

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202833Orig1s000**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA:** 202833

**Drug Name:** Pep005 (Ingenol Mebutate) gel, 0.015%

**Indication(s):** Treatment of actinic keratosis on the face and scalp

**Applicant:** Leo Pharmaceuticals

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**Review Priority:** Standard

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

The sponsor, Leo Pharmaceuticals, is seeking approval for PEP005 gel, at the concentration of 0.015% and 0.05%, for the topical treatment of actinic keratosis (AK) on face and scalp, and on trunk and extremities, respectively. A total of four pivotal clinical studies (16 and 25 for head area; 14 and 28 for non-head area) have been conducted in support of this NDA filing. This NDA review will focus on the indication for AK on face and scalp. A separate statistical review for the indication of AK lesions on trunk and extremities (Study 14 and Study 28) is carried out by Carin Kim, Ph.D.

The Pep005 gel 0.015% applied once daily to face or scalp is statistically superior to vehicle gel in the treatment of AK lesions in two Phase 3 pivotal studies. Both studies enrolled subjects with 4 to 8 visible and discrete AK lesions within a contiguous 25 cm<sup>2</sup> treatment area on either face or scalp. Enrolled subjects were randomized in a 1:1 ratio to either Pep005 gel 0.015% or vehicle gel. The primary endpoint is the complete clearance rate of AK lesions in the treatment area 8 weeks post-treatment. The efficacy data were analyzed by Cochran-Mantel-Haenszel (CMH) test controlling for study sites. The efficacy of Pep005 gel 0.015% was demonstrated to be statistically superior to vehicle gel in both studies based on the intent to treat (ITT) population at the significance level of 0.05. Efficacy results for each study are presented in Table 1.

**Table 1: Complete Clearance<sup>(1)</sup> Rates (ITT-Reviewer's Analysis)**

	<b>Pep005 Gel</b>	<b>Vehicle Gel</b>	<b><i>p</i>-value</b>
<b>Study 16</b>	50/135 (37%)	3/134 (2.2%)	<0.0001
<b>Study 25</b>	67/142 (47.2%)	7/136 (5.2%)	<0.0001

<sup>(1)</sup> Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57; P-value is calculated from CMH test stratified by sites

## 1.2 Brief Overview of Clinical Studies

The sponsor, Leo Pharmaceuticals, submitted 4 pivotal studies in support of this NDA filing for PEP005 gel, at the concentration of 0.015% and 0.05%, for two indications: AK lesions on face and scalp, or on trunk and extremities, respectively. For the indication of actinic keratosis on face and scalp, the sponsor conducted clinical studies including two pivotal Phase 3 efficacy and safety studies, Study 16 and Study 25, and one Phase 2 dose ranging study, Study 15. Study 16 and Study 25 had similar design and were conducted in the United States and Australia; Table 2 lists the studies included in the sponsor's clinical program.

**Table 2: Overview of Efficacy and Safety Studies**

Study	Development Objective	Study Population	Treatment Arms	Number of Subjects	Dates
16	Phase 3 Superiority Study	Subjects aged at least 18 years	Pep005 Gel 0.015% Vehicle Gel	135 134	6/2009—9/2009
25	Phase 3 Superiority Study	Subjects aged at least 18 years	Pep005 Gel 0.015% Vehicle Gel	142 136	6/2009—9/2009
15	Phase 2 Dose ranging	Subjects aged at least 18 years	0.005%, 0.01%, or 0.015% PEP005 Gel, Vehicle Gel	199 in Pep005 66 vehicle	6/2008—10/2008

### 1.3 Statistical Issues and Findings

The goal of this submission is to evaluate the efficacy and safety considerations of the proposed product, Pep005 0.015%, to meet the requirements for the NDA application. Two pivotal studies, Study 16 and Study 25, were submitted with the primary objective of establishing the efficacy for the topical treatment of AK lesions on face and scalp.

The randomization was stratified by study sites and anatomical location to have 80% of subjects treated on the face and 20% of subjects treated on the scalp. Actual study sites were combined to form “analysis sites” according to the proximity to ensure at least 8 subjects per arm per site. The primary endpoint is defined as the complete response rate of AK lesions 8 weeks post treatment. The AK lesion counts were collected only at baseline and Day 57 but not at the interim visits.

CMH test controlling for study sites was used to detect any difference in complete clearance rate of AK lesions between the two treatment groups. The reviewer analyzed the data based on both intent-to-treat (ITT) and per protocol (PP) populations. The ITT population included all randomized subjects and the PP population includes all subjects in the ITT population who completed the study in full compliance with the protocol. Missing final evaluation data were imputed using last observation carried forward (LOCF). As the drop out rate was very small (2% in Pep 0.015% gel, 5% in vehicle gel) for both studies, the method of imputation for handling missing data is not expected to impact the overall efficacy results. Study 16 and Study 25 both demonstrated that Pep 0.015% gel is statistically superior to vehicle gel in the topical treatment of AK lesions on face and scalp with a *p*-value less than 0.0001. Treatment effects are generally consistent across study sites

When complete clearance rates were analyzed by anatomical location, the subjects treated on face had much higher response rates in both Study 16 and Study 25. The number of subjects treated on scalp is small, however. When complete clearance rates were analyzed by gender, female subjects had higher response rate than male subjects. This result may not be conclusive due to the small number of female subjects.

## **2. INTRODUCTION**

### **2.1 Overview**

The sponsor, Leo Pharmaceuticals, is seeking approval for PEP005 gel, at the concentration of 0.015% and 0.05%, for two indications: actinic keratosis on face and scalp, or on the trunk and extremities, respectively. Originally, the sponsor was seeking indication of AK on non-head locations including trunk and extremities, and submitted the special protocol assessment (SPA). Following agreement on the SPA, the sponsor proposed two Phase 3 studies (Study 16 and Study 25), modeled upon the SPA for non-head locations, for the indication of AK lesion located in the head including face and scalp. The two studies had similar study design and both were conducted in the United States and Australia;

The following is a summary of the regulatory history regarding the proposed product under IND

(b) (4):

#### **PIND Meeting - October 28, 2003**

- The Agency noted that the sponsor should include elements of dose ranging including drug concentration, frequency and duration of application. Furthermore, in preparation of Phase 3 studies, the sponsor should evaluate clinical endpoint of percent of subjects with complete clearance of actinic keratosis lesions at a pre-specified time-point. Enrollment should be stratified by location and number of lesions. The minimum number of actinic keratosis lesions per subject enrolled should be pre-specified and agreed upon with the Agency.

#### **Guidance Meeting (End of Phase I) - March 7, 2005**

- The sponsor proposed a Phase 2a study in the treatment of AK lesions. The Agency commented that sequential dosing of cohorts is recommended rather than parallel and enrollment of subjects should be stratified according to the treatment area (e.g. trunk, extremities and head).

#### **Comments on a Single Special Protocol Assessment (Non-head Locations) - June 2, 2008**

##### **Agreement**

- The general design of the proposed study entitled “A multi-site, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of 0.05% PEP005 Topical Gel in subjects with AK lesions on non-head locations” is acceptable.
- The proposed dose regimen (once daily for two consecutive days) and the primary efficacy endpoint “Complete clearance rate of AK lesions defined as the proportion of subjects at the Day 57 visit with no clinically visible AK lesions in the selected treatment area” is acceptable

- The proposed secondary efficacy endpoint “Partial clearance rate of AK lesions defined as the proportion of subjects at the Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at Baseline, in the selected treatment area” is acceptable.
- The Division agrees on the primary analysis based on the ITT population with missing data imputed using LOCF.
- Under the sponsor's assumed response rates of 40% and 20% for PEP005 and vehicle, respectively, the sponsor's sample size calculation was verified using a two-sided type I error rate of 0.05.

#### **Non Agreement**

- The Division does not agree with the [REDACTED] (b) (4)

#### **Additional Comments**

- The sponsor only submitted a single protocol for Special Protocol Assessment without mention of conducting a second trial in subjects with AK lesions in non-head areas. Typically for an efficacy claim, we recommend results from two well-controlled trials as this provides independent substantiation of the efficacy results.
- For the assessment of multi-site trials the protocol should include a test for treatment by site interaction. In the case of significant interaction, typically conducted at  $\alpha = 0.10$  level, the protocol should specify a sensitivity analysis to assess the impact of extreme sites on efficacy. The goal of the sensitivity analysis is to ensure efficacy results are not driven by extreme site(s).
- Efficacy claims on the secondary endpoint (at least 75% reduction) cannot be made unless the primary endpoint reaches statistical significance.
- A sensitivity analysis to the method of data imputation should be proposed to ensure efficacy results are not driven by the method of data imputation.
- The analysis on the per-protocol population and the evaluable population (i.e. subjects with both baseline and end of treatment efficacy assessments) is not intended to be a sensitivity analysis to the method of data imputation, but rather as a supportive analysis to the primary analysis on the ITT population. It should be noted these two populations would be expected to yield quite similar efficacy results.

### **End of Phase 2 Meeting (Head Locations) - June 3, 2009**

- The sponsor proposed two Phase 3 studies (Study 16 and Study 25), modeled upon the SPA for non-head locations, for the indication of AK lesion located in the head including face and scalp.
- The Agency indicated that “the complete clearance of AK lesions would be a clinically meaningful endpoint however it is not clear if the secondary endpoint of 75% or greater reduction is clinically meaningful.”
- The protocol stated that if the Breslow-Day test is significant then an exploratory analysis would be conducted to assess the impact of site-by-treatment interactions on the study results. The Agency stated that such analysis should be pre-specified in the protocol. As a sensitivity analysis, the sponsor might consider deleting the most extreme site(s) and applying CMH stratified by the remaining sites to assess the robustness of efficacy conclusions.
- The proposed sensitivity analysis for handling missing data and out-of-window observations is to impute these observations as treatment failures. It should be noted that subjects who miss the Day 57 visit are essentially imputed as treatment failures using the primary method of data imputation, LOCF, as the Baseline and Day 57 visit are the only visits where efficacy is assessed. Thus, it is expected that the sensitivity analysis for the data imputation and the primary method for data imputation will yield similar results. The protocol should propose an alternative method for data imputation as a sensitivity analysis of the primary method of data imputation to ensure that efficacy results are not driven by the method of data imputation.
- The Agency noted that all subjects, regardless of AE status, should be followed for at least one year after the primary efficacy time point, to obtain recurrence and safety data.

### **Guidance Meeting - September 16, 2009**

- The sponsor proposed two extension studies, one for head location and one for non-head location, to address the Agency’s comment at the End of Phase 2 meeting that “all subjects, regardless of AE status, should be followed for at least one year after the primary efficacy time point, to obtain recurrence and safety data”.
- The Agency noted that the enrollment should include only subjects who had complete clearance of AK lesions as the information needed is the recurrence rate in subjects who had complete clearance. The follow up duration should be extended to 12 months.

### **Pre-NDA Meeting - December 15, 2010**

- The sponsor proposed to submit the pooled analysis datasets for the integrated analyses of efficacy. The Agency noted that the individual analysis dataset for each of the pivotal studies also need to be submitted. In addition, the Agency requested that the sponsor submit AK lesion counts occurred during the course of the trial in addition to the counts at baseline and at Day 57

as such data could be used to handle missing data and examine the subject response profile. However, the sponsor responded that they did not collect such data during the trial.

## 2.2 Data Sources

For the indication of AK lesion on face and scalp, the sponsor provided the electronic datasets for the two Phase 3 efficacy and safety studies (Study 16 and Study 25) evaluated in this review:

Electronic submission for Study 16 and 25: <\\CDSESUB1\EVSPROD\NDA202833\0000>

- Datasets

Study 16: <\\Cdsub1\evsprod\NDA202833\0000\m5\datasets\pep005-016\analysis\datasets>

Study 25: <\\Cdsub1\evsprod\NDA202833\0000\m5\datasets\pep005-025\analysis\datasets>

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

For the indication of actinic keratosis on face and scalp, the sponsor conducted two Phase 3 studies, Study 16 and Study 25, in support of the efficacy of safety findings of Pep005 at the concentration of 0.015%. The two studies have similar study design that is summarized below.

#### 3.1.1 Study design

Both studies were designed as multi-site, double-blind, randomized, vehicle controlled parallel group studies. Each of the study was conducted in 21 sites including 19 sites in the US and 2 sites in Australia. The sites selected to conduct the two studies were different. Subjects enrolled were male or females at least 18 years old with 4 to 8 clinically typical, visible and discrete AK lesions within a contiguous 25 cm<sup>2</sup> treatment area on the head. Enrolled subjects were randomized in a ratio of 1:1 to Pep005 gel 0.015% or vehicle gel. The randomization was stratified by site and by the location of the treatment area to enroll approximately 20% of subjects treated on the scalp and approximately 80% of subjects treated on the face. A total of 269 subjects were enrolled in Study 16: 135 to Pep005 gel 0.015% and 134 to vehicle gel, with a total of 278 subjects enrolled in Study 25: 142 to Pep005 gel 0.015% and 136 to vehicle gel. Subjects were instructed to apply the study medication once daily for three consecutive days at home with follow up visits at Days 4, 8, 15, 29 and 57. Clinical AK lesion assessments were collected at Day 1 and Day 57.

The primary endpoint was defined in the protocol as the complete clearance rate of AK lesions at the Day 57 visit. Subjects were considered complete clearance if there were no clinically visible AK lesions in the selected treatment area. The secondary endpoint was defined as partial clearance rate of AK lesions at the Day 57 visit. Subjects were considered partial clearance if they achieved a reduction of at least 75% in the number of clinically visible AK lesions.

Additional efficacy endpoint was defined as the percent change from baseline to Day 57 in AK lesion counts. No multiplicity adjustment was planned as the secondary endpoint would be tested only if the primary endpoint was significant.

The protocols stated the primary efficacy analysis would be based on the intent-to-treat (ITT) population including all randomized subjects. Supportive efficacy analyses would be based on the per-protocol (PP) population including all subjects in the ITT population who completed the study in full compliance with the protocol. All Missing complete or partial clearance assessments would be imputed using last observation carried forward (LOCF). Sensitivity analysis was performed where missing or out-of-window observations were considered not cleared. As the clinical assessments of complete or partial clearance is only carried out at baseline and Day 57. Using LOCF for imputation is the same as imputing missing as failure.

In addition, the protocols stated that in order to obtain at least 8 subjects per site per treatment group, study sites yielding fewer than 16 subjects were combined together in order of geographical proximity. The primary analysis was based on the pooled analysis sites rather than the investigational sites.

All hypothesis testing were conducted two-sided with a significance level of 0.05. Complete and partial clearance rate would be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by site. Breslow-Day test with a significance level of 0.1 would be used to investigate the heterogeneity of the odds ratios across analysis sites.

### 3.1.2 Disposition of Subjects

Study 16 enrolled 269 subjects with 135 subjects randomized to Pep005 gel 0.015% and 134 randomized to vehicle gel. Study 25 enrolled 278 subjects with 142 subjects randomized to Pep005 gel 0.015% and 136 subjects randomized to vehicle gel. For Study 16, the dropout rate is approximately 2% in Pep005 arm compared to 5% in the vehicle arm. For Study 25, no subject dropped out from Pep005 arm and 1 subject dropped out from vehicle arm. The Reasons for study discontinuations are presented in Table 3.

**Table 3: Reasons for Discontinuation (ITT-Reviewer’s Analysis)**

	Study 016		Study 025	
	PEP005	Vehicle	PEP005	Vehicle
<b>ITT <sup>(1)</sup> Subjects</b>	135	134	142	136
<b>Completed</b>	132 (97.8%)	127 (94.8%)	142 (100.0 %)	135 (99.3%)
<b>Reason for Discontinuation</b>	3 (2.2%)	7 (5.2%)	0 (0.0 %)	1 (0.7 %)
<i>Adverse Event</i>	1	1	0	0
<i>Protocol violation</i>	0	1	0	0
<i>Withdrew consent</i>	2	5	0	1

(1) ITT defined as all randomized subjects regardless of receiving any dose of study medication.

### 3.1.3 Baseline and Demographic Data

All subjects enrolled were White. Approximately 88% of subjects enrolled in Study 16 and 82% of subjects enrolled in Study 25 were males. The average age was approximately 64 years for both studies. The baseline demographic data for the two studies are presented in Table 4.

**Table 4: Baseline Demographic Data for Study 16 (ITT-Reviewer’s Analysis)**

	Study 016		Study 025	
	PEP005	Vehicle	PEP005	Vehicle
<b>ITT <sup>(1)</sup> Subjects</b>	135	134	142	136
<b>Age</b>				
<b>≤65</b>	71 (53%)	77 (58%)	73 (51%)	63 (46%)
<b>&gt;65</b>	64 (47%)	57 (43%)	69 (49%)	73 (54%)
<b>Sex</b>				
<b>Female</b>	19 (14%)	14 (10%)	25 (18%)	24 (18%)
<b>Male</b>	116 (86%)	120 (90%)	117 (82%)	112 (82%)
<b>Race</b>				
<b>White</b>	135 (100%)	134 (100%)	142 (100%)	136 (100%)

### 3.1.4 Primary Efficacy Analysis

#### 3.1.4.1 Primary Endpoint Results Based on ITT and PP Populations

The protocol defined the primary endpoint as the complete clearance rate of AK lesions at the Day 57 visit. Subjects were considered success (i.e. complete clearance) if there were no clinically visible AK lesions in the selected treatment area.

The protocol defined the intent-to-treat (ITT) population as all randomized subjects and defined the per protocol (PP) population as all subjects in the ITT population who completed the study in full compliance with the protocol. The primary endpoints were analyzed based on the ITT population with supportive analysis conducted based on PP population. Missing Day 57 efficacy evaluation were imputed using last observation carried forward (LOCF). As the clinical assessments of complete clearance was only carried out at baseline and Day 57, the LOCF for imputation is the same as imputing missing as failure. The Cochran-Mantel-Haenszel (CMH) test stratified by site was specified by the protocol for testing the difference of the success (complete clearance) rate between Pep005 gel and vehicle gel. The efficacy results obtained by the reviewer are the same as that provided by the sponsor and are presented in Table 5 and Table 6, for Study 16 and Study 25, respectively.

**Table 5: Complete Clearance Rate for Study 16 (Reviewer’s Analysis)**

	Study 016		
	PEP005	Vehicle	<i>p</i> -value <sup>(1)</sup>
<b>Complete Clearance</b>			
<b>ITT</b>	50/137 (37%)	3/134 (2.2%)	<0.0001
<b>PP</b>	44/121 (36.4%)	3/125 (2.4%)	<0.0001

(1) *p*-values based on ITT and PP populations are calculated from a CMH test stratified by sites.

**Table 6: Complete Clearance Rate for Study 25 (Reviewer’s Analysis)**

	Study 025		
	PEP005	Vehicle	<i>p</i> -value <sup>(1)</sup>
<b>Complete Clearance</b>			
<b>ITT</b>	67/142 (47.2%)	7/136 (5.2%)	<0.0001
<b>PP</b>	64/136 (47.1%)	7/130 (5.4%)	<0.0001

(1) *p*-values based on ITT and PP populations are calculated from a CMH test stratified by sites.

The efficacy results showed that Pep005 Gel 0.015% is superior to the vehicle gel with *p*-values less than 0.0001 based on both ITT and PP population for both studies. As the drop out rate is small and the treatment effect is relatively large, the method of imputation for handling missing data is not expected to impact the overall efficacy result.

#### 3.1.4.2 Efficacy Results by Site

Both Study 16 and Study 25 were conducted in 21 sites including 19 sites in the US and 2 sites in Australia. The two studies were conducted in different sites. The site-by-site plots are presented in Figure 1 and Figure 2 in Appendix A.

Treatment effects across sites are generally consistent. The result from Breslow-Day test shows that the treatment by site interaction is not significant at the level of 0.1. Analysis site 12, combined from investigational site 12 and 19, of Study 25 showed that Pep005 had a lower success rate than the vehicle gel. However, this might be by chance alone.

### 3.1.5 Secondary Endpoints Analysis

The secondary endpoint was defined as partial clearance rate of AK lesions at the Day 57 visit. Subjects were considered partial clearance if they achieved a reduction of at least 75% in the number of clinically visible AK lesions. The secondary endpoint would be tested only if the primary endpoint is significant.

The protocol indicated that secondary endpoint would be based on ITT population and analyzed the same way as the primary endpoints. Missing efficacy evaluation at Day 57 would be imputed using LOCF, and the Cochran-Mantel-Haenszel (CMH) test stratified by site would be used for

testing the difference of partial clearance rate between Pep005 gel and vehicle gel. The efficacy results of the secondary endpoints are presented in Table 7 and Table 8, for Study 16 and Study 25, respectively.

**Table 7: Partial Clearance Rate for Study 16 (Reviewer’s Analysis)**

	Study 016		
	PEP005 (N=135)	Vehicle (N=134)	<i>p</i> -value <sup>(1)</sup>
<b>Partial Clearance</b>	81/135 (60%)	9/134 (6.7%)	<0.0001

(1) *p*-value is calculated from a CMH test stratified by sites.

**Table 8: Partial Clearance Rate for Study 25 (Reviewer’s Analysis)**

	Study 025		
	PEP005 (N=142)	Vehicle (N=136)	<i>p</i> -value <sup>(1)</sup>
<b>Partial Clearance</b>	96/142 (67.6%)	11/136 (8.1%)	<0.0001

(1) *p*-value is calculated from a CMH test stratified by sites.

For the secondary endpoints of partial clearance, the results showed that Pep005 Gel 0.015% is superior to the vehicle gel with *p*-values less than 0.0001 based on ITT population for both studies.

## 3.2 Evaluation of Safety

### 3.2.1 Local Skin Reactions

At each visit, investigators evaluated each of the following six local skin reactions (LSR): erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration on 5 point scales of 0 to 4. A grade of 0 represented no reaction present in the treated area, and a grade of 4 indicated a marked and severe skin reaction. The summary of the maximal local skin reactions post baseline for Study 16 and Study 25 is presented in Table 9.

**Table 9: Summary of the Maximal Local Skin Reactions Post Baseline for Study 16 and Study25 Combined (Sponsor’s Analysis)**

Local Skin Responses	Grade	Pep005 Gel 0.015% N=274	Vehicle Gel N=271
<b>Erythema</b>	0	1 (<1%)	105 (39%)
	1	25 (9%)	129 (47%)
	2	56 (20%)	33 (12%)
	3	125 (46%)	6 (2%)
	4	66 (24%)	0 (0%)
<b>Flaking/Scaling</b>	0	7 (3%)	89 (21%)
	1	52 (19%)	142
	2	91 (33%)	36
	3	98 (36%)	4
	4	25 (9)	0 (0%)
<b>Crusting</b>	0	44 (16%)	219
	1	85 (31%)	47
	2	64 (23%)	5
	3	64 (23%)	0 (0%)
	4	16 (6%)	0 (0%)
<b>Swelling</b>	0	56 (20%)	257 (95%)
	1	88 (32%)	12 (4%)
	2	67 (25%)	2 (<1%)
	3	48 (18%)	0 (0%)
	4	14 (5%)	0 (0%)
<b>Vesiculation/Pustulation</b>	0	119 (43%)	270 (99%)
	1	36 (13%)	1 (<1%)
	2	53 (19%)	0 (0%)
	3	50 (18%)	0 (0%)
	4	15 (6%)	0 (0%)
<b>Erosion/Ulceration</b>	0	186 (68%)	267 (98%)
	1	55 (20%)	4 (2%)
	2	26 (10%)	0 (0%)
	3	5 (2%)	0 (0%)
	4	1 (<1%)	0 (0%)

### 3.2.2 Adverse Events

The adverse events were evaluated based on safety population defined as all randomized subjects who received at least one dose of study medication and who had at least one post baseline safety evaluation. A total of 93 (35%) subjects in Study 16 and 69 (%) subjects in Study 25 reported at least one adverse event (AE). In Study 16, two subjects randomized to Pep005 Gel did not apply the study medication and hence were excluded from the safety population. One subject randomized to Pep005 actually received vehicle Gel. In Study 25, all randomized subjects were included in safety population. The proportion of subjects who experienced AE is higher in the Pep005 Gel than the vehicle Gel across the two studies. Table 10 presents the number of subjects with at least one AE per treatment arm for each study.

**Table 10: Number of Subjects with at Least One Adverse Event (Reviewer's Analysis)**

	<b>Pep005 Gel 0.015%</b>	<b>Vehicle Gel</b>	<b>Total</b>
<b>Study 16</b>	62/132 (47%)	31/135 (23%)	93/267 (35%)
<b>Study 25</b>	40/142 (28%)	29/136 (21%)	69/278 (25%)

The AE rates for events occurring at least 1% of subjects per treatment arm are presented in Table 11 and Table 12 for Study 16 and Study 25, respectively. The most common adverse events are application site pain and application site Pruritus.

**Table 11: Adverse Events Occurring in at Least 1% of Subjects per Treatment Arm in Study 16 (Reviewer's Analysis)**

<b>Adverse Events (Preferred Term)</b>	<b>Pep005 Gel 0.015% N=132</b>	<b>Vehicle Gel N=135</b>	<b>Total N=267</b>
<b>Application Site Pain</b>	25 (19%)	0 (0%)	25 (9%)
<b>Application Site Pruritus</b>	5 (4%)	2 (1%)	7 (3%)
<b>Headache</b>	4 (3%)	3 (2%)	7 (3%)
<b>Application Site Infection</b>	4 (3%)	0 (0%)	4 (1%)
<b>Periorbital Oedema</b>	2 (2%)	0 (0%)	2 (<1%)
<b>Arthralgia</b>	2 (2%)	0 (0%)	2 (<1%)
<b>Contusion</b>	1 (1<%)	4 (3%)	5 (2%)
<b>Liver Function Test Abnormal</b>	0 (0%)	2 (1%)	2 (<1%)

**Table 12: Adverse Events Occurring in at Least 1% of Subjects per Treatment Arm in Study 25 (Reviewer's Analysis)**

<b>Adverse Events (Preferred Term)</b>	<b>Pep005 Gel 0.015% N=142</b>	<b>Vehicle Gel N=136</b>	<b>Total N=278</b>
<b>Application Site Pain</b>	13 (9%)	1 (<1%)	14 (5%)
<b>Application Site Pruritus</b>	4 (3%)	0 (0%)	4 (1%)
<b>Eyelid Oedema</b>	2 (1%)	0 (0%)	2 (<1%)
<b>Scratch</b>	0 (0%)	2 (1%)	2 (<1%)
<b>Pain in Extremity</b>	0 (0%)	2 (1%)	2 (<1%)
<b>Electrocardiogram QT Prolonged</b>	0 (0%)	2 (1%)	2 (<1%)

## 4. FINDINGS IN SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

In both Study 16 and Study 25, the response rate for female subjects was higher than the response rate for male subjects. However, as the number of female subjects is small in each of the two trials, the results may not be conclusive. All subjects enrolled for both studies were classified as White and hence subgroup analyses by race are not feasible. Enrolled subjects were categorized into two age groups: less than 65 years or 65 years and older. The response rate for subjects less than 65 years is slightly higher than that of subjects 65 years and older. Treatment success rates by gender and age for Study 16 and Study 25 are presented in Table 13.

**Table 13 Complete Clearance (ITT, LOCF) by Gender, Race and Age**

	Study 016		Study 025	
	PEP005	Vehicle	PEP005	Vehicle
ITT <sup>(1)</sup> Subjects	135	134	142	136
Age				
≤65	27/71 (38%)	2/77 (3%)	38/73 (52%)	5/63 (8%)
>65	23/64 (36%)	1/57 (4%)	29/69 (42%)	2/73 (3%)
Sex				
Male	40/116 (34%)	2/120 (2%)	52/117 (44%)	7/112 (6%)
Female	10/19 (53%)	1/14 (7%)	15/25 (60%)	0/24 (0%)

(1) ITT defined as all randomized subjects regardless of receiving any dose of study medication

### 4.2 Other Special/Subgroup Populations

#### 4.2.1 Anatomic Location, Baseline Lesion Counts and Fitzpatrick Skin Type

Subjects were treated for lesions on face or scalp, but not both. The randomization was stratified by anatomic location to have 80% of subjects treated on face and 20% of subjects treated on scalp. The subjects treated on face had much higher response rates in both Study 16 and Study 25. The number of subjects treated on scalp is small, however. The complete clearance rates by baseline lesion counts are calculated for two categories: subjects having 4, 5 or 6 lesions, and 7 or 8 lesions. Both baseline lesion counts and Fitzpatrick skin type do not appear to have much impact on the complete clearance rates. The complete clearance rates by each subgroup for Study 16 and Study 25 are presented in Table 14.

**Table 14: Complete Clearance Rates by Anatomic Location, Baseline Lesion Counts and Fitzpatrick Skin Type for Study 16 and Study 25 (ITT-Reviewer’s Analysis)**

	Study 016		Study 025	
	PEP005	Vehicle	PEP005	Vehicle
<b>ITT <sup>(1)</sup> Subjects</b>	135	134	142	136
<b>Anatomic Location</b>				
<b>Face</b>	46/109 (42%)	3/109 (3%)	58/111 (52%)	6/111 (5%)
<b>Scalp</b>	4/26 (15%)	0/25 (0%)	9/31 (29%)	1/25 (4%)
<b>Baseline Lesion</b>				
<b>4, 5 or 6 Lesions</b>	26/82 (32%)	2/69 (3%)	49/88 (56%)	7/89 (8%)
<b>7 or 8 Lesions</b>	24/53 (45%)	1/65 (2%)	18/54 (33%)	0/47 (0%)
<b>Fitzpatrick Skin Type</b>				
<b>I</b>	10/24 (42%)	0/16 (0%)	17/27 (63%)	1/18 (6%)
<b>II</b>	16/58 (28%)	2/53 (4%)	32/65 (49%)	3/59 (5%)
<b>III</b>	19/44 (43%)	1/59 (2%)	15/40 (38%)	3/52 (6%)
<b>IV</b>	5/9 (56%)	0/6 (0%)	3/10 (30%)	0/7 (0%)

(1) ITT defined as all randomized subjects regardless of receiving any dose of study medication.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The sponsor has submitted efficacy and safety results for two Phase 3 studies to support an efficacy claim for the indication of AK lesions on face and scalp. Originally, the sponsor was seeking the indication of AK lesions on non-head locations and submitted the special protocol assessment (SPA). Following agreement on the SPA, the sponsor proposed two Phase 3 studies (Study 16 and Study 25), modeled upon the SPA for non-head locations, for the indication of AK lesions located in the head including face and scalp.

The primary endpoints is defined as the complete response rate of AK lesions 8 weeks post treatment. The CMH test controlling for study sites was used to detect any difference in complete response rate between the two treatment groups. The AK lesion counts were collected only at baseline and Day 57 but not at the interim visits. Missing data on final evaluation were imputed using last observation carried forward (LOCF). The method of imputing missing data did not have much impact on the overall efficacy results as the drop out rate was very small (2% in Pep 0.015% gel, 5% in vehicle gel). Study 16 and Study 25 both demonstrated that Pep 0.015% gel is statistically superior to vehicle gel in the topical treatment of AK lesions on face and scalp with a *p*-value less than 0.0001. Treatment effects are generally consistent across study sites.

When complete clearance rates are analyzed by anatomical location, the subjects treated on face had much higher response rates in both Study 16 and Study 25 although the number of subjects treated on scalp is small. When complete clearance rates are analyzed by gender, female subjects

had higher response rate than male subjects, however, the results may not be conclusive due to the small number of female subjects.

The subjects treated on face had much higher response rates than subjects treated on scalp in both Study 16 and Study 25. It should be noted that the number of subjects treated on scalp is small to make reasonable conclusion. Female subjects had higher response rate than male subjects. This result may not be conclusive due to the small number of female subjects.

## 5.2 Conclusions and Recommendations

In Summary, the efficacy findings from the two pivotal studies (Study 16 and Study 25) support the efficacy claim of the superiority of Pep005 gel 0.015% applied once daily for three consecutive days for the treatment of actinic keratosis (AK) lesions on face and scalp. All enrolled subjects were White with 4 to 8 visible and discrete AK lesions within a contiguous 25 cm<sup>2</sup> treatment area on either face or scalp. The primary efficacy endpoint is complete clearance rate in the treatment area 8 weeks post-treatment (Day 57). The primary efficacy results for Study 16 and Study 25 are presented in Table 15.

**Table 65: Complete Clearance<sup>(1)</sup> Rates (ITT-Reviewer's Analysis)**

	<b>Pep005 Gel</b>	<b>Vehicle Gel</b>	<b><i>p</i>-value</b>
<b>Study 16</b>	50/135 (37%)	3/134 (2.2%)	<0.0001
<b>Study 25</b>	67/142 (47.2%)	7/136 (5.2%)	<0.0001

<sup>(1)</sup> Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57; P-value is calculated from CMH test stratified by sites

The findings of Table 15 support that Pep005 gel 0.015% is statistically superior to vehicle gel.

# APPENDICES

## A. Site-by-Site Plot

Figure 1: Center by Center Results for Study 16 (ITT)

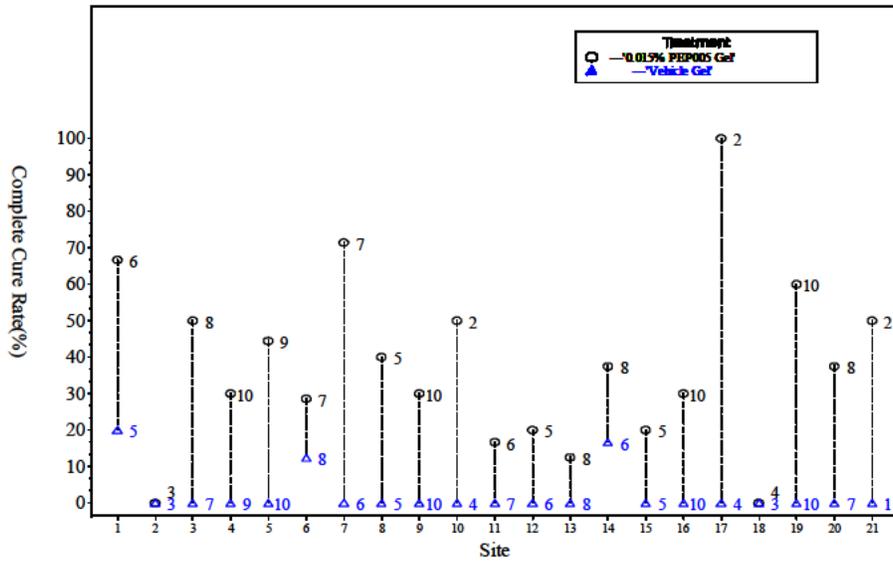
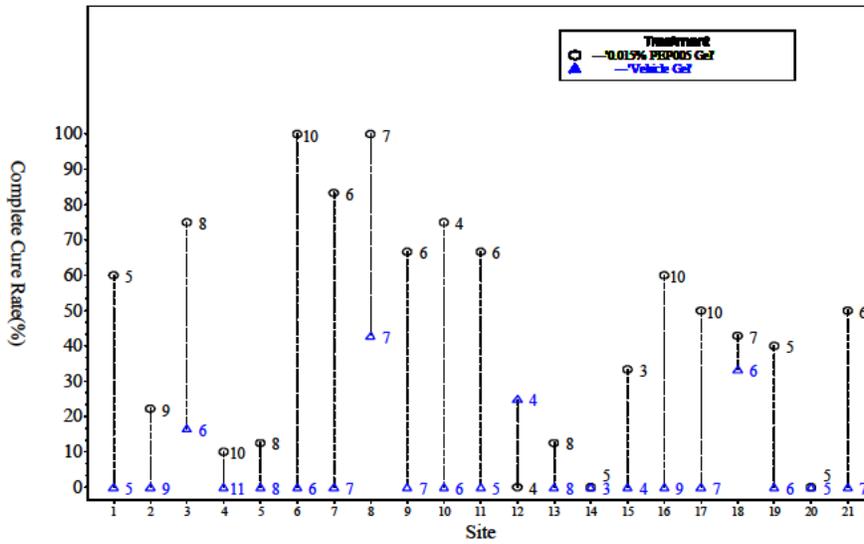


Figure 2: Center by Center Results for Study 25 (ITT)



## **SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Yuqing Tang, Ph.D.  
Date: November 15, 2011

Statistical Team Leader: Mohamed Alosch, Ph.D.

cc:

Archival NDA  
DDDP/Walker  
DDDP/Ku  
DDDP/Lindstrom  
DDDP/Phillips  
OBIO/Lavange  
OBIO/Patrician  
DBIII/Wilson  
DBIII/Alosch  
DBIII/Kim  
DBIII/Tang

November 15, 2011

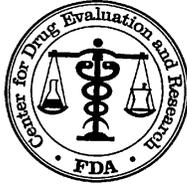
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YUQING TANG  
11/17/2011

MOHAMED A ALOSH  
11/18/2011

For biostatistics review of the clinical trials for the non-head actinic keratosis lesions please check review by Carin Kim, Ph.D., signed on 11/18/2011



U.S. 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

## CLINICAL STUDIES

**NDA/BLA Serial  
Number:**

NDA 202833 / SDN 001

**Drug Name:**

Picato (PEP005 gel, 0.05%)

**Indication(s):**

Nonhead AK lesions

**Applicant:**

Leo Pharmaceuticals

**Date(s):**

Stamp Date: 3/25/2011

PDUFA Date: 1/25/2012

**Review Priority:**

Standard

**Biometrics Division:**

DBIII

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**Project Manager:**

J. Paul Phillips, DDDP

**Keywords:**

Clinical studies, Superiority trials

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## 1. EXECUTIVE SUMMARY

The sponsor submitted results of four Phase 3 trials to support the efficacy claim for actinic keratoses (AK) on head locations, and on nonhead locations. In this review, only the Phase 3 trials for the nonhead AK lesions (PEP005-014 and PEP005-028) are reviewed, and the other two Phase 3 trials for the head AK lesions (PEP005-016 and PEP005-025) are reviewed by Yuqing Tang, Ph.D.

PEP005 topical gel, 0.05% was statistically superior to vehicle gel in two studies (PEP005-014 and PEP005-028) in the treatment of AK on nonhead locations. The primary efficacy endpoint was the complete clearance rate of AK lesions; defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the selected treatment area. It should be noted that most subjects had the nonhead treatment locations on the arm or back of hand (i.e., approximately 87% of the enrolled subjects were treated for the nonhead AK lesions on the arm or back of hand), with a small number of subjects with AK lesions on the chest, shoulder, back or leg.

Summary of efficacy results is given in the following table.

**Table 1. Complete Clearance<sup>(1)</sup> (ITT, LOCF) - Study 014 and Study 028**

	<b>PEP005</b>	<b>Vehicle</b>	<b>p-value</b>
<b>Study 014</b>	35/126 (27.8%)	6/129 (4.7%)	<0.001
<b>Study 028</b>	42/100 (42.0%)	5/103 (4.9%)	<0.001

(1) Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57; P-value is calculated from CMH test stratified by sites.

Source: Sponsor's Study Report Table 12 (Study 014), and Table 11 (Study 028).

## 2. INTRODUCTION

### 2.1 Overview

In the current development program, the sponsor is developing PEP005 gels, 0.015% and 0.05% for the treatment of actinic keratoses (AK) on the head and nonhead locations, respectively. In this review, only the Phase 3 trials for the nonhead AK lesions are reviewed, and the two Phase 3 trials for the head AK lesions are reviewed by Yuqing Tang, Ph.D.

PEP005, 0.05% is proposed to be used once daily for two consecutive days (Days 1 and 2) to a 25 cm<sup>2</sup> contiguous AK treatment area on nonhead locations (arm, back of hand, chest, back, leg or shoulder). The sponsor conducted two Phase 3 trials: PEP005-014 (from hereon referred to as Study 014) and PEP005-028 (from hereon referred to as Study 028) evaluating the safety and efficacy of PEP005 gel, 0.05% in the treatment of nonhead AK lesions.

Both studies included two arms: PEP005 gel and vehicle gel, and the objective of the trials was to demonstrate the superiority of PEP005 to vehicle.

There were several correspondences between the Agency and the sponsor during the IND 70114 phase: Pre-IND (10/28/2003), Guidance (3/7/2005), a Pre-Phase 2 Guidance (4/10/2006), Special Protocol Assessment (6/2/2008), Guidance (9/16/2009), and a Pre-NDA (12/15/2010).

For the Special Protocol Assessment (SPA), the pivotal Phase 3 trial (Study 014) was the subject of review and the SPA agreement letter was sent to the sponsor (6/2/2008). At that time, the Agency agreed to the proposed general design to conduct “a multi-center, randomized, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 gel in subjects with AK on non-head locations”, the proposed treatment area of 25 cm<sup>2</sup>, the dose regimen, the primary and the secondary endpoints, and the primary imputation method to use the last observation carried forward (LOCF). However, there were two Nonagreement items:

1. “We do not agree with the [REDACTED] (b) (4)
2. [REDACTED] (b) (4)

Per the Agency comments in the SPA letter, the sponsor revised their Phase 3 protocols and submitted the protocols for Agency comments (SDN69; stamp date: 7/28/2008). Statistical review on the amended Phase 3 protocols were completed and signed off in DARRTS on 10/29/2008, and the following statistical comments were conveyed to the sponsor in an Advice Letter on 5/13/2009.

- “A dynamic randomization scheme is now proposed that plans to seek balance within a site and on the anatomical region. The protocol does not list the levels or number of categories of the anatomical location nor has data been provided that shows efficacy varies by anatomical location to justify stratifying on this factor. In addition, it is unclear if such a randomization scheme will ensure balance as only 8 subjects per treatment arm per center are planned to be enrolled. As such, it is not clear if a dynamic randomization scheme is needed over a simpler randomization procedure which stratifies by site allocating subjects in blocks. You should consider a simpler randomization procedure or provide sufficient details and justification for the use of the more complex dynamic randomization scheme.”
- “Your proposed statistical methodology is not clear. The protocol states that CMH weighted by anatomical location will be used to calculate the complete clearance rate, yet also states logistic ANOVA will be used to test for treatment effect. Further, the weights for anatomical location are not provided and it is unclear how the weighting would be done. Should the randomization procedure be stratified by both study site and anatomical location, the use of a “logistic regression” model would be acceptable. However, if the randomization is stratified by only study site, we request that for superiority claims over vehicle tests for treatment effect use CMH stratified by study site.”

While the Agency commented that the sponsor use a simpler randomization method rather than a dynamic randomization method; however, because Study 014 was already ongoing at the time that they received the Agency comments, the sponsor could not revise the protocol regarding the randomization method. As such, for Study 014, the sponsor used a dynamic randomization method stratified by site and by anatomical location (see details regarding this randomization method in section 3.2), but for Study 028, the sponsor used a simple block randomization method stratified by site and by anatomical location.

For the two completed Phase 3 trials, eligible subjects were to be at least 18 years of age, with 4 to 8 clinically typical, visible, and discrete AK lesions within a contiguous 25 cm<sup>2</sup> treatment area on nonhead locations. Subjects applied the treatment once daily at home for two consecutive days, and had study visits on the following days: baseline, Days 3, 8, 15, 29 and 57. Study centers were located in the United States and in Australia. Features of the Phase 3 studies are presented in Table 2.

**Table 2. Nonhead AK Phase 3 studies conducted by the sponsor**

<b>Study</b>	<b>Treatment Arms</b>	<b>No. of Subjects</b>	<b>Enrollment Period</b>
<b>PEP005-014</b>	PEP005	126	9/5/2008-2/23/2009
	Vehicle	129	
<b>PEP005-028</b>	PEP005	100	7/22/2009-10/14/2009
	Vehicle	103	

Source: Reviewer's Table.

## **2.2 Data Sources**

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets in this review are archived at the following locations:

<\\cdsesub1\EVSPROD\NDA202833\0000\m5\datasets\>

## **3. STATISTICAL EVALUATION**

### **3.1 Data and Analysis Quality**

The sponsor submitted electronic analysis datasets for review. While the primary efficacy analyses could be conducted using the analysis datasets, the plots of the local skin reaction over time required some data extraction from an SDTM dataset (e.g. ss.xpt) because such information was not included in the analysis datasets.

## 3.2 Evaluation of Efficacy

### Study Design and Endpoints

The primary objective was to evaluate the efficacy and safety of 0.05% PEP005 topical gel compared to vehicle gel when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm<sup>2</sup> contiguous actinic keratoses (AK) treatment area on nonhead locations.

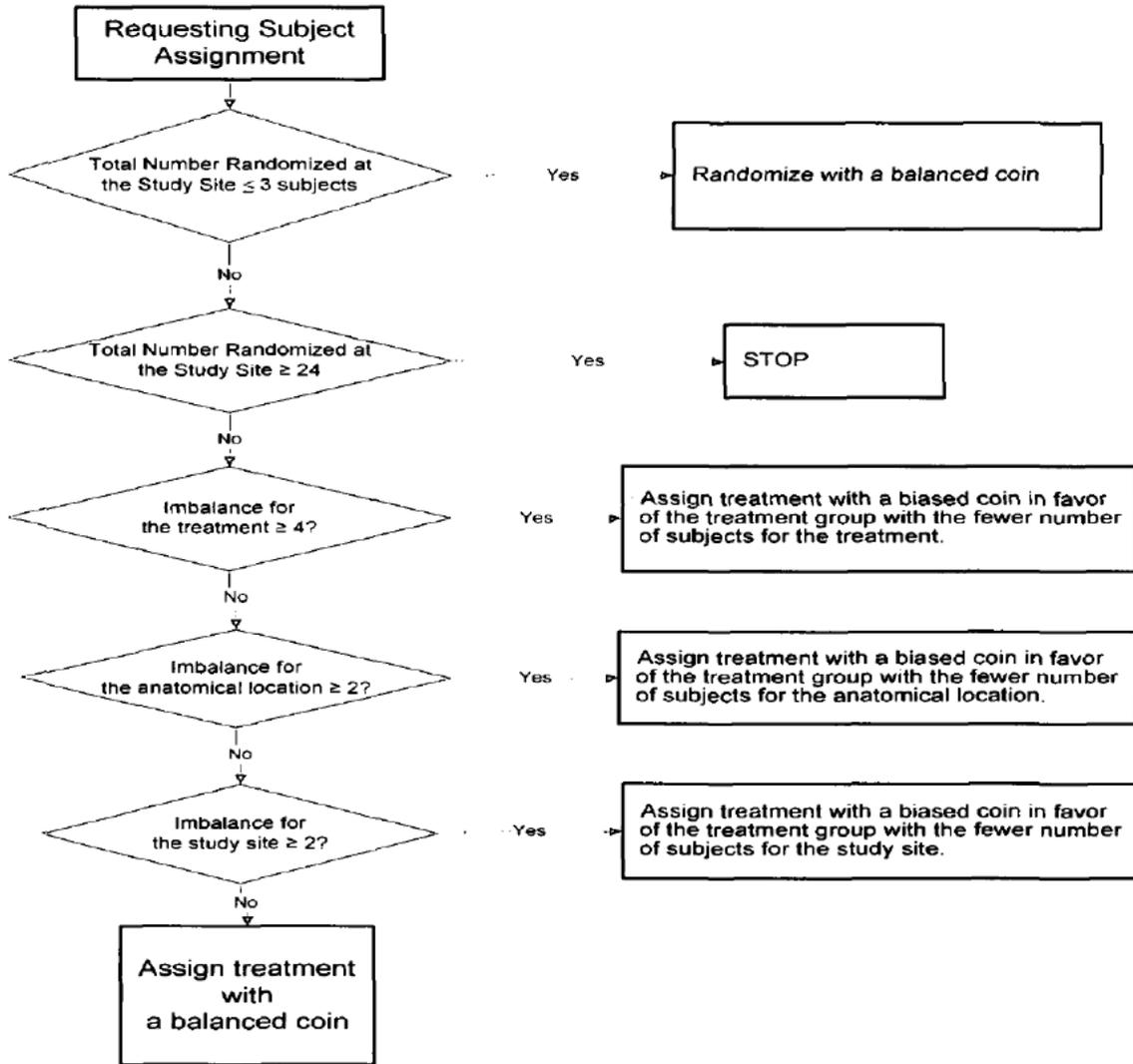
A total of 255 subjects from 19 centers who were at least 18 years of age, with 4 to 8 clinically typical, visible, and discrete AK lesions within a contiguous 25 cm<sup>2</sup> treatment area on nonhead locations were enrolled. Subjects applied the treatment once daily at home for two consecutive days, and paid visits on the following days: Days 3, 8, 15, 29 and 57.

Subjects were randomized in a 1:1 ratio to one of the following two groups:

- PEP005 0.05%
- Vehicle gel

According to the protocol, the randomization was stratified by study site and anatomical location using a “dynamic randomization algorithm”. A central Interactive Voice Response/Interactive Web Response (IVR/IWR) system was used. The Agency requested additional details regarding the dynamic randomization method as an information request to the sponsor (9/2/2011), and the sponsor provided further information regarding their “IXRS<sup>®</sup> Randomization Algorithm Specifications” on 9/9/2011 (SDN17). According to the sponsor, subjects were stratified by treatment assignment, anatomical location, and by study site. The dynamic randomization algorithm was used to achieve approximately 1:1 ratio of sample sizes across the two treatment groups for the study overall, anatomical location, and within each site, while assigning all subjects at random and as many as possible without the use of a biased coin. According to the submission, the algorithm is the hierarchical method proposed by Signorini (Signorini, D.F., Leung, O., Simes, R.J., Beller, E., and Gebski, V.J., “Dynamic Balanced Randomization for Clinical Trials”, *Statistics in Medicine*, Vol. 12, 2343-2350, 1993). The sponsor stated that the Signorini method has been generalized to allow alternative orderings of the levels in the hierarchy, as well as the use of a biased coin rather than a deterministic assignment when the imbalance at a given level exceeded the specified threshold. In addition, the sponsor used a permuted block for the first 3 subjects at each site to help ensure within site balance. See Figure 1 for flowchart of the dynamic randomization algorithm.

**Figure 1. Sponsor’s Dynamic Randomization Algorithm Flow Chart**



The protocol-specified primary efficacy endpoint is the complete clearance rate of AK lesions; defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the selected treatment area.

The protocol-specified secondary efficacy endpoint is the partial clearance rate of AK lesions; defined as the proportion of subjects at Day 57 with a 75% or greater reduction in the number of AK lesions identified at baseline, in the selected treatment area.

According to the sponsor, no interim efficacy data was collected.

## Patient Disposition, Demographic and Baseline Characteristics

Study 014 enrolled 255 subjects (126 PEP005, 129 vehicle), and Study 028 enrolled 203 subjects (100 PEP005, 103 vehicle). For Study 014, the discontinuation rate for PEP005 subjects (3.2%) was higher than for vehicle subjects (0.8%), and for Study 028, the discontinuation rate for vehicle (3.9%) was higher than for PEP005 subjects (2%). The reasons for discontinuation are presented in Table 3.

**Table 3. Subject Disposition**

	Study 014		Study 028	
	PEP005	Vehicle	PEP005	Vehicle
<b>ITT <sup>(1)</sup> Subjects</b>	126	129	100	103
<b>Completed</b>	122 (96.8%)	128 (99.2%)	98 (98.0 %)	99 (96.1%)
<b>Reason for Discontinuation</b>	4 (3.2%)	1 (0.8%)	2 (2.0 %)	4 (3.9 %)
<i>Adverse Event</i>	2	1	0	1
<i>Lost to follow-up</i>	1	0	0	0
<i>Protocol violation</i>	1	0	1	1
<i>Withdrew consent</i>	0	0	0	1
<i>Other</i>	0	0	1	1

(1) ITT defined as all randomized subjects regardless of receiving any dose of study medication.  
Source: Sponsor's Study Report 14.1.2.1 (Study 014) and Table 14.1.1.1 (Study 028).

Both studies were fairly evenly balanced across treatment arms in terms of age, however, in both studies, more male subjects than female subjects were enrolled. All subjects were white in both studies.

**Table 4. Demographics**

	Study 014		Study 028	
	PEP005	Vehicle	PEP005	Vehicle
<b>ITT <sup>(1)</sup> Subjects</b>	126	129	100	103
<b>Age</b>				
<b>≤65</b>	51 (40%)	56 (43%)	50 (50%)	53 (51%)
<b>&gt;65</b>	75 (60%)	73 (57%)	50 (50%)	50 (49%)
<b>Sex</b>				
<b>Female</b>	40 (32%)	56 (43%)	41 (41%)	35 (34%)
<b>Male</b>	86 (68%)	73 (57%)	59 (59%)	68 (66%)
<b>Race</b>				
<b>White</b>	126 (100%)	129 (100%)	100 (100%)	103 (100%)

(1) ITT defined as all randomized subjects regardless of receiving any dose of study medication.  
Source: Reviewer's table

Both studies were fairly evenly balanced across treatment arms for the baseline Fitzpatrick data and in terms of baseline lesion counts. Only a small number of subjects had baseline AK lesions ≥8.

**Table 5. Baseline severity**

	Study 014		Study 028	
	PEP005 N=126	Vehicle N=129	PEP005 N=100	Vehicle N=103
<b>Fitzpatrick</b>				
I	26 (21%)	31 (24%)	26 (26%)	24 (23%)
II	69 (55%)	73 (57%)	36 (36%)	45 (44%)
III	21 (17%)	21 (16%)	31 (31%)	27 (26%)
IV	10 (8%)	4 (3%)	5 (5%)	7 (7%)
V	-	-	2 (2%)	-
<b>Baseline Lesion Count</b>				
4	30 (24%)	35 (27%)	37 (37%)	27 (26%)
5	37 (29%)	40 (31%)	25 (25%)	21 (20%)
6	29 (23%)	26 (20%)	20 (20%)	26 (25%)
7	17 (13%)	14 (11%)	6 (6%)	15 (15%)
8	11 (9%)	14 (11%)	6 (6%)	14 (14%)
9	2 (2%)	-	-	-

### Statistical Methodologies

The efficacy analysis was based on the ITT population defined by all randomized subjects regardless of receiving any dose of study medication.

For handling of missing data, the LOCF was used as the primary imputation method which was agreed upon per the SPA letter. For sensitivity analyses, the sponsor considered the following:

- Analysis based on the within treatment group multiple imputation method
- Analysis based on a trimmed population – a subset of the ITT population (excluding patients from the sites that have the smallest and the largest treatment response differences among all sites)
- Analysis based on ‘evaluable’ population – a subset of the ITT population. Evaluable population is defined as the randomized subjects who have lesion counts at baseline and Day 57.
- Analysis based on per-protocol (PP) population where PP is defined as those with no violations of any study entry eligibility criteria, received study medication and did not receive the wrong medication or incorrect dose at any time prior to the time point evaluated, applied study medication on Days 1 and 2 per protocol, did not receive any excluded concomitant medication to the selected treatment area prior to the time point evaluated, treatment assignment was not unblinded at any time during the study, completed all required scheduled assessments.

For the analysis of primary and secondary efficacy endpoints, the sponsor proposed two methods without specifying the primary method:

- “CMH test weighted over anatomical locations” and

- “Logistic ANOVA with treatment, anatomical location, and study site as factors for treatment effect”

The Agency provided detailed comments on the proposed primary analysis methods on 5/13/2009; however, Study 014 was already ongoing at the time that the sponsor received Agency comments that the sponsor did not revise the analysis method for Study 014. For Study 028, the primary analysis method was revised per the Agency comments.

## Results and Conclusions

The following table shows the primary efficacy analysis results. Both Phase 3 trials (Studies 014 and 028) met the statistical significance level of 0.05.

The complete clearance rates for each anatomical location are shown as well. In both studies, while most subjects had their treated AK locations on the arm or on the back of hand, the complete clearance rates were higher on the arm than those of the back of hand location.

**Table 6. Complete Clearance (ITT, LOCF) - Study 014**

	Study 014		
	PEP005 (N=126)	Vehicle (N=129)	p-value
<b>Complete Clearance<sup>(1)</sup></b>	35/126 (27.8%)	6/129 (4.7%)	<0.001
<b>Arm</b>	22/84 (26.2%)	4/82 (4.9%)	-
<b>Back of hand</b>	4/25 (16.0%)	0/29 (0%)	-
<b>Chest</b>	8/9 (88.9%)	1/8 (12.5%)	-
<b>Back</b>	0/2 (0%)	0/3 (0%)	-
<b>Leg</b>	1/6 (16.7%)	1/5 (20.0 %)	-
<b>Shoulder</b>	-	0/2 (0%)	-

(1) Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by sites.

Source: Sponsor’s Study Report Table 12.

**Table 7. Complete Clearance (ITT, LOCF) - Study 028**

	Study 028		
	PEP005 (N=100)	Vehicle (N=103)	p-value
<b>Complete Clearance<sup>(1)</sup></b>	42/100 (42.0%)	5/103 (4.9%)	<0.001
<b>Arm</b>	27/59 (45.8%)	3/67 (4.5%)	-
<b>Back of hand</b>	6/28 (21.4%)	0/27 (0%)	-
<b>Chest</b>	3/5 (60.0%)	1/3 (33.3%)	-
<b>Back</b>	3/3 (100%)	-	-
<b>Leg</b>	1/3 (33.3%)	0/5 (0%)	-
<b>Shoulder</b>	2/2 (100%)	1/1 (100%)	-

(1) Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by pooled sites (protocol-specified method).

Source: Sponsor’s Study Report Table 11.

The number of subjects with missing data was very small in both studies (<4% in all treatment arms). As such, efficacy results were not impacted by the choice of imputation method for this application (i.e., using multiple imputation method yielded the same response rates and therefore, the same conclusion).

The per protocol (PP) analysis set was defined as those with no violations of any study entry eligibility criteria, received study medication and did not receive the wrong medication or incorrect dose at any time prior to the time point evaluated, applied study medication on Days 1 and 2 per protocol, did not receive any excluded concomitant medication to the selected treatment area prior to the time point evaluated, treatment assignment was not unblinded at any time during the study, completed all required scheduled assessments. For the PP population, approximately 10% of subjects were excluded from the ITT population. The results of the analyses on the PP population were very similar to those on the ITT population with similar success rates. The PP analysis results are shown in Table 8.

**Table 8. Complete Clearance (PP, LOCF) - Study 014 and Study 028**

	Study 014		Study 028	
	PEP005 (N=112)	Vehicle (N=113)	PEP005 (N=90)	Vehicle (N=95)
<b>Complete Clearance<sup>(1)</sup></b>	31/112 (27.7%)	6/113 (5.3%)	37/90 (41.1%)	3/95 (3.2%)
<b>Arm</b>	19/71 (26.7%)	4/69 (5.8%)	25/53 (47.2%)	1/61 (1.6%)
<b>Back of hand</b>	4/25 (16.0%)	0/28 (0%)	4/25 (16.0%)	0/25 (0%)
<b>Chest</b>	7/8 (87.5%)	1/7 (14.3%)	2/4 (50%)	1/3 (33.3%)
<b>Back</b>	0/1 (0%)	0/3 (0%)	3/3 (100%)	-
<b>Leg</b>	1/6 (16.7%)	1/4 (25.0%)	1/3 (33.3%)	0/5 (0%)
<b>Shoulder</b>	0/1 (0%)	0/2 (0%)	2/2 (100%)	1/1 (100%)

(1) Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57.  
Source: Reviewer's analysis.

The analysis of the secondary efficacy endpoint, the partial clearance rate of AK lesions (i.e., 75% or greater reduction in the number of AK lesions identified at baseline) at Day 57 overall and by anatomical locations, was statistically significant. Similar to the complete clearance rates, the partial clearance rates for the AK lesions on the arm was almost twice as high as those of the back of hand.

**Table 9. Partial Clearance (ITT, LOCF) - Study 014**

	Study 014		
	PEP005 (N=126)	Vehicle (N=129)	p-value
<b>Partial Clearance<sup>(1)</sup></b>	56/126 (44.4%)	9/129 (7.0%)	<0.0001
<b>Arm</b>	40/84 (47.6%)	7/82 (8.5%)	-
<b>Back of hand</b>	6/25 (24.0%)	0/29 (0%)	-
<b>Chest</b>	8/9 (88.9%)	1/8 (12.5%)	-
<b>Back</b>	1/2 (50.0%)	0/3 (0%)	-
<b>Leg</b>	1/6 (16.7%)	1/5 (20.0%)	
<b>Shoulder</b>	-	0/2 (0%)	

(1) Partial Clearance is defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by anatomical location (protocol-specified method).  
Source: Sponsor's Study Report Table 13.

**Table 10. Partial Clearance (ITT, LOCF) - Study 028**

	Study 028		
	PEP005 (N=100)	Vehicle (N=103)	p-value
<b>Partial Clearance<sup>(1)</sup></b>	55/100 (55.0%)	7/103 (6.8%)	<0.001
<b>Arm</b>	36/59 (61.0%)	4/67 (6.0%)	-
<b>Back of hand</b>	9/28 (32.1%)	1/27 (3.7%)	-
<b>Chest</b>	4/5 (80.0%)	1/3 (33.3%)	-
<b>Back</b>	3/3 (100%)	-	-
<b>Leg</b>	1/2 (50.0%)	0/5 (0%)	
<b>Shoulder</b>	2/2 (100%)	1/1 (100%)	

(1) Partial Clearance is defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by anatomical location (protocol-specified method).  
Source: Sponsor's Study Report Table 12.

### 3.3 Evaluation of Safety

The protocol stated that the assessment of local skin responses (LSR) was presented by grade (0-4) for each LSR at each scheduled visit using frequency counts and percentages. The sponsor stated that the LSR grading scale is a photographic, descriptive 5-point scale that was developed with the assistance of practicing dermatologists.

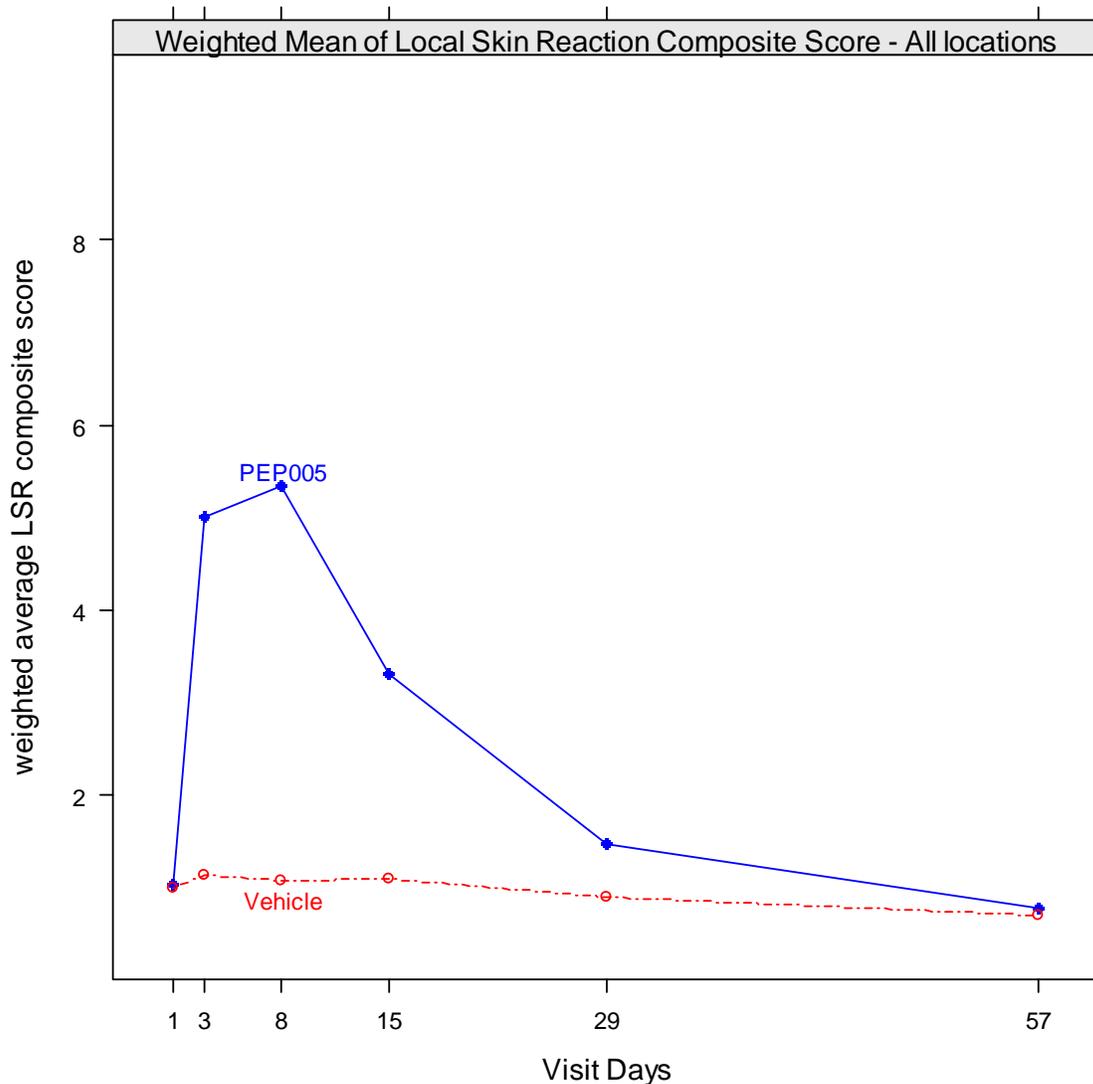
The selected treatment area was assessed for the LSR at all visits, and the following individual LSRs were recorded: erythema, flaking/scaling, crusting, swelling, vesiculation/postulation, and erosion/ulceration. The sponsor stated that skin responses other than the recorded LSRs were recorded as adverse events (AEs). The LSR composite score was defined as the sum of individual LSR grades at each scheduled visit. For handling missing data, the last observation carried forward (LOCF) was used.

As the efficacy trend over the course of the treatment is of interest to the Agency, on 9/2/2011, the Agency inquired whether the sponsor collected efficacy assessments on interim visits between Day 0 and 57. The sponsor confirmed that no efficacy results were assessed. While no

interim efficacy data were available to assess the interim efficacy, because the safety endpoints such as the local skin reactions (LSR) are thought to be correlated to the efficacy data, this reviewer plotted the LSR scores over time. With most subjects having the AK lesions on the arm or on the back of hand and a small number of subjects having the lesions elsewhere, the weighted mean of the composite LSR scores over time for all ITT subjects are plotted (Figure 2 and Figure 4). The average of the composite location skin response scores over time is plotted for each anatomical location Figures 3 and 5 for Study 014 and Study 028, respectively.

The plots show that the local skin response scores peak at Day 8 (i.e., 6 days after the last treatment), and gradually appears to subside over time. The same trend is observed in both studies.

**Figure 2. Weighted Average of Composite Location Skin Response Scores (Study 014)**



Source: Reviewer's plot (ITT, LOCF).

**Figure 3. Average Composite Local Skin Response Scores by Anatomical Location (Study 014)**

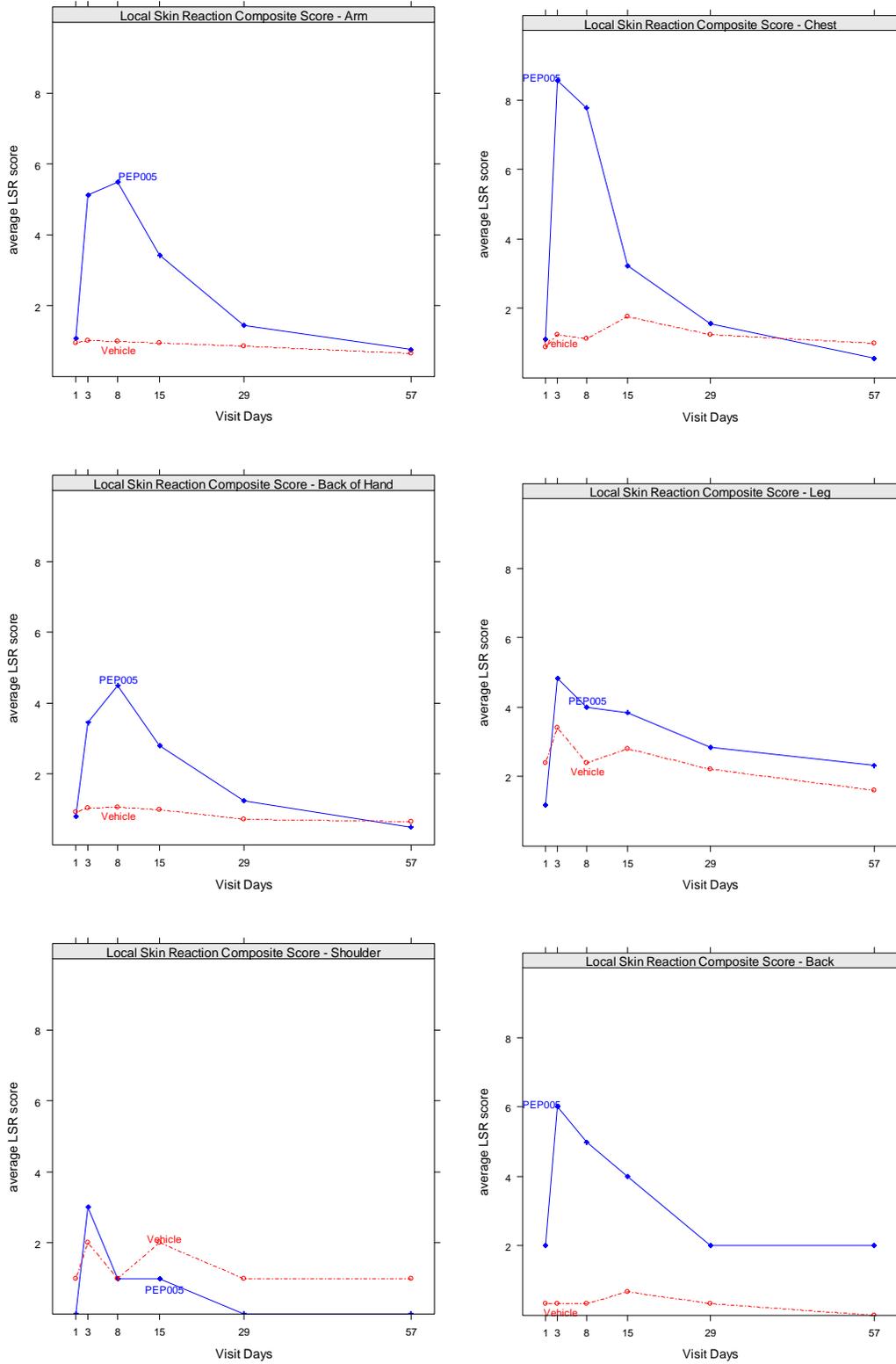
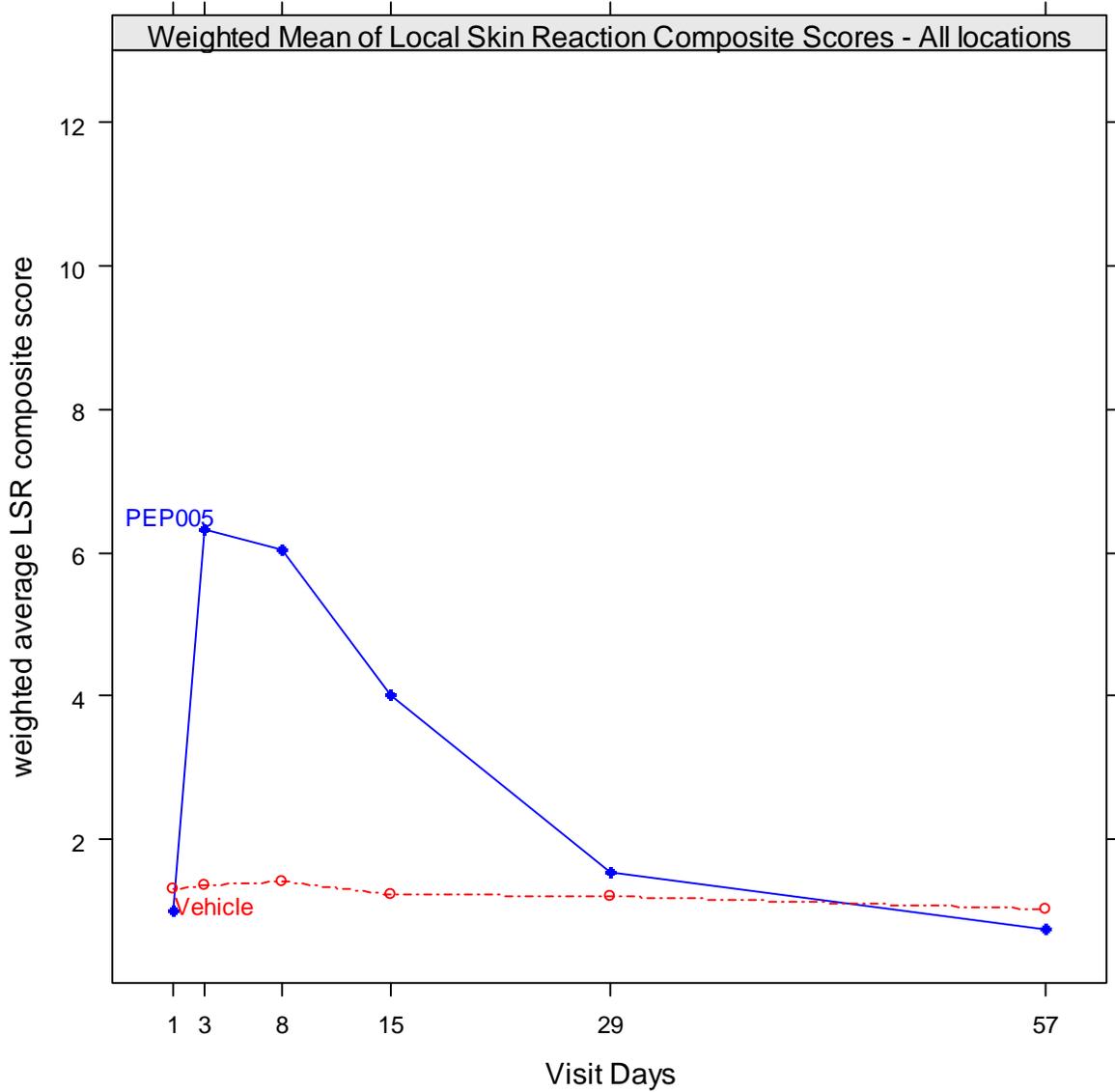
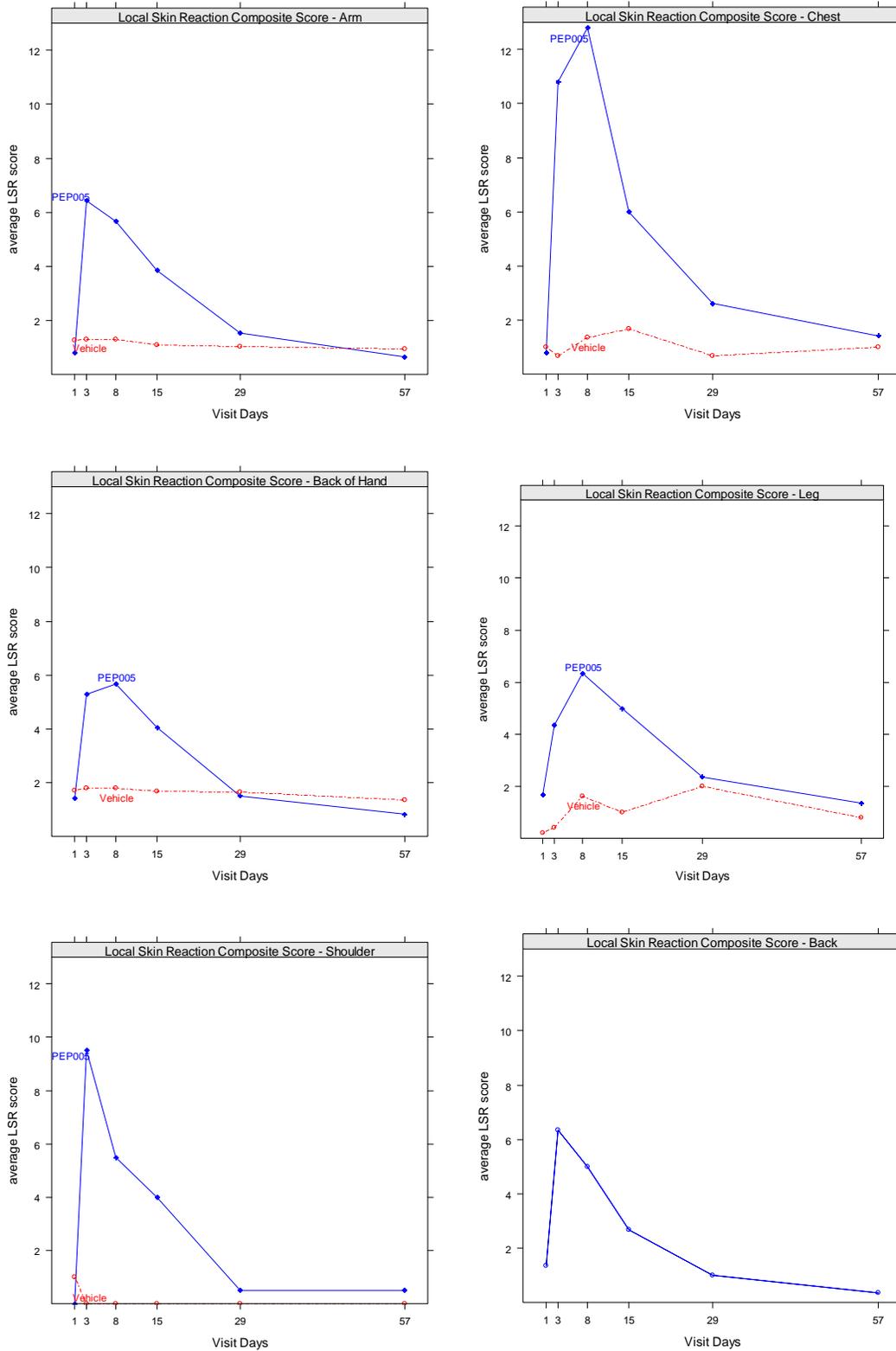


Figure 4. Weighted Average of Location Skin Reaction Composite Scores (Study 028)



Source: Reviewer's plot (ITT, LOCF)

**Figure 5. Average Composite Local Skin Reaction Scores by Anatomical Location (Study 028)**



## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age

Efficacy does not appear to be driven by gender or age, although the complete clearance rates were slightly higher for those subjects who were  $\leq 65$  of age compared to those of subjects who were  $>65$  of age. In terms of gender, the complete clearance rates for PEP005 gel were similar in females and in males, but the vehicle rates were higher in females than those in males. For the efficacy by race, it should be noted that the studies only enrolled white subjects.

**Table 11. Complete Clearance (ITT, LOCF) by Gender, Race and Age**

	Study 014		Study 028	
	PEP005	Vehicle	PEP005	Vehicle
<b>ITT <sup>(1)</sup> Subjects</b>	126	129	100	103
<b>Age</b>				
<b><math>\leq 65</math></b>	17/51 (33%)	3/56 (5%)	26/50 (52%)	1/53 (2%)
<b><math>&gt;65</math></b>	18/75 (24%)	3/73 (4%)	16/50 (32%)	4/50 (1%)
<b>Sex</b>				
<b>Female</b>	11/40 (28%)	5/56 (9%)	18/41 (44%)	2/35 (6%)
<b>Male</b>	24/86 (28%)	1/73 (1%)	24/59 (41%)	3/68 (4%)
<b>Race</b>				
<b>White</b>	35/126 (28%)	6/129 (5%)	42/100 (42%)	5/103 (4.9%)

(1) ITT defined as all randomized subjects regardless of receiving any dose of study medication

Source: Reviewer's analysis

### 4.2 Fitzpatrick type, Baseline Lesion Count

The majority of subjects had baseline lesion counts of 4-6 with a small number of subjects with baseline AK lesions  $>6$ . The subjects with baseline lesion of 4-6 appear to have higher complete clearance rates compared to those of subjects with  $>6$  lesions, but the number of subjects that had  $>6$  baseline lesions is small. Table 12 shows the complete clearance rate by Fitzpatrick type and by baseline lesion count.

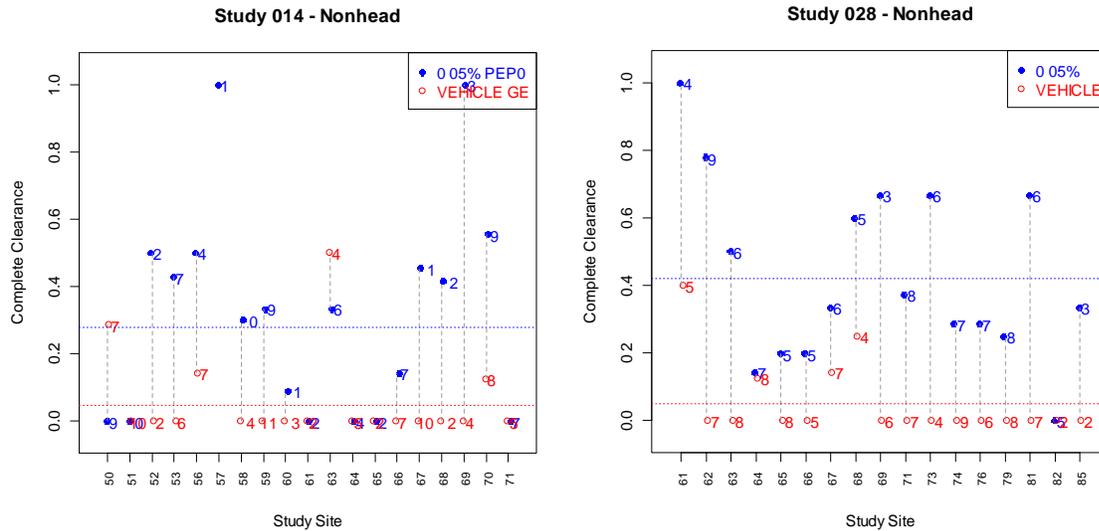
**Table 12. Complete Clearance (ITT, LOCF) by Fitzpatrick type, and by Baseline Lesion Count**

	Study 014		Study 028	
	PEP005 N=126	Vehicle N=129	PEP005 N=100	Vehicle N=103
<b>Fitzpatrick</b>				
I	11/26 (42%)	0/31 (0%)	11/26 (42%)	0/24 (0%)
II	17/69 (25%)	3/73 (4%)	13/36 (36%)	3/45 (7%)
III	4/21 (19%)	3/21 (14%)	16/31(52%)	2/27 (7%)
IV	3/10 (30%)	0/4 (0%)	2/5 (40%)	0/7 (0%)
V	-	-	0/2 (0%)	-
<b>Baseline Lesion Count</b>				
4	9/30 (30%)	3/35 (9%)	18/37 (49%)	1/27 (4%)
5	20/37 (54%)	3/40 (8%)	9/25 (36%)	2/21 (10%)
6	2/29 (7%)	0/26 (0%)	9/20 (45%)	1/26 (4%)
7	2/17 (12%)	0/14 (0%)	0/6 (0%)	1/15 (7%)
8	2/11 (18%)	0/14 (0%)	6/6 (100%)	9/14 (64%)
9	0/2 (0%)	-	-	-

### 4.3 Efficacy by Center

The efficacy results appear to be consistent across the pooled study sites, and the efficacy by center plots are presented in Figure 6.

**Figure 6. Complete Clearance Rate by Center (ITT, LOCF)**



## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

The sponsor submitted results of four Phase 3 trials to support the efficacy claim for actinic keratoses (AK) on head locations, and on nonhead locations. In this review, only the Phase 3 trials for the nonhead AK lesions (PEP005-014 and PEP005-028) are reviewed, and the other two Phase 3 trials for the head AK lesions (PEP005-016 and PEP005-025) are reviewed by Yuqing Tang, Ph.D.

For the treatment of AK on nonhead locations that include arm, back of hand, back, chest, leg and shoulder, the sponsor conducted two Phase 3 trials, Study 014 and Study 028, with PEP005 gel, 0.05%. Both studies demonstrated significance for the primary efficacy endpoint of complete clearance at Day 57. It should be noted that the two studies were identical in design except for the randomization methods that were utilized in each study. Study 014 used dynamic randomization method, and Study 028 used simple block randomization method per Agency previous comments. However, because most enrolled subjects had AK lesions on arm or back of hand with a small number of subjects having AK lesions in other anatomical locations (back, shoulder, chest, or leg), there appears to be little advantage or utility of using dynamic randomization method over a simpler randomization method. It should be noted that the efficacy results appeared to be consistent across the study sites in both studies.

Further, it should be noted that although the efficacy trend over the course of the treatment is of interest to the Agency, the sponsor only collected efficacy assessments on Days 0 and 57. While no interim efficacy data were available to assess the interim efficacy, because the safety endpoints (e.g. the local skin reactions) are thought to be correlated to the efficacy data, the weighted mean of the local skin reaction (LSR) scores over time were plotted. The plots showed that the local skin response scores peaked at Day 8 (i.e., 6 days after the last treatment), and gradually decreased over time.

### **5.2 Conclusions and Recommendations**

PEP005 topical gel, 0.05% was statistically superior to vehicle gel in two studies (PEP005-014 and PEP005-028) in the treatment of AK on nonhead locations. The primary efficacy endpoint was the complete clearance rate of AK lesions; defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the selected treatment area. It should be noted that most of the nonhead treatment locations were on the arm or on the back of hand with only a small number of subjects with AK lesions on the chest, shoulder, back or leg. Due to the small sample size in the some of the subgroups (i.e., chest, back, leg and shoulder), it would be difficult to make conclusive remarks for these anatomical locations.

Efficacy results are presented in Tables 13 and 14.

**Table 13. Complete Clearance (ITT, LOCF) - Study 014**

	Study 014		
	PEP005 (N=126)	Vehicle (N=129)	p-value
<b>Complete Clearance<sup>(1)</sup></b>	35/126 (27.8%)	6/129 (4.7%)	<0.001
<b>Arm</b>	22/84 (26.2%)	4/82 (4.9%)	-
<b>Back of hand</b>	4/25 (16.0%)	0/29 (0%)	-
<b>Chest</b>	8/9 (88.9%)	1/8 (12.5%)	-
<b>Back</b>	0/2 (0%)	0/3 (0%)	-
<b>Leg</b>	1/6 (16.7%)	1/5 (20.0 %)	-
<b>Shoulder</b>	-	0/2 (0%)	-

(1) Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by sites.  
Source: Sponsor's Study Report Table 12.

**Table 14. Complete Clearance (ITT, LOCF) - Study 028**

	Study 028		
	PEP005 (N=100)	Vehicle (N=103)	p-value
<b>Complete Clearance<sup>(1)</sup></b>	42/100 (42.0%)	5/103 (4.9%)	<0.001
<b>Arm</b>	27/59 (45.8%)	3/67 (4.5%)	-
<b>Back of hand</b>	6/28 (21.4%)	0/27 (0%)	-
<b>Chest</b>	3/5 (60.0%)	1/3 (33.3%)	-
<b>Back</b>	3/3 (100%)	-	-
<b>Leg</b>	1/3 (33.3%)	0/5 (0%)	-
<b>Shoulder</b>	2/2 (100%)	1/1 (100%)	-

(1) Complete Clearance is defined as the proportion of subjects with no clinically visible AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by pooled sites (protocol-specified method).  
Source: Sponsor's Study Report Table 11.

## SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Carin Kim, Ph.D.

Date: November 16, 2011

Concurring Reviewer(s):

Statistical Team Leader: Mohamed Alosh, Ph.D.

Biometrics Division Director: Stephen Wilson, Dr.PH.

cc:

J. Paul Phillips

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Carin Kim, Ph.D.

Mohamed Alosh, Ph.D.

Stephen Wilson, Dr. PH

Yuqing Tang, Ph.D.

Lillian Patrician

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CARIN J KIM  
11/16/2011

MOHAMED A ALOSH  
11/18/2011

For biostatistics review of the clinical trials for the head actinic keratosis lesions please check review by Yuqing Tang, Ph.D., signed on 11/18/2011

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 202833**

**Applicant: Leo Pharmaceuticals**

**Stamp Date: 3/31/2011**

**Drug Name: (Ingenol Mebutate) NDA/BLA Type: NDA  
Gel, 0.015% and 0.05%**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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File name: Stat\_filing\_checklist\_202833

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Yuqing Tang	5/11/2011
Reviewing Statistician I	Date
Carin Kim	5/11/2011
Reviewing Statistician II	Date
Mohamed Alosch	5/11/2011
Supervisor/Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YUQING TANG  
05/24/2011

MOHAMED A ALOSH  
05/24/2011