efficacy Criteria The following are the protocol defined secondary endpoints.

- 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 Noninflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT).

3.1.3 Statistical Methodology

The statistical methodologies described below correspond to those included in the protocol for Study 18113 and Study 18114. Any deviations from protocol defined methods are documented.

3.1.3.1 Populations The primary analysis population is defined as the intent-to-treat (ITT) population which includes all subjects who were randomized and dispensed medication. The per protocol (PP) population which excludes subjects with major protocol violations is planned as a supportive analysis to the primary analysis on the ITT population.

3.1.3.2 Statistical Analysis All comparisons of Differin™ to its vehicle for the co-primary endpoints will be tested at the two-sided $\alpha = 0.05$ significance level. Small centers will be pooled prior to analysis which combines the largest center with the smallest center. These pooled centers will be referred to as "analysis centers" in the statistical analyses. The trial will meet efficacy criteria if all primary analyses are shown to be statistically significant at the two-sided $\alpha = 0.05$ level.

3.1.3.2.1 Investigator Global Assessment For the analysis on the percent of subjects with an IGA success, the protocol listed CMH stratified by "analysis center" as the primary method of statistical analysis. A subject will be considered a success if IGA is at least 2 grades lower than the baseline assessment. The primary method of data imputation is LOCF with two sensitivity analyses listed as (a) impute all missing week 12 data as failures and (b) impute all missing week 12 data as successes.

3.1.3.2.2 Lesion Counts The absolute change at Week 12 (LOCF) from baseline in inflammatory, non-inflammatory, and total lesion counts between treatment groups will be tested based on either parametric or nonparametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA model with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to an ANCOVA. A test for normality of the absolute change from baseline in inflammatory, non-inflammatory, and total lesions will be based on the Shapiro-Wilk test at a significance level of $\alpha = 0.05$ and will be applied to the residuals resulting from the ANCOVA model (unranked). The primary analysis will be based on the original scaled (unranked) lesion counts if the normality assumption is met and on the rank-transformed lesion counts if not. Should a rank transformed analysis be indicated by virtue of the results of the normality testing, the absolute change in inflammatory, non-inflammatory, and/or total lesions and the baseline count covariate will be rank transformed prior to including them in the ANCOVA model. In this situation the results of both the rank-transformed and original scaled analyses will be presented with those of the rank-transformed being considered primary.

The primary method of data imputation for missing data is LOCF. As a sensitivity analysis missing data for change in lesion count at Week 12 will be imputed by the median change for the respective treatment group from the subjects with complete data. Additionally, a second sensitivity analysis of lesion counts will include 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). Analyses will be performed as outlined above for the primary analysis.

3.1.4 Patient Disposition and Baseline Characteristics

3.1.4.1 Patient Disposition In the two Phase 3 studies a total of 273 out of 2141 subjects (12.8%) discontinued from the trial (table 2). Overall, the rate of drop out in each trial was slightly higher in the vehicle arm than the Differin™ treatment arm. The reason for drop-out was similar for each treatment arm with most subjects discontinuing due to either "Lost to Follow-Up" or "Subject's Request".

Table 2: **Summary of Subject Completion/Discontinuation**

	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: Study Report Table 10.1-2; reproduced by reviewer using `ADSL.XPT`.

3.1.4.2 Baseline Demographic Factors The baseline demographics for age, gender, race, and skin phototype are provided in Table 15 in the Appendix (page 32). The following summarizes the data presented for baseline demographics for each of the Phase 3 trials.

Study 18113: Overall, the mean age of subjects was 19 years old; 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. There was no imbalance of any of the demographic factors between treatment arms.

Study 18114: Overall, the mean age of subjects was 19 years old; 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. There was no imbalance of any of the demographic factors between treatment arms.

3.1.4.3 Baseline Prognostic Factors This exploratory analysis examines *baseline* characteristics of the clinical endpoints used in the evaluation of efficacy for acne vulgaris. Ideally, one hopes to see that randomization to treatment for the two treatment arms results in similar baseline values of the prognostic characteristics as large disparities could have an effect on the efficacy claims.

Based upon the summary statistics, little differences existed between the two treatment arms for the baseline distribution (table 3). An overwhelming majority of subjects enrolled with a baseline IGA score of 'Moderate' ($> 90\%$). The distribution of baseline lesion counts was similar for both Differin™ and vehicle.

Table 3: **Baseline Prognostic Factors**

	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 42.00 55.75	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: reviewer analysis using `ADGA.XPT` and `ADLS.XPT`.

3.1.5 Populations Analyzed

The intent-to treat (ITT) population included all subjects who were randomized to treatment and to whom medication was dispensed; this was the primary population for the efficacy analyses. The per protocol (PP) population was a subset of the ITT population, which included those ITT subjects who met all major protocol criteria. Table 4 depicts the number of subjects included in the two analysis populations for each treatment arm.

Table 4: **Number of Subjects for each Analysis Population**

	Study 18113		Study 18114	
	Differin™ Lotion	Vehicle Lotion	Differin™ Lotion	Vehicle Lotion
ITT Population	533	542	535	531
PP Population	462	451	459	439

Source: Sponsor's Study Report Table 10.2-1; reproduced by reviewer using `ADGA.XPT`.

3.1.6 Primary Endpoint Results (ITT-LOCF)

The section on efficacy is broken down into two sections. The first examines efficacy results according to the investigator global assessment whereas the second examines efficacy results based upon absolute change in lesion counts (inflammatory, non-inflammatory, and total). Recall that the trial will be claimed positive regarding efficacy of adapalene for the indication of acne vulgaris if (1) IGA Success rate, and (2) at least two out of the three absolute changes in lesion counts are significant versus vehicle after addressing multiplicity. Each comparison is made at

the two-sided $\alpha = 0.05$ level for the week 12 (LOCF) data.

3.1.6.1 Investigator Global Assessment For the primary analysis, the protocol defined IGA success criteria was defined as a two grade improvement from Baseline to Week 12. 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 (table 5). IGA success rates for each treatment arm were similar in the two Phase 3 trials. Statistical comparisons met the superiority criteria of $\alpha = 0.05$.

Table 5: **Investigator Global Results (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".

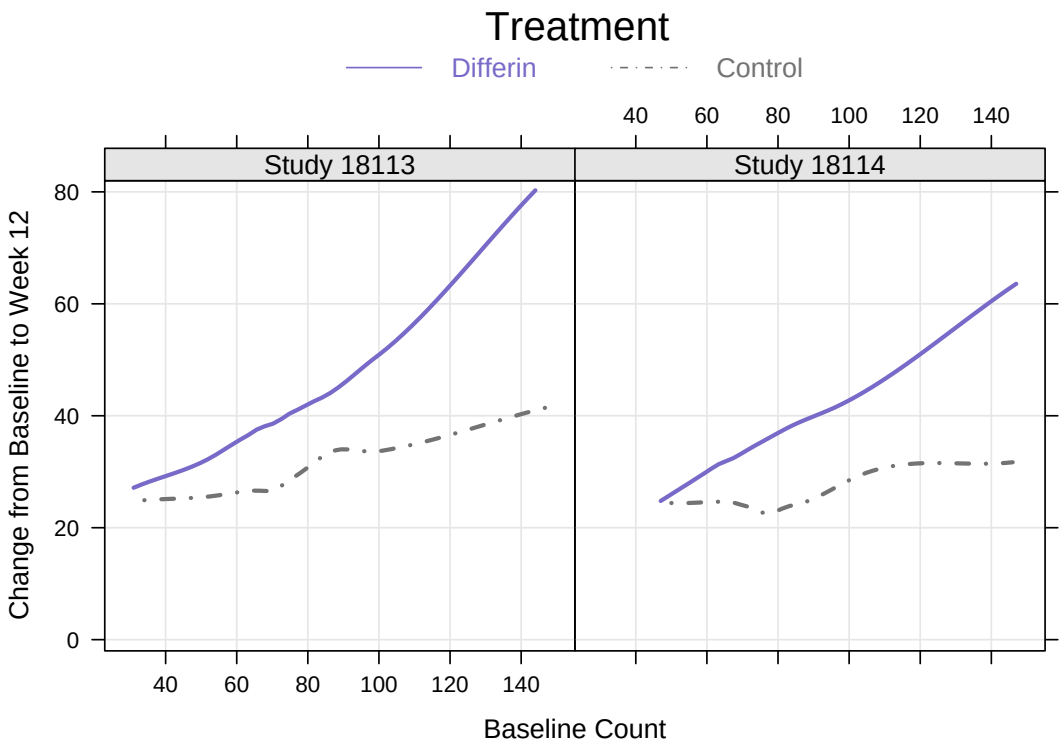
Source: Study Report Table 11.4.1.1-1; reproduced by reviewer using `ADGA.XPT`

3.1.6.2 Change in Lesion Counts For the assessment of change in lesion counts, the following sections depict a visual summary of the change from baseline based upon the baseline lesion count. This graphical summary is followed by formal statistical testing procedures as described in Section 3.1.3. Recall that the testing procedure for lesion counts is protocol specified to be a step-wise procedure; first testing the total lesion counts followed by testing inflammatory and non-inflammatory lesions. As such, the following section first starts with the comparison of Differin™ to vehicle for total lesions followed by analysis results for inflammatory and non-inflammatory lesions.

3.1.6.2.1 Total Lesion Counts Figure 1 depicts loess nonparametric regression lines[2] for the total lesion counts at baseline and the change in total lesion counts for each treatment group paneled on study. In this graphical summary of results across the range of the baseline total lesion count, both studies show a treatment effect which was largest for higher lesion counts.

ANCOVA models were used to fit the absolute change in total lesion counts with factors for treatment and analysis center and the respective baseline total lesion count as a covariate. In both studies Differin™ was superior to vehicle on the basis of the absolute change in total lesion counts (table 6). The treatment effects for the mean absolute change were 11.2 and 9.0 lesions

Figure 1: **Total Lesion Counts (ITT-LOCF)**



in Studies 18113 and 18114, respectively. The treatment effects for the mean percent change were 14.4 and 11.8 lesions in Studies 18113 and 18114, respectively.

Table 6: **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

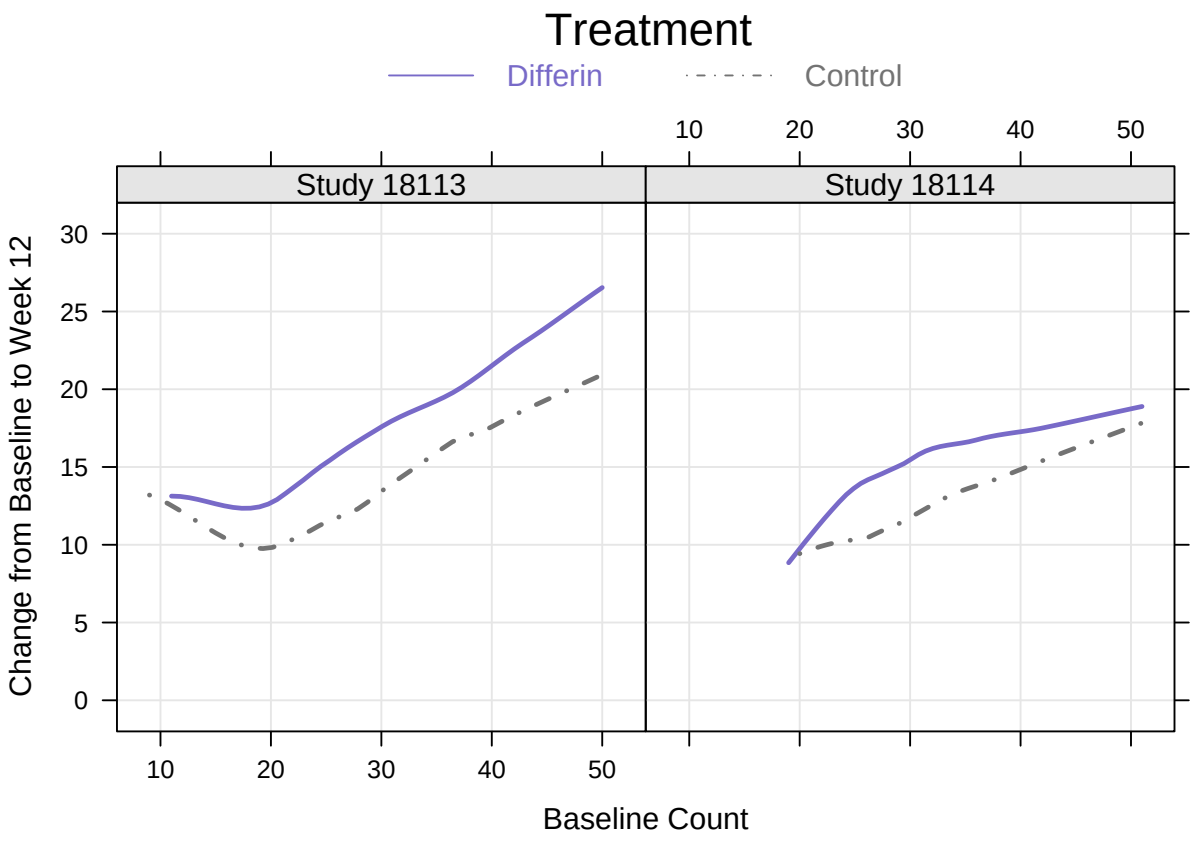
† P-value is based on the ANCOVA model on rank data of changes from baseline lesion counts, including rank data of baseline lesion count as a covariate, treatment and "analysis center" as main effects.

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

Source: Study Report Table 11.4.1.1-1; reproduced by the reviewer using `ADLS.XPT`.

3.1.6.2.2 Inflammatory Lesion Counts Figure 2 depicts loess nonparametric regression lines for the inflammatory lesion counts at baseline and the change in inflammatory lesion counts for each treatment group paneled on study. Note that in Study 18113 four subjects had baseline inflammatory lesion counts less than 20 (protocol violation) and these four subject impact the curve of the loess regression line below a baseline count of 20. Discounting these four subjects the treatment effect is constant across the range of the baseline inflammatory lesion counts in Study 18113. However, the slopes of the loess lines in Study 18114 are not parallel suggesting slightly differing differences in treatment effects across the range of the baseline inflammatory lesion counts. While this may be the case, overall, there is a trend showing a treatment effect in favor of Differin™ in Study 18114.

Figure 2: **Inflammatory Lesion Counts (ITT-LOCF)**



ANCOVA models were used to fit the absolute change in inflammatory lesion counts with factors for treatment and analysis center and the respective baseline inflammatory lesion count. In both studies, Differin™ was superior to vehicle for the absolute change in inflammatory lesions (table 7). The treatment effects for the mean absolute change were 4.1 and 2.5 lesions in Studies 18113 and 18114, respectively. The treatment effects for the mean percent change were

14.6 and 9.1 lesions in Studies 18113 and 18114, respectively.

Table 7: **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: Study Report Table 11.4.1.1-1; reproduced by the reviewer using `ADLS.XPT`.

3.1.6.2.3 Non-Inflammatory Lesion Counts Figure 3 depicts loess nonparametric regression lines for the non-inflammatory lesion counts at baseline and the change in non-inflammatory lesion counts for each treatment group paneled on study. Note that in Study 18113 three subjects had baseline non-inflammatory lesion counts less than 30 (protocol violation) and these three subjects impact the curve of the loess regression line below a baseline count of 30. Discounting these three subjects there is a clear treatment effect across the range of the baseline non-inflammatory lesion counts in Study 18113. There is also a clear treatment effect across the range of the baseline non-inflammatory lesion counts in Study 18114 though the difference is small for baseline non-inflammatory lesion counts around 30.

ANCOVA models were used to fit the absolute change in non-inflammatory lesion counts with factors for treatment and analysis center and the respective baseline non-inflammatory lesion count. In both studies, Differin™ was superior to vehicle for the absolute change in inflammatory lesions (table 7). The treatment effects for the mean absolute change were 7.1 and 6.5 lesions in Studies 18113 and 18114, respectively. The treatment effects for the mean percent change were 13.9 and 12.9 lesions in Studies 18113 and 18114, respectively. The two studies showed more consistent results for non-inflammatory lesions than for inflammatory lesions.

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

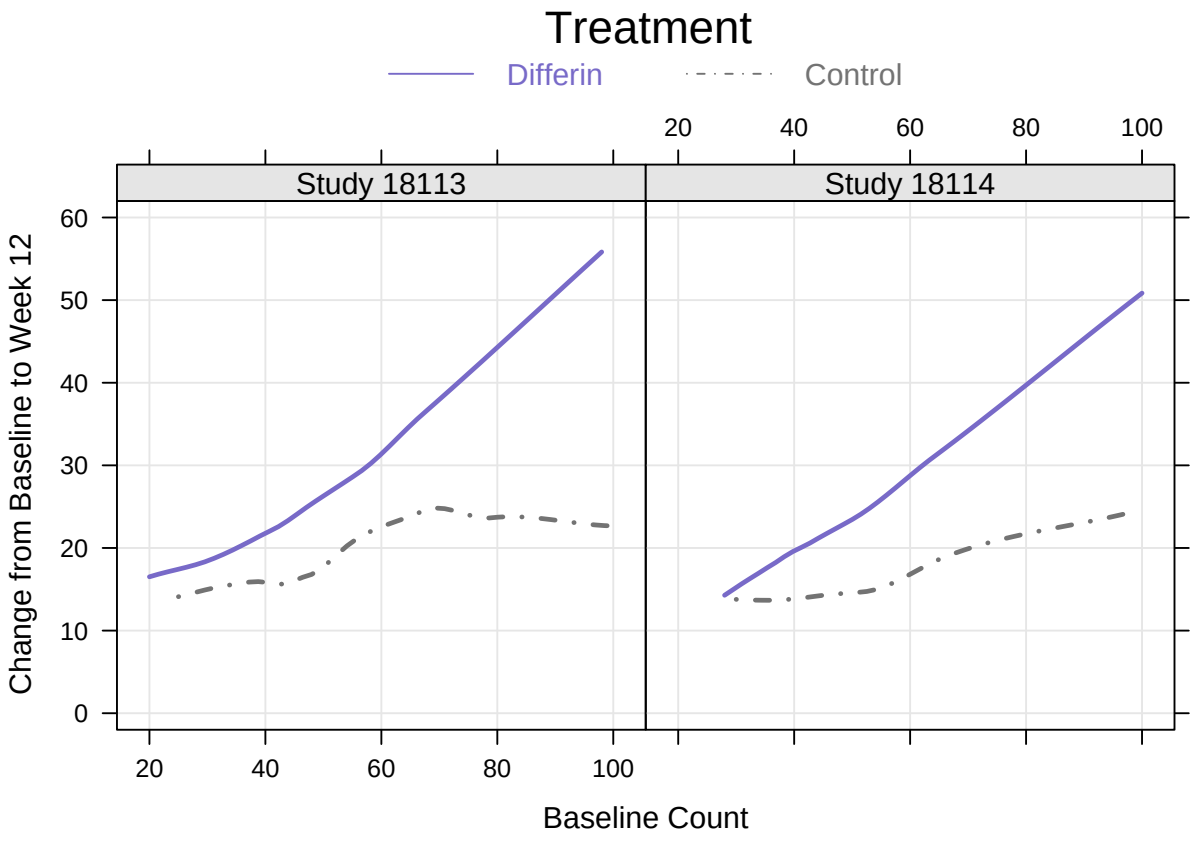


Table 8: **Change in Non-Inflammatory Lesion Counts (ITT-LOCF)**

	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: Study Report Table 11.4.1.1-1; reproduced by the reviewer using `ADLS.XPT`.

3.1.7 Primary Endpoint Results (PP-LOCF)

3.1.7.1 Investigator Global Assessment Based upon the definition of IGA success as a Week 12 two grade improvement from baseline, the efficacy results on the PP population are consistent with the ITT population (table 9). For the PP population the estimated treatment effects were 9.8% and 9.0% for Studies 18113 and 18114, respectively. Note that these observed treatment effects were larger than those reported for the ITT-LOCF population (table 5).

Table 9: **Investigator Global Results (PP)**

	Study 18113		**Study 18114**	
	Differin™ Lotion ($N = 462$)	Vehicle Lotion ($N = 451$)	Differin™ Lotion ($N = 459$)	Vehicle Lotion ($N = 439$)
IGA Success (%)	132 (28.6)	85 (18.8)	126 (27.5)	81 (18.5)
p-value†	-	< 0.001	-	< 0.001

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

Source: Study Report Table 14.2.7.2; reproduced by reviewer using `ADGA.XPT`

3.1.7.2 Change in Lesion Counts For the assessment of absolute change in lesion count in the PP population, the main effects ANCOVA model is fit with absolute change in lesion counts as the response and terms for treatment, analysis center, and baseline lesion count listed as the covariate (note that the analysis is based on the unranked data). Consistent with the ITT population, for all lesion types, Differin™ was superior to vehicle in both Phase 3 studies (table 10). Note that the observed treatment effects for each lesion type were larger in the PP population in comparison to the ITT population.

3.1.8 Additional Sensitivity Analyses of Primary Endpoints

3.1.8.1 Site Effects The clinical review team identified [redacted] as having a conflict of interest. Based upon this finding, the team recommended a DSI inspection of analysis center [redacted] which corresponds to [redacted]. However, DSI recommended that such a center not be inspected as the site had been subject to a recent inspection with no issued identified. Analysis center [redacted] enrolled a total of [redacted] subjects, [redacted] randomized to each treatment arm. To assess if this site may influence the efficacy findings, the site was removed from a sensitivity analysis of the [redacted] endpoint using the ITT population of Study [redacted] with the missing data imputed using LOCF. The original treatment effect reported in Table 5 for Study [redacted]. Deleting the data of analysis center [redacted] resulted in an estimated treatment effect of [redacted]. Thus, there is no evidence that analysis center [redacted] influenced

Table 10: **Change in Lesion Counts (PP-LOCF)**

	Study 18113		Study 18114	
	Differin™ Lotion ($N = 462$)	Vehicle Lotion ($N = 451$)	Differin™ Lotion ($N = 459$)	Vehicle Lotion ($N = 439$)
Total Lesion Count				
Mean Change	41.1	28.6	35.2	25.1
Mean Percent Change	55.6	40.0	48.7	35.6
p-value†	-	< 0.001	-	< 0.001
Inflammatory Lesion Count				
Mean Change	16.1	11.5	14.1	11.0
Mean Percent Change	59.4	43.9	51.2	40.1
p-value†	-	< 0.001	-	< 0.001
Non-Inflammatory Lesion Count				
Mean Change	25.0	17.1	21.1	14.1
Mean Percent Change	53.4	38.0	46.8	32.6
p-value†	-	< 0.001	-	< 0.001

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

Source: Study Report Table 14.2.7.2; reproduced by the reviewer using `ADLS.XPT`.

the efficacy finding of Study (b) (6) Note that efficacy results by clinical site is provided in Section 4.2.1.

3.1.8.2 Missing Data Sensitivity Analysis As a sensitivity analysis to the primary method of data imputation as LOCF, two alternate imputation approaches were provided in the protocol for both the dichotomized IGA score and the absolute change in lesion counts. The following sections provide efficacy results using these alternate imputation approaches.

3.1.8.2.1 Investigator Global Assessment For the IGA score the alternate imputation approaches are: (a) impute all missing week 12 data as failures and (b) impute all missing week 12 data as successes. While no multiplicity adjustments were included for these analyses as these analyses are considered supportive, all superiority comparisons of Differin™ to vehicle reached the nominal $\alpha = 0.05$ significance level for both studies (table 11). Thus, results based upon these sensitivity analyses were consistent with the primary efficacy analysis of IGA.

Table 11: **Investigator Global Results (ITT-Missing Sensitivity)**

	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".

Source: Study Report Table 11.4.2.2-1; reproduced by reviewer using `ADGA.XPT`

3.1.8.2.2 Change in Lesion Counts For changes in lesion counts missing values at Week 12 will be imputed by the median change for the respective treatment group from the subjects with complete data. Additionally, a second sensitivity analysis of lesion counts will include 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). No multiplicity adjustments were listed in the protocol for the multiple comparisons in this sensitivity analysis. Using a nominal $\alpha = 0.05$ significance level, for each lesion count, Differin™ was statistically superior to vehicle for each of the sensitivity analyses in both Phase 3 studies (table 12). The point estimates of the sensitivity analyses for lesion counts were similar to those of primary analysis. Thus, efficacy conclusions for the sensitivity analyses for lesion counts were similar to those of the primary analysis.

3.1.9 Secondary Endpoint Results

The protocol specified that the only secondary endpoint intended for labeling claims were the percent reductions in lesion counts. A formal statistical analysis using percent change in the ANCOVA model was not carried out as the point estimates are provided for descriptive purposes to complement labeling of absolute change for each lesion type. Point estimates for the percent reduction in lesion counts are provided in Tables 6 (total lesions), 7 (inflammatory lesions), and 8 (non-inflammatory lesions) for both Phase 3 trials.

Table 12: **Change in Lesion Counts (Missing Data Sensitivity Analysis)**

	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: Study Report Table 11.4.2.2-2; reproduced by the reviewer using `ADLS.XPT`.

3.2 Evaluation of Safety

The review of safety is based on Study 18113 and Study 18114. The adverse events are coded using the MedDRA dictionary version 10.1. For subjects that experienced an AE multiple times, only a single instance is used in the tabulations that follow.

3.2.1 MedDRA Tabulation

Table 13 contains the MedDRA preferred terms which were reported in at least 1.0% of subjects grouped according to system organ classification (SOC). A total of 15 preferred terms were reported in at least 1.0% of subjects in a total of 5 SOC's. The reported incidence rates of a specific preferred term were similar between Differin™ and vehicle with the exception of dry skin which was reported in a higher percentage of subjects treated with Differin™ (7.7% versus 3.0% for Differin™ and vehicle, respectively).

3.2.2 Serious Adverse Events

Five serious adverse events were reported in Study 18113 and none of the adverse events reported in Study 18114 were determined to be serious. Three of the five serious adverse events occurred in subjects being treated with Differin™ (table 14). Based upon the sponsor's determination none of the serious adverse events were related to study drug.

3.2.2.1 Local Skin Reactions Four local skin reactions: dryness, erythema, scaling, and stinging were actively assessed at each visit with scores of 0 = 'None', 1 = 'Mild', 2 = 'Moderate', 3 = 'Severe'. The mean score over all subjects was calculated at each visit for each treatment group. Figure 4 depicts the mean profile over time for each study and local skin reaction grouped by treatment arm. For all local skin reactions the mean profile of Differin™ is above that of each monad and vehicle. During the twelve weeks of treatment the peak of the mean for each local reaction is at week 1 with a gradual reduction thereafter.

Table 13: **Adverse Events by System Organ Class and Preferred Term**

	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: Reviewer's Analysis using `ADAE.XPT`.

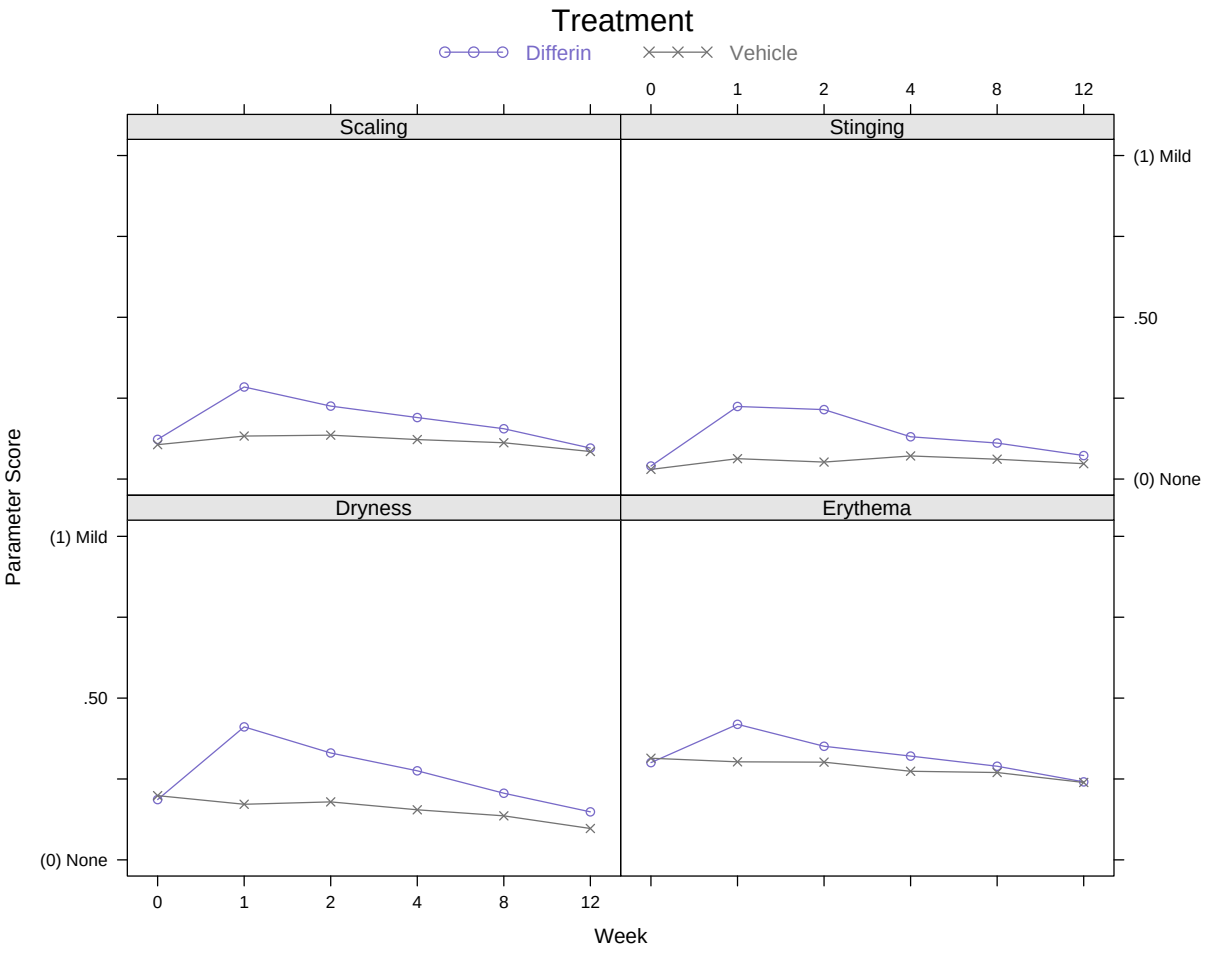
Table 14: **Serious Adverse Events**

Subject ID	Treatment	Preferred Term	Relation[†]	Time of Onset
SPR.18113-17-002	Vehicle	Suicide attempt	Not Related	>30 to ≤ 60 days
SPR.18113-19-030	Differin	Multiple drug overdose	Not Related	>60 days
SPR.18113-19-030	Differin	Depression	Not Related	>60 days
SPR.18113-24-004	Differin	Cerebral haemorrhage	Not Related	0 to ≤ 30 days
SPR.18113-28-001	Vehicle	Ovarian cyst	Not Related	>60 days

[†] Relation to study drug is listed according to the sponsor's determination.

Source: Reviewer's analysis using `ADAE.XPT`.

Figure 4: **Local Skin Reactions (Study 18113 and 18114)**



4 Findings in Special/Subgroup Populations

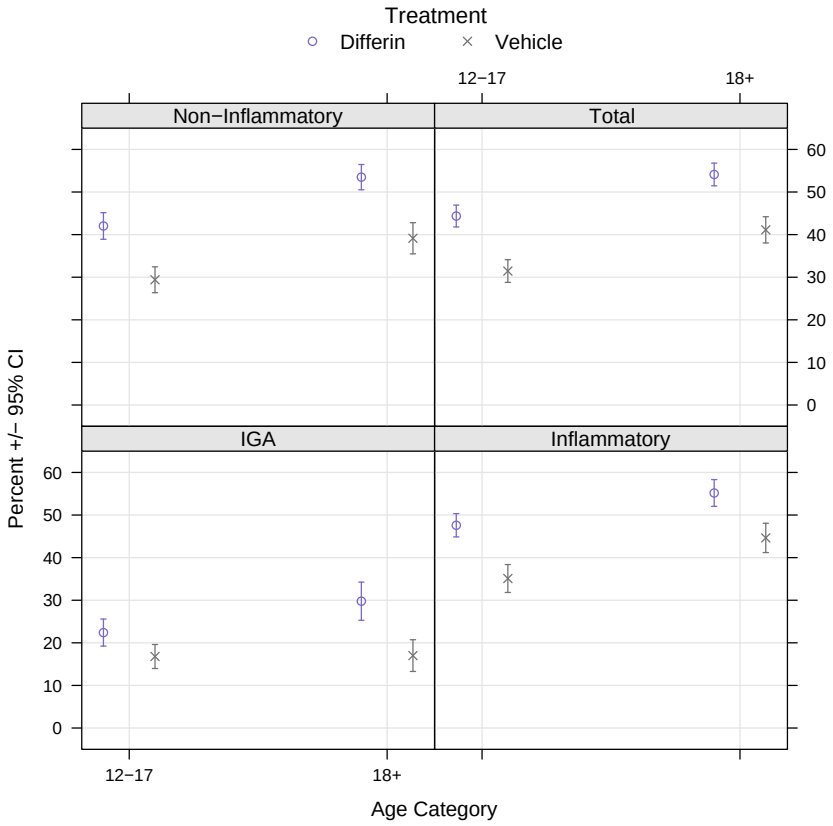
Section 4.1 provides a graphical assessment of efficacy by age, gender, and race. The data from Study 18113 and Study 18114 were combined so as to assess the general trend and patterns in the subgroups. Rather than using the absolute change from baseline in the graphical depictions, the percent change is used as this would be on a similar scale as the percent of IGA successes (Week 12 two grade improvement from baseline). The analysis population is the ITT population with missing week 12 observations imputed using LOCF as in the primary analysis. Note that the protocol did not pre-specify any subgroup analysis which controlled the overall Type I error rate. For a tabular presentation of the data refer to the Appendix, Section A.1.2.

4.1 Gender, Race, and Age

4.1.1 Age

The age of subjects was dichotomized into two categories: 12 to 17 years old and 18 years and older. Figure 5 depicts efficacy results according to age category along with unadjusted 95% confidence intervals. The figure shows that Differin™ had higher mean response rates than vehicle for both age groups for each of the endpoints. In general, subjects who were 18 and older tended to have slightly higher efficacy than subjects 12 to 17 years old.

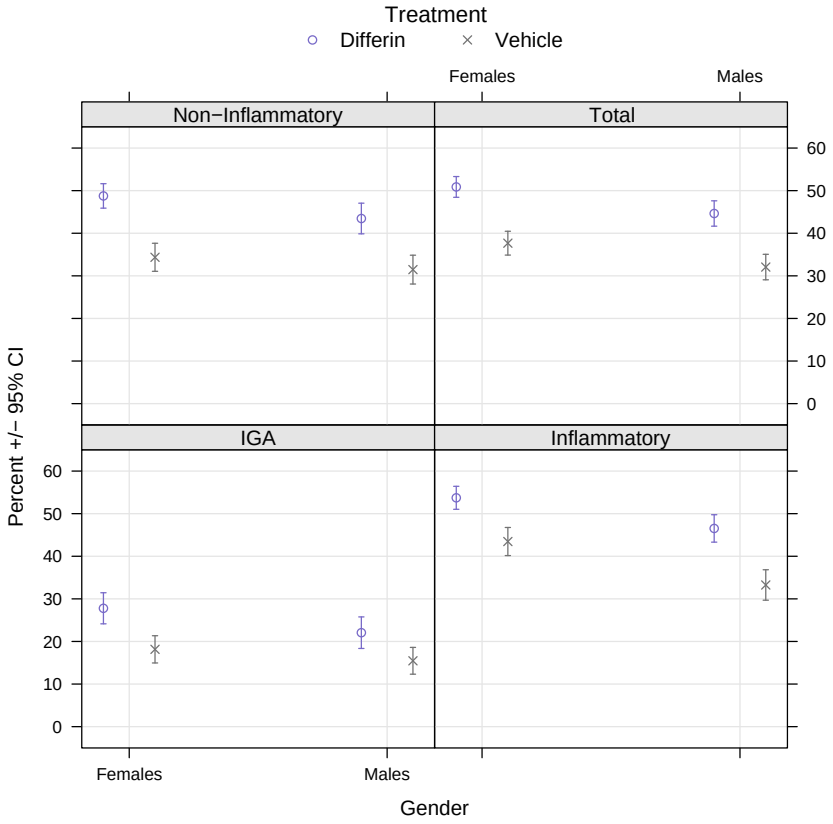
Figure 5: **Efficacy Results According to Age**



4.1.2 Gender

Figure 6 depicts efficacy results according to gender along with unadjusted 95% confidence intervals. In general efficacy results are similar for males and females where Differin™ had higher means than vehicle for both genders according to each of the co-primary endpoints. For all endpoints, females tended to have higher means than males.

Figure 6: **Efficacy Results According to Gender**



4.1.3 Race

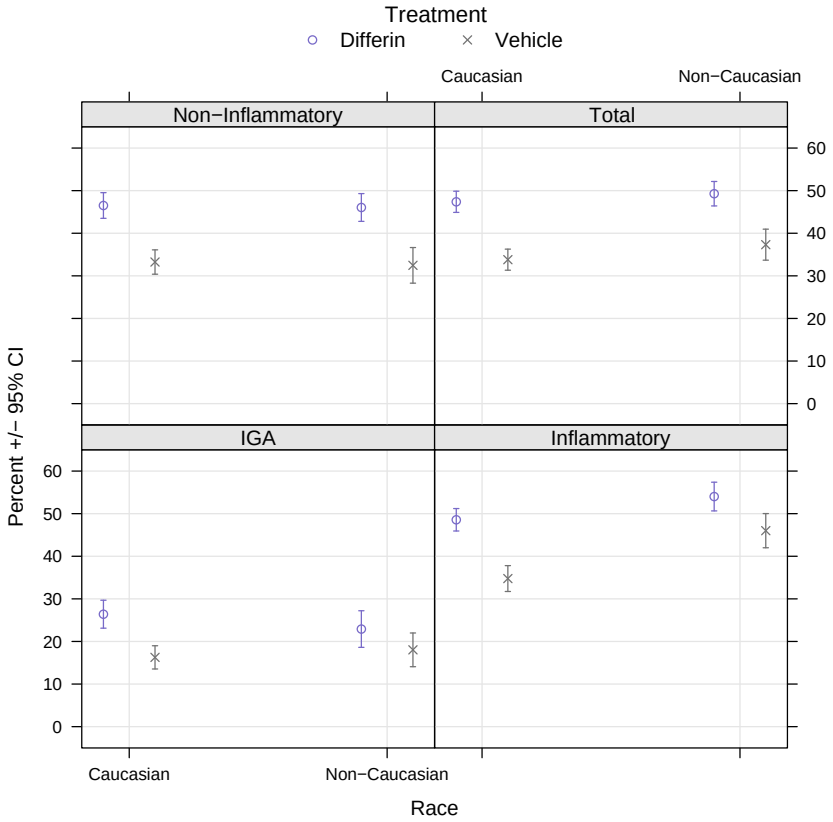
Race was dichotomized into two categories: Caucasian and Non-Caucasian due to the limited number of subjects enrolled with race categorized as either Asian, Black, Hispanic, or Other (table 15). Figure 7 depicts the means for each endpoint along with unadjusted 95% confidence intervals by race for each of the co-primary endpoints. Overall the efficacy results were quite consistent across subgroups which show higher means in subjects treated with Differin™ than vehicle.

4.2 Other Special/Subgroup Populations

4.2.1 Efficacy by Site

Study 18113 was conducted in 39 centers in the U.S. and Canada. Using the primary analysis population, Figure 8 depicts the mean percent of IGA successes for each analysis center along with the number of subjects enrolled for a given treatment arm within an analysis center. This analysis/summary was used as a descriptive analysis to identify sites for inspection. Refer to

Figure 7: **Efficacy Results According to Race**



Section 3.1.8.1 for sensitivity analysis conclusions when analysis center 25 is excluded from the analysis.

Study 18114 was conducted in 35 centers in the U.S. and Canada. Using the primary analysis population (ITT-LOCF), Figure 9 depicts the mean percent of IGA successes for each analysis center along with the number of subjects enrolled for a given treatment arm within an analysis center. This analysis/summary was used as a descriptive analysis to identify sites for inspection. Note that no sites were selected for inspection from Study 18114.

Figure 8: Efficacy Results By Pooled Investigative Site (Study 18113)

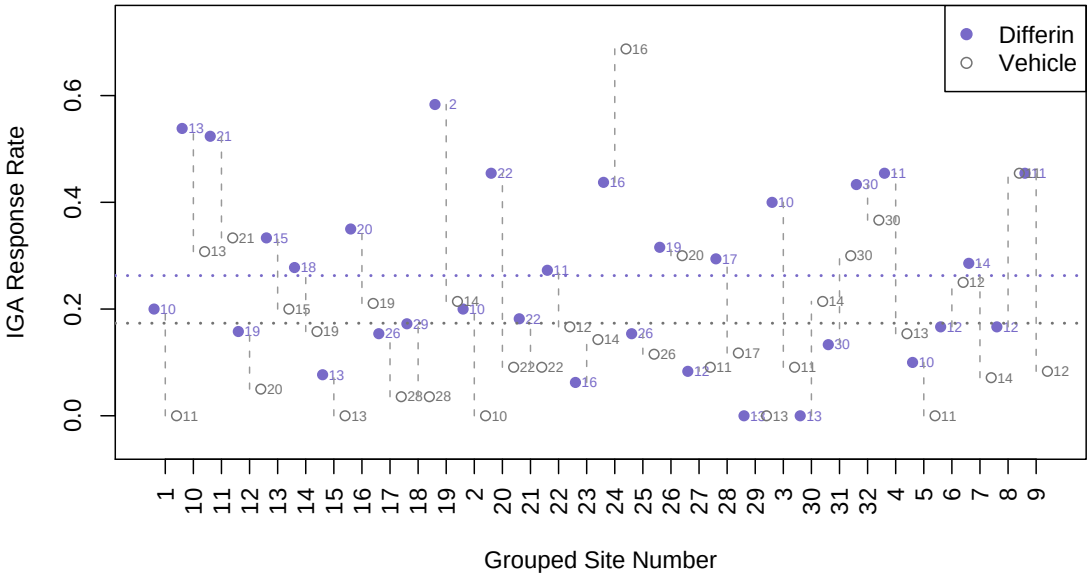
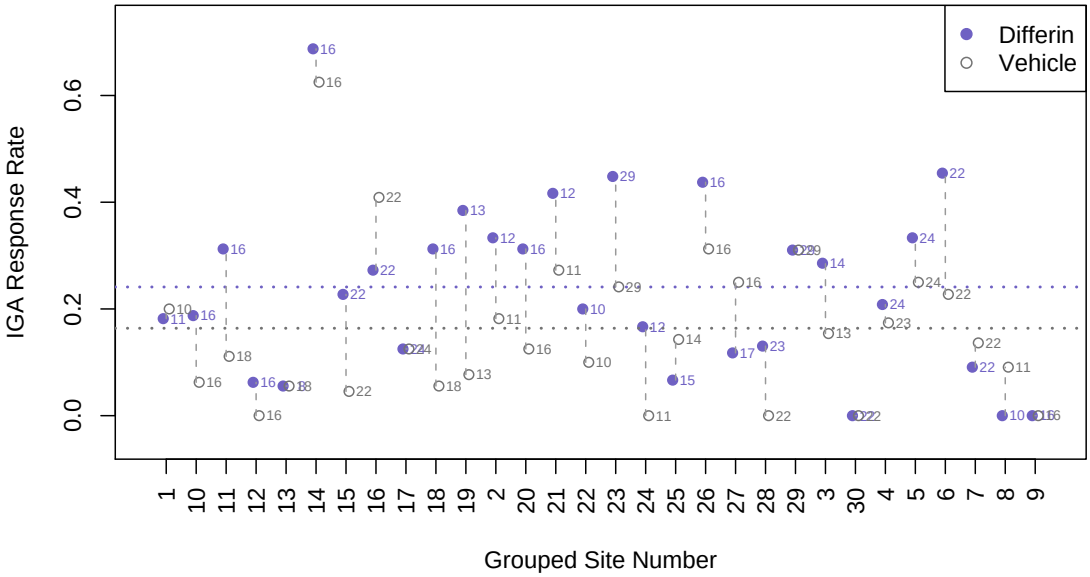


Figure 9: Efficacy Results By Pooled Investigative Site (Study 18114)



5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Based upon protocol agreed upon statistical methods, both Study 18113 and 18114 established the superiority of Differin™ over its vehicle. Determination was made upon the agreed upon co-primary endpoints.

- Success Rate is 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 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 non-inflammatory lesion counts;
  - Absolute change from baseline to Week 12 (LOCF, ITT) in total lesion counts.

Additional sensitivity and supportive analyses were conducted which were consistent with conclusions reached based upon the primary analysis.

The safety of Differin™ appears to be slightly more irritating than its vehicle with most irritation (dryness, erythema, scaling, and stinging) occurring within the first week of treatment. While the mean level of irritation for Differin™ does appear to be highest at Week 1, the mean is still scored below a mild rating. Irritation tends to resolve by the end of treatment (Week 12) reaching near baseline levels.

5.2 Conclusions and Recommendations

The Division and sponsor reached agreements on the primary statistical analysis methods applied to agreed upon co-primary endpoints: Two grade reduction in the IGA scale and absolute change in two out of three lesion counts. Two Phase 3 trials were conducted with the objective to establish the superiority of Differin™ over its vehicle. Each Phase 3 trial individually established the superiority of Differin™ based upon the primary analysis as well as several other sensitivity analyses.

References

[1] DrugsFDA (2009). Retrieved June 18, 2009, from `http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=DIFFERIN`.

[2] Cleveland, W.S. *The Elements of Graphing Data*. Hobart Press, Summit, New Jersey, 1985.

[3] Statistical Analysis and Graphics produced with R software. R Development Core Team (2007). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL `http://www.R-project.org`.

Appendix

A.1 Supplementary Information for Study 18113 and Study 18114

A.1.1 Baseline Demographic Tables

Table 15: **Subject Demographics**

	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: Study Report Table 11.2-1; reproduced by reviewer using `ADSL.XPT`.

A.1.2 Efficacy Tables by Subgroups

The following tables present point estimates of efficacy by age, gender, and race. In the reporting of lesion counts, the means and standard deviation are based upon absolute change from baseline whereas results presented in Section 4.1 were based upon the percent reduction from baseline. Note that no statistical comparisons are made as the results are presented for descriptive purposes only.

A.1.2.1 Investigator Global Assessment Tables 16, 17, and 18 depict efficacy results for the endpoint: Investigator Global Assessment. Tabular information is separated out for each study with data shown being the percent successes (two point IGA change: baseline to Week 12) as well as fraction of successes for each subgroup. The analysis population was the ITT population with missing data imputed using LOCF.

Table 16: **Investigator Global Results (ITT-LOCF) by Age**

	Study 18113		Study 18114	
	Differin	Vehicle	Differin	Vehicle
< 18 years	24.2 $\frac{79}{327}$	18.7 $\frac{64}{343}$	20.7 $\frac{70}{338}$	14.9 $\frac{50}{336}$
18 to 64 years	29.6 $\frac{61}{206}$	15.1 $\frac{30}{199}$	29.9 $\frac{59}{197}$	19 $\frac{37}{195}$

Source: Study Report Table 14.2.11.2; reproduced by reviewer using `ADGA.XPT`

Table 17: **Investigator Global Results (ITT-LOCF) by Sex**

	Study 18113		Study 18114	
	Differin	Vehicle	Differin	Vehicle
Females	30 $\frac{85}{283}$	20.7 $\frac{60}{290}$	25.7 $\frac{77}{300}$	15.4 $\frac{42}{272}$
Males	22 $\frac{55}{250}$	13.5 $\frac{34}{252}$	22.1 $\frac{52}{235}$	17.4 $\frac{45}{259}$

Source: Study Report Table 14.2.11.1; reproduced by reviewer using `ADGA.XPT`

Table 18: **Investigator Global Results (ITT-LOCF) by Race**

	Study 18113		Study 18114	
	Differin	Vehicle	Differin	Vehicle
Caucasian	27.4 $\frac{88}{321}$	15.6 $\frac{52}{334}$	25.5 $\frac{96}{376}$	16.9 $\frac{63}{373}$
Non-Caucasian	24.5 $\frac{52}{212}$	20.2 $\frac{42}{208}$	20.8 $\frac{33}{159}$	15.2 $\frac{24}{158}$

Source: Study Report Table 14.2.11.3; reproduced by reviewer using `ADGA.XPT`

A.1.2.2 Change in Inflammatory Lesion Counts Tables 19, 20, and 21 depict efficacy results for the endpoint: absolute change from baseline for inflammatory lesions. Tabular information is separated out for each study with estimates for the mean and standard deviation (shown in parentheses). The analysis population was the ITT population with missing data imputed using LOCF.

Table 19: **Change in Inflammatory Lesions (ITT-LOCF) by Age**

	Study 18113		**Study 18114**	
	Differin	Vehicle	Differin	Vehicle
< 18 years	14.3 (9.9)	10.3 (13.0)	12.3 (10.7)	9.0 (12.6)
18 to 64 years	15.4 (8.6)	11.2 (9.2)	13.5 (9.7)	12.3 (9.8)

Source: Study Report Table 14.2.11.2; reproduced by reviewer using `ADGA.XPT`

Table 20: **Change in Inflammatory Lesions (ITT-LOCF) by Sex**

	Study 18113		**Study 18114**	
	Differin	Vehicle	Differin	Vehicle
Females	15.3 (8.8)	11.4 (11.0)	13.2 (9.5)	11.2 (10.7)
Males	14.1 (10.0)	9.7 (12.5)	12.2 (11.3)	9.2 (12.7)

Source: Study Report Table 14.2.11.1; reproduced by reviewer using `ADLS.XPT`.

Table 21: **Change in Inflammatory Lesions (ITT-LOCF) by Race**

	Study 18113		**Study 18114**	
	Differin	Vehicle	Differin	Vehicle
Caucasian	14.2 (9.6)	9.3 (11.8)	12.7 (10.7)	9.4 (12.3)
Non-Caucasian	15.6 (9.2)	12.8 (11.3)	12.9 (9.5)	12.1 (10.2)

Source: Study Report Table 14.2.11.3; reproduced by reviewer using `ADLS.XPT`.

A.1.2.3 Change in Non-Inflammatory Lesion Counts Tables 22, 23, and 24 depict efficacy results for the endpoint: absolute change from baseline for non-inflammatory lesions. Tabular information is separated out for each study with estimates for the mean and standard deviation (shown in parentheses). The analysis population was the ITT population with missing data imputed using LOCF.

Table 22: **Change in Non-Inflammatory Lesions (ITT-LOCF) by Age Category**

	Study 18113		**Study 18114**	
	Differin	Vehicle	Differin	Vehicle
< 18 years	22.7 (19.1)	14.9 (20.9)	18.5 (21.4)	11.5 (20.7)
18 to 64 years	24.0 (15.6)	18.1 (18.1)	21.6 (14.1)	16.0 (16.9)

Source: Study Report Table 14.2.11.2; reproduced by reviewer using `ADLS.XPT`.

Table 23: **Change in Non-Inflammatory Lesions (ITT-LOCF) by Sex**

	Study 18113		**Study 18114**	
	Differin	Vehicle	Differin	Vehicle
Females	23.6 (18.6)	16.6 (19.7)	20.9 (16.6)	14.0 (19.5)
Males	22.7 (17.0)	15.5 (20.3)	18.1 (21.7)	12.2 (19.5)

Source: Study Report Table 14.2.11.1; reproduced by reviewer using `ADLS.XPT`.

Table 24: **Change in Non-Inflammatory Lesions (ITT-LOCF) by Race**

	Study 18113		**Study 18114**	
	Differin	Vehicle	Differin	Vehicle
Caucasian	23.1 (18.5)	15.7 (18.6)	19.2 (19.8)	13.4 (19.0)
Non-Caucasian	23.3 (16.8)	16.6 (22.0)	20.7 (17.1)	12.6 (20.6)

Source: Study Report Table 14.2.11.3; reproduced by reviewer using `ADLS.XPT`.

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DB3/Alosh
DB3/Soukup

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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