CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	**21, 753**
Drug Name:	Adapalene Gel, 0.3%
Indication(s):	Treatment Of Acne Vulgaris
Applicant:	Galderma Laboratories, L.P.
Date of Original Submission	04-01-2004
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% and the corresponding vehicle in subjects with acne vulgaris at multiple time points (week 8 and week 12). In the Analysis of the ITT population, with the last observation carried forward (LOCF) for missing values, Adapalene 0.3% demonstrated superiority over Adapalene 0.1% in IGA success rates. In percent change from baseline, Adapalene 0.3% failed to demonstrate superiority over Adapalene 0.1% for all three lesion counts (Total, Inflammatory and Non-inflammatory). However, these analyses results were sensitive to an outlier (subject #1696) and consequently, as specified in the protocol, analysis results based on the rank data were also considered in assessing the efficacy, in addition to other sensitivity analyses. Results of the rank analyses of the ITT with LOCF, failed to provide significant difference of Adapalene 0.3% over Adapalene 0.1%. In the sensitivity analyses using the completer's mean percent change and success rate (for imputation of the missing values), Adapalene 0.3% demonstrated superiority over Adapalene 0.1% based on the rank data.

Although based on the protocol, the primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1%, it was in the interest of the reviewer to see that in the same trial, Adapalene 0.1% also demonstrated superiority over the vehicle. This would be an internal control to evaluate the strength of evidence of efficacy of Adapalene 0.3% over Adapalene 0.1%.

1.2 Brief Overview of Clinical Studies

Pivotal Clinical Study:

Study 18081: The primary objective of the study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% and the corresponding vehicle in subjects with acne vulgaris.

1.3 Statistical Issues and Findings

In this review, the primary analysis was based on the correlated repeated measurements at week 8 and week 12 in the ITT population. Generalized Estimating Equation (GEE) methodology was used as the primary analysis and all tests were two-sided, each at the 0.050 significance level. Efficacy analyses were carried out for two co-primary endpoints: (a) success rates according to the protocol was defined as the percentage of subjects with "Clear" or "Almost Clear" on the Investigator's Global Assessment. (b) percent change in lesion counts (total, inflammatory and non-inflammatory) from baseline. In the analysis of the success rate using GEE, logit link functions was used to

model the marginal expectation. For percent changes in lesion counts, the identity link function with an unstructured working correlation matrix was used. For single time points (week 8 and week 12), Cochran-Mantel-Haenszel (CMH) test was used as pre-specified.

Based on the end of phase 2 meeting minutes dated December 3, 2001, the sponsor had agreed to the definition of the IIT population as all subjects randomized and dispensed study medication, LOCF. In a letter to Galderma Laboratories dated February 15, 2002, the division requested that the assumption of missing completely at random (MAR) should be justified and sensitivity analyses should be carried out for other assumptions for missing data, including imputation based on LOCF method. Accordingly, the efficacy results were assessed in this review based on observed data, LOCF and additional sensitivity analyses for the primary efficacy variables.

In the primary analyses, subject #1696 was identified as an outlier due to extreme values in percent change from baseline in non-inflammatory lesions: 325% at Week 8 and 490% at Week 12. Several FDA sensitivity analyses were performed to examine the influence of this outlier.

In this study, a total of 653 subjects were randomized (258 Adapalene Gel, 0.3%, 261 Adapalene Gel, 0.1% and 134 vehicle gel). Majority of the subjects were Caucasians (75.2% in the Adapalene Gel 0.3% group, 71.3% in the Adapalene Gel, 0.1% group and 67.9% in the vehicle gel group). Hispanics made up 12.3% of the total population; Blacks, 10.3%; Asians, 3.4%; and other races, 2.0%. The mean age was in the range of 17.8 to 18.6 years. Overall, in the ITT population, there were no statistically significant differences observed among the treatment groups with respect to demographic and baseline characteristics.

A total of 89.9% of the subjects completed the study and 88.0% in the Adapalene Gel, 0.3%, 92.0% in the Adapalene Gel, 0.1%, and 89.6% in the vehicle group. Among the subjects discontinued, 30 (4.6%) of the subjects were discontinued due to subject request and 25 (3.8%) due to lost to follow-up. Eight subjects were withdrawn from the study due to an AE: 5 subjects (1.9%) in Adapalene Gel, 0.3% group; 2 subjects (0.8%) in the Adapalene Gel, 0.1% group; and 1 subject (0.7%) in the vehicle group. According to sponsor, of these 8 subjects, 1 subject (Adapalene Gel, 0.3% group) was withdrawn due to a non-dermatologic AE (spherocytosis), and 7 were withdrawn due to dermatologic AEs. There were relatively more subjects discontinued in Adapalene 0.3% arm compared to the Adapalene Gel, 0.1% and vehicle; and majority of the discontinued (16/31) were based on subject request.

Based on the protocol, the primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% (previously approved product) and the corresponding vehicle in subjects with acne vulgaris. However, it was in the interest of the reviewer to see that in the same trial, Adapalene 0.1% also demonstrated superiority over the vehicle, which would substantiate the strength of evidence of efficacy of Adapalene 0.3%.

Single time points (week 8, week 12)- Observed Data

Evaluating the treatment success rates at week 8 (Table 7), the rates were 32/229 (14%) in the Adapalene 0.3% arm, 20/242(8.3%) in the Adapalene 0.1% arm and 13/122(10.7%) in the Vehicle arm, respectively. At week 12, success rates of 53/227(23.3%) in the Adapalene 0.3% arm, 40/237(16.9%) in the Adapalene 0.1% arm and 12/120(10.0%) in the Vehicle arm were reported.

At week 8, success rate in Adapalene 0.3% arm demonstrated superiority over Adapalene 0.1% (p=0.04). However, Adapalene 0.3% failed to show superiority over the vehicle (p=0.29) and Adapalene 0.1% failed to show superiority over the vehicle (p=0.50). In percent change from baseline, Adapalene Gel, 0.3% failed to demonstrate superiority over Adapalene 0.1% for all three lesion counts (Total, Inflammatory and Non-inflammatory) and the superiority over the vehicle was only established for non-Inflammatory lesion counts.

At week 12, Adapalene 0.3% failed to show superiority over Adapalene 0.1% (p=0.07) in success rates. For total and non-inflammatory lesions, Adaplaene 0.3% demonstrated superiority over Adaplaene 0.1%. However, Adapalene 0.1% achieved only border line significance over vehicle (p=0.05) for non-inflammatory lesion counts. Similar conclusions were drawn based on the LOCF data.

Repeated Measures (week 8 and week 12) - Observed Data

In the GEE analyses (Table 9) at multiple time points (Week 8 and Week 12), Adapalene Gel, 0.3% was superior to Adaplaene Gel, 0.1% (p=0.02) in IGA success rates. However, Adapalene 0.1% failed to show superiority over vehicle (p=0.41). In the analysis of the total lesion counts, Adapalene Gel, 0.3% failed to demonstrate superiority in percent reduction over Adapalene Gel, 0.1% (p=0.19). In the analysis of the inflammatory lesion counts, Adapalene Gel, 0.3% achieved a border-line significance in percent reduction over Adapalene Gel, 0.1% (p=0.05). In the analysis of the non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.49).

In the Rank analyses for Week 8 and Week 12 (Table 9), for total lesion counts, Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% (p=0.02). In the analysis of the inflammatory lesion counts, Adapalene Gel, 0.3% showed a significant percent reduction over Adapalene Gel, 0.1% (p=0.02). However, Adapalene 0.1% failed to demonstrate superiority over vehicle (p=0.15). In the analysis of the non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.06).

In the GEE analyses of the ITT population (Table 10, LOCF-including 45 subjects) at multiple time points (Week 8 and Week 12), Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% in IGA success rates (p=0.028). However,

Adapalene 0.1% failed to demonstrate superiority over vehicle (p=0.42). For total lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene Gel, 0.1% (p=0.33). For inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significant difference in percent reduction over Adapalene Gel, 0.1% (p=0.164). For non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction in non-inflammatory lesion counts over Adapalene Gel, 0.1% (p=0.56). In the rank analyses of the LOCF data, Adapalene 0.3% failed to show superiority over Adapalene 0.1% in all three lesion counts.

Following the Agency's request on October 13, 2004, the sponsor carried out two additional sensitivity analyses. In the sensitivity analyses-I (Table 12), the missing values were imputed by using completer's mean percent change and success rate at week 8 and week 12. In the GEE analyses of IGA success rates at multiple time points, Adapalene Gel, 0.3% was superior to Adapalene Gel, 0.1% (p=0.017). However, Adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.258). For total lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene Gel, 0.1% (p=0.105). For inflammatory lesion counts, Adapalene Gel, 0.3% demonstrated a significant difference in percent reduction over Adapalene Gel, 0.1% (p=0.03). For non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.344). In the analyses using the Rank data, Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% in all three lesion counts.

In the sensitivity analysis-II (Table 13), the missing values were imputed by using completer's mean percent change and success rate with similar baseline counts and IGA score at week 8 and week 12. In the GEE analyses of IGA success rates, Adapalene Gel, 0.3% was significantly superior to Adapalene Gel, 0.1% (p=0.021). However, Adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.229). For total lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene Gel, 0.1% (p=0.11). For inflammatory lesion counts, Adapalene Gel, 0.3% demonstrated a significant difference in percent reduction over Adapalene Gel, 0.1% (p=0.03). For non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.33). In the analyses using the Rank data, Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% in all three lesion counts. However, for Inflammatory lesion counts, Adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.05)

In the special/sub group populations, there were no significant differences observed in success rates between Adapalene 0.3% and Adapalene 0.1% for both male and female groups. The success rates were slightly higher in Caucasians versus non-Caucasians across all three treatment groups. It should be noted that there were 72% Caucasians overall in the study compared to other ethnic groups. Comparing the age groups, success rates in the Adapalene Gel, 0.3% and vehicle gel groups were lower numerically in the 12-17 year-old age group compared with the 18-64 year-old age group. There was no

significant difference between Adapalene Gel, 0.3% and Adapalene Gel, 0.1% at week 8 and 12 in the 12-17 age group.

As regards to the safety, based on sponsor's study report, there were reports of erythema worest than at baseline was present in 24.5% and 26.8% of subjects in the Adapalene Gel, 0.3% and 0.1% groups, respectively, at Week 1, and in 12.3% and 13.2%, respectively, at the final visit. Although majority of AEs were mild or moderate in severity, dermatological AEs were more frequently reported in the Adapalene Gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). The majority of dermatological AEs were considered related to study drug treatment. Four subjects (all in the Adapalene Gel, 0.3% group) had non-dermatological AEs that were considered related to study treatment; these events were facial edema, pain, keratoconjunctivitis, and eye pain.

2. INTRODUCTION

2.1 Overview

Acne vulgaris is a very common skin disorder, affecting the majority of the teenage population. Adapalene 0.1% gel was approved in the US for the topical treatment of acne vulgaris. The submitted pivotal Phase 3 study (study 18081) has been designed to provide evidence of the superior therapeutic effect of Adapalene Gel, 0.3% compared to Adapalene Gel, 0.1% and corresponding vehicle gel.

The primary objective of the study was to demonstrate superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% and the corresponding vehicle gel. The study subjects were 12 years of age and older with 20 to 100 non-inflammatory lesions, 20 to 50 inflammatory lesions, and no nodules or cysts. The planned treatment duration was 12 weeks and the study drug was applied once daily in the evening. Blood and urine samples collected at Screening and Week 12 (or at the time of discontinuation) at specified sites were evaluated for blood chemistries, hematology, and urinalysis.

2.2 Data Sources

The sponsor's submitted data was available on the EDR. The directory link is \\CDSESUB1\N21753\N_000\2004-03-31. There were additional data and analyses results submitted to the agency based on subsequent requests to aid the review and were reviewed. The applicable comments were incorporated in this review document.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 18081

3.1.1.1 Study Description

Study Design: This was a multi-center, randomized, active and vehicle-controlled, double-blind and parallel-group study comparing between Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle gel in subjects with acne vulgaris. The subjects were randomized in a 2:2:1 ratio to receive either Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, or vehicle gel.

Study Objectives: The primary objective of the study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% and the corresponding vehicle in subjects with acne vulgaris.

The primary efficacy variables:

- Percent lesion reduction from baseline (inflammatory, non-inflammatory, and total)

- IGA Success rate, the percentage of subjects with "Clear" or "Almost Clear" on the Investigator's Global Assessment.

Primary Analysis/population: Based on the protocol, the primary endpoints will be analyzed using the ITT population at multiple time-points (Week 8 and Week 12) based on the following criteria:

- Two of the three (total, inflammatory, non-inflammatory) percent lesion reductions and
- IGA Success rate

Secondary efficacy variables:

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

The sponsor's safety variables were:

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

Table 1: Analyzed Subjects

Disposition	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Vehicle Gel	Total
ITT	258	261	134	653
Safety	258	261	134	653

Sponsor's Statistical Methods

Based on the protocol, the Generalized Estimating Equation (GEE) methodology was used as the primary analysis for the correlated repeated measurements at Week 8 and Week 12. All tests were two-sided, each at the 0.050 significance level. Treatment by center interaction were assessed for all primary efficacy variables using a significance level of 0.15 as specified in the protocol. However, the division recommends that the center interactions be tested using a significance level of 0.10 and was tested accordingly. For success rates, the logit link function was used to model the marginal expectation. For percent changes in lesion counts, the identity link function with an unstructured working correlation matrix was used. For single time points (week 8 and week 12), Cochran-Mantel-Haenszel (CMH) test was used. Based on the end of phase 2 meeting minutes

dated December 3, 2001, the sponsor had agreed to the definition of the ITT population as all subjects randomized and dispensed study medication, LOCF. In a letter to Galderma Laboratories dated February 15, 2002, the division requested that the assumption of missing completely at random should be justified and a sensitivity analysis should be carried out for other assumptions for missing data, including imputation based on LOCF method. Accordingly, the efficacy results were assessed in this review based on both types of analyses (observed data, LOCF) for the primary efficacy variables.

Dropouts or Missing Data

Based on the Sponsor's analysis, missing values were estimated using the LOCF method. For cases where no post-baseline values were available, baseline values were carried forward to all post-baseline visits. For the three lesion counts (total, inflammatory, and non-inflammatory), the LOCF estimation was applied to the individual item (open comedone, close comedone, papules, pustules, nodules/cysts) prior to the totals. The observed data at Week 8 and Week 12 were used in the GEE analyses, assuming that the missing data were missing completely at random (MAR). Sensitivity analyses were submitted and reviewed based on the division recommendations as stated in the protocol.

Sponsor's Outlier

According to the sponsor, in performing the analyses, subject #1696 was identified as an outlier due to extreme values in percent change from baseline in non-inflammatory lesions: 325% at Week 8 and 490% at Week 12. Several FDA sensitivity analyses were performed to examine the influence of the outlier, as reported by the sponsor.

Pooling of centers

According to the sponsor, small centers that have <10 subjects were pooled in the Adapalene Gel, 0.3% or Adapalene Gel, 0.1% treatment arm based on the ITT population. Within the group of small centers, pooling was done from the largest center to the smallest center, and by center number within those having the same size. Small centers were pooled until the pooled center has ≥10 subjects in the Adapalene Gel, 0.3% and Adapalene Gel, 0.1% treatment group. Any leftover centers from this procedure that do not have a sufficient number of subjects to form a pooled center were pooled with the last pooled center.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

Table 2 presents the demographic and baseline characteristic of subjects enrolled in the study and Table 3 represents the subjects continued/discontinued in the study ITT population.

Table 2: Demographic and Baseline Characteristics – ITT Population

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

Sponsor's Table

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

Table 3: Subjects Completed/Discontinued the Study: ITT Population

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

Sponsor's Table/Edited

Statistical Reviewer's Comments:

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

Table 4 presents summary of patient's treatment duration across all the three treatments. The protocol specified treatment duration was for 12 weeks (plus or minus 5-7 days (77-84 days) to assist with subject compliance). The proportion of subjects within this window is similar across the three treatment arms. Subjects treated beyond 91 days were protocol violators. There were a total of 39 subjects treated beyond 91 days. Among these subjects, 17(6.6%) of the Adapalene treated subjects, 12(4.6%) of the Adaplene 0.1% treated subjects and 10(7.5%) of the vehicle were treated more than 91 days.

Table 4: Summary of Treatment Duration: ITT population

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

Reviewer's Table

Statistical Reviewer's Comments:

Based on the above table, 535/653(82%) of the patients were received treatment in the 77-91 days window of treatment duration. Among these patients, 209/258(81.0%) were in the Adapalene 0.3% and 218/261(83.5%) were in the Adapalene 0.1% and 108/134(80.6%) in the vehicle arm, respectively.

According to the protocol, subjects with Inflammatory lesion counts<20 or >50 and non-inflammatory lesion counts<20 and >100 should have been excluded from this analysis. There were 29 subjects violated the criteria were included in the analysis. Also, based on Table 4, there were a total of 39 subjects treated beyond 91 days. Sensitivity analyses were performed after excluding these cases to assess the impact on the efficacy results (refer Table 11 for analyses results).

3.1.1.3 Efficacy Analyses

3.1.1.3.1 Univariate Analysis

Table 5: Observed data: Summary of Success Rate and ITT at final study point (week 12)

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Baseline Total	258	(100.0%)	261	(100.0%)	134	(100.0%)	-	-
Week1 Success	3/241	(1.2%)	0/246	(0.0%)	1/126	(0.8%)	0.105	0.676
Week2 Success	10/241	(4.1%)	6/245	(2.4%)	5/128	(3.9%)	0.197	0.824
Week4 Success	16/240	(6.7%)	11/239	(4.6%)	12/124	(9.7%)	0.332	0.312
Week8 Success	32/229	(14.0%)	20/242	(8.3%)	13/122	(10.7%)	0.037	0.292
Week12 Success	53/227	(23.3%)	40/237	(16.9%)	12/120	(10.0%)	0.072	0.002
ITT Success (LOCF)	53/258	(20.5%)	41/261	(15.7%)	12/134	(9.0%)	0.156	0.002

LOCF: the last observation for a subject during the treatment period, including baseline if no post baseline data is available. P-value was assessed based on the CMH row mean difference statistic, controlling for the center.

Dr. [redacted]'s Site:

The sponsor reported that one site (n=19 subjects) belonged to Dr. [redacted] used the draft Investigators Global Assessment (IGA) score prior to finalization, instead of the final IGA score. The results based on a sensitivity analyses by excluding these patients were given below.

Table 6: Summary of Success Rate: Observed Data (excluding Dr. [redacted]'s site; n=19 subjects):

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	30/222	(13.5%)	19/236	(8.1%)	12/118	(10.2%)	0.042	0.290
Week12 Success	48/220	(21.8%)	39/231	(16.9%)	11/117	(9.4%)	0.157	0.003
ITT Success	48/250	(19.2%)	40/254	(15.7%)	11/130	(8.5%)	0.307	0.004

Statistical Reviewer's Comments:

The statistical conclusions were the same based on excluding the subjects for sensitivity analyses as compared to the observed subjects (as given in Table 5*). At week 8, although the success rate for Adapalene 0.3% demonstrated superiority to Adapalene 0.1% (p=0.04), Adapalene 0.3% failed to show superiority over the vehicle (p=0.29).*

At week 12, the success rate was not significantly different compared to Adapalene 0.1% (p=0.16) although Adapalene 0.3% demonstrated superiority over the vehicle (p=0.003). The LOCF analysis provided consistent results at week 12.

Table 7: Observed Data: Univariate Analysis of Percent change in Total, Inflammatory, Non-Inflammatory and IGA Success rates for Week 8 and Week 12

	Adapalene 0.3%	Adapalene 0.1%	Vehicle	P-Values		
				0.3% vs. 0.1%	0.3% vs. Vehicle	0.1% vs. Vehicle
WEEK 8						
Total						
Absolute Change	-27.6	-27.9	-22.1	0.967	0.092	0.093
% Change	-41.5%	-40.9%	-34.7%	0.320	0.070	0.290
Inflammatory						
Absolute Change	-13.3	-12.7	-11.7	0.432	0.324	0.686
% Change	-48.2%	-45.0%	-43.9%	0.240	0.630	0.700
Non-Inflammatory						

Absolute Change % Change	-14.5 -35.6%	-15.2 -36.6%	-10.5 -26.9%	0.802 0.570	0.040 0.030	0.020 0.090
IGA Success Success	32/229(14.0%)	20/242(8.3%)	13/122 (10.7%)	0.037	0.290	0.500
WEEK 12						
Total Absolute Change % Change	 -33.3 -49.5%	 -30.6 -43.9%	 -21.8 -34.7%	 0.110 0.003	 <0.001 <0.001	 0.001 0.006
Inflammatory Absolute Change % Change	 -15.5 -55.8%	 -14.5 -51.7%	 -11.2 -41.5%	 0.126 0.099	 <0.001 <0.001	 0.002 0.007
Non-Inflammatory Absolute Change % Change	 -17.8 -43.5%	 -16.2 -37.2%	 -10.7 -27.9%	 0.164 0.003	 <0.001 <0.001	 0.007 0.050
IGA Success	53/227(23.3%)	40/237(16.9%)	12/120(10.0%)	0.070	0.002	0.100

P values are based on CMH row mean difference statistic, controlling for center

Table 8: ITT (LOCF): Univariate analysis of percent change in Total, Inflammatory, Non-Inflammatory and IGA Success rates at Week 12

WEEK 12	P-Values		
	*Ada 0.3% vs. 0.1%	Ada 0.3% vs. Vehicle	Ada 0.1% vs. Vehicle
Total Lesions	0.020	<0.001	0.010
Inflammatory	0.376	<0.001	0.007
Non-inflammatory	0.011	<0.001	0.051
IGA Success	0.160	0.002	0.105

*Ada=Adapalene

3.1.1.3.2 Repeated Measures Analysis

The sponsor pointed out in their study report that subject #1696 was an outlier. Based on the protocol, due to the concerns of not meeting the parametric assumptions (normality, $p<0.0001$), models based on rank data were also submitted and reviewed in addition to all other analyses.

Table 9: Observed Cases (assuming MAR): Repeated Measures Analysis (GEE) of Week 8 and Week 12

GEE Analyses of multiple timepoints	Mean Difference Estimates (week 8,12)*			P-Values		
	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.1% vs. Vehicle	0.3% vs. 0.1%	0.3% vs. Vehicle	0.1% vs. Vehicle
Total						
Absolute change	-1.78	-8.69	-6.91	0.33	<0.001	<0.02
% change	-3.66	-10.6	-6.90	0.19	0.001	0.02
Rank	-30.16	-65.67	-35.51	0.02	<0.001	0.01
Inflammatory						
Absolute change	-1.15	-3.32	-2.17	0.14	0.001	0.04
% change	-5.05	-10.93	-5.87	0.05	0.001	0.08
Rank	-30.33	-51.59	-21.26	0.02	<0.001	0.15
Non-Inflammatory						
Absolute change	-0.68	-5.45	-4.76	0.64	0.004	0.001
% change	-2.64	-11.30	-8.66	0.49	0.014	0.02
Rank	-24.40	-60.65	-36.25	0.06	<0.001	0.01
IGA Success *	1.67	2.11	1.27	0.02	0.007	0.41

- For IGA(success), estimate is the odds ratio

Table 10: ITT Population (LOCF): Repeated Measures Analysis (GEE) of Week 8 and Week 12 (included 45 missing subjects)

GEE Analyses of multiple timepoints (Adapalene)	Mean Difference Estimates (week 8,12)*			P-Values		
	Ada 0.3% vs. 0.1%	Ada 0.3% vs. Vehicle	Ada 0.1% vs. Vehicle	0.3% vs. 0.1%	0.3% vs. Vehicle	0.1% vs. Vehicle
Total						
Absolute change	-1.24	-8.26	-7.03	0.480	<0.001	<0.001
% change	-2.55	-10.08	-7.54	0.326	0.001	0.010
Rank	-23.33	-63.34	-39.82	0.072	<0.001	0.006
Inflammatory						
Absolute change	-0.78	-2.96	-2.18	0.301	0.003	0.030
% change	-3.42	-9.62	-6.20	0.164	0.003	0.050
Rank	-23.61	-47.59	-23.98	0.064	0.002	0.110
Non-Inflammatory						
Absolute change	-0.50	-5.37	-4.88	0.747	<0.001	<0.001
% change	-2.04	-11.47	-9.44	0.560	0.007	0.010
Rank	-20.24	-60.36	-40.12	0.120	<0.001	0.006
IGA Success *	1.61	2.03	1.26	0.028	0.010	0.420

- For IGA(success), estimate is the odds ratio

There were few protocol violations/compliance issues and post-hoc analyses of the observed data were performed (by the sponsor based on Agency's request). These include Subjects with baseline inflammatory lesion counts between 20 and 50, and non-inflammatory lesion counts between 20 and 100, and subjects whose Week 8 efficacy evaluation between days 49 and 63 and week 12 efficacy evaluation between days 77 and 91 days. Based on the GEE analyses of the multiple time points (weeks 8 and 12), Adapalene 0.3% failed to demonstrate superiority over Adapalene 0.1% in percent change from baseline for total and non-inflammatory counts. IGA success rate and the percent change in inflammatory lesion counts achieved only border-line significance. The analyses of the ITT using LOCF and the rank data (LOCF), failed to provide evidence of superiority of Adapalene 0.3% over Adapalene 0.1% in all three lesion counts. The results of these analyses are given below in Table 11.

Table 11: Observed Data, ITT(LOCF): Repeated Measures Analysis (GEE) of Week 8 and Week 12 (Subjects with baseline inflammatory (20-50 counts), non-inflammatory (20-100 counts), efficacy assessment of week 8(49-63 days), week 12 (77-91 days)

	Mean Difference Estimates (week 8,12)*		P-Values	
% Change	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	0.3% vs. 0.1%	0.3% vs. Vehicle
Total				
Observed	-3.56	-12.37	0.297	0.004
Observed-Rank	-27.29	-63.75	0.025	<0.001
LOCF	-1.87	-10.54	0.476	0.002
LOCF-Rank	-19.00	-61.12	0.134	<0.001
Inflammatory				
Observed	-5.57	-13.62	0.050	0.002
Observed-Rank	-28.44	-47.56	0.013	0.002
LOCF	-2.88	-10.25	0.246	0.003
LOCF-Rank	-20.38	-48.09	0.100	0.002
Non-Inflammatory				
Observed	-1.22	-11.61	0.800	0.035
Observed-Rank	-19.27	-62.05	0.121	<0.001
LOCF	-1.24	-11.87	0.726	0.011
LOCF-Rank	-16.41	-57.61	0.192	<0.001
IGA Success *	1.62	2.52	0.051	0.004
LOCF	1.63	1.87	0.026	0.022

Sponsor's analysis

- IGA(success) of the observed data; estimate is the odds ratio

Sponsor's Sensitivity Analyses:

The Agency had requested for two additional sensitivity analyses for the imputation of the missing data.

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

Sensitivity Analysis-II:
Imputed missing data by using Completer's mean percent change and success rate with similar baseline counts and IGA score at week 8 and Week 12 in the ITT population.

Table 12 and Table 13 provide the sensitivity analysis results.

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

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

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

Table 13: Sensitivity Analyses-II: Imputed missing data by using Completer's mean percent change and success rate with similar baseline counts and IGA score at week 8 and Week 12 in the ITT population

GEE Analyses of multiple timepoints	Mean Difference Estimates (week 8 and 12)		P-Values		
	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.3% vs. 0.1%	Adapalene 0.3% vs. Vehicle	Adapalene 0.1% vs. Vehicle
IGA (Success)*	1.590	2.210	0.021	0.001	0.229
Total Lesion Count					
Percent change	-3.820	-11.790	0.113	<0.001	0.002
Rank	-35.430	-86.690	0.008	<0.001	0.001

Inflammatory Count					
Percent change	-4.870	-11.370	0.030	<0.001	0.031
Rank	-35.080	-66.240	0.007	<0.001	0.046
Non-Inflammatory Count	-3.260	-13.000	[redacted]	0.002	0.006
Percent change	-29.330	-82.240	0.030	<0.001	0.001
Rank					

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

3.2 Evaluation of Safety

The safety review was based on the ITT population, which included subjects who had applied the study medication at least once.

Adverse Events

An AE was defined as any unfavorable and unintended sign *(e.g., including a clinically relevant abnormal laboratory finding)*, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Table 14: Highest Erythema Severity Score (Worse Than Baseline)

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

Source: Sponsor's Table, Section 14, Table SAF 2.1

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

Table 15: Overall Summary of Adverse Events

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

Source: Sponsor's Table, Section 14

Statistical Reviewer's Comments:

According to the sponsor, at baseline, erythema of mild or moderate severity was present in 67 (26.0%), 62 (23.7%), and 30 (22.4%) of subjects in the Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle gel groups, respectively. The majority of these subjects had mild erythema (58 in the Adapalene Gel, 0.3% group, 53 in the Adapalene Gel, 0.1% group, and 25 in the vehicle gel group). The subjects whose erythema worsened from baseline, the majority developed erythema of mild severity. Across treatment groups, 26.1%, 29.6%, and 21.1% of subjects in the Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle groups had, as the highest severity score, mild erythema; 13.0%, 10.5%, and 4.5%, respectively, had, as the highest severity score, moderate erythema; and few subjects (0.0% to 0.8% across treatment groups) developed severe erythema with treatment.

The percentage of subjects with erythema worse than at baseline in the two Adapalene treatment groups was highest at Week 1, and decreased over time during treatment. Erythema worse than at baseline was present in 24.5% and 26.8% of subjects in the Adapalene Gel, 0.3% and 0.1% groups, respectively, at Week 1, and in 12.3% and 13.2%, respectively, at the final visit. This decrease in erythema over time was not present in the vehicle group. At the final visit, the precentages of subjects with erythema worse than baseline were comparable across the Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle gel treatment groups.

Based on sponsor's study report, dermatological AEs were more frequently reported (Table 15) in the Adapalene Gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). The majority of dermatological AEs were considered related to study drug treatment. Four subjects (all in the Adapalene Gel,

0.3% group) had non-dermatological AEs that were considered related to study treatment; these events were facial edema, pain, keratoconjunctivitis, and eye pain.

Three subjects had SAEs (See sponsor's Section 12.4.2 for full discussion): 1 subject in the Adapalene Gel, 0.3% group (spherocytosis) and 2 subjects in the Adapalene Gel, 0.1% group (accidental displacement of mediport; and, paralytic migraine; See Section 12.4.1 for narratives). According to the sponsor, none of the SAEs was considered related to study treatment. Eight subjects (5 in the Adapalene Gel, 0.3% group, 2 in the Adapalene Gel, 0.1% group, and 1 in the vehicle group) discontinued due to an AE. Dermatological AEs that led to discontinuation were reported in 4 (1.6%), 2 (0.8%), and 1 (0.7%) subjects in the Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle gel groups, respectively. The majority of AEs were mild or moderate in severity. The percentages of subjects with severe AEs was low: 0.4%, 2.3%, and 1.5% in the Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle gel groups, respectively. The percentage of subjects with drug-related AEs increased with gel concentration: 22.1%, 11.9%, and 4.5% in the Adapalene Gel, 0.3%, Adapalene Gel, 0.1%, and vehicle gel groups, respectively. However, according to the sponsor, the drug-related AEs were generally mild or moderate in severity and transient, occurring predominantly in the early weeks of treatment, and generally did not limit further treatment with Adapalene Gel.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were performed for the primary efficacy variables for the following subgroups of subjects: center, gender, race, and age. These data were summarized for the observed data, ITT (LOCF) population using the CMH test. It should be noted that the study was not powered for subgroup analysis and thus the p-values should be interpreted appropriately.

4.1 Gender, Race and Age

Table 16: Summary of Success Rate by Gender: Male (Observed data and ITT)

Success Rate	Adapalene Gel 0.3% (n/N)		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	13/113	(11.5%)	6/126	(4.8%)	4/57	(7.0%)	0.055	0.359
Week12 Success	22/114	(19.3%)	15/124	(12.1%)	4/59	(6.8%)	0.126	0.029
ITT Success	22/129	(17.1%)	15/132	(11.4%)	4/62	(6.5%)	0.188	0.046

P-value was assessed based on the CMH row mean difference statistic

Table 17: Summary of Success Rate by Gender: Female (Observed data and ITT)

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	19/116	(16.4%)	14/116	(12.1%)	9/65	(13.8%)	0.348	0.652
Week12 Success	31/113	(27.4%)	25/113	(22.1%)	8/61	(13.1%)	0.356	0.031
ITT Success	31/129	(24.0%)	26/129	(20.2%)	8/72	(11.1%)	0.454	0.027

P-value was assessed based on the CMH row mean difference statistic.

Table 18: Summary of Success Rate by Race: Caucasian (Observed data and ITT)

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	30/174	(17.2%)	14/172	(8.1%)	9/84	(10.7%)	0.011	0.171
Week12 Success	43/172	(25.0%)	29/167	(17.4%)	8/82	(9.8%)	0.086	0.005
ITT Success	43/194	(22.2%)	30/186	(16.1%)	9/91	(9.9%)	0.136	0.013

P-value was assessed based on the CMH row mean difference statistic.

Table 19: Summary of Success Rate by Race: Non-Caucasian (Observed data and ITT)

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	2/55	(3.6%)	6/70	(8.6%)	4/38	(10.5%)	0.265	0.186
Week12 Success	10/55	(18.2%)	11/70	(15.7%)	4/38	(10.5%)	0.715	0.313
ITT Success	10/64	(15.6%)	11/75	(14.7%)	3/43	(7.0%)	0.875	0.181

P-value was assessed based on the CMH row mean difference statistic.

Table 20: Summary of Success Rate by Age: 12-17 years (Observed data and ITT)

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	18/150	(12.0%)	11/168	(6.5%)	6/74	(8.1%)	0.092	0.377
Week12 Success	27/151	(17.9%)	27/164	(16.5%)	5/75	(6.7%)	0.739	0.023
ITT Success	27/162	(16.7%)	28/178	(15.7%)	5/79	(6..3%)	0.815	0.027

P-value was assessed based on the CMH row mean difference statistic.

Table 21: Summary of Success Rate by Age: 18-64 years (Observed data and ITT)

Success Rate	Adapalene Gel 0.3%		Adapalene Gel 0.1%		Vehicle Gel		P-value 0.3%-0.1%	P-value 0.3%-Veh
Week8 Success	14/79	(17.7%)	9/74	(12.2%)	7/48	(14.6%)	0.338	0.646
Week12 Success	26/76	(34.2%)	13/73	(17.8%)	7/45	(15.6%)	0.023	0.027
ITT Success	26/96	(27.1%)	13/83	(15.7%)	7/55	(12.7%)	0.066	0.041

P-value was assessed based on the CMH row mean difference statistic.

Statistical Reviewer's Comments:

Based on special /sub group populations (Table 16), *overall, there was no significant difference in success rates between Adapalene 0.3% and Adapalene 0.1% at for both male and female groups.*

The success rates were slightly higher in Caucasians versus non-Caucasians across all three treatment groups. It should be noted that there were 72% Caucasians overall in the study compared to other ethnic groups. Comparing the age groups, success rates in the Adapalene Gel, 0.3% and vehicle gel groups were lower numerically in the 12-17 year-old age group compared with the 18-64 year-old age group. There was no significant difference between Adapalene Gel, 0.3% and Adapalene Gel, 0.1% at week 8 and 12 in the 12-17 age group. However, in the 18-64 age group, the difference was significant at week 12.

4.2 Other Special /Subgroup Populations

Other several sub-groups have been reviewed but are not included in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In this review, the primary analysis was based on the correlated repeated measurements at week 8 and week12 in the ITT population. Generalized Estimating Equation (GEE) methodology was used as the primary analysis and all tests were two-sided, each at the 0.050 significance level. Efficacy analyses was carried out for two co-primary endpoints: (a) success rates according to the protocol was defined as the percentage of subjects with "Clear" or "Almost Clear" on the Investigator's Global Assessment. (b) percent change in lesion counts (total, inflammatory and non-inflammatory) from baseline. In the analyses of the success rate using GEE, logit link functions was used to model the

marginal expectation. For percent changes in lesion counts, the identity link function with an unstructured working correlation matrix was used. For single time points (week 8 and week 12), Cochran-Mantel-Haenszel (CMH) test was used as pre-specified.

Based on the end of phase 2 meeting minutes dated December 3, 2001, the sponsor had agreed to the definition of the IIT population as all subjects randomized and dispensed study medication, LOCF. In a letter to Galderma Laboratories dated February 15, 2002, the division requested that the assumption of missing completely at random (MAR) should be justified and sensitivity analyses should be carried out for other assumptions for missing data, including imputation based on LOCF method. Accordingly, the efficacy results were assessed in this review based on observed data, LOCF and additional sensitivity analyses for the primary efficacy variables.

In the primary analyses, subject #1696 was identified as an outlier due to extreme values in percent change from baseline in non-inflammatory lesions: 325% at Week 8 and 490% at Week 12. Several FDA sensitivity analyses were performed to examine the influence of this outlier. Based on evaluating various analyses and examining the leverage (H value), observation #1696 was appeared slightly as an influential outlier (although not very extreme) based on the GEE primary analysis model. It should be noted that adjusted Pearson residual was slightly higher for week 8 and week 12 based on the leverage suggesting that the estimates for the model parameters were sensitive to this observation.

In this study, a total of 653 subjects were randomized (258 Adapalene Gel, 0.3%, 261 Adapalene Gel, 0.1% and 134 vehicle gel). Majority of the subjects were Caucasians (75.2% in the Adapalene Gel 0.3% group, 71.3% in the Adapalene Gel, 0.1% group and 67.9% in the vehicle gel group). Hispanics made up 12.3% of the total population; Blacks, 10.3%; Asians, 3.4%; and other races, 2.0%. The mean age across treatment group was in the range of 17.8 to 18.6 years. Overall, in the ITT population, there were no statistically significant differences observed among the treatment groups with respect to demographic and baseline characteristics.

A total of 89.9% of the subjects completed the study and 88.0% in the Adapalene Gel, 0.3%, 92.0% in the Adapalene Gel, 0.1%, and 89.6% in the vehicle group. Among the subjects discontinued, 30 (4.6%) of the subjects were discontinued due to subject request and 25 (3.8%) due to lost to follow-up. Eight subjects were withdrawn from the study due to an AE: 5 subjects (1.9%) in Adapalene Gel, 0.3% group; 2 subjects (0.8%) in the Adapalene Gel, 0.1% group; and 1 subject (0.7%) in the vehicle group. According to sponsor, of these 8 subjects, 1 subject (Adapalene Gel, 0.3% group) was withdrawn due to a non-dermatologic AE (spherocytosis), and 7 were withdrawn due to dermatologic AEs. There were relatively more subjects discontinued in Adapalene 0.3% arm compared to the Adapalene Gel, 0.1% and vehicle; and majority of the discontinued (16/31) were based on subject request.

Based on the protocol, the primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% (previously approved product) and the corresponding vehicle in subjects with acne vulgaris. However, it was in

the interest of the reviewer to see that in the same trial, Adapalene 0.1% also demonstrated superiority over the vehicle, which would substantiate the strength of evidence of efficacy of Adapalene 0.3%.

Single time points (week 8, week 12)- Observed Data

Evaluating the treatment success rates at week 8 (Table 7), the rates were 32/229 (14%) in the Adapalene 0.3% arm, 20/242(8.3%) in the Adapalene 0.1% arm and 13/122(10.7%) in the Vehicle arm, respectively. At week 12, success rates of 53/227(23.3%) in the Adapalene 0.3% arm, 40/237(16.9%) in the Adapalene 0.1% arm and 12/120(10.0%) in the Vehicle arm were reported.

At week 8, success rate in Adapalene 0.3% arm demonstrated superiority over Adapalene 0.1% (p=0.04). However, Adapalene 0.3% failed to show superiority over the vehicle (p=0.29) and Adapalene 0.1% failed to show superiority over the vehicle (p=0.50). In percent change from baseline, Adapalene Gel, 0.3% failed to demonstrate superiority over Adapalene 0.1% for all three lesion counts (Total, Inflammatory and Non-Inflammatory) and the superiority over the vehicle was only established for Non-Inflammatory lesion counts.

At week 12, Adapalene 0.3% failed to show superiority over Adapalene 0.1% (p=0.07) in success rates. For total and non-inflammatory lesions, Adaplaene 0.3% demonstrated superiority over Adaplaene 0.1%. However, Adapalene 0.1% achieved only border line significance over vehicle (p=0.05) for non-inflammatory lesion counts. Similar conclusions were drawn based on the LOCF data.

Repeated Measures (week 8 and week 12) - Observed Data

In the GEE analyses of the observed cases (Table 9) at multiple time points (Week 8 and Week 12), Adapalene Gel, 0.3% was superior to Adaplaene Gel, 0.1% (p=0.02) in IGA success rates. However, Adapalene 0.1% failed to show superiority over vehicle (p=0.41). In the analysis of the total lesion counts, Adapalene Gel, 0.3% failed to demonstrate superiority in percent reduction over Adapalene Gel, 0.1% (p=0.19). In the analysis of the inflammatory lesion counts, Adapalene Gel, 0.3% achieved a border-line significance in percent reduction over Adapalene Gel, 0.1% (p=0.05). In the analysis of the non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.49).

In the analyses of the observed cases using Rank data for Week 8 and Week 12 (Table 9), for total lesion counts, Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% (p=0.02). In the analysis of the inflammatory lesion counts, Adapalene Gel, 0.3% showed a significant percent reduction over Adapalene Gel, 0.1% (p=0.02). However, Adapalene 0.1% failed to demonstrate superiority over vehicle (p=0.15). In the analysis of the non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.06).

In the GEE analyses of the ITT population (Table 10, LOCF-including 45 subjects) at multiple time points (Week 8 and Week 12), Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% in IGA success rates (p=0.028). However, Adapalene 0.1% failed to demonstrate superiority over vehicle (p=0.42). For total lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene Gel, 0.1% (p=0.33). For inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significant difference in percent reduction over Adapalene Gel, 0.1% (p=0.164). For non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction in non-inflammatory lesion counts over Adapalene Gel, 0.1% (p=0.56). In the analyses of the rank data, Adapalene 0.3% failed to show superiority over Adapalene 0.1% in all three lesion counts.

Following the Agency's request on October 13, 2004, the sponsor carried out two additional sensitivity analyses. In the sensitivity analyses-I (Table 12), the missing values were imputed by using completer's mean percent change and success rate at week 8 and week 12. In the GEE analyses of IGA success rates at multiple time points, Adapalene Gel, 0.3% was superior to Adapalene Gel, 0.1% (p=0.017). However, Adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.258). For total lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene Gel, 0.1% (p=0.105). For inflammatory lesion counts, Adapalene Gel, 0.3% demonstrated a significant difference in percent reduction over Adapalene Gel, 0.1% (p=0.03). For non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.344). In the analyses of the Rank data, Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% in all three lesion counts.

In the sensitivity analysis-II (Table 13), the missing values were imputed by using completer's mean percent change and success rate with similar baseline counts and IGA score at week 8 and week 12. In the GEE analyses of IGA success rates, Adapalene Gel, 0.3% was significantly superior to Adapalene Gel, 0.1% (p=0.021). However, Adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.229). For total lesion counts, Adapalene Gel, 0.3% failed to demonstrate a significantly greater percent reduction over Adapalene Gel, 0.1% (p=0.11). For inflammatory lesion counts, Adapalene Gel, 0.3% demonstrated a significant difference in percent reduction over Adapalene Gel, 0.1% (p=0.03). For non-inflammatory lesion counts, Adapalene Gel, 0.3% failed to demonstrate a statistically significant percent reduction over Adapalene Gel, 0.1% (p=0.33). In the analyses using the Rank data, Adapalene Gel, 0.3% demonstrated superiority over Adapalene Gel, 0.1% in all three lesion counts. However, for Inflammatory lesion counts, Adapalene 0.1% failed to demonstrate superiority to Vehicle (p=0.05).

There were few protocol violations/compliance issues and post-hoc analyses of the observed data were performed (by the sponsor based on Agency's request) for the subjects with baseline inflammatory lesion counts between 20 and 50, and non-inflammatory lesion counts between 20 and 100, and subjects whose Week 8 efficacy

evaluation between days 49 and 63 and week 12 efficacy evaluation between days 77 and 91 days. Based on the GEE analyses of the multiple time points (weeks 8 and 12), Adapalene 0.3% failed to demonstrate superiority over Adapalene 0.1% in percent change from baseline for Total and non-inflammatory counts. IGA success rate and the percent change in inflammatory lesion counts achieved only border-line significance. The analyses of the ITT using LOCF and the rank data (LOCF), failed to provide evidence of superiority of Adapalene 0.3% over Adapalene 0.1% in all three lesion counts (Table 11).

In the special/sub group populations, there were no significant differences observed in success rates between Adapalene 0.3% and Adapalene 0.1% for both male and female groups. The success rates were slightly higher in Caucasians versus non-Caucasians across all three treatment groups. It should be noted that there were 72% Caucasians overall in the study compared to other ethnic groups. Comparing the age groups, success rates in the Adapalene Gel, 0.3% and vehicle gel groups were lower numerically in the 12-17 year-old age group compared with the 18-64 year-old age group. There was no significant difference between Adapalene Gel, 0.3% and Adapalene Gel, 0.1% at week 8 and 12 in the 12-17 age group.

As regards to the safety issues, based on sponsor's study report, there were reports of erythema worst than at baseline was present in 24.5% and 26.8% of subjects in the Adapalene Gel, 0.3% and 0.1% groups, respectively, at Week 1, and in 12.3% and 13.2%, respectively, at the final visit. Although majority of AEs were mild or moderate in severity, dermatological AEs were more frequently reported in the Adapalene Gel, 0.3% and 0.1% groups (26.7% and 16.1% of subjects, respectively) than in the vehicle group (9.0%). The majority of dermatological AEs were considered related to study drug treatment. Four subjects (all in the Adapalene Gel, 0.3% group) had non-dermatological AEs that were considered related to study treatment; these events were facial edema, pain, keratoconjunctivitis, and eye pain.

5.2 Conclusions and Recommendations

In this study, the primary analysis was based on the correlated repeated measurements at week 8 and week 12, although analyses based on single time points were reviewed and assessed. The primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% and the corresponding vehicle in subjects with acne vulgaris. As per the protocol, Generalized Estimating Equation (GEE) methodology was used as the primary analysis and all statistical tests were two-sided and each at the 0.050 significance level.

The primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1% and the corresponding vehicle in subjects with acne vulgaris at multiple time points (week 8 and week 12). In the Analysis of the ITT population for week 8 and week 12, with the last observation carried forward (LOCF) for missing values, Adapalene 0.3% demonstrated superiority over Adapalene 0.1% in IGA success rates. In percent change from baseline, Adapalene 0.3% failed to demonstrate superiority over Adapalene 0.1% for all three lesion counts (Total,

Inflammatory and Non-inflammatory). However, these analyses results were sensitive to an outlier (subject #1696) and consequently, as specified in the protocol, analyses results based on the rank data were also considered in assessing the efficacy, in addition to other sensitivity analyses. Results of the rank analyses of the ITT with LOCF, failed to provide significant difference of Adapalene 0.3% over Adapalene 0.1%. In the sensitivity analyses using the completer's mean percent change and success rate (for imputation of the missing values), Adapalene 0.3% demonstrated superiority over Adapalene 0.1% based on the rank data. There was no major safety issues reported.

Although based on the protocol, the primary objective of this study was to provide evidence of the superiority of Adapalene Gel, 0.3% over Adapalene Gel, 0.1%, it was in the interest of the reviewer to see that in the same trial, Adapalene 0.1% also demonstrated superiority over the vehicle. This would be an internal control to evaluate the strength of evidence of efficacy of Adapalene 0.3% over Adapalene 0.1%.

6. APPENDIX

Outlier Assessment:

Table 22: The outlier (subject #1696) and few other subjects enrolled by the same investigator (#2179) for comparison

Patno	Baseline			Week 8			Week 12		
	Inf	Non-Inf	Total	Inf*	Non-inf*	Total*	Inf*	Non-inf*	Total*
1003	21	59	80	28(33%)	42(-29%)	70(-13%)	12(-43%)	12(-80%)	24(-70%)
1004	40	74	114	43(8%)	23(-69%)	67(-41%)	17(-57%)	38(-49%)	55(-52%)
1005	23	23	46	23(0%)	39(70%)	63(37%)	5(-78%)	15(-35%)	20(-57%)
1696	20	20	40	29(45%)	65(325%)	94(135%)	37(85%)	118(490%)	155(288%)
1697	42	99	141	13(-69%)	72(-27%)	85(-40%)	24(-43%)	62(-37%)	87(-38%)
1698	20	31	51	10(-50%)	29(-6%)	39(-24%)	22(10%)	48(55%)	70(37%)

Statistical Reviewer's Comments:

Based on evaluating few subjects enrolled by the investigator (#2179) who enrolled subject #1696 (outlier)), there was nothing unusual noticed in his assessment which would classify it as an outlier. Subject #1696 was evaluated like any other subject in the data with the exception that the baseline non-inflammatory counts were low, inflating the percent reduction from baseline.

Note: of these results, it can be inferred that small baseline values would inflate the percent reduction from baseline creating an increased skewness in the distribution and the statistical tests were basically capturing the difference in the tail distribution between the treatment groups showing a significant result. The absolute change from baseline counts will be a more reliable endpoint compared to percent change from baseline.

Table 22: Summary of Number of Subjects (sponsor's Analyses)

opulation	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Gel Vehicle	Total
ITT population	258	261	134	653
Baseline inflammatory lesion: 20-50	250	251	133	634
Baseline non-inflammatory lesion: 20-100	251	254	133	638
Baseline inflammatory lesion: 20-50 **AND** Non-inflammatory lesion: 20-100	246	246	132	624
Baseline inflammatory lesion: 20-50 **AND** Non-inflammatory lesion: 20-100 **AND** Week 8 (Day 49-63) data available	208*	220	110	538*
Baseline inflammatory lesion: 20-50 **AND** Non-inflammatory lesion: 20-100 **AND** Week 12 (Day 77-91) data available	204	209	107	520
Baseline inflammatory lesion: 20-50 **AND** Non-inflammatory lesion: 20-100 **AND** Both Week 8 (Day 49-63) **AND** Week 12 (Day 77-91) data available	194*	201	96	491*

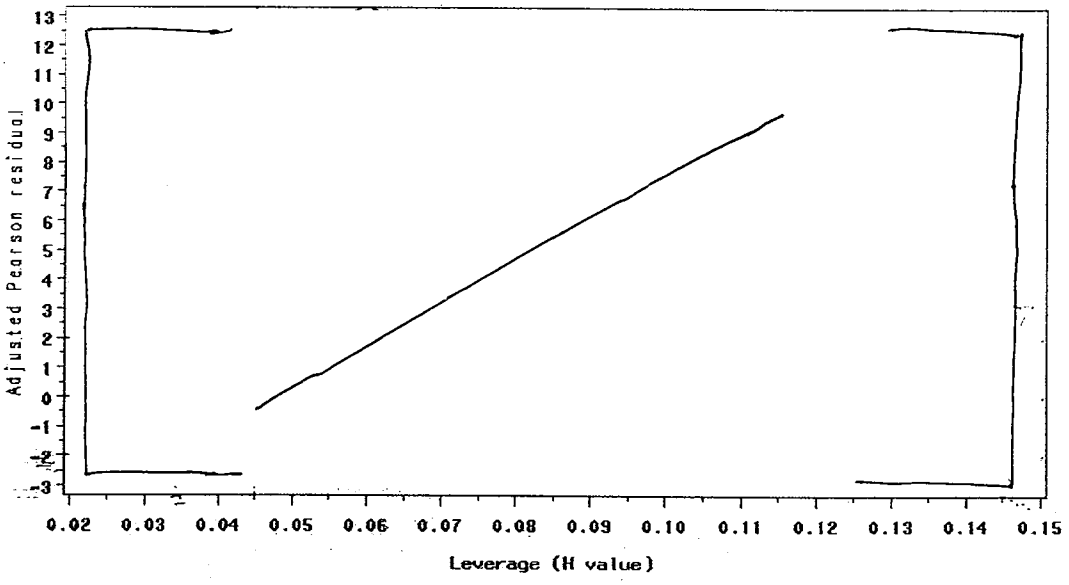
* One subject had lesion counts evaluated at Week 8 but did not have IGA data available.

Table 23: Summary of Success Rate and Median Percent Changes in Lesion Counts (sponsor's table)

	Adapalene Gel, 0.3%	Adapalene Gel, 0.1%	Gel Vehicle
Week 8 (Population C)*	**N=208**	**N=220**	**N=110**
Success Rate	14.5%	7.3%	10.9%
Median % Lesion Changes			
Total	-47.8	-43.8	-33.7
Inflammatory	-51.9	-48.3	-53.5
Non-Inflammatory	-43.5	-42.9	-26.9
Week 12 (Population D)**	**N=204**	**N=209**	**N=107**
Success Rate	21.6%	15.8%	9.3%
Median % Lesion Changes			
Total	-54.1	-48.1	-37.5
Inflammatory	-61.5	-56.8	-42.9
Non-Inflammatory	-50.0	-44.0	-28.1

* Population C: Week 8 efficacy between days 49-63, 20<=inf<=50, 20<=noninf<=100
Population D: Week 12 efficacy between days 77-91, 20<=inf<=50, 20<=noninf<=100

Non-inflammatory Lesions: Week 8 and Week 12

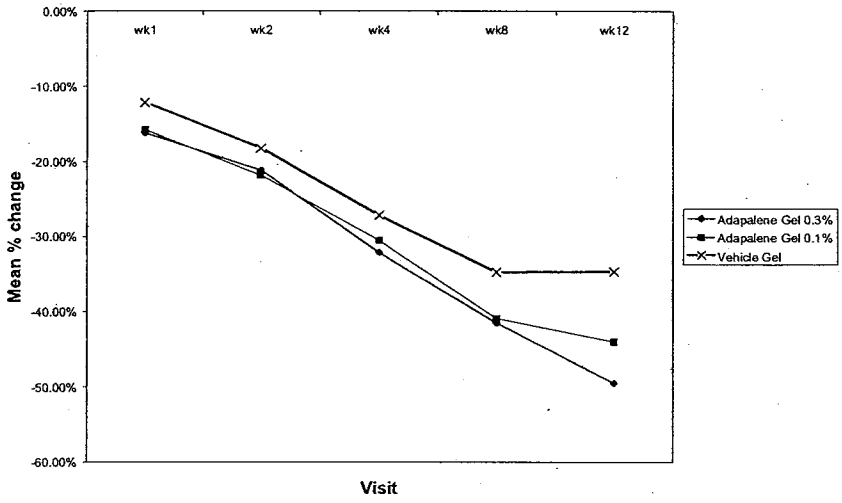


Statistical Reviewer's Comments:

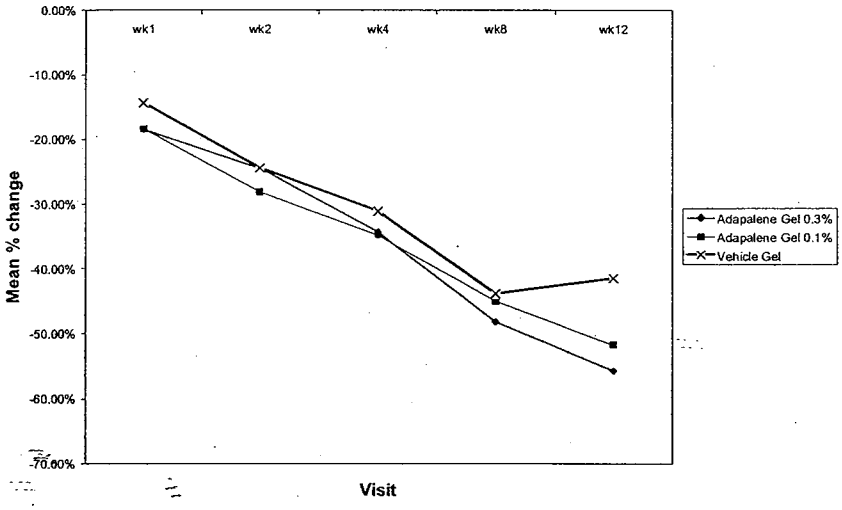
Based on evaluating various analyses and examining the leverage (H value), the observation #1696 was not appeared as a very influential outlier based on the GEE primary analysis model. The baseline non-inflammatory count was very low for this subject (20) which inflated value of the percent reduction from baseline. It should be

noted that adjusted pearson residual was moderately higher for week 8 and week 12 based on the leverage suggesting that this observation did impact the model parameters.

ITT: Mean % Change in Total Lesion Count



ITT: Mean % Change in Inflammatory Lesion Count



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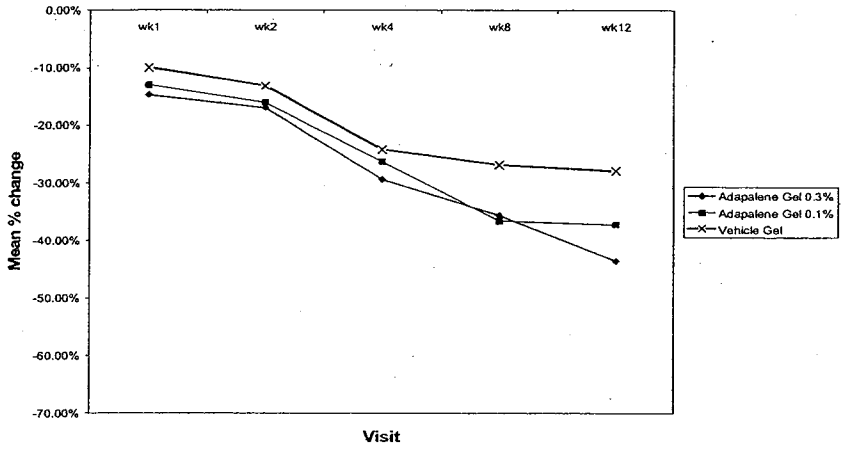
ITT: Mean % Change in Non-Inflammatory Lesion Count



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Statistical Review of NDA 21753

Mohamed Alosh
1/14/05 12:09:14 PM
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Concur with review

Biostatistical Team Leader Secondary Review
NDA 21-753 Differin (adapalene) Gel 0.3%

(Sponsor's submission stamp date: December 18, 2006)

February 5, 2007

As agreed to with the Division, the sponsor conducted one clinical trial to provide evidence of the superiority of adapalene gel 0.3% over adapalene gel 0.1% in acne treatment, which is currently approved for this indication. The protocol-specified primary analysis is based on using the Generalized Estimating Equation (GEE) methodology applied to repeated measurements for Week 8 and Week 12 data. Further, the protocol specified that if data did not meet the normality assumption, an analysis based on ranks would be used.

The analyses as summarized in the biostatistical review (carried out by Dr. Valappil) showed that success rates for the 0.3% were higher for the Investigator Global Assessment (IGA) and for percent change of inflammatory, non-inflammatory and total lesions than those for the 0.1% concentration, however, comparative results did not establish significant differences for some of the co-primary endpoints. The failure to establish superiority of the 0.3% over the 0.1% can be attributed, to a large extent, to the method of handling dropouts and the impact of one extreme outlier (subject #1696) as summarized in Dr. Valappil's review. Based on the efficacy findings, the Agency issued a not approval (NA) letter on February 1, 2005. Following the NA letter the sponsor held a teleconference with the Agency on April 13, 2005 to discuss deficiencies in the letter and a meeting with Agency on October 12, 2005. The goals of the meeting, as stated in the meeting minutes were: "(1) to provide adequate evidence that the higher concentration of adapalene gel offers benefits over the currently available concentration of adapalene gel when used in the treatment of acne vulgaris, and (2) to propose a risk management program (labeling) to address the increased potential for teratogenicity given the systemic levels of adapalene seen in the submitted pharmacokinetics study."

As the GEE methodology assumes missingness is not related to outcome, or what usually is denoted as missing at random (MAR), it deals with observed cases. Results of the repeated measures analysis (GEE) for Week 8 and Week 12 are presented in Table 9 of Dr. Valappil's statistical review. The results of this analysis show that the 0.3 % is superior to the 0.1% for the co-primary endpoint of success on the Investigator Global Assessment (IGA). However, analysis results of change and percent change of inflammatory, non-inflammatory and total lesions, although marginally in favor of the 0.3% do not reach statistical significance. Analysis based on ranks results in the following p-values (0.02, 0.02 and 0.06) for the comparison of inflammatory, non-inflammatory and total lesions. An analysis based on the ITT population with last-observation-carried-forward shows that none of the comparisons for lesion counts (inflammatory, non-inflammatory and total lesions) reach statistical significance for the 0.3% vs. the 0.1% (whether one analyzes change, percent change or ranks). These results are provided in Table 10 of the biostatistical review. To address the impact of handling dropouts and to have efficacy results based on the total study population, the Agency requested the sponsor submit analysis results for two sensitivity analyses with underlying assumptions that might be

considered close to those of the GEE methodology. In the first analysis missing data were to be imputed using the completers' mean percent change and in the second analysis missing data were to be imputed using the completers mean percent change and success rate for subjects with similar baseline counts and IGA score at Week 8 and Week 12. The results of these analyses were reported in the biostatistical review in Tables 12 and 13, respectively. These analyses resulted in smaller p-values than the analysis based on the observed cases addressed in the GEE original results. This might be attributed to the increase in the sample size with the imputation of data for missing observations. Under the first analysis the reported p-values are significant for analysis based on ranks and for percent change in inflammatory lesions. However, analyses of percent changes for non-inflammatory and total lesions are not significant, although trending in favor of the 0.3% concentration.

The meeting minutes of the October 12, 2005 meeting stated that "the Agency agreed that based on GEE analysis statistical superiority was demonstrated. However, the clinical benefit of 0.3% adapalene gel is small compared to 0.1%". Also the meeting minutes stated that: "While the Agency's recommendations regarding what is needed for approval are documented in the NA letter and in minutes of our last meeting, the sponsor's proposal may be submitted to the Agency for formal review as a complete response to the NA letter". The sponsor's current submission represents their response to the NA letter.

While repeated measurements data for Week 8 and Week 12 are used in the pre-specified statistical analysis to reduce the impact of outliers and to base analysis on two efficacy assessments for each subject, however, we recommend efficacy results for Week 12 only to be presented in labeling for consistency with labeling of other drugs for acne.

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cc:
Archival NDA 21753
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HFD-540/Ms. Lutwak
HFD-700/Dr. O'Neill
HFD- / Dr. Wilson
HFD-700 /Ms. Patrician
HFD-/ Dr. Alosh

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