CONFIDENTIAL

PEP005 (Ingenol Mebutate) Gel

2.7.3 Summary of Clinical Efficacy for Actinic Keratosis

LEO Pharma A/S
Clinical Development

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LIST OF ABBREVIATIONS

5-FU 5-fluorouracil
AE adverse event
AK actinic keratosis
AUS Australia
CI confidence interval
C_{max} maximum plasma concentration
CMH Cochran-Mantel-Haenszel
DLT dose-limiting toxicity
DMC Data Monitoring Committee
ECG Electrocardiogram
EU European Union
FDA Food and Drug Administration
FET Fisher's exact test
GCP Good Clinical Practice
ICH International Conference on Harmonisation
ITT intent-to-treat
IVR interactive voice response
IWR interactive web response
LOCF last observation carried forward
LSR local skin response
mITT modified intent-to-treat
MTD maximum tolerated dose
PK pharmacokinetic
PP per protocol
SAE serious adverse event
SAP statistical analysis plan
SCC squamous cell carcinoma
SD standard deviation
TSQM Treatment Satisfaction Questionnaire for Medication
US United States

DEFINITION OF TERMS

Efficacy Endpoints

Anatomical Location	Study	Primary	Secondary	Additional
Head Non-Head	PEP005-016 PEP005-025 PEP005-015 PEP005-014 PEP005-028	Complete clearance rate was defined as the proportion of patients at Day 57 with no clinically visible actinic keratosis (AK) lesions in the selected treatment area.	Partial clearance rate was defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline in the selected treatment area.	The percent change from baseline to Day 57 in the total number of AK lesions was calculated.
Head (Scalp patients only) Non-Head (Non-scalp patients)	PEP005-006	Partial clearance rate was defined as the proportion of patients at Day 57 who had a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area.	Baseline clearance rate was defined as the proportion of patients at Day 57 who had a 100% reduction in the number of AK lesions identified at baseline in the selected treatment area. Complete clearance rate was defined as the proportion of patients at Day 57 who had no clinically visible AK lesions in the selected treatment area. Percent reduction in the number of AK lesions from baseline was calculated. Number and proportion of emergent subclinical AK lesions within the treatment area was documented. Time to complete AK lesion clearance was calculated. Patient's global impression of study treatment was assessed.	Not specified

Efficacy Endpoints

Anatomical Location	Study	Primary	Secondary	Additional
Head	PEP005-007	Not specified	Complete clearance rate was defined as the proportion of patients at Day 57 with no clinically visible AK lesions. Baseline clearance rate was defined as the proportion of patients at Day 57 with 100% reduction in the number of AK lesion identified at baseline. Patient satisfaction to treatment outcomes at Day 57 was assessed.	Not specified
Non-Head	PEP005-017	Not specified	Complete clearance rate was defined as proportion of patients no clinically visible AK lesions in the selected treatment area. Percent reduction in the number of AK lesions at Day 57 compared to baseline in the selected treatment area was calculated.	Partial clearance rate was defined as ≥ 75% reduction in the number of clinically visible AK lesions in the selected treatment area.

Efficacy Endpoints

Anatomical Location	Study	Primary	Secondary	Additional
Non-Head	PEP005-018	Complete clearance rate was defined as proportion of patients at Day 57 with no clinically visible AK lesions in the selected AK treatment area. Partial clearance rate was defined as proportion of patients at Day 57 with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected AK treatment area. Baseline clearance rate was defined as proportion of patients at Day 57 with 100% reduction in the number of AK lesions identified at baseline in the selected AK treatment area.	Not specified	Complete, partial, and baseline clearance rates by number of doses received Percent reduction in AK lesions Number and percentage of patients with subclinical AK lesions, visible AK lesions, and remaining baseline AK lesions within the treatment area
Non-Head	PEP005-020	Complete clearance rate was defined as proportion of patients at Day 57 with no clinically visible AK lesions in the selected treatment area.	Partial clearance rate was defined as proportion of patients at Day 57 with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area.	The percent change from baseline to Day 57 in the total number of AK lesions was calculated.
Head	PEP005-030	Not specified	Not specified	Not specified
Non-Head	PEP005-031 PEP005-032	Recurrence was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study.		

Efficacy Endpoints

Anatomical Location	Study	Primary	Secondary	Additional
Non-Head	PEP005-004	Not specified	Clinical response at Day 29 was assessed as extent of AK lesion clearance compared to baseline using a 6-point scale.	Not specified
Non-Head	AGN204332-004	Not specified	Not specified	Not specified
		Global response to treatment at Day 14 or thereafter using an 8-point scale.		
		The proportion of patients with complete clearance of all 5 selected lesions.		
Head and Non-Head	PEP005-001	Histological response was assessed by a central dermatopathologist for biopsy specimens obtained on Day 85; this assessment was used to determine complete lesion clearance.	Cosmetic assessment was performed but is not included in this efficacy summary.	Not specified
		Clinical response to treatment was based on an assessment of each lesion compared with the baseline assessment using a 6-point scale.		

Local Skin Response

The Applicant, at the direction of the United States Food and Drug Administration's Division of Dermatology and Dental Products and with the assistance of a number of practicing dermatologists, developed a photographic and clearly defined scale, the Local Skin Response (LSR) Grading Scale, to ensure that a clear and unified assessment of LSRs related to the selected treatment area was performed. The LSR Grading Scale employed a 0 to 4 scoring system for each category to be assessed with photographs and definitions of each grade. Investigators were trained on this scale to ensure consistency in reporting of LSRs. As the clinical development programme evolved, so did the LSR Grading Scale. Below is a summary of specific LSR aspects for each study included in this efficacy summary.

Anatomical Location	Study	LSR Grading Scale Components	Maximum Composite Score	Pigmentation and Scarring Evaluations Included
Head Non-Head	PEP005-016 PEP005-025 PEP005-015 PEP005-014 PEP005-028 PEP005-017 PEP005-020	• Erythema • Flaking/scaling • Crusting • Swelling • Vesiculation/pustulation • Erosion/ulceration	24 No;	Evaluated Separately
Head Non-Head Head (Scalp patients only) Non-Head (Non-scalp patients)	PEP005-007 PEP005-018 PEP005-006	• Erythema • Flaking/scaling • Crusting • Swelling • Vesiculation/pustulation • Erosion/ulceration • Hypopigmentation and hyperpigmentation • Scarring	32 Yes	

Anatomical Location	Study	LSR Grading Scale Components	Maximum Composite Score	Pigmentation and Scarring Evaluations Included
Non-Head	PEP005-004	Study conducted prior to development of LSR grading scale; local skin *reactions* for each treated lesion were evaluated as the number and percentage of patients with mild, moderate or severe occurrences of the following: • Erythema • Oedema • Erosion/ulceration • Scabbing/crusting • Weeping/exudates • Vesicles • Flaking/scaling/dryness • Hypopigmentation • Hyperpigmentation	Not applicable	Pigmentation included; scarring evaluated separately
Head	PEP005-030	LSRs were not assessed (no study medication was administered)	Not applicable	Not applicable
Non-Head	PEP005-031 PEP005-032			

Anatomical Location	Study	LSR Grading Scale Components	Maximum Composite Score	Pigmentation and Scarring Evaluations Included
Non-Head	AGN204332-004	Study conducted prior to development of LSR grading scale; local skin *reactions* for each treated lesion were evaluated as the number and percentage of patients with mild, moderate or severe occurrences of the following: • Erythema • Oedema • Erosion/ulceration • Scabbing/crusting • Weeping/exudates • Vesicles • Flaking/scaling/dryness	Not applicable	No; scarring evaluated separately
Head and Non-Head	PEP005-001	Study conducted prior to development of LSR grading scale; local skin *reactions* for each treated lesion were evaluated as the number and percentage of patients with mild, moderate or severe occurrences of the following: • Itch • Erythema • Oedema • Erosion/ulceration • Scabbing/crusting • Weeping/exudates • Vesicles • Flaking/scaling/dryness • Hypopigmentation • Hyperpigmentation • Scarring	Not applicable	Yes

1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

1.1 BACKGROUND

1.1.1 Actinic Keratosis

Actinic keratosis (AK) is a common skin condition visible as thickened, cornified, scaly lesions and characterised histologically by atypical epithelial proliferation.(1) Actinic keratosis lesions usually develop on the face, lips, ears, scalp, neck, forearms, and back of the hands—areas that are most commonly exposed to the sun. Patients endure a psychological burden due to AK, expressing embarrassment, irritation, and annoyance that lesions are unsightly, particularly when located on the face.(2,3) In addition to the emotional strain, AK lesions may be painful and pruritic, and are easily traumatised which can result in bleeding.(3,4,5,6)

It is estimated that AK occurs in 11–50% of the population aged 40 or older in the United States (US) and Australia.(1) In Europe the prevalence rate is from 11-25% for people aged 40 or older.(7,8) Patients with AK tend to have Fitzpatrick type I or II skin (fair skin) which burns and does not tan.(5)

In the US and Australia, the majority of patients who develop AK lesions have fair skin with Fitzpatrick skin types I and II.(9,10) The same is true for Northern European populations, such as the English, Irish, Scottish, and Scandinavians.(11)

There is increasing evidence that AK represents squamous cell carcinoma (SCC) in situ in its earliest stages.(1,12,13) Histological evidence shows that contiguous AK is present in 97% of SCC lesions on sun-damaged skin.(12) If left untreated, AK may progress to SCC, with significant morbidity and death.(12)

1.1.2 Current Treatment Practice

Current treatment options for AK lesions consist of cryotherapy, photodynamic therapy, curettage, excisional surgery and topical products.

1.1.2.1 Lesion-Specific Treatment

Lesion-specific treatments include photodynamic therapy, cryotherapy, curettage, and excisional surgery. Photodynamic therapy and cryotherapy can be painful, and patients are

often left with hypopigmented spotting where cryotherapy is applied.(14,15) Curettage (with or without electrosurgery) and excisional surgery are alternatives to cryosurgery.(16)

1.1.2.2 Topical Products for Field Treatment

Topical products include 5-fluorouracil (5-FU), diclofenac, and imiquimod, and are commonly used as field treatment for multiple lesions over larger skin areas. 5-Fluorouracil is approved in the US under the brand names of Efudex®, Fluoroplex®, and Carac® (17,18,19) and in some European countries under the brand name of Efudix®.(20) Diclofenac is approved in the US as Solaraze® and in some European countries as Solaraze™.(21,22) Imiquimod in approved in the US under the brand names of Aldara® (23) and Zyclara™ (24) and in the EU under the brand name of Aldara®.(25)

Two 5-FU products (Efudex®/Efudix® and Fluoroplex®) are approved without restriction to anatomical location (17,18) and one product (Carac®) is approved for treatment on the face and scalp.(19) When Carac® is applied once daily for two to four weeks, complete clearance rates range from 15-58%.(19) Three other studies were identified where 5-FU was evaluated in the treatment of AK. One study suggested a complete clearance rate (no AK lesions in the treated area) of 40% (26) and a second study stated no patients showed complete clearance.(27) In a third study, complete clearance was not measured; the number of AK lesions was reported as a mean of 15.3 ± 6.9 at baseline and 4.2 ± 2.5 after 3 months.(28) In these studies, 5-FU 1% or 5% cream was applied once or twice a day for approximately 2 to 8 weeks.

Diclofenac (Solaraze®) is marketed as a 3% gel and is approved for treatment without anatomical restriction, it requires twice daily application for 60-90 days, and complete clearance rates of 34-47% have been reported.(21)

Imiquimod is approved for treatment on the face and scalp, and is available in two strengths (3.75% and 5%). The first is a 5% cream (Aldara®) which in the US is approved for application twice weekly for 16 weeks; complete clearance rates range from 44-46%.(23) In the EU, the approved regimen for Aldara® 5% cream is three times per week for 4 weeks. After a 4-week no-treatment period another 4-week course can be applied if required.(25) The other strength is a 3.75% cream (Zyclara™) which is only approved in the US and is applied once daily before bedtime to the skin of the affected area (entire face or balding scalp) for two 2-week treatment cycles separated by a 2-week no-treatment period; complete clearance rates range from 26-46%.(24)

Measurable plasma concentrations have been documented with use of 5-FU, diclofenac, and imiquimod.(17,19,21,23,24) Irritation resulting from 5-FU treatment can be unsightly during and after therapy,(29) diclofenac has the potential to cause allergic reactions (30), and imiquimod, in addition to having significant local irritation, has been associated with systemic side effects, such as fatigue, flu-like symptoms, and angioedema.(23,31,32,33) Study medication discontinuation rates due to adverse events (AEs) (primarily skin irritation and application site reactions) during Phase 3 clinical trials have been reported to be 12% for 5-FU (19) and 18% for diclofenac.(21) For imiquimod, a rest period was required during treatment with Aldara® for 16% of patients due to local skin reactions and for 3% of patients due to treatment site infections; additionally, 2% of patients discontinued due to skin reactions.(23) With Zyclara™, 11% of patients required a rest period.(24) Lengthy treatment durations and adverse effects can reduce a patient's ability to complete a full course of therapy and can lead to treatment failure.(12)

Observational studies have evaluated recurrence after imiquimod treatment. Recurrence was defined as at least one AK lesion in the treatment area or receipt of an intervention related to AKs or SCC in the treatment area after the patient finished treatment and achieved complete clearance. In one study, patients who had complete clearance 4 weeks after one or two treatment courses (3 times/week for 4 weeks) were assessed 12 months later. The patient-based recurrence rate was 39% in the imiquimod group and 57% in the vehicle group.(34) In a second study, patients received imiquimod three times a week for 16 weeks or two times a week for 16 weeks. After a median follow-up time of 16 months, the recurrence rate was 25% for the patients who received imiquimod 3 times a week and 43% for those who received treatment two times a week.(35)

1.1.3 PEP005 (ingenol mebutate) Gel

Ingenol mebutate is an ingenol derivative extracted from *Euphorbia peplus* L. *(E. peplus)*, a member of the Spurge family. The sap of *E peplus* has been used to treat a number of conditions including warts, corns, waxy growths, and skin cancer since the 1800s.(36,37,38) Results from an early proof of concept study using the crude sap of *E. peplus* (known as study PEP001) confirmed anecdotal community-based evidence of activity against AK and non-melanoma skin cancer when used topically. Ingenol mebutate was identified as the principal active component responsible for the selective cytotoxic effects of *E. peplus* sap, based on its antitumour effects both in vitro and in vivo.(39) Ingenol mebutate is a pleiotrophic effector with a dual mechanism of action involving rapid (24-48 hours) primary necrosis followed by a tumour cell-specific immune response characterised by antibody-dependent cellular

cytotoxicity, which removes residual disease.(40,41,42,43,44,45,46) This mechanism of action distinguishes ingenol mebutate from current therapeutic options and provides a rationale for substantially shorter durations of treatment (two to three days) compared to approved topical AK products.

The AK clinical development programme for PEP005 (ingenol mebutate) Gel includes Phase 1 through Phase 3 studies that explored varying treatment regimens for AK lesions located on the most common sun-exposed areas of the body. Early AK studies focused on treatment of individual AK lesions (i.e., lesion-specific therapy) (AGN 204332-004 and PEP005-001). Data from these early studies established the safety of PEP005 Gel when used as lesion specific therapy and allowed for further assessment of PEP005 Gel on a small field of skin (9 cm^2) containing a single target AK lesion in study PEP005-004. Subsequent studies used to determine optimal dosing for AK (PEP005-006, PEP005-007, PEP005-015) were conducted using field treatment application as well, except that the area treated was larger (i.e., a contiguous 25 cm^2 area) and contained multiple AK lesions (four to eight); these studies were more consistent with trials conducted with other topical products marketed for treatment of AK. Data from the AK studies also suggested that different concentrations and treatment regimens of PEP005 Gel would be needed to treat AK lesions depending on the anatomic location of the lesion (head versus non-head). Actinic keratosis lesions located on the face and scalp required lower concentrations applied for three days compared with AK lesions located on the trunk and extremities (non-head), which required higher concentrations of PEP005 Gel applied for only two days.

Based on the results of the Phase 2b dose ranging studies (PEP005-015 for head and PEP005-006 for non-head), two Phase 3 studies (PEP005-016 and PEP005-025) for the treatment of AK lesions on the head (face and scalp) and two Phase 3 studies (PEP005-014 and PEP005-028) for the treatment of AK lesions on non-head locations (trunk and extremities) were conducted.

This efficacy summary presents all available clinical information relevant to the efficacy of PEP005 Gel for treatment of AK lesions on the head (face and scalp) and non-head (trunk and extremities). Sources of efficacy data are listed in Table 1 for head and Table 2 for non-head. Narrative summaries of individual studies are provided in Section 2.1.2 for head and Section 2.2.2 for non-head. An integrated comparison and analysis of relevant efficacy information is provided in Sections 3.2.1 and 3.3.1 for head and Sections 3.2.2 and 3.3.2 for non-head. An evaluation of efficacy information in subpopulations based on pooled data from clinical

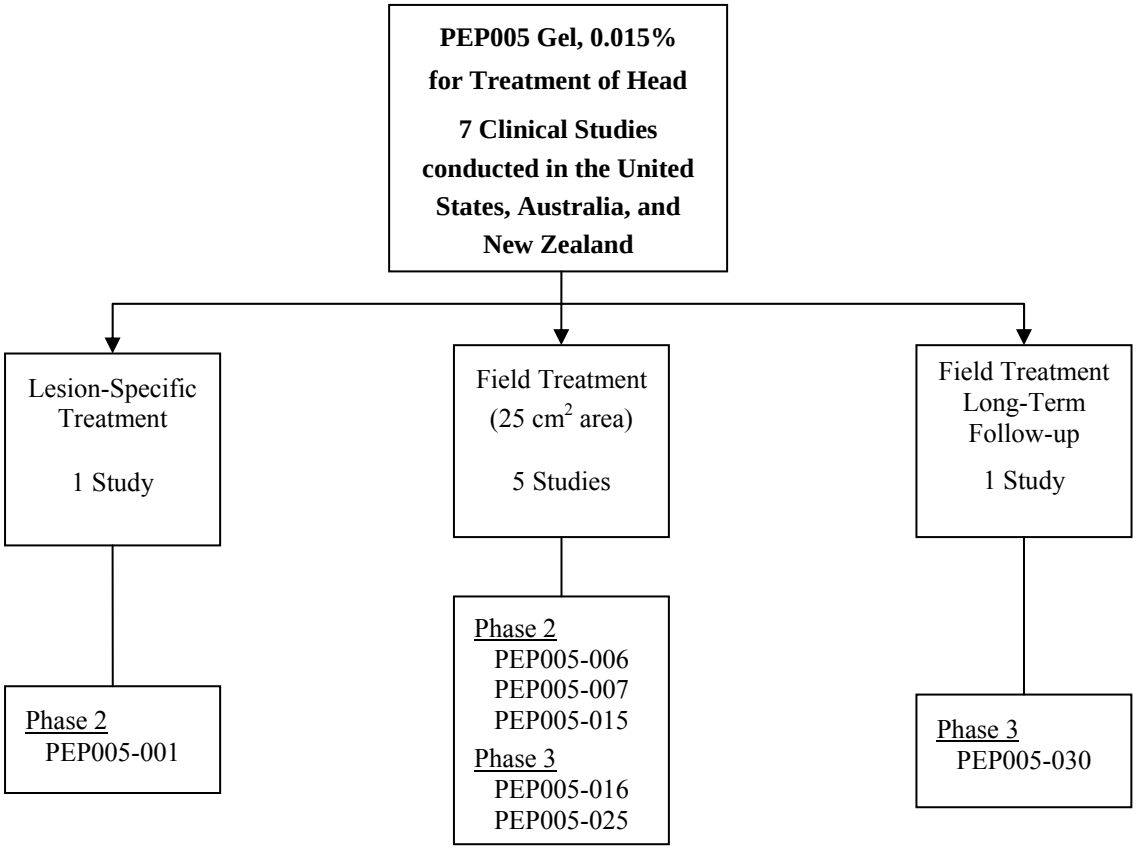
studies is provided in Section 3.4.1 for head and Section 3.4.2 for non-head. An analysis of clinical information relevant to dosing recommendations is provided in Section 4.1 for head and Section 4.2 for non-head. Information from a long-term follow-up study relevant to the persistence of efficacy is provided in Section 5.1 for head and Section 5.2 for non-head.

1.2 OVERVIEW OF CLINICAL EFFICACY STUDIES

1.2.1 Head (Face and Scalp) Locations

In total, there are seven studies in the clinical development programme that evaluated PEP005 Gel on head locations, as shown in Figure 1. Five studies (PEP005-016, PEP005-025, PEP005-015, PEP005-006, and PEP005-007) provide efficacy data for field treatment of PEP005 Gel to a defined 25 cm^2 skin area containing four to eight AK lesions located on the head with the primary endpoint of complete clearance assessed at Day 57; all five are included in the comparative efficacy results in Sections 3.2.1 and 3.3.1. The sixth trial was a long-term follow-up study (PEP005-030) where no study medication was administered and is relevant to the persistence of efficacy (Section 5.1). The seventh trial was a lesion-specific study (PEP005-001) which allowed up to five lesions to be treated on multiple anatomical sites (head and non-head locations). This study did not evaluate efficacy for the indication sought, and therefore, is not presented in Section 3 but is included in description of clinical efficacy studies (Table 1) with a study narrative provided in Section 2.1.2.5.1.

Figure 1: Overview of PEP005 Gel Clinical Development Programme for the Head (Face and Scalp) Locations



A summary of each study is provided in Table 1.

All clinical studies were conducted in full conformance with the principles of International Conference on Harmonisation (ICH) (ICH E6 1997) Good Clinical Practice (GCP) and the Declaration of Helsinki (1964 as amended in Edinburgh [2000]). Two studies, PEP005-016 and PEP005-025, meet the criteria for adequate and well-controlled studies and together data from these two studies satisfy the regulatory requirements for submission of PEP005 Gel for treatment of the head locations. The proposed dosage regimen is PEP005 Gel, 0.015% applied topically once daily for three consecutive days on the face or scalp.

1.2.1.1 Adequate and Well-Controlled Studies (PEP005-016 and PEP005-025)

PEP005-016 and PEP005-025 are multi-centre, double-blind, randomised, parallel group, vehicle-controlled studies with identical study designs. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within

a 25 cm^2 contiguous treatment area on the face or scalp. Exclusion criteria stipulated restrictions for prohibited treatments and procedures prior to study entry. Patients were randomised centrally to treatment using a simple stratified randomisation in a 1:1 ratio through an interactive voice/web response (IVR/IWR) system. Randomisation was stratified by study site and by the location of the treatment area (face or scalp). The percentage of scalp and face treated patients was controlled so that it represented the patient population which would be treated. Approximately 80% of patients enrolled were to be treated on the face and 20% were to be treated on the scalp. This ratio was selected based on published survey results which tabulated the anatomical location of AK lesions in patients seeking treatment for AK.(47,48) The IVR/IWR system assigned a study medication kit number for each patient randomised into the study. Study medication (PEP005 Gel, 0.015% or vehicle gel) was applied topically once daily on three consecutive days to the selected treatment area by the patient at home.

The primary efficacy endpoint was complete clearance rate of AK lesions, defined as the proportion of patients with no clinically visible AK lesions in the selected treatment area. Day 57 was selected as the optimal endpoint for assessment of complete clearance based on early study data suggesting that responding patients had not reached complete clearance by Day 15/29 (AGN 204332-004) and other evidence suggesting little difference in complete clearance rates observed between Day 57 and Day 85 (PEP005-001). A Day 57 assessment (2 months following treatment completion) is also consistent with the timing of endpoint evaluations conducted during trials of other approved agents. The primary efficacy analyses were based on the intent-to-treat (ITT) population (all randomised patients).

The secondary efficacy endpoint was partial clearance rate of AK lesions, defined as the proportion of patients with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area at Day 57. Percent reduction from baseline in the number of AK lesions at Day 57 was also determined. Partial clearance and percent reduction from baseline in the number of AK lesions were included because they are sensitive to the change in individual lesions and therefore provide clinically meaningful information to dermatologists.(49) These additional endpoints have also been used in clinical trials of other topical agents for treatment of AK.(31,50,51,52)

For studies PEP005-016 and PEP005-025, the primary efficacy analysis compared complete clearance rates across treatment groups (active vs. vehicle) using the Cochran-Mantel-Haenszel (CMH) test statistic. In each of these studies, in order to obtain at least eight

patients per site per active treatment group, study sites yielding fewer than 16 patients were combined together in order of geographical proximity, known as "analysis sites". The exact composition of these "analysis sites" was determined and documented prior to breaking the study blind. The stratification for CMH analyses was based on the analysis sites, not on the actual study sites. A sensitivity analysis of complete clearance assumed that all patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) did not achieve complete clearance. In addition, complete clearance rates were compared across treatment groups by location of treatment area (face or scalp). Statistical tests were two-sided with a significance level of $\alpha = 0.05$. Missing values were imputed using the last observation carried forward (LOCF) method. Analyses of study results were prespecified prior to database lock and unblinding.

As part of this efficacy summary, two additional analyses of complete clearance were performed for each study. An additional sensitivity analysis was performed for complete clearance rates in which all active treatment patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) were considered as not achieving complete clearance and all vehicle patients who missed the Day 57 visit or were outside the visit window were considered as achieving complete clearance. Clearance rates were compared across treatment groups using a logistic analysis of variance model with terms for treatment, analysis site, and anatomical location, consistent with Guidance for Industry: E9 Statistical Principles for Clinical Trials.

1.2.1.2 Other Controlled Studies (PEP005-006 and PEP005-015)

There are two other controlled clinical studies that included an efficacy assessment relevant to field treatment for treatment of the head locations (PEP005-006 and PEP005-015). PEP005-015 was a multi-centre, randomised, double-blind, vehicle-controlled, dose-ranging Phase 2b study which provided the primary basis for dosage selection of PEP005 Gel in the Phase 3 studies of AK lesions on the head (face and scalp) regions. In PEP005-015, PEP005 Gel concentrations (0.005%, 0.01%, 0.015%) or vehicle gel were applied once daily for either two or three consecutive days to a 25 cm^2 contiguous treatment area. PEP005-006, a Phase 2b, dose-ranging study included patients with AK lesions on the scalp as well as non-head areas. In PEP005-006, PEP005 Gel was applied as two different concentrations for two or three days, including 0.025% for three days, 0.05% for two or three days, and vehicle gel for three days; study medication was applied to a 25 cm^2 contiguous treatment area. Only the patients who were treated on the scalp were of interest for this efficacy summary.

1.2.1.3 Uncontrolled Study (PEP005-007)

In an uncontrolled dose escalation study, PEP005-007 (Phase 2a), PEP005 Gel concentrations ranging from 0.0025% to 0.025% were evaluated with study medication applied once daily for two or three consecutive days. The maximum tolerated dose (MTD) on the face only, or the face and scalp (for example, forehead) was established as PEP005 Gel, 0.025%, applied daily for two consecutive days.

1.2.1.4 Long-Term Follow-up Study (PEP005-030)

The long-term follow-up study, PEP005-030, was conducted in patients who achieved complete clearance of their AK lesions at Day 57 in the Phase 3 studies. PEP005-030 was a follow-up study of patients who participated in PEP005-016 or PEP005-025 (double-blind treatment with PEP005 Gel, 0.015% or vehicle gel). No study medication was administered in PEP005-030, thus this study did not contribute information relevant to clearance rates following treatment with PEP005 Gel. The original protocol dated 01 Jul 2009, allowed for eligibility criteria to include patients if they completed the Day 57 visit. With implementation of Amendment #1, dated 28 Sep 2009, eligibility was modified to include only patients who achieved complete clearance at Day 57. This study was designed to provide 1-year, follow-up data on recurrence of AK lesions and other safety data in the previously treated area. The double-blind status of patients who were treated in PEP005-016 and PEP005-025 was maintained until completion of PEP005-030. Assessments of AK lesion recurrence were performed at Months 3, 6, 9, and 12. Information from PEP005-030 relevant to the persistence of efficacy is provided in Section 5.1.

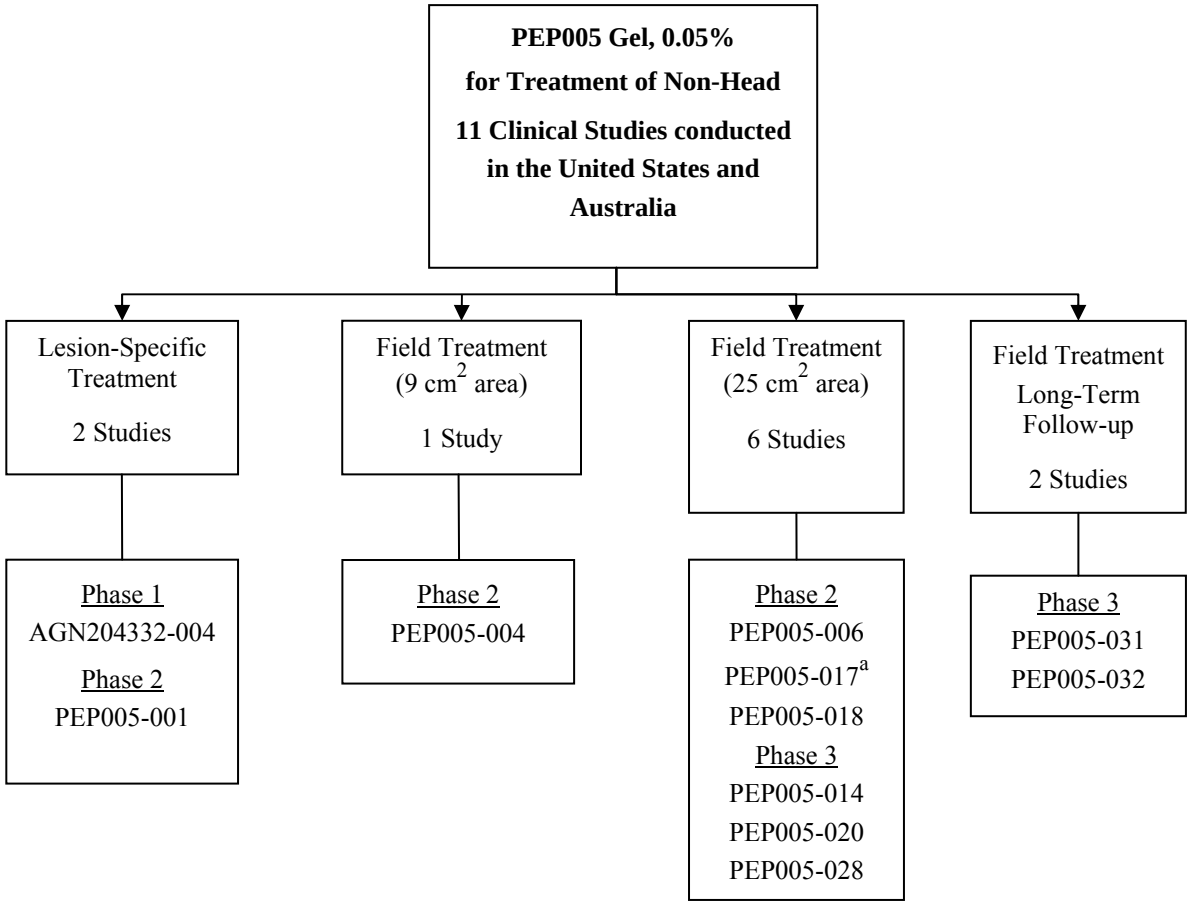
1.2.1.5 Lesion-Specific Treatment Study (PEP005-001)

In a controlled study, PEP005-001 (Phase 2a), study medication was applied to individual AK lesions (i.e., lesion-specific therapy) rather to a field of skin containing multiple lesions. Up to five lesions on multiple anatomical locations (arms, shoulders, chest, face, and scalp) were allowed to be treated. This study was designed primarily to evaluate local skin reactions (safety) following topical administration of PEP005 Gel using different drug concentrations and regimens. Efficacy was evaluated at Day 85. This study is not presented in Section 3 but is included in the description of clinical efficacy studies (Table 1) and has a study narrative provided in Section 2.1.2.5.1.

1.2.2 Non-Head (Trunk and Extremities) Locations

In total, there are 11 studies in the clinical development programme that evaluated PEP005 Gel on non-head locations, as shown in Figure 2. Six studies (PEP005-014, PEP005-028, PEP005-006, PEP005-018, PEP005-020, and PEP005-017) provide efficacy data for field treatment of PEP005 Gel to a defined skin area containing four to eight AK lesions located on the trunk or extremities with an assessment of complete clearance assessed at Day 57. The treatment area size for all these studies is 25 cm^2 except PEP005-017 where the treatment area was larger (100 cm^2). All six studies are included in the comparative efficacy results in Sections 3.2.2 and 3.3.2. Two studies (PEP005-031 and PEP005-032) were long-term follow-up studies where no study medication was administered and are relevant to the persistence of efficacy (Section 5.2). There was one study (PEP005-004) where PEP005 Gel was applied to a small field of treatment (9 cm^2) that included a single target lesion with efficacy endpoints assessed at Day 29. There were two lesion-specific studies (AGN204332-004 and PEP005-001). In both, study medication was applied to individual AK lesions (i.e., lesion-specific therapy) rather than to a field of skin. These last three studies (PEP005-004, AGN204332-004 and PEP005-001) did not evaluate efficacy for the indication sought, and therefore, are not presented in Sections 3.2.2 and 3.3.2 but are included in description of clinical efficacy studies (Table 2) with study narratives provided. See Sections 2.2.2.5.1, 2.2.2.6.1, and 2.2.2.6.2 for narrative summaries of PEP005-004, AGN204332-004 and PEP005-001, respectively.

Figure 2: Overview of PEP005 Gel Clinical Development Programme for the Non-Head (Trunk and Extremities) Locations



[a] For PEP005-017, an area of 100 cm^2 was treated and assessed for safety; efficacy was assessed in a 25 cm^2 area within the 100 cm^2 treatment area.

A summary of each study is provided in Table 2.

All clinical studies were conducted in conformance with the principles of ICH (ICH E6 1997) GCP and the Declaration of Helsinki (1964 as amended in Edinburgh [2000]). Two studies, PEP005-014 and PEP005-028, meet the criteria for adequate and well-controlled studies, and together data from these two studies satisfy the regulatory requirements for submission of PEP005 Gel for treatment of the non-head locations. The proposed dosage regimen is PEP005 Gel, 0.05% applied topically once daily for two consecutive days on the trunk or extremities.

1.2.2.1 Adequate and Well-Controlled Studies (PEP005-014 and PEP005-028)

PEP005-014 and PEP005-028 are multi-centre, double-blind, randomised, parallel group, vehicle-controlled studies with identical study designs. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the trunk or extremities. Exclusion criteria stipulated restrictions for prohibited treatments and procedures prior to study entry. Study medication (PEP005 Gel, 0.05% or vehicle gel) was applied topically once daily on two consecutive days to the selected treatment area by the patient at home.

The primary efficacy endpoint was complete clearance rate of AK lesions, defined as the proportion of patients with no clinically visible AK lesions in the selected treatment area. Day 57 was selected as the optimal endpoint for assessment of complete clearance based on early study data suggesting that responding patients had not reached complete clearance by Day 14/21 (AGN 204332-004) and other evidence suggesting little difference in observed complete clearance rates between Day 57 and Day 85 (PEP005-001). A Day 57 assessment (approximately two months following completion of treatment course) is also consistent with the timing of endpoint evaluations conducted during trials of other approved agents. The primary efficacy analyses were based on the ITT population (all randomised patients).

The secondary efficacy endpoint was partial clearance rate of AK lesions, defined as the proportion of patients with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area at Day 57. Percent reduction from baseline in the number of AK lesions at Day 57 was also determined. Partial clearance and percent reduction in the number of AK lesions were included because they are sensitive to change in individual lesions and therefore provide clinically meaningful information to dermatologists.(49) These additional endpoints have also been used in clinical trials of other topical agents for treatment of AK.(31,50,51,52)

The primary efficacy analysis compared complete clearance rates across treatment groups (active vs. vehicle) using the CMH test statistic. The CMH analysis for PEP005-014 was stratified on anatomical location and the CMH analysis for study PEP005-028 was stratified on analysis site. A sensitivity analysis of complete clearance assumed that all patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) did not achieve complete clearance. In addition, complete clearance rates were compared across treatment groups by location of treatment area (arm, back of hand, or other). Statistical tests were two-sided with a significance level of $\alpha = 0.05$. Missing values were imputed using the

LOCF method. Analyses of study results were prespecified prior to database lock and unblinding.

As part of this efficacy summary, two additional analyses of complete clearance were performed for each study. An additional sensitivity analysis was performed for complete clearance rates in which all active treatment patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) were considered as not achieving complete clearance and all vehicle patients who missed the Day 57 visit or were outside the visit window were considered as achieving complete clearance. The treatment groups were compared using the CMH test stratifying on analysis site. Clearance rates were compared across treatment groups using a logistic analysis of variance model with terms for treatment, analysis site, and anatomical location, consistent with Guidance for Industry: E9 Statistical Principles for Clinical Trials.

1.2.2.2 Other Controlled Studies (PEP005-006 and PEP005-017)

There are two other controlled clinical studies that included an efficacy assessment relevant to treatment of the non-head locations (PEP005-006 and PEP005-017). PEP005-017 was a single-centre, pharmacokinetic (PK) study designed primarily to determine the potential for systemic exposure of topically applied ingenol mebutate. In PEP005-017, PEP005 Gel, 0.05% was applied once daily for two consecutive days to a 100 cm^2 contiguous treatment area. PEP005-006, a Phase 2b, dose-ranging study included patients with AK lesions on non-head locations and on the scalp. PEP005-006 was the study that provided the primary basis for dosage selection of PEP005 Gel in Phase 3 studies of AK lesions on non-head locations. PEP005 Gel was applied as two different concentrations for two or three days, including 0.025% for three days, 0.05% for two or three days, and vehicle gel for three days; study medication was applied to a 25 cm^2 contiguous treatment area. Only the patients who were treated on non-head locations were of interest for this efficacy summary.

1.2.2.3 Uncontrolled Studies (PEP005-018 and PEP005-020)

There are two open-label, uncontrolled studies of PEP005 Gel that provided efficacy information relevant to treatment of the non-head locations (PEP005-018, and PEP005-020). PEP005-018 and PEP005-020 were uncontrolled, single-arm studies designed primarily to investigate the safety of PEP005 Gel, 0.05% applied once daily for two consecutive days to a 25 cm^2 treatment area of AK lesions; efficacy was evaluated at Day 57.

1.2.2.4 Long-Term Follow-up Studies (PEP005-031 and PEP005-032)

There are two long-term follow-up studies conducted in patients who achieved complete clearance of their AK lesions at Day 57 in previous AK studies. PEP005-031 was a follow-up study of patients who participated in PEP005-020 (open-label treatment with PEP005 Gel, 0.05%). PEP005-032 was a follow-up study of patients who participated in PEP005-028 (double-blind treatment with PEP005 Gel, 0.05% or vehicle gel). The double-blind status of patients treated in PEP005-028 was maintained until completion of PEP005-032. No study medication was administered in PEP005-031 and PEP005-032, thus they do not contribute information relevant to clearance rates following treatment with PEP005 Gel. These studies were designed to provide 1-year, follow-up data on AK recurrence and safety in the previously treated area. Assessments were performed at Months 3, 6, 9, and 12. Information from PEP005-031 and PEP005-032 relevant to the persistence of efficacy is provided in Section 5.2.

1.2.2.5 Field Treatment (Small Area, 9 cm^2) Study (PEP005-004)

PEP005-004 was an early (Phase 2a) dose escalation study designed primarily to determine MTD. In PEP005-004, study drug was applied once daily for two consecutive days to a 9 cm^2 treatment area that included a single target AK lesion and efficacy was evaluated at Day 29. This study is not presented in Section 3 but is included in the description of clinical efficacy studies (Table 2) and each has a study narrative provided in Section 2.2.2.5.

1.2.2.6 Lesion-Specific Treatment Studies (AGN 204332-004, and PEP005-001)

In two studies, AGN 204332 004 (Phase 1) and PEP005-001 (Phase 2a), study drug was applied to individual AK lesions (i.e., lesion-specific therapy) rather than to a field of skin containing multiple lesions. These studies were designed primarily to evaluate local skin reactions (safety) following topical administration of PEP005 Gel using different drug concentrations and regimens. Efficacy was evaluated at Day 14 in AGN 204332-004 and Day 85 in PEP005-001. PEP005-001 included patients with AK lesions on the scalp as well as non-head locations.

These studies are not presented in Section 3 but are included in the description of clinical efficacy studies (Table 2) and each has a study narrative provided in Section 2.2.2.6.

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

This section includes a tabular listing and narrative descriptions of the seven clinical studies that provide information relevant to the efficacy of PEP005 Gel for treatment of AK lesions on the head (face and scalp) locations (Section 2.1) and the 11 clinical studies that provide information relevant to the efficacy of PEP005 Gel for treatment of AK lesions on non-head (trunk and extremities) locations (Section 2.2).

2.1 HEAD (FACE AND SCALP) LOCATIONS

2.1.1 Tabular Listing of Clinical Efficacy Studies

A tabular description of all clinical studies that provide information relevant to the efficacy of PEP005 Gel for treatment of the head locations is provided in Table 1.

Table 1: Description of Clinical Efficacy Studies of Actinic Keratosis on Head (Face and Scalp) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Adequate and Well-Controlled Studies – Field Treatment										
PEP005-016	21 total 19 (US) 2 (AUS)	05 Jun 09 Completed 10 Sep 09 269/250	Double-blind, parallel group, vehicle-controlled (Phase 3)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 contiguous area on head (face or scalp)	0.015% x 3 d Vehicle x 3 d	135/132 134/127	116/19 120/14 38 – 88	3 days 57 days	Complete clearance rate[g], partial clearance rate, percent reduction in AK lesion counts at D57
PEP005-025	21 total 19 (US) 2 (AUS)	05 Jun 09 Completed 02 Sep 09 278/250	Double-blind, parallel group, vehicle-controlled (Phase 3)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 contiguous area on head (face or scalp)	0.015% x 3 d Vehicle x 3 d	142/142 136/135	117/25 112/24 34 – 89	3 days 57 days	Complete clearance rate[g], partial clearance rate, percent reduction in AK lesion counts at D57

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male; US = United States

[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group
[g] Complete clearance rate at Day 57 was the primary efficacy endpoint.

Table 1: Description of Clinical Efficacy Studies of Actinic Keratosis on Head (Face and Scalp) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Other Controlled Studies – Field Treatment										
PEP005-006	22 US	11 Sep 06 Completed 19 Jun 07 222 / 200	Double-blind, double dummy, parallel group, vehicle-controlled, dose ranging (Phase 2b)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 contiguous area on arm, shoulder, chest, back, and/or scalp	0.025% x 3 d 0.05% x 2 d 0.05% x 3 d Vehicle	50/50 55/54 57/57 60/59	40/10 46/9 48/9 44/16 43 – 85	2 or 3 days 57 days	Partial clearance rate[g], baseline clearance rate, complete clearance rate, percent reduction in AK lesion counts at D57

AE = adverse events; AK = actinic keratosis; AUS = Australia; d = day; F = female; LSR = local skin response; M = male; US = United States

[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group
[g] Partial clearance rate at Day 57 was the primary efficacy endpoint.

Table 1: Description of Clinical Efficacy Studies of Actinic Keratosis on Head (Face and Scalp) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Other Controlled Studies – Field Treatment (continued)										
PEP005-015	28 total 25 (US) 3 (AUS)	24 Jun 08 Completed 20 Oct 08 265 / 260	Double-blind, parallel group, dose-ranging, vehicle-controlled (Phase 2b)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 contiguous area on head (face or scalp)	0.005% x 2 d 0.01% x 2 d 0.015% x 2 d vehicle x 2 d 0.005% x 3 d 0.01% x 3 d 0.015% x 3 d vehicle x 3 d	33/32 34/34 33/33 33/31 33/31 34/34 32/32 33/33	30/3 32/2 32/1 29/4 27/6 31/3 28/4 28/5 45-90	2 or 3 days 57 days	Complete clearance rate[g], partial clearance rate, percent reduction in AK lesion counts at D57

AE = adverse events; AK = actinic keratosis; AUS = Australia; d = day; F = female; LSR = local skin response; M = male; US = United States

[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group
[g] Complete clearance rate at Day 57 was the primary efficacy endpoint.

Table 1: Description of Clinical Efficacy Studies of Actinic Keratosis on Head (Face and Scalp) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Uncontrolled Study – Field Treatment										
PEP005-007	9 AUS; New Zealand	18 Jan 07 Completed 13 Nov 07 94 / 86	Open-label, dose-escalation, maximum tolerated dose (Phase 2a)	Safety, Efficacy	4–8 AK lesions in 25 cm^2 contiguous area on the face or face and scalp	0.0125% x 2 d 0.0175% x 2 d 0.025% x 2 d 0.0025% x 3 d 0.005% x 3 d 0.0075% x 3 d 0.0125% x 3 d 0.0175% x 3 d 0.025% x 3 d	3/3 3/3 30/30 8/8 8/8 9/9 11/10 10/9 6/6	3/0 3/0 23/7 6/2 5/3 5/4 8/3 8/2 4/2 42 - 89	2 or 3 days 57 days	Complete clearance rate and baseline clearance rate at D57, patient satisfaction to treatment
Long-Term Follow-up Study- No Treatment										
PEP005-030	42 total 38 (US) 4 (AUS)	29 Jul 2009 Completed 16 Sep 2010 108/160	Observational Recurrence	Safety	Achieved complete clearance at Day 57 in previous Phase 3 study	0.015% x 3 d vehicle x 3 d (previous treatment)	108/102 9/8	83/25 8/1 37-88	1 year follow-up	Recurrence

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male; US = United States
[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] For PEP005-007, no control (vehicle) group was used. All study medications (PEP005 Gel concentrations) were applied topically.
[e] Number of patients entered / number of patients completed. For PEP005-030, the number of patients completed includes patients who remained on study at the 6-month visit.
[f] By dose group; for PEP005-030, dose groups are from the previous studies.

Table 1: Description of Clinical Efficacy Studies of Actinic Keratosis on Head (Face and Scalp) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Lesion-Specific Treatment Study										
PEP005-001	7 AUS	17 Mar 05 Completed 14 Oct 05 63 / 60	Double-blind, parallel group, vehicle-controlled, dose ranging (Phase 2a)	Safety, Efficacy	≥5 AK lesions on arm, shoulder, chest, face, and/or scalp	0.0025%xd1&2 0.01% x d1&2 0.05% x d1&2 Vehicle x d1&2 0.0025%xd1&8 0.01% x d1&8 0.05% x d1&8 Vehicle x d1&8	9/8 8/7 9/8 6/6 8/7 8/8 9/7 6/6	9/0 8/0 8/1 4/2 7/1 7/1 9/0 5/1 44 – 86	2 days (Days 1 and 2 or Days 1 and 8) 85 days	Histological response at D85, clinical response at each visit using a 6-point scale

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male

[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group

2.1.2 Narrative Descriptions of Clinical Efficacy Studies

Narrative descriptions of clinical studies that provide information relevant to the efficacy of PEP005 Gel for treatment of the head locations are grouped as follows: adequate and well-controlled studies (PEP005-016 and PEP005-025 [Section 2.1.2.1]), other completed controlled studies (PEP005-006, and PEP005-015 [field treatment; Section 2.1.2.2], an uncontrolled study (PEP005-007; Section 2.1.2.3), a long-term follow-up study (PEP005-030; Section 2.1.2.4), and a lesion-specific controlled study PEP005-001 [Section 2.1.2.5]).

2.1.2.1 Adequate and Well-Controlled Studies

2.1.2.1.1 PEP005-016 (Module 5.3.5.1\PEP005-016)

Objectives: To evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel when administered once daily for three consecutive days to a contiguous 25 cm^2 area of skin on the head (face or scalp).

Methods: This was a Phase 3, multi-centre, randomised, parallel group, double-blind, vehicle-controlled study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the head (face or scalp). Patients were randomised to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Randomisation was stratified by study site and by anatomical location. Study medication was patient applied at home on Days 1, 2 and 3. Subsequent follow-up visits for safety assessments were conducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline and on Day 57. For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until resolved or assessed as clinically stable.

The primary efficacy endpoint was complete clearance rate of AK lesions at Day 57. The secondary endpoint was partial clearance rate of AK lesions; percent reduction from baseline in the number of AK lesions at Day 57 was an additional endpoint.

Statistical Methods: The primary efficacy analyses were based on the ITT population (all randomised patients). Complete clearance rate was compared between treatment groups using the CMH test, stratified by analysis site.

Results: In total, 269 patients were randomised to treatment (135 to PEP005 Gel and 134 to vehicle gel); all were included in the ITT population. A high percentage of patients applied study medication once daily for three consecutive days (96% of patients in the PEP005 Gel, 0.015% group and 100% of patients in the vehicle gel group). In the PEP005 Gel, 0.015%

group, two patients never applied study medication, two patients applied study medication for one day, and one patient applied medication for two days.

Efficacy

Patients treated with PEP005 Gel, 0.015% demonstrated a statistically significantly higher complete clearance rate compared to vehicle gel patients (37% versus 2%, respectively; $p < 0.001$). The partial clearance rate was also statistically significant (60% in PEP005 Gel-treated patients compared to 7% in vehicle gel patients; $p < 0.001$). Additionally, an 83% median reduction in the number of AK lesions compared to baseline was observed for the PEP005 Gel group versus 0% in the vehicle group.

Patient Reported Outcomes

Patient reported outcomes included the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Skindex-16 Dermatology Survey; both are validated, self-administered instruments. Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group compared to vehicle gel ($p < 0.001$). For the Skindex-16 Dermatology Survey, a statistically significant difference was seen with PEP005 Gel-treated patients less bothered about their skin condition for each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 for all three domains and continued at Day 57 ($p < 0.001$ at Day 57 for each domain).

Conclusions: The efficacy of PEP005 Gel, 0.015% was demonstrated in this study when compared to vehicle gel as measured by complete and partial clearance rates; a substantial reduction in the number of AK lesions was also seen in PEP005 Gel-treated patients.

2.1.2.1.2 **PEP005-025 (Module 5.3.5.1\PEP005-025)**

Objectives: To evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel when administered once daily for three consecutive days to a contiguous 25 cm^2 area of skin on the head (face or scalp).

Methods: This was a Phase 3, multi-centre, randomised, parallel group, double-blind, vehicle-controlled study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the head (face or scalp). Patients were randomised to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Randomisation was stratified by study site and by anatomical location. Study medication was patient applied at home on Days 1, 2 and 3. Subsequent follow-up visits for safety assessments were con-

ducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline and on Day 57. For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until resolved or assessed as clinically stable.

The primary efficacy endpoint was complete clearance rate of AK lesions at Day 57. The secondary endpoint was partial clearance rate of AK lesions; percent reduction from baseline in the number of AK lesions at Day 57 was an additional endpoint.

Statistical Methods: The primary efficacy analyses were based on the ITT population (all randomised patients). Complete clearance rate was compared between treatment groups using the CMH test, stratified by analysis site.

Results: In total, 278 patients were randomised to treatment (142 to PEP005 Gel and 136 to vehicle gel); all were included in the ITT population. A high percentage of patients applied study medication once daily for three consecutive days (99% of patients in the PEP005 Gel, 0.015% group and 100% of patients in the vehicle gel group). In the PEP005 Gel, 0.015% group, one patient applied study medication for only one day and one patient applied medication for two days.

Efficacy

Patients treated with PEP005 Gel, 0.015% demonstrated a statistically significantly higher complete clearance rate compared to vehicle gel patients (47% versus 5%, respectively; $p < 0.001$). The partial clearance rate was also statistically significant (68% of PEP005 Gel-treated patients versus 8% of vehicle gel-treated patients, $p < 0.001$). Additionally, an 87% median reduction in the number of AK lesions compared to baseline was observed for the PEP005 Gel group versus 0% in the vehicle group.

Patient Reported Outcomes

Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey; both are validated, self-administered instruments. Patient reported outcomes showed statistically significant higher mean patient global satisfaction scores, measured by the TSQM, in the PEP005 Gel group compared to vehicle gel ($p < 0.001$). For the Skindex-16 Dermatology Survey, a statistically significant difference was seen with PEP005 Gel-treated patients less bothered about their skin condition for each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 for all three domains and continued at Day 57 ($p < 0.001$ at Day 57 for each domain).

Conclusions: A statistically significant treatment effect was seen in the PEP005 Gel, 0.015% group as evident by the complete and partial clearance rates; a substantial reduction in the number of AK lesions was seen in PEP005 Gel-treated patients.

2.1.2.2 Other Controlled Studies

2.1.2.2.1 **PEP005-006 (Module 5.3.5.1\PEP005-006)**

Objectives: The primary objectives were to evaluate the safety/tolerability and efficacy (assessed by partial clearance rate) of 0.025% and 0.05% PEP005 Gel compared with vehicle gel, administered once daily for two (0.05%) or three (0.025% and 0.05%) consecutive days to a 25 cm^2 contiguous AK treatment area. Secondary objectives were to evaluate the efficacy of PEP005 Gel administered as above compared with vehicle gel assessed by baseline clearance rate and complete clearance rate.

Methods: This was a Phase 2b, multi-centre, randomised, double-blind, double-dummy, vehicle-controlled, sequential cohort study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 treatment area on the arm, shoulder, chest, back or scalp. During Treatment Phase 1, patients were randomly assigned to one of three treatment groups: (1) vehicle gel on Days 1, 2, and 3; (2) 0.025% PEP005 Gel on Days 1, 2, and 3; or (3) vehicle gel on Day 1 and 0.05% PEP005 Gel on Days 2 and 3. After all patients reached Day 29, an independent Data Monitoring Committee (DMC) reviewed safety data and recommended continued enrolment of new patients into Treatment Phase 2. The 0.025% PEP005 Gel dose was eliminated and patients were randomly assigned to one of the three following treatment groups: (1) vehicle gel on Days 1, 2, and 3; (2) vehicle gel on Day 1 and 0.05% PEP005 Gel on Days 2 and 3; (3) or 0.05% PEP005 Gel on Days 1, 2, and 3. Study medication was patient applied at home. Safety and efficacy were assessed at follow-up visits on Days 8, 15, 29, and 57. Patient satisfaction was assessed at Day 57 using a 7-point Likert scale (1 = very negative to 7 = very positive). For patients with unresolved safety concerns at Day 57, follow-up visits were required until resolved or assessed as clinically stable.

The primary efficacy endpoint was partial clearance. Key secondary efficacy endpoints were baseline clearance rate, complete clearance rate, and percent change from baseline in AK lesions.

Statistical Methods: Efficacy analyses were primarily based on the modified ITT (mITT) population (i.e., all patients who were dosed and had at least one postbaseline assessment of lesion clearance). The chi-square test was used to analyse the primary endpoint of partial clearance rate at Day 57.

Results: In total, 222 patients were enroled and treated, 50 patients received 0.025% PEP005 Gel for three consecutive days, 55 patients received 0.05% PEP005 Gel for two consecutive

days, 57 patients received 0.05% PEP005 Gel for three consecutive days, and 60 patients received vehicle gel. All 222 patients also had at least one postbaseline assessment of lesion clearance (mITT). Of the 222 patients, 61 received treatment on the scalp.

Overall, 97% of patients in the PEP005 Gel groups applied all doses of study medication as instructed. For patients treated on the scalp, 30 of the 44 PEP005 Gel-treated patients (68%) applied all doses of study medication as instructed.

Efficacy

Overall, the partial clearance rates were statistically significantly higher in each of the PEP005 Gel groups (range: 56-75%) compared with the vehicle gel group (22%) ($p \leq 0.0002$). Baseline clearance rates were statistically significantly higher in each of the PEP005 Gel treatment groups (range: 42-58%) compared with the vehicle gel group (13%) ($p \leq 0.0007$). Complete clearance rates were statistically significantly higher in each of the PEP005 Gel treatment groups (range: 40-54%) compared with vehicle gel (12%) ($p \leq 0.0006$). Median percent reductions in the number of AK lesions were statistically significantly higher in the PEP005 Gel treatment groups (range: 75-100%) compared with vehicle gel (0%) ($p < 0.0001$). The majority of patients had lesion clearance between Day 29 and Day 57. The percentage of patients with emergent subclinical AK lesions was low (≤ 8%) across PEP005 Gel treatment groups and study visits.

For patients who received treatment on the scalp, the partial clearance rates were statistically significantly higher in the 0.025% and 0.05% PEP005 Gel three day groups (69% and 78%, respectively) compared with the vehicle gel group (24%) ($p = 0.0123$ and $p = 0.0013$, respectively). The comparison of the 0.05% PEP005 Gel two day group and the vehicle gel group was not statistically significant (46%, $p = 0.193$). Complete clearance rates showed statistical significance at Day 57 for all three PEP005 Gel groups (range: 38-72%) compared with the vehicle gel group (6%) ($p \leq 0.027$).

The median overall patient satisfaction score was 7.0 for all three PEP005 Gel treatment groups versus 4.0 for the vehicle gel group.

Conclusions: PEP005 Gel applied for up to three consecutive days as a field treatment of AK lesions on the scalp showed significant benefit when compared with vehicle gel in clearance of AK lesions. Scalp-treated patients were less compliant with the administration of study medication than non-scalp-treated patients.

2.1.2.2.2 **PEP005-015 (Module 5.3.5.1\PEP005-015)**

Objectives: The primary objectives of the study were to evaluate the safety, tolerability, and efficacy (complete clearance) of PEP005 Gel, 0.005%, 0.01%, and 0.015%, compared to vehicle gel, administered once daily as either a two or three consecutive day treatment regimen, to a 25 cm^2 contiguous AK treatment area on the face or scalp. The secondary objective was to evaluate efficacy (partial clearance) of the treatment groups described above.

Methods: This was a Phase 2, multi-centre, randomised, double-blind, vehicle-controlled, dose-ranging study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the head (face or scalp). Patients were randomised to receive one of three PEP005 Gel concentrations (0.005%, 0.01%, 0.015%) or vehicle gel with study medication applied daily for either two or three consecutive days. Patients were randomised to treatment in a 1:1:1:1:1:1:1:1 fashion and were stratified across treatment groups based on location of AK lesions on the head (i.e., face or scalp). Study medication was patient-applied at home. Subsequent follow-up visits for safety assessments were conducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline and on Day 57. For patients with unresolved safety concerns at Day 57, follow-up visits were required until resolved or assessed as clinically stable.

The primary efficacy endpoint was complete clearance rate of AK lesions at Day 57. The secondary endpoint was partial clearance rate of AK lesions; percent change from baseline in total number of AK lesions at Day 57 was an additional endpoint.

Statistical Methods: As a Phase 2 dose-ranging study, the per protocol (PP) population was identified as the population of primary interest. The results for the ITT (all randomised patients) and PP population were similar, thus, the results of the ITT population were presented in the CSR and are described below. Complete clearance rate was compared between treatment groups using the CMH test, adjusting for treatment location (face or scalp). As a secondary analysis, Fisher's exact test (FET) with a Hochberg adjustment was used to compare each PEP005 Gel group and the vehicle gel group.

Results: In total, 265 patients were randomised and 260 (98%) completed the study. Overall, 97% (258 of 265) of patients were able to complete study medication application according to their randomised treatment regimen, once daily for two or three consecutive days.

Efficacy

There were statistically significant differences in the complete clearance rate of the face and scalp at Day 57 for all PEP005 Gel groups compared with vehicle gel based on the CMH test,

except for the 0.01% three-day group. The results of the comparison of the 0.01% and 0.015% groups versus vehicle gel based on the FET were similar to the results based on the CMH test. Neither of the comparisons of the 0.005% groups versus vehicle gel was significant based on FET sensitivity analysis ($p < 0.065$). The highest concentration and regimen, 0.015% for three consecutive days, resulted in complete and partial clearance rates of 50% and 72%, respectively, and a median reduction in the number of AK lesion count of 85%.

Complete and partial clearance rates and median percent reduction in the number of AK lesions in the 0.01% three-day treatment group were lower compared to other PEP005 Gel three-day groups. (The complete clearance rate for the 0.01% three-day group was 18% compared to 33% for the 0.005% group and 50% for the 0.015% group). A review of the patients within this treatment group demonstrated no difference with respect to age, gender, skin type, AK history, or baseline number of AK lesions compared with other PEP005 Gel three-day groups. In addition, patients randomised to this group were evenly distributed among study sites, and there were approximately 20% scalp-treated and 80% face-treated patients in this group. The Sponsor is unable to determine a reason for the lower efficacy observed in this 0.01% three-day PEP005 Gel group.

Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were shown for all PEP005 Gel groups, relative to vehicle gel; the mean satisfaction scores were highest in the 0.01% and 0.015% two-day groups, followed by the 0.01% and 0.015% three-day groups. No statistically significant differences from vehicle gel were noted for the three domains (symptoms, emotions, and functioning) of the Skindex-16 Dermatology Survey at Day 57.

Conclusions: The treatment regimen, PEP005 Gel, 0.015% once daily for three consecutive days, was found to provide the optimum balance between AK lesion clearance and local skin irritation in the PEP005-015 study.

2.1.2.3 Uncontrolled Study

2.1.2.3.1 **PEP005-007 (Module 5.3.5.2\PEP005-007)**

Objectives: The primary objective was to determine the optimal tolerated regimen of PEP005 Gel, administered once daily as a two or three consecutive day application to a 25 cm^2 contiguous AK treatment area on the face or face and scalp. Secondary objectives were to determine the partial clearance, complete clearance, and baseline clearance rates.

Methods: This was a Phase 2a, multi-centre, open-label, nonrandomised, uncontrolled, dose-escalation, cohort study. Eligible patients were male or female, ≥ 18 years of age, with four to

eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the face or face and scalp. A cohort of three patients was planned at each escalation level. The original protocol started dosing with 0.025% PEP005 Gel; at this concentration, the two day dosing was established as the MTD and the three day dosing was established as the dose limiting toxicity (DLT). Two subsequent protocol amendments were implemented to evaluate lower concentrations of PEP005 Gel (0.0175%, 0.0125%, 0.0075%, 0.0050%, and 0.0025%) with similar treatment regimens (once daily for two or three consecutive days). Study medication was patient applied under the supervision of the investigator on Days 1 and 2 or Days 1, 2, and 3. Subsequent follow-up visits for safety assessments were conducted on Days 2, 3, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline and on Day 57.

Efficacy endpoints included partial clearance, complete clearance, and baseline clearance rates at Day 57.

Statistical Methods: Clinical response was reported for the modified ITT population (all patients who received at least one dose of study medication and had at least one postbaseline measurement of efficacy). Patients were categorised into 2 analysis groups. Analysis Group 1 consisted of all patients who received dosing for two days (PEP005 Gel concentrations of 0.025%, 0.0175%, and 0.0125%) and Analysis Group 2 consisted of all patients who received dosing for three days (PEP005 Gel concentrations of 0.025%, 0.0175%, 0.0125%, 0.0075%, 0.0050%, and 0.0025%).

Results: Ninety-four patients were enroled in the study and 88 were treated with at least one dose of study medication. Of the 88 patients treated, 36 were in Analysis Group 1 (two day dosing) and 52 were in Analysis Group 2 (three day dosing). Study medication was patient-applied under the supervision of the investigator. In Analysis Group 1, the percentage of patients who applied study medication according to their treatment regimen of once daily for two consecutive days ranged from 33% for PEP005 Gel 0.0125% to 100% for PEP005 Gel 0.0175%. In Analysis Group 2, the percentage of patients who applied study medication according to their treatment regimen of once daily for three consecutive days ranged from 40% for PEP005 Gel 0.0175% to 100% for PEP005 Gel 0.0025%.

Efficacy

For the MTD (PEP005 Gel 0.025% once daily for two consecutive days), the percentage of patients with partial clearance was 67%; complete clearance was 37%; and baseline clearance was 37%. The 0.0175% concentration achieved the highest complete (100% Analysis Group 1; 80% Analysis Group 2) and baseline (100% Analysis Group 1; 80% Analysis Group 2) AK lesion clearance. The 0.0125% concentration achieved the best partial clearance (100%) in

Analysis Group 1 and shared the designation with the 0.025% in Analysis Group 2 (100%). The lowest concentration (0.0025%) underperformed other concentrations.

Conclusions: The MTD was determined by the Dose Escalation Steering Committee to be 0.025% PEP005 Gel, once daily for two consecutive days for application on the face or face and scalp.

2.1.2.4 Long-Term Follow-up Study

2.1.2.4.1 **PEP005-030 (Module 5.3.5.2\PEP005-030)**

Objectives: To summarise treatment area recurrence of AK lesions and long-term safety data, in the selected treatment area, during a 12-month follow-up period for patients who achieved complete clearance of AKs at Day 57 in studies PEP005-016 and PEP005-025.

Methods: This was a prospective, longitudinal, follow-up study in patients who achieved complete clearance at Day 57 in either study PEP005-016 and PEP005-025. No study medication was administered during the study. The original protocol dated 01 Jul 2009, allowed for eligibility criteria to include patients if they completed the Day 57 visit. With implementation of Amendment #1, dated 28 Sep 2009, eligibility was modified to include only patients who achieved complete clearance at Day 57. Therefore patients who had not achieved complete clearance at Day 57 but were already enroled at the time Amendment #1 was implemented were terminated from the study at the next regularly scheduled study visit or sooner, if feasible.

Patients returned to the study clinic for follow-up visits at Months 3, 6, 9, and 12 after the Day 57 visit in the previous study (PEP005-016 or PEP005-025). Information was collected for all patients on AEs in the selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. The number of AK lesions in the selected treatment area was counted at each visit. Recurrence was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study (PEP005-016 or PEP005-025). The double-blind status of patients who were treated in PEP005-016 and PEP005-025 was maintained until completion of PEP005-030.

Statistical Methods: The recurrence of AK was analysed for the population of patients who had complete clearance at Day 57 of the previous Phase 3 study (PEP005-016 and PEP005-025). Kaplan-Meier estimates were used for time to event analyses. At each visit, the number of patients showing AK recurrence during the visit window, the number of patients censored during the visit window, and the number of patients at risk during the visit window

were presented. AK recurrence rates based on baseline lesion counts (obtained at the baseline visit from study PEP005-016 or PEP005-025) were determined. For this analysis, to account for treatment of recurrent AK lesions within the treatment area (between follow-up visits), the lesion count at a follow-up visit was carried forward in the event that subsequent lesion counts were zero.

Results: The population of interest was patients with complete clearance at Day 57 of the previous study. For this population, a total of 108 patients from the previous PEP005 Gel treatment groups and 9 patients from the previous vehicle gel groups from Studies PEP005-016 and PEP005-025 were enroled. Eight patients (7%) in the previous PEP005 Gel group and one patient (11%) in the previous vehicle group prematurely discontinued.

AK Recurrence

At 12 months of follow-up, 54% of patients who had been treated with PEP005 Gel in the previous Phase 3 studies, had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 365 days. Based on the number of lesions observed within the treatment area during 12 months of follow-up relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 studies), the mean lesion-based recurrence rate was 13%.

At 12 months of follow-up, 72% of vehicle-treated patients had a new or recurrent AK lesion, with a median time to recurrence of 183 days. For this group of patients, the mean lesion-based recurrence rate at 12 months was 16%.

Conclusions: During 12 months of follow-up, 54% of patients previously treated with PEP005 Gel had at least one new or recurrent AK lesion within the treatment area; the median time to recurrence was 365 days. Relative to the total number of AK lesions observed prior to treatment in either study PEP005-016 or PEP005-025, the lesion recurrence rate at 12 months was 13% for previously treated PEP005 Gel patients.

2.1.2.5 Lesion-Specific Treatment Study

2.1.2.5.1 PEP005-001 (Module 5.3.5.1\PEP005-001)

Objectives: The primary objective was to determine the safety of PEP005 Gel 0.0025%, 0.01%, and 0.05% administered on Days 1 and 2 or Days 1 and 8 to AK lesions on the arms, shoulders, chest, face, and/or scalp. Secondary objectives were (1) to evaluate the efficacy of PEP005 Gel administered as above, (2) to determine a recommended treatment regimen for

AK, and (3) to evaluate patients for cosmetic outcome (not discussed in this narrative; see Module 5.3.5.1\PEP005-001).

Methods: This was a Phase 2a, multi-centre, double-blind, randomised, vehicle-controlled, parallel group study. Eligible patients were men (≥ 18 years of age) with at least five individual AK lesions on the arm, shoulders, chest, face, and/or scalp. Patients were randomised to one of two treatment schedules, Day 1 and Day 2 (Arm A) or Day 1 and Day 8 (Arm B) and within Arm A or B to one of three PEP005 Gel concentrations (0.0025%, 0.01%, and 0.05%). Two single applications of study medication were applied directly to each of the selected lesions by a licensed practitioner. Safety and efficacy were assessed at visits on Days 2, 8, 15, 29, 57, and 85 following the last day of study medication application. Post-Day 85 safety visits were scheduled until local skin AEs were resolved or to confirm adequate healing of the punch biopsy areas.

Histological clearance of each individual lesion was determined by central dermatopathologist review of punch biopsy specimens obtained on Day 85. Clinical response to treatment of each lesion was assessed at each scheduled visit as follows: complete clearance (100% improvement, no evidence of residual disease), marked clearance (50% to 90% improvement), slight clearance (10% to 50% improvement), unchanged (±10%), worsened (clinically observable growth), or unable to be assessed (e.g., heavy scabbing, bruise, trauma, inflammatory response).

Statistical Methods: Efficacy data were summarised descriptively by treatment group. Fisher's exact test was used to compare treatment groups. Histological clearance analysis was based on the ITT population (all randomised patients). Clinical response analyses were based on the mITT population (all patients who met the screening eligibility criteria and received at least one dose of study medication).

Results: In total, 63 patients were randomised and analysed for histological clearance (ITT); 58 patients received study medication and were analysed for clinical response. All patients were scheduled to receive two doses of study medication, applied by a licensed practitioner on Days 1 and 2 in Arm A and on Days 1 and 8 in Arm B. All patients received both doses; one patient randomised to the Arm A 0.05% PEP005 Gel group experienced a dose delay and received the second dose on Day 8 instead of Day 2.

Efficacy

In the histological review, there was no significant difference in the presence or absence of AK lesions at Day 85 between each of the PEP005 Gel dose groups and vehicle gel in either

Arm A or Arm B. Between treatment arms, there was no significant difference in the presence or absence of AK lesions within dose groups.

Although not statistically significant, the complete clearance rate of AK lesions (Arm A vs. Arm B patients) at the end of study was 38% vs. 43% for the 0.05% PEP005 Gel group, 0% vs. 13% for the 0.01% PEP005 Gel group, 13% vs. 29% for the 0.0025% PEP005 Gel group, and 17% vs. 0% for the vehicle gel group.

A statistically significant difference in the percentage of patients who had complete clearance of ≥ 80% of AK lesions was observed when all treatment groups were compared ($p = 0.0082$). A statistically significant difference was also observed for the percentage of patients in the 0.05% PEP005 Gel group who had complete clearance of ≥ 80% of AK lesions when compared to vehicle gel ($p = 0.0185$). No statistically significant difference for pooled treatment arms data was observed for 100% complete AK lesion clearance for any PEP005 Gel dose group, when compared to vehicle gel or when all treatment groups were compared.

Conclusions: Evidence of improved lesion clearance with 0.05% PEP005 Gel compared with vehicle gel was observed.

2.2 NON-HEAD (TRUNK AND EXTREMITIES) LOCATIONS

2.2.1 Tabular Listing of Clinical Efficacy Studies

A tabular description of all clinical studies that provide information relevant to the efficacy of PEP005 Gel for treatment of the non-head locations is provided in Table 2.

Table 2: Description of Clinical Efficacy Studies of Actinic Keratosis on Non-Head (Trunk and Extremities) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment[c]	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Adequate and Well-Controlled Studies – Field Treatment										
PEP005-014	19 total 17 (US) 2 (AUS)	05 Sep 08 Completed 23 Feb 09 255/250	Double-blind, parallel group, vehicle-controlled (Phase 3)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 conti-guous area on trunk or extremities	0.05% x 2 d Vehicle x 2 d	126/122 129/128	86/40 73/56 36 – 88	2 days 57 days	Complete clearance rate[g], partial clearance rate, % reduction in AK lesion counts at D57
PEP005-028	17 US	22 Jul 09 Completed 14 Oct 09 203/200	Double-blind, parallel group, vehicle-controlled (Phase 3)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 conti-guous area on trunk or extremities	0.05% x 2 d Vehicle x 2 d	100/98 103/99	59/41 68/35 34 – 89	2 days 57 days	Complete clearance rate[g], partial clearance rate, % reduction in AK lesion counts at D57
Other Controlled Studies – Field Treatment										
PEP005-006	22 US	11 Sep 06 Completed 19 Jun 07 222/200	Double-blind, double dummy, parallel group, vehicle-controlled, dose ranging (Phase 2b)	Efficacy, Safety	4–8 AK lesions in 25 cm^2 conti-guous area on arm, shoulder, chest, back, and/or scalp	0.025% x 3 d 0.05% x 2 d 0.05% x 3 d Vehicle x 2 d	50/50 55/54 57/57 60/59	40/10 46/9 48/9 44/16 43 – 85	2 or 3 days 57 days	Partial clearance rate[g], baseline clearance rate, complete clearance rate, % reduction in AK lesion counts at D57

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male; US = United States
[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group
[g] Indicates primary efficacy endpoint

Table 2: Description of Clinical Efficacy Studies of Actinic Keratosis on Non-Head (Trunk and Extremities) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment[c]	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Other Controlled Studies – Field Treatment (Cont'd.)										
PEP005-017	1 US	18 Mar 09 Completed 27 May 09 16/15	Double-blind, parallel group, vehicle-controlled (Phase 2)	PK, Safety, Efficacy	Multiple AK lesions in a 100 cm^2 contiguous area on dorsal aspect of one forearm	0.05% x 2 d Vehicle x 2 d	13/13 3/3	6/7 0/3 48 – 79	2 days 57 days	Complete clearance, partial clearance, percent reduction in AK lesion counts at D57
Uncontrolled Studies – Field Treatment										
PEP005-018	4 US	11 Oct 07 Completed 18 Dec 07 12/12	Open-label, single arm, uncontrolled (Phase 2)	Safety, Efficacy	4–8 AK lesions in 25 cm^2 conti-guous area dorsum of hand	0.05% x 2 d	11/11	11/0 57 – 82	2 days 57 days	Complete clearance, partial clearance, baseline clearance at D57
PEP005-020	11 total 8 (US) 3 (AUS)	08 Jun 09 Completed 2 Sep 09 102/100	Open-label, single arm, uncontrolled (Phase 3b)	Safety, Efficacy	4–8 AK lesions in 25 cm^2 conti-guous area on trunk or extremities	0.05% x 2 d	102/102	68/34 38 – 88	2 days 57 days	Complete clearance rate[g], partial clearance rate, percent reduction in AK lesion counts at D57

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male; PK = pharmacokineitcs; US = United States
[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group
[g] Indicates primary efficacy endpoint

Table 2: Description of Clinical Efficacy Studies of Actinic Keratosis on Non-Head (Trunk and Extremities) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment[c]	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Long-Term Follow-up Studies – No Treatment										
PEP005-031	11 total 8 (US) 3 (AUS)	29 Jul 09 Completed 14 Sep 10 38/30	Observational	Recurrence, Safety	Achieved complete clearance at Day 57 in PEP005-020	0.05% x 2 d (previous treatment)	38/34 25/	13 38 - 80	1 year follow-up	Recurrence
PEP005-032	15 US	09 Sep 09 Completed 11 Oct 10 43/40	Observational	Recurrence, Safety	Achieved complete clearance at Day 57 in PEP005-028	0.05% x 2 d vehicle x 2 d (previous treatment)	38/38 5/5	22/16 3/2 44 – 79	1 year follow-up	Recurrence
Field Treatment (Small Area, 9 cm^2) Study										
PEP005-004	1 US	7 Sep 05 Completed 14 Mar 06 22/up to 34	Open-label, nonrandomised, uncontrolled, dose escalation (Phase 2a)	Safety (MTD), Efficacy, PK	Single target AK lesion diameter 3 mm to 15 mm on the shoulder, chest, back, or arm.	0.01% x 2 d 0.025% x 2 d 0.05% x 2 d 0.075% x 2 d (applied to 9 cm^2 area with 1 target lesion)	3/3 3/3 10/10 6/6	2/1 2/1 7/3 5/1 64 – 87	2 days 29 days	Extent of lesion clearance at D29 on a 6-point scale (complete, marked, slight, unchanged, worsened, unable to assess)

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male; MTD = maximum tolerated dose; PK =pharmacokinetics; US = United States

[a] First patient enroled/randomised/treated

[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies

[c] Total enroled / enrolment goal.

[d] All study and control medications were applied topically.

[e] Number of patients entered / number of patients completed. For PEP005-031 and PEP005-032, the number of patients completed includes patients who remained on study at the 6-month visit.

[f] By dose group; for PEP005-031 and PEP005-032, dose groups are from previous studies.

Table 2: Description of Clinical Efficacy Studies of Actinic Keratosis on Non-Head (Trunk and Extremities) Locations

Study ID (Protocol No.)	Number of Study Centres Location	Start Date[a] Enrolment Status, Date[b] Enrolment[c]	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 Gel and Vehicle Dose, Regimen[d]	Number of Patients by Dose Group[e]	Gender M/F[f] Age Range (years)	Treatment Duration Study Duration	Efficacy Endpoints
Lesion-Specific Treatment Studies										
AGN204332-004	4 US	12 Aug 04 Completed 15 Oct 04 16/16	Double-blind, parallel group, vehicle-controlled (Phase 1)	Safety	≥5 AK lesions on shoulder, chest back, and/or arm	0.01% x 1 d Vehicle x 1 d	11/11 5/4	10/1 4/1 42 – 82	1 day 14 days	Global response on an 8-point scale from 0 (completely cleared) to 7 (unable to determine)
PEP005-001 7	AUS	17 Mar 05 Completed 14 Oct 05 63/60	Double-blind, parallel group, vehicle-controlled, dose ranging (Phase 2a)	Safety, Efficacy	≥5 AK lesions on arm, shoulder, chest, face, and/or scalp	0.0025%x d 1&2 0.01% x d 1&2 0.05% x d 1&2 Vehicle x d 1&2 0.0025%x d 1&8 0.01% x d 1&8 0.05% x d 1&8 Vehicle x d 1&8	9/8 8/7 9/8 6/6 8/7 8/8 9/7 6/6	9/0 8/0 8/1 4/2 7/1 7/1 9/0 5/1 44 – 86	2 days (Days 1 and 2 or Days 1 and 8) 85 days	Histological response at D85, clinical response at each visit using a 6-point scale

AK = actinic keratosis; AUS = Australia; d = day; F = female; M = male; US = United States
[a] First patient enroled/randomised/treated
[b] Last patient/last follow-up for completed studies; cutoff date for data analysis for ongoing studies
[c] Total enroled / enrolment goal.
[d] All study and control medications were applied topically.
[e] Number of patients entered / number of patients completed
[f] By dose group

2.2.2 Narrative Descriptions of Clinical Efficacy Studies

Narrative descriptions of clinical studies that provide information relevant to the efficacy of PEP005 Gel for treatment of the non-head locations are group as follows: adequate and well-controlled studies (PEP005-014 and PEP005-028 [Section 2.2.2.1]), other controlled studies (PEP005-006, and PEP005-017 [Section 2.2.2.2]), uncontrolled studies (PEP005-018 and PEP005-020 [Section 2.2.2.3]), long-term follow-up studies (PEP005-031 and PEP005-032 [Section 2.2.2.4]), small field treatment (PEP005-004 [Section 2.2.2.5]), and lesion-specific treatment studies (AGN204332-004 and PEP005-001 [Section 2.2.2.6]).

2.2.2.1 Adequate and Well-Controlled Studies

2.2.2.1.1 PEP005-014 (Module 5.3.5.1\PEP005-014)

Objectives: To evaluate the efficacy and safety of PEP005 Gel, 0.05% compared with vehicle gel when administered once daily for two consecutive days to a 25 cm^2 contiguous AK treatment area on non-head locations.

Methods: This was a Phase 3, multicentre, randomised, double-blind, parallel group, vehicle-controlled study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the trunk or extremities. Randomisation was stratified by study site and by anatomical location. Patients received PEP005 Gel, 0.05% or vehicle gel once daily on Days 1 and 2. Study medication was patient-applied at home. The primary efficacy endpoint was complete clearance rate of AK lesions at Day 57. The secondary endpoint was partial clearance rate of AK lesions at Day 57; percent reduction from baseline in the number of AK lesions at Day 57 was an additional endpoint. Efficacy assessments were conducted at baseline and Day 57 following treatment. For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until resolved or assessed as clinically stable.

Statistical Methods: Efficacy analyses were based on the ITT population. Complete and partial clearance rates were calculated using observed rates and using weighted estimates based on the weights for the CMH test statistic. Treatment groups were compared using the CMH test stratifying on anatomical location and using a logistic regression model with terms for treatment, country (US versus Australia), and anatomical location (back of hand versus non-back of hand).

Results: In total, 255 patients were randomised and treated, 126 patients received PEP005 Gel, 0.05% and 129 patients received vehicle gel. All were included in the ITT population.

All patients in the vehicle gel group and 124 (98%) patients in the PEP005 Gel, 0.05% group were compliant with the treatment regimen, i.e., applied study medication on both days of dosing.

Efficacy

Complete clearance rate at Day 57 was statistically significantly higher in the PEP005 Gel, 0.05% group compared with the vehicle gel group ($p < 0.0001$; CMH stratified on anatomical location and based on logistic regression model). The observed complete clearance rate in the PEP005 Gel, 0.05% group was 28% versus 5% in the vehicle gel group. The observed partial clearance rate at Day 57 in the PEP005 Gel, 0.05% group was 44% versus 7% in the vehicle gel group ($p < 0.0001$, CMH). Median percent reduction from baseline in the number of AK lesions at Day 57 in the PEP005 Gel, 0.05% group was 69% versus 0% in the vehicle gel group.

Patient Reported Outcomes

Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey; both are validated, self-administered instruments. Patient-reported mean overall Satisfaction score at Day 57, as measured by the TSQM, was significantly higher in the PEP005 Gel, 0.05% group (71) relative to the vehicle group (48) ($p < 0.0001$, analysis of variance with treatment, anatomical location, and study site). Skindex-16 scores in the Symptoms domain were increased from baseline at Day 8 in the PEP005 Gel, 0.05% group, indicating increased concern ("bothersomeness") ($p < 0.0001$ for difference between treatment groups). At Day 57, all three domain scores (Symptoms, Emotions, and Functioning) were decreased from baseline, with no statistically significant differences between treatment groups.

Conclusions: PEP005 Gel, 0.05% demonstrated statistically significant improvement compared to vehicle gel for both primary and secondary efficacy endpoints.

2.2.2.1.2 **PEP005-028 (Module 5.3.5.1\PEP005-028)**

Objectives: To evaluate the efficacy and safety of PEP005 Gel, 0.05% compared with vehicle gel when administered once daily for two consecutive days to a 25 cm^2 contiguous AK treatment area on non-head locations.

Methods: This was a Phase 3, multicentre, randomised, double-blind, parallel group, vehicle-controlled study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the trunk or extremities. Randomisation was stratified by study site and by anatomical location. Patients received PEP005 Gel, 0.05% or vehicle gel once daily on Days 1 and 2.

Study medication was patient-applied at home. The primary efficacy endpoint was complete clearance rate of AK lesions at Day 57. The secondary endpoint was partial clearance rate of AK lesions at Day 57; percent reduction from baseline in the number of AK lesions at Day 57 was an additional endpoint. Efficacy assessments were conducted at baseline and Day 57 following treatment. For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until resolved or assessed as clinically stable.

Statistical Methods: The primary efficacy analyses were based on the ITT population. Complete and partial clearance rates were compared between treatment groups using the CMH test stratifying on analysis site.

Results: In total, 203 patients were randomised and treated, 100 patients received PEP005 Gel, 0.05% and 103 patients received vehicle gel. All were included in the ITT population. All patients in the vehicle group and 99 (99%) of patients in the PEP005 Gel, 0.05% group were compliant with the treatment regimen, i.e., applied study medication on both days of dosing. One patient in the PEP005 Gel, 0.05% group missed the second dose due to losing the study medication tube.

Efficacy

Complete clearance rate of AK lesions at Day 57 was statistically significantly higher in the PEP005 Gel, 0.05% group (42%) than the vehicle gel group (5%) ($p < 0.001$). The partial clearance rate at Day 57 in the PEP005 Gel, 0.05% group was 55% versus 7% in the vehicle gel group ($p < 0.001$). Median percent reduction from baseline in the number of AK lesions at Day 57 in the PEP005 Gel, 0.05% group was 75% versus 0% in the vehicle group.

Patient Reported Outcomes

Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey; both are validated, self-administered instruments. Patient-reported mean overall Satisfaction score at Day 57, as measured by the TSQM, was significantly higher in the PEP005 Gel, 0.05% group (72) relative to the vehicle gel group (34) ($p < 0.001$, analysis of variance with treatment, analysis site, and anatomical location). Skindex-16 scores in the Symptoms domain were increased from baseline at Day 8 in the PEP005 Gel, 0.05% group, indicating increased concern ("bothersomeness") ($p < 0.001$ for difference between treatment groups). At Day 57, mean scores for all three domains (Symptoms, Emotions, and Functioning) were decreased from baseline to a significantly greater degree in the PEP005 Gel, 0.05% group relative to the vehicle gel group ($p \leq 0.013$), indicating a greater improvement in patient concern regarding their skin condition in the PEP005 Gel, 0.05% group relative to the vehicle gel group.

Conclusions: PEP005 Gel, 0.05% demonstrated statistically significant improvement compared to vehicle gel for both primary and secondary efficacy endpoints.

2.2.2.2 Other Controlled Studies

2.2.2.2.1 PEP005-006 (Module 5.3.5.1\PEP005-006)

Objectives: Primary objectives were to evaluate the safety/tolerability and efficacy (assessed by partial clearance rate) of 0.025% and 0.05% PEP005 Gel compared with vehicle gel, administered once daily for two or three consecutive days to a 25 cm^2 contiguous AK treatment area. Secondary objectives were to evaluate the efficacy of PEP005 Gel at above dosages with vehicle gel assessed by baseline clearance rate and complete clearance rate.

Methods: This was a Phase 2b, multicentre, randomised, double-blind, double-dummy, vehicle-controlled, sequential cohort study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 treatment area on the arm, shoulder, chest, back, or scalp. The PEP005 Gel dosage regimens evaluated were 0.025% for three days, 0.05% for two days, and 0.05% for three days. Study medication was patient-applied under supervision at the clinic on Day 1 and at home on Days 2 and 3. Safety and efficacy were assessed at follow-up visits on Days 8, 15, 29, and 57. The primary efficacy endpoint was partial clearance rate; secondary endpoints were baseline clearance rate and complete clearance rate. Patient satisfaction was assessed at Day 57 using a 7-point Likert scale (1 = very negative to 7 = very positive). For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until resolved or assessed as clinically stable.

Statistical Methods: Efficacy analyses were based primarily on the mITT population (i.e., all patients who were dosed and had at least one postbaseline assessment of lesion clearance). The chi-square test was used to analyse partial clearance, complete clearance, and baseline lesion clearance rates at Day 57.

Results: In total, 222 patients were enroled and treated: 60 patients received vehicle gel, 50 patients received 0.025% PEP005 Gel for three days, 55 patients received 0.05% PEP005 Gel for two days, and 57 patients received 0.05% PEP005 Gel for three days. All 222 patients were included in the mITT population. Overall, 97% of patients in the PEP005 Gel groups applied all doses of study medication as instructed.

One hundred sixty-one patients were treated on non-head locations: 43 patients received vehicle gel, 37 patients received 0.025% PEP005 Gel for three days, 42 patients received 0.05% PEP005 Gel for two days, and 39 patients received 0.05% PEP005 Gel for three days.

In the highest PEP005 Gel dose group (0.05% for three days), 85% of patients treated on non-head locations applied all three daily doses, while 97% of patients applied drug for at least two days. In the PEP005 Gel, 0.05% two day group, 93% of patients applied the two daily doses.

Study results are presented by treatment group in the following order: vehicle gel, 0.025% PEP005 Gel for three days, 0.05% PEP005 Gel for two days, and 0.05% PEP005 Gel for three days groups, respectively.

Efficacy

Partial clearance rates were 22%, 56%, 62%, and 75%, respectively ($p \leq 0.0001$ for PEP005 Gel groups compared to vehicle gel). Baseline clearance rates were 13%, 42%, 44%, and 58%, respectively ($p \leq 0.0001$ for PEP005 Gel groups compared to vehicle gel). Complete clearance rates were 12%, 40%, 44%, and 54%, respectively ($p \leq 0.0001$ for PEP005 Gel groups compared to vehicle gel). Median percent reductions in the number of AK lesions were 0%, 75%, 83%, and 100%, respectively ($p \leq 0.0001$ for PEP005 Gel groups compared to vehicle gel).

For patients who received treatment on non-head locations, partial clearance rates by treatment group were 21%, 51%, 67%, and 74%, respectively ($p \leq 0.0001$ for PEP005 Gel groups compared to vehicle gel). Complete clearance rates were 14%, 35%, 45%, and 46%, respectively ($p < 0.006$ for PEP005 Gel groups compared to vehicle gel).

The median overall patient satisfaction score was 7.0 for all three PEP005 Gel treatment groups versus 4.0 for vehicle gel group.

Conclusions: Overall, clearance of AK lesions showed a dose response relationship across PEP005 Gel treatment groups where observed clearance rates increased with increasing dose. Local skin responses also showed a dose response relationship with PEP005 Gel treatment (mean composite LSR score increased with increasing dose) and were transient. Similar study results were observed for the subset of patients who were treated on non-head locations.

2.2.2.2.2 **PEP005-017 (Module 5.3.3.2\PEP005-017)**

Objectives: Primary objective was to evaluate the potential for systemic exposure of ingenol mebutate when applied in a maximal use setting to the dorsal aspect of the forearm in patients with AK (not discussed in this narrative; see Module 2.7.2). Secondary objectives were to evaluate the safety and efficacy of PEP005 Gel, 0.05%.

Methods: This was a Phase 2, single-centre, randomised, double-blind, vehicle-controlled study. Eligible patients were male or female, ≥ 18 years of age, with multiple AK lesions

within a 100 cm^2 contiguous treatment area on the dorsal aspect of one forearm. Patients were randomised to receive PEP005 Gel, 0.05% or vehicle gel in a 4:1 ratio, respectively. Study medication was applied on Days 1 and 2 in the clinic by site staff. Efficacy was assessed in a 25 cm^2 area within the 100 cm^2 treatment area. The entire 100 cm^2 treatment area was evaluated for safety. Safety and efficacy were assessed on Days 2, 3, 8, 15, 29 and 57. Efficacy parameters included complete and partial clearance rates and percent reduction from baseline in the number of AK lesions at Day 57. For patients with unresolved safety concerns at Day 57, follow-up visits were required until resolved or assessed as clinically stable.

Statistical Methods: Efficacy and safety data were summarised descriptively by treatment group. Efficacy analyses were based on the ITT population.

Results: Sixteen patients were enroled and randomised, 13 patients to PEP005 Gel, 0.05% and three patients to vehicle gel. All patients received the scheduled treatment of two consecutive once-daily doses of study medication.

Efficacy

Of the 13 patients treated with PEP005 Gel, 0.05%, 10 patients (77%) achieved complete clearance and 13 (100%) achieved partial clearance. None of the three patients randomised to vehicle gel had complete or partial clearance. Median percent reduction in the number of AK lesions was 100% in the PEP005 Gel, 0.05% group and 0% in the vehicle gel group.

Conclusions: Complete and partial clearance of AK lesions (25 cm^2 area) was observed in 10 out of 13 patients (77%) and 13 out of 13 patients (100%) who received PEP005 Gel, 0.05%, respectively.

2.2.2.3 Uncontrolled Studies

2.2.2.3.1 **PEP005-018 (Module 5.3.5.2\PEP005-018)**

Objectives: Primary objective was to examine the safety and tolerability of PEP005 Gel, 0.05% administered on two consecutive days to a 25 cm^2 contiguous AK treatment area on the dorsum of a single hand. Secondary objective was to examine the efficacy of PEP005 Gel, 0.05% administered as above.

Methods: This was a Phase 2, multicentre, open-label, single-arm, uncontrolled study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the dorsum of one hand. PEP005 Gel, 0.05% was applied topically by a board-certified dermatologist.

Safety and efficacy assessments were conducted on Days 2, 8, 15, 29, and 57. Primary efficacy endpoints included complete clearance rate, partial clearance rate, and baseline clearance rate at the Day 57. For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until the event resolved or was assessed as clinically stable.

Statistical Methods: Efficacy data were summarised descriptively. Efficacy analyses were based on the mITT population (all patients who received at least one dose of study medication and had at least one postbaseline measurement of efficacy).

Results: Eleven patients were enroled and received the scheduled treatment of two consecutive once-daily doses of PEP005 Gel, 0.05%.

Efficacy

At Day 57, the complete clearance rate was 27%, and the partial clearance rate was 46%. Median percent reduction in the number of AK lesions from baseline to Day 57 was 67%. Treatment emergent subclinical lesions were identified in three patients (27%) on Day 57, based on a comparison of the total number of lesions at Day 57 with the lesions identified at baseline.

Conclusions: Complete and partial clearance of AK lesions was observed in 27% and 46% of patients, respectively.

2.2.2.3.2 **PEP005-020 (Module 5.3.5.2\PEP005-020)**

Objectives: Primary objective was to evaluate the safety of PEP005 Gel, 0.05% administered once daily for two consecutive days to a 25 cm^2 contiguous treatment area on non-head locations. Secondary objective was to evaluate the efficacy of PEP005 Gel, 0.05% as administered above.

Methods: This was a Phase 3b, multicentre, open-label, single-arm, uncontrolled study. Eligible patients were male or female, ≥ 18 years of age, with four to eight clinically typical, visible, and discrete AK lesions within a 25 cm^2 contiguous treatment area on the trunk or extremities. PEP005 Gel, 0.05% was applied topically by the patient at home. The primary efficacy endpoint was complete clearance rate of AK lesions at Day 57. The secondary endpoint was partial clearance rate of AK lesions at Day 57; percent reduction from baseline in the number of AK lesions at Day 57 was an additional endpoint. Efficacy assessments were conducted at baseline and Day 57 following treatment. For patients with unresolved safety concerns at Day 57, poststudy follow-up visits were required until resolved or assessed as clinically stable.

Statistical Methods: Efficacy and safety data were summarised descriptively. Efficacy analyses were based primarily on the ITT population.

Results: A total of 102 patients were enroled in the study and all were included in the ITT population. A high percentage of patients (99%) applied study medication once daily for two days. One patient applied only one dose of study medication.

Efficacy

In this open-label study, 39% of patients achieved complete clearance and 55% had partial clearance. Median percent reduction in the number of AK lesions from baseline to Day 57 was 75%.

Conclusions: Complete and partial clearance of AK lesions was observed in 39% and 55% of patients, respectively. The median reduction in the number of AK lesions was 75%.

2.2.2.4 Long-Term Follow-up Studies

2.2.2.4.1 **PEP005-031 (Module 5.3.5.2\PEP005-031)**

Objectives: To summarise treatment area recurrence of AK lesions and long-term safety data, in the selected treatment area, during a 12-month follow-up period for patients who achieved complete clearance of AKs at Day 57 in open-label study PEP005-020.

Methods: This was a prospective, longitudinal, follow-up study in patients who achieved complete clearance at Day 57 in study PEP005-020. No study medication was administered during the study. The original protocol dated 01 Jul 2009, allowed for eligibility criteria to include patients if they completed the Day 57 visit. With implementation of Amendment #1, dated 30 Sep 2009, eligibility was modified to include only patients who achieved complete clearance at Day 57. Therefore patients who had not achieved complete clearance at Day 57 but were already enroled at the time Amendment #1 was implemented were terminated from the study at the next regularly scheduled study visit or sooner, if feasible.

Patients returned to the study clinic for follow-up visits at Months 3, 6, 9, and 12 after the Day 57 visit in study PEP005-020. Information was collected for all patients on AEs in the selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. The number of AK lesions in the selected treatment area was counted at each visit. Recurrence was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study (PEP005-020).

Statistical Methods: The recurrence of AK was analysed for the population of patients who had complete clearance at Day 57 of the previous Phase 3 study (PEP005-020). Kaplan-Meier estimates were used for time to event analyses. At each visit, the number of patients showing AK recurrence during the visit window, the number of patients censored during the visit window, and the number of patients at risk during the visit window were presented. AK recurrence rates based on baseline lesion counts (obtained at the baseline visit from study PEP005-020) were determined. For this analysis, to account for treatment of recurrent AK lesions within the treatment area (between follow-up visits), the lesion count at a follow-up visit was carried forward in the event that subsequent lesion counts were zero.

Results: The population of interest was patients with complete clearance at Day 57 of the previous study. For this population, a total of 38 patients previously treated with PEP005 Gel from the open-label study (PEP005-020) were enroled. Four patients (11%) prematurely discontinued.

AK Recurrence

At 12 months of follow-up, 63% of patients treated with PEP005 Gel in study PEP005-020 had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 274 days. Based on the number of lesions observed within the treatment area during 12 months of follow-up relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 study), the mean lesion-based recurrence rate was 11%.

Conclusions: During 12 months of follow-up, 63% of patients had a new or recurrent AK lesion within the treatment area, with a median time to recurrence of 274 days. Relative to the total number of AK lesions at baseline in study PEP005-020, the lesion recurrence rate at 12 months was 11%.

2.2.2.4.2 **PEP005-032 (Module 5.3.5.2\PEP005-032)**

Objectives: To summarise treatment area recurrence of AK lesions and long-term safety data, in the selected treatment area, during a 12-month follow-up period for patients who achieved complete clearance of AKs at Day 57 in study PEP005-028.

Methods: This was a prospective, longitudinal, follow-up study in patients who achieved complete clearance at Day 57 in study PEP005-028. No study medication was administered during the study.

Patients returned to the study clinic for follow-up visits at Months 3, 6, 9, and 12 after the Day 57 visit in study PEP005-028. Information was collected for all patients on AEs in the

selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. The number of AK lesions in the selected treatment area was counted at each visit. Recurrence was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study (PEP005-028). The double-blind status of patients who were treated in PEP005-028 was maintained until completion of PEP005-032.

Statistical Methods: The recurrence of AK was analysed for the population of patients who had complete clearance at Day 57 of the previous Phase 3 study (PEP005-028). Kaplan-Meier estimates were used for time to event analyses. At each visit, the number of patients showing AK recurrence during the visit window, the number of patients censored during the visit window, and the number of patients at risk during the visit window were presented. AK recurrence rates based on baseline lesion counts (obtained at the baseline visit from study PEP005-028) were determined. For this analysis, to account for treatment of recurrent AK lesions within the treatment area (between follow-up visits), the lesion count at a follow-up visit was carried forward in the event that subsequent lesion counts were zero.

Results: The population of interest was patients with complete clearance at Day 57 of the previous study. For this population, a total of 38 patients from the previous PEP005 Gel treatment group and five patients from the previous vehicle gel group from study PEP005-028 were enroled. One (3%) PEP005 Gel-treated patient prematurely discontinued.

AK Recurrence

At 12 months of follow-up, 50% of patients who had been treated with PEP005 Gel in the previous Phase 3 study, had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was >183 days. Based on the number of lesions observed within the treatment area during 12 months of follow-up relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 study), the mean lesion-based recurrence rate was 15%.

At 12 months of follow-up, 80% of vehicle-treated patients had a new or recurrent AK lesion, with a median time to recurrence of 183 days. For this group of patients, the mean lesion-based recurrence rate at 12 months was 19%.

Conclusions: During 12 months of follow-up, 50% of patients previously treated with PEP005 Gel had at least one new or recurrent AK lesion within the treatment area; the median time to recurrence was >183 days. Relative to the total number of AK lesions observed at baseline in study PEP005-028, the lesion recurrence rate at 12 months was 15% for patients previously treated with PEP005 Gel.

2.2.2.5 Small Field Treatment (9 cm^2) Study

2.2.2.5.1 PEP005-004 (Module 5.3.5.2\PEP005-004)

Objectives: Primary objective was to determine the maximum tolerated dose for PEP005 Gel applied once daily for two consecutive days to a 9 cm^2 field surrounding a target AK lesion. Secondary objectives were to: (1) evaluate the clinical efficacy of PEP005 Gel as assessed by complete clinical response and (2) determine the systemic absorption of PEP005 Gel following application once daily for two consecutive days (not discussed in this narrative; see Module 2.7.2).

Methods: This was a Phase 2a, single-centre, open-label, nonrandomised, uncontrolled, dose-escalation cohort study. Eligible patients were male or female, ≥ 18 years of age, with one AK lesion with a diameter between 3 mm and 15 mm on the shoulders, chest, back, or arms. PEP005 Gel 0.01%, 0.025%, 0.05%, or 0.075% was applied at the study site by a licensed medical practitioner. Safety and efficacy were assessed at follow-up visits on Days 1, 2, 8, 15, and 29. Maximum tolerated dose was the primary endpoint. Clinical response was assessed as extent of clearance of the treated AK lesion compared to baseline using a 6 point scale as follows: complete clearance, marked clearance (50-90% improvement), slight clearance (10-50% improvement), unchanged (±10%), worsened (clinically observable growth), or unable to be assessed (e.g., heavy scabbing, bruising, trauma, inflammatory response). If local skin AEs were present at Day 29, follow-up visits were required until resolution of the event.

Statistical Methods: Efficacy and safety data were summarised descriptively by treatment group. Clinical response was reported for patients who met screening eligibility, received at least one dose of study medication, and had at least one postbaseline measurement of efficacy. Safety analyses included all patients who met screening eligibility and received at least one dose of study medication.

Results: Twenty-two patients were enroled and treated, three patients received 0.01% PEP005 Gel, three patients received 0.025% PEP005 Gel, 10 patients received 0.05% PEP005 Gel, and six patients received 0.075% PEP005 Gel. All patients received the scheduled treatment of two consecutive once-daily doses of study medication.

Efficacy

Complete clearance of the treated AK lesion at Day 29 was reported in two (67%) patients in the 0.01% PEP005 Gel cohort, one (33%) patient in the 0.025% PEP005 Gel cohort, six (60%) patients in the 0.05% PEP005 Gel cohort, and three (50%) patients in the 0.075%

PEP005 Gel cohort. Marked clearance was reported in two (20%) patients in the 0.05% PEP005 Gel cohort and two (33%) patients in the 0.075% PEP005 Gel cohort.

Conclusions: The MTD of 0.05% PEP005 Gel administered once daily for two consecutive days appeared to be a safe and effective treatment for clearance of AK lesions.

2.2.2.6 Lesion-Specific Treatment Studies

2.2.2.6.1 **AGN204332-004 (Module 5.3.5.1\AGN204332-004)**

Objectives: To determine the safety of 0.01% PEP005 Gel after a single application to AK lesions on the shoulders, chest, back and/or arms.

Methods: This was a Phase 1, multicentre, randomised, double-blind, parallel group, vehicle-controlled study. Eligible patients were male or female, ≥ 18 years of age, with at least five individual AK lesions on the shoulders, chest, back, and/or arms. Study drug (0.01% PEP005 Gel or vehicle gel) was applied to each of five AK lesions by a licensed physician or trained personnel at the study site. Safety and efficacy were assessed at follow-up visits. Efficacy was assessed using an 8-point global response to treatment scale ranging from 0 (completely cleared) to 8 (unable to determine due to inflammatory response), based on the investigator's visual assessment of each lesion compared with the lesion at the baseline visit (using the photographs taken at baseline as a reference). Blood samples for PK testing were collected from consenting patients at selected sites on the day of treatment prior to and approximately 3 to 9 hours after treatment application (see Module 2.7.2).

Statistical Methods: Efficacy and safety data were summarised descriptively by treatment group. Efficacy analyses were based on the ITT population. Safety analyses included all patients who received at least one dose of study medication.

Results: Sixteen patients were enroled and treated, 11 patients received 0.01% PEP005 Gel and five patients received vehicle gel. All patients received the scheduled single application of study treatment.

Efficacy

A total of 80 AK lesions were treated (55 with 0.01% PEP005 Gel; 25 with vehicle gel). In the 0.01% PEP005 Gel group, complete clearance was reported for 8 lesions (15%) at Day 14 and 16 lesions (29%) at last available follow-up (i.e., Day 14 or Day 21). In addition, six lesions were classified as almost cleared (≥ 90% clearance) at last available follow-up. The combined rate of almost and complete clearance at last follow-up for lesions treated with 0.01% PEP005 Gel was 40%. In the vehicle gel group, complete clearance was reported for

10% of lesions at Day 14 (no Day 14 data was available for one patient with five lesions; no patients had follow-up data after Day 14). The combined rate of almost and complete clearance for lesions treated with vehicle gel was 15%. In the 0.01% PEP005 Gel group, complete clearance of all five lesions was reported for one patient; another patient had complete clearance in four out of five treated lesions. In the vehicle group, no patient had complete clearance of all five lesions.

Conclusions: Clinical response to 0.01% PEP005 Gel was observed, notably in patients with > 14-day follow-up.

2.2.2.6.2 **PEP005-001 (Module 5.3.5.1\PEP005-001)**

Study PEP005-001 is relevant to the efficacy of both head and non-head locations. The narrative description is provided in Section 2.1.2.5.1.

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1 STUDIES INCLUDED FOR COMPARISON AND ANALYSES

3.1.1 Head (Face and Scalp) Locations

For the head locations, five studies (PEP005-016, PEP005-025, PEP005-015, PEP005-006, and PEP005-007) which provide efficacy data for field treatment of PEP005 Gel to a defined 25 cm^2 area of skin containing four to eight AK lesions are included in the comparison and analyses of efficacy results. Of these five studies, three were selected to be included in the populations of combined studies (PEP005-016, PEP005-025, and PEP005-015). Data from all five studies are provided in supporting summary tables in Module 5.3.5.3. Efficacy results are summarised for the ITT population (all randomised patients) unless specified otherwise.

The rationale for selecting these three studies for inclusion in the populations of combined studies is based on the similarity of design across studies as it relates to the study population, selected treatment area, dose and treatment regimen, and endpoint for assessing efficacy following treatment. These three studies were double-blind, vehicle-controlled, parallel group studies. For all three studies, study medication was patient-applied at home to a contiguous 25 cm^2 treatment area and a 57-day endpoint was used for efficacy evaluation. PEP005-016 and PEP005-025 evaluated the proposed dosage regimen for approval of PEP005 Gel for treatment of the head locations, i.e., 0.015% applied for three consecutive days (Days 1, 2, and 3). PEP005-015 was a dose-ranging study that included the proposed dosage regimen for approval of PEP005 Gel.

Reasons for not selecting the other two studies for inclusion in the populations of combined studies are as follows:

- PEP005-006 was a double-blind, parallel group, vehicle-controlled study. The proposed dosage regimen for treatment of the head locations (PEP005 Gel, 0.015% applied topically once daily for three consecutive days) was not investigated in PEP005-006. See Section 2.1.2.2.1 for efficacy information.
- PEP005-007 was an uncontrolled, open-label, dose-escalation study. The proposed dosage regimen for treatment of the head locations (PEP005 Gel, 0.015% applied topically once daily for three consecutive days) was not investigated in PEP005-007. See Section 2.1.2.3.1 for efficacy information.

It was also decided that two populations of combined studies were important for comparison and analysis of efficacy results. These populations are as follows:

- The two controlled Phase 3 studies (PEP005-016 and PEP005-025).
- The controlled Phase 2 and Phase 3 studies (PEP005-015, PEP005-016, and PEP005-025). In this population, for study PEP005-015 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.015% three day) and the corresponding vehicle gel three day group were included.

The studies were evaluated as combined populations in order to better: (1) estimate the clearance rate for PEP005 Gel, 0.015% and (2) investigate factors related to clearance rate for PEP005 Gel, 0.015% with larger sample sizes than provided in the individual studies. The studies for the first combined population (PEP005-016 and PEP005-025) had identical study designs. The studies for the second population were similar in terms of the dosage regimen of PEP005 Gel used, size of the treatment area, duration of follow-up, the type of efficacy data collected, and the type of patients treated. Efficacy data for each of the combined studies populations were summarised by treatment group.

For this efficacy summary, the Statistical Analysis Plan (SAP) for the head (face and scalp) locations, dated 03 Nov 2009, is provided in Module 5.3.5.3. Changes to the planned analyses are described in the text of this efficacy summary, when applicable.

Although the SAP stated no inferential analyses were to be performed to compare efficacy results across treatment groups in the combined studies populations, it was subsequently decided that these analyses should be performed for the combined Phase 3 studies population for complete and partial clearance. These analyses were performed for completeness and to confirm the consistency and significance of the results of the individual studies.

3.1.2 Non-Head (Trunk and Extremities) Locations

For the non-head locations, six studies (PEP005-014, PEP005-028, PEP005-006, PEP005-018, PEP005-020, and PEP005-017) which provide efficacy data for field treatment of PEP005 Gel to an area of skin containing four to eight AK lesions are included in the comparison and analyses of efficacy results. Of these six studies, five were selected to be included in the populations of combined studies (PEP005-014, PEP005-028, PEP005-006, PEP005-018, and PEP005-020). Data from all six studies are provided in supporting summary tables in Module 5.3.5.3. Efficacy results are summarised for the ITT population (all randomised patients for studies PEP005-014, PEP005-028, and PEP005-006; all patients

enroled and dispensed medication for studies PEP005-020 and PEP005-018) unless specified otherwise.

The rationale for selecting these five studies for inclusion in the populations of combined studies is based on the similarity of design across studies as it relates to the study population, selected treatment area, dose and treatment regimen, and endpoint for assessing efficacy following treatment. For all five studies, study medication was patient-applied at home to a contiguous 25 cm^2 treatment area and a 57-day endpoint was used for efficacy evaluation. Three of the five studies were double-blind, vehicle-controlled, parallel group studies (PEP005-014, PEP005-028, and PEP005-006). PEP005-014 and PEP005-028 evaluated the proposed dosage regimen for treatment of the non-head locations, i.e., PEP005 Gel, 0.05% applied for two consecutive days. PEP005-006 was a dose-ranging study that included the proposed dosage regimen for PEP005 Gel. The other two studies (PEP005-018 and PEP005-020) were open-label, uncontrolled, single arm studies which investigated the proposed dosage regimen for PEP005 Gel, and had a 57 day efficacy assessment. In PEP005-018, the treatment area was on back of hand only. The open-label studies were conducted in similar geographic locations and similar time frames as the controlled studies. In all five studies except PEP005-006, study medication was applied once daily on Day 1 and Day 2 of the study. In PEP005-006, which had a double-blind, double-dummy design, study medication was applied once daily for three consecutive days. In the PEP005 Gel, 0.05% two day group, vehicle gel was applied on Day 1 and PEP005 Gel, 0.05% was applied on Day 2 and Day 3. PEP005-006 included patients with AK lesions on the scalp as well as non-head locations. Only patients with AK lesions on non-scalp locations are included in the integrated tables and listings for this section.

The other study was not selected as a study of interest (PEP005-017) because it was a single-centre, PK study and study drug was applied to a 100 cm^2 treatment area. See Section 2.2.2.2.2 for efficacy information.

It was also decided that three populations of combined studies were important for comparison and analysis of efficacy results. These populations are as follows:

- The two controlled Phase 3 studies (PEP005-014 and PEP005-028).
- The controlled Phase 2 and Phase 3 studies (PEP005-006, PEP005-014, and PEP005-028). In this population, for study PEP005-006 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included.

- The controlled and uncontrolled Phase 2 and Phase 3 studies (PEP005-006, PEP005-014, PEP005-028, PEP005-018, and PEP005-020). In this population, for study PEP005-006 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included.

The studies were evaluated as combined populations in order to better: (1) estimate the clearance rate for PEP005 Gel, 0.05% and (2) investigate factors related to clearance rate for PEP005 Gel, 0.05% with larger sample sizes than provided in the individual studies. The studies for the first combined population (PEP005-014 and PEP005-028) had identical study designs. Although there were differences among studies combined for the other two populations, particularly with regard to control and blinding in the third population, the studies were similar in terms of PEP005 Gel dosage regimen, size of the treatment area, duration of follow-up, type of efficacy data collected, and type of patients treated. Efficacy data for each of the combined studies populations were summarised by treatment group.

For this efficacy summary, the SAP for the non-head (trunk and extremities) locations, dated 03 Nov 2009, is provided in Module 5.3.5.3. Changes to the planned analyses are described in the text of this efficacy summary, when applicable.

Although the SAP stated no inferential analyses were to be performed to compare efficacy results across treatment groups in the combined studies populations, it was subsequently decided that these analyses should be performed for the combined Phase 3 studies population for complete and partial clearance. These analyses were performed for completeness and to confirm the consistency and significance of the results of the individual studies.

3.2 STUDY POPULATION

3.2.1 Head (Face and Scalp) Locations

3.2.1.1 Patient Disposition of Head (Face and Scalp) Locations

Patient disposition for individual studies of interest is summarised in Table 3. Patient disposition for the combined studies populations is summarised in Table 4.

For studies PEP005-016 and PEP005-025, a high percentage of randomised patients completed the study as specified in the protocol at Day 57 (96% and 99%, respectively). Study PEP005-015 also had a high percentage of patients (98%) who completed the study at Day 57. Two patients in PEP005-016 who were randomised to PEP005 Gel withdrew consent and never applied study medication; both are included in the ITT population.

The combined study populations reflect the high percentage of completed patients. For the combined Phase 3 studies, only three PEP005 Gel patients (1%) discontinued. Two patients withdrew consent prior to applying study medication and each terminated on Day 4. The third patient applied all three doses of study medication and experienced treatment-related AEs (application site pain/eye pain/periorbital oedema) that resolved by Day 11 but led to termination on Day 29. Eight vehicle gel patients (3%) discontinued (six due to patient decision, one due to abnormal lab test/adverse event, and one due to protocol deviation).

Treatment compliance for the combined Phase 3 studies was also high; only five PEP005 Gel-treated patients did not apply all three doses of study medication. (These five patients did complete the study.) In PEP005-016, two patients applied study medication for one day and one patient applied medication for two days. In PEP005-025, one patient applied study medication for one day and one patient applied study medication for two days. Thus, including the two patients in PEP005-016 who withdrew consent and never applied study medication, in the combined Phase 3 studies, seven patients (3%) were not compliant with the three day treatment regimen.

When the combined Phase 2 and 3 studies were assessed for treatment compliance, 12 patients (4%) were not compliant (five patients in PEP005-015 did not apply all three doses of study medication but did complete the study). See Modules 5.3.5.1\PEP005-016, 5.3.5.1\PEP005-025, and 5.3.5.1\PEP005-015 for details concerning premature discontinuations and exposure data on these three studies.

Patient disposition for studies PEP005-006 and PEP005-007 is presented in Module 5.3.5.3, Tables 1.1 and 1.2, respectively. Across these two studies, all patients completed except two in PEP005-007 (one was lost to follow-up and the other withdrew consent). See Modules 5.3.5.1\PEP005-006 and 5.3.5.2\PEP005-007 for details concerning premature discontinuations and exposure data on these two studies.

For studies PEP005-015, PEP005-006, and PEP005-007, patients who participated in one PEP005 study were allowed to participate in a subsequent PEP005 study as long as the treatment areas did not overlap. For studies PEP005-016 and PEP005-025, patients who previously received PEP005 Gel were not eligible to participate. Patients who received treatment with PEP005 Gel in more than one clinical study are presented in Module 5.3.5.3, Table 1.8. Across the studies conducted for treatment of the head locations, 29 patients received treatment with PEP005 Gel in two clinical studies. Of these 29 patients, five received field treatment on the same anatomical location but none of the five were treated in

the same selected treatment area. Additionally, none of five patients received the proposed dosage regimen (0.015% applied daily for three consecutive days) in both studies. Thus, the impact on the efficacy analyses is minimal.

Table 3: Patient Disposition in Individual Studies of Interest: Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		PEP005-015							
					Two Day Dosing				Three Day Dosing			
	PEP005, 0.015% (N=135)	Vehicle (N=134)	PEP005, 0.015% (N=142)	Vehicle (N=136)	PEP005, 0.005% (N=33)	PEP005, 0.01% (N=34)	PEP005, 0.015% (N=33)	Vehicle (N=33)	PEP005, 0.005% (N=33)	PEP005, 0.01% (N=34)	PEP005, 0.015% (N=32)	Vehicle (N=33)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Enroled/randomised (ITT)	135 (100)	134 (100)	142 (100)	136 (100)	33 (100)	34 (100)	33 (100)	33 (100)	33 (100)	34 (100)	32 (100) 33	(100)
Received at least 1 dose of study medication (Safety Population)	133 (98.5)	134 (100)	142 (100)	136 (100)	32 (97.0)	34 (100)	33 (100)	33 (100)	33 (100)	34 (100)	32 (100)	33 (100)
Discontinued early from study	3 (2.2)	7 (5.2)	0	1 (0.7)	1 (3.0)	0	0	2 (6.1)	2 (6.1)	0	0	0
Reason for discontinuation												
Abnormal Lab Test/ Adverse event	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (3.0)	0	0	0
Consent Withdrawn/ Subject Decision	2 (1.5)	5 (3.7)	0	1 (0.7)	0	0	0	1 (3.0)	1 (3.0)	0	0	0
Protocol Deviation/ Violation	0	1 (0.7)	0	0	0 0		0	0	0 0 0 0			
Other	0	0	0	0	1 (3.0)	0	0	1 (3.0)	0	0	0	0

ITT = intent-to-treat

All study medication was administered once-daily for three consecutive days on Days 1, 2 and 3 in PEP005-016 and PEP005-025.

Source: Module 5.3.5.3, Tables 1.3, 1.4 and 1.5

Table 4: Patient Disposition in Combined Studies Populations: Head (Face and Scalp) Locations

	Controlled Phase 3 Studies[a]		**Controlled Phase 2 and 3 Studies[b]**	
	PEP005, 0.015% (N=277)	**Vehicle (N=270)**	**PEP005, 0.015% (N=309)**	**Vehicle (N=303)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Enroled/randomised (ITT)	277 (100)	270 (100)	309 (100)	303 (100)
Received at least 1 dose of study medication (Safety Population)	275 (99.3)	270 (100)	307 (99.4)	303 (100)
Discontinued early from study	3 (1.1)	8 (3.0)	3 (1.0)	8 (2.6)
Reason for discontinuation				
Abnormal Lab Test/ Adverse event	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Consent Withdrawn/ Subject Decision	2 (0.7)	6 (2.2)	2 (0.6)	6 (2.0)
Protocol Deviation / Violation	0	1 (0.4)	0	1 (0.3)
Other 0		0	0	0

ITT = intent-to-treat

[a] Controlled Phase 3 studies (PEP005-016 and PEP005-025)

[b] Controlled Phase 2 and 3 studies (PEP005-015, PEP005-016, and PEP005-025); for study PEP005-015 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.015% three day) and the corresponding vehicle gel three day group were included.

Source: Module 5.3.5.3, Tables 1.6 and 1.7

3.2.1.2 Patient Demographics of Head (Face and Scalp) Locations

Patient demographics in individual studies of interest are summarised in Table 5. Patient demographics in the combined studies populations are summarised in Table 6.

For demography, although the SAP (Module 5.3.5.3) indicated that age categories of ≤65 and >65 years would be summarised, categories of <65, ≥65 to ≤75, and >75 years were summarised to be consistent with regulatory recommendations.

For individual studies PEP005-016, PEP005-025, and PEP005-015, patient demographics were similar. Most patients were located in the United States (range across all treatment group in the three studies: 78-94%), the majority were male (range: 82-97%), mean age ranged from 63.0-68.8 years, and all patients were white.

The main eligibility criteria included four to eight clinically typical, visible, and discrete AK lesions within a contiguous 25 cm^2 treatment area on the face or scalp. In addition, the location of the selected treatment area could not be within 5 cm of an incompletely healed wound or within 10 cm of a suspected BCC or SCC. Patients were not allowed to have been previously treated with PEP005 Gel, treatment area lesions were not allowed to have an atypical clinical appearance (e.g., hypertrophic, hyperkeratotic, recalcitrant disease [had cryosurgery on two previous occasions] and/or cutaneous horns), and evidence of skin conditions other than the study indication that would interfere with evaluation of the study medication (e.g., eczema, unstable psoriasis, xeroderma pigmentosum) were not allowed. Exclusion criteria also stipulated restrictions for prohibited treatments and procedures prior to study entry. Across these three studies, > 90% of the patients met the inclusion and exclusion criteria. This patient sample is representative of the population which will use PEP005 Gel.(54)

The combined studies populations reflect these findings. For the combined Phase 3 studies, 92% of the PEP005 Gel and 93% of the vehicle gel patients were located in the US. In the PEP005 Gel and vehicle gel groups, 84% and 86% were male, respectively. Mean age was 64.2 years in the PEP005 Gel group and 64.0 years in the vehicle gel group. The controlled Phase 2 and 3 study population showed similar results. No apparent differences in demographic characteristics were seen across the treatment groups.

For studies PEP005-006 and PEP005-007, demographics are presented in Module 5.3.5.3, Tables 2.1 and 2.2, respectively. Study PEP005-007 was conducted in Australia and study

PEP005-006 was conducted in the US. The majority of patients were male (range across all treatment group in the two studies: 56-100%), mean age ranged from 53.3-76.9 years, and all patients were white.

Table 5: Patient Demographics in Individual Studies of Interest: Intent-to-treat Population, Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		PEP005-015							
					Two Day Dosing				Three Day Dosing			
Parameter	PEP005, 0.015% (N=135)	Vehicle (N=134)	PEP005, 0.015% (N=142)	Vehicle (N=136)	PEP005, 0.005% (N=33)	PEP005, 0.01% (N=34)	PEP005, 0.015% (N=33)	Vehicle (N=33)	PEP005, 0.005% (N=33)	PEP005, 0.01% (N=34)	PEP005, 0.015% (N=32)	Vehicle (N=33)
Geographic region (n [%])												
United States	125 (92.6)	126 (94.0)	131 (92.3)	124 (91.2)	30 (90.9)	29 (85.3)	31 (93.9)	29 (87.9)	29 (87.9)	31 (91.2)	25 (78.1)	28 (84.8)
Australia	10 (7.4)	8 (6.0)	11 (7.7)	12 (8.8)	3 (9.1)	5 (14.7)	2 (6.1)	4 (12.1)	4 (12.1)	3 (8.8)	7 (21.9)	5 (15.2)
Age (years)												
n	135	134	142	136	33	34	33	33	33	34	32	33
Mean (SD)	63.5 (10.5)	63.0 (10.0)	64.8 (11.2)	65.0 (10.1)	65.7 (10.3)	67.1 (10.5)	67.3 (7.0)	64.7 (9.7)	68.2 (11.0)	67.2 (9.0)	66.8 (10.1)	68.8 (10.7)
Minimum, Maximum	37-88	40-85	34-88	46-89	49-85	47-87	56-80	46-85	45-90	50-85	48-85	51-90
Age categories (years) (n [%])												
<65 years	71 (52.6)	77 (57.5)	73 (51.4)	63 (46.3)	16 (48.5)	13 (38.2)	16 (48.5)	18 (54.5)	11 (33.3)	13 (38.2)	13 (40.6)	11 (33.3)
65-75 years	47 (34.8)	39 (29.1)	36 (25.4)	49 (36.0)	8 (24.2)	14 (41.2)	14 (42.4)	9 (27.3)	15 (45.5)	15 (44.1)	11 (34.4)	14 (42.4)
>75 years	17 (12.6)	18 (13.4)	33 (23.2)	24 (17.6)	9 (27.3)	7 (20.6)	3 (9.1)	6 (18.2)	7 (21.2)	6 (17.6)	8 (25.0)	8 (24.2)
Sex (n [%])												
Male	116 (85.9)	120 (89.6)	117 (82.4)	112 (82.4)	30 (90.9)	32 (94.1)	32 (97.0)	29 (87.9)	27 (81.8)	31 (91.2)	28 (87.5)	28 (84.8)
Female	19 (14.1)	14 (10.4)	25 (17.6)	24 (17.6)	3 (9.1)	2 (5.9)	1 (3.0)	4 (12.1)	6 (18.2)	3 (8.8)	4 (12.5)	5 (15.2)
Race (n [%])												
White	135 (100)	134 (100)	142 (100)	136 (100)	33 (100)	34 (100)	33 (100)	33 (100)	33 (100)	34 (100)	32 (100)	33 (100)
Ethnicity (n [%])												
Non-Hispanic	135 (100)	132 (98.5)	141 (99.3)	135 (99.3)	33 (100)	34 (100)	33 (100)	33 (100)	33 (100)	34 (100)	31 (96.9)	33 (100)
Hispanic	0	2 (1.5)	1 (0.7)	1 (0.7)	0	0	0	0	0	0	1 (3.1)	0

SD = standard deviation

All study medication was administered once-daily for three consecutive days on Days 1, 2 and 3 in PEP005-016 and PEP005-025.

Source: Module 5.3.5.3, Tables 2.3, 2.4 and 2.5

Table 6: Patient Demographics in Combined Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

Parameter	Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
	PEP005, 0.015% (N=277)	Vehicle (N=270)	PEP005, 0.015% (N=309)	Vehicle (N=303)
Geographic region (n [%])				
United States	256 (92.4)	250 (92.6)	281 (90.9)	278 (91.7)
Australia	21 (7.6)	20 (7.4)	28 (9.1)	25 (8.3)
Age (years)				
n	277 2	70	309 3	03
Mean (SD)	64.2 (10.8)	64.0 (10.1)	64.4 (10.8)	64.6 (10.3)
Minimum, Maximum	34-88	40-89 34	-88 40	-90
Age categories (years) (n [%])				
<65 years	144 (52.0)	140 (51.9)	157 (50.8)	151 (49.8)
65-75 years	83 (30.0)	88 (32.6)	94 (30.4)	102 (33.7)
>75 years	50 (18.1)	42 (15.6)	58 (18.8)	50 (16.5)
Sex (n [%])				
Male	233 (84.1)	232 (85.9)	261 (84.5)	260 (85.8)
Female	44 (15.9)	38 (14.1)	48 (15.5)	43 (14.2)
Race (n [%])				
White	277 (100)	270 (100)	309 (100)	303 (100)
Ethnicity (n [%])				
Non-Hispanic	276 (99.6)	267 (98.9)	307 (99.4)	300 (99.0)
Hispanic	1 (0.4)	3 (1.1)	2 (0.6)	3 (1.0)

SD = standard deviation

[a] Controlled Phase 3 studies (PEP005-016 and PEP005-025)

[b] Controlled Phase 2 and 3 studies (PEP005-015, PEP005-016, and PEP005-025); for study PEP005-015 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.015% three day) and the corresponding vehicle gel three day group were included.

Source: Module 5.3.5.3, Tables 2.6 and 2.7

3.2.1.3 Baseline Disease Characteristics of Head (Face and Scalp) Locations

Baseline disease characteristics of patients in individual studies of interest are summarised in Table 7. Baseline disease characteristics of patients in the combined studies populations are summarised in Table 8.

For individual studies PEP005-016, PEP005-025, and PEP005-015, baseline disease characteristics were similar across the treatment groups of the three studies. Most patients received treatment on the face (range across all treatment groups in the 3 studies: 73-82%), the majority had Fitzpatrick skin type I, II or III (range: 88-96%), and most had four to six lesions at baseline (range: 62-83%). A positive history of skin cancer was documented for approximately 50% of patients (range: 29-64%). Approximately 80% received prior treatment with cryotherapy (range: 73-94%), approximately 15% received prior imiquimod (range: 5-36%), and approximately 20% received prior 5-FU (range: 12-27%).

The combined studies populations showed consistency with the individual studies. For the combined Phase 3 studies, 79% and 82% of the PEP005 Gel and vehicle gel patients, respectively, received treatment on the face. In the PEP005 Gel and vehicle gel groups, 93% and 95% had Fitzpatrick skin type I, II, or III. The baseline lesion count was four to six in 65% of PEP005 Gel patients and 74% of vehicle gel patients. A history of skin cancer was present in 46% of PEP005 Gel patients and 44% of vehicle gel patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 81% and 84%; imiquimod: 9% and 12%; 5-FU: 20% and 19%, respectively). Results for the combined Phase 2 and 3 studies were similar. Across the treatment groups, no apparent differences were seen for baseline disease characteristics.

For studies PEP005-006 and PEP005-007, baseline characteristics are presented in Module 5.3.5.3, Tables 2.1 and 2.2, respectively. In PEP005-007, the majority of patients (78%) received treatment on the face. In study PEP005-006, scalp was the only head location allowed to be treated. Fitzpatrick skin type was I, II or III for the majority of patients (range across all treatment groups in the two studies: 76-100%), most had four to six lesions at baseline (50-100%), and 39-100% had a positive history of skin cancer. Prior treatment with cryotherapy was seen in 72-100% of patients, prior imiquimod use was reported in 8-50% of patients, and prior 5 FU use was reported in 6-67%.

Table 7: Baseline Disease Characteristics in Individual Studies of Interest: Intent-to-treat Population, Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		PEP005-015							
					Two Day Dosing				Three Day Dosing			
	PEP005, 0.015% (N=135)	Vehicle (N=134)	PEP005, 0.015% (N=142)	Vehicle (N=136)	PEP005, 0.005% (N=33)	PEP005, 0.01% (N=34)	PEP005, 0.015% (N=33)	Vehicle (N=33)	PEP005, 0.005% (N=33)	PEP005, 0.01% (N=34)	PEP005, 0.015% (N=32)	Vehicle (N=33)
Parameter	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Anatomical location												
Face	109 (80.7)	109 (81.3)	111 (78.2)	111 (81.6)	24 (72.7)	27 (79.4)	26 (78.8)	26 (78.8)	26 (78.8)	26 (76.5)	24 (75.0)	25 (75.8)
Scalp	26 (19.3)	25 (18.7)	31 (21.8)	25 (18.4)	9 (27.3)	7 (20.6)	7 (21.2)	7 (21.2)	7 (21.2)	8 (23.5)	8 (25.0)	8 (24.2)
Fitzpatrick skin type												
I	24 (17.8)	16 (11.9)	27 (19.0)	18 (13.2)	9 (27.3)	6 (17.6)	4 (12.1)	9 (27.3)	7 (21.2)	7 (20.6)	9 (28.1)	3 (9.1)
II	58 (43.0)	53 (39.6)	65 (45.8)	59 (43.4)	11 (33.3)	18 (52.9)	16 (48.5)	8 (24.2)	10 (30.3)	12 (35.3)	14 (43.8)	14 (42.4)
III	44 (32.6)	59 (44.0)	40 (28.2)	52 (38.2)	9 (27.3)	6 (17.6)	9 (27.3)	14 (42.4)	13 (39.4)	11 (32.4)	6 (18.8)	12 (36.4)
IV	9 (6.7)	6 (4.5)	10 (7.0)	7 (5.1)	4 (12.1)	4 (11.8)	3 (9.1)	2 (6.1)	2 (6.1)	4 (11.8)	3 (9.4)	4 (12.1)
V	0 0		0 0		0	0	1 (3.0)	0	1 (3.0)	0	0	0
Baseline lesion count												
4	27 (20.0)	32 (23.9)	21 (14.8)	25 (18.4)	7 (21.2)	6 (17.6)	7 (21.2)	5 (15.2)	3 (9.1)	7 (20.6)	10 (31.3)	9 (27.3)
5	36 (26.7)	44 (32.8)	39 (27.5)	35 (25.7)	9 (27.3)	12 (35.3)	11 (33.3)	11 (33.3)	12 (36.4)	10 (29.4)	6 (18.8)	8 (24.2)
6	28 (20.7)	35 (26.1)	28 (19.7)	29 (21.3)	10 (30.3)	6 (17.6)	7 (21.2)	8 (24.2)	8 (24.2)	11 (32.4)	8 (25.0)	9 (27.3)
7	27 (20.0)	15 (11.2)	27 (19.0)	21 (15.4)	5 (15.2)	7 (20.6)	5 (15.2)	4 (12.1)	4 (12.1)	2 (5.9)	5 (15.6)	5 (15.2)
8	17 (12.6)	8 (6.0)	27 (19.0)	26 (19.1)	2 (6.1)	3 (8.8)	3 (9.1)	5 (15.2)	6 (18.2)	4 (11.8)	3 (9.4)	2 (6.1)
Skin cancer history	65 (48.1)	63 (47.0)	61 (43.0)	57 (41.9)	14 (42.4)	20 (58.8)	16 (48.5)	21 (63.6)	16 (48.5)	10 (29.4)	16 (50.0)	16 (48.5)
Prior treatment												
Cryotherapy	112 (83.0)	108 (80.6)	112 (78.9)	119 (87.5)	28 (84.8)	32 (94.1)	24 (72.7)	26 (78.8)	26 (78.8)	25 (73.5)	26 (81.3)	26 (78.8)
Imiquimod	7 (5.2)	15 (11.2)	18 (12.7)	16 (11.8)	11 (33.3)	10 (29.4)	7 (21.2)	10 (30.3)	9 (27.3)	5 (14.7)	8 (25.0)	12 (36.4)
5-Fluorouracil	26 (19.3)	25 (18.7)	29 (20.4)	27 (19.9)	5 (15.2)	7 (20.6)	6 (18.2)	8 (24.2)	4 (12.1)	9 (26.5)	4 (12.5)	4 (12.1)

All study medication was administered once-daily for three consecutive days on Days 1, 2 and 3 in PEP005-016 and PEP005-025.
Source: Module 5.3.5.3, Tables 2.3, 2.4 and 2.5

Table 8: Baseline Disease Characteristics in Combined Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

	Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
	PEP005, 0.015% (N=277)	Vehicle (N=270)	PEP005, 0.015% (N=309)	Vehicle (N=303)
Parameter	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Anatomical location				
Face	220 (79.4)	220 (81.5)	244 (79.0)	245 (80.9)
Scalp	57 (20.6)	50 (18.5)	65 (21.0)	58 (19.1)
Fitzpatrick skin type				
I	51 (18.4)	34 (12.6)	60 (19.4)	37 (12.2)
II	123 (44.4)	112 (41.5)	137 (44.3)	126 (41.6)
III	84 (30.3)	111 (41.1)	90 (29.1)	123 (40.6)
IV	19 (6.9)	13 (4.8)	22 (7.1)	17 (5.6)
Baseline lesion count				
4	48 (17.3)	57 (21.1)	58 (18.8)	66 (21.8)
5	75 (27.1)	79 (29.3)	81 (26.2)	87 (28.7)
6	56 (20.2)	64 (23.7)	64 (20.7)	73 (24.1)
7	54 (19.5)	36 (13.3)	59 (19.1)	41 (13.5)
8	44 (15.9)	34 (12.6)	47 (15.2)	36 (11.9)
Skin cancer history	126 (45.5)	120 (44.4)	142 (46.0)	136 (44.9)
Prior treatment				
Cryotherapy	224 (80.9)	227 (84.1)	250 (80.9)	253 (83.5)
Imiquimod	25 (9.0)	31 (11.5)	33 (10.7)	43 (14.2)
5-Fluorouracil	55 (19.9)	52 (19.3)	59 (19.1)	56 (18.5)

[a] Controlled Phase 3 studies (PEP005-016 and PEP005-025)

[b] Controlled Phase 2 and 3 studies (PEP005-015, PEP005-016, and PEP005-025); for study PEP005-015 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.015% three day) and the corresponding vehicle gel three day group were included.

Source: Module 5.3.5.3, Tables 2.6 and 2.7

3.2.2 Non-Head (Trunk and Extremities) Locations

3.2.2.1 Patient Disposition of Non-Head (Trunk and Extremities) Locations

Patient disposition for individual studies of interest is summarised in Table 9. Patient disposition for the combined studies populations is summarised in Table 10.

For the Phase 3 controlled studies (PEP005-014 and PEP005-028), a high percentage of randomised patients completed the study as specified in the protocol at Day 57 (98% and 97%, respectively). The Phase 2 controlled study, PEP005-006, also had a high percentage of patients (99%) who completed the study.

The combined study populations reflect the high percentage of completed patients. Across all five studies, seven patients randomised to PEP005 Gel and six patients randomised to vehicle gel were prematurely withdrawn. Of these 13 patients, four patients were withdrawn due to an AE or abnormal laboratory value (two PEP005 Gel patients and two vehicle gel patients). The other nine patients were terminated early due to protocol violation (three patients), lost to follow-up (two patients), withdrawn consent (two patients), or other reasons (two patients).

Treatment compliance was high across all five studies; only six PEP005 Gel patients (2%) did not apply both daily doses of study medication. For the two controlled Phase 3 studies, compliance with the treatment regimen was 99%. Only three PEP005 Gel, 0.05% treated patients did not apply study medication on both days of treatment, and of these, one patient in PEP005-028 missed the second dose due to losing the study medication tube. See Module 5.3.5.1\PEP005-014, Module 5.3.5.1\PEP005-028, Module 5.3.5.1\PEP005-006, Module 5.3.5.2\PEP005-018, and Module 5.3.5.2\PEP005-020 for further information on treatment compliance.

Analyses based on combined studies populations focus on patients treated with PEP005 Gel, 0.05% for two days (the proposed dosage regimen for treatment of the non-head locations) or vehicle gel. As shown in Table 10, 458 patients were included in the controlled Phase 3 studies population, 226 patients in the PEP005 Gel, 0.05% group and 232 patients in the vehicle gel group. In total, 543 patients were included in the controlled Phase 2 and 3 studies population (PEP005 Gel, 0.05%, 268 patients; vehicle gel, 275 patients) and 656 patients were included in the controlled and uncontrolled Phase 2 and 3 studies population (PEP005 Gel, 0.05%, 381 patients; vehicle gel, 275 patients).

Patient disposition for study PEP005-017 is presented in Module 5.3.5.3, Table 7.3. Sixteen patients were enroled and randomised, 13 patients received PEP005 Gel, 0.05% and three patients received vehicle gel. All patients received study medication as planned per protocol and all patients completed the study. See Module 5.3.5.1\PEP005-017 for further information on patient disposition and extent of exposure for this study.

Patients who participated in one PEP005 study were allowed to participate in a subsequent PEP005 study as long as the treatment areas did not overlap. Patients who received treatment with PEP005 Gel in more than one clinical study are presented in Module 5.3.5.3, Table 7.10. Across the studies conducted for treatment of the non-head locations, 16 patients received treatment with PEP005 Gel in two clinical studies. Of these 16 patients, five received field treatment on the same anatomical location and only two of these patients received treatment that possibly overlapped in the selected treatment area. Thus, the impact on the efficacy analyses is minimal.

Table 9: Patient Disposition in Individual Studies of Interest, Non-Head (Trunk and Extremities) Locations

	PEP005-014		PEP005-028		PEP005-006				PEP005-018	PEP005-020
	PEP005, 0.05% (N=126)	Vehicle (N=129)	PEP005, 0.05% (N=100)	Vehicle (N=103)	PEP005, 0.25% x 3d (N=37)	PEP005, 0.05% x 2 d[a] (N=42)	PEP005, 0.05% x 3d (N=39)	Vehicle x 3d (N=43)	PEP005, 0.05% (N=11)	PEP005, 0.05% (N=102)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ITT (enroled/randomised)	126 (100)	129 (100)	100 (100)	103 (100)	37 (100)	42 (100)	39 (100)	43 (100)	11 (100)	102 (100)
Safety population[b]	125 (99.2)	129 (100)	100 (100)	103 (100)	37 (100)	42 (100)	39 (100)	43 (100)	11 (100)	102 (100)
Discontinued early from study	4 (3.2)	1 (0.8)	2 (2.0)	4 (3.9)	0	1 (2.4)	0	1 (2.3)	0	0
Reason for discontinuation										
Adve rse event/abnormal lab test	2 (1.6)	1 (0.8)	0	1 (1.0)	0	0	0	0	0	0
Prot ocol devia-tion/violation	1 (0.8)	0	1 (1.0)	1 (1.0)	0	0	0	0	0	0
Consent withdrawn/ subject decision	0	0	0	1 (1.0)	0	0	0	1 (2.3)	0	0
Lost to follow-up	1 (0.8)	0	0	0	0	1 (2.4)	0	0	0	0
Other	0	0	1 (1.0)	1 (1.0)	0	0	0	0	0	0

d = day; ITT = intent-to-treat

Percentages based on number of patients enroled/randomised.

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except as indicated in PEP005-006 (double-blind, double-dummy). For PEP005-006, only patients with AK lesions on non-scalp locations are included in the analysis.

[a] PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1)

[b] Safety population for PEP005-014, PEP005-028 and PEP005-020 included all patients who received at least one dose of study medication and had at least one postbaseline safety evaluation; and for PEP005-006 and PEP005-018 included all patients who received at least one dose of study medication.

Source: Module 5.3.5.3, Table 7.1, Table 7.2, Table 7.4, Table 7.5, Table 7.6

Table 10: Patient Disposition in Combined Studies Populations, Non-Head (Trunk and Extremities) Locations

	Controlled Phase 3 Studies		Controlled Phase 2 and 3 Studies		Controlled and Uncontrolled Phase 2 and 3 Studies	
	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)	PEP005, 0.05% (N=381)	Vehicle (N=275)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ITT (enroled/randomised)	226 (100)	232 (100)	268 (100)	275 (100)	381 (100)	275 (100)
Safety population[a]	225 (99.6)	232 (100)	267 (99.6)	275 (100)	380 (99.7)	275 (100)
Discontinued early from study	6 (2.7)	5 (2.2)	7 (2.6)	6 (2.2)	7 (1.8)	6 (2.2)
Reason for discontinuation						
Adverse event/abnormal lab test	2 (0.9)	2 (0.9)	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.7)
Consent withdrawn/ subject decision	0	1 (0.4)	0	2 (0.7)	0	2 (0.7)
Lost to follow-up	1 (0.4)	0	2 (0.7)	0	2 (0.5)	0
Other	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.4)
Protocol deviation/violation	2 (0.9)	1 (0.4)	2 (0.7)	1 (0.4)	2 (0.5)	1 (0.4)

d = day; ITT = intent-to-treat

Percentages based on number of patients enroled/randomised.

Controlled Phase 3 studies (PEP005-014 and PEP005-028); controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); controlled and uncontrolled Phase 2 and 3 studies (PEP005-006, PEP005-014, PEP005-028, PEP005-018, and PEP005-020). For PEP005-006 (non-scalp patients), only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included in the controlled Phase 2 and 3 studies and the Controlled and Uncontrolled Phase 2 and 3 studies.

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except in PEP005-006 (double-blind, double-dummy) where study medication was administered on three consecutive days; PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1).

[a] Safety population for PEP005-014, PEP005-028 and PEP005-020 included all patients who received at least one dose of study medication and had at least one postbaseline safety evaluation; and for PEP005-006 and PEP005-018 included all patients who received at least one dose of study medication.

Source: Module 5.3.5.3, Table 7.7, Table 7.8, Table 7.9

3.2.2.2 Patient Demographics of Non-Head (Trunk and Extremities) Locations

Patient demographics in individual studies of interest are summarised in Table 11. Patient demographics in the combined studies populations are summarised in Table 12.

For demography, although the SAP (Module 5.3.5.3) indicated that age categories of ≤65 and >65 years would be summarised, categories of <65, ≥65 to ≤75, and >75 years were summarised to be consistent with regulatory recommendations.

The majority of patients participating in these five studies were treated at study sites in the United States (range across all treatment groups in the five studies: 74-100%). Fifty-six patients were treated in Australia (29 patients in PEP005-014 and 27 patients in PEP005-020). Across the five studies of interest, the majority of patients were male (57-100%), white (98-100%), and non-Hispanic (95-100%). The mean age ranged from 62.7-70.6 years.

For the controlled Phase 3 studies, the main eligibility criteria included four to eight clinically typical, visible, and discrete AK lesions within a contiguous 25 cm^2 treatment area on the trunk or extremities. In addition, the location of the selected treatment area could not be within 5 cm of an incompletely healed wound or within 10 cm of a suspected BCC or SCC. Patients were not allowed to have been previously treated with PEP005 Gel, treatment area lesions were not allowed to have an atypical clinical appearance (e.g., hypertrophic, hyperkeratotic, recalcitrant disease [had cryosurgery on two previous occasions] and/or cutaneous horns), and evidence of skin conditions other than the study indication that would interfere with evaluation of the study medication (e.g., eczema, unstable psoriasis, xeroderma pigmentosum) were not allowed. Exclusion criteria also stipulated restrictions for prohibited treatments and procedures prior to study entry. For both of the Phase 3 studies, > 90% of the patients met the inclusion and exclusion criteria. This patient sample is representative of the population which will use PEP005 Gel.(54)

Patient demographics in the combined studies populations reflect the patient sample in the individual studies. For the combined Phase 3 studies, 93% of the PEP005 Gel and 94% of the vehicle gel patients were located in the US. In the PEP005 Gel and vehicle gel groups, 64% and 61% were male, respectively. Mean age was 66.4 years in the PEP005 Gel group and 66.0 years in the vehicle gel group. The other two combined studies populations showed similar results. No apparent differences in demographic characteristics were seen across the treatment groups.

Patient demographics for study PEP005-017 are presented in Module 5.3.5.3, Table 8.3. Study PEP005-017 was conducted in the US. In the PEP005 Gel group, 54% of patients were female and all patients in the vehicle group were female. The mean age was 63.0 years in the PEP005 Gel group and 64.7 years in the vehicle gel group, and all patients were white.

Table 11: Patient Demographics in Individual Studies of Interest: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

	PEP005-014		PEP005-028		PEP005-006				PEP005-018	PEP005-020
Parameter	**PEP005, 0.05% (N=126)**	**Vehicle (N=129)**	**PEP005, 0.05% (N=100)**	**Vehicle (N=103)**	**PEP005, 0.25% x 3d (N=37)**	**PEP005, 0.05% x 2d[a] (N=42)**	**PEP005, 0.05% x 3d (N=39)**	**Vehicle x 3d (N=43)**	**PEP005, 0.05% (N=11)**	**PEP005, 0.05% (N=102)**
Geographic region (n [%])										
United States	110 (87.3)	116 (89.9)	100 (100)	103 (100)	37 (100)	42 (100)	39 (100)	43 (100)	11 (100)	75 (73.5)
Australia	16 (12.7)	13 (10.1)	0	0	0	0	0	0	0	27 (26.5)
Age (years)										
n	126	129	100	103	37	42	39	43	11	102
Mean (SD)	67.3 (10.6)	66.9 (9.9)	65.3 (10.2)	64.9 (10.7)	67.1 (8.5)	65.1 (9.4)	66.4 (10.2)	67.2 (8.9)	70.6 (8.9)	62.7 (10.9)
Range	43–88	36–87 4	3–87	34–89 5	0–82	43–84 4	3–85	47–82	57–82	38–88
Age category (years) (n [%])										
<65 years	46 (36.5)	48 (37.2)	48 (48.0)	52 (50.5)	15 (40.5)	22 (52.4)	18 (46.2)	18 (41.9)	3 (27.3)	53 (52.0)
65–75 years	51 (40.5)	55 (42.6)	33 (33.0)	30 (29.1)	16 (43.2)	13 (31.0)	14 (35.9)	16 (37.2)	5 (45.5)	34 (33.3)
≥75 years	29 (23.0)	26 (20.2)	19 (19.0)	21 (20.4)	6 (16.2)	7 (16.7)	7 (17.9)	9 (20.9)	3 (27.3)	15 (14.7)
Sex (n [%])										
Male	86 (68.3)	73 (56.6)	59 (59.0)	68 (66.0)	27 (73.0)	33 (78.6)	30 (76.9)	27 (62.8)	11 (100)	68 (66.7)
Female	40 (31.7)	56 (43.4)	41 (41.0)	35 (34.0)	10 (27.0)	9 (21.4)	9 (23.1)	16 (37.2)	0	34 (33.3)
Race (n [%])										
White	126 (100)	129 (100)	100 (100)	103 (100)	37 (100)	42 (100)	39 (100)	43 (100)	11 (100)	100 (98.0)
Other	0	0 0		0 0		0 0		0	0	2 (2.0)
Ethnicity (n [%])										
Non-Hispanic	125 (99.2)	127 (98.4)	98 (98.0)	103 (100)	37 (100)	41 (97.6)	37 (94.9)	43 (100)	11 (100)	102 (100)
Hispanic	1 (0.8)	2 (1.6)	2 (2.0)	0	0	1 (2.4)	2 (5.1)	0	0	0

d = day

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except as indicated in PEP005-006 (double-blind, double-dummy). For PEP005-006, only patients with AK lesions on non-scalp locations are included in the analysis.

[a] PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1)

Source: Module 5.3.5.3, Table 8.1, Table 8.2, Table 8.4, Table 8.5, Table 8.6.

Table 12: Patient Demographics in Combined Studies Populations: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

Parameter	Controlled Phase 3 Studies		Controlled Phase 2 and 3 Studies		Controlled and Uncontrolled Phase 2 and 3 Studies	
	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)	PEP005, 0.05% (N=381)	Vehicle (N=275)
Geographic region (n [%])						
United States	210 (92.9)	219 (94.4)	252 (94.0)	262 (95.3)	338 (88.7)	262 (95.3)
Australia	16 (7.1)	13 (5.6)	16 (6.0)	13 (4.7)	43 (11.3)	13 (4.7)
Age (years)						
n	226	232	268 2	75 3	81 2	75
Mean (SD)	66.4 (10.4)	66.0 (10.3)	66.2 (10.3)	66.2 (10.1)	65.4 (10.5)	66.2 (10.1)
Range	43–88 3	4–89 4	3–88	34–89	38–88	34–89
Age category (years) (n [%])						
<65 years	94 (41.6)	100 (43.1)	116 (43.3)	118 (42.9)	172 (45.1)	118 (42.9)
65–75 years	84 (37.2)	85 (36.6)	97 (36.2)	101 (36.7)	136 (35.7)	101 (36.7)
≥75 years	48 (21.2)	47 (20.3)	55 (20.5)	56 (20.4)	73 (19.2)	56 (20.4)
Sex (n [%])						
Male	145 (64.2)	141 (60.8)	178 (66.4)	168 (61.1)	257 (67.5)	168 (61.1)
Female	81 (35.8)	91 (39.2)	90 (33.6)	107 (38.9)	124 (32.5)	107 (38.9)
Race (n [%])						
White	226 (100)	232 (100)	268 (100)	275 (100)	379 (99.5)	275 (100)
Other	0 0 0			0	2 (0.5)	0
Ethnicity (n [%])						
Non-Hispanic	223 (98.7)	230 (99.1)	264 (98.5)	273 (99.3)	377 (99.0)	273 (99.3)
Hispanic	3 (1.3)	2 (0.9)	4 (1.5)	2 (0.7)	4 (1.0)	2 (0.7)

Controlled Phase 3 studies (PEP005-014 and PEP005-028); controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); controlled and uncontrolled Phase 2 and 3 studies (PEP005-006, PEP005-014, PEP005-028, PEP005-018, and PEP005-020). For PEP005-006 (non-scalp patients), only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included in the controlled Phase 2 and 3 studies and the Controlled and Uncontrolled Phase 2 and 3 studies.
All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except in PEP005-006 (double-blind, double-dummy) where study medication was administered on three consecutive days; PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1).

Source: Module 5.3.5.3, Table 8.7, Table 8.8, Table 8.9.

3.2.2.3 Baseline Disease Characteristics of Non-Head (Trunk and Extremities) Locations

Baseline disease characteristics of patients in individual studies of interest are summarised in Table 13. Baseline disease characteristics of patients in the combined studies populations are summarised in Table 14.

Across the five studies, most patients were treated on the arm (range across all treatment groups in the five studies: 50-95%) followed by the back of hand (21-100%). The majority of patients had four to six lesions in the treatment area at baseline (68-82%). Most patients had Fitzpatrick skin type I, II or III (92-100%). A positive history of skin cancer was documented for approximately 50% of patients (range: 43-91%). Approximately 80% received prior treatment with cryotherapy (range: 73-100%), approximately 10% received prior imiquimod (range: 7-28%), and approximately 25% received prior 5-FU (range: 21-46%).

The combined studies populations showed consistency with the individual studies. For the combined Phase 3 studies, 63% and 64% of the PEP005 Gel and vehicle gel patients, respectively, received treatment on the arm. In the PEP005 Gel and vehicle gel groups, 93% and 95% had Fitzpatrick skin type I, II, or III. The baseline lesion count was four to six in 79% of PEP005 Gel patients and 75% of vehicle gel patients. A history of skin cancer was present in 54% of PEP005 Gel patients and 52% of vehicle gel patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 75% and 77%; imiquimod: 9% and 14%; 5-FU: 22% and 24%, respectively). Results for the other two combined studies populations were similar. Across the treatment groups, no apparent differences were seen for baseline disease characteristics.

Baseline disease characteristics for study PEP005-017 are presented in Module 5.3.5.3, Table 8.3. In PEP005-017, all patients received treatment on the arm. Fitzpatrick skin type was I, II or III for all patients except one in the PEP005 Gel group, all had four to six lesions at baseline except one in the PEP005 Gel group, and only two patients had a positive history of skin cancer (both were in the PEP005 Gel group). Prior treatment with cryotherapy was seen in two patients (both were in the PEP005 Gel group), prior 5-FU use was reported in 15-33%, and no patients had used imiquimod in the past.

Table 13: Baseline Disease Characteristics in Individual Studies of Interest: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

Parameter	PEP005-014		PEP005-028		PEP005-006				PEP005-018	PEP005-020
	PEP005, 0.05% (N=126)	Vehicle (N=129)	PEP005, 0.05% (N=100)	Vehicle (N=103)	PEP005, 0.25% x 3d (N=37)	PEP005, 0.05% x 2d[a] (N=42)	PEP005, 0.05% x 3d (N=39)	Vehicle x 3d (N=43)	PEP005, 0.05% (N=11)	PEP005, 0.05% (N=102)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment location										
Arm	83 (65.9)	82 (63.6)	59 (59.0)	67 (65.0)	35 (94.6)	39 (92.9)	35 (89.7)	38 (88.4)	0	51 (50.0)
Back of hand	26 (20.6)	29 (22.5)	28 (28.0)	27 (26.2)	0	0	0	0	11 (100)	41 (40.2)
Chest	9 (7.1)	8 (6.2)	5 (5.0)	3 (2.9)	2 (5.4)	1 (2.4)	1 (2.6)	3 (7.0)	0	7 (6.9)
Leg	6 (4.8)	5 (3.9)	3 (3.0)	5 (4.9)	0	0	0	0	0	1 (1.0)
Back	1 (0.8)	3 (2.3)	3 (3.0)	0	0	0	1 (2.6)	0	0	1 (1.0)
Shoulder	1 (0.8)	2 (1.6)	2 (2.0)	1 (1.0)	0	2 (4.8)	2 (5.1)	2 (4.7)	0	1 (1.0)
Fitzpatrick skin type										
I	26 (20.6)	31 (24.0)	26 (26.0)	24 (23.3)	6 (16.2)	10 (23.8)	6 (15.4)	6 (14.0)	0	18 (17.6)
II	69 (54.8)	73 (56.6)	36 (36.0)	45 (43.7)	21 (56.8)	18 (42.9)	21 (53.8)	29 (67.4)	4 (36.4)	52 (51.0)
III	21 (16.7)	21 (16.3)	31 (31.0)	27 (26.2)	7 (18.9)	12 (28.6)	11 (28.2)	5 (11.6)	7 (63.6)	28 (27.5)
IV	10 (7.9)	4 (3.1)	5 (5.0)	7 (6.8)	3 (8.1)	2 (4.8)	1 (2.6)	3 (7.0)	0	4 (3.9)
V	0	0	2 (2.0)	0	0	0	0	0	0	0

d = day

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except as indicated in PEP005-006 (double-blind, double-dummy). For PEP005-006, only patients with AK lesions on non-scalp locations are included in the analysis.

[a] PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1)

Source: Module 5.3.5.3, Table 8.1, Table 8.2, Table 8.4, Table 8.5, Table 8.6.

Table 13: Baseline Disease Characteristics in Individual Studies of Interest: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

	PEP005-014		PEP005-028		PEP005-006				PEP005-018	PEP005-020
Parameter	**PEP005, 0.05% (N=126)**	**Vehicle (N=129)**	**PEP005, 0.05% (N=100)**	**Vehicle (N=103)**	**PEP005, 0.25% x 3d (N=37)**	**PEP005, 0.05% x 2d[a] (N=42)**	**PEP005, 0.05% x 3d (N=39)**	**Vehicle x 3d (N=43)**	**PEP005, 0.05% (N=11)**	**PEP005, 0.05% (N=102)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Baseline lesion count										
4	30 (23.8)	35 (27.1)	37 (37.0)	27 (26.2)	13 (35.1)	12 (28.6)	11 (28.2)	10 (23.3)	4 (36.4)	24 (23.5)
5	37 (29.4)	40 (31.0)	25 (25.0)	21 (20.4)	10 (27.0)	11 (26.2)	11 (28.2)	11 (25.6)	1 (9.1)	27 (26.5)
6	29 (23.0)	26 (20.2)	20 (20.0)	26 (25.2)	6 (16.2)	10 (23.8)	8 (20.5)	10 (23.3)	3 (27.3)	18 (17.6)
7	17 (13.5)	14 (10.9)	6 (6.0)	15 (14.6)	5 (13.5)	7 (16.7)	7 (17.9)	5 (11.6)	1 (9.1)	18 (17.6)
8	11 (8.7)	14 (10.9)	12 (12.0)	14 (13.6)	3 (8.1)	2 (4.8)	2 (5.1)	6 (14.0)	2 (18.2)	15 (14.7)
9[b]	2 (1.6)	0	0	0	0	0	0	1 (2.3)	0	0
Skin cancer history										
Yes	69 (54.8)	77 (59.7)	52 (52.0)	44 (42.7)	25 (67.6)	19 (45.2)	20 (51.3)	28 (65.1)	10 (90.9)	61 (59.8)
Prior treatment										
Cryotherapy	97 (77.0)	99 (76.7)	73 (73.0)	79 (76.7)	34 (91.9)	35 (83.3)	34 (87.2)	34 (79.1)	11 (100)	86 (84.3)
5-Fluorouracil	27 (21.4)	30 (23.3)	23 (23.0)	26 (25.2)	13 (35.1)	11 (26.2)	11 (28.2)	12 (27.9)	5 (45.5)	33 (32.4)
Imiquimod	14 (11.1)	17 (13.2)	7 (7.0)	15 (14.6)	6 (16.2)	11 (26.2)	7 (17.9)	12 (27.9)	3 (27.3)	17 (16.7)

d = day

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except as indicated in PEP005-006 (double-blind, double-dummy).
For PEP005-006, only patients with AK lesions on non-scalp locations are included in the analysis.

[a] PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1)

[b] Inclusion criteria specified that patients have 4 to 8 AK lesions within the treatment area.

Source: Module 5.3.5.3, Table 8.1, Table 8.2, Table 8.4, Table 8.5, Table 8.6.

Table 14: Baseline Disease Characteristics in Combined Studies Populations: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

Parameter	Controlled Phase 3 Studies		Controlled Phase 2 and 3 Studies		Controlled and Uncontrolled Phase 2 and 3 Studies	
	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)	PEP005, 0.05% (N=381)	Vehicle (N=275)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment location						
Arm	142 (62.8)	149 (64.2)	181 (67.5)	187 (68.0)	232 (60.9)	187 (68.0)
Back of hand	54 (23.9)	56 (24.1)	54 (20.1)	56 (20.4)	106 (27.8)	56 (20.4)
Chest	14 (6.2)	11 (4.7)	15 (5.6)	14 (5.1)	22 (5.8)	14 (5.1)
Leg	9 (4.0)	10 (4.3)	9 (3.4)	10 (3.6)	10 (2.6)	10 (3.6)
Back	4 (1.8)	3 (1.3)	4 (1.5)	3 (1.1)	5 (1.3)	3 (1.1)
Shoulder	3 (1.3)	3 (1.3)	5 (1.9)	5 (1.8)	6 (1.6)	5 (1.8)
Fitzpatrick skin type						
I	52 (23.0)	55 (23.7)	62 (23.1)	61 (22.2)	80 (21.0)	61 (22.2)
II	105 (46.5)	118 (50.9)	123 (45.9)	147 (53.5)	179 (47.0)	147 (53.5)
III	52 (23.0)	48 (20.7)	64 (23.9)	53 (19.3)	99 (26.0)	53 (19.3)
IV	15 (6.6)	11 (4.7)	17 (6.3)	14 (5.1)	21 (5.5)	14 (5.1)
V	2 (0.9)	0	2 (0.7)	0	2 (0.5)	0

Controlled Phase 3 studies (PEP005-014 and PEP005-028); controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); controlled and uncontrolled Phase 2 and 3 studies (PEP005-006, PEP005-014, PEP005-028, PEP005-018, and PEP005-020). For PEP005-006 (non-scalp patients), only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included in the controlled Phase 2 and 3 studies and the Controlled and Uncontrolled Phase 2 and 3 studies.

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except in PEP005-006 (double-blind, double-dummy) where study medication was administered on three consecutive days; PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1).

Source Module 5.3.5.3, Table 8.7, Table 8.8, Table 8.9.

Table 14: Baseline Disease Characteristics in Combined Studies Populations: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

Parameter	Controlled Phase 3 Studies		Controlled Phase 2 and 3 Studies		Controlled and Uncontrolled Phase 2 and 3 Studies	
	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)	PEP005, 0.05% (N=381)	Vehicle (N=275)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline lesion count						
4	67 (29.6)	62 (26.7)	79 (29.5)	72 (26.2)	107 (28.1)	72 (26.2)
5	62 (27.4)	61 (26.3)	73 (27.2)	72 (26.2)	101 (26.5)	72 (26.2)
6	49 (21.7)	52 (22.4)	59 (22.0)	62 (22.5)	80 (21.0)	62 (22.5)
7	23 (10.2)	29 (12.5)	30 (11.2)	34 (12.4)	49 (12.9)	34 (12.4)
8	23 (10.2)	28 (12.1)	25 (9.3)	34 (12.4)	42 (11.0)	34 (12.4)
9[a]	2 (0.9)	0	2 (0.7)	1 (0.4)	2 (0.5)	1 (0.4)
Skin cancer history						
Yes	121 (53.5)	121 (52.2)	140 (52.2)	149 (54.2)	211 (55.4)	149 (54.2)
Prior treatment						
Cryotherapy	170 (75.2)	178 (76.7)	205 (76.5) 2	12 (77.1) 3	02 (79.3) 2	12 (77.1)
5-Fluorouracil	50 (22.1)	56 (24.1)	61 (22.8)	68 (24.7)	99 (26.0)	68 (24.7)
Imiquimod	21 (9.3)	32 (13.8)	32 (11.9)	44 (16.0)	52 (13.6)	44 (16.0)

Controlled Phase 3 studies (PEP005-014 and PEP005-028); controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); controlled and uncontrolled Phase 2 and 3 studies (PEP005-006, PEP005-014, PEP005-028, PEP005-018, and PEP005-020). For PEP005-006 (non-scalp patients), only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included in the controlled Phase 2 and 3 studies and the Controlled and Uncontrolled Phase 2 and 3 studies.

All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except in PEP005-006 (double-blind, double-dummy) where study medication was administered on three consecutive days; PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1).

[a] Inclusion criteria specified that patients have 4 to 8 AK lesions within the treatment area.

Source Module 5.3.5.3, Table 8.7, Table 8.8, Table 8.9.

3.3 COMPARISON OF EFFICACY RESULTS OF ALL STUDIES

3.3.1 Head (Face and Scalp) Locations

The following efficacy endpoints were selected for comparison and analysis across studies: complete clearance rate, partial clearance rate, and percent change from baseline in the number of AK lesions. In addition, percent change in total AK lesion count was presented for the combined studies populations. Data are presented for the ITT population.

Efficacy results in individual studies of interest are summarised in Table 15. Efficacy results in the combined studies populations are summarised in Table 16.

For the individual studies, the complete clearance rate was 37%, 47%, and 50% for PEP005 Gel-treated patients compared to 2%, 5%, and 9% for vehicle gel-treated patients in PEP005-016, PEP005-025, and PEP005-015, respectively ($p < 0.001$ for each study). Partial clearance rate was also statistically significant (60%, 68%, and 72% for PEP005 Gel-treated patients compared to 7%, 8%, and 12% for vehicle gel-treated patients in PEP005-016, PEP005-025, and PEP005-015, respectively [$p < 0.001$ for each study]). The median reduction in the number of AK lesions compared to baseline was >80% for the PEP005 Gel, 0.015% versus 0% in the vehicle gel group for each of the three studies.

The complete clearance rate for PEP005-016 was lower than the rate seen in PEP005-025. As shown in Table 5 and Table 7, no difference was apparent between the two studies for geographic region, age, sex, race, ethnicity, anatomical location, Fitzpatrick skin type, baseline AK lesion count, history of skin cancer or prior treatment. Thus, no reason could be identified for this variation between the complete clearance rates. However, even with this variation between the two studies, the findings were consistent in that each study was statistically significant in favour of PEP005 Gel and the results were clinically meaningful.

For each of the two Phase 3 studies, an additional sensitivity analysis was performed for complete clearance rates in which all active treatment patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) were considered as not achieving complete clearance and all vehicle gel patients who missed the Day 57 visit or were outside the visit window were considered as achieving complete clearance. Results are presented in Module 5.3.5.3, Tables 3.8 and 3.9 for PEP005-016 and PEP005-025, respectively. Even applying this "worst case scenario", a treatment effect similar to the outcome of the ITT analyses was evident; complete clearance was 36% and 47% for PEP005 Gel-treated patients

compared to 8% and 7% for vehicle gel-treated patients in PEP005-016 and PEP005-025, respectively ($p < 0.001$ for each study).

The combined study populations showed a consistent treatment effect. For the controlled Phase 3 study population, 42% of the PEP005 Gel patients compared to only 4% of the vehicle gel patients achieved complete clearance ($p < 0.001$). Partial clearance was seen in 64% of PEP005 Gel-treated patients and 7% of vehicle gel-treated patients ($p < 0.001$). The median reduction in the number of AK lesions compared to baseline was 83% for the PEP005 Gel group versus 0% for the vehicle gel group. The reduction in total lesion count was substantially greater in the PEP005 Gel group (72% compared to 14% in the vehicle gel group). Results for the combined controlled Phase 2 and 3 studies were consistent with the findings of the combined Phase 3 studies.

Of the 12 patients randomised to PEP005 Gel, 0.015% in the combined Phase 2 and 3 studies population who were not compliant (Section 3.2.1.1), two never applied any amount of study medication. Of the remaining 10 patients who applied one or two doses of PEP005 Gel, 0.015%, nine achieved complete clearance at Day 57 (Modules 5.3.5.1\PEP005-016, 5.3.5.1\PEP005-025, and 5.3.5.1\PEP005-015).

For studies PEP005-006, and PEP005-007, efficacy results are presented in Module 5.3.5.3, Tables 3.1 and 3.2, respectively. These two studies investigated various strengths of PEP005 Gel ranging from 0.0025-0.05% for two or three consecutive days. Complete clearance rates in PEP005-006 ranged from 46-72% in the PEP005 Gel groups versus 6% in the vehicle group. In the PEP005-007 study, complete clearance rates ranged from 0-100% across the PEP005 Gel concentrations studied.

Table 15: Efficacy Results in Individual Studies of Interest: Intent-to-treat Population, Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		PEP005-015							
					Two Day Dosing				Three Day Dosing			
	PEP005, 0.015%	Vehicle	PEP005, 0.015%	Vehicle	PEP005, 0.005%	PEP005, 0.01%	PEP005, 0.015%	Vehicle	PEP005, 0.005%	PEP005, 0.01%	PEP005, 0.015%	Vehicle
Efficacy Parameter	**(N=135)**	**(N=134)**	**(N=142)**	**(N=136)**	**(N=33)**	**(N=34)**	**(N=33)**	**(N=33)**	**(N=33)**	**(N=34)**	**(N=32)**	**(N=33)**
Complete Clearance												
n (%)	50 (37.0)	3 (2.2)	67 (47.2)	7 (5.1)	5 (15.2)	10 (29.4)	12 (36.4)	0	11 (33.3)	6 (17.6)	16 (50.0)	3 (9.1)
95% CI	28.9, 45.8	0.5, 6.4	38.8, 55.7	2.1, 10.3	5.1, 31.9	15.1, 47.5	20.4, 54.9	0, 10.6	18.0, 51.8	6.8, 34.5	31.9, 68.1	1.9, 24.3
P value	<0.001		<0.001		0.053	<0.001	<0.001		0.033	0.476	<0.001	
Partial Clearance												
n (%)	81 (60.0)	9 (6.7)	96 (67.6)	11 (8.1)	11 (33.3)	17 (50.0)	17 (51.5)	3 (9.1)	14 (42.4)	9 (26.5)	23 (71.9)	4 (12.1)
95% CI	51.2, 68.3	3.1, 12.4	59.2, 75.2	4.1, 14.0	18.0, 51.8	32.4, 67.6	33.5, 69.2	1.9, 24.3	25.5, 60.8	12.9, 44.4	53.3, 86.3	3.4, 28.2
P value	<0.001		<0.001		0.033	<0.001	<0.001		0.012	0.217	<0.001	
Percent Reduction in AK Lesions												
n	131	133	142	136	33 34 33	32 31 34 32 33						
Median	83	0	87	0	50 73 75			0	67 55 94			0
Range	-50, 100	-100, 100	-25, 100	-100, 100	-20, 100	0, 100	0, 100	-17, 86	-17, 100	0, 100	0, 100	-25, 100

CI = confidence interval

All study medication was administered once-daily for three consecutive days on Days 1, 2 and 3 in PEP005-016 and PEP005-025.

Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)

For PEP005-016 and PEP005-025, P value is for comparing active treatment vs. vehicle, using the CMH test stratifying on site. For PEP005-015, P value is for comparing active treatment vs. vehicle, using Fisher's Exact test.

The 95% CI uses the exact binomial method.

Source: Module 5.3.5.3, Table 3.3, 3.4 and 3.5

Table 16: Efficacy Results in Combined Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

Efficacy Parameter	Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
	PEP005, 0.015% (N=277)	**Vehicle (N=270)**	**PEP005, 0.015% (N=309)**	**Vehicle (N=303)**
Complete Clearance				
n (%)	117 (42.2)	10 (3.7)	133 (43.0)	13 (4.3)
95% CI	36.4, 48.3	1.8, 6.7	37.4, 48.8	2.3, 7.2
P value	<0.001			
Partial Clearance				
n (%)	177 (63.9)	20 (7.4)	200 (64.7)	24 (7.9)
95% CI	57.9, 69.6	4.6, 11.2	59.1, 70.1	5.1, 11.6
P value	<0.001			
Percent Reduction in AK Lesions				
n	273	269 3	05 3	02
Median	83 0		83 0	
Range	-50, 100	-100, 100	-50, 100	-100, 100
Total AK Lesion Count				
Baseline	1607 1	526	1784 1	707
End of study (Day 57)	444 1	310 4	81 1	454
Percent change	72 14		73 15	

CI = confidence interval

[a] Controlled Phase 3 studies (PEP005-016 and PEP005-025)

[b] Controlled Phase 2 and 3 studies (PEP005-015, PEP005-016, and PEP005-025); for study PEP005-015 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.015% three day) and the corresponding vehicle gel three day group were included.

Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)

P value is for comparing active treatment vs. vehicle, using a logistic regression model with treatment, study, and anatomical location.

The 95% CI uses the exact binomial method.

Source: Module 5.3.5.3, Tables 3.6, 3.7, and 3.12

3.3.2 Non-Head (Trunk and Extremities) Locations

The following efficacy endpoints were selected for comparison and analysis across studies: complete clearance rate, partial clearance rate, and percent change from baseline in the number of AK lesions. In addition, percent change in total AK lesion count was presented for the combined studies populations. Efficacy results in individual studies of interest are summarised in Table 17. Efficacy results in the combined studies populations are summarised in Table 18.

Across the five studies of interest, complete clearance rates for PEP005 Gel treated patients ranged from 27–46% versus 5–14% for vehicle gel-treated patients. In the Phase 2 and 3 controlled studies (PEP005-014, PEP005-028, and PEP005-006), the difference between PEP005 Gel, 0.05% (the proposed dosage regimen for treatment of the non-head locations) and vehicle gel was statistically significant ($p < 0.001$, $p < 0.001$, and $p = 0.002$, respectively). Partial clearance rates for PEP005 Gel treated patients ranged from 44–74% versus 7–21% for vehicle gel-treated patients, and in all comparative studies the difference between PEP005 Gel, 0.05% and vehicle gel was statistically significant ($p < 0.001$ for each study). Median reduction in the number of AK lesions compared to baseline for PEP005 Gel treated patients ranged from 69–86% versus 0% for vehicle gel-treated patients.

The complete clearance rate for PEP005-014 was lower than the rate seen in PEP005-028. As shown in Table 11 and Table 13, no difference was apparent between the two studies for geographic region, age, sex, race, ethnicity, anatomical location, Fitzpatrick skin type, baseline AK lesion count, history of skin cancer or prior treatment. Thus, no reason could be identified for this variation between the complete clearance rates. However, even with this variation between the two studies, the findings were consistent in that each study was statistically significant in favour of PEP005 Gel and the results were clinically meaningful.

For each of the two pivotal Phase 3 studies, an additional sensitivity analysis was performed for complete clearance rates in which all PEP005 Gel, 0.05% treated patients who missed the Day 57 visit or were outside the visit window (≤ Day 50 or ≥ Day 85) were considered as not achieving complete clearance and all vehicle gel patients who missed the Day 57 visit or were outside the visit window were considered as achieving complete clearance. Results are presented in Module 5.3.5.3, Table 9.10 and Table 9.11 for PEP005-014 and PEP005-028, respectively. Even applying this "worst case scenario," a treatment effect similar to the outcome of the ITT analyses was evident; i.e., complete clearance rate for PEP005 Gel, 0.05%

treated patients was 27% and 41% versus 5% and 9% for vehicle gel-treated patients in PEP005-014 and PEP005-028, respectively ($p < 0.001$ for each study).

The combined study populations showed a consistent treatment effect across all efficacy endpoints. For the controlled Phase 3 studies populations, 34% of the PEP005 Gel patients compared to only 5% of the vehicle gel-patients achieved complete clearance ($p < 0.001$). Partial clearance was seen in 49% of PEP005 Gel-treated patients and 7% of vehicle gel-treated patients ($p < 0.001$). The median reduction in the number of AK lesions compared to baseline was 75% for the PEP005 Gel group versus 0% for the vehicle gel group. The reduction in total lesion count was substantially greater in the PEP005 Gel group (63% compared to 15% in the vehicle gel group). Results for the other two combined studies populations were consistent with the findings of the combined Phase 3 studies.

Efficacy results for study PEP005-017 are presented in Module 5.3.5.3, Table 9.3. In PEP005-017, the complete clearance rate for PEP005 Gel, 0.05% treated patients was 77% versus 0% for vehicle gel-treated patients.

Table 17: Efficacy Results in Individual Studies of Interest: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

	PEP005-014		PEP005-028		PEP005-006				PEP005-018	PEP005-020
Efficacy Parameter	**PEP005, 0.05% (N=126)**	**Vehicle (N=129)**	**PEP005, 0.05% (N=100)**	**Vehicle (N=103)**	**PEP005, 0.25% x 3d (N=37)**	**PEP005, 0.05% x 2d[a] (N=42)**	**PEP005, 0.05% x 3d (N=39)**	**Vehicle x 3d (N=43)**	**PEP005, 0.05% (N=11)**	**PEP005, 0.05% (N=102)**
Complete Clearance										
n (%)	35 (27.8)	6 (4.7)	42 (42.0)	5 (4.9)	12 (32.4)	19 (45.2)	18 (46.2)	6 (14.0)	3 (27.3)	40 (39.2)
95% CI	20.2, 36.5	1.7, 9.8	32.2, 52.3	1.6, 11.0	18.0, 49.8	29.8, 61.3	30.1, 62.8	5.3, 27.9	6.0, 61.0	29.7, 49.4
P value	<0.001 <0		.001		0.062	0.002	0.002			
Partial Clearance										
n (%)	56 (44.4)	9 (7.0)	55 (55.0)	7 (6.8)	20 (54.1)	27 (64.3)	29 (74.4)	9 (20.9)	5 (45.5)	56 (54.9)
95% CI	35.6, 53.6	3.2, 12.8	44.7, 65.0	2.8, 13.5	36.9, 70.5	48.0, 78.4	57.9, 87.0	10.0, 36.0	16.7, 76.6	44.7, 64.8
P value	<0.001 <0		.001		0.003	<0.001	<0.001			
Percent Reduction in AK Lesions										
N	120 12	8 10	0	101	37	41	39	42	11	102
Median	69 0		75 0		75	83	86 0		67	75
Range	-25, 100	-33, 100	0, 100	-33, 100	0, 100	-57, 100	0, 100	-20, 100	-13, 100	-80, 100

CI = confidence interval; d = day
All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except as indicated in PEP005-006 (double-blind, double-dummy). For PEP005-006, only patients with AK lesions on non-scalp locations are included in the analysis.
[a] PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1)
Percent reduction = 100 · (baseline AK lesion count – Day 57 AK lesion count)/(baseline AK lesion count)
p-values comparing active treatment vs. vehicle using the CMH test stratifying on site for PEP005-014 and PEP005-028 and using Fisher's Exact test in PEP005-006.
The 95% CI using the exact binomial method.
Source: Module 5.3.5.3, Table 9.1, Table 9.2, Table 9.4, Table 9.5, Table 9.6.

Table 18: Efficacy Results in Combined Studies Populations: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

Efficacy Parameter	Controlled Phase 3 Studies		Controlled Phase 2 and 3 Studies		Controlled and Uncontrolled Phase 2 and 3 Studies	
	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)	PEP005, 0.05% (N=381)	Vehicle (N=275)
Complete Clearance						
n (%)	77 (34.1)	11 (4.7)	96 (35.8)	17 (6.2)	139 (36.5)	17 (6.2)
95% CI	27.9, 40.6	2.4, 8.3	30.1, 41.9	3.6, 9.7	31.6, 41.5	3.6, 9.7
P value	<0.001					
Partial Clearance						
n (%)	111 (49.1)	16 (6.9)	138 (51.5)	25 (9.1)	199 (52.2)	25 (9.1)
95% CI	42.4, 55.8	4.0, 11.0	45.3, 57.6	6.0, 13.1	47.1, 57.3	6.0, 13.1
P value	<0.001					
Percent Reduction in AK Lesions						
N	220	229	261 2	71 3	74 2	71
Median	75 0	75		0	75	0
Range	-25 – 100	-33 – 100	-57 – 100	-33 – 100	-80 – 100	-33 – 100
Total AK Lesion Count						
Baseline	1204 1	274 1	426	1513	2073	1513
End of study (Day 57)	441	1078	508	1255	736	1256
Percent change	63 15	64		17	64	17

CI = confidence interval
Controlled Phase 3 studies (PEP005-014 and PEP005-028); controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); controlled and uncontrolled Phase 2 and 3 studies (PEP005-006, PEP005-014, PEP005-028, PEP005-018, and PEP005-020). For PEP005-006 (non-scalp patients), only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and the vehicle gel group were included in the controlled Phase 2 and 3 studies and the Controlled and Uncontrolled Phase 2 and 3 studies.
All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except in PEP005-006 (double-blind, double-dummy) where study medication was administered on three consecutive days; PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1).
Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)
P value is for comparing active treatment vs. vehicle, using a logistic regression model with treatment, study, and anatomical location.
The 95% CI using the exact binomial method.
Source: Module 5.3.5.3, Table 9.7, Table 9.8, Table 9.9, Table 9.14.

3.3.3 Summary of Analyses to Investigate Combined Phase 3 Studies Population

3.3.3.1 Head (Face and Scalp) Locations

Although the SAP did not include an analysis to compare the treatment groups in terms of complete clearance for the combined Phase 3 studies population, a logistic regression model with treatment, anatomical location, and study as independent variables was performed for the combined Phase 3 studies (PEP005-016 and PEP005-025). Two analyses were performed; the first investigated potential study by treatment and anatomical location by treatment interactions (interaction model). If there was no evidence of significant interactions using a significance level of 0.10, then a second model investigated treatment effects without the interaction terms (main effects model). The results of the analysis are presented in Module 5.3.5.3, Tables 3.10, 3.11, and 3.12.

Findings indicate that there is no evidence of significant study by treatment interaction or anatomical location by treatment interaction for the combined Phase 3 studies based on the logistic regression model ($p \geq 0.592$). The treatment effect remained significant ($p < 0.001$).

3.3.3.2 Non-Head (Trunk and Extremities) Locations

Similarly, for non-head, the SAP did not include an analysis to compare the treatment groups in terms of complete clearance for the combined Phase 3 studies population. The same logistic regression model with treatment, anatomical location, and study as independent variables was performed for the combined Phase 3 studies (PEP005-014 and PEP005-028). Two analyses were performed; the first investigated potential study by treatment and anatomical location by treatment interactions (interaction model). If there was no evidence of significant interactions using a significance level of 0.10, then a second model investigated treatment effects without the interaction terms (main effects model). The results of the analysis are presented in Module 5.3.5.3, Tables 9.12, 9.13, and 9.14.

Findings indicate that there is no evidence of significant study by treatment interaction or anatomical location by treatment interaction for the combined Phase 3 studies based on the logistic regression model ($p \geq 0.356$). The treatment effect remained significant ($p < 0.001$).

3.4 COMPARISON OF RESULTS IN SUBPOPULATIONS

A paediatric subpopulation was not included in the studies conducted with PEP005 Gel because AK does not occur in the paediatric population except in rare cases. These include a few rare genetic diseases (54), e.g., albinism (especially in near-equatorial countries in Africa)

(53,55,56) genodermatoses such as xeroderma pigmentosum (57,58,59,60) and Rothmund-Thomson syndrome (61).

Subpopulations containing pregnant or lactating women were not included in the studies conducted with PEP005 Gel because both pregnancy and lactation were exclusion criteria in all protocols.

The subpopulation of elderly was defined as patients ≥65 years old and the subpopulation of very elderly was defined as patients ≥75 years old. Both were included in the PEP005 studies and are analysed in the following sections.

3.4.1 Head (Face and Scalp) Locations

3.4.1.1 Complete Clearance by Subpopulations of Demographic and Baseline Characteristics

The efficacy endpoint of interest for comparison of the subgroups is complete clearance. The combined studies populations were used for the prospectively planned analyses. Only patients who received PEP005 Gel were included in these subgroup analyses; patients who received vehicle gel were omitted since the focus was on differences in clearance rates among subgroups; the complete clearance rate for the vehicle gel-treated patients was minimal (10 patients for the combined Phase 3 studies population). The objective of the subgroup analyses was to investigate the observed effects of PEP005 Gel, 0.015% for consistency across all subgroups. All summaries and analyses were based on the ITT population.

A logistic regression model was used to compare subgroups in the univariate analyses. The odds ratio with 95% CI and p value from the Wald Chi-square statistic were reported in addition to summary statistics for each subgroup. These were a priori planned exploratory analyses to investigate any apparent differences between various subgroups of patients in terms of complete clearance rate for PEP005 Gel, 0.015% applied to a contiguous 25 cm^2 treatment area for three consecutive days on the head (face and scalp). As exploratory analyses, they do not carry the same statistical or clinical weight as the treatment group comparisons conducted for the adequate and well controlled studies. The information in this section was examined for consistency of effect among subsets of the overall population.

Additional exploratory analyses were performed after the findings from the univariate logistic regressions were assessed. These additional exploratory analyses included multiple logistic regression analyses performed for the combined studies populations, summaries of demo-

graphic, baseline disease characteristics, and efficacy by anatomical location, and univariate subgroup and multiple logistic regression analyses by anatomical location. Exploratory analyses are further explained prior to presentation in the sections where presented (Sections 3.4.1.1.2 and 3.4.1.1.3). All subgroup analyses are provided in Module 5.3.5.3, Tables 4.1.1 through 4.6.2.

3.4.1.1.1 **Univariate Analyses of Subpopulations**

A summary of complete clearance rates in subgroups defined by demographic factors, baseline characteristics, and prior therapies based on the combined controlled Phase 3 studies population is presented in Table 19.

For the combined Phase 3 studies, there were statistically significant differences between the subgroups defined by sex, anatomical location, baseline AK lesions, history of skin cancer, and prior use of 5-FU in terms of the complete clearance rate. These findings are as follows:

- Women were more likely than men to achieve complete clearance (odds ratio = 2.02; 95% CI: 1.05, 3.87; p = 0.035).
- Patients treated on the face were more likely than patients treated on the scalp to achieve complete clearance rate (odds ratio = 3.03; 95% CI: 1.55, 5.95; p = 0.001).
- Patients with fewer baseline AK lesions (four to six) were more likely to achieve complete clearance than patients with seven to eight lesions at baseline (odds ratio = 1.74; 95% CI: 1.04, 2.90; p = 0.034). However, a positive treatment effect is still evident in patients treated with PEP005 Gel who have more baseline lesions. In studies PEP005-016 and PEP005-025, subgroup analyses comparing the difference between PEP005 Gel and vehicle gel groups by baseline lesion count (four to six vs. seven to eight) was performed. Complete clearance was statistically significantly higher in the PEP005 Gel patients compared to vehicle for both subgroups. In PEP005-016, for the subgroup with fewer baseline lesions (four to six), 39% of PEP005 Gel and 3% of vehicle patients had complete clearance ($p < 0.001$) and for the subgroup with more baseline lesions (seven to eight), 34% of PEP005 Gel and 0% of vehicle patients had complete clearance ($p = 0.001$). In PEP005-025, for the subgroup with fewer baseline lesions (four to six), 56% of PEP005 Gel and 8% of vehicle patients had complete clearance ($p < 0.001$) and for the subgroup with more baseline lesions (seven to eight), 33% of PEP005 Gel and 0% of vehicle patients had complete clearance ($p < 0.001$). (See Module 5.3.5.1\PEP005-016 and \PEP005-025)

- Patients with no history of skin cancer were more likely to have complete clearance compared to patients with a history of skin cancer (odds ratio = 2.10; 95% CI: 1.29, 3.43; p = 0.003).
- Patients who had not previously used 5 FU were more likely to achieve complete clearance as those who had used 5 FU in the past (odds ratio = 2.27; 95% CI: 1.18, 4.34; p = 0.014).
- Other factors did not show statistically significant differences.

A summary of complete clearance rates in subgroups by demographic factors, baseline characteristics, and prior therapies based on the combined controlled Phase 2 and 3 studies population is presented in Module 5.3.5.3, Table 4.1.2. Results were similar to the findings for the combined Phase 3 studies.

Table 19: Univariate Subgroup Analyses of Complete Clearance Rate: Combined Controlled Phase 3 Studies (Intent-to-treat Population), Head (Face and Scalp) Locations

Subgroup[a]	Number of Patients	PEP005, 0.015% (N=277)				
		Complete Clearance		Odds Ratio		
	N	n (%)	95% CI	Ratio	95% CI	p value
Geographic region				1.51	0.59, 3.86	0.393
United States	256	110 (43.0)	36.8, 49.3			
Australia	21	7 (33.3)	14.6, 57.0			
Age Group						
<65 years	144	65 (45.1)	36.8, 53.6	1.28	0.79, 2.07	0.309
≥65 years	133	52 (39.1)	30.8, 47.9			
≤75 years	227	101 (44.5)	37.9, 51.2	1.70	0.89, 3.26	0.108
>75 years	50	16 (32.0)	19.5, 46.7			
Sex				2.02	1.05, 3.87	0.035
Fem ale	44	25 (56.8)	41.0, 71.7			
M ale	233	92 (39.5)	33.2, 46.1			
Fitzpatrick Skin Type[b]				1.10	0.67, 1.80	0.705
I and II	174	75 (43.1)	35.6, 50.8			
III and IV	103	42 (40.8)	31.2, 50.9			
Anatomical location				3.03	1.55, 5.95	0.001
Face	220	104 (47.3)	40.5, 54.1			
Scalp	57	13 (22.8)	12.7, 35.8			
Baseline AK lesions				1.74	1.04, 2.90	0.034
4, 5, 6 lesions	179	84 (46.9)	39.4, 54.5			
7, 8 lesions	98	33 (33.7)	24.4, 43.9			
History of skin cancer				2.10	1.29, 3.43	0.003
No	151	76 (50.3)	42.1, 58.6			
Yes	126	41 (32.5)	24.5, 41.5			
Prior cryotherapy				1.55	0.85, 2.82	0.155
No	53	27 (50.9)	36.8, 64.9			
Yes	224	90 (40.2)	33.7, 46.9			

[a] Race and ethnicity were included as subgroups but not presented here; all patients were Caucasian and only one of the 277 patients was Hispanic.

[b] Fitzpatrick Skin Type categories have been previously grouped and discussed as I, II and III versus IV, V, and VI; in these subgroup analyses they are grouped as I and II versus III and IV because the sample sizes in the subgroups would not be adequate to analyse otherwise (Type III, N = 84).

CI = confidence interval

Controlled Phase 3 studies (PEP005-016 and PEP005-025); only PEP005 Gel-treated patients were included in analyses.

The 95% CI for complete clearance uses the exact binomial method.

Odds Ratio = (odds of complete clearance in first subgroup)/(odds of complete clearance in second subgroup).

P value is for testing H_0: odds ratio = 1, using the Wald chi-square test from a 1-factor logistic regression model.

Source: Module 5.3.5.3, Table 4.1.1

Table 19: Univariate Subgroup Analyses of Complete Clearance Rate: Combined Controlled Phase 3 Studies (Intent-to-treat Population), Head (Face and Scalp) Locations

Subgroup[a]	Number of Patients	PEP005, 0.015% (N=277)				
		Complete Clearance		Odds Ratio		
	N	n (%)	95% CI	Ratio	95% CI	p value
Prior imiquimod				1.33	0.57, 3.13	0.509
No	252	108 (42.9)	36.7, 49.2			
Yes	25	9 (36.0)	18.0, 57.5			
Prior 5-fluorouracil				2.27	1.18, 4.34	0.014
No	222	102 (45.9)	39.3, 52.7			
Yes	55	15 (27.3)	16.1, 41.0			

[a] Race and ethnicity were included as subgroups but not presented here; all patients were Caucasian and only one of the 277 patients was Hispanic.
CI = confidence interval
Controlled Phase 3 studies (PEP005-016 and PEP005-025); only PEP005 Gel-treated patients were included in analyses.
The 95% CI for complete clearance uses the exact binomial method.
Odds Ratio = (odds of complete clearance in first subgroup)/(odds of complete clearance in second subgroup).
P value is for testing H_0: odds ratio = 1, using the Wald chi-square test from a 1-factor logistic regression model.
Source: Module 5.3.5.3, Table 4.1.1

3.4.1.1.2 Multiple Regression Analyses of Significant Factors

Based on the univariate logistic regression analyses presented in Section 3.4.1.1.1 , the variables with a p-value of 0.10 or less were used in a multiple logistic regression analysis. The objective of this exploratory analysis was to identify the subset of factors that best predicted complete clearance in the PEP005 Gel patients in this population. The analysis used a 0.05 significance level for the selection of factors to be included in the final model. In order to investigate the effect of the variable selection algorithm on the factors selected for inclusion in the final model, models using no variable selection, forward selection, backward selection, and stepwise selection were compared. Analyses were done for both the combined controlled Phase 3 studies population and the combined controlled Phase 2 and 3 studies population.

Results of the analyses for the combined Phase 3 studies population are presented in Table 20. Regardless of the method of variable selection for the multiple regression model (none, forward selection, backward selection, stepwise selection), the results were consistent. Three factors were significant in the multiple regression model: anatomical location, history of skin cancer, and prior use of 5 FU. Both sex and the number of lesions at baseline were not significant in the multiple regression model. The most significant factor in all multiple

regression models was anatomical location and therefore, more detailed analyses were performed, as provided in Section 3.4.1.1.3.

The multiple regression analyses for the combined Phase 2 and 3 studies population are provided in Module 5.3.5.3, Table 4.2.2. Results of the combined Phase 2 and 3 studies population were consistent with the results for the combined Phase 3 studies population.

Table 20: Summary of Multiple Regression Analyses of Complete Clearance Rate: Combined Controlled Phase 3 Studies (Intent-to-treat Population), Head (Face and Scalp) Locations

	Number of Observations = 277		
Model	**Odds Ratio**	**p-value**	**95% CI**
No Variable Selection			
Anatomical location	3.13	0.002	1.53, 6.41
Sex 0.	62	0.179	0.31, 1.24
Baseline AK lesions	1.47	0.168	0.85, 2.53
History of Skin Cancer	2.25	0.002	1.33, 3.80
Prior 5-fluorouracil	2.23	0.021	1.13, 4.41
Backward, Forward, and Stepwise Selection			
Anatomical location	3.59 <0.	001	1.78, 7.23
History of Skin Cancer	2.39 <0.	001	1.43, 4.00
Prior 5-fluorouracil	2.13 0.	028	1.09, 4.18

Controlled Phase 3 studies (PEP005-016 and PEP005-025); only PEP005 Gel-treated patients were included in analyses.
Source: Module 5.3.5.3, Table 4.2.1

3.4.1.1.3 **Analysis by Anatomical Location**

In both the univariate and multiple logistic regression models, anatomical location was the strongest predictor of complete clearance ($p = 0.001$ in the univariate analysis and $p \leq 0.002$ in the multiple regression analyses). Anatomical location was therefore further explored for patients treated on the face and scalp separately for the individual Phase 3 studies and each of the combined studies populations. Based on the combined Phase 3 studies population, the treatment groups were compared in terms of complete and partial clearance using the CMH test stratified on analysis site. The objectives of these exploratory summaries and analyses were 1) to investigate potential differences between the treatment groups separately for patients treated on the face and scalp, and 2) to identify any potential differences in complete clearance rates for subgroups defined by demographic and baseline disease characteristics separately for patients treated on the face and scalp.

Patient Demographics and Baseline Disease Characteristics by Anatomical Location

Demographic and baseline disease characteristics in individual Phase 3 studies and the combined Phase 3 studies population are summarised in Table 21 for patients treated on the face and in Table 22 for patients treated on the scalp.

For patients treated on the face, there were no apparent differences between the treatment groups for demographic and baseline disease characteristics in the individual studies (PEP005-016 and PEP005-025). Similar results were seen in the combined Phase 3 studies population. For the combined studies, 91% of the PEP005 Gel and 92% of the vehicle gel patients treated on the face were located in the US. Mean age was 63.8 years in the PEP005 Gel group and 64.5 years in the vehicle gel group. Approximately 80% of patients treated on the face were male (80% of PEP005 Gel and 83% of vehicle gel patients) and all were white. Over 90% of patients had Fitzpatrick skin type I, II or III (94% and 96% of the PEP005 Gel and vehicle gel patients treated on the face, respectively). The baseline lesion count was four to six in 66% of PEP005 Gel patients and 75% of vehicle gel patients. A history of skin cancer was present in 49% of PEP005 Gel patients and 47% of vehicle gel patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 81% and 84%, respectively; imiquimod: 9% and 11%, respectively; 5-FU: 19% in each treatment group).

When patients treated on the scalp were assessed, there were also no apparent differences between the treatment groups for demographic and baseline disease characteristics in the individual studies (PEP005-016 and PEP005-025). The combined Phase 3 studies population results were consistent with the results of the individual studies. In the combined Phase 3 studies, 97% of the PEP005 Gel and 96% of the vehicle gel scalp-treated patients were located in the US. Mean age was 65.7 years in the PEP005 Gel group and 62.2 years in the vehicle gel group. All scalp-treated patients were male and white. Over 90% of patients had Fitzpatrick skin type I, II, or III (91% and 92% of the PEP005 Gel and vehicle gel patients, respectively). The baseline lesion count was four to six in 58% of PEP005 Gel patients and 72% of vehicle gel patients. A history of skin cancer was present in 33% of PEP005 Gel patients and 32% of vehicle gel patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 81% and 84%; imiquimod: 11% and 12%; 5-FU: 23% and 22%, respectively).

For the combined Phase 2 and 3 studies population, demographic and baseline disease characteristics are provided in Module 5.3.5.3, Table 4.3.4. Results were similar to the combined Phase 3 studies population for patients in each anatomical location.

Table 21: Demographic and Baseline Disease Characteristics for Patients Treated on the Face in Individual Phase 3 Studies and Combined Phase 3 Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		Controlled Phase 3 Studies	
Parameter	**PEP005, 0.015% (N=109)**	**Vehicle (N=109)**	**PEP005, 0.015% (N=111)**	**Vehicle (N=111)**	**PEP005, 0.015% (N=220)**	**Vehicle (N=220)**
Geographic region (n [%])						
United States	101 (92.7)	101 (92.7)	100 (90.1)	101 (91.0)	201 (91.4)	202 (91.8)
Australia	8 (7.3)	8 (7.3)	11 (9.9)	10 (9.0)	19 (8.6)	18 (8.2)
Age (years)						
N	109 109		111 111		220	220
Mean (standard deviation)	63.3 (10.5)	63.6 (10.1)	64.2 (11.0)	65.4(10.2)	63.8 (10.8)	64.5 (10.1)
Minimum, Maximum	37-88 40-85		34-88 46-89		34-88	40-89
Sex (n [%])						
Male	90 (82.6)	95 (87.2)	86 (77.5)	87 (78.4)	176 (80.0)	182 (82.7)
Female	19 (17.4)	14 (12.8)	25 (22.5)	24 (21.6)	44 (20.0)	38 (17.3)
Fitzpatrick skin type (n [%])						
I	23 (21.1)	15 (13.8)	22 (19.8)	16 (14.4)	45 (20.5)	31 (14.1)
II	47 (43.1)	47 (43.1)	49 (44.1)	45 (40.5)	96 (43.6)	92 (41.8)
III	33 (30.3)	43 (39.4)	32 (28.8)	45 (40.5)	65 (29.5)	88 (40.0)
IV	6 (5.5)	4 (3.7)	8 (7.2)	5 (4.5)	14 (6.4)	9 (4.1)
Baseline lesion count (n [%])						
4	24 (22.0)	28 (25.7)	17 (15.3)	22 (19.8)	41 (18.6)	50 (22.7)
5	28 (25.7)	31 (28.4)	33 (29.7)	27 (24.3)	61 (27.7)	58 (26.4)
6	22 (20.2)	31 (28.4)	22 (19.8)	25 (22.5)	44 (20.0)	56 (25.5)
7	22 (20.2)	13 (11.9)	20 (18.0)	18 (16.2)	42 (19.1)	31 (14.1)
8	13 (11.9)	6 (5.5)	19 (17.1)	19 (17.1)	32 (14.5)	25 (11.4)
Skin cancer history (n [%])	55 (50.5)	56 (51.4)	52 (46.8)	48 (43.2)	107 (48.6)	104 (47.3)
Prior treatment (n [%])						
Cryotherapy	91 (83.5)	87 (79.8)	87 (78.4)	98 (88.3)	178 (80.9)	185 (84.1)
Imiquimod	6 (5.5)	10 (9.2)	13 (11.7)	15 (13.5)	19 (8.6)	25 (11.4)
5-Fluorouracil	20 (18.3)	19 (17.4)	22 (19.8)	22 (19.8)	42 (19.1)	41 (18.6)

Age by category, race, and ethnicity are provided in Module 5.3.5.3, Tables 4.3.1, 4.3.2, and 4.3.3.
Controlled Phase 3 studies (PEP005-016 and PEP005-025)
Source: Module 5.3.5.3, Tables 4.3.1, 4.3.2, and 4.3.3

Table 22: Demographic and Baseline Disease Characteristics for Patients Treated on the Scalp in Individual Phase 3 Studies and Combined Phase 3 Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		Controlled Phase 3 Studies	
Parameter	**PEP005, 0.015% (N=26)**	**Vehicle (N=25)**	**PEP005, 0.015% (N=31)**	**Vehicle (N=25)**	**PEP005, 0.015% (N=57)**	**Vehicle (N=50)**
Geographic region (n [%])						
United States	24 (92.3)	25 (100)	31 (100)	23 (92.0)	55 (96.5)	48 (96.0)
Australia	2 (7.7)	0	0	2 (8.0)	2 (3.5)	2 (4.0)
Age (years)						
n	26 25		31 25		57	50
Mean (standard deviation)	64.5 (10.4)	60.8 (9.5)	66.8 (11.7)	63.6 (9.9)	65.7 (11.1)	62.2 (9.7)
Minimum, Maximum	40-86 45-80		44-85 46-84		40-86	45-84
Sex (n [%])						
Male	26 (100)	25 (100)	31 (100)	25 (100)	57 (100)	50 (100)
Female	0 0		0 0		0	0
Fitzpatrick skin type (n [%])						
I	1 (3.8)	1 (4.0)	5 (16.1)	2 (8.0)	6 (10.5)	3 (6.0)
II	11 (42.3)	6 (24.0)	16 (51.6)	14 (56.0)	27 (47.4)	20 (40.0)
III	11 (42.3)	16 (64.0)	8 (25.8)	7 (28.0)	19 (33.3)	23 (46.0)
IV	3 (11.5)	2 (8.0)	2 (6.5)	2 (8.0)	5 (8.8)	4 (8.0)
Baseline lesion count (n [%])						
4	3 (11.5)	4 (16.0)	4 (12.9)	3 (12.0)	7 (12.3)	7 (14.0)
5	8 (30.8)	13 (52.0)	6 (19.4)	8 (32.0)	14 (24.6)	21 (42.0)
6	6 (23.1)	4 (16.0)	6 (19.4)	4 (16.0)	12 (21.1)	8 (16.0)
7	5 (19.2)	2 (8.0)	7 (22.6)	3 (12.0)	12 (21.1)	5 (10.0)
8	4 (15.4)	2 (8.0)	8 (25.8)	7 (28.0)	12 (21.1)	9 (18.0)
Skin cancer history (n [%])	10 (38.5)	7 (28.0)	9 (29.0)	9 (36.0)	19 (33.3)	16 (32.0)
Prior treatment (n [%])						
Cryotherapy	21 (80.8)	21 (84.0)	25 (80.6)	21 (84.0)	46 (80.7)	42 (84.0)
Imiquimod	1 (3.8)	5 (20.0)	5 (16.1)	1 (4.0)	6 (10.5)	6 (12.0)
5-Fluorouracil	6 (23.1)	6 (24.0)	7 (22.6)	5 (20.0)	13 (22.8)	11 (22.0)

Age by category, race, and ethnicity are provided in Module 5.3.5.3, Tables 4.3.1, 4.3.2, and 4.3.3.
Controlled Phase 3 studies (PEP005-016 and PEP005-025)
Source: Module 5.3.5.3, Tables 4.3.1, 4.3.2, and 4.3.3

Efficacy Results by Anatomical Location

The same efficacy endpoints as analysed for the overall study populations (Section 3) were selected for comparison by anatomical location and included complete clearance rate, partial clearance rate, and percent change in AK lesion count. Percent change in total AK lesion count was also presented by anatomical location for the combined studies populations. Data are presented for the ITT population.

Efficacy results in the individual Phase 3 studies and combined Phase 3 studies population are summarised in Table 23 for patients treated on the face and in Table 24 for patients treated on the scalp. It should be noted that the sample size in these analysis of the combined Phase 3 studies for patients treated on the face is larger than for patients treated on the scalp (n = 440 and n = 107, respectively).

For patients treated on the face, the complete clearance rate was 42%, 52%, and 47% for PEP005 Gel-treated patients compared to 3%, 5%, and 4% for vehicle gel-treated patients in PEP005-016, PEP005-025, and the combined Phase 3 studies, respectively ($p < 0.001$ for each study). The difference between the treatment groups for partial clearance rate was also statistically significant (69%, 74%, and 71% for PEP005 Gel-treated patients compared to 7%, 9%, and 8% for vehicle gel-treated patients in PEP005-016, PEP005-025, and the combined Phase 3 studies respectively [$p < 0.001$ for each study]). The median reduction in the number of AK lesions compared to baseline was 83%, 100%, and 88% for the PEP005 Gel, 0.015% versus 0% in the vehicle gel group for PEP005-016, PEP005-025, and the combined Phase 3 studies, respectively. Percent change in total lesion count which was analysed for the combined Phase 3 studies but not the individual studies, showed a reduction that was substantially greater in the PEP005 Gel group (77% compared to 14% in the vehicle gel group).

For patients treated on the scalp, the complete clearance rate was 15%, 29%, and 23% for PEP005 Gel-treated patients compared to 0%, 4%, and 2% for vehicle gel-treated patients in PEP005-016, PEP005-025, and the combined Phase 3 studies, respectively. Results were statistically significant for PEP005-025 ($p = 0.031$) and the combined Phase 3 studies ($p = 0.001$) but not for PEP005-016 ($p = 0.110$). Partial clearance rate was 23%, 45%, and 35% for PEP005 Gel-treated patients compared to 4% for each of the vehicle gel groups in PEP005-016, PEP005-025, and the combined Phase 3 studies respectively. Results were statistically significant for PEP005-025 ($p < 0.001$) and the combined Phase 3 studies ($p < 0.001$) but not for PEP005-016 ($p = 0.099$). The median reduction in the number of AK

lesions compared to baseline was 49%, 63%, and 57% for the PEP005 Gel, 0.015% versus 25%, 0%, and 0% in the vehicle gel group for PEP005-016, PEP005-025, and the combined Phase 3 studies, respectively. Percent change in total lesion count which was analysed for the combined Phase 3 studies but not the individual studies, showed a reduction that was substantially greater in the PEP005 Gel group (54% compared to 16% in the vehicle gel group).

For the combined Phase 2 and 3 studies population by anatomical location, efficacy results are presented in Module 5.3.5.3, Table 4.4.4. Results were consistent with the combined Phase 3 studies population.

Table 23: Efficacy Results for Patients Treated on the Face in Individual Phase 3 Studies and Combined Phase 3 Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

Efficacy Parameter	PEP005-016		PEP005-025		Controlled Phase 3 Studies	
	PEP005, 0.015% (N=109)	Vehicle (N=109)	PEP005, 0.015% (N=111)	Vehicle (N=111)	PEP005, 0.015% (N=220)	Vehicle (N=220)
Complete Clearance						
n (%)	46 (42.2)	3 (2.8)	58 (52.3)	6 (5.4)	104 (47.3)	9 (4.1)
95% CI	32.8, 52.0	0.6, 7.8	42.6, 61.8	2.0, 11.4	40.5, 54.1	1.9, 7.6
P value	<0.001		<0.001		<0.001	
Partial Clearance						
n (%)	75 (68.8)	8 (7.3)	82 (73.9)	10 (9.0)	157 (71.4)	18 (8.2)
95% CI	59.2, 77.3	3.2, 14.0	64.7, 81.8	4.4, 15.9	64.9, 77.2	4.9, 12.6
P value	<0.001		<0.001		<0.001	
Percent Reduction in AK Lesions						
n	107	108 1	11	111 2	18	219
Median	83 0		100	0 8	8 0	
Range	-50, 100 -	100, 100 -	25, 100	-100, 100 -	50, 100 -	100, 100
Total AK Lesion Count						
Baseline	not done	not done	not done	not done	1271	1238
End of study (Day 57)	not done	not done	not done	not done	290	1069
Percent change	not done	not done	not done	not done	77	14

CI = confidence interval
Controlled Phase 3 studies (PEP005-016 and PEP005-025)
Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)
P value is for comparing active treatment vs. vehicle, using Fisher's Exact test.
The 95% CI uses the exact binomial method.
Source: Module 5.3.5.3, Tables 4.4.1, 4.4.2, and 4.4.3

Table 24: Efficacy Results for Patients Treated on the Scalp in Individual Phase 3 Studies and Combined Phase 3 Studies Populations: Intent-to-treat Population, Head (Face and Scalp) Locations

	PEP005-016		PEP005-025		Controlled Phase 3 Studies	
Efficacy Parameter	**PEP005, 0.015% (N=26)**	**Vehicle (N=25)**	**PEP005, 0.015% (N=31)**	**Vehicle (N=25)**	**PEP005, 0.015% (N=57)**	**Vehicle (N=50)**
Complete Clearance						
n (%)	4 (15.4)	0	9 (29.0)	1 (4.0)	13 (22.8)	1 (2.0)
95% CI	4.4, 34.9	0.0, 13.7	14.2, 48.0	0.1, 20.4	12.7, 35.8	0.1, 10.6
P value	0.110		0.031		0.001	
Partial Clearance						
n (%)	6 (23.1)	1 (4.0)	14 (45.2)	1 (4.0)	20 (35.1)	2 (4.0)
95% CI	9.0, 43.6	0.1, 20.4	27.3, 64.0	0.1, 20.4	22.9, 48.9	0.5, 13.7
P value	0.099		<0.001		<0.001	
Percent Reduction in AK Lesions						
n	24 25	31		25 55	50	
Median	49 25	63		0	57	0
Range	-25, 100	-40, 75	-17, 100	-60, 100	-25, 100	-60, 100
Total AK Lesion Count						
Baseline	not done	not done	not done	not done	336	288
End of study (Day 57)	not done	not done	not done	not done	156	243
Percent change	not done	not done	not done	not done	54	16

CI = confidence interval
Controlled Phase 3 studies (PEP005-016 and PEP005-025); controlled Phase 2 and 3 studies (PEP005-015, PEP005-016, and PEP005-025)
Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)
P value is for comparing active treatment vs. vehicle, using Fisher's Exact test.
The 95% CI uses the exact binomial method.
Source: Module 5.3.5.3, Tables 4.4.1, 4.4.2, and 4.4.3.

Subpopulation Evaluation by Anatomical Location

In order to fully understand the factors which may influence treatment in each anatomical location, univariate subgroup analyses were performed by anatomical location for the combined Phase 3 studies population and the combined Phase 2 and 3 studies population. In addition, multiple regression analyses were also performed by anatomical location for these combined studies populations.

The univariate subgroup and multiple regression n analyses by anatomical location are provided in Module 5.3.5.3, Tables 4.5.1 and 4.5.2 for the combined Phase 3 studies population and combined Phase 2 and 3 studies population, respectively. The multiple regression analyses by anatomical location are provided in Module 5.3.5.3, Tables 4.6.1 and 4.6.2 for the same populations. The objective of the subgroup analyses by anatomical location was to investigate whether the observed effects of PEP005 Gel, 0.015% were consistent across other factors when face and scalp patients were evaluated separately.

For patients treated on the face, in the combined Phase 3 studies population, the univariate analyses showed three factors that were significant. Patients with fewer baseline AK lesions (four to six) were more likely to achieve complete clearance than patients with seven to eight lesions at baseline (odds ratio = 2.12; 95% CI: 1.19, 3.77; p = 0.011). Patients with no history of skin cancer were more likely to have complete clearance compared to patients with a history of skin cancer (odds ratio = 2.98; 95% CI: 1.72, 5.17; p <= 0.001). Patients who had not previously used 5-FU were more likely to achieve complete clearance as those who had used 5 FU in the past (odds ratio = 2.67; 95% CI: 1.29, 5.56; p = 0.008). Other factors did not show statistically significant differences. In particular, there was no significant difference in complete clearance rates between males and females treated on the face. In the multiple regression model, these three factors were also statistically significant (baseline AK lesions; p = 0.046; history of skin cancer, p < 0.001; prior 5 FU treatment, p = 0.014). The findings of the univariate and multiple regression analyses in the combined Phase 2 and 3 studies population were consistent with the results of the combined Phase 3 studies for patients treated on the face except in the multiple regression analyses, baseline AK lesion count was not significant.

In the combined Phase 3 studies population, the univariate analyses showed that there were no significant differences in clearance rates between the subgroups defined by the demographic and baseline characteristics of the scalp-treated patients. The multiple regression model provided the same results; no factors significantly impacted treatment on the scalp. The

findings of the univariate and multiple regression analyses in the combined Phase 2 and 3 studies population are consistent with the results of the combined Phase 3 studies.

3.4.1.2 Exploratory Analyses of Local Skin Response with Efficacy

Exploratory analyses were performed to examine the association of LSR with efficacy for patients treated with PEP005 Gel in the combined controlled Phase 3 studies and combined controlled Phase 2 and 3 studies population. The vehicle gel patients were not included. These analyses were not included in the SAP (Module 5.3.5.3).

Two types of exploratory analyses were performed, as follows:

1. The correlation of complete clearance, partial clearance, and percent reduction in AK lesion count with the maximum composite LSR score, erythema, swelling, crusting, flaking/scaling, vesiculation/pustulation, and erosion/ulceration was investigated using Spearman rank correlations.
2. For each LSR variable, the value of the maximum score which provided the greatest difference between patients who achieved complete clearance and those who did not achieve complete clearance was determined. The two subgroups defined by the value which provided the greatest difference (scores < value with greatest difference versus scores ≥ value with greatest difference) were compared in terms of the percentage of patients achieving complete clearance using Fisher's exact test for each LSR variable.

Results of the analyses of maximum composite LSR scores versus complete clearance status for patients treated with PEP005 Gel in the combined Phase 3 studies are presented in Table 25.

The mean maximum composite LSR score was 9.1 for all PEP005 Gel-treated patients. When patients were evaluated by complete clearance status, the mean maximum composite LSR scores were greater for patients with complete clearance than for patients who did not achieve complete clearance.

Table 25: Maximum Composite LSR Scores in PEP005 Gel Patients for Combined Controlled Phase 3 Studies Population: Safety Population, Head (Face and Scalp) Locations

		N	Mean
All PEP005 Gel Patients	2	73	9.1
Achieved Complete Clearance	Yes 1	17	10.1
N	o	156	8.4

Controlled Phase 3 studies (PEP005-016 and PEP005-025)

Source: Module 5.3.5.3, Table 4.7.1

The significant results ($p \leq 0.05$) based on Spearman rank correlations are summarised in Table 26.

All correlations between the three efficacy endpoints and composite LSR scores were positive with higher LSR scores associated with achieving complete clearance, partial clearance, and greater percent reduction in the number of AK lesions. The strongest correlations were observed for maximum scores of composite LSR and swelling, followed by erythema.

Table 26: Significant Correlations for Efficacy Endpoints and Local Skin Responses in PEP005 Gel Patients for Combined Controlled Phase 3 Studies Population: Safety Population, Head (Face and Scalp) Locations

(N = 273)

Efficacy Endpoint	Local Skin Response Variable	Correlation	P value
Complete clearance (N = 273)	Maximum Composite	0.211	<0.001
M	aximum Vesiculation	0.123	0.043
M	aximum Erythema	0.129	0.033
M	aximum Swelling	0.250	<0.001
Partial clearance (N = 273)	Maximum Composite	0.279	<0.001
M	aximum Vesiculation	0.168	0.005
M	aximum Erosion	0.131	0.030
Max	imum Erythema	0.224	<0.001
M	aximum Crusting	0.135	0.026
M	aximum Swelling	0.279	<0.001
Percent Reduction in AK lesions (N = 272)	Maximum Composite	0.292	<0.001
M	aximum Vesiculation	0.171	0.005
M	aximum Erosion	0.130	0.032
M	aximum Erythema	0.209	0.001
M	aximum Crusting	0.143	0.018
M	aximum Swelling	0.295	<0.001

Controlled Phase 3 studies (PEP005-016 and PEP005-025)

P-value is for testing if Spearman rank correlation between each efficacy endpoint and each LSR variable is significantly different from zero.

Source: Module 5.3.5.3, Table 4.8.1

Since there was consistent evidence to suggest a positive association between maximum LSR score and efficacy, an analysis was performed to determine the value of the maximum score for each LSR variable which provided the greatest difference between achieving or not achieving complete clearance. This determination was based on the p value for comparing the two subgroups defined by the value. The analysis was restricted to values that resulted in no more than 75% of the patients (e.g., 204 out of 273) in each subgroup. Table 27 summarises the results of these analyses when the difference was significant ($p \leq 0.05$) or approached significance ($0.10 \leq p < 0.05$).

Composite LSR and erythema were the variables with scores that provided the greatest difference between the complete clearance rates. For the maximum composite LSR score, the value which provided the greatest difference was 10. For maximum erythema, the value which provided the greatest difference was 3. Similar to the results for the correlations, a maximum swelling value of 2 was associated with a large difference between the complete clearance rates.

Table 27: Values of Maximum Local Skin Response Scores with Greatest Difference Between Achieving and Not Achieving Complete Clearance in PEP005 Gel Patients for Combined Controlled Phase 3 Studies Population: Safety Population, Head (Face and Scalp) Locations

(N = 273)

Local Skin Response Variable	Value of LSR Score with Greatest Difference	Clearance Rate < Value with Greatest Difference	Clearance Rate ≥ Value with Greatest Difference	P value
		n/N (%)	n/N (%)	
Maximum Composite	10	55/159 (34.6)	62/114 (54.4)	0.001
Maximum Erythema	3	24/82 (29.3)	93/191 (48.7)	0.003
Maximum Swelling	2	46/144 (31.9)	71/129 (55.0)	<0.001
Maximum Vesiculation	2	59/155 (38.1)	58/118 (49.4)	0.084

Controlled Phase 3 studies (PEP005-016 and PEP005-025)

P value is Fisher's Exact test comparing the two subgroups defined by the value of the maximum LSR score which provided the greatest difference (scores < value with greatest difference versus scores ≥ value with greatest difference) in terms of the percentage of patients achieving complete clearance.
Source: Module 5.3.5.3, Table 4.9.1

A summary of the association of maximum LSR scores with efficacy for the combined controlled Phase 2 and 3 studies population is presented in Module 5.3.5.3, Tables 4.7.2, 4.8.2, and 4.9.2. The results were consistent with the findings of the combined Phase 3 studies population.

3.4.1.3 Summary

The univariate subgroup analyses that were planned and specified in the SAP (Module 5.3.5.3) for this efficacy summary showed five factors appeared to impact complete clearance in patients who received PEP005 Gel. These five factors included anatomical location, history of skin cancer, prior 5-FU use, number of baseline AK lesions, and sex.

Although sex first appeared to be a significant factor, upon further exploration, it became clear this effect was driven by the fact that all scalp patients were male. When the univariate subgroup and the multiple regression analyses by anatomical location were performed for patients treated on the face, there was no statistically significant effect seen for sex.

For baseline AK lesions, the univariate subgroup analyses showed statistical significance but it was not a significant factor in the multiple regression analyses. Baseline AK lesions remained significant in the univariate and multiple regression analyses for patients treated on the face. In both of the Phase 3 studies (PEP005-016 and PEP005-025), the PEP005 Gel group was compared to vehicle by baseline lesion count; a statistically significant treatment effect was evident in PEP005 Gel patients compared to vehicle for both subgroups of baseline lesion count (four to six and seven to eight). Yet, studies suggest that keratoses which are numerous and thick may only partially respond to treatment.(51,62) Thus, clinically it is reasonable to conclude that fields of AK with a higher number of lesions may not achieve complete clearance as often as fields with fewer AKs.

Published research also support the concept that patients who have had an occurrence of skin cancer, or who have had to previously resort to treatment with 5-FU, may have had more UV exposure without sunscreen protection.(63) History of skin cancer and prior 5-FU use as significant factors most likely represent patients who have more severe disease.

Anatomical location was the strongest predictor of complete clearance, with patients treated on the face having a higher likelihood of achieving complete clearance ($p = 0.001$ in the univariate and $p \leq 0.002$ in the multiple regression analyses). It should also be noted that the sample size in these analysis of the combined Phase 3 studies for patients treated on the face was larger than for patients treated on the scalp ($n = 440$ and $n = 107$, respectively). Previous reports have documented a higher response rate for facial AKs, which are typically thinner and less severe than those located on the scalp.(64) Scalp AKs are known to be much less responsive to treatment.(65)

In summary, when the subgroup analyses were performed separately for each anatomical location, no factors influenced the rate of complete clearance in scalp patients, whereas, the factors that influenced complete clearance in the overall combined studies (baseline AK lesions, history of skin cancer, and prior use of 5-FU) also influenced complete clearance of patients treated on the face. Nonetheless, for patients who received PEP005 Gel treatment on the face, a consistent treatment effect was seen in each individual Phase 3 study and in the combined studies ($p < 0.001$ in each). A treatment effect was also seen in the patients who

received PEP005 Gel on the scalp. In the scalp-treated patients, the results of study PEP005-016 were not statistically significant for the complete clearance rate but were numerically in favour of PEP005 Gel. Results of study PEP005-025 and the combined populations were statistically significant, and taken collectively, showed a consistent effect. Even though the clearance rates for face and scalp were significantly different for the PEP005 Gel-treated patients when the prespecified univariate analyses were performed, it is evident that PEP005 Gel is effective for each anatomical location based on evaluating patients treated on the face and scalp separately.

The results of the exploratory analyses of LSR with efficacy showed there were consistent, significant positive associations of maximum composite LSR score, maximum swelling score, and maximum erythema score with complete clearance, partial clearance, and percent reduction in AK lesion count. Patients with a maximum composite score of at least 10 had a complete clearance rate of 54% versus 35% for patients with a score less than 10. The maximum vesiculation scores showed a trend for association with complete clearance that was sometimes statistically significant. The maximum flaking and crusting scores did not seem to be associated with achieving complete clearance.

3.4.2 Non-Head (Trunk and Extremities) Locations

3.4.2.1 Complete Clearance by Subpopulations of Demographic and Baseline Characteristics

The efficacy endpoint of interest for comparison of subgroups is complete clearance. The combined studies populations were used for the prospectively planned analyses. Only patients who received PEP005 Gel were included in these subgroup analyses; patients who received vehicle gel were omitted since the focus was on differences in clearance rates among subgroups; the complete clearance rate for the vehicle gel-treated patients was minimal (11 patients for the combined Phase 3 studies population). The objective of the subgroup analyses was to investigate the observed effects of PEP005 Gel, 0.05% for consistency across all subgroups. All summaries and analyses were based on the ITT population.

A logistic regression model was used to compare subgroups in the univariate analyses. The odds ratio with 95% CI and p value from the Wald Chi-square statistic were reported in addition to summary statistics for each subgroup. These were a priori planned exploratory analyses to investigate any apparent differences between various subgroups of patients in terms of complete clearance rate for PEP005 Gel, 0.05% applied to a contiguous 25 cm^2

treatment area for two consecutive days on non-head (trunk and extremities) locations. As exploratory analyses, they do not carry the same statistical or clinical weight as the treatment group comparisons conducted for the adequate and well controlled studies. The information in this section was examined for consistency of effect among subsets of the overall population.

Additional exploratory analyses were performed after the findings from the univariate logistic regressions were assessed. These additional exploratory analyses included multiple logistic regression analyses performed for the combined studies populations, summaries of demographic, baseline disease characteristics, and efficacy by anatomical location, and univariate subgroup analyses by anatomical location. Exploratory analyses are further explained prior to presentation in the sections where presented (Sections 3.4.2.1.2 and 3.4.2.1.3). All subgroup analyses are provided in Module 5.3.5.3, Tables 10.1.1 through 10.5.3.

3.4.2.1.1 **Univariate Analyses of Subpopulations**

A summary of complete clearance rates in selected subpopulations in the combined controlled Phase 3 studies population is presented in Table 28.

For the combined Phase 3 studies, there were statistically significant differences ($p \leq 0.05$) between subgroups defined by anatomical location (back of hand vs. not back of hand), number of baseline AK lesions (4–6 vs. 7–8), and age group (< 65 vs. ≥ 65 years) in terms of the complete clearance rate. These findings are as follows:

- Patients treated with PEP005 Gel on the back of hand were less likely to achieve complete clearance than patients treated on other non-head locations (odds ratio for non-back of hand versus back of hand = 2.81; 95% CI: 1.32, 5.96; p = 0.007).
- Patients with fewer baseline lesions (4–6) were more likely to achieve complete clearance than patients with more baseline lesions (7–8) (odds ratio = 2.29; 95% CI: 1.07, 4.90; p = 0.032). However, a positive treatment effect is still evident in patients treated with PEP005 Gel who have more baseline lesions. In study PEP005-028, a subgroup analyses comparing the difference between PEP005 Gel and vehicle gel groups by baseline lesion count (4-6 vs. 7-8) was performed. Complete clearance was statistically significantly higher in the PEP005 Gel patients compared to vehicle for both subgroups. For the subgroup with fewer baseline lesions (4-6), 44% of PEP005 Gel and 5% of vehicle patients had complete clearance (p < 0.001) and for the subgroup with more baseline lesions (7-8),

33% of PEP005 Gel and 3% of vehicle patients had complete clearance (p = 0.009). (See Module 5.3.5.1/PEP005-028)

- Patients < 65 years were more likely to achieve complete clearance than older (≥ 65 years) patients (odds ratio = 1.75; 95% CI: 1.00, 3.06; p = 0.048). The difference between patients < 75 and ≥ 75 years was not statistically significant.

A summary of complete clearance rates in subgroups by demographic factors, baseline characteristics, and prior therapies based on the combined controlled Phase 2 and 3 studies population is presented in Module 5.3.5.3, Table 10.1.2 and for the combined controlled and uncontrolled Phase 2 and 3 studies in Module 5.3.5.3, Table 10.1.3. Overall, statistically significant differences between subgroups defined by anatomical location (back of hand vs. not back of hand) and number of baseline AK lesions (4–6 vs. 7–8) were seen across the three combined analysis populations. Statistically significant differences between age groups (< 65 vs. ≥ 65 years) were not evident in the combined controlled and uncontrolled Phase 2 and 3 studies population (p = 0.078). Other subgroups with an observed difference in complete clearance rates were country (US vs. Australia) and history of skin cancer (yes vs. no) and were observed only in the combined controlled and uncontrolled Phase 2 and 3 studies population.

Table 28: Subgroup Analyses of Complete Clearance Rate: Combined Controlled Phase 3 Studies (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations

Subgroup[a]	Number of Patients	PEP005 Gel, 0.05% (N=226)				
		Complete Clearance		Odds Ratio		
		n (%)	95% CI	Ratio	95% CI	p value
Geographic region						
United States	210	72 (34.3)	27.9, 41.1	1.15	0.38, 3.43	0.805
Australia	16	5 (31.3)	11.0, 58.7			
Age Group						
< 65 years	94	39 (41.5)	31.4, 52.1	1.75	1.00, 3.06	0.048
≥ 65 years	132	38 (28.8)	21.2, 37.3			
< 75 years	178	65 (36.5)	29.4, 44.0	1.73	0.84, 3.55	0.138
≥ 75 years	48	12 (25.0)	13.6, 39.6			
Sex						
Female	81	29 (35.8)	25.4, 47.2	1.13	0.64, 1.99	0.681
M ale	145	48 (33.1)	25.5, 41.4			
Fitzpatrick Skin Type[b]						
I and II	157	52 (33.1)	25.8, 41.1	0.87	0.48, 1.58	0.650
III, IV, V, VI	69	25 (36.2)	25.0, 48.7			
Anatomical location						
Not arm	84	28 (33.3)	23.4, 44.5	0.95	0.54, 1.68	0.858
Arm	142	49 (34.5)	26.7, 42.9			
Not back of hand	172	67 (39.0)	31.6, 46.7	2.81	1.32, 5.96	0.007
Back of hand	54	10 (18.5)	9.3, 31.4			
Baseline AK lesions						
4, 5, 6	178	67 (37.6)	30.5, 45.2	2.29	1.07, 4.90	0.032
7, 8	48	10 (20.8)	10.5, 35.0			
History of skin cancer						
No	105	42 (40.0)	30.6, 50.0	1.64	0.94, 2.85	0.081
Yes	121	35 (28.9)	21.0, 37.9			

CI = confidence interval
Controlled Phase 3 studies: PEP005-014 and PEP005-028.
[a] Race and ethnicity are included as subgroups in Module 5.3.5.3, Table 10.1.1; all patients were Caucasian and only 3 of the 266 patients were Hispanic.
[b] Fitzpatrick Skin Type categories have been previously grouped and discussed as I, II and III versus IV, V, and VI; in these analyses they are grouped as I and II versus III, IV, V, VI because the sample sizes in the sub-groups would not be distributed sufficiently to analyse otherwise.
Percentages based number of patients in each subgroup.
The 95% CI for complete clearance using the exact binomial method.
Odds Ratio = (odds of complete clearance in first subgroup)/(odds of complete clearance in second subgroup).
p-value testing H0: odds ratio = 1, using the Wald chi-square test from a 1-factor logistic regression model. Only PEP005 Gel-treated patients were included in analyses
Source: Module 5.3.5.3, Table 10.1.1.

Table 28: Subgroup Analyses of Complete Clearance Rate: Combined Controlled Phase 3 Studies (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations

Subgroup[a]	Number of Patients	PEP005 Gel, 0.05% (N=226)				
		Complete Clearance		Odds Ratio		
		n (%)	95% CI	Ratio	95% CI	p value
Prior cryotherapy						
No	56	23 (41.1)	28.1, 55.0	1.50	0.80, 2.79	0.204
Yes	170	54 (31.8)	24.8, 39.3			
Prior imiquimod						
No	205	67 (32.7)	26.3, 39.6	0.53	0.22, 1.32	0.174
Yes	21	10 (47.6)	25.7, 70.2			
Prior 5-fluorouracil						
No	176	59 (33.5)	26.6, 41.0	0.90	0.46, 1.73	0.744
Yes	50	18 (36.0)	22.9, 50.8			

CI = confidence interval
Controlled Phase 3 studies: PEP005-014 and PEP005-028.
[a] Race and ethnicity are included as subgroups in Module 5.3.5.3, Table 10.1.1; all patients were Caucasian and only 3 of the 266 patients were Hispanic.
Percentages based number of patients in each subgroup.
The 95% CI for complete clearance using the exact binomial method.
Odds Ratio = (odds of complete clearance in first subgroup)/(odds of complete clearance in second subgroup).
p-value testing H0: odds ratio = 1, using the Wald chi-square test from a 1-factor logistic regression model. Only PEP005 Gel-treated patients were included in analyses
Source: Module 5.3.5.3, Table 10.1.1.

3.4.2.1.2 **Multiple Regression Analyses of Significant Factors**

Multiple regression analyses were performed to further explore the factors found to be significant ($p \leq 0.05$) in the planned univariate analyses (Section 3.4.2.1.1). Four factors were included in the multiple regression models: the two factors found to be consistently significant in the univariate analyses (anatomical location and number of baseline AK lesions); age group, which was significant in two of the three combined analysis populations; and history of skin cancer, which was significant in one of the three combined analysis populations and was also a significant factor in the head (face and scalp) studies (see Section 3.4.1). Four multiple regression models were performed using no variable selection, backward selection, forward selection, and stepwise selection. Analyses were performed for the three combined analysis populations: controlled Phase 3 studies population, controlled Phase 2 and 3 studies population, and controlled and uncontrolled Phase 2 and 3 studies population.

Results of the analyses for the combined controlled Phase 3 studies population are presented in Table 29. As shown in the table, anatomical location was a significant factor regardless of the method of variable selection in the multiple regression model (none, forward selection, backward selection, stepwise selection).

Anatomical location, number of baseline AK lesions, and age (<65 versus ≥65 years) were significant in the multiple regression model for the combined controlled Phase 2 and 3 studies population. Anatomical location and number of baseline AK lesions were significant in each multiple regression model for the combined controlled and uncontrolled Phase 2 and 3 studies population. The multiple regression analyses for the combined controlled Phase 2 and 3 studies population and combined controlled and uncontrolled Phase 2 and 3 studies population are provided in Module 5.3.5.3, Table 10.2.2 and Table 10.2.3, respectively.

Table 29: Multiple Regression Analyses of Complete Clearance Rate: Combined Controlled Phase 3 Studies (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations

	Number of Observations = 226		
Model	**Odds Ratio**	**p-value**	**95% CI**
No Variable Selection			
Anat omical location (back of hand vs. not back of hand)	2.48 0.	020	1.15, 5.33
No. baseline AK lesions (4–6 vs. 7–8)	1.99 0.	086	0.91, 4.36
Age group (< 65 vs. ≥ 65 years)	1.59 0.	115	0.88, 2.85
History of skin cancer (y es vs. no)	1.35 0.	314	0.75, 2.41
Backward, Forward, and Stepwise Selection			
Anat omical location (back of hand vs. not back of hand)	2.51 0.	018	1.17, 5.40

CI = confidence interval
Controlled Phase 3 studies: PEP005-014 and PEP005-028. Only PEP005 Gel-treated patients were included in analyses.
Source: Module 5.3.5.3, Table 10.2.1.

3.4.2.1.3 **Analysis by Anatomical Location**

In both the univariate and multiple logistic regression models, anatomical location was a significant factor (p = 0.007 in the univariate analysis and p = 0.018 in the multiple regression analyses). Anatomical location was therefore further explored for patients treated on the arm, back of hand, and other non-head locations (back, shoulder, leg, chest) separately for the individual Phase 3 studies and each of the combined studies populations. Based on the combined Phase 3 studies population, the treatment groups were compared in terms of complete and partial clearance using the CMH test stratified on analysis site. The objectives of these exploratory summaries and analyses were 1) to investigate potential differences between the treatment groups separately for patients treated on the arm, back of hand, and other non-head locations, and 2) to identify any potential differences in complete clearance

rates for subgroups defined by demographic and baseline disease characteristics separately for patients treated on the arm, back of hand, and other non-head locations.

Patient Demographics and Baseline Disease Characteristics by Anatomical Location
Summaries of demographic and baseline disease characteristics by anatomic location (arm, back of hand, and other non-head locations [back, shoulder, leg, chest]) for the individual Phase 3 studies and the combined analysis populations are provided in Module 5.3.5.3, Table 10.3.1 (PEP005-014), Table 10.3.2 (PEP005-028), Table 10.3.3 (combined controlled Phase 3 studies population), Table 10.3.4 (combined controlled Phase 2 and 3 studies population), and Table 10.3.5 (combined controlled and uncontrolled Phase 2 and 3 studies population).

For patients treated on the arm, there were no apparent differences between the treatment groups for demographic and baseline disease characteristics in the individual studies (PEP005-014 and PEP005-028). Similar results were seen in the combined Phase 3 studies population. For the combined studies, 93% of the PEP005 Gel and 95% of the vehicle gel patients treated on the arm were located in the US. Mean age was 65.4 years in the PEP005 Gel group and 66.0 years in the vehicle gel group. Approximately 65% of patients treated on the arm were male (68% of PEP005 Gel and 62% of vehicle gel patients) and all were white. Over 90% of patients had Fitzpatrick skin type I, II or III (93% and 95% of the PEP005 Gel and vehicle gel patients treated on the arm, respectively). The baseline lesion count was four to six in 81% of PEP005 Gel patients and 79% of vehicle gel patients. A history of skin cancer was present in 49% of PEP005 Gel patients and 53% of vehicle gel patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 68% and 77%, respectively; imiquimod: 8% and 11%, respectively; 5-FU: 18% and 24%, respectively).

When patients treated on the back of hand were assessed, no apparent differences between the treatment groups for demographic and baseline disease characteristics were noted in the individual studies (PEP005-014 and PEP005-028). Similar results were seen in the combined Phase 3 studies population. For the combined studies, 94% of the PEP005 Gel and 93% of the vehicle gel patients treated on the back of hand were located in the US. Mean age was 68.6 years in the PEP005 Gel group and 66.9 years in the vehicle gel group. Approximately 70% of patients treated on the back of hand were male (67% of PEP005 Gel and 73% of vehicle gel patients) and all were white. Over 90% of patients had Fitzpatrick skin type I, II or III (91% and 96% of the PEP005 Gel and vehicle gel patients treated on the back of hand, respectively). The baseline lesion count was four to six in 69% of PEP005 Gel patients and

63% of vehicle gel patients. A history of skin cancer was present in 61% of PEP005 Gel patients and 46% of vehicle gel patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 89% and 75%, respectively; imiquimod: 11% and 20%, respectively; 5-FU: 32% and 27%, respectively).

Although the sample sizes were smaller, when patients treated on other non-head locations (back, shoulder, leg, chest) were assessed, no clear differences between the treatment groups for demographic and baseline disease characteristics were noted in the individual studies (PEP005-014 and PEP005-028). Similar results were seen in the combined Phase 3 studies population. For the combined studies, 90% of the PEP005 Gel and 96% of the vehicle gel patients treated on other non-head areas were located in the US. Mean age was 67.1 years in the PEP005 Gel group and 64.2 years in the vehicle gel group. In the PEP005 Gel group, 40% were male and in the vehicle group, 26% were male; all were white. Over 90% of patients had Fitzpatrick skin type I, II or III (93% and 96% of the PEP005 Gel and vehicle gel patients, respectively). The baseline lesion count was four to six in 87% of PEP005 Gel patients and 85% of vehicle gel patients. A history of skin cancer was present in 63% of the PEP005 Gel patients and 59% of the vehicle patients; prior therapy was documented in similar percentages of PEP005 Gel and vehicle gel patients (cryotherapy: 83% and 78%, respectively; imiquimod: 13% and 19%, respectively; 5-FU: 23% and 22%, respectively).

For the other two combined studies population, results of demographic and baseline disease characteristics were similar to the combined Phase 3 studies population for patients in each anatomical location.

Efficacy Results by Anatomical Location

The same efficacy endpoints analysed for the overall study populations (see Section 3) were used for comparison by anatomical location: complete clearance rate, partial clearance rate, and percent change in the number of AK lesions. Percent change in total AK lesion count was presented by anatomical location for the combined studies populations. Efficacy results in the individual Phase 3 studies and combined controlled Phase 3 studies population are summarised in Table 30 for patients treated on the arm, Table 31 for patients treated on the back of hand, and Table 32 for patients treated on other non-head locations.

As shown in Table 30, for patients treated on the arm, complete clearance rates in PEP005 Gel, 0.05% group were 27%, 46%, and 35% compared with 5% in each of the vehicle gel groups ($p < 0.001$ for each analysis) in PEP005-014, PEP005-028, and the combined Phase 3 studies, respectively. Similarly, partial clearance rates in PEP005 Gel, 0.05% group were

47%, 61%, and 53% compared with 9%, 6%, and 7% in the vehicle group, respectively ($p < 0.001$ for each analysis). The median reduction in the number of AK lesions compared to baseline in PEP005 Gel, 0.05% group was 73%, 80%, and 75% versus 0% in the vehicle gel group for PEP005-014, PEP005-028, and the combined Phase 3 studies, respectively. In the combined Phase 3 studies population, percent reduction in total lesion count in the PEP005 Gel, 0.05% group was 67% versus 16% in the vehicle gel group.

Response rates for patients treated on the back of hand are shown in Table 31. Complete clearance rates in PEP005 Gel, 0.05% group were 15%, 21%, and 19% compared with 0% in the vehicle gel group ($p < 0.05$ across analyses) in PEP005-014, PEP005-028, and the combined Phase 3 studies, respectively. Similarly, partial clearance rates in PEP005 Gel, 0.05% group were 27%, 32%, and 30% compared with 0%, 4%, and 2% in the vehicle gel group, respectively ($p \leq 0.012$ across analyses). The median reduction in the number of AK lesions compared to baseline in PEP005 Gel, 0.05% group was 54%, 59%, and 57% versus 0% in the vehicle group for PEP005-014, PEP005-028, and the combined Phase 3 studies, respectively. In the combined Phase 3 studies population, percent reduction in total lesion count in the PEP005 Gel, 0.05% group was 49% versus 9% in the vehicle gel group.

Response rates for patients treated on other non-head locations (back, shoulder, leg, chest) are shown in Table 32. Complete clearance rates in PEP005 Gel, 0.05% group were 53%, 69%, and 60% compared with 11%, 22%, and 15% in the vehicle group ($p = 0.012$, $p = 0.080$, $p < 0.001$, respectively) in PEP005-014, PEP005-028, and the combined Phase 3 studies, respectively. The results of the PEP005-028 study may have been impacted by the small sample size. Partial clearance rates in PEP005 Gel, 0.05% group were 59%, 77%, and 67% compared with 11%, 22%, and 15% in the vehicle gel group, respectively ($p < 0.03$ across analyses). The median reduction in the number of AK lesions compared to baseline in PEP005 Gel, 0.05% group was 100% versus 0% in the vehicle gel group for PEP005-014, PEP005-028, and the combined Phase 3 studies. In the combined Phase 3 studies population, percent reduction in total lesion count in the PEP005 Gel, 0.05% group was 72% versus 25% in the vehicle gel group.

Efficacy results by anatomical location for the combined controlled Phase 2 and 3 studies population and the combined controlled and uncontrolled Phase 2 and 3 studies population are summarised in Module 5.3.5.3, Table 10.4.4 and Table 10.4.5, respectively. Results were consistent with the combined controlled Phase 3 studies population.

Table 30: Efficacy Results for Patients Treated on the Arm in Individual Controlled Phase 3 Studies and Combined Controlled Phase 3 Studies Population: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

	PEP005-014		PEP005-028		Combined Phase 3 Studies	
Efficacy Parameter	**PEP005, 0.05% (N=83)**	**Vehicle (N=82)**	**PEP005, 0.05% (N=59)**	**Vehicle (N=67)**	**PEP005, 0.05% (N=142)**	**Vehicle (N=149)**
Complete Clearance						
n (%)	22 (26.5)	4 (4.9)	27 (45.8)	3 (4.5)	49 (34.5)	7 (4.7)
95% CI	17.4, 37.3	1.3, 12.0	32.7, 59.2	0.9, 12.5	26.7, 42.9	1.9, 9.4
P value	<0.001 <0		.001		<0.001	
Partial Clearance						
n (%)	39 (47.0)	7 (8.5)	36 (61.0)	4 (6.0)	75 (52.8)	11 (7.4)
95% CI	35.9, 58.3	3.5, 16.8	47.4, 73.5	1.7, 14.6	44.3, 61.2	3.7, 12.8
P value	<0.001 <0		.001		<0.001	
Percent Reduction in AK Lesions						
N	78 82		59 66		137	148
Median	73 0		80 0	75		0
Range	-20, 100	-33, 100	0, 100	-25, 100	-20, 100	-33, 100
Total AK Lesion Count						
Baseline	not done	not done	not done	not done	742	806
End of study (Day 57)	not done	not done	not done	not done	242	676
Percent change	not done	not done	not done	not done	67	16

CI = confidence interval
Controlled Phase 3 studies: PEP005-014 and PEP005-028
The 95% CI using the exact binomial method.
p-values comparing active treatment vs. vehicle using Fisher's Exact test.
Percent reduction = 100 · (baseline AK lesion count – Day 57 AK lesion count)/(baseline AK lesion count)
Source: Module 5.3.5.3, Table 10.4.1, Table 10.4.2, Table 10.4.3.

Table 31: Efficacy Results for Patients Treated on the Back of Hand in Individual Controlled Phase 3 Studies and Combined Controlled Phase 3 Studies Population: Intent-to-treat Population, Non-Head (Trunk and Extremities) Locations

	PEP005-014		PEP005-028		Combined Phase 3 Studies	
Efficacy Parameter	**PEP005, 0.05% (N=26)**	**Vehicle (N=29)**	**PEP005, 0.05% (N=28)**	**Vehicle (N=27)**	**PEP005, 0.05% (N=54)**	**Vehicle (N=56)**
Complete Clearance						
n (%)	4 (15.4)	0 (0%)	6 (21.4)	0 (0)	10 (18.5)	0 (0)
95% CI	4.4, 34.9	0.0, 11.9	8.3, 41.0	0.0, 12.8	9.3, 31.4	0.0, 6.4
P value	0.044 0		.023		<0.001	
Partial Clearance						
n (%)	7 (26.9)	0 (0)	9 (32.1)	1 (3.7)	16 (29.6)	1 (1.8)
95% CI	11.6, 47.8	0.0, 11.9	15.9, 52.4	0.1, 19.0	18.0, 43.6	0.0, 9.6
P value	0.003 0		.012		<0.001	
Percent Reduction in AK Lesions						
n	26 29		28 26	54		55
Median	54 0		59 0	57		0
Range	-25, 100	-33, 71	0, 100	-33, 86	-25, 100	-33, 86
Total AK Lesion Count						
Baseline	not done	not done	not done	not done	316	330
End of study (Day 57)	not done	not done	not done	not done	161	301
Percent change	not done	not done	not done	not done	49	9

CI = confidence interval
Controlled Phase 3 studies: PEP005-014 and PEP005-028
The 95% CI using the exact binomial method.
p-values comparing active treatment vs. vehicle using Fisher's Exact test.
Percent reduction = 100 · (baseline AK lesion count – Day 57 AK lesion count)/(baseline AK lesion count)
Source: Module 5.3.5.3, Table 10.4.1, Table 10.4.2, Table 10.4.3.

Table 32: Efficacy Results for Patients Treated on Other Anatomical Locations (back, shoulder, leg, chest) in Individual Controlled Phase 3 Studies and Combined Controlled Phase 3 Studies Population: Intent-to-treat Population, Non-Head (Trunk and Extremities) Location

	PEP005-014		PEP005-028		Combined Phase 3 Studies	
Efficacy Parameter	**PEP005, 0.05% (N=17)**	**Vehicle (N=18)**	**PEP005, 0.05% (N=13)**	**Vehicle (N=9)**	**PEP005, 0.05% (N=30)**	**Vehicle (N=27)**
Complete Clearance						
n (%)	9 (52.9)	2 (11.1)	9 (69.2)	2 (22.2)	18 (60.0)	4 (14.8)
95% CI	27.8, 77.0	1.4, 34.7	38.6, 90.9	2.8, 60.0	40.6, 77.3	4.2, 33.7
P value	0.012 0		.080		<0.001	
Partial Clearance						
n (%)	10 (58.8)	2 (11.1)	10 (76.9)	2 (22.2)	20 (66.7)	4 (14.8)
95% CI	32.9, 81.6	1.4, 34.7	46.2, 95.0	2.8, 60.0	47.2, 82.7	4.2, 33.7
P value	0.005 0		.027		<0.001	
Percent Reduction in AK Lesions						
N	16	17	13 9	29		26
Median	100 0		100 0		100	0
Range	0, 100	0, 100	40, 100	0, 100	0, 100	0, 100
Total AK Lesion Count						
Baseline	not done	not done	not done	not done	146	138
End of study (Day 57)	not done	not done	not done	not done	41	104
Percent change	not done	not done	not done	not done	72	25

CI = confidence interval
Controlled Phase 3 studies: PEP005-014 and PEP005-028)
The 95% CI using the exact binomial method.
p-values comparing active treatment vs. vehicle using Fisher's Exact test.
Percent reduction = 100 · (baseline AK lesion count – Day 57 AK lesion count)/(baseline AK lesion count)
Source: Module 5.3.5.3, Table 10.4.1, Table 10.4.2, Table 10.4.3.

Subpopulation Evaluation by Anatomical Location

Univariate subgroup analyses by anatomical location were performed to determine if any disparity in the treatment effect of PEP005 Gel, 0.05% could be detected among subsets of patients treated on the arm, back of hand, and other locations (back, shoulder, leg, chest). The same subgroups (demographic factors, baseline disease characteristics, prior AK therapies), efficacy endpoint (complete clearance rate), and patient populations (combined studies populations) analysed for the overall study populations (see Section 3.4.2.1.1) were used for comparison by anatomical location.

The results of the univariate subgroup analyses by anatomical location are provided in Module 5.3.5.3, Table 10.5.1 (combined controlled Phase 3 studies population), Table 10.5.2 (combined controlled Phase 2 and 3 studies population), and Table 10.5.3 (combined controlled and uncontrolled Phase 2 and 3 studies population). There were no significant differences in complete clearance rates between subgroups defined by any of the selected factors, for any anatomic location, in any analysis population, with the single exception of age group (< 65 vs. ≥ 65 years) in patients treated on the arm in the combined Phase 3 studies population.

3.4.2.2 Exploratory Analyses of Local Skin Response with Efficacy

Exploratory analyses were performed to examine the association of LSR with efficacy for patients treated with PEP005 Gel in the combined controlled Phase 3 studies and combined controlled Phase 2 and 3 studies population. The vehicle gel patients were not included. These analyses were not included in the SAP (Module 5.3.5.3).

Two types of exploratory analyses were performed, as follows:

- The correlation of complete clearance, partial clearance, and percent reduction in AK lesion count with the maximum composite LSR score, erythema, swelling, crusting, flaking/scaling, vesiculation/pustulation, and erosion/ulceration was investigated using Spearman rank correlations.
- For each LSR variable, the value of the maximum score which provided the greatest difference between patients who achieved complete clearance and those who did not achieve complete clearance was determined. The two subgroups defined by the value which provided the greatest difference (scores < value with greatest difference versus scores ≥ value with greatest difference) were compared in terms of the percentage of patients achieving complete clearance using Fisher's exact test for each LSR variable.

Results of the analyses of maximum composite LSR scores versus complete clearance status for patients treated with PEP005 Gel in the combined Phase 3 studies are presented in Table 33.

The mean maximum composite LSR score was 6.8 for all PEP005 Gel-treated patients. When patients were evaluated by complete clearance status, the mean maximum composite LSR scores were greater for patients with complete clearance than for patients who did not achieve complete clearance.

Table 33: Maximum Composite LSR Scores in PEP005 Gel Patients for Combined Controlled Phase 3 Studies Population: Safety Population, Non-Head (Trunk and Extremities)

		N	Mean
All PEP005 Gel Patients	2	25	6.8
Achieved Complete Clearance	Yes 78		7.5
N	o	147	6.4

Controlled Phase 3 studies (PEP005-014 and PEP005-028)
Source: Module 5.3.5.3, Table 10.6.1

The significant results ($p \leq 0.05$) based on Spearman rank correlations are summarised in Table 34.

All correlations between the three efficacy endpoints and composite LSR scores were positive with higher LSR scores associated with achieving complete clearance, partial clearance, and greater percent reduction in the number of AK lesions. The strongest correlations were observed for maximum scores of composite LSR and erythema, followed by swelling.

Table 34: Significant Correlations for Efficacy Endpoints and Local Skin Responses in PEP005 Gel Patients for Combined Controlled Phase 3 Studies Population: Safety Population, Non-Head (Trunk and Extremities) Locations

(N = 225)

Efficacy Endpoint	Local Skin Response Variable	Correlation	P value
Complete clearance (N = 225)	Maximum Composite	0.153	0.022
M	aximum Erythema	0.227	0.001
M	aximum Swelling	0.136	0.041
Partial clearance (N = 225)	Maximum Composite	0.153	0.022
M	aximum Erosion	0.147	0.028
M	aximum Erythema	0.203	0.002
Percent Reduction in AK lesions (N = 220)	Maximum Composite	0.239	<0.001
M	aximum Vesiculation	0.139	0.039
M	aximum Erosion	0.145	0.031
Max	imum Erythema	0.282	<0.001
Max	imum Flaking	0.165	0.014
M	aximum Swelling	0.174	0.010

Controlled Phase 3 studies (PEP005-014 and PEP005-028)
P-value is for testing if Spearman rank correlation between each efficacy endpoint and each LSR variable is significantly different from zero.
Source: Module 5.3.5.3, Table 10.7.1

Since there was consistent evidence to suggest a positive association between maximum LSR score and efficacy, an analysis was performed to determine the value of the maximum score for each LSR variable which provided the greatest difference between achieving or not achieving complete clearance. This determination was based on the p value for comparing the two subgroups defined by the value. The analysis was restricted to values that resulted in no more than 75% of the patients (e.g., 168 out of 225) in each subgroup. Table 35 summarises the results of these analyses when the difference was significant ($p \leq 0.05$) or approached significance ($0.10 \leq p < 0.05$).

Composite LSR and erythema were the variables with scores that provided the greatest difference between the complete clearance rates. For the maximum composite LSR score, the value which provided the greatest difference was 6. For maximum erythema, the value which provided the greatest difference was 2. For maximum swelling, the value which provided the greatest difference was 3 and for maximum vesiculation, the maximum value was 4.

Table 35: Values of Maximum Local Skin Response Scores with Greatest Difference Between Achieving and Not Achieving Complete Clearance in PEP005 Gel Patients for Combined Controlled Phase 3 Studies Population: Safety Population, Non-Head (Trunk and Extremities) Locations

(N = 225)

Local Skin Response Variable	Value of LSR Score with Greatest Difference	Clearance Rate < Value with Greatest Difference	Clearance Rate ≥ Value with Greatest Difference	P value
		n/N (%)	n/N (%)	
Maximum Composite	6	24/92 (26.1)	54/133 (40.6)	0.032
Maximum Erythema	2	3/36 (8.3)	75/189 (39.7)	<0.001
Maximum Swelling	3	63/198 (31.8)	15/27 (55.6)	0.018
Maximum Crusting	4	74/217 (34.1)	4/8 (50.0)	0.453
Maximum Flaking	3	44/141 (31.2)	34/84 (40.5)	0.192
Maximum Vesiculation	4	75/222 (33.8)	3/3 (100.0)	0.041

Controlled Phase 3 studies (PEP005-014 and PEP005-028)

P value is Fisher's Exact test comparing the two subgroups defined by the value of the maximum LSR score which provided the greatest difference (scores < value with greatest difference versus scores ≥ value with greatest difference) in terms of the percentage of patients achieving complete clearance.
Source: Module 5.3.5.3, Table 10.8.1

A summary of the association of maximum LSR scores with efficacy for the combined controlled Phase 2 and 3 studies population is presented in Module 5.3.5.3, Tables 10.6.2, 10.7.2, and 10.8.2. The results were consistent with the findings of the combined Phase 3 studies population.

3.4.2.3 Summary

The univariate subgroup analyses that were planned and specified in the SAP (Module 5.3.5.3) for this efficacy summary showed three factors appeared to impact complete clearance in patients who received PEP005 Gel. These three factors included anatomical location, number of baseline AK lesions, and age.

Age in PEP005 Gel, 0.05% treated patients was an inconsistent and marginally significant factor affecting complete clearance in univariate subgroup analyses, as well as an inconsistent predictor of complete clearance in regression analyses. It is probable that older patients, simply by a prolonged interval for sun exposure, may have more extensive AK lesions compared with younger patients. Patients with extensive keratoses are more likely to only partially respond to treatment.(51,62)

For baseline AK lesions, univariate subgroup analyses in all three combined analysis populations and multiple regression analyses in the combined controlled Phase 2 and 3 population and the combined controlled and uncontrolled Phase 2 and 3 population suggested that patients with fewer baseline lesions were more likely to achieve complete clearance. In one of the Phase 3 studies (PEP005-028), the PEP005 Gel group was compared to vehicle by baseline lesion count; a statistically significant treatment effect was evident in PEP005 Gel patients compared to vehicle for both subgroups of baseline lesion count (4-6 and 7-8). Yet, studies suggest that keratoses which are numerous and thick may only partially respond to treatment.(51,62) Thus, clinically it is reasonable to conclude that fields of AK with a higher number of lesions may not achieve complete clearance as often as fields with fewer AKs.

Anatomical location was the strongest predictor of complete clearance in all regression analyses. Reduced responsiveness to treatment of AK lesions on the extremities, particularly back of hand and forearm, is well documented in the published literature.(66,67) Across available treatments, it is generally observed that AK lesions on the face have the highest response rates, whereas, lesions on the back of hands and forearms are the most difficult to treat.(66,68)

Exploratory analyses by anatomical locations showed that PEP005 Gel, 0.05% consistently had a numerically greater treatment effect relative to vehicle gel, as measured by complete clearance, partial clearance, percent reduction in the number of AK lesions, and percent reduction in total lesion count, regardless of whether the treatment area was located on the arm, back of hand, or other non-head locations (back, shoulder, leg, or chest). PEP005 Gel, 0.05% had a statistically significant treatment effect relative to vehicle gel as measured by both complete clearance rate and partial clearance rate in patients treated on arm and patients treated on the back of hand. Patients treated on other non-head locations (combined) also showed a statistically significant treatment effect with PEP005 Gel, 0.05% relative to vehicle gel except for study PEP005-028. A higher complete clearance rate was observed in the PEP005 Gel, 0.05% group (69%; N=13) relative to the vehicle group (22%; N=9) but the difference was not significant ($p = 0.080$). These results may have been impacted by the small sample size.

In summary, it is evident that PEP005 Gel is effective for each anatomical location based on evaluating patients treated on the arm, back of hand, and other non-head locations. The results of the efficacy comparison in selected subgroups defined by demographic factors, disease characteristics, and prior AK therapies did not reveal any clinically meaningful trends

that might potentially limit the effectiveness of PEP005 Gel, 0.05% in specific subsets of patients with AK on non-head locations.

The results of the exploratory analyses of LSR with efficacy showed there were consistent, significant positive associations of maximum composite LSR score, maximum swelling score, and maximum erythema score with complete clearance, partial clearance, and percent reduction in the number of AK lesions. Patients with a maximum composite score of at least 6 had a complete clearance rate of 41% versus 26% for patients with a score less than 6. The maximum erosion and vesiculation scores showed a trend for association with complete clearance that was sometimes statistically significant. The maximum flaking and crusting scores did not seem to be associated with achieving complete clearance.

4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

4.1 HEAD (FACE AND SCALP) LOCATIONS

The proposed dosage regimen for the treatment of the head is PEP005 Gel, 0.015% applied topically once daily for three consecutive days

The key clinical studies that support the dosing recommendations of PEP005 Gel for treatment of the head locations are PEP005-007 and PEP005-015. For this product, dose selection was based on identifying a concentration and regimen that balanced local skin responses as well as efficacy. For these reasons, clinical safety data pertinent to dose selection has been included in this section. PEP005-007 was an uncontrolled, Phase 2a, dose-escalation study designed to determine the MTD of PEP005 Gel on the face or face and scalp and studied concentrations ranging from 0.0025% to 0.025% applied once daily for two and three consecutive days. PEP005-015 was a controlled, Phase 2b, dose-ranging study that investigated three concentrations (0.005%, 0.01%, and 0.015%) applied once daily for two and three consecutive days. PEP005-015 provided the primary basis for dosage selection in the pivotal Phase 3 head clinical studies.

4.1.1 Early Non-Clinical and Clinical Information

In the non-clinical dermal toxicology programme, studies were conducted with single doses of 1833 µg/kg in rats and 143 µg/kg in mini-pigs or three consecutive daily repeat doses of ≤600 µg/kg/day or ≤60 µg/kg/day, in rats or mini-pigs, respectively. These dose levels and dosage regimens did not produce mortality or systemic toxicity. Based on the total applied topical dose, a single PEP005 Gel dose was 1018-fold (1833 µg/kg) and 79-fold (143 µg/kg) higher for rats and mini-pigs respectively, than the intended clinical therapeutic dose (1.8 µg/kg/day for a 70 kg human).

Additionally, chronic dermal application of PEP005 Gel for three consecutive days, repeated monthly at ≤100 µg/kg/day for six months in rats and ≤12 µg/kg/day for nine months in mini-pigs also demonstrated an absence of systemic toxicity. Furthermore, toxicokinetic analysis in these studies demonstrated that ingenol mebutate, and its two isomers, PEP015 and PEP025, are not quantifiable in whole blood following repeated dermal dosing at less than ~100 µg/kg/day in rats and ~64 µg/kg/day in mini-pigs. Based on the total applied topical dose, the maximum three day repeat PEP005 Gel doses were ~333-fold (600 µg/kg/day) and

33-fold (60 µg/kg/day) higher for rats and mini-pigs respectively, than the intended clinical therapeutic dose (1.8 µg/kg/day for a 70 kg human).

No clinical pharmacokinetic studies were conducted to support dose selection for the head locations because PEP005 Gel applied topically is not systemically detected (see Module 2.7.2).

Earlier studies (PEP005-006, PEP005-007, and PEP005-001) demonstrated that treatment with PEP005 Gel, at various strengths ranging from 0.0125% to 0.025% for two or three consecutive days when applied to an area of skin on the face or scalp was well tolerated. Study narratives are located in Sections 2.1.2.2.1, 2.1.2.3.1, and 2.1.2.5.1 , respectively.

4.1.2 Clinical Data Relevant to the Dosing Recommendations from Study PEP005-007

PEP005-007 was a multi-centre, open-label, dose-escalation study. PEP005 Gel was applied to a 25 cm^2 contiguous treatment area on the face or face and scalp. PEP005 Gel was applied daily for two consecutive days at concentrations of 0.025%, 0.0175%, and 0.0125% and applied daily for three consecutive days at concentrations of 0.025%, 0.0175%, 0.0125%, 0.0075%, 0.0050%, and 0.0025%. Eighty-eight patients were treated, 36 with three different concentrations of two day dosing and 52 with six different concentrations of three day dosing. Study medication was patient-applied under the supervision of the investigator. Treatment compliance for the two day dosing regimens ranged from 33% to 100% and for the three day dosing regimens, 40% to 100%.

PEP005 Gel 0.025% once daily for two consecutive days was established to be the MTD. At the MTD, complete clearance was 39%. The 0.0175% concentration achieved the highest complete clearance; 100% with two day dosing and 80% with three day dosing. The 0.0125% concentration achieved the best partial clearance; 100% with both two and three day dosing. The lowest concentration (0.0025%) underperformed the other concentrations.

The most common AEs were application site conditions, such as application site reactions, followed by application site irritation, pain, paresthesia and pruritus. The LSR composite score was the highest value on Day 3 pre-dose and Day 8, improved markedly by Day 15, and returned to the baseline level or better on Day 57. Neither time to onset nor duration of LSR Grade 2 or above seemed to be consistently correlated with concentration or number of applications. In summary, there appeared to be no dose-dependent increase in the number of patients with at least one treatment-related AE, the number of treatment-related AEs, or the LSR profile.

Although the PEP005-007 study was not statistically powered to evaluate efficacy, the concentrations of 0.0125% and 0.0175% appeared to provide the greatest balance between patient tolerability of the treatment regimen and AK lesion clearance.

4.1.3 Clinical Data Relevant to the Dosing Recommendations from Study PEP005-015

PEP005-015 was a multi-centre, randomised, double-blind, vehicle-controlled, dose-ranging study (see Section 2.1.2.2.2 for study narrative). PEP005 Gel dosage regimens of 0.005%, 0.01%, and 0.015% applied daily for either two or three consecutive days were evaluated. Study medication was applied to a 25 cm^2 contiguous treatment area with four to eight clinically typical, visible, and discrete AK lesions on the face or scalp.

As shown in Table 36, the 0.015% three-day treatment group resulted in a complete clearance rate of 50%. This treatment group exhibited the highest complete clearance rate compared to the all other PEP005 Gel groups, including the two- and three-day regimens. Patients in the other PEP005 Gel groups achieved complete clearance rates which ranged from 15% in the 0.005% two-day group to 36% in the 0.015% two-day group. Furthermore, the 0.015% three-day group was statistically significant when compared to vehicle ($p < 0.001$).

Table 36: Complete Clearance Rate by Treatment Group: PEP005-015 (Intent-to-treat Population), Head (Face and Scalp) Locations

	Two Day Dosing				Three Day Dosing			
Complete Clearance	**PEP005, 0.005%**	**PEP005, 0.01%**	**PEP005, 0.015%**	**Vehicle**	**PEP005, 0.005%**	**PEP005, 0.01%**	**PEP005, 0.015%**	**Vehicle**
	(N=33)	**(N=34)**	**(N=33)**	**(N=33)**	**(N=33)**	**(N=34)**	**(N=32)**	**(N=33)**
n (%)	5 (15.2)	10 (29.4)	12 (36.4)	0	11 (33.3)	6 (17.6)	16 (50.0)	3 (9.1)
95% CI	5.1, 31.9	15.1, 47.5	20.4, 54.9	0, 10.6	18.0, 51.8	6.8, 34.5	31.9, 68.1	1.9, 24.3
P value	0.053	<0.001	<0.001		0.033	0.476	<0.001	

CI = confidence interval
The 95% CI uses the exact binomial method.
P-value is for comparing Active vs. Vehicle, using Fisher's Exact test.
Source: Module 5.3.5.3, Table 3.3.

An analysis of the treatment effect by PEP005 Gel concentration and regimen as measured by complete clearance rate is presented in Table 37. Based on the findings of this logistic regression analysis, there was a significant effect due to higher concentration ($p = 0.037$). The complete clearance for patients treated with 0.015% was 43% compared to 24% in each of the lower concentrations (0.005% and 0.01%). For regimen, there was no statistically

significant difference, however, the complete clearance rate for patients treated with the three day regimen was numerically higher (33% versus 27% for patients treated with the two day regimen).

Table 37: Comparison of Complete Clearance Rate by PEP005 Gel Dosage Regimen: PEP005-015 (Intent-to-treat Population), Head (Face and Scalp) Locations

	Number of Patients	PEP005 Gel (N=199)				
		Complete Clearance		Odds Ratio		
PEP005 Gel	**N**	**n (%)**	**95% CI**	**Ratio**	**95% CI**	**p value**
Concentration				1.68	1.03, 2.74	0.037
0.005%	66 16	(24.2)	14.5, 36.4			
0.01%	68 16	(23.5)	14.1, 35.4			
0.015%	65 28	(43.1)	30.8, 56.0			
Regimen				0.73	0.40, 1.35	0.320
2 days	100 27	(27.0)	18.6, 36.8			
3 days	99 33	(33.3)	24.2, 43.5			

CI = confidence interval

The 95% CI for complete clearance uses the exact binomial method.

Concentration: Odds Ratio = (odds of complete clearance at Con'c = 2x)/(odds of complete clearance at Con'c = x).

Regimen: Odds Ratio = (odds of complete clearance in 2 day regimen)/(odds of complete clearance in 3 day regimen).

P value is for testing H_0: odds ratio = 1, using the Wald chi-square test from a 2-factor logistic regression model, with factors log2 (Concentration) and Regimen.

Source: Module 5.3.5.3, Table 5.1.

Safety and tolerability measures also showed dose related treatment effects in the three day regimen. Common AEs included application site irritation and application site pruritus. Application site reactions were also the most common treatment-related AEs reported, and included irritation, pruritus, discomfort, swelling, and pain at the application site. All treatment-related events resolved without sequelae. As shown in Table 38, the incidence of AEs and treatment-related AEs was higher in the three day PEP005 Gel treatment groups compared with the vehicle gel, with the highest incidence in patients receiving PEP005 Gel 0.015% for three days.

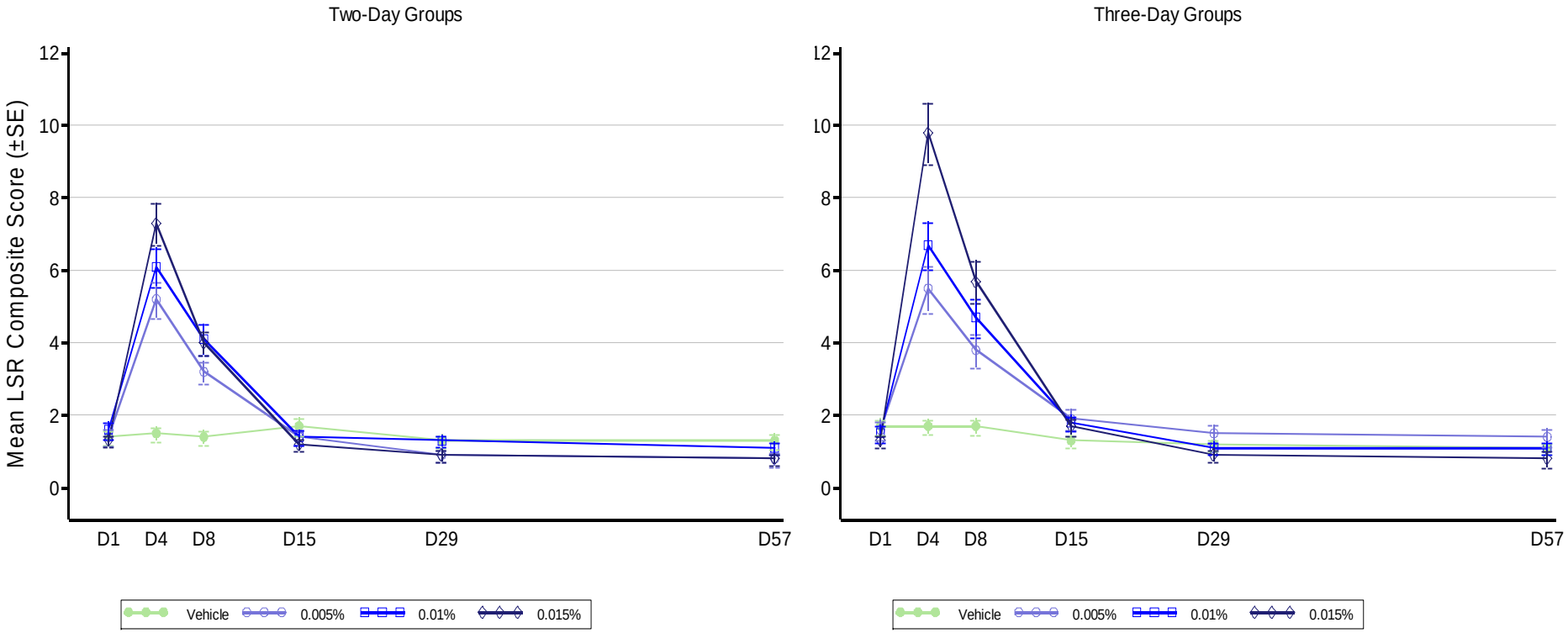
Table 38: Incidence of Adverse Events by PEP005 Gel Dosage Regimen: PEP005-015 (Safety Population), Head (Face and Scalp) Locations

Regimen Concentration	**N**	**Adverse Events**	**Treatment-related Adverse Events**
		n (%)	**n (%)**
Two Day Dosing			
PEP005 Gel 0.005%	32	12 (37.5)	6 (18.8)
PEP005 Gel 0.01%	34	12 (35.3)	8 (23.5)
PEP005 Gel 0.015%	33	8 (24.2)	6 (18.2)
Vehicle gel	33	11 (33.3)	2 (6.1)
Three Day Dosing			
PEP005 Gel 0.005%	33	11 (33.3)	6 (18.2)
PEP005 Gel 0.01%	34	14 (41.2)	10 (29.4)
PEP005 Gel 0.015%	32	22 (68.8)	17 (53.1)
Vehicle gel	33	6 (18.2)	4 (12.1)

Source: Module5.3.5.1\PEP005-015\Table 20

Similar findings were observed for LSRs (Figure 3). The mean composite LSR scores peaked on Day 4 for all PEP005 Gel groups, but not for the vehicle gel groups, and returned to baseline levels or lower by Day 57. The highest mean composite score of 9.8 was observed in the 0.015% three-day group (maximum score of 24). Maximum mean composite LSR scores were concentration-dependent for both the two-day and three-day groups.

Figure 3: Comparison of Mean Composite Local Skin Response Score by PEP005 Gel Dosage Regimen: PEP005-015 (Safety Population), Head (Face and Scalp) Locations



As shown in Table 39, patient compliance with the treatment regimen also showed a tendency to be regimen related. In the PEP005 Gel, 0.015% three day dose group, 27 of the 32 patients (84%) randomised to the three-day regimen applied all three daily doses, while 97-100% of patients randomised to all other treatment groups applied all doses. Of the five patients in the PEP005 Gel, 0.015% three day dose group who did not apply all three doses, three patients received only one application and two patients received only two applications. All five of these patients completed the study and achieved complete clearance at Day 57.

Table 39: Patient Compliance by PEP005 Gel Dosage Regimen: PEP005-015 (Intent-to-treat Population), Head (Face and Scalp) Locations

Regimen Concentration	**Compliance to the Regimen**
	n/N (%)
Two Day Dosing	
PEP005 Gel 0.005%	32/33 (97.0)
PEP005 Gel 0.01%	34/34 (100)
PEP005 Gel 0.015%	33/33 (100)
Vehicle gel	33/33 (100)
Three Day Dosing	
PEP005 Gel 0.005%	33/33 (100)
PEP005 Gel 0.01%	33/34 (97.1)
PEP005 Gel 0.015%	27/32 (84.4)
Vehicle gel	33/33 (100)

Source: Module5.3.5.1\PEP005-015\Table 19

For subgroup analyses in PEP005-015, the SAP (Module 5.3.5.3) indicated that a logistic regression model would be used to compare complete clearance rates in subgroups stratified by demographic and baseline disease characteristics. Instead, for subgroup analyses, summaries of the observed complete clearance rates with 95% confidence intervals were provided for each of the dose groups since these summaries better addressed the objective of investigating the consistency of concentration and regimen-related effects within subgroups. In addition, the SAP did not indicate that history of skin cancer, prior cryotherapy, prior imiquimod, and prior 5-FU would be evaluated; these factors were included for completeness. In the final analyses, subgroups included geographic region, age, sex, race, ethnicity, Fitzpatrick skin type, treatment location, baseline AK lesion count, history of skin cancer, and prior therapy

(including cryotherapy, imiquimod, and 5-FU). The results of these analyses are provided in Module 5.3.5.3, Table 5.2.

The concentration-related trends for the subgroups were consistent with the trends for the entire population. Although the sample sizes are small, these results indicate that the selection of the 0.015% three-day treatment group as the dosage regimen for the Phase 3 studies was appropriate.

4.1.4 Conclusions Relevant to the Dosing Recommendation

4.1.4.1 Treatment Regimen for Application to Head (Face and Scalp) Locations

PEP005-007, the open-label dose-escalation study, established PEP005 Gel 0.025% once daily for two consecutive days as the maximum tolerated dose for AK lesions treated on the head. No clear dose dependent pattern was seen in the incidence of AEs or LSRs across concentrations or regimens evaluated. Although PEP005-007 was not statistically powered to evaluate efficacy, the 0.0125% and 0.0175% concentrations achieved high clearance rates and were well tolerated.

In order to evaluate various concentrations and treatment regimens prior to initiating the Phase 3 studies, PEP005-015 was conducted. This Phase 2b study was designed as a randomised, double-blind, vehicle-controlled, dose-ranging trial to assess potential regimens for treating AK lesions on the head (face and scalp). The concentrations and treatment regimens selected for investigation (0.005%, 0.01%, and 0.015% applied once daily for two or three consecutive days) were based on the findings of PEP005-007, the dose-escalation study.

The PEP005-015 results indicated that the highest concentration and regimen, 0.015% for three consecutive days, resulted in the best complete and partial clearance rates of 50% and 72%, respectively. Efficacy results for the 0.01% three-day treatment group were inconsistent, however, the other five treatment regimens reported dose-dependent results. At all treatment regimens evaluated (0.005%, 0.01%, and 0.015% applied once daily for two or three consecutive days), PEP005 Gel appeared safe and well-tolerated when used to treat AK lesions on the face or scalp.

The treatment regimen, PEP005 Gel, 0.015%, applied once daily for three consecutive days, was found to provide the optimum balance between AK lesion clearance, local skin irritation, and treatment compliance in the PEP005-015 study. This dosage regimen was therefore selected to treat AK lesion on the head in the Phase 3 trials.

4.1.4.2 Instructions for Patients

In PEP005-007, the open-label dose-escalation study, investigational product was patient-applied under the supervision of an Investigator. In PEP005-015, the randomized, double-blind Phase 2b study and in the adequate and well-controlled Phase 3 studies, investigational product was patient-applied at home. Patients were instructed to protect their hand with a glove or finger cot, as appropriate, when applying investigational product. Specific instructions stated that the patient should squeeze the entire contents of the unit dose investigational product tube onto a covered finger (using the glove or finger cot provided), then spread the investigational product evenly over the treatment area, and allow the medication to dry for at least 15 minutes. Patients were to avoid touching or washing the treated area for 6 hours following application. Patients were provided with instructions for handling an accidental/inadvertent exposure (e.g., healthy skin, eyes, inhalation, ingestion) to the gel.

Instructions for the use of gloves or finger cots to protect the palmar (i.e., ventral) surface of the hand and finger were incorporated in the clinical protocols because the Sponsor decided it was the most cautious and prudent approach for conducting the clinical protocols. At the time these instructions were implemented, no data or information existed that suggested this precaution was required.

4.2 NON-HEAD (TRUNK AND EXTREMITIES) LOCATIONS

The proposed dosage regimen for the treatment of non-head (trunk and extremities) is PEP005 Gel, 0.05% applied topically once daily for two consecutive days.

The key clinical studies that support the dosing recommendations for PEP005 Gel for treatment of the non-head locations are PEP005-004 and PEP005-006 (non-scalp patients). For this product, dose selection was based on identifying a concentration and regimen that balanced local skin responses as well as efficacy. For these reasons, clinical safety data pertinent to dose selection has been included in this section. PEP005-004 was an uncontrolled, Phase 2a, dose-escalation study designed to determine the MTD of PEP005 Gel. PEP005-004 had a shorter efficacy endpoint (Day 29) and evaluated a smaller treatment area (9 cm^2) with a single target lesion whereas PEP005-006 investigated field treatment in a 25 cm^2 area with four to eight lesions. PEP005-006 was a controlled, Phase 2b, dose-ranging study that provided the primary basis for dosage selection for the non-head pivotal Phase 3 studies.

4.2.1 Early Non-Clinical and Clinical Information

In the non-clinical dermal toxicology programme, studies were conducted with single doses of 1833 µg/kg in rats and 143 µg/kg in mini-pigs or three consecutive daily repeat doses of ≤600 µg/kg/day or ≤60 µg/kg/day, in rats or mini-pigs, respectively. These dose levels and dosage regimens did not produce mortality or systemic toxicity. Based on the total applied topical dose, a single PEP005 Gel dose was 1018-fold (1833 µg/kg) and 79-fold (143 µg/kg) higher for rats and mini-pigs respectively, than the intended clinical therapeutic dose (1.8 µg/kg/day for a 70 kg human).

Additionally, chronic dermal application of PEP005 Gel for three consecutive days, repeated monthly at ≤100 µg/kg/day for six months in rats and ≤12 µg/kg/day for nine months in mini-pigs also demonstrated an absence of systemic toxicity. Furthermore, toxicokinetic analysis in these studies demonstrated that ingenol mebutate, and its two isomers, PEP015 and PEP025, are not quantifiable in whole blood following repeated dermal dosing at less than ~100 µg/kg/day in rats and ~64 µg/kg/day in mini-pigs. Based on the total applied topical dose, the maximum three day repeat PEP005 Gel doses were ~333-fold (600 µg/kg/day) and 33-fold (60 µg/kg/day) higher for rats and mini-pigs respectively, than the intended clinical therapeutic dose (1.8 µg/kg/day for a 70 kg human).

No clinical PK studies were conducted to support dose selection because PEP005 Gel applied topically is not systemically detected (see Module 2.7.2).

Phase 1 and 2 studies (AGN 204332-004, PEP005-001, PEP005-004, and PEP005-018) demonstrated that treatment with PEP005 Gel, 0.05% for two consecutive days when applied either directly to an AK lesion or to an area of skin was well tolerated. Study narratives are located in Sections 2.2.2.6.1, 2.2.2.6.2, 2.2.2.5.1 and 2.2.2.3.1, respectively.

4.2.2 Clinical Data Relevant to the Dosing Recommendations from Study PEP005-004

PEP005-004 was a single-centre, open-label, dose-escalation study (see Section 2.2.2.5.1 for study narrative). PEP005 Gel was applied to a 9 cm^2 area around a target AK lesion on two consecutive days on the shoulders, chest, back, or arms. PEP005 Gel doses of up to 0.1% were planned. Twenty-two patients were enroled in the study, three patients received PEP005 Gel, 0.01%; three patients received PEP005 Gel, 0.025%; 10 patients received PEP005 Gel, 0.05%; and six patients received PEP005 Gel, 0.075%. Two patients treated with PEP005 Gel, 0.075% experienced dose-limiting toxicities and, therefore, PEP005 Gel, 0.05% once daily for two consecutive days was set as the MTD.

PEP005 Gel appeared to be well tolerated. All treated patients received the scheduled treatment of two consecutive once-daily doses of study medication. At Day 29, complete clearance of the target lesion was reported in two of three (67%) patients treated with PEP005 Gel, 0.01%; one of three (33%) patients treated with PEP005 Gel, 0.025%; six of 10 (60%) patients treated with PEP005 Gel, 0.05%; and three of six (50%) patients treated with PEP005 Gel, 0.075%. The most common AEs were related to the application site (skin cracked on lesion site, bleeding, discharge, irritation, pain, and pruritus) and showed a dose-related trend, i.e., patient frequencies were 33% (one patient) for PEP005 Gel, 0.01%; 60% (six patients) for PEP005 Gel, 0.05%; and 83% (five patients) for PEP005 Gel, 0.075%. A similar trend was observed for local skin reactions. Moderate local skin reactions occurred predominately in the 0.05% and 0.075% PEP005 Gel cohorts, and severe local skin reactions occurred only in the 0.05% and 0.075% PEP005 Gel cohorts (one patient and two patients, respectively).

4.2.3 Clinical Data Relevant to the Dosing Recommendations from Study PEP005-006

PEP005-006 was a multicentre, randomised, double-blind, double-dummy, vehicle-controlled, sequential cohort study (see Section 2.2.2.2.1 for study narrative). Eligible patients had four to eight clinically typical, visible, and discrete AK lesions within the selected 25 cm^2 treatment area on the arm, shoulder, chest, back or scalp. Only patients with AK lesions on non-scalp locations (arm, shoulder, chest, back) are included in analyses presented in this section. Study medication was patient-applied at home. One hundred sixty-one non-scalp patients were evaluable for efficacy and safety: 43 patients received vehicle gel, 37 patients received PEP005 Gel, 0.025% for three consecutive days, 42 patients received PEP005 Gel, 0.05% for two consecutive days, and 39 patients received PEP005 Gel, 0.05% for three consecutive days.

As shown in Table 17, treatment effects were dose dependent over all 3 measures of efficacy tested. From lowest to highest PEP005 Gel concentration, complete clearance rates were 32%, 45%, and 46%, respectively, compared with 14% for vehicle gel ($p = 0.002$ for the two PEP005 Gel, 0.05% groups vs. vehicle gel); partial clearance rates were 54%, 64%, and 74%, respectively, compared with 21% for vehicle gel ($p < 0.001$ for the two PEP005 Gel, 0.05% groups vs. vehicle gel); and the median reductions in the number of AK lesions were 75%, 83%, and 86%, respectively, compared with 0% for vehicle gel.

A logistic regression analysis of the treatment effect by PEP005 Gel concentration and regimen as measured by complete clearance rate is presented in Table 40. Although a

statistically significant treatment effect across the two PEP005 Gel concentrations (0.025% and 0.05%) was not detected, there was a clear dose-response effect observed in the clinical study results and only the 0.05% dose was consistently significant relative to vehicle gel across efficacy measures tested (Table 17). There was no significant treatment effect across dosage regimen (two-day and three-day).

Table 40: Comparison of Complete Clearance Rate by PEP005 Gel Dosage Regimen: PEP005-006 Non-Scalp Patients (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations

PEP005 Gel	Number of Patients	PEP005 Gel, 0.05% (N=118)				
		Complete Clearance		Odds Ratio		
		n (%)	95% CI	Ratio	95% CI	p value
Concentration				1.79	0.70, 4.54	0.223
0. 025%	37	12 (32.4)	18.0, 49.8			
0. 05%	81	37 (45.7)	34.6, 57.1			
Regimen				0.96	0.40, 2.31	0.934
2 days	42	19 (45.2)	29.8, 61.3			
3 days	76	30 (39.5)	28.4, 51.4			

CI = confidence interval
Only patients with AK lesions on non-scalp locations are included in the analysis.
The 95% CI using the exact binomial method.
Concentration (C): Odds Ratio = (odds of complete clearance at C = 2x) / (odds of complete clearance at C = x).
Regimen: Odds Ratio = (odds of complete clearance in the two day regimen) / (odds of complete clearance in the three day regimen).
P value for testing H_0: odds ratio = 1, using the Wald chi-square test from a 2-factor logistic regression model, with factors $\log_2$(concentration) and regimen.
Source: Module 5.3.5.3, Table 11.1.

As shown in Table 41, the incidence of treatment-related AEs was higher in the PEP005 Gel treatment groups compared with the vehicle gel, with the highest incidence in patients receiving PEP005 Gel, 0.05% for three days. All treatment-related AEs in the PEP005 Gel group resolved during the study.

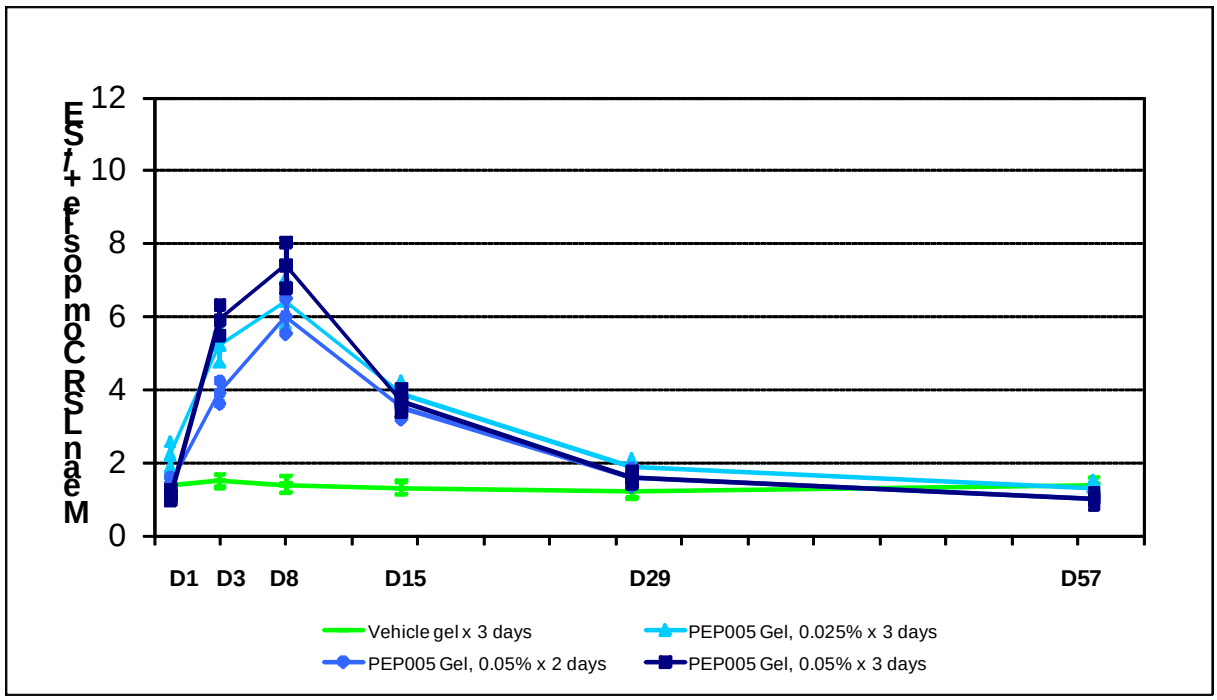
Table 41: Incidence of Adverse Events by PEP005 Gel Dosage Regimen: PEP005-006 Non-Scalp Patients (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations

Study Medication	N	Treatment-related Adverse Events
		n (%)
Vehicle gel	43	2 (4.7)
PEP005 Gel 0.025% x 3 days	37	8 (21.6)
PEP005 Gel, 0.05% x 2 days	42	6 (14.3)
PEP005 Gel, 0.05% x 3 days	39	10 (25.6)

Treatment-related AEs were those assessed as either unknown relation, possibly, probably, or definitely related to study drug.
Source: Module 5.3.5.1\PEP005-006\Tables 32 and 44.

Local skin responses also showed a dose-response relationship with PEP005 Gel treatment and were transient (Figure 4). The mean composite LSR scores were higher in the PEP005 Gel treatment groups compared with the vehicle gel. The highest mean composite LSR score occurred in patients receiving PEP005 Gel, 0.05% for three days.

Figure 4: Comparison of Mean Composite Local Skin Response Score by PEP005 Gel Dosage Regimen: PEP005-006 Non-Scalp Patients (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations



Source: Module 5.3.5.1\PEP005-006, Section 14.3, Additional Table 14

As shown in Table 42, patient compliance to the treatment regimen showed a tendency to be regimen related. In the PEP005 Gel, 0.05% dose group, 85% of patients randomised to the three day regimen applied all three daily doses, while 93% of patients randomised to the two day group applied the two daily doses.

Table 42: Patient Compliance by PEP005 Gel Dosage Regimen: PEP005-006 Non-Scalp Patients (Intent-to-treat Population), Non-Head (Trunk and Extremities) Locations

Study Medication	**Compliance to the Regimen**
	n/N (%)
Vehicle gel	42/43 (97.7)
PEP005 Gel, 0.025% x 3 days	35/37 (94.6)
PEP005 Gel, 0.05% x 2 days	39/42 (92.9)
PEP005 Gel, 0.05% x 3 days	33/39 (84.6)

Source: Module 5.3.5.1\PEP005-006\Table 31.

For subgroup analyses in PEP005-006, the SAP (Module 5.3.5.3) indicated that a logistic regression model would be used to compare complete clearance rates in subgroups stratified by demographic and baseline disease characteristics. Instead, for subgroup analyses, summaries of the observed complete clearance rates with 95% confidence intervals were provided for each of the dose groups since these summaries better addressed the objective of investigating the consistency of concentration and regimen-related effects within subgroups. In addition, the SAP did not indicate that history of skin cancer, prior cryotherapy, prior imiquimod, and prior 5-FU would be evaluated; these factors were included for completeness. In the final analyses, subgroups included geographic region, age, sex, race, ethnicity, Fitzpatrick skin type, treatment location, baseline AK lesion count, history of skin cancer, and prior therapy (including cryotherapy, imiquimod, and 5-FU). The results of these analyses are provided in Module 5.3.5.3, Table 11.2.

The concentration-related trends for the subgroups were consistent with the trends for the entire population. Although the sample sizes are small, these results indicate that the selection of the 0.05% two-day treatment group as the dosage regimen for the Phase 3 studies was appropriate.

4.2.4 Conclusions Relevant to the Dosing Recommendation

4.2.4.1 Treatment Regimen for Application to Non-Head (Trunk and Extremities) Locations

In PEP005-004, an open-label dose-escalation study, dose-limiting toxicities were observed in patients receiving PEP005 Gel, 0.075%; therefore, PEP005 Gel, 0.05% was established as the maximum tolerated dose. All treated patients received the scheduled dosages of PEP005 Gel. Although the number of patients in this study was too small for meaningful assessment of

dose-dependent treatment effects (N = 3 to 10 across dose groups), a dose-related trend was observed for AEs and LSRs.

PEP005-006, a randomised, double-blind, double-dummy, vehicle-controlled, sequential cohort study, provided the primary basis for dosage selection in the non-head pivotal Phase 3 studies. The PEP005 Gel concentrations and treatment regimens selected for investigation (0.025%, 0.05%, and 0.05% applied once daily for two or three consecutive days) were based on the findings of PEP005-004. The PEP005-006 results indicated that the highest concentration, 0.05%, resulted in the best therapeutic response rates with little difference between the two-day and three-day regimens, i.e., 45% and 46% complete response rates and 64% and 74% partial response rates for the two-day and three-day regimens, respectively. Safety and tolerability measures also showed dose-related treatment trends. The incidence of treatment-related AEs was higher in the PEP005 Gel treatment groups compared with the vehicle gel, with the highest incidence in patients receiving PEP005 Gel, 0.05% for three days. Local skin responses showed a similar dose-response relationship across PEP005 Gel dose groups. Patient compliance showed a tendency to be better in the PEP005 Gel, 0.05% two day regimen (93%) compared with the PEP005 Gel, 0.05% three day regimen (85%).

The treatment regimen, PEP005 Gel, 0.05% applied topically once daily for two consecutive days, was found to provide the optimum balance between AK lesion clearance, local skin irritation, and treatment compliance in the PEP005-006 study. This dosage regimen was therefore selected to treat AK lesion on non-head locations in the Phase 3 trials.

4.2.4.2 Instructions for Patients

In PEP005-004, the open-label dose-escalation study and in PEP005-006, the randomized, double-blind Phase 2 study, investigational product was patient-applied under the supervision of an Investigator. In the adequate and well-controlled Phase 3 studies, investigational product was patient-applied at home. Patients were instructed to protect their hand with a glove or finger cot, as appropriate, when applying investigational product. Specific instructions stated that the patient should squeeze the entire contents of the unit dose investigational product tube onto a covered finger (using the glove or finger cot provided), then spread the investigational product evenly over the treatment area, and allow the medication to dry for at least 15 minutes. Patients were to avoid touching or washing the treated area for 6 hours following application. Patients were provided with instructions for handling an accidental/inadvertent exposure (e.g., healthy skin, eyes, inhalation, ingestion) to the gel.

Instructions for the use of gloves or finger cots to protect the palmar (i.e., ventral) surface of the hand and finger were incorporated in the clinical protocols because the Sponsor decided it was the most cautious and prudent approach for conducting the clinical protocols. At the time these instructions were implemented, no data or information existed that suggested this precaution was required.

5 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

5.1 HEAD (FACE AND SCALP) LOCATIONS

A long-term (1-year) study (PEP005-030) was conducted to assess the recurrence rate of AK lesions following short-term treatment with PEP005 Gel. See Section 2.1.2.4.1 for the PEP005-030 study narrative.

PEP005-030 was a prospective, follow-up study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025. No study medication was administered during PEP005-030. The original protocol dated 01 Jul 2009, allowed for eligibility criteria to include patients if they completed the Day 57 visit. With implementation of Amendment #1, dated 28 Sep 2009, eligibility was modified to include only patients who achieved complete clearance at Day 57. Therefore patients who had not achieved complete clearance at Day 57 but were already enroled at the time Amendment #1 was implemented were terminated from the study at the next regularly scheduled study visit or sooner, if possible.

Patients returned to the study clinic for follow-up visits at Months 3, 6, 9, and 12 after the Day 57 visit in the previous study (PEP005-016 or PEP005-025). The outcome of interest was recurrence rate in the selected treatment area at these time points. For recurrence rate, the population of interest was all patients who achieved complete clearance of AK lesions in the selected treatment area at Day 57 of the previous study (PEP005-016 or PEP005-025). Recurrence was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study (PEP005-016 or PEP005-025). The double-blind status of patients who were treated in PEP005-016 and PEP005-025 was maintained until completion of PEP005-030.

Patient disposition is summarised in Table 43. The population of interest was patients with complete clearance at Day 57 of the previous study. For this population, a total of 108 patients from the previous PEP005 Gel treatment groups and 9 patients from the previous vehicle gel groups from Studies PEP005-016 and PEP005-025 were enroled. Eight patients (7%) in the previous PEP005 Gel group and one patient (11%) in the previous vehicle gel group prematurely discontinued.

Table 43: Patient Disposition: PEP005-030, Head (Face and Scalp) Locations

	PEP005, 0.015%	**Vehicle**
Patients Enroled	250	215
Patients without Complete Clearance at Day 57 (n [%])	142 (56.8)	206 (95.8)
Patients with Complete Clearance at Day 57 [a] (n [%])	108 (43.2)	9 (4.2)
Early Termination (n [%])[b]	8 (7.4)	1 (11.1)
Patient Withdrew Consent (n [%])	5 (4.6)	1 (11.1)
Protocol Violation (n [%])	2 (1.9)	0
Lost to Follow-up (n [%])	1 (0.9)	0

[a] Patients with complete clearance at Day 57 of the previous study is the population of interest for recurrence.

[b] The denominator is based on the number of patients with complete clearance at Day 57 of the previous study.

Source: Module 5.3.5.3, Table 6.1.

Demographic and baseline characteristics are presented in Table 44. Mean age was 63.0 years in the PEP005 Gel group and 61.4 years in the vehicle gel group. The majority of patients were male (77% in the PEP005 Gel group and 89% in the vehicle gel group). Over 90% of patients had Fitzpatrick skin type I, II or III (94% and 100% of the PEP005 Gel and vehicle gel patients, respectively). Most patients had been treated on the face in the previous study (89% in each group). The baseline lesion count was four to six in 70% of PEP005 Gel patients and 100% of vehicle gel patients.

Table 44: Demographic and Baseline Characteristics for Patients with Complete Clearance at Day 57: PEP005-030, Head (Face and Scalp) Locations

Parameter	**PEP005, 0.015% (N=108)**	**Vehicle (N=9)**
Age (years)		
N	108	9
Mean (standard deviation)	63.0 (9.9)	61.4 (10.5)
M inimum, Maximum	37, 88	47, 79
Sex (n [%])		
Male	83 (76.9)	8 (88.9)
Female	25 (23.1)	1 (11.1)
Fitzpatrick skin type (n [%])		
I	27 (25.0)	1 (11.1)
II	43 (39.8)	5 (55.6)
III	31 (28.7)	3 (33.3)
IV	7 (6.5)	0
Location of Treatment Area (n [%])		
Face 96	(88.9) 8	(88.9)
Scalp 12	(11.1)	1 (11.1)
Baseline lesion count (n [%])		
4	18 (16.7)	4 (44.4)
5	38 (35.2)	3 (33.3)
6	20 (18.5)	2 (22.2)
7	22 (20.4)	0
8	10 (9.3)	0

Source: Module 5.3.5.3, Table 6.2

A summary of recurrence rates is presented in Table 45.

At 12 months of follow-up, 54% of patients who had been treated with PEP005 Gel in the previous Phase 3 studies had at least one new or recurrent AK lesion within the selected treatment area. For vehicle patients, 72% of patients had a new or recurrent AK lesion within the selected treatment area.

Table 45: Recurrence Rates: PEP005-030, Head (Face and Scalp) Locations

Follow-up Period	**PEP005, 0.015% (N=108)**	**Vehicle (N=9)**
Recurrence Rate[a]		
3-month		
N	107	9
Perce nt	16.8	44.4
95 % CI	11.0, 25.4 19.5,	79.6
6-month		
N	86	4
Perce nt	33.3	58.3
95 % CI	25.1, 43.2 29.2,	89.1
9-month		
N	68	3
Perce nt	46.0	72.2
95 % CI	37.0, 56.1 40.9,	95.6
12-month		
N	55	2
Perce nt	53.9	72.2
95 % CI	44.6, 63.7 40.9,	95.6

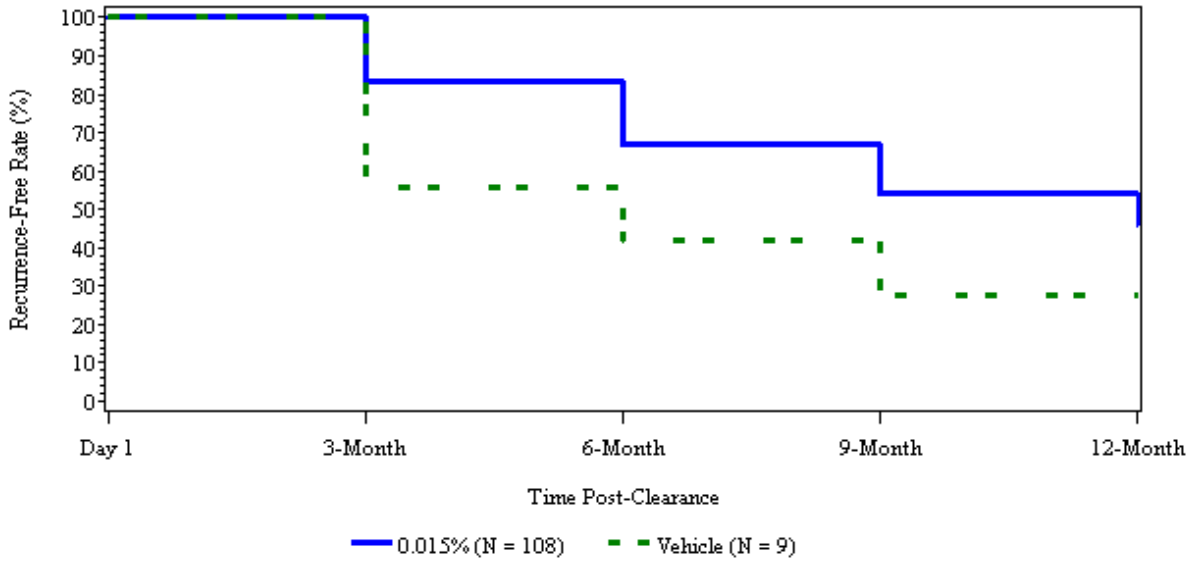
CI = confidence interval

[a] Recurrence rate = the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage.

Source: Module 5.3.5.3, Table 6.3.

The time to recurrence for patients who achieved complete clearance at Day 57 of the previous study is displayed graphically in the Kaplan-Meier plot shown in Figure 5. Kaplan-Meier estimates of the median time to recurrence (i.e., appearance of a new or recurrent lesion within the treatment area) were 365 days and 183 days for PEP005 Gel-treated patients and vehicle-treated patients, respectively.

Figure 5: Time to Recurrence (Kaplan-Meier Estimate) vs. Days Post-Clearance, Patients with Complete Clearance at Day 57: PEP005-030, Head (Face and Scalp) Locations



Source: Module 5.3.5.3, Table 6.3.

Recurrence rates based on baseline lesion counts (obtained at the baseline visit from study PEP005-016 or PEP005-025) were determined, as shown in Table 46. For this analysis, to account for treatment of recurrent AK lesions within the treatment area (between follow-up visits), the lesion count at a follow-up visit was carried forward in the event that subsequent lesion counts were zero. Based on this analysis, patients in the PEP005 Gel group had mean lesion-based AK recurrence rates that ranged from 4% at 3 months of follow-up to 13% at 12 months. Patients in the vehicle group had lesion-based AK recurrence rates of 11% and 16% at 3 and 12 months of follow-up, respectively.

Table 46: Lesion Based Recurrence: PEP005-030, Head (Face and Scalp) Locations

Follow-up Period	**PEP005, 0.015% (N=108)**	**Vehicle (N=9)**
3-Month Follow-up		
N 1	07	9
Mean (SD), %	3.8 (9.2)	10.9 (13.5)
Median 0.	0	0.0
Min, Max	0.0, 50.0	0.0, 33.3
6-Month Follow-up		
N 1	03	8
Mean (SD), %	8.8 (15.2)	12.7 (15.2)
Median 0.	0	8.3
Min, Max	0.0, 80.0	0.0, 40.0
9-Month Follow-up		
N 1	02	8
Mean (SD), %	9.5 (14.4)	19.0 (19.0)
Median 0.	0	18.3
Min, Max	0.0, 62.5	0.0, 50.0
12-Month Follow-up		
N 1	00	8
Mean (SD), %	12.8 (19.1)	16.3 (21.6)
Median 0.	0	8.3
Min, Max	0.0, 120.0	0.0, 60.0

Note: The lesion-based recurrence rate for each patient with an assessment in the visit window was defined as the ratio of the number of new/recurred lesions at the visit to the number of lesions at Baseline in the previous Phase 3 study, and expressed as a percentage. For patients who received treatment for lesions in the treatment area, the number of new/recurred lesions was carried forward to visits following the administration of treatment, if no lesions were observed at these visits.

Source: Module 5.3.5.3, Table 6.3.

5.2 NON-HEAD (TRUNK AND EXTREMITIES) LOCATIONS

Long-term (1-year) studies (PEP005-031 and PEP005-032) were conducted to assess recurrence rates following short-term treatment with PEP005 Gel. See Sections 2.2.2.4.1 and 2.2.2.4.2 for the study narratives for PEP005-031 and PEP005-032, respectively.

PEP005-031 was a follow-up study in patients who achieved complete clearance at Day 57 in PEP005-020 (open-label treatment with PEP005 Gel, 0.05%), and PEP005-032 was a follow-

up study of patients who achieved complete clearance at Day 57 in PEP005-028 (double-blind treatment with PEP005 Gel, 0.05% or vehicle gel). The double-blind status of PEP005-028 was maintained until completion of PEP005-032. No study medication was administered in either PEP005-031 or PEP005-032.

For PEP005-031, the original protocol dated 01 Jul 2009, allowed for eligibility criteria to include patients if they completed the Day 57 visit. With implementation of Amendment #1, dated 30 Sep 2009, eligibility was modified to include only patients who achieved complete clearance at Day 57. Therefore patients who had not achieved complete clearance at Day 57 but were already enroled at the time Amendment #1 was implemented were terminated from the study at the next regularly scheduled study visit or sooner, if possible. For PEP005-032, no patients were enroled prior to the amendment which modified eligibility to include only patients who achieved complete clearance at Day 57.

In both PEP005-031 and PEP005-032, patients returned to the study clinic for follow-up visits at Months 3, 6, 9, and 12 after the Day 57 visit in the previous study. The outcome of interest was recurrence rate in the selected treatment area at these time points for patients who achieved complete clearance of AK lesions at Day 57 of the previous study. Recurrence was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study.

For this efficacy summary, data are presented for each study and for both studies combined.

Patient disposition for each study and combined study data is summarised in Table 47. The population of interest was patients with complete clearance at Day 57 of the previous study. For the PEP005-031 study, a total of 38 PEP005 Gel patients from study PEP005-020 were enroled and for PEP005-032, a total of 38 patients from the previous PEP005 Gel treatment group and five patients from the previous vehicle gel group from study PEP005-028 were enroled. Across both studies, five patients (7%) in the previous PEP005 Gel groups and no patients in the previous vehicle gel group prematurely discontinued.

Table 47: Patient Disposition: PEP005-031, PEP005-032, and Combined Study Population, Non-Head (Trunk and Extremities) Locations

	PEP005-031	PEP005-032		Combined Studies (PEP005-031 and PEP005-032)	
	PEP005, 0.05%	PEP005, 0.05%	Vehicle	PEP005, 0.05%	Vehicle
Patients Enroled	98	38	5	136	5
Patients without Complete Clearance at Day 57 (n [%])	60 (61.2)	0	0	60 (44.1)	0
Patients with Complete Clearance at Day 57 [a] (n [%])	38 (38.8)	38 (100)	5 (100)	76 (55.9)	5 (100)
Early Termination (n [%])[b]	4 (10.5)	1 (2.6)	0	5 (6.6)	0
Patient Withdrew Consent (n [%])	3 (7.9)	0	0	3 (3.9)	0
Investigator's decision (n [%])	1 (2.6)	0	0	1 (1.3)	0
Protocol Violation (n [%])	0	0	0	0	0
Lost to Follow-up (n [%])	0	0	0	0	0
Other (n [%])	0	1 (2.6)	0	1 (1.3)	0

[a] Patients with complete clearance at Day 57 of the previous study is the population of interest for recurrence.
[b] The denominator is based on the number of patients with complete clearance at Day 57 of the previous study.
Source: Module 5.3.5.3, Table 12.1, Table 12.2, Table 12.3.

Demographic and baseline characteristics are presented in Table 48. Across both studies, the mean age ranged from 62.3-67.6 years, the majority of patients were male (range for treatment groups across both studies: 58-66%). Approximately 95% of patients had Fitzpatrick skin type I, II or III, and most patients had been treated on the arm in the previous study (range: 60-66%). The baseline lesion count was four to six in the majority of patients (range: 80-87%).

Table 48: Demographic and Baseline Characteristics for Patients with Complete Clearance at Day 57: PEP005-031, PEP005-032, and Combined Study Population, Non-Head (Trunk and Extremities) Locations

	PEP005-031	PEP005-032		Combined Studies (PEP005-031 and PEP005-032)	
Parameter	**PEP005, 0.05% (N=38)**	**PEP005, 0.05% (N=38)**	**Vehicle (N=5)**	**PEP005, 0.05% (N=76)**	**Vehicle (N=5)**
Age (years)					
N	38	38 5	76	5	
Mean (standard deviation)	62.3 (10.6)	64.6 (8.6)	67.6 (10.6)	63.4 (9.7)	67.6 (10.6)
M inimum, Maximum	38, 80	44, 79	50, 77	38, 80	50, 77
Sex (n [%])					
Male	25 (65.8)	22 (57.9)	3 (60.0)	47 (61.8)	3 (60.0)
Female	13 (34.2)	16 (42.1)	2 (40.0)	29 (38.2)	2 (40.0)
Fitzpatrick skin type (n [%])					
I	6 (15.8)	10 (26.3) 0	16	(21.1) 0	
II	17 (44.7)	12 (31.6)	3 (60.0)	29 (38.2)	3 (60.0)
III	12 (31.6)	15 (39.5)	2 (40.0)	27 (35.5)	2 (40.0)
IV	3 (7.9)	1 (2.6)	0	4 (5.3)	0
Location of Treatment Area (n [%])					
Arm	25 (65.8)	23 (60.5)	3 (60.0)	48 (63.2)	3 (60.0)
Shoulder	1 (2.6)	2 (5.3)	1 (20.0)	3 (3.9)	1 (20.0)
Chest	6 (15.8)	3 (7.9)	1 (20.0)	9 (11.8)	1 (20.0)
Back	1 (2.6)	3 (7.9)	0	4 (5.3)	0
Back of hand	4 (10.5)	6 (15.8)	0	10 (13.2)	0
Leg	1 (2.6)	1 (2.6)	0	2 (2.6)	0
Baseline lesion count (n [%])					
4	11 (28.9)	16 (42.1)	1 (20.0)	27 (35.5)	1 (20.0)
5	13 (34.2)	8 (21.1)	2 (40.0)	21 (27.6)	2 (40.0)
6	7 (18.4)	9 (23.7)	1 (20.0)	16 (21.1)	1 (20.0)
7	5 (13.2)	0	1 (20.0)	5 (6.6)	1 (20.0)
8	2 (5.3)	5 (13.2)	0	7 (9.2)	0

Source: Module 5.3.5.3, Table 13.1, Table 13.2, Table 13.3.

A summary of recurrence rates is presented in Table 49.

For PEP005-031, at 12 months of follow-up, 63% of patients had at least one new or recurrent AK lesion in the selected treatment area. For PEP005-032, at 12 months of follow-up, 50% of patients in the PEP005 Gel group and 80% of patients in the vehicle group had at least one new or recurrent AK lesion in the selected treatment area.

When the two studies were combined, at 12 months of follow-up, 56% of patients in the PEP005 Gel group and 80% of patients in the vehicle group had at least one new or recurrent AK lesion in the selected treatment area.

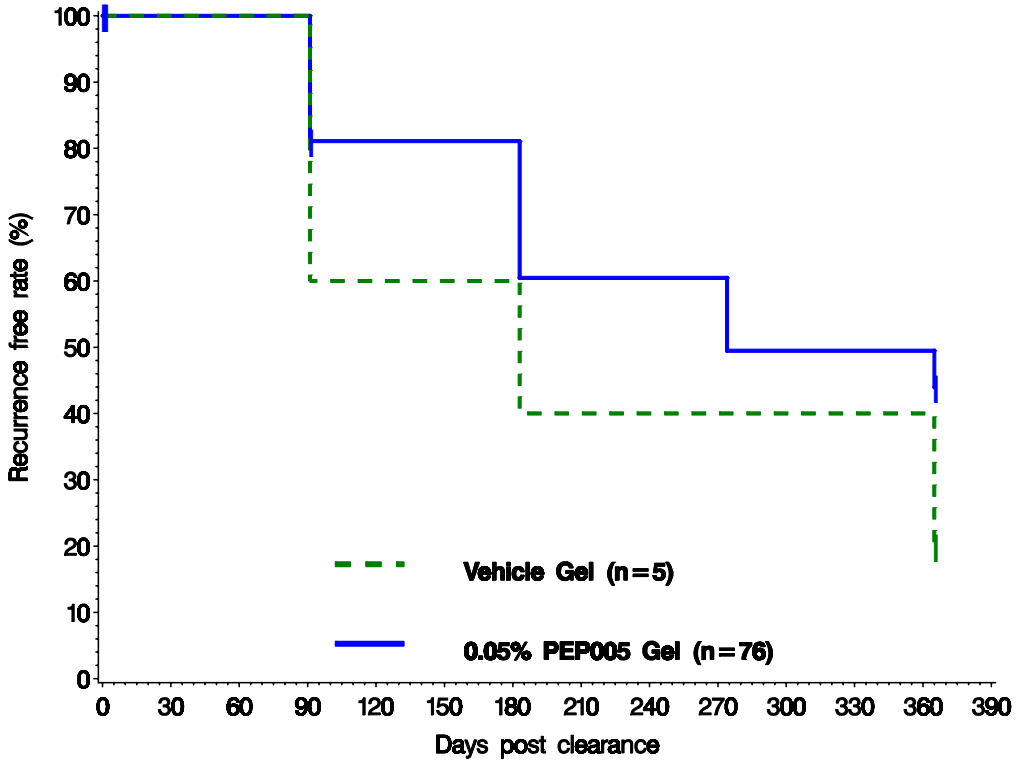
Table 49: Recurrence Rates: PEP005-031, PEP005-032, and Combined Study Population, Non-Head (Trunk and Extremities) Locations

	PEP005-031	PEP005-032		Combined Studies (PEP005-031 and PEP005-032)	
Follow-up Period	**PEP005, 0.05% (N=38)**	**PEP005, 0.05% (N=38)**	**Vehicle (N=5)**	**PEP005, 0.05% (N=76)**	**Vehicle (N=5)**
Recurrence Rate[a]					
3-month					
N	36	38 5	74	5	
Perce nt	25.0	13.2 40	.0 18	.9 40	.0
95 % CI	13.9, 42.5	5.7, 28.8	11.8, 87.4	11.7, 29.8	11.8, 87.4
6-month					
N	26	33 3	59	3	
Perce nt	48.1	31.6 60	.0 39	.5 60	.0
95 % CI	33.2, 65.5	19.3, 48.9	24.7, 94.8	29.4, 51.7	24.7, 94.8
9-month					
N	18	26 2	44	2	
Perce nt	59.6	42.1 60	.0 50	.5 60	.0
95 % CI	44.1, 75.7	28.3, 59.2	24.7, 94.8	39.7, 62.4	24.7, 94.8
12-month					
N	14	22 2	36	2	
Perce nt	62.5	50.0 80	.0 56	.0 80	.0
95 % CI	46.9, 78.1	35.5, 66.6	41.8, 99.2	45.1, 67.6	41.8, 99.2

CI = confidence interval
[a] Recurrence rate = the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage.
Source: Module 5.3.5.3, Table 14.1, Table 14.2, Table 14.3.

The time to recurrence for patients who achieved complete clearance at Day 57 of the previous study is displayed graphically for both studies combined in the Kaplan-Meier plot shown in Figure 6. Kaplan-Meier estimates of the median time to recurrence (i.e., appearance of a new or recurrent lesion within the treatment area) were 274 days and 183 days for PEP005 Gel-treated patients and vehicle-treated patients, respectively, for both PEP005-031 and PEP005-032 combined.

Figure 6: Time to Recurrence (Kaplan-Meier Estimate) vs. Days Post-Clearance, Patients with Complete Clearance at Day 57: PEP005-031 and PEP005-032 Combined, Non-Head (Trunk and Extremities) Locations



Source: Module 5.3.5.3, Table 14.3

Recurrence rates based on baseline lesion counts were determined, as shown in Table 50. For this analysis, to account for treatment of recurrent AK lesions within the treatment area (between follow-up visits), the lesion count at a follow-up visit was carried forward in the event that subsequent lesion counts were zero. Based on this analysis, in study PEP005-031, PEP005 Gel patients had mean lesion-based AK recurrence rates that ranged from 9% at 3 months of follow-up to 11% at 12 months. For study PEP005-032, patients in the PEP005 Gel group had mean lesion-based AK recurrence rates that ranged from 5% at 3 months of follow-up to 15% at 12 months. Patients in the vehicle group had lesion-based AK recurrence rates of 7% and 19% at 3 and 12 months of follow-up, respectively.

For both studies combined, patients in the PEP005 Gel group had mean lesion-based AK recurrence rates that ranged from 7% at 3 months of follow-up to 13% at 12 months. Patients in the vehicle group had lesion-based AK recurrence rates of 7% and 19% at 3 and 12 months of follow-up, respectively.

Table 50: Lesion Based Recurrence: PEP005-031, PEP005-032, and Combined Study Population, Non-Head (Trunk and Extremities) Locations

	PEP005-031	PEP005-032		Combined Studies (PEP005-031 and PEP005-032)	
Follow-up Period	**PEP005, 0.05% (N=38)**	**PEP005, 0.05% (N=38)**	**Vehicle (N=5)**	**PEP005, 0.05% (N=76)**	**Vehicle (N=5)**
3-Month Follow-up					
N	36	38 5	74	5	
Mean (SD), %	8.8 (21.2)	4.7 (13.7)	6.9 (9.6)	6.7 (17.7)	6.9 (9.6)
Median	0.0	0.0 0.	0 0.	0 0.	0
Min, Max	0.0, 100.0	0.0, 60.0	0.0, 20.0	0.0, 100.0	0.0, 20.0
6-Month Follow-up					
N	33	38 5	71	5	
Mean (SD), %	19.1 (28.4)	12.9 (27.7)	16.9 (20.5)	15.7 (28.0)	16.9 (20.5)
Median	0.0	0.0 14	.3 0.	0 14	.3
Min, Max	0.0, 125.0	0.0, 140.0	0.0, 50.0	0.0, 140.0	0.0, 50.0
9-Month Follow-up					
N	33	38 5	71	5	
Mean (SD), %	18.5 (24.7)	13.9 (25.3)	14.2 (16.4)	16.1 (25.0)	14.2 (16.4)
Median	16.7	0.0 14	.3 0.	0 14	.3
Min, Max	0.0, 125.0	0.0, 140.0	0.0, 40.0	0.0, 140.0	0.0, 40.0
12-Month Follow-up					
N	34	37 5	71	5	
Mean (SD), %	11.3 (16.5)	14.9 (27.7)	19.2 (14.7)	13.2 (23.0)	19.2 (14.7)
Median	0.0	0.0 16	.7 0.	0 16	.7
Min, Max	0.0, 75.0	0.0, 140.0	0.0, 40.0	0.0, 140.0	0.0, 40.0

Note: The lesion-based recurrence rate for each patient with an assessment in the visit window was defined as the ratio of the number of new/recurred lesions at the visit to the number of lesions at Baseline in the previous Phase 3 study, and expressed as a percentage. For patients who received treatment for lesions in the treatment area, the number of new/recurred lesions was carried forward to visits following the administration of treatment, if no lesions were observed at these visits.

Source: Module 5.3.5.3, Table 14.1, Table 14.2, Table 14.3.

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