Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ingenol Mebutate

Proprietary Product Name: Picato Gel

Sponsor: Leo Pharmaceutical Products Ltd

Date of CER: 23 February 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. Clinical rationale

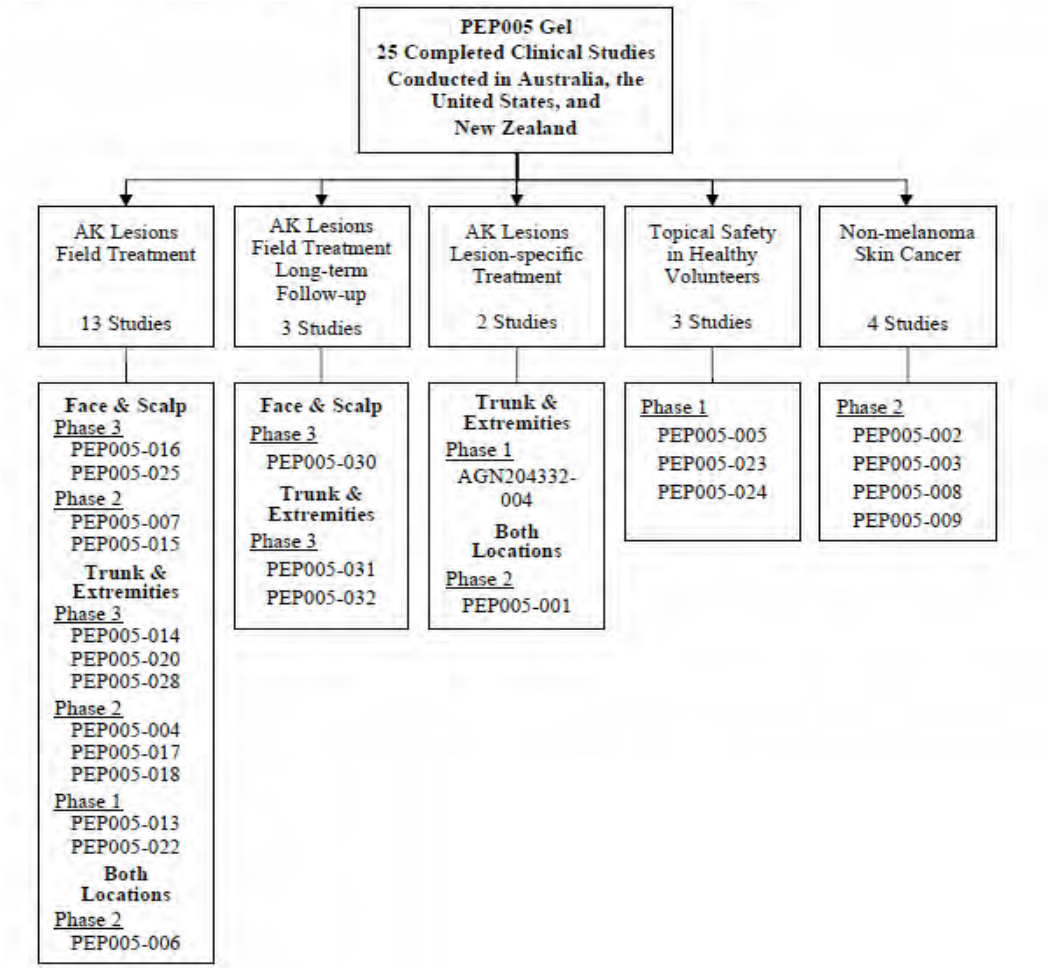
This application is for Category 1 Australian registration of Picato Gel, a new chemical entity. The active pharmaceutical ingredient in Picato Gel is ingenol mebutate. The finished product is available in 2 strengths of active ingredient, 0.015% w/w and 0.05% w/w. The proposed indication for the 0.015% strength is for the treatment of solar (actinic) keratoses (SK) on the face and scalp, while the proposed indication for the 0.05% strength is for the treatment of SK on the body (non-head regions). The recommended dosage for the treatment of SK lesions on the face and scalp is 0.015% Picato Gel topically applied to the affected area once daily for 3 consecutive days. The recommended dosage for the treatment of SK lesions on the trunk and extremities is 0.05% Picato Gel topically applied to the affected area once daily for 2 days.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

A total of 25 clinical studies were provided in support of this application as illustrated below. In these studies, Picato Gel was identified as PEP005 Gel. In addition, there were noted to be three ongoing safety studies, PEP005-033, PEP005-036 and LP0041-01. Minimal information was provided on these ongoing studies.

Figure 1. Overview of the Completed Clinical studies for PEP005 Gel



Of these 25 completed studies, 18 were conducted in patients with SK lesions. The remaining 7 studies contributed data to the safety profile of Picato Gel and included 3 topical safety studies

performed in healthy volunteers and 4 safety studies in patients with non malignant skin cancer (NMSC).

The minimum effective dose for both indications was identified in 2 dose-ranging studies, PEP005-015 for the head and neck indication (0.015% Picato Gel) and PEP005-006 for the trunk and extremities indication (0.05% Picato Gel). These studies are further described *Dose repose studies and Main clinical studies* and *Supportive studies* below.

Information provided on pharmacology focussed on demonstrating that PEP005 was not systemically absorbed. Pharmacokinetic information was obtained from a total of 32 subjects as well as predicted using allometric scaling from *in vivo* animal PK and *in vitro* percutaneous absorption data. This is further discussed under *Pharmacokinetics*. This information is consistent with that provided in the draft PI. The precise mechanism of action of PEP005 gel is unknown, although possible mechanisms were postulated in the draft PI.

The dose proposed in the draft PI was used in the pivotal studies. The pivotal studies were all placebo-controlled, with a clinically acceptable superiority margin. This is further discussed under *Dose repose studies and Main clinical studies* and *Supportive studies* below. There were no active controlled studies. Data on recurrence was provided from 3 long term studies (PEP005-030, PEP005-031 and PEP005-032) and is discussed further under *Analysis performed across trials (pooled analyses and meta-analysis)* and *Supporting studies*.

Limited information on histological confirmation of clearance was provided, and is further discussed in the *Introduction* to *Clinical Efficacy*, including results from study PEP005-001. Efficacy endpoints are also discussed in this section, and were consistently applied across all pivotal studies. Limited objective measures were used.

2.2. Paediatric data

Not applicable.

2.3. Good clinical practice

No significant GCP aspects were identified in the development of this product.

3. Pharmacokinetics

3.1. Introduction

Picato Gel is applied topically and not absorbed systemically. Ingenol mebutate, at the concentrations applied topically for treatment of SK lesions, has no detectable systemic absorption. The human PK profile was predicted using allometric scaling from *in vivo* animal PK and *in vitro* percutaneous absorption data. This profile suggested that the maximum intended clinical dose (2 micrograms/kg/day) would not produce measurable systemic blood levels of ingenol mebutate, and that a minimum topical dose of 2000 micrograms/kg/day would be required.

3.2. Methods

3.2.1. Analytical methods

Pharmacokinetic samples were collected from a total of 32 patients (25 on Picato Gel and 7 on vehicle) enrolled in 4 independent Picato Gel clinical studies for the treatment of non-head SK lesions (AGN 204332-004, PEP005-004, PEP005-013 and PEP005-017). These studies are described in the section on *Clinical Efficacy*, as they were primarily designed as efficacy or safety studies.

3.2.2. Pharmacokinetic data analysis

The highest concentration and treatment area evaluated was 0.05% microgram/mm^2 of 0.05% Picato Gel applied once daily to a 100 cm^2 area for 2 consecutive days (PEP005-013 and PEP005-017). No systemic levels of ingenol mebutate or its 2 isomers PEP015 or PEP025 were quantifiable in any of the blood samples collected for PK analysis.

3.2.3. Statistical analysis

Statistical analysis was limited to descriptive analysis only.

3.3. Absorption

Not applicable.

3.4. Distribution

Not applicable.

3.5. Elimination

Not applicable.

3.6. Dose proportionality and time dependency

Not applicable.

3.7. Intra- and inter-individual variability

Not applicable.

3.8. Pharmacokinetics in the target population

Not applicable.

3.9. Pharmacokinetics in special populations

Not applicable.

3.10. Pharmacokinetic drug interactions

Not applicable.

3.11. Exposure relevant for safety evaluation

Not applicable.

3.12. Evaluator's overall conclusions on pharmacokinetics

Picato Gel is applied topically and not absorbed systemically. Ingenol mebutate, at the concentrations applied topically for treatment of SK lesions, has no detectable systemic absorption. This is supported by the human PK profile from allometric scaling, as well as some limited PK data obtained from subjects in 4 clinical studies.

4. Pharmacodynamics

4.1. Introduction

No clinical studies on human pharmacodynamics (PDs) were conducted. As such, human PD data was not available, and no PK/PD correlation studies were performed nor PK/PD relationship established. The mode of action of PEP005 has been established on preclinical models using cell lines and animal models.

4.2. Mechanism of action

Ingenol mebutate is a pleiotropic effector which possesses a novel, dual mechanism of action in neoplastic conditions. Initially, ingenol mebutate rapidly induces necrosis, resulting in the debulking of locally affected tumour cells. Secondarily, it induces a tumour cell-specific immune response characterised by antibody dependent cellular cytotoxicity which results in removal of residual disease. Ingenol mebutate also stimulates cluster of differentiation (CD) 8+ T-cells and CD4+ T-cell responses, resulting in further anti-tumour activity and possible long-term immunity. The mechanism of action in SK is not fully understood, but appears to be a combination of induction of local lesion cell death and promotion of an inflammatory response with neutrophils and other immuno-competent cells.

4.3. Primary pharmacology

Not applicable.

4.4. Secondary pharmacology

Not applicable.

4.5. Relationship between plasma concentration and effect

Not applicable.

4.6. Pharmacodynamic drug-drug interactions

Not applicable.

4.7. Genetic differences in pharmacodynamic response

Not applicable.

4.8. Evaluator's overall conclusions on pharmacodynamics

No clinical studies on human pharmacodynamics were conducted. The mechanism of action in SK is not fully understood, but appears to be a combination of induction of local lesion cell death and promotion of an inflammatory response with neutrophils and other immuno-competent cells.

5. Dosage selection for the pivotal studies

See sections under *Clinical Efficacy* below.

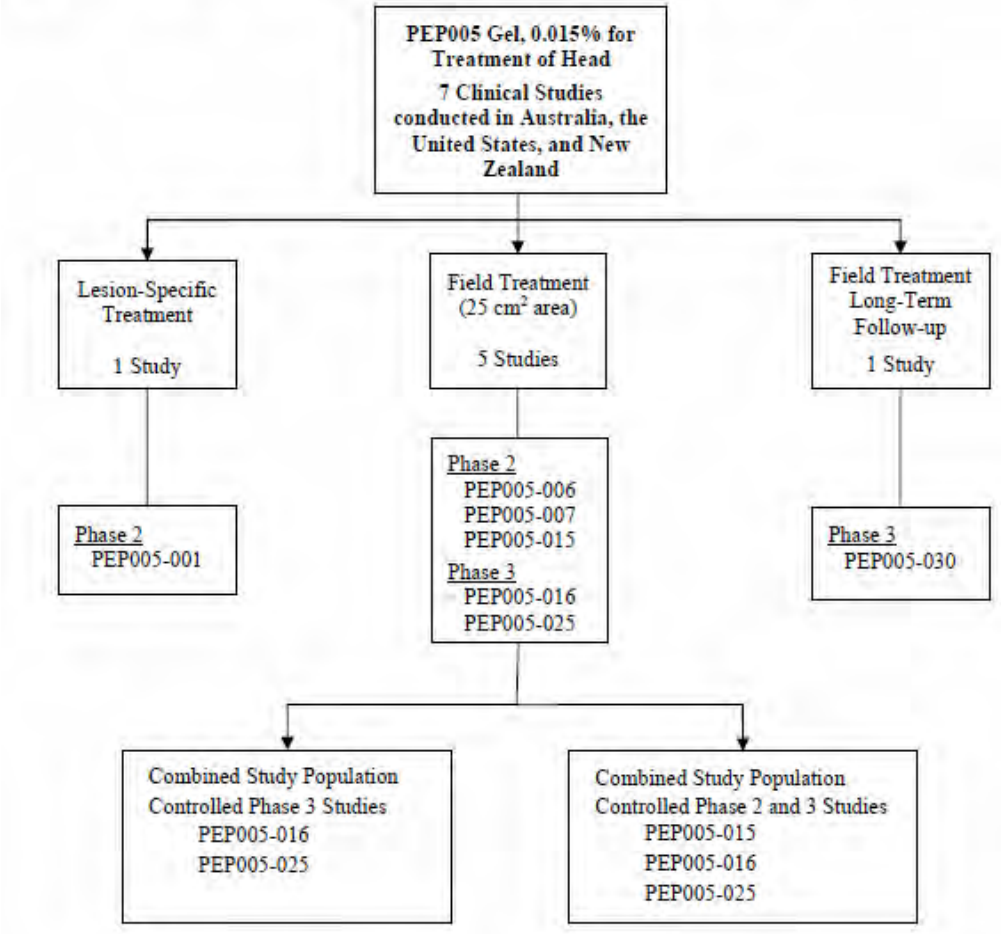
6. Clinical efficacy

6.1. Introduction

Information on clinical efficacy was provided for the 2 specific indications, the treatment of solar (actinic) keratoses (SK) on the face and scalp (0.015% Picato Gel), and for the treatment of SK on the body (non-head regions) (0.05% Picato Gel). For the first indication, there were 7 studies that evaluated Picato Gel. Of these studies, five (PEP005-016, PEP005-025, PEP005-015, PEP005-006 and PEP005-007) provided efficacy data for field treatment of Picato Gel to a defined 25 cm2 skin area containing 4 to 8 SK lesions located on the head with efficacy assessed at Day 57 (study exit). The sixth trial (PEP005-030) was a long-term 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 this study. The seventh trial was a lesion specific study (PEP005-001) which allowed up to five lesions to be treated on multiple anatomical sites.

Of these studies, PEP005-015, PEP005-016 and PEP005-025 were randomised, double-blind, vehicle-controlled, parallel-group studies, and were the pivotal studies for this indication. PEP005-015 was a dose-ranging study that included the proposed dosage regimen treatment on head locations. PEP005-016 and PEP005-025 were Phase III studies that evaluated the proposed dosage regimen of Picato Gel for treatment of head locations. This study development program is summarised below.

Figure 2. Clinical studies included in the efficacy evaluation of Head Locations

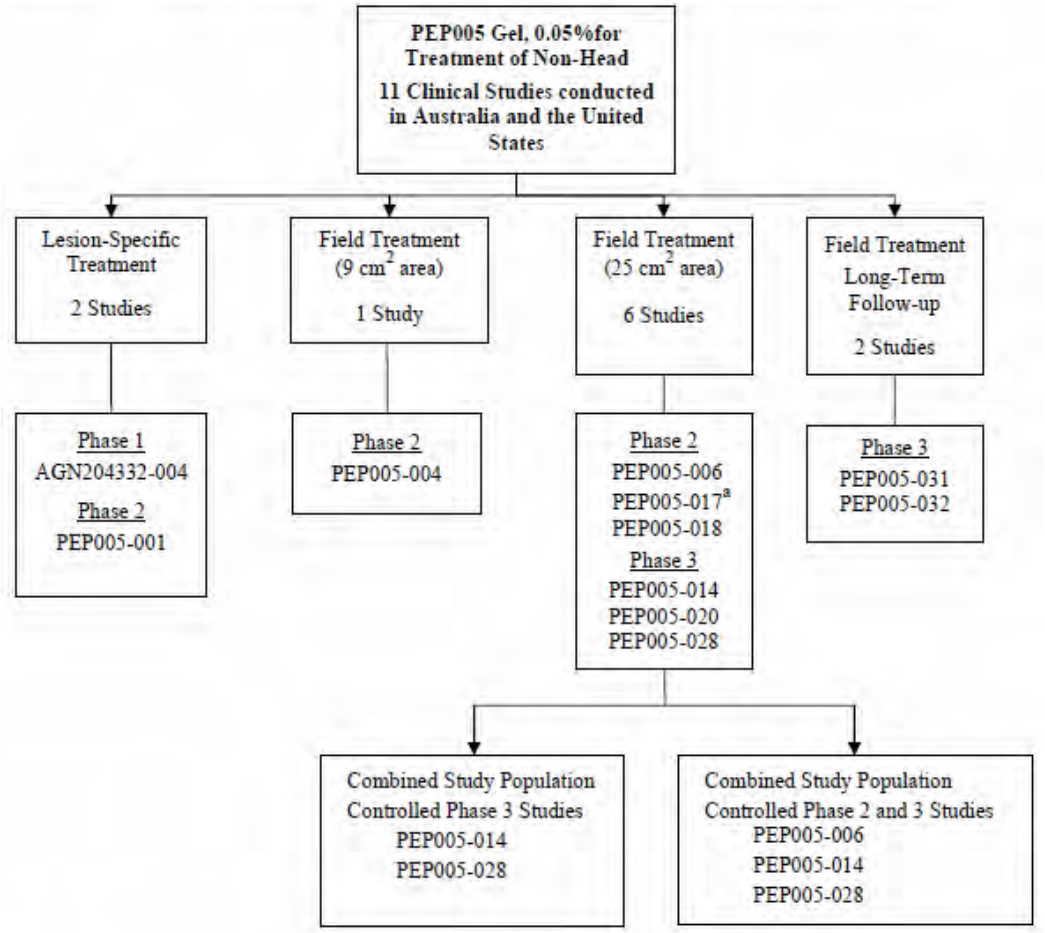


For the second indication (trunk and extremities), 11 studies evaluated Picato Gel. Of these studies, six provided efficacy data for field treatment of Picato Gel to a defined 25 cm² skin area containing four to 8 SK lesions located on trunk and extremities with efficacy assessed at Day 57 (PEP005-014, PEP005-028, PEP005-006, PEP005-017, PEP005-018, and PEP005-020). Two trials (PEP005-031 and PEP005-032) were long-term follow-up studies in patients who achieved complete clearance at

Day 57 in previous trials. One study (PEP005-004) assessed efficacy where Picato 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 also two lesion-specific studies where Picato Gel was applied to individual SK lesions rather than to a field of skin (AGN204332-004 and PEP005-001).

Of these studies, PEP005-014 and PEP005-028 were well-controlled Phase III studies that evaluated the proposed dosage regimen application of Picato Gel for treatment of non-head locations, and should be regarded as the pivotal studies for this indication. This study development is summarised below.

Figure 3. Clinical studies included in the Efficacy evaluation of Non-Head 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.

For the pivotal studies, a study design using an active comparator was not employed because of the potential to introduce bias with regard to the selection and timing of study endpoints. PEP005 Gel and any available active comparator used in the same patient population represent different modalities of treatment. As a result, efficacy endpoints would have been measured at different times during a comparator trial. The duration of treatment for PEP005 Gel is 2 or 3 days with efficacy assessment at Day 57 following study medication application. Other products have longer durations of treatment, may require repeat treatment periods and take longer to achieve efficacy. Therefore, the Applicant considered that an unbiased comparator trial would not be feasible.

For the pivotal studies, the majority of SKs were diagnosed clinically, not histologically. In a study where 271 lesions were biopsied to correlate SK and SCC, clinical diagnosis and histopathologic findings agreed in 91% of the biopsies further supporting the appropriateness of a clinical diagnosis for SK. Punch biopsies of 220 clinically diagnosed untreated AKs were performed at baseline plus 51 lesions unresponsive to treatment (total, 271). Clinical diagnosis and

histopathologic findings agreed in 91% (246/271) of the lesions biopsied. The results of the biopsied lesions were: (1) benign changes 4% (11/271) and (2) occult cutaneous malignancy in 5% (14/271) of the cases, 12 squamous cell carcinomas and 2 basal cell carcinomas.

Early in this clinical development programme, histological data were evaluated in a Phase I, lesion-specific study (PEP005-001). Two single applications of study medication were applied directly to each selected lesion using PEP005 Gel at concentrations of 0.0025%, 0.01%, 0.05%, or vehicle gel. Punch biopsy samples were obtained pre-treatment to confirm the presence of SK, and post-treatment on Day 85 to determine lesion clearance. All biopsies were reviewed by a central dermatopathologist. Results showed absence of SK lesions on post-treatment biopsy for approximately 50% of the biopsies performed across all treatment groups. Results from this study are further described under *Supportive studies*, including proportion of pre- and post-treatment biopsies, and the number who had complete clearance. Although based on few patients these findings provide evidence of histological clearance.

For the pivotal studies, the comparative efficacy analyses for head and non-head locations used the same efficacy endpoints. For the combined studies populations, the primary efficacy endpoint was complete clearance, defined as the proportion of patients at Day 57 with no clinically visible SK lesions in the selected treatment area. For the head location, this endpoint was pre-specified as the primary endpoint in the two adequate and well-controlled Phase III studies (PEP005-016 and PEP005-025) and the Phase II dose-ranging study (PEP005-015). For the non-head location, this endpoint was pre-specified as the primary endpoint in the two adequate and well controlled Phase III studies (PEP005-014 and PEP005-028) but was a secondary endpoint in the Phase II dose-ranging study (PEP005-006). The secondary endpoint was partial clearance rate, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of clinically visible SK lesions identified at baseline in the selected treatment area. Percent reduction from baseline in the total number of SK lesions at Day 57 was an additional endpoint.

For the head locations, the primary efficacy analysis in the Phase III studies (PEP005-016 and PEP005-025) 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 treatment group, study sites yielding fewer than 16 patients were combined in order of geographical proximity, referred to 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. For the non-head locations, the primary efficacy analysis in the Phase III studies (PEP005-014 and PEP005-028) also 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. As part of this efficacy summary a CMH analysis for PEP005-014 stratified on analysis site is also presented.

For each Phase III study for the head and non-head locations, missing values were imputed using the last observation carried forward (LOCF) method. 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 for head and arm, back of hand, or “other” [back, shoulder, leg or chest] for non-head). Statistical tests were two-sided with a significance level of $\alpha = 0.05$. 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. Furthermore, clearance rates were compared across treatment groups using a logistic regression model with terms for treatment, analysis site, and anatomical location.

Table 1. Tabular Listing of Clinical Studies.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	PEP005-017	5.3.3.2	PK, safety, efficacy	Randomized, vehicle-controlled	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (100 cm^2 treatment area)	16 13 PEP005 Gel 3 vehicle	AK lesions trunk and extremities	2 Days	Complete; Full
PK	PEP005-013	5.3.3.2	PK, safety	Open-label	0.05% PEP005 Gel, qd Topical field application (100 cm^2 treatment area)	8	AK lesions trunk and extremities	2 Days	Complete; Full
Efficacy	PEP005-016	5.3.5.1 head	Efficacy, safety	Randomized, vehicle-controlled	0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	269 135 PEP005 Gel 134 vehicle	AK lesions face and scalp	3 Days	Complete; Full
Efficacy	PEP005-025	5.3.5.1 head	Efficacy, safety	Randomized, vehicle-controlled	0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	278 142 PEP005 Gel 136 vehicle	AK lesions face and scalp	3 Days	Complete; Full
Safety	PEP005-006	5.3.5.1 head 5.3.5.1 non-head	Safety, efficacy (dose ranging)	Randomized, vehicle-controlled	0.025% or 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	222 162 PEP005 Gel 60 vehicle	AK lesions scalp, trunk, and extremities	2 Days or 3 Days	Complete; Full

Table 1 continued. Tabular Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-015	5.3.5.1 head	Safety, efficacy (dose ranging)	Randomized, vehicle-controlled	0.005%, 0.01%, or 0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	265 199 PEP005 Gel 66 vehicle	AK lesions face and scalp	2 Days or 3 Days	Complete; Full
Safety	PEP005-001	5.3.5.1 head 5.3.5.1 non-head	Safety, efficacy	Randomized, vehicle-controlled	0.0025%, 0.01%, or 0.05% PEP005 Gel, qd Vehicle Gel, qd Lesion-specific topical application on Day 1 and Day 2 or 8	63 51 PEP005 Gel 12 vehicle	AK lesions face, scalp, trunk and extremities	2 Days	Complete; Full
Efficacy	PEP005-014	5.3.5.1 non-head	Efficacy, safety	Randomized, vehicle-controlled	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	255 126 PEP005 Gel 129 vehicle	AK lesions trunk and extremities	2 Days	Complete; Full
Efficacy	PEP005-028	5.3.5.1 non-head	Efficacy, safety	Randomized, vehicle-controlled	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	203 100 PEP005 Gel 103 vehicle	AK lesions trunk and extremities	2 Days	Complete; Full
Safety	AGN-204332-004	5.3.5.1 non-head	Pilot safety	Randomized, vehicle-controlled	0.01% PEP005 Gel, qd Vehicle Gel, qd Lesion-specific topical application	16 11 PEP005 Gel 5 vehicle	AK lesions trunk and extremities	1 Day	Complete; Full

Table 1 continued. Tabular Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-004	5.3.5.2	Determine MTD, safety, efficacy	Open-label	0.01%, 0.025%, 0.05%, 0.075% PEP005 Gel, qd Topical field application (9 cm^2 treatment area)	22	AK lesions trunk and extremities	2 Days	Complete; Full
Safety	PEP005-018	5.3.5.2	Safety, efficacy	Open-label	0.05% PEP005 Gel, qd Topical field application (25 cm^2 treatment area)	12	AK lesions trunk and extremities	2 Days	Complete; Full
Safety	PEP005-020	5.3.5.2	Safety, efficacy	Open-label	0.05% PEP005 Gel, qd Topical field application (25 cm^2 treatment area)	102	AK lesions trunk and extremities	2 Days	Complete; Full
Safety	PEP005-007	5.3.5.2	Determine optimal dosing regimen, safety, efficacy	Open-label	0.0025%, 0.005%, 0.0075%, 0.0125%, 0.0175%, or 0.025% PEP005 Gel, qd Topical field application (25 cm^2 treatment area)	94	AK lesions face and scalp	2 Days or 3 Days	Complete; Full
Safety	PEP005-022	5.3.5.2	Safety	Open-label	0.05% PEP005 Gel, qd Topical field application, treatment areas ranging from 25–100 cm^2	74	AK lesions trunk and extremities	2 Days	Complete; Full

Table 1 continued. Tabular Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-030	5.3.5.2	Long-term safety in treatment area	Prospective, longitudinal, observational	None Patients had received PEP005 Gel or vehicle in study PEP005-016 or PEP005-025	117	AK lesions face and scalp	NA	Complete; Full
Safety	PEP005-031	5.3.5.2	Long-term safety in treatment area	Prospective, longitudinal, observational	None Patients had received PEP005 Gel or vehicle in study PEP005-020	38	AK lesions trunk and extremities	NA	Complete; Full
Safety	PEP005-032	5.3.5.2	Long-term safety in treatment area	Prospective, longitudinal, observational	None Patients had received PEP005 Gel or vehicle in study PEP005-028	43	AK lesions trunk and extremities	NA	Complete; Full
Safety	PEP005-002	5.3.5.4	Safety, efficacy	Randomized, vehicle-controlled	0.0025%, 0.01%, 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical application on Day 1 and Day 2 or 8	58 46 PEP005 Gel 12 vehicle	NMSC nodular BCC on the face, scalp, trunk and extremities	2 Days	Complete; Full
Safety	PEP005-003	5.3.5.4	Safety, efficacy	Randomized, vehicle-controlled	0.0025%, 0.01%, 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical application on Day 1 and Day 2 or 8	60 48 PEP005 Gel 12 vehicle	NMSC superficial BCC on the face, scalp, trunk and extremities	2 Days	Complete; Full

Table 1 continued. Tabular Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-005	5.3.5.4	Dermal sensitization	Randomized, vehicle-controlled	0.01% PEP005 Gel Vehicle Gel Topical application (4 cm^2 treatment area)	238	Healthy subjects	10 doses of both PEP005 Gel and vehicle over 6–8 weeks	Complete; Full
Efficacy	PEP005-008	5.3.5.4	Efficacy, safety	Open-label	0.05% PEP005 Gel, qd Topical application	25	NMSC SCCIS on the face, trunk, and extremities	2 Days	Complete; Abbreviated
Safety	PEP005-009	5.3.5.4	Determine MTD, safety, efficacy	Open-label	0.025%, 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, 0.175%, 0.2%, 0.225% or 0.25% PEP005 Gel Topical application on Day 1 or Days 1 and 8	101	NMSC superficial BCC on the trunk	1 Day or 2 Days	Complete; Full
Safety	PEP005-023	5.3.5.4	Dermal photo-irritation	Randomized, within subject comparison to vehicle	0.01% PEP005 Gel Vehicle Gel Topical application (two 4 cm^2 treatment areas)	34	Healthy subjects	1 Day	Complete; Full

Table 1 continued. Tabular Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-024	5.3.5.4	Dermal photo-sensitization	Randomized, within subject comparison to vehicle	0.01% PEP005 Gel Vehicle Gel Topical application (two 4 cm^2 treatment areas)	60	Healthy subjects	7 doses of both PEP005 Gel and vehicle over 6–8 weeks	Complete; Full
Safety	PEP005-033	NA. Study in progress	Safety, efficacy	Open-label	0.05% PEP005 Gel, qd Lesion-specific topical application	24 planned	Seborrhoeic keratosis on the trunk and extremities	3 Days	In progress, completion by Q4 2011; No report included
Safety	PEP005-036	NA. Study in progress	Safety, efficacy	Open-label	0.015% PEP005 Gel, qd Topical field application (25 cm^2 treatment area)	24 planned	Photo-damaged skin on the face	3 Days	In progress, completion by Q4 2011; No report included
Safety	LP0041-01	NA. Study in progress	Tolerability on the finger following exposure to PEP005 Gel and hand washing	Randomized, 2-arm, open-label	0.015% or 0.05% PEP005 Gel, qd Application via dominant index finger to an external test surface over a 25 cm^2 area	100 planned	Healthy subjects	2 Days or 3 Days	In progress, completion by Q3 2011; No report included

6.2. Dose response studies and main clinical studies

6.2.1. Head and scalp indication

6.2.1.1. *PEP005-015*

This study was a multi-centre, randomized, double-blind, vehicle-controlled, dose ranging study conducted in the USA and Australia between June 2008 and October 2008. The primary objective of the study was to evaluate the safety, tolerability and efficacy 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 SK treatment area on the face or scalp. The primary efficacy variable was the complete clearance rate, defined as the proportion of patients at the Day 57 visit with no clinically visible SK lesions in the selected treatment area. The secondary efficacy variable was the partial clearance rate, defined as the proportion of patients at the Day 57 visit with a 75% or greater reduction in the number of SK lesions identified at baseline, in the selected treatment area. Patients were screened and randomized to one of three PEP005 Gel concentrations (0.005%, 0.01%, 0.015%) or vehicle gel and were treated once daily for either two or three consecutive days. Patients were evaluated on the basis of safety, tolerability, and efficacy for 57 days following study treatment.

A total of 265 patients were randomized and 260 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 250 patients were included in the per-protocol (PP) population. The safety population included 264 patients. Subjects were male or female patients at least 18 years of age with four to eight clinically typical, visible, and discrete SK lesions within a contiguous 25 cm^2 treatment area on the face or scalp. Patients were randomized centrally, to treatment in a 1:1:1:1:1:1:1:1 fashion and were stratified across treatment groups (as per the Table 2 below) based on location of SK lesions on the head (i.e., face or scalp).

Table 2. Treatment groups

Treatment Group	Study Medication Concentration	Regimen	Number of Patients
1	0.005%	Day 1, 2	30
2	0.01%	Day 1, 2	30
3	0.015%	Day 1, 2	30
4	vehicle gel	Day 1, 2	30
5	0.005%	Day 1, 2, 3	30
6	0.01%	Day 1, 2, 3	30
7	0.015%	Day 1, 2, 3	30
8	vehicle gel	Day 1, 2, 3	30

Approximately 240 patients (30 per group) were sufficient to detect an odds ratio of 10.45 in 2 strata with 0.2:0.8 proportion and 6%:6% vehicle response rates in the complete clearance of AK lesions at Day 57, assuming a 15% attrition rate. This would detect a difference in the *complete clearance rate* of AK lesions, allowing for at least a 34% difference between the treatment group and vehicle group (40% vs. 6%). Based on clinical judgment and results of prior PEP005 Topical Gel AK clinical studies, this sample size would provide at least 85% power with a two-sided alpha=0.05 using a continuity corrected CMH test of OR=10.45 for 2x2 tables in 2 strata, assuming 15% attrition rate.

All hypotheses were tested for statistical significance with two-tailed tests. Results of all tests were considered statistically significant if their p-value was less than or equal to 0.05, with the exception of Hochberg's multiple comparison procedure. Results of Hochberg's multiple comparisons were considered statistically significant if the p-value was less than or equal to

0.05, 0.025, or 0.0167, according to the procedure. The primary efficacy endpoint was the *complete clearance rate* of SK lesions at Day 57. A Cochran-Mantel-Haenszel (CMH) test, adjusting for treatment area (face, scalp), was used to test for treatment effect. The secondary efficacy endpoint was the *partial clearance rate* of SK lesions at Day 57. The statistical analysis was the same as the one used for the primary efficacy endpoint. Dose effect was explored by inspection of observed means or rates for the PEP005 Gel and vehicle gel groups within each treatment regimen. Results from this study are included below.

Table 3. Observed Complete Clearance Rate of the Face and Scalp at Day 57. ITT population.

	Two-Day Groups				Three-Day Groups			
	Vehicle Gel (N = 33)	0.005% (N = 33)	0.01% (N = 34)	0.015% (N = 33)	Vehicle Gel (N = 33)	0.005% (N = 33)	0.01% (N = 34)	0.015% (N = 32)
Observed complete clearance rate [n/N (%)][a]	0/33	5/33 (15.2)	10/34 (29.4)	12/33 (36.4)	3/33 (9.1)	11/33 (33.3)	6/34 (17.6)	16/32 (50.0)
Difference (%) Active - Vehicle[a]		15.2	29.4	36.4		24.2	8.6	40.9
CMH Weighted Difference (95% CI)[a]		14.8 (-0.2, 29.8)	29.4 (11.1, 47.7)	36.4 (17.0, 55.7)		23.7 (3.1, 44.3)	8.5 (-10.2, 27.2)	41.0 (18.1, 55.8)
Hochberg Adjusted P-value from CMH test[a]	--	0.025	0.002	<0.001	--	0.036	0.311	0.001

[a] Using LOCF.

Table 4. Observed Partial Clearance Rate of the Face and Scalp at Day 57. ITT population.

	Two-Day Groups				Three-Day Groups			
	Vehicle Gel (N = 33)	0.005% (N = 33)	0.01% (N = 34)	0.015% (N = 33)	Vehicle Gel (N = 33)	0.005% (N = 33)	0.01% (N = 34)	0.015% (N = 32)
Observed partial clearance rate [n/N (%)][a]	3/33 (9.1)	11/33 (33.3)	17/34 (50.0)	17/33 (51.5)	4/33 (12.1)	14/33 (42.4)	9/34 (26.5)	23/32 (71.9)
Difference (%) Active - Vehicle[a]	--	24.2	40.9	42.4	--	30.3	14.3	59.8
CMH Weighted Difference (95% CI)[a]	--	25.1 (3.4, 46.7)	40.8 (15.8, 63.2)	42.4 (19.9, 65.0)	--	29.8 (7.3, 52.3)	14.2 (-6.6, 35.0)	59.8 (37.7, 65.0)
Hochberg Adjusted P-value from CMH test[a]	--	0.014	<.001	<.001	--	0.013	0.139	<.001

[a] Using LOCF.

Table 5. Summary of the Number if AK lesions on the Face and Scalp and Percent Change from baseline at Day 57. PP population.

Study Day/ Statistics	Two-Day Groups				Three-Day Groups			
	Vehicle Gel (N = 29)	0.005% (N = 32)	0.01% (N = 34)	0.015% (N = 33)	Vehicle Gel (N = 33)	0.005% (N = 30)	0.01% (N = 33)	0.015% (N = 26)
Number of AK Lesions at:								
Baseline (Day 1)								
Median	6.0	6.0	5.0	5.0	5.0	6.0	6.0	5.5
Min to Max	4 to 8	4 to 8	4 to 8	4 to 8	4 to 8	4 to 8	4 to 8	4 to 8
Day 57								
Median	5.0	3.0	2.0	2.0	4.0	2.0	3.0	1.0
Min to Max	1 to 8	0 to 7	0 to 7	0 to 6	0 to 8	0 to 8	0 to 8	0 to 7
Percent Change from Baseline in AK Lesions at:								
Day 57								
Median	0.0	-50.0	-73.2	-75.0	0.0	-69.0	-50.0	-84.5
Min to Max	-80.0 to 16.7	-100.0 to 20.0	-100.0 to 0.0	-100.0 to 0.0	-100.0 to 25.0	-100.0 to 16.7	-100.0 to 0.0	-100.0 to 0.0

Five of the six PEP005 Gel groups demonstrated statistically significant, higher complete clearance rates versus vehicle gel (CMH test corrected for multiple comparisons) based on both the PP and ITT populations. Observed complete clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed complete clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 15% in the 0.005% two-day group to 50% in the 0.015% three-day group. Five of the six PEP005 Gel groups demonstrated statistically significant, higher partial clearance rates versus vehicle gel (CMH test corrected for multiple comparisons) based on both the PP and ITT populations. Partial clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed partial clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 33.3% in the 0.005% two-day group to 71.9% in the 0.015% three-day group. Overall PEP005 Gel, at a concentration of 0.01% once daily for two consecutive days and at a concentration of 0.015% once daily for two or three consecutive days, demonstrated statistically significant and clinically meaningful improvements in complete clearance of SK lesions on the face and scalp compared to vehicle gel. The median number of SK lesions was reduced with all PEP005 Gel concentrations and regimens tested with the highest reduction in the 0.015% two-day and three-day groups.

6.2.1.2. ***PEP005-016***

This study was a multi-centre, randomized, double-blind, vehicle-controlled, dose ranging study[1] conducted in the USA and Australia between June 2009 and September 2009. The objective of the study was 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). Patients were randomized to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (End of Study). A total of 269 patients were randomized (135 to PEP005 Gel 0.015% and 134 to vehicle gel); 259 patients completed the study. All randomized patients were included in the intent-to-treat (ITT)

[1] Erratum: Phase III study

population; 246 patients were included in the per-protocol (PP) population. Subjects were male or female patients at least 18 years of age with four to eight clinically typical, visible and discrete SK lesions within a contiguous 25 cm^2 treatment area on the head (face or scalp). The primary efficacy endpoint was complete clearance rate of SK lesions at the Day 57 visit. A patient with no clinically visible SK lesions in the selected treatment area was defined to have complete clearance. The secondary efficacy endpoint was the partial clearance rate of SK lesions at the Day 57 visit. A patient with a 75% or greater reduction in the number of clinically visible SK lesions identified at baseline, in the selected treatment area was defined to have partial clearance. The primary efficacy analysis was based on the intent-to-treat (ITT) population. All treatment comparisons were tested with two-tailed tests and a 0.05 significance level.

Sample size was based on the Phase IIb study, PEP005-015, which demonstrated a complete clearance rate of 50% for PEP005 Gel, 0.015%, compared to a 9% clearance rate for vehicle gel, 57 days following treatment for three consecutive days in a study design similar to PEP005-016. Thus, statistical power greater than 95% may be achieved in a sample as small as 25 patients per treatment group. The choice of a sample size of 125 patients per group, in this Phase III study was not, therefore, motivated by statistical considerations of efficacy, but rather by the need to treat a sufficient number of individuals in pre-marketing studies to be able to estimate the incidence of common adverse drug events. Enrolment of 125 patients per group in each of two Phase III pivotal studies (PEP005-016 and PEP005-025) was consistent with this goal.

The complete clearance rate was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. The secondary efficacy endpoint was the partial clearance rate of SK lesions at Day 57. The statistical analysis was the same as that used for the primary efficacy endpoint. Results from this study are included below.

Table 6. Complete Clearance Rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population.

	PEP005 Gel 0.015% (N = 135)	Vehicle Gel (N = 134)	*P* value
Overall			
Complete Clearance Rate [n/N (%)]	50/135 (37.0)	3/134 (2.2)	<0.001[a]
95% Confidence Interval [b]	28.9, 45.8	0.5, 6.4	
Breslow Day *P* value [c]			0.574
Face			
Complete Clearance Rate [n/N (%)]	46/109 (42.2)	3/109 (2.8)	<0.001[d]
95% Confidence Interval [b]	32.8, 52.0	0.6, 7.8	
Scalp			
Complete Clearance Rate [n/N (%)]	4/26 (15.4)	0/25	0.110[d]
95% Confidence Interval [b]	4.4, 34.9	0.0, 13.7	

[a] *P* values are from Cochran-Mantel-Haenszel test, stratified by analysis site. The *P* values ≤ 0.05 are considered statistically significant.

[b] Confidence intervals are calculated using the exact binomial distribution (Clopper-Pearson).

[c] *P* values ≤ 0.10 are considered statistically significant.

[d] *P* values are from Fisher's Exact test treatment group comparison. The *P* values ≤ 0.05 are considered statistically significant.

Table 7. Partial Clearance Rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population.

	PEP005 Gel 0.015% (N = 135)	Vehicle Gel (N = 134)	*P* value
Overall			
Partial Clearance Rate [n/N (%)]	81/135 (60.0)	9/134 (6.7)	<0.001[a]
95% Confidence Interval [b]	51.2, 68.3	3.1, 12.4	
Face			
Partial Clearance Rate [n/N (%)]	75/109 (68.8)	8/109 (7.3)	<0.001[c]
95% Confidence Interval [b]	59.2, 77.3	3.2, 14.0	
Scalp			
Partial Clearance Rate [n/N (%)]	6/26 (23.1)	1/25 (4.0)	0.099[c]
95% Confidence Interval [b]	9.0, 43.6	0.1, 20.4	

[a] *P* values are from Cochran-Mantel-Haenszel test, stratified by analysis site. The *P* values ≤ 0.05 are considered statistically significant.

[b] Confidence intervals are calculated using the exact binomial distribution (Clopper-Pearson).

[c] *P* values are from Fisher's Exact test treatment group comparison. The *P* values ≤ 0.05 are considered statistically significant.

Table 8. Percent change from baseline in Actinic Keratosis Lesion count at Day 57. Overall and by Anatomical Location. ITT population.

	PEP005 Gel 0.015% (N = 135)	Vehicle Gel (N = 134)
Overall		
N	131	133
Mean Percent Change (SD)	-72.6 (32.0)	-16.4 (31.5)
Median Percent Change	-83.3	0
Minimum, Maximum	-100.0, 50.0	-100.0, 100.0
Face	(N = 109)	(N = 109)
N	107	108
Mean Percent Change (SD)	-77.7 (29.0)	-14.7 (31.3)
Median Percent Change	-83.3	0.0
Minimum, Maximum	-100.0, 50.0	-100.0, 100.0
Scalp	(N = 26)	(N = 25)
N	24	25
Mean Percent Change (SD)	-50.1 (35.5)	-23.6 (31.8)
Median Percent Change	-48.6	-25.0
Minimum, Maximum	-100.0, 25.0	-75.0, 40.0

Note: Percent change = 100* (Day 57 AK Lesion Count – Baseline AK Lesion Count)/(Baseline AK Lesion Count).

The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (37% compared to 2%, p<0.001, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population. For the secondary endpoint the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (60% compared to 7%, p<0.001, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population.

6.2.1.3. ***PEP005-025***

This study was a multi-centre, randomized, double-blind, vehicle-controlled, dose ranging study[2] conducted in the USA and Australia between June 2009 and September 2009. The objective of the study was 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). Patients were randomized to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (End of Study). A total of 278 patients were randomized (142 to PEP005 Gel 0.015% and 136 to vehicle gel); 277 patients completed the study. Subjects were male or female patients at least 18 years of age with four to eight clinically typical, visible and discrete SK lesions within a contiguous 25 cm^2 treatment area on the head (face or scalp). The primary efficacy endpoint was the complete clearance rate of SK lesions at the Day 57 visit. A patient with no clinically visible SK lesions in the selected treatment area was defined to have complete clearance. The secondary efficacy endpoint was the partial clearance rate of SK lesions at the Day 57 visit. A patient with a 75% or greater reduction in the number of clinically visible SK lesions identified at baseline, in the selected treatment area was defined to have partial clearance.

Sample size was based on the Phase IIb study, PEP005-015, which demonstrated a complete clearance rate of 50% for PEP005 Gel, 0.015%, compared to a 9% clearance rate for vehicle gel, 57 days following treatment for three consecutive days in a study design similar to PEP005-016. Thus, statistical power greater than 95% may be achieved in a sample as small as 25 patients per treatment group. The choice of a sample size of 125 patients per group, in this Phase III study was not, therefore, motivated by statistical considerations of efficacy, but rather by the need to treat a sufficient number of individuals in pre-marketing studies to be able to estimate the incidence of common adverse drug events. Enrolment of 125 patients per group in each of two Phase III pivotal studies (PEP005-016 and PEP005-025) was consistent with this goal.

The complete clearance rate was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. The statistical analysis for the secondary efficacy endpoint was the same as that used for the primary efficacy endpoint. All treatment comparisons were tested with two-tailed tests and a 0.05 significance level. Results from this study are included below.

[2] Erratum: Phase III study

Table 9. Complete clearance rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population.

	PEP005 Gel 0.015% (N = 142)	Vehicle Gel (N = 136)	*P* value
Overall			
Complete Clearance Rate [n/N (%)]	67/142 (47.2)	7/136 (5.1)	<0.001[a]
95% Confidence Interval [b]	38.8, 55.7	2.1, 10.3	
Breslow Day *P* value [c]			0.306
Face			
Complete Clearance Rate [n/N (%)]	58/111 (52.3)	6/111 (5.4)	<0.001[d]
95% Confidence Interval [b]	42.6, 61.8	2.0, 11.4	
Scalp			
Complete Clearance Rate [n/N (%)]	9/31 (29.0)	1/25 (4.0)	0.031[d]
95% Confidence Interval [b]	14.2, 48.0	0.1, 20.4	

[a] P values are from Cochran-Mantel-Haenszel test, stratified by analysis site. The P values ≤ 0.05 are considered statistically significant.

[b] Confidence intervals are calculated using the exact binomial distribution (Clopper-Pearson).

[c] P values ≤ 0.10 are considered statistically significant.

[d] P values are from Fisher's Exact test treatment group comparison. The P values ≤ 0.05 are considered statistically significant.

Table 10. Partial clearance rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population.

	PEP005 Gel 0.015% (N = 142)	Vehicle Gel (N = 136)	*P* value
Overall			
Partial Clearance Rate [n/N (%)]	96/142 (67.6)	11/136 (8.1)	<0.001[a]
95% Confidence Interval [b]	59.2, 75.2	4.1, 14.0	
Face			
Partial Clearance Rate [n/N (%)]	82/111 (73.9)	10/111 (9.0)	<0.001[c]
95% Confidence Interval [b]	64.7, 81.8	4.4, 15.9	
Scalp			
Partial Clearance Rate [n/N (%)]	14/31 (45.2)	1/25 (4.0)	<0.001[c]
95% Confidence Interval [b]	27.3, 64.0	0.1, 20.4	

[a] *P* values are from Cochran-Mantel-Haenszel test, stratified by analysis site. The *P* values ≤ 0.05 are considered statistically significant.

[b] Confidence intervals are calculated using the exact binomial distribution (Clopper-Pearson).

[c] *P* values are from Fisher's Exact test treatment group comparison. The *P* values ≤ 0.05 are considered statistically significant.

Table 11. Percent change from baseline in Actinic Keratosis Lesion count at Day 57. Overall and by Anatomical Location. ITT population.

	PEP005 Gel 0.015% (N = 142)	Vehicle Gel (N = 136)
Overall		
N	142	136
Mean Percent Change (SD)	-72.8 (35.7)	-12.7 (32.5)
Median Percent Change	-86.6	0.0
Minimum, Maximum	-100.0, 25.0	-100.0, 100.0
Face	(N = 111)	(N = 111)
N	111	111
Mean Percent Change (SD)	-77.7 (32.8)	-13.7 (33.5)
Median Percent Change	-100.0	0.0
Minimum, Maximum	-100.0, 25.0	-100.0, 100.0
Scalp	(N = 31)	(N = 25)
N	31	25
Mean Percent Change (SD)	-55.0 (40.3)	-8.6 (28.3)
Median Percent Change	-62.5	0.0
Minimum, Maximum	-100.0, 16.7	-100.0, 60.0

Note: Percent change = 100* (Day 57 AK Lesion Count – Baseline AK Lesion Count)/(Baseline AK Lesion Count)

The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (47% compared to 5%, $p < 0.001$, CMH test stratified by analysis site) based on the ITT population. The results for the PP population were consistent with the results for the ITT population. For the secondary efficacy endpoint, the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (68% compared to 8%, $p < 0.001$, CMH test stratified by analysis site) based on the ITT population. The results for the PP population were consistent with the results for the ITT population. Overall, the treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days was shown to be effective in completely clearing a contiguous 25cm2 treatment area of SK lesions on the head (face and scalp).

6.2.2. Trunk and extremities indication

6.2.2.1. *PEP005-014*

This study was a multi-centre, randomized, parallel group, double-blind, vehicle-controlled, study conducted in the USA and Australia between September 2008 and February 2009. The objective of the study was to evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel, when administered once daily for two consecutive days (Day 1 and Day 2) to a 25 cm2 contiguous SK treatment area on non-head locations. Efficacy assessments were performed at baseline (Day 1 predose) and Day 57 (end of study). A total of 255 patients were enrolled (126 to PEP005 Gel, 0.05% and 129 to vehicle gel). Subjects were male or female patients at least 18 years of age with 4 to 8 clinically typical, visible, and discrete SK lesions within a contiguous 25 cm^2 treatment area on the trunk and extremities (i.e., non-head locations). The primary efficacy endpoint was complete clearance rate of SK lesions at Day 57, defined as the proportion of patients with no clinically visible SK lesions in the selected treatment area at Day 57. The secondary efficacy endpoint was the partial clearance rate of SK lesions at Day 57, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of SK lesions identified at baseline in the selected treatment area.

A study population of approximately 250 patients (125 patients per treatment group) was considered sufficient to detect a difference in the complete clearance rate of AK lesions, allowing for at least a 20% difference between the treatment group and vehicle group (40% versus 20%)

at Day 57. These rates correspond to an active-to-vehicle odds ratio of clearance rates of 2.67. Based on previous results of clinical studies, this sample size would provide at least 90% power with a two-sided α = 0.05 using Fisher's exact test, assuming a 5% drop-out rate.

Complete clearance rates were calculated using observed rates and using weighted estimates based on the Cochran-Mantel-Haenszel (CMH) test statistic stratifying on anatomical location. Treatment groups were compared using the CMH test. A logistic analysis of variance (ANOVA) with treatment, anatomical location, and country as factors was also used to test for treatment effect. Partial clearance rates were calculated and the treatment groups were compared using the same methods as those used for the primary efficacy endpoint. All statistical tests were two-sided with a significance level of α = 0.05, unless specified otherwise. Results from this study are included below.

Table 12. Complete clearance rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population.

Clinical Assessment	PEP005, 0.05% (N = 126)	Vehicle (N = 129)	p-value
All Anatomical Locations			
Observed complete clearance, n (%) [95% CI][a]	35 (27.8%) [20.2%, 36.46%]	6 (4.7%) [1.7%, 9.9%]	<0.0001[c]
Difference between treatment groups [95% CI][b]	23.13% [14.5%, 31.8%]		
CMH weighted complete clearance rate [95% CI][d]	27.3% [20.2%, 34.5%]	4.9% [1.2%, 8.7%]	
Difference between treatment groups [95% CI][e]	22.4% [14.3%, 30.5%]		<0.0001[e]
Anatomical Location			
Arm			
Observed complete clearance, n/N (%) [95% CI][a]	22/84 (26.2%) [17.2%, 36.9%]	4/82 (4.9%) [1.3%, 12.0%]	
Difference between treatment groups [95% CI][b]	21.3% [10.8%, 31.8%]		
Back of hand			
Observed complete clearance, n/N (%) [95% CI][a]	4/25 (16.0%) [4.5%, 36.1%]	0/29 [0, 11.9%]	
Difference between treatment groups [95% CI][b]	16.0% [01.6%, 30.4%]		
Chest			
Observed complete clearance, n/N (%) [95% CI][a]	8/9 (88.9%) [51.8%, 99.7%]	1/8 (12.5%) [0.3%, 52.7%]	
Difference between treatment groups [95% CI][b]	76.4% [45.6%, 100.0%]		
Other[f]			
Observed complete clearance, n/N (%) [95% CI][a]	1/8 (12.5%) [0.3%, 52.7%]	1/10 (10.0%) [0.2%, 44.5%]	
Difference between treatment groups [95% CI][b]	2.5% [-27.0%, 32.0%]		

CI = confidence interval

Complete clearance defined as no clinically visible AK lesions in the treatment area at Day 57. Missing values and values outside analysis windows were imputed using the last observation carried forward method.

[a] Exact CI for complete clearance rate
[b] Asymptotic CI for the difference in complete clearance rate between treatment groups (active – vehicle).
[c] p-value for the difference from Cochran-Mantel-Haenszel (CMH) test controlling for anatomical location.
[d] Asymptotic CI. Complete clearance rate weighted over anatomical location.
[e] Asymptotic CI for the difference between treatment groups (active – vehicle); p-value from Cochran chi-square test.
[f] Other = shoulder, back, and leg.

Table 13. Partial clearance rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population

Clinical Assessment	PEP005, 0.05% (N = 126)	Vehicle (N = 129)	p-value
All Anatomical Locations			
Observed partial clearance, n (%) [95% CI][a]	56 (44.4%) [35.6%, 53.6%]	9 (7.0%) [3.2%, 12.8%]	<0.0001[c]
Difference between treatment groups [95% CI][b]	37.5% [27.73%, 47.19%]		
CMH weighted partial clearance rate [95% CI][d]	44.1% [35.9%, 52.3%]	7.3% [2.8%, 11.9%]	
Difference between treatment groups [95% CI][e]	36.8% [27.4%, 46.1%]		<0.0001[e]
Anatomical Location			
Arm			
Observed partial clearance, n/N (%) [95% CI][a]	40/84 (47.6%) [36.6%, 58.8%]	7/82 (8.5%) [3.50%, 16.8%]	
Difference between treatment groups [95% CI][b]	39.1% [26.8%, 51.4%]		
Back of hand			
Observed partial clearance, n/N (%) [95% CI][a]	6/25 (24.0%) [9.4%, 45.1%]	0/29 [0, 11.9%]	
Difference between treatment groups [95% CI][b]	24.0% [7.3%, 40.7%]		
Chest			
Observed partial clearance, n/N (%) [95% CI][a]	8/9 (88.9%) [51.8%, 99.7%]	1/8 (12.5%) [0.3%, 52.6%]	
Difference between treatment groups [95% CI][b]	76.4% [45.6%, 100%]		
Other[f]			
Observed partial clearance, n/N (%) [95% CI][a]	2/8 (25.0%) [3.2%, 65.1%]	1/10 (10.0%) [0.3%, 44.5%]	
Difference between treatment groups [95% CI][b]	15.0% [-20.3%, 50.3%]		

CI = confidence interval

Partial clearance defined as ≥75% reduction in the number of AK lesions identified at baseline in the treatment area at Day 57. Missing values and values outside analysis windows were imputed using the last observation carried forward method.

[a] Exact CI for complete clearance rate

[b] Asymptotic CI for the difference in partial clearance rate between treatment groups (active – vehicle).

[c] p-value for the difference from Cochran-Mantel-Haenszel (CMH) test controlling for anatomical location.

[d] Asymptotic CI. Partial clearance rate weighted over anatomical location.

[e] Asymptotic CI for the difference between treatment groups (active – vehicle); p-value from Cochran chi-square test.

[f] Other = shoulder, back, and leg.

Table 14. Percent reduction from Baseline in Actinic Keratosis Lesion count at Day 57. Overall and by Anatomical Location. ITT population

	PEP005, 0.05% (N = 126)	Vehicle (N = 129)
All Anatomical Locations		
n	120	128
Median	69.05	0
Range	-25.0 – 100	-33.3 – 100
Anatomical Location		
Arm	(N = 84)	(N = 82)
n	79	82
Median	75.00	0
Range	-20.0 – 100	-33.3 – 100
Back of hand	(N = 25)	(N = 29)
n	25	29
Median	50.00	0
Range	-25.0 – 100	-33.3 – 71.4
Chest	(N = 9)	(N = 8)
n	9	8
Median	100	0
Range	0 – 100	0 – 100
Other[a]	(N = 8)	(N = 10)
n	7	9
Median	57.14	0
Range	0 – 100	0 – 100

Only patients with available data at both baseline and Day 57 (n) were used in the analysis.

Percent reduction calculated as [(Baseline AK lesions – Day 57 AK lesions) / Baseline AK lesions] × 100.

[a] Other = shoulder, back, and leg.

The observed complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (28%) than the vehicle group (5%) ($p < 0.0001$). Sensitivity analyses, including a multiple imputation method for handling missing data and analyses based on evaluable and PP populations, all demonstrated a statistically significantly higher complete clearance rate in the PEP005 Gel, 0.05% group than in the vehicle group ($p < .0001$ for all comparisons). The observed partial clearance rate at Day 57 overall in the PEP005 Gel, 0.05% group was 44% (56/126) versus 7% (9/129) in the vehicle group ($p < 0.0001$). Overall, the complete clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. In addition, the other efficacy variables supported the results of the primary efficacy endpoint. The partial clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. Median percent reduction from baseline in lesion count at Day 57 was substantially reduced in the PEP005 Gel, 0.05% group relative to the vehicle groups.

6.2.2.2. *PEP005-028*

This study was a multi-centre, randomized, parallel group, double-blind, vehicle-controlled, study conducted in the USA between July 2009 and October 2009. The objective of the study was to evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous SK treatment area on non-head locations. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (end of study). A total of 203 patients were enrolled (100 PEP005 Gel, 0.05%; 103 vehicle gel). Subjects were male or female patients at least 18 years of age with 4 to 8 clinically typical, visible and discrete SK lesions within a contiguous 25 cm^2 treatment area on

non-head locations. The primary efficacy endpoint was the complete clearance rate of SK lesions at the Day 57 visit, defined as the proportion of patients with no clinically visible SK lesions in the selected treatment area at Day 57. The secondary efficacy endpoint was the partial clearance rate of SK lesions at the Day 57 visit, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of SK lesions identified at baseline in the selected treatment area.

Approximately 200 patients (100 per group) were to be randomized in this study. This sample size was based on comparing the treatment groups in terms of complete clearance rate of AK lesions. It was assumed that a 20% difference between the treatment group and vehicle group (30% vs. 10%) at Day 57 was of clinical interest. The assumed 10% complete clearance rate for the vehicle group was observed in a previous Peplin study in non-head AK (PEP005-014). This sample size provided at least 90% power with a two-sided significance level of 0.05 (α=0.05) using the Chi-square test for homogeneity of proportions.

The complete clearance rate at Day 57 was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. The partial clearance rate at Day 57 was compared using the same analysis as that used for the primary efficacy endpoint. The number of AK lesions and percent change from baseline were summarized for each treatment group. All treatment comparisons were tested with two-tailed tests and a 0.05 significance level. Results from this study are included below.

Table 15. Complete clearance rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population

Clinical Assessment	PEP005, 0.05% (N = 100)	Vehicle (N = 103)	p-value
All Anatomical Locations			
Complete clearance rate, n (%)	42 (42.0%)	5 (4.9%)	<0.001[a]
[95% CI][b]	[32.2%, 52.3%]	[1.6%, 11.0%]	
Breslow Day p-value[c]	0.579		
Anatomical Location			
Arm			
Complete clearance rate, n/N (%)	27/59 (45.8%)	3/67 (4.5%)	<0.001[d]
[95% CI][b]	[32.7%, 59.2%]	[0.9%, 12.5%]	
Back of hand			
Complete clearance rate, n/N (%)	6/28 (21.4%)	0/27	0.023[d]
[95% CI][b]	[8.3%, 41.0%]	[0, 12.8%]	
Chest			
Complete clearance rate, n/N (%)	3/5 (60.0%)	1/3 (33.3%)	1.000[d]
[95% CI][b]	[14.7%, 94.7%]	[0.8%, 90.6%]	
Other[e]			
Complete clearance rate, n/N (%)	6/8 (75.0%)	1/6 (16.7%)	0.103[d]
[95% CI][b]	[34.9%, 96.8%]	[0.4%, 64.1%]	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

Complete clearance defined as no clinically visible AK lesions in the treatment area at Day 57. Missing values and values outside analysis windows were imputed using the last observation carried forward method.

[a] p-value from CMH test, stratified by analysis site; p-values ≤0.05 are statistically significant.

[b] Confidence intervals calculated using the exact bionomical distribution (Clopper-Pearson)

[c] p-values ≤0.10 are statistically significant.

[d] p-value from Fisher's Exact test; p-values ≤0.05 are statistically significant.

[e] Other = leg, back, and shoulder.

Table 16. Partial clearance rate of Actinic Keratosis Lesions at Day 57. Overall and by Anatomical Location. ITT population

Clinical Assessment	PEP005, 0.05% (N = 100)	Vehicle (N = 103)	p-value
All Anatomical Locations			
Partial clearance rate, n (%)	55 (55.0%)	7 (6.8%)	<0.001[a]
[95% CI][b]	[44.7%, 65.0%]	[2.8%, 13.5%]	
Anatomical Location			
Arm			
Partial clearance rate, n/N (%)	36/59 (61.0%)	4/67 (6.0%)	<0.001[c]
[95% CI][b]	[47.4%, 73.5%]	[1.7%, 14.6%]	
Back of hand			
Partial clearance rate, n/N (%)	9/28 (32.1%)	1/27 (3.7%)	0.012[c]
[95% CI][b]	[15.9%, 52.4%]	[0.1%, 19.0%]	
Chest			
Partial clearance rate, n/N (%)	4/5 (80.0%)	1/3 (33.3%)	0.464[c]
[95% CI][b]	[28.4%, 99.5%]	[0.8%, 90.6%]	
Other[d]			
Partial clearance rate, n/N (%)	6/8 (75.0%)	1/6 (16.7%)	0.103[c]
[95% CI][b]	[34.9%, 96.8%]	[0.4%, 64.1%]	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

Partial clearance defined as ≥75% reduction in the number of AK lesions identified at baseline in the treatment area at Day 57. Missing values and values outside analysis windows were imputed using the last observation carried forward method.

[a] p-value from CMH test, stratified by analysis site; p-values ≤0.05 are statistically significant.

[b] Confidence intervals calculated using the exact bionomical distribution (Clopper-Pearson)

[c] p-value from Fisher's Exact test; p-values ≤0.05 are statistically significant.

[d] Other = leg, back, and shoulder.

Table 17. Percent reduction from Baseline in Actinic Keratosis Lesion count at Day 57. Overall and by Anatomical Location. ITT population

	PEP005, 0.05% (N = 100)	Vehicle (N = 103)
All Anatomical Locations		
N	100	101
Median	-75.0	0.0
Range	-100 – 0	-100 – 33.3
Anatomical Location		
Arm	(N = 59)	(N = 67)
N	59	66
Median	-80.0	0
Range	-100 – 0	-100 – 25.0
Back of hand	(N = 28)	(N = 27)
n	28	26
Median	-58.6	0
Range	-100 – 0	-85.7 – 33.3
Chest	(N = 5)	(N = 3)
n	5	3
Median	-100.0	0
Range	-100 – -40.0	-100 – 0
Other[a]	(N = 8)	(N = 6)
n	8	6
Median	-100.0	0
Range	-100 – -40.0	-100 – 0

Only patients with available data at both baseline and Day 57 (n) were used in the analysis.

[a] Other = leg, back, and shoulder.

The complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (42%) than the vehicle group (5%) ($p < 0.001$). The results of the analysis of the secondary efficacy endpoint, partial clearance (≥75% reduction) in SK lesions at Day 57, support the results of the analysis of complete clearance. The partial clearance rate at Day 57 overall was statistically significantly higher in the PEP005 Gel, 0.05% group (55%) than the vehicle group (7%) ($p < 0.001$). Overall, the complete clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. In addition, other efficacy variables supported the results of the primary efficacy endpoint. Partial clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. Median percent change from baseline in lesion count at Day 57 was substantially reduced in the PEP005 Gel, 0.05% group relative to the vehicle group.

6.3. Clinical studies in special populations

No clinical studies in special populations were performed.

6.4. Analysis performed across trials (pooled analyses and meta-analysis)

In order to further evaluate the efficacy of PEP005 Gel for the head and scalp indication, data were pooled across studies and referred to as "combined studies populations". Two combined studies populations were presented. One combined studies population pooled data from PEP005-016 and PEP005-025 and another pooled data PEP005-016, PEP005-025, and PEP005-015. PEP005-016 and PEP005-025 were the adequate and well-controlled Phase III studies that evaluated the proposed dosage regimen of PEP005 Gel for treatment of the head locations, i.e., 0.015% applied topically for three consecutive days (Days 1, 2, and 3).

PEP005-015 was a dose-ranging study that included the proposed dosage regimen treatment on head locations. These three studies were randomised, double-blind, vehicle-controlled, parallel

group studies. Study medication was supplied as unit-dose tubes and patient-applied at home to a contiguous 25 cm^2 treatment area. Results are included below.

Table 18. Efficacy Results in Individual Studies of Interest and Combined Studies Populations. Head Locations. ITT population.

	PEP005-016		PEP005-025		PEP005-015		Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
Efficacy Parameter	PEP005, 0.015% (N=135)	Vehicle (N=134)	PEP005, 0.015% (N=142)	Vehicle (N=136)	PEP005, 0.015% (N=32)	Vehicle (N=33)	PEP005, 0.015% (N=277)	Vehicle (N=270)	PEP005, 0.015% (N=309)	Vehicle (N=303)
Complete Clearance										
n (%)	50 (37.0)	3 (2.2)	67 (47.2)	7 (5.1)	16 (50.0)	3 (9.1)	117 (42.2)	10 (3.7)	133 (43.0)	13 (4.3)
95% Confidence Interval	28.9, 45.8	0.5, 6.4	38.8, 55.7	2.1, 10.3	31.9, 68.1	1.9, 24.3	36.4, 48.3	1.8, 6.7	37.4, 48.8	2.3, 7.2
P value	<0.001		<0.001		<0.001		<0.001			
Partial Clearance										
n (%)	81 (60.0)	9 (6.7)	96 (67.6)	11 (8.1)	23 (71.9)	4 (12.1)	177 (63.9)	20 (7.4)	200 (64.7)	24 (7.9)
95% Confidence Interval	51.2, 68.3	3.1, 12.4	59.2, 75.2	4.1, 14.0	53.3, 86.3	3.4, 28.2	57.9, 69.6	4.6, 11.2	59.1, 70.1	5.1, 11.6
P value	<0.001		<0.001		<0.001		<0.001			
Percent Reduction in AK Lesions										
n	131	133	142	136	32	33	273	269	305	302
Median	83	0	87	0	94	0	83	0	83	0
Range	-50, 100	-100, 100	-25, 100	-100, 100	0, 100	-25, 100	-50, 100	-100, 100	-50, 100	-100, 100

[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)

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% Confidence Interval uses the exact binomial method.

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

Table 19. Recurrence: Head Locations

Patient-Based Recurrence[a]		Lesion-Based Recurrence[b]	
	PEP005, 0.015% (N=108)		PEP005, 0.015% (N=108)
3-month		*3-month*	
N	107	N	107
Percent	16.8	Mean (SD), %	3.8 (9.2)
95% CI	11.0, 25.4	Min, Max	0.0, 50.0
6-month		*6-month*	
N	86	N	103
Percent	33.3	Mean (SD), %	8.8 (15.2)
95% CI	25.1, 43.2	Min, Max	0.0, 80.0
9-month		*9-month*	
N	68	N	102
Percent	46.0	Mean (SD), %	9.5 (14.4)
95% CI	37.0, 56.1	Min, Max	0.0, 62.5
12-month		*12-month*	
N	55	N	100
Percent	53.9	Mean (SD), %	12.8 (19.1)
95% CI	44.6, 63.7	Min, Max	0.0, 120.0

CI = confidence interval

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

[b] 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.

In order to further evaluate efficacy for the trunk and extremities indication, data were pooled across studies and referred to as “combined studies populations”. Two combined studies populations were presented. One combined studies population pooled data from PEP005-014 and PEP005-028 and another pooled data from PEP005-014, PEP005-028, and PEP005-006. PEP005-014 and PEP005-028 were the adequate and well-controlled Phase III studies that evaluated the proposed dosage regimen for approval of PEP005 Gel for treatment of non-head locations, i.e., 0.05% applied topically for two consecutive days (Days 1 and 2). Unit-dose tubes were used for study medication application by the patient at home in these two studies (PEP005-014 and PEP005-28). PEP005-006 was a dose-ranging study that included the proposed dosage regimen for approval of PEP005 Gel. Results are included below.

Table 20. Efficacy Results in Individual Studies of Interest and Combined Studies Populations. Non-Head Locations. ITT population

	PEP005-014		PEP005-028		PEP005-006		Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
Efficacy Parameter	PEP005, 0.05% (N=126)	Vehicle (N=129)	PEP005, 0.05% (N=100)	Vehicle (N=103)	PEP005, 0.05% (N=42)	Vehicle (N=43)	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)
Complete Clearance										
n (%)	35 (27.8)	6 (4.7)	42 (42.0)	5 (4.9)	19 (45.2)	6 (14.0)	77 (34.1)	11 (4.7)	96 (35.8)	17 (6.2)
95% Confidence Interval	20.2, 36.5	1.7, 9.8	32.2, 52.3	1.6, 11.0	29.8, 61.3	5.3, 27.9	27.9, 40.6	2.4, 8.3	30.1, 41.9	3.6, 9.7
P value	<0.001		<0.001		0.002		<0.001			
Partial Clearance										
n (%)	56 (44.4)	9 (7.0)	55 (55.0)	7 (6.8)	27 (64.3)	9 (20.9)	111 (49.1)	16 (6.9)	138 (51.5)	25 (9.1)
95% Confidence Interval	35.6, 53.6	3.2, 12.8	44.7, 65.0	2.8, 13.5	48.0, 78.4	10.0, 36.0	42.4, 55.8	4.0, 11.0	45.3, 57.6	6.0, 13.1
P value	<0.001		<0.001		<0.001		<0.001			
Percent Reduction in AK Lesions										
n	120	128	100	101	41	42	220	229	261	271
Median	69	0	75	0	83	0	75	0	75	0
Range	-25, 100	-33, 100	0, 100	-33, 100	-57, 100	-20, 100	-25 – 100	-33 – 100	-57 – 100	-33 – 100

[a] Controlled Phase 3 studies (PEP005-014 and PEP005-028)

[b] Controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); for study PEP005-006 only non-scalp patients in the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and vehicle gel group were included.

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

For PEP005-014 and PEP005-028, P value is for comparing active treatment vs. vehicle, using the CMH test stratifying on site. For PEP005-006, P value is for comparing active treatment vs. vehicle, using Fisher's Exact test. The 95% Confidence Interval uses the exact binomial method.

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

Table 21. Recurrence: Non-Head Locations

Patient-Based Recurrence[a]		Lesion-Based Recurrence[b]	
	PEP005, 0.05% (N=76)		PEP005, 0.05% (N=76)
3-month		*3-month*	
N	74	N	74
Percent	18.9	Mean (SD), %	6.7 (17.7)
95% CI	11.7, 29.8	Min, Max	0.0, 100.0
6-month		*6-month*	
N	59	N	71
Percent	39.5	Mean (SD), %	15.7 (28.0)
95% CI	29.4, 51.7	Min, Max	0.0, 140.0
9-month		*9-month*	
N	44	N	71
Percent	50.5	Mean (SD), %	16.1 (25.0)
95% CI	39.7, 62.4	Min, Max	0.0, 140.0
12-month		*12-month*	
N	36	N	71
Percent	56.0	Mean (SD), %	13.2 (23.0)
95% CI	45.1, 67.6	Min, Max	0.0, 140.0

CI = confidence interval

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

[b] 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.

6.5. Supportive studies

6.5.1. Head and scalp indication

6.5.1.1. *PEP005-006*

This study was a multi-centre, randomised, double-blind, double dummy, vehicle-controlled sequential cohort study conducted in the USA between September 2006 and June 2007. The primary objectives of the study were to evaluate the safety and tolerability of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel, administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous SK treatment area, and to evaluate the efficacy of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel when administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous SK treatment area. The study included 2 treatment phase cohorts. During Treatment Phase I, patients were randomly assigned to 1 of 3 treatment groups: vehicle gel applied on Days 1, 2, and 3; 0.025% PEP005 Topical Gel applied on Days 1, 2, and 3; or vehicle gel applied on Day 1 and 0.05% PEP005 Topical Gel applied on Days 2 and 3. During Treatment Phase II, the 0.025% PEP005 Topical Gel dose was eliminated and patients were randomly assigned to 1 of the 3 following treatment groups: vehicle gel applied on Days 1, 2, and 3; vehicle gel applied on Day 1 and 0.05% PEP005 Topical Gel applied on Days 2 and 3; or 0.05% PEP005 Topical Gel applied on Days 1, 2, and 3. This is illustrated in Table 22 below.

Table 22. Treatment in Phase 1 and Phase 2: 3 dosing groups

Treatment Phase 1: 3 dosing groups:

Study Gel Concentration	Treatment Regimen	Dose per Application [Volume]	PEP005 Applied per mm^2 per Dose (µg)
Vehicle	Day 1, 2, 3	250 µL	0
0.025%	Day 1, 2, 3	250 µL	0.025
0.05%	Day 1: Vehicle Gel Days 2 and 3: 0.05%	250 µL 250 µL	0 0.05

Treatment Phase 2: 3 dosing groups:

Study Gel Concentration	Treatment Regimen	Dose per Application [Volume]	PEP005 Applied per mm^2 per Dose (µg)
Vehicle	Day 1, 2, 3	250 µL	0
0.05%	Day 1, 2, 3	250 µL	0.05
0.05%	Day 1: Vehicle Gel Days 2 and 3: 0.05%	250 µL 250 µL	0 0.05

Clinical response to treatment with PEP005 Topical Gel was determined at each post-treatment visit by assessing the clearance of SK lesions identified at baseline (presence/absence), assessing the number of subclinical lesions appearing/emerging that were not clinically identifiable at baseline within the selected treatment area, and assessing patient satisfaction of treatment outcome at Day 57. A total of 222 patients were enrolled in the study. Subjects were male and postmenopausal female patients who were at least 18 years of age with 4 to 8 clinically typical, visible and discrete SK lesions within a contiguous 25 cm^2 treatment area on the arm, shoulder, chest, back, or scalp. Clinical response to treatment with PEP005 Topical Gel was determined at each post-treatment visit by assessing the clearance of SK lesions identified at baseline (presence/absence), assessing the number of subclinical lesions appearing/emerging that were not clinically identifiable at baseline within the selected treatment area, and assessing patient satisfaction of treatment outcome at Day 57. Efficacy endpoints were analysed for the modified Intent-to-Treat (mITT) Population with a Per Protocol (PP) Population as supplemental information for the primary and secondary efficacy endpoints. The chi-square test was used to analyse complete SK clearance, baseline SK lesion clearance, and partial clearance rate at end of study. The 95% CIs were determined using binomial approximation to the normal distribution. Median percentage reduction was analysed across treatment groups using the Kruskal-Wallis test and between treatment groups using the Wilcoxon Rank Sum test. The time to initial complete SK lesion clearance was estimated by the Kaplan-Meier product-limit method. Results from this study are included below.

Table 23. Partial clearance rate at Day 57. mITT Population

		PEP005 Topical Gel			
	Vehicle Gel N = 60	0.025% Days 1, 2, & 3 N = 50	0.05% Days 2 & 3 N = 55	0.05% Days 1, 2, & 3 N = 57	
Parameter	n (%)	n (%)	n (%)	n (%)	p-Value[a]
≥75% clearance[b]	13 (21.7)	28 (56.0)	34 (61.8)	43 (75.4)	<0.0001
95% CI[c]	11.24, 32.09	42.24, 69.76	48.98, 74.66	64.26, 86.61	
<75% clearance[b]	47 (78.3)	22 (44.0)	21 (38.2)	14 (24.6)	
95% CI[c]	67.91, 88.76	30.24, 57.76	25.34, 51.02	13.39, 35.74	
Difference PEP005 versus Vehicle	-	-34.33	-40.15	-53.77	
95% CI[c]	-	-51.60, -17.07	-56.69, -23.61	-69.05, -38.49	
p-Value[d]	-	0.0002	<0.0001	<0.0001	

CI = confidence interval.

[a] P-value calculated using chi-square test across dose levels.

[b] Proportions are based on the number of nonmissing patients within each treatment group.

[c] Two-sided CI from binomial approximation to the normal distribution.

[d] P-value calculated using chi-square test for comparing differences in the clearance rate between the vehicle gel group and PEP005 Topical Gel group for each dose level.

Table 24. Complete clearance rate at Day 57. mITT Population

		PEP005 Topical Gel			
	Vehicle Gel N = 60	0.025% Days 1, 2, & 3 N = 50	0.05% Days 2 & 3 N = 55	0.05% Days 1, 2, & 3 N = 57	
Parameter	n (%)	n (%)	n (%)	n (%)	p-Value[a]
Complete clearance[b]	7 (11.67)	20 (40.00)	24 (43.64)	31 (54.39)	<0.0001
95% CI[c]	3.54, 19.79	26.42, 53.58	30.53, 56.74	41.46, 67.32	
Incomplete clearance[b]	53 (88.33)	30 (60.00)	31 (56.36)	26 (45.61)	
95% CI[c]	80.21, 96.46	46.42, 73.58	43.26, 69.47	32.68, 58.54	
Difference PEP005 versus vehicle gel	-	-28.33	-31.97	-42.72	
95% CI[c]	-	-44.16, -12.51	-47.39, -16.55	-57.99, -27.45	
p-Value[d]	-	0.0006	0.0001	<0.0001	

CI = confidence interval.

[a] P-value calculated using chi-square test across dose levels.

[b] Proportions are based on the number of nonmissing patients within each treatment group.

[c] Two-sided CI from binomial approximation to the normal distribution.

[d] P-value calculated using chi-square test for comparing differences in the clearance rate between the vehicle gel group and PEP005 Topical Gel group for each dose level.

Table 25. Median percent reduction in AK lesions at the end of Study. mITT population.

		PEP005 Topical Gel			
Parameter	Vehicle Gel N = 60	0.025% Days 1, 2, & 3 N = 50	0.05% Days 2 & 3 N = 55	0.05% Days 1, 2, & 3 N = 57	p-Value[a]
Median	0.0	75.0	83.3	100.0	<0.0001
Min, max	-20.0, 100.0	0.0, 100.0	-57.1, 100.0	0.0, 100.0	
p-Value[b]		<0.0001	<0.0001	<0.0001	

[a] P-value calculated using Kruskal-Wallis test across dose levels.

[b] P-value calculated using Wilcoxon Rank Sum test between vehicle gel and each PEP005 Topical Gel dose level.

A statistically significant difference in partial clearance rate (≥75%) was observed for patients treated with PEP005 Topical Gel compared with vehicle gel. The partial clearance rate for patients treated with PEP005 Topical Gel ranged from 56.0% to 75.4% compared with vehicle gel (21.7%) ($p = 0.0002$ to $p < 0.0001$). This ≥75% clearance of baseline SK lesions was statistically significant across all dose levels ($p < 0.0001$). Baseline clearance rate was statistically significantly higher ($p<0.0007$) in the PEP005 Topical Gel treatment groups (range: 42.0% to 57.9% of patients) compared with the vehicle gel group (13.3% of patients). Baseline clearance rate was statistically significant across all dose levels ($p < 0.0001$). Complete clearance rate was also statistically higher ($p<0.0006$) for patients in the PEP005 Topical Gel treatment groups (range: 40.0% to 54.4%) compared with vehicle gel (11.7%). Complete clearance rate was statistically significant across all dose levels ($p < 0.0001$). The median percent reduction in the number of SK lesions was statistically significantly higher ($p < 0.0001$) in the PEP005 Topical Gel treatment groups (range: 75.0% to 100.0%) compared with vehicle gel (0.0%) and was statistically significant across all dose levels and the majority of patients had lesion clearance between Day 29 and Day 57. Overall, the proportion of patients with emergent subclinical SK lesions was low (8.3%) across treatment groups and study visits.

6.5.1.2. *PEP005-007*

This study was an open-label, multi-centre, dose-escalation, cohort study conducted in Australia and New Zealand between January and November 2007. The primary objective was to determine the optimal tolerated regimen of PEP005 Topical Gel when administered to patients once daily as a two or three consecutive day application schedule to a 25 cm^2 contiguous SK treatment area on the face or face and scalp. The secondary objectives were to evaluate the efficacy of a two or three consecutive day application of PEP005 Topical Gel, when applied once daily to a 25 cm^2 contiguous SK treatment area on the face or face and scalp. Efficacy assessments were based on the following:

- Determination of the partial clearance rate, defined as the proportion of patients at the Day 57 post-treatment visit with a 75% or greater reduction in the number of SK lesions identified at baseline in the treatment area.
- Determination of the complete clearance rate, defined as the proportion of patients at the Day 57 post-treatment visit with no clinically visible SK lesions in the treatment area.
- Determination of the baseline clearance rate, defined as the proportion of patients at the Day 57 post-treatment visit with 100% reduction in the number of SK lesions identified at baseline in the treatment area.

A dose escalation design was chosen with a cohort of three patients at each escalation level. Application of 0.025% PEP005 Topical Gel applied once daily for three days and for two days was established as the dose limiting toxicity (DLT) and the maximally tolerated dose (MTD), respectively, for treatment of the face or face and scalp. There was no intra-patient dose

escalation in this study and no randomization to assign dose levels. Two subsequent protocol amendments were introduced to evaluate the safety and tolerability of lower concentrations of PEP005 Topical Gel (0.0175%, 0.0125%, 0.0075%, 0.0050%, and 0.0025%) with similar treatment regimens (once daily for two or three consecutive days). A total of 94 patients were actually enrolled with 88 patients treated with at least one dose of PEP005 Topical Gel. Subjects were male patients at least 18 years of age or post-menopausal female patients, (i.e., no menses for at least 12 consecutive months, or post-hysterectomy) with four to eight clinically typical, visible, and discrete SK lesions within a contiguous 25 cm^2 treatment area on the face or face and scalp. Analysis was mostly descriptive in nature. No hypothesis/inferential testing was conducted. Results from this study are included below.

Table 26. Number and percentage of patients with AK lesion clearance for Analysis Group 1: Full Analysis Set, mIIT and PP populations.

AK Lesion Clearance	0.025% PEP005 Day 1 & 2 n (%)	0.0175% PEP005 Day 1 & 2 n (%)	0.0125% PEP005 Day 1 & 2 n (%)
mITT	**(N = 30)**	**(N = 3)**	**(N = 3)**
PP	**(N = 26)**	**(N = 3)**	**(N = 3)**
Complete AK lesion clearance[a]			
mITT	11 (36.7)	3 (100.0)	0
95% CI[b]	19.4%–3.9%	100.0%–100.0%	0.0%–0.0%
PP	11 (42.3)	3 (100.0)	0
95% CI[b]	23.3%–61.3%	100.0%–100.0%	0.0%–0.0%
Partial AK lesion clearance[c]			
mITT	20 (66.7)	3 (100.0)	3 (100.0)
95% CI[b]	49.8%–83.5%	100.0%–100.0%	100.0%–100.0%
PP	20 (76.9)	3 (100.0)	3 (100.0)
95% CI[b]	60.7%–93.1%	100.0%–100.0%	100.0%–100.0%
Baseline AK lesion clearance[d]			
mITT	11 (36.7)	3 (100.0)	0
95% CI[b]	19.4%–53.9%	100.0%–100.0%	0.0%–0.0%
PP	11 (42.3)	3 (100.0)	0
95% CI[b]	23.3%–61.3%	100.0%–100.0%	0.0%–0.0%

Note: Percentages were based on the number of patients in each as treated group within each treatment group.

[a] Complete AK lesion clearance included patients with no clinically visible lesions in the selected AK treatment area.

[b] The 95% CI is the CI for the percentage of patients with AK clearance (complete, partical, or baseline).

[c] Partial AK lesion clearance included patients with 75% or greater clearance of baseline lesions in the selected AK treatment area.

[d] Baseline AK lesion clearance included patients with no clinically visible remaining baseline lesions in the selected AK treatment area.

Table 27. Number and percentage of patients with AK lesion clearance for Analysis Group 2: Full Analysis Set, mIIT and PP populations.

AK Lesion Clearance	0.025% PEP005 Day 1, 2, & 3 n (%)	0.0175% PEP005 Day 1, 2, & 3 n (%)	0.0125% PEP005 Day 1, 2, & 3 n (%)	0.0075% PEP005 Day 1, 2 & 3 n (%)	0.0050% PEP005 Day 1, 2, & 3 n (%)	0.0025% PEP005 Day 1, 2, & 3 n (%)
mITT	(N = 6)	(N = 10)	(N = 11)	(N = 8)	(N = 8)	(N = 8)
PP	(N = 5)	(N = 9)	(N = 10)	(N = 7)	(N = 7)	(N = 8)
Complete AK lesion clearance[a]						
mITT	3 (50.0)	8 (80.0)	6 (54.6)	3 (37.5)	3 (37.5)	0
95% CI[b]	10.0%–90.0%	55.2%–100.0%	25.1%–84.0%	4.0%–71.1%	4.0%–71.1%	0.0%–0.0%
PP	3 (60.0)	7 (77.8)	5 (50.0)	2 (28.6)	2 (28.6)	0
95% CI[b]	17.1%–100.0%	50.6%–100.0%	19.0%–81.0%	0.0%–62.0%	0.0%–62.0%	0.0%–0.0%
Partial AK lesion clearance[c]						
mITT	6 (100.0)	8 (80.0)	11 (100.0)	6 (75.0)	5 (62.5)	2 (25.0)
95% CI[b]	100.0%–100.0%	55.2%–100.0%	100.0%–100.0%	45.0%–100.0%	29.0%–96.1%	0.0%–55.0%
PP	5 (100.0)	7 (77.8)	10 (100.0)	5 (71.4)	4 (57.1)	2 (25.0)
95% CI[b]	100.0%–100.0%	50.6%–100.0%	100.0%–100.0%	38.0%–100.0%	20.5%–93.8%	0.0%–55.0%
Baseline AK lesion clearance[d]						
mITT	3 (50.0)	8 (80.0)	6 (54.6)	3 (37.5)	3 (37.5)	0
95% CI[b]	10.0%–90.0%	55.2%–100.0%	25.1%–84.0%	4.0%–71.1%	4.0%–71.1%	0.0%–0.0%
PP	3 (60.0)	7 (77.8)	5 (50.0)	2 (28.6)	2 (28.6)	0
95% CI[b]	17.1%–100.0%	50.6%–100.0%	19.0%–81.0%	0.0%–62.0%	0.0%–62.0%	0.0%–0.0%

Note: Percentages were based on the number of patients in each as treated group within each treatment group.

[a] Complete AK lesion clearance included patients with no clinically visible lesions in the selected AK treatment area.

[b] The 95% CI is the CI for the percentage of patients with AK clearance (complete, partical, or baseline).

[c] Partial AK lesion clearance included patients with 75% or greater clearance of baseline lesions in the selected AK treatment area.

[d] Baseline AK lesion clearance included patients with no clinically visible remaining baseline lesions in the selected AK treatment area.

The study was not statistically powered to evaluate efficacy, and the resulting groups have a small number of patients. For the MTD, 0.025% PEP005 Topical Gel, once daily for two consecutive days, the percentage of patients with partial clearance (PC) was 66.7%; complete clearance (CC) was 38.9%; and baseline clearance (BC) was 36.7%. 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 0.025% in Analysis Group 2 (100%).

6.5.1.3. *PEP005-030*

This study was a 12-month, long-term follow-up study of patients with SK on the head (face or scalp) who have completed Day 57 in studies PEP005-016 or PEP005-025, and was conducted in the USA and Australia between July 2009 and September 2010. The objectives of the study

were to summarize treatment area recurrence of SK lesions, in the selected treatment area, during a 12-month follow-up period for patients who achieved complete clearance of SKs at Day 57 in studies PEP005-016 and PEP005-025, and to summarize long-term safety data, in the selected treatment area over a 12-month follow-up period for patients who completed Day 57 in studies PEP005-016 and PEP005-025. This was a prospective, longitudinal, observational 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. A total of 117 patients who had demonstrated complete clearance of SK lesions in either study PEP005-016 or PEP005-025 were enrolled in this long-term follow-up study. Of these 117 patients, 108 had received 0.015% PEP005 Gel and 9 had received vehicle in the previous study. Criteria for evaluation was the number of SK lesions in the selected treatment area (with recurrence defined as any identified SK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase III study) and concomitant therapies (medications and procedures) for treatment of SK lesions in the selected treatment area. For the CC57 (complete clearance at 57 days) population, SK recurrence was summarized using Kaplan-Meier methods. All event times were imputed to their target study day prior to performing the calculations. The recurrence rate was estimated by the Kaplan-Meier "failure" estimate at the target study day expressed as a percentage. The estimates, along with 95% confidence intervals, were calculated at Days 91, 183, 274, and 365. The time to recurrence was also summarized. The recurrence rate at Day 365 (12 months) was summarized for the subgroups of treatment location, geographic region, Fitzpatrick skin type, gender, age group, and baseline lesion count. The number of AK lesions in the treatment area was summarized at each visit. Results from this study are included below.

Table 28. Recurrence Rate: Overall and by Treatment Location (CC57 Population)

	Previous Treatment Group					
	PEP005 Gel, 0.015%			Vehicle		
	N	Estimate	95% CI	N	Estimate	95% CI
Overall						
3-month followup	107	16.8	9.7, 23.9	9	44.4	12.0, 76.9
6-month followup	86	33.3	24.2, 42.3	4	58.3	24.4, 92.2
9-month followup	68	46.0	36.4, 55.6	3	72.2	40.5, 103.9
12-month followup	55	53.9	44.3, 63.5	2	72.2	40.5, 103.9
Face						
3-month followup	95	15.8	8.5, 23.1	8	50.0	15.4, 84.6
6-month followup	78	32.0	22.5, 41.4	3	50.0	15.4, 84.6
9-month followup	62	45.1	35.0, 55.3	3	66.7	31.4, 102.0
12-month followup	50	52.8	42.6, 63.0	2	66.7	31.4, 102.0
Scalp						
3-month followup	12	25.0	0.5, 49.5	1	0	--
6-month followup	8	43.8	14.7, 72.8	1	100.0	100.0, 100.0
9-month followup	6	53.1	23.7, 82.6	0	100.0	100.0, 100.0
12-month followup	5	62.5	33.8, 91.2	0	100.0	100.0, 100.0

N = number of patients at risk at the start of the visit window

Note: the recurrence rate is the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage

Table 29. Summary of Lesion-based Recurrence (CC57 Population)

Lesion-based Recurrence (%)	Previous Treatment Group	
	PEP005 Gel, 0.015%	Vehicle
3-Month Followup		
N	107	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 Followup		
N	103	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 Followup		
N	102	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 Followup		
N	100	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.

At 12 months of follow-up, 53.9% of patients who had been treated with PEP005 Gel in the previous Phase III studies (N=108), had at least one new or recurrent SK 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 III studies), the mean lesion-based recurrence rate was 12.8%. At 12 months of follow-up, 72.2% of vehicle-treated patients (N=9) had a new or recurrent SK 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 16.3%.

6.5.1.4. *PEP005-001*

This study was a multi-centre, randomized, double-blind, parallel-group, vehicle-controlled study conducted in Australia between March and October 2005. The primary objective of the study was to determine the safety of PEP005 Topical Gel at 0.0025%, 0.01%, and 0.05% administered as two applications to patients with SK on the arms, shoulders, chest, face, and/or scalp under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. The secondary objectives of the study were to evaluate the efficacy of PEP005 0.0025%, 0.01% and 0.05% Topical Gel administered under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8, to determine a recommended treatment regimen for SK, and to evaluate patients for cosmetic outcome.

This was a multi-centre, double-blind, randomized, vehicle-controlled, parallel-group comparison of two treatment schedules, Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B) of three concentrations (0.0025%, 0.01%, and 0.05%) of PEP005 Topical

Gel in patients with at least five SK lesions located on the arms, shoulders, chest, face, and/or scalp. A total of 72 patients were screened, 63 were randomized and analysed for efficacy, and 58 were analysed for safety. Subjects were adults with at least five individual SK lesions on the arm, shoulders, chest, face, and/or scalp. The histological clearance of each individual lesion was determined by assessing the extent of SK lesion clearance based on the histology results from Day 85 for patients included in the ITT population. Clinical response to treatment of each selected lesion was evaluated at each scheduled visit until End of Study (Day 85) for patients included in the mITT population. Clinical response was evaluated as: 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). The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing. Results are included below.

Table 30. Histological response to Treatment (punch biopsy) at end of study (Day 85): ITT population

Treatment	Vehicle Gel N=12		PEP005 0.0025% N=17		PEP005 0.01% N=16		PEP005 0.05% N=18	
Timepoint/Histological Response	Arm A N=6	Arm B N=6	Arm A N=9	Arm B N=8	Arm A N=8	Arm B N=8	Arm A N=9	Arm B N=9
End of Study								
Number of 2 mm Punch Biopsies	6	6	8	7	7	8	8	7
Presence of AK	3	4	7	4	3	5	6	3
Absence of AK	3	2	1	3	4	3	2	4
Difference								
PEP005 vs. Vehicle	-	-	0.3750	-0.0952	-0.0714	-0.0417	0.2500	-0.2381
95% CI[a]	-	-	(-0.1332, 0.8832)	(-0.6800, 0.4895	(-0.6747, 0.5318)	(-0.5981, 0.5147)	(-0.3012, 0.8012)	(-0.8228, 0.3466)
P-value[b]	-	-	0.2448	1.0000	1.0000	1.000	0.5804	0.5921
P-value[c] Treatment Arm A	0.2637							
P-value[c] Treatment Arm B	0.9126							

Note: Percentages are based on the number of non-missing biopsies within each treatment group.
[a] Two-sided confidence interval from normal approximation to the binomial.
[b] P-value from Fisher's exact test comparing individual doses to vehicle gel.
[c] P-value from Fisher's exact test comparing all treatment groups.

Table 31. AK lesion clearance rate. Pooled treatment arms A and B at end of study (Day 85): mITT population.

Clinical Assessment / Global Response to Treatment[a]	Vehicle Gel	0.0025% PEP005	0.01% PEP005	0.05% PEP005
End of Study	**N = 12**	**N = 15**	**N = 16**	**N = 15**
Global response to treatment[a]				
Total lesions	60	75	75	75
Complete clearance	19 (31.67%)	30 (40.00%)	19 (25.33%)	53 (70.67%)
95% CI	(19.65%, 43.68%)	(28.73%, 51.27%)	(15.33%, 35.34%)	(60.19%, 81.14%)
Non-complete clearance[b]	41 (68.33%)	45 (60.00%)	56 (74.67%)	22 (29.33%)
95% CI	(56.32%, 80.35%)	(48.73%, 71.27%)	(64.66%, 84.67%)	(18.86%, 39.81%)
Difference in proportion between respective dose level and vehicle gel for complete clearance of AK	-	0.0833	-0.0633	0.3900
95% CI for the difference in proportion between respective dose level and vehicle gel for complete clearance of AK[c]	-	(-7.98%, 24.65%)	(-21.82%, 9.15%)	(23.21%, 54.79%)
Pairwise p-values[d]	-	0.3696	0.4460	<0.0001
p-value[e] (all treatment groups)	<0.0001			
End of Study	**N = 12**	**N = 15**	**N = 16**	**N = 15**
Global response to treatment				
80% of lesion complete clearance[f]	2 (16.67%)	5 (33.33%)	2 (12.50%)	10 (66.67%)
95% CI	(-7.01%, 40.35%)	(7.23%, 59.44%)	(-5.12%, 30.12%)	(40.56%, 92.77%)
Difference in proportion between respective dose level and vehicle gel for complete clearance of 80% AK		0.1667	-0.0417	0.5000
95% CI for the difference in proportion between respective dose level and vehicle gel for complete clearance of 80% AK[c]		(-16.72%, 50.06%)	(-32.01%, 23.67%)	(16.61%, 83.39%)
Pairwise p-values[d]		0.4082	1.0000	0.0185
p-value[e] (all treatment groups)	0.0082			

CI = confidence interval; AK = actinic keratosis.
[a] Proportions were calculated using the number of lesions within each treatment group.
[b] Non-complete clearance includes marked clearance, slight clearance, unchanged, worsened, and unable to determine.
[c] Two-sided confidence interval from normal approximation to the binomial.
[d] P-value calculated from Fisher's exact test comparing individual doses to vehicle gel.
[e] P-value calculated from Fisher's exact test comparing all treatment groups.
[f] Proportions were calculated using the number of patients with complete clearance for ≥80% of AK lesions within each treatment group.

When data from both treatment arms were pooled, a statistically significant (p <0.0001) difference in the percentage of lesions cleared was observed when all treatment groups were compared. A statistically significant (p <0.0001) difference was also observed for the percentage of lesions cleared for the 0.05% PEP005 Topical Gel group when compared to vehicle gel. A statistically significant difference (p =0.0082) in the percentage of patients who had complete clearance of 80% of SK lesions was observed when all treatment groups were compared. A statistically significant difference (p =0.0185) was also observed for the percentage of patients in the 0.05% PEP005 Topical Gel group who had complete clearance of 80% of SK lesions when compared to vehicle gel. No statistically significant difference for pooled treatment arms data was observed for 100% complete SK lesion clearance for any PEP005 Topical Gel dose group, when compared to vehicle gel or when all treatment groups were compared.

6.5.2. Trunk and extremities indication

6.5.2.1. *PEP005-006*

This study was described above, as it included both head/ scalp and trunk/ extremities subjects. 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. For patients who received treatment on non-head locations, partial clearance rates by treatment group were 21%, 51%, 67%, and 74%, respectively (p ≤ 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). Results from this study are included below.

Table 32. Partial Clearance rates at Day 57 for lesions located in non-scalp areas: mITT population.

		PEP005 Topical Gel			
Parameter	Vehicle Gel N = 43 n (%)	0.025% Days 1, 2, & 3 N = 37 n (%)	0.05% Days 2 & 3 N = 42 n (%)	0.05% Days 1, 2, & 3 N = 39 n (%)	p-Value[a]
≥75% clearance[b]	9 (20.9)	19 (51.4)	28 (66.7)	29 (74.4)	<0.0001
95% CI[c]	8.8, 33.1	35.3, 67.5	52.4, 80.9	60.7, 88.1	
<75% clearance[b]	34 (79.1)	18 (48.7)	14 (33.3)	10 (25.6)	
95% CI[c]	66.9, 91.2	32.5, 64.8	19.1, 47.6	11.9, 39.4	
Difference PEP005 versus Vehicle	-	-30.4	-45.7	-53.4	
95% CI[c]	-	-50.6, -10.2	-64.5, -27.0	-71.8, -35.1	
p-Value[d]	-	0.0045	<0.0001	<0.0001	

CI = Confidence interval.

[a] P-value calculated using chi-square test across dose levels.

[b] Proportions are based on the number of nonmissing patients within each treatment group.

[c] Two-sided CI from binomial approximation to the normal distribution.

[d] P-value calculated using chi-square test for comparing differences in the clearance rate between the vehicle gel group and PEP005 Topical Gel group for each dose level.

Table 33. Complete Clearance rates at Day 57 for lesions located in non-scalp areas: mITT population.

			PEP005 Topical Gel					
			0.025%		0.05%		0.05%	
	Vehicle Gel		Days 1, 2, & 3		Days 2 & 3		Days 1, 2, & 3	
Lesion Location	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Scalp	17	1 (5.9)	13	7 (53.9)	13	5 (38.5)	18	13 (72.2)
Nonscalp	43	6 (14.0)	37	13 (35.1)	42	19 (45.2)	39	18 (46.2)

6.5.2.2. *PEP005-017*

This study was a randomized, double-blind, vehicle-controlled study to evaluate the pharmacokinetics of PEP005 (ingenol mebutate) Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis. It was conducted in the USA between March 2009 and May 2009. The 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 actinic keratosis. The secondary objectives were to evaluate the safety and efficacy of PEP005 Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis. A total of 16 patients were randomized (analysed) (13 patients randomized to PEP005 Gel and three to vehicle gel). Subjects were male or female patients at least 18 years of age with multiple SK lesions within a contiguous 100 cm^2 treatment area on the dorsal aspect of one forearm. The primary criteria for evaluation were whole blood samples, quantified (C_{max}, T_{max} and $AUC_{(0-24)}$) for ingenol mebutate and PEP015 and PEP025. The secondary criteria for evaluation were; incidence rate of AEs, serious adverse events (SAEs) and AEs leading to discontinuation through Day 57; incidence rate and grade of LSRs, pigmentation and scarring, following study treatment through Day 57; complete clearance rate, defined as no clinically visible SK lesions in a 25 cm^2 area within the selected treatment area; and percentage (%) reduction in SK lesions at Day 57, compared to baseline, in a 25 cm^2 area within the selected treatment area. Results were summarized into tabulations, case listings, plots, and histograms for comparison. Descriptive summaries were created to include the mean, standard deviation, median, and range for continuous variables, and counts and percentages for categorical variables. Results are included below.

Table 34. Summary of AK lesion counts (ITT population)

Lesion Clearance at Day 57 (25 cm^2 area)	PEP005 Gel, 0.05% N = 13	Vehicle Gel N = 3
Patients with lesion clearance		
Complete clearance	10 (77%)	0
Partial clearance	13 (100%)	0
Median lesion count		
Baseline	5.0	4.0
Day 57	0	5.0
Change from baseline lesion count (%)		
Mean (SD)	–95.8 (8.0)	+33.3 (57.7)
Median	–100	0
Min	–80	0
Max	–100	+100

N = number of patients; SD = standard deviation.

No systemic absorption was detected. Levels of ingenol mebutate and its acyl isomers were below the LLOQ in samples from all patients following two consecutive once-daily applications of PEP005 Gel, 0.05%.SK lesion clearance was assessed at Day 57 in a 25 cm^2 contiguous area of

skin located within the larger treatment area. Of the patients who received treatment with PEP005 Gel, 0.05%, 77% (10/13) had complete clearance of all SK lesions, and all patients had partial clearance. None of the three patients treated with vehicle gel had complete or partial clearance of their AK lesions. The percentage change from baseline in the total SK lesion count in the selected 25 cm^2 area was also assessed at Day 57. The median percentage reduction in SK lesion count was 100% in patients treated with PEP005 Gel, 0.05%, and zero in those patients treated with vehicle gel.

6.5.2.3. ***PEP005-018***

This study was a multicentre, open-label study to examine the safety and toleration of 0.05% PEP005 Topical Gel in patients with actinic keratoses on the dorsum of the hand, conducted in the USA between October and December 2007. The objectives of the study were to examine the safety and toleration of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm^2 contiguous SK treatment area on the dorsum of a single hand, and to examine the efficacy of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm^2 contiguous SK treatment area on the dorsum of a single hand as determined by the complete clearance rate (the proportion of patients at the Day 57 post-treatment visit with no clinically visible SK lesions in the selected SK treatment area), partial clearance rate (the proportion of patients at the Day 57 post-treatment visit with a 75% or greater reduction in the number of SK lesions identified at baseline in the selected SK treatment area) and baseline clearance rate (the proportion of patients at the Day 57 post-treatment visit with a 100% reduction in the number of SK lesions identified at baseline in the selected SK treatment area). A total of 12 patients were enrolled, 11 of which were treated with study medication and analysed. Male and/or postmenopausal female patients at least 18 years of age with 4–8 clinically typical, visible, and discrete SK lesions within a contiguous 25 cm^2 treatment area on the dorsum of one hand. The analysis was primarily descriptive in nature. Results are included below.

Table 35. Percentage of patients with complete lesion clearance (mITT population).

	PEP005 Gel, 0.05%, on Days 1 and 2 (N = 11)				
Complete Lesion Clearance[a]	**Day 2**	**Day 8**	**Day 15**	**Day 29**	**Day 57**
Complete clearance	0	0	5 (45.5%)	4 (36.4%)	3 (27.3%)
95% CI	0, 0	0, 0	16.0%, 74.9%	7.9%, 64.8%	1.0%, 53.6%
Incomplete clearance	11 (100.0%)	11 (100.0%)	6 (54.6%)	7 (63.6%)	8 (72.7%)
95% CI	100%, 100%	100%, 100%	25.1%, 84.0%	35.2%, 92.1%	46.4%, 99.1%

CI = confidence interval; N = number of patients.

Note: The per-protocol population was identical to the modified intent-to-treat population, and the per-protocol analysis yielded identical results (Table 14.2.1.2).

[a] Complete clearance includes patients with no clinically visible lesions (100% clearance) in the treatment area. Incomplete clearance includes all other patients.

Table 36. Percentage of patients with partial lesion clearance (mITT population).

	PEP005 Gel, 0.05%, on Days 1 and 2 (N = 11)				
Partial Lesion Clearance[a]	Day 2	Day 8	Day 15	Day 29	Day 57
≥ 75% lesion clearance	0	0	5 (45.5%)	7 (63.6%)	5 (45.5%)
95% CI	0, 0	0, 0	16.0%, 74.9%	35.2%, 92.1%	16.0%, 74.9%
< 75% lesion clearance	11 (100.0%)	11 (100.0%)	6 (54.6%)	4 (36.4%)	6 (54.6%)
95% CI	100%, 100%	100%, 100%	25.1%, 84.0%	7.9%, 64.8%	25.1%, 84.0%

CI = confidence interval; N = number of patients.

Note: The per-protocol population was identical to the modified intent-to-treat population, and the analysis of the per-protocol population provided identical results (Table 14.2.2.2).

[a] Partial clearance includes patients with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline in the treatment area.

Table 37. Percentage of patients with complete clearance of baseline lesions (mITT population).

	PEP005 Gel, 0.05%, on Days 1 and 2 (N = 11)				
Baseline Lesion Clearance[a]	Day 2	Day 8	Day 15	Day 29	Day 57
Complete baseline clearance	1 (9.1%)	0	5 (45.5%)	4 (36.4%)	3 (27.3%)
95% CI	0%, 26.1%	0, 0	16.0%, 74.9%	7.9%, 64.8%	1.0%, 53.6%
Incomplete baseline clearance	10 (90.9%)	11 (100.0%)	6 (54.6%)	7 (63.6%)	8 (72.7%)
95% CI	73.9%, 100%	100%, 100%	25.1%, 84.0%	35.2%, 92.1%	46.4%, 99.1%

CI = confidence interval; N = number of patients.

Note: The per-protocol population was identical to the modified intent-to-treat population, and the analysis of the per-protocol population provided identical results (Table 14.2.3.2).

[a] Baseline clearance includes patients with no clinically visible baseline lesions remaining in the treatment area.

At Day 57, the complete clearance rate was 27.3% (3/11 patients), and the partial clearance rate was 45.5% (5/11 patients). The complete clearance rate was highest on Day 15 (45.5%; 5/11 patients), while the partial clearance rate was highest on Day 29 (63.6%; 7/11 patients). The median percentage reduction in SK lesion count from baseline to Day 57 ranged from an increase of 12.5% to a decrease of 100.0%, with an overall median reduction of 66.7%. The median lesion count in the treatment area decreased from 6.0 on Day 2 to 0.0 on Day 15, increasing to 2.0 by Day 57. However, SK lesions were unable to be determined/assessed in a percentage of patients on Days 8 (5/11; 45.5%) and 15 (4/11; 36.4%). Treatment-emergent subclinical lesions were identified in three patients (27.3%) on Day 57, based on a comparison of the total number of lesions at Day 57 with the lesions identified at baseline.

6.5.2.4. *PEP005-020*

This study was a multi-centre, open-label study to evaluate the safety and efficacy of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses on non-head locations (trunk and extremities), and was conducted in the USA and Australia between June and September 2009. The objectives of the study were to evaluate the safety of PEP005 Gel, 0.05% when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous actinic keratosis treatment area on non-head locations, and to evaluate the efficacy of PEP005 Gel, 0.05% when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous SK treatment area on non-head locations. A total of 102 patients were enrolled, received treatment and completed the study. Subjects were male or female patients at least 18 years of age with 4 to 8 clinically typical, visible and discrete SK lesions within a contiguous 25 cm^2 treatment area on non-head locations (trunk and extremities). Criteria for evaluation included complete clearance rate of SK lesions at the Day 57 visit (defined as no clinically visible SK lesions in the selected treatment area), partial clearance rate of SK lesions at the Day 57 visit

(defined as a 75% or greater reduction in the number of SK lesions in the selected treatment area), and the percent change from baseline to Day 57 in the total number of SK lesions. No hypotheses were tested and no inferential analyses were performed in this study. Results are included below.

Table 38. Complete Clearance rate of AK lesions at Day 57-Overall and by Anatomical location: ITT population.

Clinical Assessment	PEP005 Gel, 0.05%
Overall	
Complete Clearance Rate, n (%)	40/102 (39.2)
95% confidence interval [a]	29.7, 49.4
Anatomic Location	
Arm	
Complete Clearance Rate, n (%)	26/51 (51.0)
95% confidence interval [a]	36.6, 65.2
Back of Hand	
Complete Clearance Rate, n (%)	5/41 (12.2)
95% confidence interval [a]	5.6, 29.2
Chest	
Complete Clearance Rate, n (%)	6/7 (85.7)
95% confidence interval [a]	42.1, 99.6
Back, Shoulder, Leg	
Complete Clearance Rate, n (%)	3/3 (100.0)
95% confidence interval [a]	29.2, 100.0

[a] Confidence intervals were calculated using the exact binomial distribution (Clopper-Pearson)

Table 39. Partial Clearance rate of AK lesions at Day 57-Overall and by Anatomical location: ITT population.

Clinical Assessment	PEP005 Gel, 0.05%
Overall	
Partial Clearance Rate, n (%)	56/102 (54.9)
95% confidence interval [a]	44.7, 64.8
Anatomic Location	
Arm	
Partial Clearance Rate, n (%)	36/51 (70.6)
95% confidence interval [a]	56.2, 82.5
Back of Hand	
Partial Clearance Rate, n (%)	11/41 (26.8)
95% confidence interval [a]	14.2, 42.9
Chest	
Partial Clearance Rate, n (%)	6/7 (85.7)
95% confidence interval [a]	42.1, 99.6
Back, Shoulder, Leg	
Partial Clearance Rate, n (%)	3/3 (100.0)
95% confidence interval [a]	29.2, 100.0

[a] Confidence intervals were calculated using the exact binomial distribution (Clopper-Pearson)

Table 40. Percentage change from baseline in AK lesion count at Day 57-Overall and by Anatomical location (ITT population).

	PEP005 Gel, 0.05% % Change from Baseline
Overall (N=102)	
Median	−75.0
Minimum, Maximum	−100.0, 80.0
Anatomic Location	
Arm (N=51)	
Median	−100.0
Range	−100.0, 80.0
Back of Hand (N=41)	
Median	−50.0
Range	−100.0, 0.0
Chest (N=7)	
Median	−100.0
Range	−100.0, 42.9
Back, Shoulder, Leg (N=3)	
Median	−100.0
Range	−100.0, −100.0

Overall, 40/102 (39.2%) patients had a complete clearance of SK lesions at Day 57. By treatment location, complete clearance was observed in 26/51(51%) patients treated on the arm, 5/41 (12.2%) patients treated on the back of the hand, 6/7 (85.7%) patients treated on the chest, and 3/3 (100%) patients treated in other locations (i.e., back, shoulder, or leg). There were no meaningful differences across the subgroups of gender, age, Fitzpatrick skin type, and baseline lesion count with respect to overall clearance rate; there was an apparent difference by geographic region, but this was confounded by treatment location. Partial clearance (≥75% reduction) of SK lesions at Day 57, support the results observed for complete clearance. The overall partial clearance rate was 54.9%, and by treatment location, the rates were 70.6% for the arm, 26.8% for the back of the hand, 85.7% for the chest, and 100% for the combined locations of the back, shoulder, and leg. The median percent reduction in SK lesion count over the course of the study was 75%; the median percent reduction by anatomic location was 50% for the back of the hand and 100% for all other locations.

6.5.2.5. ***PEP005-004***

This study was an open-label, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel when applied on Day 1 and Day 2 to actinic keratoses on the shoulders, chest, back, or arms followed by a post-treatment follow-up period lasting at least four weeks. The study was conducted in the USA between September 2005 and March 2006. The primary objective of this study was to determine the maximum tolerated dose (MTD) for PEP005 Topical Gel, administered once daily for two consecutive days, by applying 90 µL of PEP005 Topical Gel over a 3 cm x 3 cm field surrounding a target actinic keratosis lesion comprising both diseased and perilesional skin. The secondary objectives of this study were to evaluate the clinical efficacy of PEP005 Topical Gel by determining the complete clinical response rate, and to determine the systemic absorption of PEP005 Topical Gel following application once daily for two consecutive days. A total of 23 patients were screened, 22 patients were enrolled and analysed for efficacy and safety, and two patients provided data for the pharmacokinetic (PK) analysis. Subjects were male or female patients who were at least 18 years of age and had one SK lesion with a diameter between 3 mm and 15 mm on the shoulders, chest, back, or arms. Clinical response to treatment with PEP005 Topical Gel was determined by assessing the extent of SK lesion clearance at each post-Day 1 visit compared with the Baseline assessment. Clinical response was evaluated as: complete clearance (100% improvement, no evidence of residual disease), 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). No hypothesis/inferential testing was conducted for this study. Results are included below.

Table 41. Clinical response to treatment. ITT population.

	PEP005 Topical Gel			
	0.01% N=3	0.025% N=3	0.05% N=10	0.075% N=6
TEAE reporting by patients[a]				
With at least one AE	2 (66.7%)	1 (33.3%)	8 (80.0%)	5 (83.3%)
With any serious AE[b]	0	0	1 (10.0%)	0
With any severe AE	0	0	1 (10.0%)	0
With any AE deemed drug related[c]	1 (33.3%)	0	6 (60.0%)	5 (83.3%)
TEAE reporting by event				
Total[d]	5 (100.0%)	1 (100.0%)	19 (100.0%)	12 (100.0%)
Severity				
Mild	5 (100.0%)	1 (100.0%)	16 (84.2%)	12 (100.0%)
Moderate	0	0	2 (10.5%)	0
Severe	0	0	1 (5.3%)	0
Number of AEs deemed drug related	2 (40.0%)	0	13 (68.4%)	9 (75.0%)

TEAE = treatment emergent adverse event
[a] Percentages were based on the number of patients within each treatment group.
[b] AEs that were fatal, life threatening, persistent or significant disability, hospitalization, or congenital anomaly/birth defect.
[c] AEs with a relationship to the study drug of unknown, possible, probable, or definite.
[d] Percentages were based on the total number of TEAEs reported, including those reported more than once by the same patient.

Table 42. Overall treatment emergent adverse event information. Safety population.

	PEP005 Topical Gel			
Time point **Clinical response to treatment**	0.01% N=3	0.025% N=3	0.05% N=10	0.075% N=6
Day 2 - pre-dose				
Complete clearance	0	0	0	0
Marked clearance	0	0	0	0
Slight clearance	0	0	0	0
Unchanged	2 (66.7%)	3 (100.0%)	7 (70.0%)	6 (100.0%)
Worsened	0	0	0	0
Unable to be assessed	1 (33.3%)	0	3 (30.0%)	0
Day 8				
Complete clearance	0	0	0	0
Marked clearance	2 (66.7%)	0	1 (10.0%)	0
Slight clearance	1 (33.3%)	3 (100.0%)	1 (10.0%)	1 (16.7%)
Unchanged	0	0	1 (10.0%)	0
Worsened	0	0	0	0
Unable to be assessed	0	0	7 (70.0%)	5 (83.3%)
Day 15				
Complete clearance	0	0	3 (30.0%)	2 (33.3%)
Marked clearance	2 (66.7%)	0	4 (40.0%)	1 (16.7%)
Slight clearance	1 (33.3%)	3 (100.0%)	1 (10.0%)	1 (16.7%)
Unchanged	0	0	1 (10%)	0
Worsened	0	0	0	0
Unable to be assessed	0	0	1 (10.0%)	2 (33.3%)
Day 29 (End of Study)				
Complete clearance	2 (66.7%)	1 (33.3%)	6 (60.0%)	3 (50.0%)
Marked clearance	0	0	2 (20.0%)	2 (33.3%)
Slight clearance	1 (33.3%)	2 (66.7%)	1 (10.0%)	1 (16.7%)
Unchanged	0	0	1 (10.0%)	0
Worsened	0	0	0	0
Unable to be assessed	0	0	0	0

Clinical response to treatment with PEP005 Topical Gel was reported for the Intent-to-Treat (ITT) population. At the Day 8 assessment, complete clearance was not reported in any of the treatment groups; marked clearance was reported for two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort and for one (10.0%) patient in the 0.05% PEP005 Topical Gel cohort. At the Day 15 assessment, complete clearance was reported for three (30.0%) patients in the 0.05% PEP005 Topical Gel cohort, and two (33.3%) patients in the PEP005 Topical Gel 0.075% cohort; marked clearance was reported for two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, four (40.0%) patients in the 0.05% PEP005 Topical Gel cohort, and one (16.7%) patient in the 0.075% PEP005 Topical Gel cohort. At the Day 29 (End of Study) assessment, complete clearance was reported in two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, one (33.3%) patient in the 0.025% PEP005 Topical Gel cohort, six (60.0%) patients in the 0.05% PEP005 Topical Gel cohort, and three (50.0%) patients in the 0.075% PEP005 Topical Gel cohort. Marked clearance was reported in only the 0.05% PEP005 Topical Gel and 0.075% PEP005 Topical Gel cohorts; two (20.0%) patients and two (33.3%) patients, respectively. Four patients (one in the 0.05% PEP005 Topical Gel cohort and three in the 0.075% PEP005 Topical Gel cohort) had an unscheduled follow-up visit 12 to 15 days after the End of Study assessment. Three of the four patients had complete clearance and one had marked clearance.

6.5.2.6. ***PEP005-031***

This study was a 12-month, long-term follow-up study of patients with actinic keratosis on non-head areas (trunk and extremities) who have completed Day 57 in study PEP005-020, and was conducted in the USA and Australia between July 2009 and September 2010. The objectives of the study were to summarize treatment area recurrence of actinic keratosis lesions, in the selected treatment area, during a 12-month follow-up period for patients with complete clearance who completed Day 57 in study PEP005-020, and to summarize long-term safety data, in selected treatment area over a 12-month follow-up period for patients who completed Day 57 in study PEP005-020. This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in study PEP005-020. No study medication was administered during PEP005-031. A total of 38 patients who had demonstrated complete clearance of SK lesions in study PEP005-020 were enrolled in the study. Subjects were patients had to achieve complete clearance of SK lesions (lesion count = 0) at Day 57 in study PEP005-020. Criteria for evaluation included number of SK lesions in the selected treatment area, recurrence (defined as any identified SK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase III study) and concomitant therapies (medications and procedures) in the selected treatment area. For the CC57 (complete clearance at day 57) population, SK recurrence was summarized using Kaplan-Meier methods. All event times were imputed to their target study day prior to performing the calculations. The recurrence rate was estimated by the Kaplan-Meier “failure” estimate at the target study day expressed as a percentage. The estimates, along with 95% confidence intervals, were calculated at Days 91, 183, 274, and 365. The time to recurrence was also summarized. The recurrence rate at Day 365 (12 months) was summarized for the subgroups of treatment location, geographic region, Fitzpatrick skin type, gender, age group, and baseline lesion count. The number of SK lesions in the treatment area was summarized at each visit. Results are included below.

Table 43. Recurrence rate: Overall and by Treatment Location (CC57 population)

	Previous Treatment: 0.05% PEP005 Gel,		
	N	Estimate	95% CI
Overall			
3-month followup	36	25.0	10.9, 39.1
6-month followup	26	48.1	31.6, 64.6
9-month followup	18	59.6	43.4, 75.9
12-month followup	14	62.5	46.4, 78.6
Arm			
3-month followup	23	30.4	11.6, 49.2
6-month followup	15	58.3	37.7, 78.9
9-month followup	9	76.8	59.1, 94.6
12-month followup	5	81.4	65.1, 97.8
Back of Hand			
3-month followup	4	50.0	1.0, 99.0
6-month followup	2	75.0	32.6, 117.4
9-month followup	1	75.0	32.6, 117.4
12-month followup	1	75.0	32.6, 117.4
Chest			
3-month followup	6	0	--
6-month followup	6	0	--
9-month followup	6	0	--
12-month followup	6	0	--
Back, Shoulder, Leg			
3-month followup	3	0	--
6-month followup	3	33.3	0.0, 86.7
9-month followup	2	33.3	0.0, 86.7
12-month followup	2	33.3	0.0, 86.7

N = number of patients at risk at the start of the visit window

Note: the recurrence rate is the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage

Table 44. Summary of lesion based recurrence (CC57 population)

Lesion-based Recurrence (%)	Previous Treatment Group
	PEP005 Gel, 0.05%
3-Month Followup	
N	36
Mean (SD), %	8.8 (21.2)
Median	0.0
Min, Max	0.0, 100.0
6-Month Followup	
N	33
Mean (SD), %	19.1 (28.4)
Median	0.0
Min, Max	0.0, 125.0
9-Month Followup	
N	33
Mean (SD), %	18.5 (24.7)
Median	16.7
Min, Max	0.0, 125.0
12-Month Followup	
N	34
Mean (SD), %	11.3 (16.5)
Median	0.0
Min, Max	0.0, 75.0

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.

At 12 months of follow-up, 62.5% of patients in the CC57 population treated with PEP005 Gel, 0.05% in study PEP005-020 (N=38) 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 III study), the mean lesion-based recurrence rate was 11.3%.

6.5.2.7. ***PEP005-032***

This study was a 12 month, long-term follow-up study of patients with actinic keratosis on non-head locations (trunk and extremities) who completed Day 57 in study PEP005-028. It was conducted in the USA between September 2009 and October 2010. The objectives of the study were to summarize treatment area recurrences of actinic keratosis lesions, in the selected treatment area during a 12-month follow-up period for patients with complete clearance, who completed Day 57 in study PEP005-028, and to summarize long-term safety data, in selected treatment area over a 12-month follow-up period for patients with complete clearance, who completed Day 57 in study PEP005-028. This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in study PEP005-028. No study medication was administered during PEP005-032. A total of 43 patients were enrolled (38 received PEP005 Gel 0.05% and 5 received vehicle gel in the previous study [PEP005-028]). Subjects were patients had to achieve complete clearance of SK lesions at Day 57 in the previous study, PEP005-028. Criteria for evaluation included number of SK lesions in the selected treatment area, recurrence (defined as any identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase III study), and

concomitant therapies (medications and procedures) for treatment of SK lesions in the selected treatment area. For the CC57 population, AK recurrence was summarized using Kaplan-Meier methods. All event times were imputed to their target study day prior to performing the calculations. The recurrence rate was estimated by the Kaplan-Meier "failure" estimate at the target study day expressed as a percentage. The estimates, along with 95% confidence intervals, were calculated at Days 91, 183, 274, and 365. Time to recurrence was also summarized. The recurrence rate at Day 365 was summarized for subgroups of interest. The number of AK lesions in the treatment area was summarized at each visit. Results are included below.

Table 45. Recurrence rate: Overall and by treatment location (CC57 population)

	Previous Treatment Group					
	PEP005 Gel, 0.05%			Vehicle		
	N	Estimate	95% CI	N	Estimate	95% CI
Overall						
3-month followup	38	13.2	2.4, 23.9	5	40.0	0.0, 82.9
6-month followup	33	31.6	16.8, 46.4	3	60.0	17.1, 100.0
9-month followup	26	42.1	26.4, 57.8	2	60.0	17.1, 100.0
12-month followup	22	50.0	34.1, 65.9	2	80.0	44.9, 100.0
Arm						
3-month followup	23	8.7	0.0, 20.2	3	66.7	13.3, 100.0
6-month followup	21	30.4	11.6, 49.2	1	66.7	13.3, 100.0
9-month followup	16	39.1	19.2, 59.1	1	66.7	13.3, 100.0
12-month followup	14	47.8	27.4, 68.2	1	100.0	100.0, 100.0
Back of Hand						
3-month followup	6	16.7	0.0, 46.5	--	--	--
6-month followup	5	50.0	10.0, 90.0	--	--	--
9-month followup	3	83.3	53.5, 100.0	--	--	--
12-month followup	1	83.3	53.5, 100.0	--	--	--
Chest						
3-month followup	3	0	--	1	0	--
6-month followup	3	0	--	1	0	--
9-month followup	3	0	--	1	100.0	100.0, 100.0
12-month followup	3	0	--	1	100.0	100.0, 100.0
Back, Shoulder, Leg						
3-month followup	6	33.3	0.0, 71.1	1	0	--
6-month followup	4	33.3	0.0, 71.1	1	0	--
9-month followup	4	33.3	0.0, 71.1	1	0	--
12-month followup	4	50.0	10.0, 90.0	1	0	--

N = number of patients at risk at the start of the visit window

Note: The recurrence rate is the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage.

Table 46. Summary of lesion-based recurrence (CC57 population)

Lesion-based Recurrence (%)	Previous Treatment Group	
	PEP005 Gel, 0.05%	Vehicle
3-Month Followup		
N	38	5
Mean (SD), %	4.7 (13.7)	6.9 (9.6)
Median	0.0	0.0
Min, Max	0.0,60.0	0.0, 20.0
6-Month Followup		
N	38	5
Mean (SD), %	12.9 (27.7)	16.9 (20.5)
Median	0.0	14.3
Min, Max	0.0, 140.0	0.0, 50.0
9-Month Followup		
N	38	5
Mean (SD), %	13.9 (25.3)	14.2 (16.4)
Median	0.0	14.3
Min, Max	0.0, 140.0	0.0, 40.0
12-Month Followup		
N	37	5
Mean (SD), %	14.9 (27.7)	19.2 (14.7)
Median	0.0	16.7
Min, Max	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

At 12 months of follow-up, 50% of patients treated with PEP005 Gel, 0.05% in study PEP005-028 (N=38) had at least one new or recurrent SK lesion within the selected treatment area. The estimated median time to 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 III studies), the mean lesion-based recurrence rate was 14.9%. At 12 months of follow-up, 80% of patients treated with vehicle gel in the previous study (N=5) had a new or recurrent SK lesion, with a median time to recurrence of 183 days, and the mean lesion-based recurrence rate at 12 months was 19.2%.

6.5.2.8. *AGN204332-004*

This study was a multicentre, double-blind, parallel, randomised, vehicle-controlled study of the safety of a single application of up to 0.2 ml of 0.01% PEP005 gel to actinic keratoses on the shoulders, chest, back and/or arms followed by a post-treatment follow-up period lasting at least 2 weeks. It was conducted in the USA between August 2004 and September 2004. The objective of the study was to determine the safety of 0.01% PEP005 gel after a single application in patients with SKs on the shoulders, chest, back and/or arms. This study was a two-arm, multicentre, double-blind, parallel, randomised, vehicle-controlled Phase I trial, conducted in the USA, evaluating the safety of PEP005 0.01% gel in patients with SK. Patients received a single application of 0.01% PEP005 gel or PEP005 vehicle gel to five SK lesions. A total of 16 patients were entered and treated, however 11 received treatment with active gel and 5 received treatment with vehicle. Subjects were male or female patients, at least 18 years of age,

with at least 5 individual SK lesions on the shoulders, chest, back and/or arms. The global response to treatment was to be evaluated by the investigator at each post-baseline visit to determine response to treatment for each of the 5 selected lesions. The global response to treatment score was to be based on the investigator's visual assessment of each lesion compared to the lesion at the baseline visit (using the photographs taken at baseline as a reference) using an 8-point scale.

Response was analysed in the intent-to-treat population (all randomised patients). Efficacy was analysed at all visits and also using the last available data (i.e. Day 14 or Day 21). Results are included below.

Table 47. Extent of clearance by lesion in patients treated with 0.01% PEP005

	Day 1 [a]		Day 7		Day 14		Last overall follow-up [b]	
N lesions	50	100%	55	100%	55	100%	55	100%
Complete clearance	0	-	1	2%	8	15%	16	29%
Almost cleared	1	2%	4	7%	5	9%	6	11%
Marked clearance	3	6%	4	7%	11	20%	8	15%
Moderate clearance	3	6%	5	9%	5	9%	3	5%
Slight clearance	8	16%	12	22%	10	18%	9	16%
Unchanged	17	34%	14	25%	13	24%	12	22%
Worsened	0	-	3	5%	2	4%	0	-
Unable to determine	18	36%	12	22%	1	2%	1	2%

Data Source: Tables 14.2.3, 14.2.3.1 of Section 14.2.1.
[a] Patient #1002 did not undergo the Day 1 visit.
[b] Data taken from Day 21 follow-up visits where available (4 patients treated with 0.01% PEP005) or from Day 14 for other patients.

Table 48. Summary of skin adverse events irrespective of relationship, by patient

	0.01% PEP005		Vehicle	
N patients	11	100%	5	100%
N patients with ≥1 AE	9	82%	2	40%
N patients with				
1 AE	2	18%	2	40%
2 AEs	6	55%	0	0%
3 AEs	1	9%	0	0%

A total of 80 lesions were treated (55 with 0.01% PEP005; 25 with PEP005 vehicle). Complete clearance in all five lesions at last available follow-up was reported for one patient treated with 0.01% PEP005. Another 0.01% PEP005 patient had complete clearance in 4/5 treated lesions. Extent of lesion clearance according to individual lesions showed that at Day 14, 8/55 lesions (15%) treated with active gel had complete clearance and by the last available follow-up, this had increased to 16/55 lesions (29%) treated with active gel. In addition, 6/55 lesions were classified as almost cleared (i.e. >90% clearance) at last available follow-up. The combined rate of almost and complete clearance at last follow-up in lesions treated with 0.01% active gel is 40% (26/55). In the vehicle group, of the 25 treated lesions, 2 had complete clearance at last follow-up and 1 was classified almost cleared, giving a combined rate of almost and complete clearance of 15% (no data for one patient with 5 lesions). Of the 12 lesions with an inflammatory response at Day 7, seven (58%) had complete clearance at the last available follow-up.

6.5.2.9. *PEP005-013*

This study was a Phase I, pharmacokinetic study to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel to a 100 cm^2 (5 cm x 20 cm) contiguous

actinic keratosis treatment area on the extensor (dorsal aspect) forearm. The study was conducted in Australia between October 2007 and April 2008. The primary objective of the study was to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel on two consecutive days (Day 1 and Day 2) to a 100 cm^2 (5 cm x 20 cm) contiguous SK treatment area on the extensor (dorsal aspect) forearm. The secondary objective of the study was to evaluate the safety and tolerability of two consecutive days' application of 0.05% PEP005 Topical Gel, when applied to a 100 cm^2 (5 cm x 20 cm) contiguous SK treatment area on the extensor (dorsal aspect) forearm. Eight patients were enrolled. Six of the eight patients completed the study and were included in the safety analysis. Subjects were male patients who were at least 18 years of age with a contiguous 100 cm^2 treatment area containing at least five SK lesions on either the right or left extensor (dorsal aspect) forearm. The pharmacokinetic (PK) blood samples (Days 1, 2, and 3) were to be quantified for PEP005 and the two major metabolites, PEP015 and PEP025. Following administration of PEP005 Topical Gel, C_{max}, T_{max}, and $AUC_{(0-24)}$ were to be evaluated for PEP005, PEP015, and PEP025 to determine systemic exposure to PEP005 Topical Gel in patients receiving two consecutive days of treatment. Data were summarized and listed only. Results from this study are included below.

Table 49. Summary of Adverse events. APT population

Parameter	0.05% PEP005 Topical Gel (N = 6) n (%)
Number of patients who had a TEAE	6 (100.0)
Number of TEAEs	63
Number of Patients Who had a Treatment-related AE	6 (100.0)
Number of Treatment-related AEs	53
Number of Patients Who had at least one Severe TEAE	2 (33.3)
Number of Severe TEAEs	2
Number of Patients Who had a SAE	1 (16.7)
Number of SAEs	1
Number of Patients Who had a TEAE with an Outcome of Fatal	0
Number of Patients Who had a TEAE Leading to Discontinuation from Dosing	1 (16.7)
Number of Patients Who had a TEAE Leading to Discontinuation from Study	0
Note: Percentages are based on the number of patients treated. Treatment-related are those AEs with a relatedness to study drug of unknown, possible, probable, or definite. Severe AEs included intensity of TEAEs that are unknown.	

The PK data suggest that treatment of a 100 cm^2 area of skin with 0.05% of PEP005, once daily for one or two consecutive days does not demonstrate systemic absorption of PEP005 or its metabolites PEP015 or PEP025. No efficacy results were provided.

6.5.2.10. ***PEP005-022***

This study was a multicentre, open-label, dose-area escalation, cohort study to evaluate the safety and tolerability of 0.05% PEP005 Topical Gel applied for two consecutive days to treatment area(s) of up to a total of 100 cm^2 in patients with actinic keratoses on the extensor (dorsal aspect) forearm(s). The study was conducted in the USA and Australia between April 2008 and September 2008. The objective of the study was to evaluate the safety and tolerability of two, once-daily, consecutive applications of PEP005 Gel, 0.05%, when applied to 25, 50, 75, or 100 cm^2 actinic keratosis treatment area(s) on the dorsal forearm(s). Patients were assigned to escalating treatment Cohorts starting with Cohort 1 and escalating through to Cohort 8. Patients in each Cohort were evaluated on the basis of safety and tolerability to study treatment. A total

of 74 patients were enrolled in the study, 65 of whom were assigned to treatment. Eight patients were assigned to Cohorts 1–5, 7, and 8, and 9 patients to Cohort 6. There were 64 patients who received at least one dose of study medication and were included in the safety analysis. Of these, 63 patients completed the treatment phase (screening to Day 57). Subjects were male patients who were at least 18 years of age with a contiguous 100 cm^2 treatment area on both the right and left dorsal forearms, each containing a minimum of five SK lesions No statistical hypothesis testing was planned. For LSRs, the treatment effect was explored by inspection of observed means across treatment Cohorts, least squares (LS) mean difference, and two-sided 95% confidence intervals (CI) of the LS mean difference with control groups. All LSR, pigmentation and scarring data were also summarized descriptively and listed. Results from this study are included below.

Table 50. Summary of Overall Adverse Events (Safety population)

	Total Body Exposure[a]				
	25 cm^2 (N = 8) n (%)	50 cm^2 (N = 16) n (%)	75 cm^2 (N = 16) n (%)	100 cm^2 (N = 24) n (%)	Total (N = 64) n (%)
Patients who had a TEAE	1 (12.5)	10 (62.5)	12 (75.0)	13 (54.2)	36 (56.3)
Number of TEAEs	1	15 32 26			74
Patients who had a treatment-related AE[b]	1 (12.5)	6 (37.5)	10 (62.5)	10 (41.7)	27 (42.2)
Number of treatment-related AEs	1	8	23	17	49
Patients who had at least one severe TEAE	0	1 (6.3)	0	0	1 (1.6)
Number of severe TEAEs	0	1	0	0	1
Patients who had an SAE	0	1 (6.3)	2 (12.5)	0	3 (4.7)
Number of SAEs	0	1 2 0			3
Patients who had a TEAE with a fatal outcome	0	0	0	0	0
Patients who had a TEAE leading to discontinuation of dosing	0	0	1 (6.3)	1 (4.2)	2 (3.1)
Patients who had a TEAE leading to discontinuation from study	0	0 0 0			0

Note: Percentages are based on the number of patients in each total body exposure group.
AE = adverse event; N = number of patients; n = number of observations within a group;
SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Total body exposure: 25 cm^2 = Cohort 1; 50 cm^2 = Cohorts 2 and 3; 75 cm^2 = Cohorts 4 and 5; 100 cm^2 = Cohorts 6, 7, and 8.

[b] Treatment-related AEs are those AEs with an unknown, possible, probable, or definite relationship to the study drug.

PEP005 Gel, 0.05%, was safe and well tolerated when applied once daily for two consecutive days to a dorsal forearm treatment area of up to 100 cm^2 in patients with SK. Five of 64 (7.8%) patients did not receive the full treatment course of two days due to LSRs and/or AEs at the treatment site; of these five patients, one patient each had reactions in: a single 25 cm^2 treatment area, two 25 cm^2 areas, one 25 cm^2 and one 50 cm^2 area, two 50 cm^2 areas, and a single 75 cm^2 area. All eight patients with a single contiguous treatment area of 100 cm^2 were able to tolerate two consecutive daily applications. For Cohorts with a single contiguous treatment area, an apparent dose response was observed for the mean composite LSR score, which peaked during Days 3 and 8. Increasing the drug load by including a second treatment area on the opposite arm did not influence the intensity of LSRs in the base treatment area. No efficacy results were provided.

6.5.2.11. ***PEP005-001***

This study was described above, as it included both head/ scalp and trunk/ extremities subjects.

6.6. Evaluator's overall conclusions on clinical efficacy

- Information on clinical efficacy was provided for the 2 specific indications, the treatment of solar (actinic) keratoses (SK) on the face and scalp (0.015% Picato Gel), and for the treatment of SK on the body (non-head regions) (0.05% Picato Gel).
- PEP005-015, PEP005-016 and PEP005-025 were randomised, double-blind, vehicle-controlled, parallel-group studies, and were the pivotal studies for the face and scalp indication. PEP005-015 was a dose-ranging study that included the proposed dosage regimen treatment on head locations.
- **PEP005-015** was a multi-centre, randomized, double-blind, vehicle-controlled, dose ranging study. The primary objective of the study was to evaluate the safety, tolerability and efficacy 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 SK treatment area on the face or scalp. A total of 265 patients were randomized and 260 patients completed the study. Observed complete clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed complete clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 15% in the 0.005% two-day group to 50% in the 0.015% three-day group. Partial clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed partial clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 33.3% in the 0.005% two-day group to 71.9% in the 0.015% three-day group.
- **PEP005-016** was a multi-centre, randomized, double-blind, vehicle-controlled, dose ranging study[3]. The objective of the study was 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). A total of 269 patients were randomized (135 to PEP005 Gel 0.015% and 134 to vehicle gel); 259 patients completed the study. The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (37% compared to 2%, $p<0.001$, CMH test stratified by analysis site) based on the ITT population. For the secondary endpoint the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (60% compared to 7%, $p<0.001$, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population.
- **PEP005-025** was a multi-centre, randomized, double-blind, vehicle-controlled, dose ranging study[4]. The objective of the study was 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). A total of 278 patients were randomized (142 to PEP005 Gel 0.015% and 136 to vehicle gel); 277 patients completed the study. The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (47% compared to 5%, $p < 0.001$, CMH test stratified by analysis site) based on the ITT population. The results for the PP population were consistent with the results for the ITT population. For the secondary efficacy endpoint, the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (68% compared to 8%, $p < 0.001$, CMH test stratified by analysis site) based on the ITT population.

[3] Erratum: Phase III study.
[4] Erratum: Phase III study.

- PEP005-014 and PEP005-028 were well-controlled Phase III studies that evaluated the proposed dosage regimen application of Picato Gel for treatment of non-head locations, and were the pivotal studies for the trunk and extremities indication. Dose-ranging information for this indication was provided by PEP005-006, which involved subjects for both indications.
- **PEP005-014** was a multi-centre, randomized, parallel group, double-blind, vehicle-controlled, study. The objective of the study was to evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel, when administered once daily for two consecutive days (Day 1 and Day 2) to a 25 cm^2 contiguous SK treatment area on non-head locations. A total of 255 patients were enrolled (126 to PEP005 Gel, 0.05% and 129 to vehicle gel).The observed complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (28%) than the vehicle group (5%) ($p < 0.0001$). Sensitivity analyses, including a multiple imputation method for handling missing data and analyses based on evaluable and PP populations, all demonstrated a statistically significantly higher complete clearance rate in the PEP005 Gel, 0.05% group than in the vehicle group ($p < .0001$ for all comparisons). The observed partial clearance rate at Day 57 overall in the PEP005 Gel, 0.05% group was 44% (56/126) versus 7% (9/129) in the vehicle group ($p < 0.0001$).
- **PEP005-028** was a multi-centre, randomized, parallel group, double-blind, vehicle-controlled, study. The objective of the study was to evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous SK treatment area on non-head locations. A total of 203 patients were enrolled (100 PEP005 Gel, 0.05%; 103 vehicle gel). The complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (42%) than the vehicle group (5%) ($p < 0.001$). The results of the analysis of the secondary efficacy endpoint, partial clearance (≥75% reduction) in SK lesions at Day 57, supported the results of the analysis of complete clearance. The partial clearance rate at Day 57 overall was statistically significantly higher in the PEP005 Gel, 0.05% group (55%) than the vehicle group (7%) ($p < 0.001$).
- **PEP005-006** was a multi-centre, randomised, double-blind, double dummy, vehicle-controlled sequential cohort study. The primary objectives of the study were to evaluate the safety and tolerability of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel, administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous SK treatment area, and to evaluate the efficacy of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel when administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous SK treatment area. 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. 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).
- Three clinical studies provided information on long-term efficacy. PEP005-030 was a long-term follow-up study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025 for the head and scalp indication. Two trials (PEP005-031 and PEP005-032) were long-term follow-up studies in patients who achieved complete clearance at Day 57 in previous trials for the trunk and extremities indication. No study medication was administered during these studies.

- **PEP005-030** was a 12-month, long-term follow-up study of patients with SK on the head (face or scalp) who completed Day 57 in studies PEP005-016 or PEP005-025. The objectives of the study were to summarize treatment area recurrence of SK lesions, in the selected treatment area, during a 12-month follow-up period for patients who achieved complete clearance of SKs at Day 57 in studies PEP005-016 and PEP005-025, and to summarize long-term safety data, in the selected treatment area over a 12-month follow-up period for patients who completed Day 57 in studies PEP005-016 and PEP005-025. A total of 117 patients who had demonstrated complete clearance of SK lesions in either study PEP005-016 or PEP005-025 were enrolled in this long-term follow-up study. Of these 117 patients, 108 had received 0.015% PEP005 Gel and 9 had received vehicle in the previous study. At 12 months of follow-up, 53.9% of patients who had been treated with PEP005 Gel in the previous Phase III studies (N=108), had at least one new or recurrent SK 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 III studies), the mean lesion-based recurrence rate was 12.8%. At 12 months of follow-up, 72.2% of vehicle-treated patients (N=9) had a new or recurrent SK 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 16.3%.
- **PEP005-031** was a 12-month, long-term follow-up study of patients with actinic keratosis on non-head areas (trunk and extremities) who have completed Day 57 in study PEP005-020. The objectives of the study were to summarize treatment area recurrence of actinic keratosis lesions, in the selected treatment area, during a 12-month follow-up period for patients with complete clearance who completed Day 57 in study PEP005-020, and to summarize long-term safety data, in selected treatment area over a 12-month follow-up period for patients who completed Day 57 in study PEP005-020. A total of 38 patients who had demonstrated complete clearance of SK lesions in study PEP005-020 were enrolled in the study. At 12 months of follow-up, 62.5% of patients in the CC57 population treated with PEP005 Gel, 0.05% in study PEP005-020 (N=38) 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 III study), the mean lesion-based recurrence rate was 11.3%.
- **PEP005-032** was a 12 month, long-term follow-up study of patients with actinic keratosis on non-head locations (trunk and extremities) who completed Day 57 in study PEP005-028. The objectives of the study were to summarize treatment area recurrences of actinic keratosis lesions, in the selected treatment area during a 12-month follow-up period for patients with complete clearance, who completed Day 57 in study PEP005-028, and to summarize long-term safety data, in selected treatment area over a 12-month follow-up period for patients with complete clearance, who completed Day 57 in study PEP005-028. A total of 43 patients were enrolled (38 received PEP005 Gel 0.05% and 5 received vehicle gel in the previous study [PEP005-028]). At 12 months of follow-up, 50% of patients treated with PEP005 Gel, 0.05% in study PEP005-028 (N=38) had at least one new or recurrent SK lesion within the selected treatment area. The estimated median time to 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 III studies), the mean lesion-based recurrence rate was 14.9%. At 12 months of follow-up, 80% of patients treated with vehicle gel in the previous study (N=5) had a new or recurrent SK lesion, with a median time to recurrence of 183 days, and the mean lesion-based recurrence rate at 12 months was 19.2%.

- In addition to the studies mentioned above, a further 9 clinical studies provided supporting information on efficacy. These studies were PEP005-007, PEP005-020, PEP005-004, PEP005-017, PEP005-018, PEP005-013, PEP005-022, AGN204332-004 and PEP005-001.
- **PEP005-007** was an open-label, multi-centre, dose-escalation, cohort study. The primary objective was to determine the optimal tolerated regimen of PEP005 Topical Gel when administered to patients once daily as a two or three consecutive day application schedule to a 25 cm^2 contiguous SK treatment area on the face or face and scalp. The study was not statistically powered to evaluate efficacy, and the resulting groups had a small number of patients.
- **PEP005-020** was a multi-centre, open-label study to evaluate the safety and efficacy of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses on non-head locations (trunk and extremities). The objectives of the study were to evaluate the safety of PEP005 Gel, 0.05% when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous actinic keratosis treatment area on non-head locations, and to evaluate the efficacy of PEP005 Gel, 0.05% when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous SK treatment area on non-head locations. No hypotheses were tested and no inferential analyses were performed in this study. Overall, 40/102 (39.2%) patients had a complete clearance of SK lesions at Day 57. The overall partial clearance rate was 54.9%.
- **PEP005-004** was an open-label, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel when applied on Day 1 and Day 2 to actinic keratoses on the shoulders, chest, back, or arms followed by a post-treatment follow-up period lasting at least four weeks. The primary objective of this study was to determine the maximum tolerated dose (MTD) for PEP005 Topical Gel, administered once daily for two consecutive days, by applying 90 µL of PEP005 Topical Gel over a 3 cm x 3 cm field surrounding a target actinic keratosis lesion comprising both diseased and perilesional skin. No hypothesis/inferential testing was conducted for this study. At the Day 29 (End of Study) assessment, complete clearance was reported in two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, one (33.3%) patient in the 0.025% PEP005 Topical Gel cohort, six (60.0%) patients in the 0.05% PEP005 Topical Gel cohort, and three (50.0%) patients in the 0.075% PEP005 Topical Gel cohort.
- **PEP005-017** was a randomized, double-blind, vehicle-controlled study to evaluate the pharmacokinetics of PEP005 (ingenol mebutate) Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis. The 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 actinic keratosis. The secondary objectives were to evaluate the safety and efficacy of PEP005 Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis. Of the patients who received treatment with PEP005 Gel, 0.05%, 77% (10/13) had complete clearance of all SK lesions, and all patients had partial clearance.
- **PEP005-018** was a multicentre, open-label study to examine the safety and tolerability of 0.05% PEP005 Topical Gel in patients with actinic keratoses on the dorsum of the hand. The objectives of the study were to examine the safety and toleration of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm^2 contiguous SK treatment area on the dorsum of a single hand, and to examine the efficacy of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm^2 contiguous SK treatment area on the dorsum of a single hand. At Day 57, the complete clearance rate was 27.3% (3/11 patients), and the partial clearance rate was 45.5% (5/11 patients).
- **PEP005-013** was a Phase I, pharmacokinetic study to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel to a 100 cm^2 (5 cm x 20

cm) contiguous actinic keratosis treatment area on the extensor (dorsal aspect) forearm. No efficacy results were provided.

- **PEP005-022** was a multicentre, open-label, dose-area escalation, cohort study to evaluate the safety and tolerability of 0.05% PEP005 Topical Gel applied for two consecutive days to treatment area(s) of up to a total of 100 cm^2 in patients with actinic keratoses on the extensor (dorsal aspect) forearm(s). The objective of the study was to evaluate the safety and tolerability of two, once-daily, consecutive applications of PEP005 Gel, 0.05%, when applied to 25, 50, 75, or 100 cm^2 actinic keratosis treatment area(s) on the dorsal forearm(s). No efficacy results were provided.
- **AGN204332-004** was a multicentre, double-blind, parallel, randomised, vehicle-controlled study of the safety of a single application of up to 0.2 ml of 0.01% PEP005 gel to actinic keratoses on the shoulders, chest, back and/or arms followed by a post-treatment follow-up period lasting at least 2 weeks. A total of 80 lesions were treated (55 with 0.01% PEP005; 25 with PEP005 vehicle). Complete clearance in all five lesions at last available follow-up was reported for one patient treated with 0.01% PEP005. Another 0.01% PEP005 patient had complete clearance in 4/5 treated lesions. Extent of lesion clearance according to individual lesions showed that at Day 14, 8/55 lesions (15%) treated with active gel had complete clearance and by the last available follow-up, this had increased to 16/55 lesions (29%) treated with active gel.
- **PEP005-001** was a multi-centre, randomized, double-blind, parallel-group, vehicle-controlled study conducted in Australia between March and October 2005. The primary objective of the study was to determine the safety of PEP005 Topical Gel at 0.0025%, 0.01%, and 0.05% administered as two applications to patients with SK on the arms, shoulders, chest, face, and/or scalp under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. The study was not statistically powered to conduct formal hypothesis/inferential testing.

7. Clinical safety

7.1. Introduction

Information on safety was available from all clinical studies detailed above. In addition, a further 7 studies provided additional safety information. Of these studies, three assessed safety in healthy volunteers (PEP005-005, PEP005-023, and PEP005-024), and four provided safety data in patients receiving treatment for non-malignant skin cancer (NMSC) (PEP005-002, PEP005-003, PEP005-008 and PEP005-009). These studies are described below.

7.2. PEP005-005

This study was a randomized, controlled study to evaluate the sensitizing potential of PEP005 Topical Gel (0.01% concentration) in healthy volunteers using a repeat insult patch test design. The primary objective of this study was to determine the sensitization potential of PEP005 Topical Gel (0.01% concentration) on normal skin. The secondary objective was to evaluate skin irritation. Additionally, safety was assessed by evaluation of adverse events reported during the study. A total of 238 subjects were enrolled. Two hundred twenty were evaluable for sensitization analysis and 226 were evaluable for irritation analysis. Subjects were healthy male and female subjects 18 to 65 years of age with Fitzpatrick skin types of I, II, III, and IV. PEP005 Topical Gel (0.01% concentration) was applied topically in the amount sufficient to cover a 4 cm^2 area of skin (10 µL) 3 times weekly for 3 weeks (9 applications total) during the induction phase, and 1 time during the challenge phase. The determination of dermal sensitization

potential was based on specific scoring criteria derived from observations in the challenge phase of the study, and confirmed in the rechallenge phase, if necessary. The mean and total irritation scores during induction were tested pairwise for product differences using Fisher's protected least significant differences in the context of the 2-way analysis of variance (ANOVA), including main effects of subject and product, without interaction. Pairwise differences were tested only if the null hypothesis of a common mean score for all products was rejected at the 5% level. Results from this study are included below. There was no evidence of a sensitization potential or significant irritation following repeated applications of PEP005 Topical Gel (0.01% concentration).

Table 51. Summary of Challenging responses to PEP topical gel (0.01%)

	Time post-challenge			
Response	**Immediate (n=220)**	**24 hr (n=220)**	**48 hr (n=220)**	**72 hr (n=220)**
-	210	212	217	218
?	9	6	1	0
+D	1	2	2	2

Table 52. Mean cumulative irritation scores

Product Tested	**Mean Score (±SD)**	**Total Score**
PEP005 Topical Gel (0.01% concentration)	0.04 (0.15)	0.34 (1.31)
Vehicle control	0.00 (0.00)	0.00 (0.00)
P value	*P*<.001	*P*<.001

Table 53. Summary of Treatment-Emergent Adverse Events.

	n (%)
All Enrolled Subjects	
Number of AEs	3 (1.3)
Subjects with AEs - n (%)	3 (1.3)
Deaths – n (%)	0
Subjects with serious AEs – n (%)	0
Subjects with severe AEs – n (%)	0
Subjects discontinued due to AEs – n (%)	1 (0.4)

7.3. PEP005-023

This study was a 4-day, randomized, controlled, open application study to evaluate the photo-irritation potential of PEP005 (ingenol mebutate) Gel, 0.01% in healthy volunteers, using a phototoxicity test design. The primary objective of this study was to determine the photo-irritation potential of PEP005 Gel, 0.01% and its vehicle when topical application to skin was followed by light exposure. In addition, the safety of PEP005 Gel, 0.01% was assessed by evaluation of any adverse events (AEs) reported during the study. This was a single-centre, randomized, within-subject comparison study of PEP005 Gel, 0.01% and vehicle. Each subject received applications of the study medications at 4 separate treatment areas, of which 2 were irradiated and 2 remained non-irradiated. A fifth untreated area was also irradiated. A total of 34 subjects were enrolled; 33 subjects completed the study and were evaluable. Subjects were healthy males or females between the ages of 18 and 65 with Fitzpatrick Skin Type I, II or III who were free of any visible skin disease at the treatment area. Assessment of the treatment areas was performed once daily, on Days 2 through 4. Assessment of the untreated, irradiated control area was performed once daily, on Days 3 and 4. Selected pairwise comparisons were

performed on the mean of the ordinal response scores assigned on Day 3 and Day 4 in the context of the analyses of variance (ANOVA). Pairs compared were: Study medications irradiated versus non-irradiated and study medications irradiated versus untreated irradiated control. Results from this study are included below. There were no statistically significant differences between these irradiated treatment areas with respect to signs of photo-irritation. There was no significant irritation observed at the non-irradiated areas treated with the study medication or vehicle, and there was no statistically significant difference in signs of the photo-irritation between non-irradiated treatment areas. Irradiated treatment areas showed significantly more photo-irritation than non-irradiated treatment areas. There were no adverse events during the study.

Table 54. Summary of Photo-irritation

Study Medication	Irradiated Average of Day 3 and 4 Mean (± SD)	Non-Irradiated Average of Day 3 and 4 Mean (± SD)	*P*-values				
			A Irrd vs B Irrd	A Irrd vs A Non-Irrd	A Irrd vs C Irrd	B Irrd vs. B Non-Irrd	B Irrd vs. C Irrd
PEP005 Gel, 0.01% (A)	0.20 (0.35)	0.02 (0.09)	0.558	<0.001	0.769		
Vehicle (B)	0.17 (0.35)	0.00 (0.00)				0.002	0.380
Untreated (C)	0.21 (0.38)	NA					

7.4. PEP005-024

This study was a randomized, controlled study to evaluate the photo-allergic potential of PEP005 (ingenol mebutate) Gel, 0.01% in healthy volunteers using an open application photo-allergic test design. The primary objective of this study was to determine the photo-allergic (sensitizing) potential of PEP005 Gel, 0.01% on normal skin. In addition, the safety of PEP005 Gel, 0.01% was assessed by evaluation of any adverse events (AEs) reported during the study. The trial design was a single-centre, randomized within-subject comparison study. A total of 60 subjects were enrolled; 55 subjects completed the study and were evaluable. Subjects were healthy males or females between the ages of 18 and 65 with Fitzpatrick Skin Type I, II or III who were free of any visible skin disease at the treatment area. PEP005 Gel, 0.01% was applied topically twice weekly for 3 weeks in an amount sufficient to cover a 4 cm^2 (10 µL) area of skin during the induction phase, and 1 time at challenge phase. The incidence of photosensitization reactions were summarized by frequency counts for each treatment. For tolerability, the mean numerical equivalent score by subject and treatment, including all scores assigned during induction, was analysed in the analysis of variance with factors subject and treatment. All pairwise treatment comparisons were performed. Results from this study are included below. Neither PEP005 Gel 0.01% nor the vehicle showed any potential for photosensitization. Mean scores showed moderate erythema at the treatment areas irradiated after the application of PEP005 Gel, 0.01% and the vehicle. Non-irradiated treatment areas showed mild irritation for PEP005 Gel, 0.01% and no irritation to vehicle.

Table 55. Summary of Local Tolerability

Study Medication	Irradiated Mean (± SD)	Non-Irradiated Mean (± SD)	P-Value A vs B Irr	P-Value A vs B Non-Irr	P-Value A Irr vs A Non-Irr	P-Value B Irr vs B Non-Irr
PEP005 Gel, 0.01% (A)	0.47 (0.27)	0.11 (0.17)	0.035	0.003	<0.001	
Vehicle (B)	0.39 (0.28)	0.00 (0.02)				<0.001

Table 56. Number (%) of subjects with most frequent adverse events (≥2%)

Adverse Event	N=60 (%)
Subjects with any AE, n (%)	13 (21.7)
Vomiting	2 (3.3)
Nasopharyngitis	2 (3.3)
Back pain	2 (3.3)

7.5. PEP005-002

This study was a multi-centre, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 Topical Gel, 0.0025%, 0.01%, and 0.05%, with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to nodular basal cell carcinoma. The primary objective of this study was to determine the safety of PEP005 Topical Gel at 0.0025%, 0.01%, and 0.05% administered as two applications to patients with nodular basal cell carcinoma (nBCC) under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. A total of 58 patients were enrolled and all 58 patients were included in the Intent-to-Treat and Safety analyses, with 29 patients randomized to each treatment Arm. Subjects were male or female patients who were at least 18 years of age who had at least one nBCC lesion on the arm, shoulder, chest, face, neck, abdomen, back, leg, or scalp. Safety was evaluated by monitoring the incidence of AEs (including the incidence and severity of local skin reactions following study medication treatment); changes in haematology, serum chemistry, and urinalysis test results; vital signs measurements; and physical examination results during the study. The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing. Results from this study are included below. Results obtained in this study demonstrate that the application of PEP005 Topical Gel at concentrations of 0.0025%, 0.01%, and 0.05% is safe and well tolerated. Due to the small numbers of patients per treatment group, no statistically significant differences were observed among treatment groups. A higher frequency of moderate or severe local skin reactions were reported for the 0.01% and 0.05% PEP005 Topical Gel groups of Arm A and Arm B.

Table 57. Overall Treatment Emergent Adverse Event information for Treatment arm A and B-mITT population

	Vehicle Gel		0.0025% PEP005		0.01% PEP005		0.05% PEP005	
	Arm A N = 6	Arm B N = 6	Arm A N = 7	Arm B N = 7	Arm A N = 8	Arm B N = 8	Arm A N = 8	Arm B N = 8
Number of patients who had a TEAE	3 (50.0%)	1 (16.7%)	2 (28.6%)	6 (85.7%)	5 (62.5%)	2 (25.0%)	4 (50.0%)	6 (75.0%)
Number of TEAEs	9	1	9	9	16	4	16	23
Number of patients who had a treatment-related TEAE	1 (16.7%)	0	1 (14.3%)	2 (28.6%)	3 (37.5%)	1 (12.5%)	3 (37.5%)	3 (37.5%)
Number of treatment-related TEAEs	1	0	6	3	7	1	13	9
Number of patients who had a least one moderate or severe TEAE	3 (50.0%)	0	1 (14.3%)	2 (28.6)	3 (37.5%)	2 (25.0%)	3 (37.5%)	4 (50.0%)
Number of moderate or severe TEAEs	9	0	1	4	4	2	11	8
Number of patients who had a SAE	1 (16.7%)	0	0	0	0	0	1 (12.5%)	1 (12.5%)
Number of Serious TEAEs[a]	1	0	0	0	0	0	1	1
Number of patients who had a TEAE leading to discontinuation from study or treatment	0	0	0	0	1 (12.5%)	0	0	0

Arm A = Treatment Arm A (Day 1, Day 2); Arm B = Treatment Arm B (Day 1, Day 8); TEAE = treatment-emergent adverse event.

Percentages were calculated using the number of patients in each treatment group. A treatment-related event was defined as any event that was assessed as having an unknown relationship to study medication, or any event that was possibly, probably, or definitely-related to study medication. Moderate or severe events included those that were classified as unknown.

[a]The number of TEAEs was taken from recorded events at each visit assessment.

Table 58. Treatment Emergent adverse events in ≥2 patients by Preferred Term in Decreasing Frequency-mITT population

	Vehicle Gel		0.0025% PEP005		0.01% PEP005		0.05% PEP005	
Preferred Term	Arm A N = 6	Arm B N = 6	Arm A N = 7	Arm B N = 7	Arm A N = 8	Arm B N = 8	Arm A N = 8	Arm B N = 8
Number of patients with at least one event	3 (50.0%)	1 (16.7%)	2 (28.6%)	6 (85.7%)	5 (62.5%)	2 (25.0%)	4 (50.0%)	6 (75.0%)
Number of events	9	1	9	9	16	4	16	23
Erythema extending outside of the treatment area	0	0	0	0	0	0	3 (37.5%)	2 (25.0%)
Application site irritation	0	0	0	0	1 (12.5%)	0	1 (12.5%)	0
Application site pain	0	0	0	0	2 (12.5%)	0	0	2 (25.0%)
Basal cell carcinoma	1 (16.7%)	1 (16.7%)	0	1 (14.3%)	1 (12.5%)	1 (12.5%)	0	0
Contusion	1 (16.7%)	0	0	0	0	0	1 (12.5%)	0
Postoperative infection	1 (16.7%)	0	1 (14.3%)	0	0	0	0	0
Urinary tract infection	0	0	1 (14.3%)	0	1 (12.5%)	0	0	0
Folliculitis	0	0	0	1 (14.3%)	1 (12.5%)	0	0	0
Neoplasm progression	0	0	0	1 (14.3%)	1 (12.5%)	0	0	0
Skin exfoliation	0	0	0	0	0	0	1 (12.5%)	1 (12.5%)

Arm A = Treatment Arm A (Day 1, Day 2); Arm B = Treatment Arm B (Day 1, Day 8).
Percentages were calculated using the number of patients in each treatment group.
Patients were counted once for each preferred term and may have had more than one TEAE.
All AE terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary Version 8.0.

7.6. PEP005-003

This study was a multi-centre, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to superficial basal cell carcinoma. The primary objective of this study was to determine the safety of 0.0025%, 0.01%, and 0.05% PEP005 Topical Gel, administered as two applications to patients with superficial basal cell carcinoma (sBCC) under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. A total of 92 patients were screened, 60 were analysed for efficacy, and 60 were analysed for safety. Subjects were male or female patients, who were at least 18 years of age, who had at least one sBCC lesion on the arm, shoulder, chest, face, neck, abdomen, back, leg or scalp. Safety was evaluated by monitoring the incidence of AEs (including the incidence and severity of local skin reactions to study medication); and changes in haematology, serum chemistry and urinalysis test results; vital signs measurements; and physical examination during the study. The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing. Results from this study are included below. Overall, the incidence of AEs was low. No patients enrolled in this study had any serious adverse events (SAEs). Of the 60 patients enrolled in this study, four patients had a wound infection and three patients experienced a fall. Each of the following AEs were experienced by two patients: application site pain, erythema, back pain, increased blood glucose, headache, postoperative infection and viral infection. Most treatment-emergent AEs were classified as mild or moderate in intensity.

Table 59. Overall Treatment Emergent Adverse Event information for Treatment arm A and B-mITT population

	Vehicle Gel		0.0025% PEP005 Topical Gel		0.01% PEP005 Topical Gel		0.05% PEP005 Topical Gel	
	Arm A N = 6	Arm B N = 6	Arm A N = 8	Arm B N = 8	Arm A N = 8	Arm B N = 8	Arm A N = 8	Arm B N = 8
Number of patients who had a TEAE	3 (50.0%)	2 (33.3%)	6 (75.0%)	6 (75.0%)	3 (37.5%)	4 (50.0%)	6 (75.0%)	2 (25.0%)
Number of TEAEs	3	5	29	11	7	13	12	7
Number of patients who had a treatment-related TEAE	0	0	3 (37.5%)	1 (12.5%)	0	2 (25.0%)	3 (37.5%)	2 (25.0%%)
Number of treatment-related TEAEs	0	0	16	1	0	3	9	3
Number of patients who had a least one moderate or severe TEAE	2 (33.3%)	1 (16.7%)	4 (50.0%)	1 (12.5%)	1 (12.5%)	2 (25.0%)	4 (50.0%)	1 (12.5%)
Number of moderate or severe TEAEs	2	2	6	1	1	4	7	3

Arm A = Treatment Arm A (Day 1, Day 2); Arm B = Treatment Arm B (Day 1, Day 8); TEAE = treatment-emergent adverse event.
Percentages were calculated using the number of patients in each treatment group.
A treatment-related event was defined as any event that was assessed as having an unknown relationship to study medication, or any event that was possibly, probably, or definitely related to study medication.
Moderate or severe events included those that were classified as unknown.

Table 60. Treatment Emergent adverse events in ≥2 patients by Preferred Term in Decreasing Frequency-mITT population

	Vehicle Gel		0.0025% PEP005 Topical Gel		0.01% PEP005 Topical Gel		0.05% PEP005 Topical Gel	
Preferred Term	Arm A N = 6	Arm B N = 6	Arm A N = 8	Arm B N = 8	Arm A N = 8	Arm B N = 8	Arm A N = 8	Arm B N = 8
Wound infection	2 (33.3%)	0	1 (12.5%)	0	1 (12.5%)	0	0	0
Fall	0	0	2 (25.0%)	0	1 (12.5%)	0	0	0
Application site pain	0	0	0	0	0	0	0	2 (25.0%)
Erythema	0	0	0	0	0	0	2 (25.0%)	0
Back pain	0	0	1 (12.5%)	1 (12.5%)	0	0	0	0
Blood glucose increased	0	0	1 (12.5%)	1 (12.5%)	0	0	0	0
Headache	0	0	1 (12.5%)	0	0	1 (12.5%)	0	0
Postoperative infection	0	0	0	1 (12.5%)	0	0	0	1 (12.5%)
Viral infection	0	0	0	1 (12.5%)	0	0	0	1 (12.5%)

Arm A = Treatment Arm A (Day 1, Day 2); Arm B = Treatment Arm B (Day 1, Day 8).
Percentages were calculated using the number of patients in each treatment group.
Patients were counted once for each preferred term and may have had more than one TEAE.
All AE terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) Dictionary Version 8.0.

7.7. PEP005-008

This study was a multi-centre, open-label study to determine the safety and efficacy of PEP005 0.05% Topical Gel in patients with cutaneous Squamous Cell Carcinoma in situ (SCCIS, Bowen's Disease).A secondary objective of the study was to evaluate the safety and tolerability of PEP005 0.05% Topical Gel applied once daily for two days. A total of 34 subjects were screened and 25 were enrolled in the study. All 25 subjects received at least one dose of PEP005 0.05% Topical Gel and also had at least one post-baseline assessment of lesion clearance (Intent-To-Treat [ITT] population). All 25 subjects were included in the analyses of efficacy and safety. Subjects were male subjects or post-menopausal female subjects (no menses for at least 12 consecutive months or without a uterus) of at least 18 years of age were to have a histological diagnosis of a primary, clinically diagnosed SCCIS lesion within 90 days of the screening visit. The longest diameter of the SCCIS lesion was to be between 5 mm and 20 mm. Safety was evaluated by (1) the incidence and severity of drug-related Local Skin Responses (LSRs), (2) the incidence of treatment-related AEs and (3) the incidence of changes in vital signs from baseline (Day 1) through to the End of Study Visit (Day 57 or 85). Safety parameters were assessed using summary statistics. Local Skin Responses were summarised using descriptive statistics and the incidence of AEs was summarised by frequency tables. Vital signs were presented for each study visit. Results from this study are included below. All 25 subjects experienced at least one expected LSR greater than baseline within the first week after receiving PEP005 0.05% Topical Gel. Of these, the most frequently reported responses were erythema (25 / 25; 100%), skin desquamation (20 / 25; 80%) and swelling (14 / 25; 56%). Scarring was not reported. Most LSRs were mild in severity and resolved by the end of the study. Of the 25 subjects who received treatment, 12 (48%) reported 17 AEs; all events were mild to moderate in severity and only one, diarrhoea, was considered to be possibly related to the study treatment. One serious adverse event (SAE) was reported in the study but this event (worsening of chronic heart failure) was a result of the subject's medical condition before enrolment and was considered to be unrelated to the study medication. There were no reported deaths. There were no clinically relevant changes in vital signs throughout the study.

Table 61. Summary of expected local skin responses (Lsrs) that increased in severity from baseline.*

LSR	Frequency n (%)	Median Time to Onset (Days) (Min, Max)	Median Duration (Days) (Min, Max)
Erythema	25 (100%)	1 (1 , 7)	27 (6 , 83)
Desquamation	20 (80%)	1 (1 , 7)	24 (6 , 77)
Swelling	14 (56%)	1 (1 , 28)	27 (6 , 56)
Vesiculation / Pustulation	8 (32%)	1 (1 , 7)	21 (6 , 77)
Erosion / Ulceration	7 (28%)	7 (1 , 7)	21 (21 , 55)
Pigmentation	2 (8%)	56 (28 , 84)	28 (28 , 28)
Scarring	0 (0%)	NA	NA

* Baseline = Day 1 before treatment.
NA = not applicable.
Percentages calculated are based on N = 25.

Table 62.Highest rated severity of expected local skin responses (LSRs).

LSR	Frequency n (%)				
	Mild Grade 1	Mild Grade 2	Moderate Grade 3	Severe Grade 4	Severe Grade 5
Erythema	8 (32%)	14 (56%)	3 (12%)	NA	NA
Desquamation	7 (28%)	10 (40%)	4 (16%)	NA	NA
Swelling	7 (28%)	1 (4%)	1 (4%)	NA	NA
Vesiculation / Pustulation	3 (12%)	0 (0%)	3 (12%)	2 (8%)	0 (0%)
Erosion / Ulceration	4 (16%)	6 (24%)	0 (0%)	0 (0%)	0 (0%)
Pigmentation	3 (12%)	1 (4%)	NA	NA	NA
Scarring	NA	NA	0 (0%)	0 (0%)	0 (0%)

NA = not applicable.
Definitions of grading scales for each LSR are provided in Appendix 16.1.5
Percentages calculated are based on N = 25

Table 63. Summary of Adverse Events (AEs)

Adverse Event Type	Subjects (N = 25)
No. of subjects with an AE	12 (48%)
No. of subjects with a treatment related AE	1 (4%)*
No. of subjects with a severe AE	0 (0%)
No. of subjects with a serious adverse event	1 (4%)
No. of subjects that withdrew from the study because of an AE	0 (0%)

* Assessed by the investigator as possibly related to the study medication.
Percentages calculated were based on N = 25.

7.8. PEP005-009

This study was an open-label, multicentre, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel given as either a single application (on Day 1) or as two applications (on Day 1 and Day 8) to a superficial basal cell carcinoma

(sBCC) on the trunk. The primary objective was to determine the maximum tolerated dose (MTD) of PEP005 (ingenol mebutate) Gel when administered either as a single application or as two applications to a selected superficial basal cell carcinoma (sBCC) lesion (dose-escalation phase). This was a multicenter, open-label study consisting of two phases, a dose-escalation phase to determine the MTD of PEP005 Gel for the treatment of sBCC, and an expansion phase to evaluate the efficacy of PEP005 Gel in the treatment of sBCC at the MTD. Three patients were enrolled and treated in each of the following PEP005 Gel dose-escalation cohorts for Arm 1 and Arm 2: 0.025%, 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, 0.175%, 0.2%, 0.225% and 0.25%. A total of 30 patients were treated in each arm during the dose-escalation phase. PEP005 Gel, 0.25%, was the maximum concentration used in the dose-escalation phase; despite the fact that no dose-limiting toxicities (DLTs) were reported at this concentration, for the purposes of the analyses this concentration was defined as the MTD in the tables and listings of the study. Additional patients were then enrolled at this concentration in the expansion phase. Twenty-five patients in Arm 1 and 22 patients in Arm 2 were treated at the MTD (PEP005 Gel, 0.25%). These totals included three patients in each arm from the dose-escalation phase. The total number of patients treated in the study was 101 (52 in Arm 1 and 49 in Arm 2). Eligible patients were men and women of non-childbearing potential (i.e., postmenopausal or without a uterus) who were aged at least 18 years and had a clinically diagnosed and histologically confirmed 4 to 15 mm sBCC lesion located on the trunk that was suitable for excision. The initial biopsy for histological confirmation should have removed no more than 20% of the total tumour mass.

The following safety variables were assessed; extent of study medication exposure, based on the total number of doses administered and the total volume (a calculation of volume [mL] of gel applied based on lesion size); incidence of AEs and serious AEs (SAEs); grade and change from baseline for LSRs; grade and change from baseline for GSR; incidence of abnormal proliferation within the treatment area; incidence of abnormalities in laboratory tests (urinalysis, haematology, and chemistry);and incidence of change in vital signs and physical examination. The safety analysis was performed using the all patients treated (APT) population. Due to the large number of cohorts in each treatment arm, safety assessments for AEs, LSRs, and GSRs were summarized by grouping the cohorts into three categories based on the concentration of PEP005 Gel used: low (0.025% to 0.1%), medium (0.125% to 0.175%), and high (0.2% to 0.25%). Results from this study are included below.

Table 64. Summary of Adverse Events (All patients treated)

	PEP005 Gel Concentration[a], Day 1				PEP005 Gel Concentration[a], Days 1 and 8			
	Low (N = 12)	Medium (N = 9)	High (N = 31)	Total (N = 52)	Low (N = 12)	Medium (N = 9)	High (N = 28)	Total (N = 49)
Patients who had an AE	4 (33.3%)	5 (55.6%)	15 (48.4%)	24 (46.2%)	9 (75.0%)	5 (55.6%)	19 (67.9%)	33 (67.3%)
Num ber of AEs	12	11	32	55	29	15	53	97
Patients who had a treatment-related AE[b]	0	2 (22.2%)	12 (38.7%)	14 (26.9%)	6 (50.0%)	4 (44.4%)	17 (60.7%)	27 (55.1%)
Number of treatment-related AEs	0	5	19	24	13	11	28	52
Patients who had at least one severe AE	0	1 (11.1%)	1 (3.2%)	2 (3.8%)	0	0	2 (7.1%)	2 (4.1%)
Number of severe AEs	0	1	1	2	0	0	6	6
Patients who had an SAE	0	0	1 (3.2%)	1 (1.9%)	0	0	2 (7.1%)	2 (4.1%)
Num ber of SAEs	0	0	1	1	0	0	2	2
Patients who had an AE with a fatal outcome	0	0 0		0 0 0			0 0	
Patients who had an AE leading to discontinuation from dosing	0	0 0		0 0 0			1 (3.6%)	1 (2.0%)
Patients who had an AE leading to discontinuation from study	0	0 0		0 0 0			1 (3.6%)	1 (2.0%)

AE = adverse event; N = number of patients; SAE = serious adverse event.
[a] PEP005 Gel concentration: Low = 0.025%, 0.05%, 0.075%, and 0.1%; Medium = 0.125%, 0.15%, and 0.175%; High = 0.2%, 0.225%, and 0.25%.
[b] Treatment-related AEs are those AEs with an unknown, possible, probable or definite relationship to the study drug.

Table 65. Adverse Events at the maximum tolerated dose (all patients treated)

	PEP005 Gel, 0.25%		
	Day 1 (N = 25)	Days 1 and 8 (N = 22)	P-value[a]
Patients who had an AE	12 (48.0%)	14 (63.6%)	0.3806
Number of AEs	22	33	
Patients who had a treatment-related AE[b]	9 (36.0%)	13 (59.1%)	0.1484
Number of treatment-related AEs	13	18	
Patients who had at least one severe AE	0	1 (4.5%)	0.4681
Number of severe AEs	0	5	
Patients who had an SAE	1 (4.0%)	1 (4.5%)	1.000
Number of SAEs	1	1	
Patients who had an AE with a fatal outcome	0 0		–
Patients who had an AE leading to discontinuation from dosing	0 1	(4.5%)	0.4681
Patients who had an AE leading to discontinuation from study	0 1	(4.5%)	0.4681

AE = adverse event; N = number of patients; SAE = serious adverse event.
[a] P-value from a Chi-squared test comparing percentages between arms at the maximum tolerated dose.
[b] Treatment-related AEs were those AEs with an unknown, possible, probable or definite relationship to study drug.

Overall, treatment-related AEs occurred in 27% (14/52) of patients in Arm 1 and 55% (27/49) of patients in Arm 2. The most common treatment-related AEs among 47 patients treated at the 0.25% concentration were application-site reactions (36% of patients in Arm 1 and 50% in Arm 2); these included pruritus, irritation and, less frequently, pain. Other possibly treatment-related AEs in the overall study population were limited to influenza and arthralgia in one patient each. All treatment-related AEs were mild or moderate except for the one case of severe lymphangitis, and all had resolved or improved by the end of the study.

7.9. Patient exposure

In total, 1774 patients/subjects received PEP005 Gel across the 25 completed studies in the clinical development programme. The safety overview provided focused on the 13 studies in which patients received PEP005 Gel across a selected area of skin (i.e., field) for treatment of SK lesions. Within this group of patients, 1165 received PEP005 Gel and 632 received vehicle gel. Data from the controlled Phase III studies by treatment location (i.e., face and scalp, or trunk and extremities) was also presented. Safety data from 9 additional studies, in which patients/subjects received PEP005 Gel, provided supportive information; these additional studies included 2 lesion-specific SK studies and 7 non-SK studies (consisting of 3 topical safety studies and 4 NMSC studies). In addition, long-term safety from 3 observational studies was presented. As of 31 March 2011, PEP005 (ingenol mebutate) Gel is not marketed in any country; postmarketing data was therefore not available.

Table 66. Summary of number of patients doses with PEP005 gel or vehicle gel for field treatment of AK lesions.

Population	No. of Patients/Subjects who Received at least One Dose of Study Medication	
	PEP005 Gel	Vehicle Gel
AK Lesions, Field Treatment (13 studies)	1165	632
Controlled Phase 3 Studies (PEP005-016 and PEP005-025) with PEP005 Gel, 0.015%, for Face and Scalp Locations	274	271
Controlled Phase 3 Studies (PEP005-014 and PEP005-028), with PEP005 Gel, 0.05%, for Trunk and Extremity Locations	225	232

7.10. Adverse events

Across all SK field treatment studies, 42.5% of PEP005 Gel-treated patients had an AE compared with 24.2% of vehicle-treated patients. The higher incidence of AEs in the PEP005 Gel-treated group was attributed to a higher rate of application site reactions occurring in patients treated with active rather than vehicle gel. The SOC of general disorders and administration site conditions had the highest incidence of AEs for patients treated with PEP005 Gel (22.7% vs. 2.8% for patients treated with vehicle). Within this SOC, application site pruritus, application site pain, and application site irritation were the most frequently reported AEs and were predominantly reported for patients treated with PEP005 Gel rather than patients treated with vehicle. For PEP005 Gel-treated patients, AEs were more likely considered by the investigator as related to treatment compared with those for vehicle-treated patients (also attributed to the higher rate of application site reactions in the PEP005 Gel-treated patients). For PEP005 Gel-treated patients, the most frequently reported AEs considered related to study medication included application site pruritus (10.7%), application site pain (7.8%), and application site irritation (7.0%). Differences were noted with respect to the incidence of treatment-related AEs between treatment locations. In the controlled Phase III studies, patients treated with PEP005 Gel on the face or scalp had a higher incidence of application site pain than patients treated on the trunk or extremities (13.9% vs. 1.8%, respectively). Similarly, patients treated on the face or scalp had eye-associated disorders, such as eyelid oedema (1.1%) and periorbital oedema (2.6%), whereas patients treated on the trunk or extremities had no reports of these events.

The majority of patients had an AE with maximum severity of mild or moderate intensity. Severe AEs were reported by 3.2% of PEP005 Gel-treated patients and 1.6% of vehicle-treated patients. Severe events occurred at a higher frequency for patients treated with PEP005 Gel compared to vehicle in the SOC of general disorders and administrative site conditions, with application site reactions (e.g., irritation, pain and pruritus) attributed for this difference between treatment groups. A summary of adverse events appears below.

Table 67. Overview of Adverse Events

	Controlled Phase 3 Studies						All AK Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=499)	Vehicle (N=503)	PEP005 Gel (N=1165)	Vehicle (N=632)
Patients with one or more AEs	102 (37.2%)	60 (22.1%)	75 (33.3%)	63 (27.2%)	177 (35.5%)	123 (24.5%)	495 (42.5%)	153 (24.2%)
Patients with one or more treatment-related AEs	72 (26.3%)	11 (4.1%)	29 (12.9%)	2 (0.9%)	101 (20.2%)	13 (2.6%)	312 (26.8%)	22 (3.5%)
Patients with one or more severe AEs	8 (2.9%)	4 (1.5%)	5 (2.2%)	4 (1.7%)	13 (2.6%)	8 (1.6%)	37 (3.2%)	10 (1.6%)
Patients with one or more severe treatment-related AEs	4 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	17 (1.5%)	0 (0.0%)
Patients with one or more AEs leading to discontinuation of study drug	3 (1.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	37 (3.2%)	0 (0.0%)
Patients with one or more AEs leading to discontinuation from the study	1 (0.4%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.1%)	2 (0.3%)
Patients with one or more SAEs	6 (2.2%)	5 (1.8%)	8 (3.6%)	12 (5.2%)	14 (2.8%)	17 (3.4%)	49 (4.2%)	23 (3.6%)

Table 68. Summary of Treatment Emergent adverse events with an incidence of ≥1% in any group.

	Controlled Phase 3 Studies						All Field Application AK Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
System Organ Class Preferred Term	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=499)	Vehicle (N=503)	PEP005 Gel (N=1165)	Vehicle (N=632)
Any AE All Systems	102 (37.2%)	60 (22.1%)	75 (33.3%)	63 (27.2%)	177 (35.5%)	123 (24.5%)	495 (42.5%)	153 (24.2%)
General Disorders & Administration Site Conditions	52 (19.0%)	7 (2.6%)	27 (12.0%)	6 (2.6%)	79 (15.8%)	13 (2.6%)	264 (22.7%)	18 (2.8%)
Application Site Pruritus	22 (8.0%)	3 (1.1%)	19 (8.4%)	0 (0.0%)	41 (8.2%)	3 (0.6%)	126 (10.8%)	4 (0.6%)
Application Site Pain	38 (13.9%)	1 (0.4%)	5 (2.2%)	0 (0.0%)	43 (8.6%)	1 (0.2%)	92 (7.9%)	2 (0.3%)
Application Site Irritation	5 (1.8%)	0 (0.0%)	8 (3.6%)	1 (0.4%)	13 (2.6%)	1 (0.2%)	81 (7.0%)	2 (0.3%)
Application Site Paraesthesia	2 (0.7%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	21 (1.8%)	1 (0.2%)
Application Site Discomfort	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	15 (1.3%)	0 (0.0%)
Application Site Reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (1.2%)	0 (0.0%)
Infections and Infestations	20 (7.3%)	12 (4.4%)	15 (6.7%)	14 (6.0%)	35 (7.0%)	26 (5.2%)	88 (7.6%)	35 (5.5%)
Nasopharyngitis	0 (0.0%)	1 (0.4%)	4 (1.8%)	2 (0.9%)	4 (0.8%)	3 (0.6%)	13 (1.1%)	3 (0.5%)
Application Site Infection	7 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	7 (1.4%)	1 (0.2%)	10 (0.9%)	1 (0.2%)
Upper Respiratory Tract Infection	0 (0.0%)	0 (0.0%)	3 (1.3%)	4 (1.7%)	3 (0.6%)	4 (0.8%)	9 (0.8%)	7 (1.1%)
Skin and Subcutaneous Tissue Disorders	11 (4.0%)	3 (1.1%)	10 (4.4%)	7 (3.0%)	21 (4.2%)	10 (2.0%)	56 (4.8%)	14 (2.2%)
Periorbital Oedema	7 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.4%)	0 (0.0%)	12 (1.0%)	0 (0.0%)
Actinic Keratosis	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (1.3%)	1 (0.2%)	3 (0.6%)	10 (0.9%)	4 (0.6%)
Injury, Poisoning and Procedural Complications	10 (3.6%)	16 (5.9%)	8 (3.6%)	3 (1.3%)	18 (3.6%)	19 (3.8%)	45 (3.9%)	21 (3.3%)
Back Injury	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Contusion	1 (0.4%)	5 (1.8%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	6 (1.2%)	2 (0.2%)	6 (0.9%)
Nervous System Disorders	11 (4.0%)	6 (2.2%)	2 (0.9%)	2 (0.9%)	13 (2.6%)	8 (1.6%)	41 (3.5%)	8 (1.3%)
Headache	6 (2.2%)	3 (1.1%)	1 (0.4%)	2 (0.9%)	7 (1.4%)	5 (1.0%)	24 (2.1%)	5 (0.8%)

Table 68 continued. Summary of Treatment Emergent adverse events with an incidence of ≥1% in any group.

System Organ Class Preferred Term	Controlled Phase 3 Studies						All Field Application AK Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=499)	Vehicle (N=503)	PEP005 Gel (N=1165)	Vehicle (N=632)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	4 (1.5%)	3 (1.1%)	7 (3.1%)	10 (4.3%)	11 (2.2%)	13 (2.6%)	35 (3.0%)	17 (2.7%)
Basal Cell Carcinoma	3 (1.1%)	1 (0.4%)	3 (1.3%)	4 (1.7%)	6 (1.2%)	5 (1.0%)	17 (1.5%)	7 (1.1%)
Squamous Cell Carcinoma	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (1.3%)	1 (0.2%)	3 (0.6%)	11 (0.9%)	5 (0.8%)
Musculoskeletal and Connective Tissue Disorders	4 (1.5%)	7 (2.6%)	6 (2.7%)	3 (1.3%)	10 (2.0%)	10 (2.0%)	32 (2.7%)	12 (1.9%)
Back Pain	0 (0.0%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	8 (0.7%)	3 (0.5%)
Investigations	5 (1.8%)	8 (3.0%)	10 (4.4%)	9 (3.9%)	15 (3.0%)	17 (3.4%)	31 (2.7%)	20 (3.2%)
Electrocardiogram QT Prolonged	3 (1.1%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	3 (0.6%)	3 (0.3%)	3 (0.5%)
Electrocardiogram T Wave Biphasic	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	3 (0.5%)
Gastrointestinal Disorders	5 (1.8%)	1 (0.4%)	3 (1.3%)	1 (0.4%)	8 (1.6%)	2 (0.4%)	29 (2.5%)	4 (0.6%)
Respiratory, Thoracic and Mediastinal Disorders	4 (1.5%)	3 (1.1%)	5 (2.2%)	6 (2.6%)	9 (1.8%)	9 (1.8%)	28 (2.4%)	11 (1.7%)
Eye Disorders	8 (2.9%)	2 (0.7%)	1 (0.4%)	0 (0.0%)	9 (1.8%)	2 (0.4%)	27 (2.3%)	2 (0.3%)
Eyelid Oedema	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	9 (0.8%)	0 (0.0%)
Cardiac Disorders	2 (0.7%)	7 (2.6%)	9 (4.0%)	8 (3.4%)	11 (2.2%)	15 (3.0%)	20 (1.7%)	18 (2.8%)
Myocardial Infarction	1 (0.4%)	0 (0.0%)	2 (0.9%)	4 (1.7%)	3 (0.6%)	4 (0.8%)	3 (0.3%)	4 (0.6%)
Atrioventricular Block First Degree	0 (0.0%)	2 (0.7%)	3 (1.3%)	0 (0.0%)	3 (0.6%)	2 (0.4%)	3 (0.3%)	2 (0.3%)
Vascular Disorders	2 (0.7%)	2 (0.7%)	2 (0.9%)	1 (0.4%)	4 (0.8%)	3 (0.6%)	14 (1.2%)	4 (0.6%)
Hypertension	2 (0.7%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	3 (0.6%)	2 (0.4%)	12 (1.0%)	3 (0.5%)
Psychiatric Disorders	4 (1.5%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	4 (0.8%)	2 (0.4%)	10 (0.9%)	2 (0.3%)
Insomnia	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	7 (0.6%)	0 (0.0%)
Ear and Labyrinth Disorders	1 (0.4%)	3 (1.1%)	3 (1.3%)	1 (0.4%)	4 (0.8%)	4 (0.8%)	6 (0.5%)	4 (0.6%)

Table 69. Summary of treatment Emergent Adverse Events considered related to study medication with an incidence ≥1% in any group.

	Controlled Phase 3 Studies						All Field Application AK Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
System Organ Class Preferred Term	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=499)	Vehicle (N=503)	PEP005 Gel (N=1165)	Vehicle (N=632)
Any AE All Systems	72 (26.3%)	11 (4.1%)	29 (12.9%)	2 (0.9%)	101 (20.2%)	13 (2.6%)	312 (26.8%)	22 (3.5%)
General Disorders and Administration Site Conditions	51 (18.6%)	4 (1.5%)	25 (11.1%)	1 (0.4%)	76 (15.2%)	5 (1.0%)	259 (22.2%)	8 (1.3%)
Application Site Pruritus	22 (8.0%)	3 (1.1%)	18 (8.0%)	0 (0.0%)	40 (8.0%)	3 (0.6%)	125 (10.7%)	4 (0.6%)
Application Site Pain	38 (13.9%)	1 (0.4%)	4 (1.8%)	0 (0.0%)	42 (8.4%)	1 (0.2%)	91 (7.8%)	2 (0.3%)
Application Site Irritation	5 (1.8%)	0 (0.0%)	8 (3.6%)	1 (0.4%)	13 (2.6%)	1 (0.2%)	81 (7.0%)	2 (0.3%)
Application Site Paraesthesia	2 (0.7%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	21 (1.8%)	1 (0.2%)
Application Site Discomfort	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	15 (1.3%)	0 (0.0%)
Application Site Reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (1.2%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	7 (2.6%)	0 (0.0%)	5 (2.2%)	0 (0.0%)	12 (2.4%)	0 (0.0%)	23 (2.0%)	2 (0.3%)
Periorbital Oedema	7 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (1.4%)	0 (0.0%)	12 (1.0%)	0 (0.0%)
Nervous System Disorders	5 (1.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)	1 (0.2%)	23 (2.0%)	1 (0.2%)
Headache	5 (1.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	5 (1.0%)	1 (0.2%)	18 (1.5%)	1 (0.2%)
Eye Disorders	7 (2.6%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	7 (1.4%)	1 (0.2%)	22 (1.9%)	1 (0.2%)
Eyelid Oedema	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	9 (0.8%)	0 (0.0%)
Infections and Infestations	7 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	7 (1.4%)	1 (0.2%)	18 (1.5%)	1 (0.2%)
Application Site Infection	7 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	7 (1.4%)	1 (0.2%)	10 (0.9%)	1 (0.2%)
Investigations	3 (1.1%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	3 (0.6%)	5 (0.4%)	4 (0.6%)

Table 70. Summary Of Severe Treatment Emergent Adverse Events reported by ≥2 patients in either treatment arm (All fields application AK studies).

Severe AEs System Organ Class Preferred Term	All Field Application AK Studies PEP005 Gel (N=1165)	 Vehicle (N=632)
Severe AEs: All Systems	37 (3.2%)	10 (1.6%)
General Disorders and Administration Site Conditions	16 (1.4%)	0 (0.0%)
Application Site Irritation	5 (0.4%)	0 (0.0%)
Application Site Pain	5 (0.4%)	0 (0.0%)
Application Site Pruritus	2 (0.2%)	0 (0.0%)
Musculoskeletal and Connective Tissue Disorders	6 (0.5%)	1 (0.2%)
Muscle Spasms	2 (0.2%)	0 (0.0%)
Cardiac Disorders	4 (0.3%)	4 (0.6%)
Gastrointestinal Disorders	4 (0.3%)	0 (0.0%)
Injury, Poisoning and Procedural Complications	3 (0.3%)	2 (0.3%)
Infections and Infestations	3 (0.3%)	0 (0.0%)
Eye Disorders	3 (0.3%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.2%)	1 (0.2%)
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	1 (0.1%)	2 (0.3%)

Table 71. Summary of all severe treatment-emergent adverse events considered related to study medication (All fields application AK studies)

Severe Related AEs System Organ Class Preferred Term	All Field Application AK Studies PEP005 Gel (N=1165)	 Vehicle (N=632)
Severe Related AEs: All Systems	17 (1.5%)	0 (0.0%)
General Disorders and Administration Site Conditions	15 (1.3%)	0 (0.0%)
Application Site Irritation	5 (0.4%)	0 (0.0%)
Application Site Pain	5 (0.4%)	0 (0.0%)
Application Site Pruritus	2 (0.2%)	0 (0.0%)
Application Site Erosion	1 (0.1%)	0 (0.0%)
Application Site Oedema	1 (0.1%)	0 (0.0%)
Application Site Scab	1 (0.1%)	0 (0.0%)
Application Site Swelling	1 (0.1%)	0 (0.0%)
Eye Disorders	3 (0.3%)	0 (0.0%)
Eyelid Oedema	1 (0.1%)	0 (0.0%)
Eye Oedema	1 (0.1%)	0 (0.0%)
Eye Pain	1 (0.1%)	0 (0.0%)
Eyelid Ptosis	1 (0.1%)	0 (0.0%)
Nervous System Disorders	1 (0.1%)	0 (0.0%)
Headache	1 (0.1%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	1 (0.1%)	0 (0.0%)
Periorbital Oedema	1 (0.1%)	0 (0.0%)

Table 72. Summary of adverse events with an incidence ≥1% for the PEP005 gel-treated patients in the all AK population by PEP005 gel concentrations

System Organ Class Preferred Term	< 0.015% PEP005 Gel (N=175)	0.015% PEP005 Gel (N=339)	> 0.015% & < 0.05% PEP005 Gel (N=102)	0.05% PEP005 Gel (N=543)	> 0.05% PEP005 Gel (N=6)
All Systems	79 (45.1%)	132 (38.9%)	48 (47.1%)	231 (42.5%)	5 (83.3%)
General Disorders and Administration Site Conditions	47 (26.9%)	71 (20.9%)	21 (20.6%)	120 (22.1%)	5 (83.3%)
Application Site Pruritus	21 (12.0%)	23 (6.8%)	5 (4.9%)	72 (13.3%)	5 (83.3%)
Application Site Pain	7 (4.0%)	43 (12.7%)	7 (6.9%)	33 (6.1%)	2 (33.3%)
Application Site Irritation	16 (9.1%)	16 (4.7%)	4 (3.9%)	43 (7.9%)	2 (33.3%)
Application Site Paraesthesia	8 (4.6%)	3 (0.9%)	2 (2.0%)	8 (1.5%)	0 (0.0%)
Application Site Discomfort	7 (4.0%)	3 (0.9%)	2 (2.0%)	3 (0.6%)	0 (0.0%)
Application Site Reaction	1 (0.6%)	0 (0.0%)	4 (3.9%)	9 (1.7%)	0 (0.0%)
Infections and Infestations	12 (6.9%)	26 (7.7%)	8 (7.8%)	40 (7.4%)	2 (33.3%)
Nasopharyngitis	3 (1.7%)	1 (0.3%)	0 (0.0%)	9 (1.7%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	5 (2.9%)	16 (4.7%)	6 (5.9%)	28 (5.2%)	1 (16.7%)
Periorbital Oedema	1 (0.6%)	9 (2.7%)	2 (2.0%)	0 (0.0%)	0 (0.0%)
Injury, Poisoning and Procedural Complications	4 (2.3%)	12 (3.5%)	4 (3.9%)	25 (4.6%)	0 (0.0%)
Nervous System Disorders	7 (4.0%)	14 (4.1%)	7 (6.9%)	13 (2.4%)	0 (0.0%)
Headache	6 (3.4%)	9 (2.7%)	6 (5.9%)	3 (0.6%)	0 (0.0%)
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	2 (1.1%)	5 (1.5%)	5 (4.9%)	23 (4.2%)	0 (0.0%)
Basal Cell Carcinoma	1 (0.6%)	4 (1.2%)	2 (2.0%)	10 (1.8%)	0 (0.0%)
Investigations	5 (2.9%)	5 (1.5%)	3 (2.9%)	18 (3.3%)	0 (0.0%)

System Organ Class Preferred Term	< 0.015% PEP005 Gel (N=175)	0.015% PEP005 Gel (N=339)	> 0.015% & < 0.05% PEP005 Gel (N=102)	0.05% PEP005 Gel (N=543)	> 0.05% PEP005 Gel (N=6)
Musculoskeletal and Connective Tissue Disorders	7 (4.0%)	6 (1.8%)	0 (0.0%)	19 (3.5%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	2 (1.1%)	7 (2.1%)	6 (5.9%)	13 (2.4%)	0 (0.0%)
Gastrointestinal Disorders	5 (2.9%)	8 (2.4%)	2 (2.0%)	14 (2.6%)	0 (0.0%)
Cardiac Disorders	2 (1.1%)	3 (0.9%)	2 (2.0%)	13 (2.4%)	0 (0.0%)
Eye Disorders	5 (2.9%)	16 (4.7%)	4 (3.9%)	2 (0.4%)	0 (0.0%)
Vascular Disorders	2 (1.1%)	2 (0.6%)	3 (2.9%)	7 (1.3%)	0 (0.0%)
Hypertension	2 (1.1%)	2 (0.6%)	2 (2.0%)	6 (1.1%)	0 (0.0%)

Table 73. Summary of treatment-emergent Adverse Events and Local Skin reactions in the Controlled Phase III studies with an incidence ≥1% in any group (continued)

System Organ Class Preferred Term	0.015% PEP005 Gel (N=274)	0.05% PEP005 Gel (N=225)	PEP005 Gel (N=499)	Vehicle (N=503)
Nervous System Disorders	11 (4.0%)	2 (0.9%)	13 (2.6%)	8 (1.6%)
Headache	6 (2.2%)	1 (0.4%)	7 (1.4%)	5 (1.0%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	4 (1.5%)	7 (3.1%)	11 (2.2%)	13 (2.6%)
Basal Cell Carcinoma	3 (1.1%)	3 (1.3%)	6 (1.2%)	5 (1.0%)
Musculoskeletal and Connective Tissue Disorders	4 (1.5%)	6 (2.7%)	10 (2.0%)	10 (2.0%)
Investigations	5 (1.8%)	10 (4.4%)	15 (3.0%)	17 (3.4%)
Electrocardiogram QT Prolonged	3 (1.1%)	0 (0.0%)	3 (0.6%)	3 (0.6%)
Gastrointestinal Disorders	5 (1.8%)	3 (1.3%)	8 (1.6%)	2 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders	4 (1.5%)	5 (2.2%)	9 (1.8%)	9 (1.8%)
Eye Disorders	8 (2.9%)	1 (0.4%)	9 (1.8%)	2 (0.4%)
Eyelid Oedema	3 (1.1%)	0 (0.0%)	3 (0.6%)	0 (0.0%)
Cardiac Disorders	2 (0.7%)	9 (4.0%)	11 (2.2%)	15 (3.0%)
Atrioventricular Block First Degree	0 (0.0%)	3 (1.3%)	3 (0.6%)	2 (0.4%)
Psychiatric Disorders	4 (1.5%)	0 (0.0%)	4 (0.8%)	2 (0.4%)
Insomnia	3 (1.1%)	0 (0.0%)	3 (0.6%)	0 (0.0%)
Ear and Labyrinth Disorders	1 (0.4%)	3 (1.3%)	4 (0.8%)	4 (0.8%)

7.11. Serious adverse events and deaths

Among the patients who received field applications of PEP005 Gel or vehicle for treatment of AK lesions, SAEs were identified (by both the investigator and Applicant) for 4.2% of patients in the PEP005 Gel group and 3.6% of patients in the vehicle group. Of these SAEs, BCC (occurring in 1.5% of PEP005 Gel-treated patients and 1.1% of vehicle-treated patients) and SCC (0.9% of PEP005 Gel-treated patients and 0.8% of vehicle-treated patients) were the most frequently reported for both treatment groups (reflecting both investigator- and Applicant-identified events; all serious events of BCC and approximately half of the reported SCCs were reclassified as SAEs by the Applicant). Three patients (all treated with PEP005 Gel, 0.05%) had an SAE that was assessed as treatment-related; 1 patient had Bowen's disease, graded as mild and 2 patients had SCC, 1 graded as mild and the other graded as moderate. For all 3 patients, the SAE resolved following excision. Across all studies, there was one death, which occurred in a patient who received PEP005 Gel, 0.005% in study PEP005-015. The patient, a [information redacted] white male, died of coronary artery atherosclerosis and hypertension approximately 4 months after receiving study treatment. The investigator judged the death as not related to study medication. A summary of SAEs appears below.

Table 74. Summary of serious adverse events (including both investigator-determined and applicant determined events).

	Controlled Phase 3 Studies						All Field Application AK Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
System Organ Class Preferred Term	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=499)	Vehicle (N=503)	PEP005 Gel (N=1165)	Vehicle (N=632)
Serious AEs – All Systems	6 (2.2%)	5 (1.8%)	8 (3.6%)	12 (5.2%)	14 (2.8%)	17 (3.4%)	49 (4.2%)	23 (3.6%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	3 (1.1%)	3 (1.1%)	5 (2.2%)	9 (3.9%)	8 (1.6%)	12 (2.4%)	30 (2.6%)	16 (2.5%)
Basal Cell Carcinoma	3 (1.1%)	1 (0.4%)	3 (1.3%)	4 (1.7%)	6 (1.2%)	5 (1.0%)	17 (1.5%)	7 (1.1%)
Squamous Cell Carcinoma	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (1.3%)	1 (0.2%)	3 (0.6%)	11 (0.9%)	5 (0.8%)
Bowen's Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Malignant Melanoma	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	1 (0.1%)	1 (0.2%)
Neoplasm Skin	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Basosquamous Carcinoma	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Breast Cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Lymphoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Cardiac Disorders	1 (0.4%)	0 (0.0%)	1 (0.4%)	3 (1.3%)	2 (0.4%)	3 (0.6%)	6 (0.5%)	5 (0.8%)
Angina Pectoris	0 (0.0%)	0 (0.0%)	1 (0.4%)	2 (0.9%)	1 (0.2%)	2 (0.4%)	2 (0.2%)	2 (0.3%)
Atrial Fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.2%)
Myocardial Infarction	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.1%)	1 (0.2%)
Aortic Valve Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Coronary Artery Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Acute Coronary Syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Injury, Poisoning & Procedural Complications	1 (0.4%)	2 (0.7%)	1 (0.4%)	0 (0.0%)	2 (0.4%)	2 (0.4%)	4 (0.3%)	2 (0.3%)
Cervical Vertebral Fracture	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Meniscus Lesion	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Muscle Strain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Upper Limb Fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Injury	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Vascular Pseudoaneurysm	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)

Table 74 continued. Summary of serious adverse events (including both investigator-determined and applicant determined events)

	Controlled Phase 3 Studies						All Field Application AK Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
System Organ Class Preferred Term	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=499)	Vehicle (N=503)	PEP005 Gel (N=1165)	Vehicle (N=632)
Gastrointestinal Disorders	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Abdominal Pain	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Gastrooesophageal Reflux Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Pancreatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Small Intestinal Obstruction	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Musculoskeletal and Connective Tissue Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.3%)	0 (0.0%)
Back Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Muscle Spasms	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Muscular Weakness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.4%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
Chronic Obstructive Pulmonary Disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Hypoxia	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Pulmonary Embolism	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Infections and Infestations	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Campylobacter Infection	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Cellulitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Vascular Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Aortic Aneurysm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
General Disorders &Administration Site Conditions	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Surgical and Medical Procedures	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Hip Arthroplasty	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

Table 75. Summary of Investigator-determined and Applicant determined SAEs for All Field Application AK studies.

	Investigator-determined SAEs[a]		Additional Applicant-determined SAEs[b]	
System Organ Class Preferred Term	PEP005 Gel (N=1165)	Vehicle (N=632)	PEP005 Gel (N=1165)	Vehicle (N=632)
Serious AEs – All Systems	28 (2.4%)	11 (1.7%)	24 (2.1%)	12 (1.9%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts & Polyps)	8 (0.7%)	4 (0.6%)	24 (2.1%)	12 (1.9%)
Basal Cell Carcinoma	--	--	17 (1.5%)	7 (1.1%)
Squamous Cell Carcinoma	7 (0.6%)	2 (0.3%)	5 (0.4%)	3 (0.5%)
Bowen's Disease	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Malignant Melanoma	--	--	1 (0.1%)	1 (0.2%)
Neoplasm Skin	--	--	1 (0.1%)	0 (0.0%)
Basosquamous Carcinoma	--	--	0 (0.0%)	1 (0.2%)
Breast Cancer	0 (0.0%)	1 (0.2%)	--	--
Lymphoma	0 (0.0%)	1 (0.2%)	--	--

Table 76. Summary of patients with an SCC by location (All Field Application AK studies.)

Population	No. (%) of Patients	
	PEP005 Gel (N=1165)	Vehicle (n=632)
No. (%) of patients with an SCC[a]	11 (0.9%)	5 (0.8%)
Location of SCC[b]		
Outside treatment area	8 (0.7%)	3 (0.5%)
Inside or possibly inside treatment area	3 (0.3%)	2 (0.3%)

7.12. Laboratory findings

The vast majority of clinical laboratory parameters (haematology and serum chemistry) were within normal limits at the time points measured in the studies. The proportion of patients with normal laboratory values at baseline followed by shifts away from this normal range at later time points was generally similar between treatment groups, with no apparent trend. There were no meaningful shifts or trends in any of the clinical laboratory parameters.

7.13. Safety in special populations

Not applicable.

7.14. Immunological events

Not applicable.

7.15. Safety related to drug-drug interactions and other interactions

Not applicable.

7.16. Discontinuation due to adverse events

In the 13 studies that evaluated field treatment of PEP005 Gel for SK lesions, a total of 3 patients (1 treated with PEP005 Gel and 2 treated with vehicle) discontinued from the study due to one

or more AEs. The patient treated with PEP005 Gel discontinued study PEP005- 016 due to severe application site (face) pain, severe eye pain, and severe periorbital oedema.

The vehicle-treated patients discontinued due to multiple trauma and loss of consciousness after falling off a ladder (1 patient) and severe myocardial infarction (MI; 1 patient). Across the 9 additional studies (lesion-specific and non-SK), 1 patient (who received PEP005 Gel, 0.05% in study PEP005-008) discontinued from the study due to diarrhoea, which was moderate in intensity.

In the 13 SK field treatment studies, a total of 37 patients (37 treated with PEP005 Gel and 0 treated with vehicle) discontinued study medication due to one or more AEs. Although patients discontinued study medication, most remained in the study for observation of SK lesion disposition and safety assessments through Day 57. Discontinuation of study medication was primarily attributed to application site reactions, notably application site irritation and application site pain, reported by 16 patients each. Across the 9 additional studies, 4 patients discontinued dosing due to application site pain, erythema and skin exfoliation, lymphangitis, and pregnancy.

7.17. Postmarketing experience

Postmarketing data was not available.

7.18. Evaluator's overall conclusions on clinical safety

- Information on safety was available from all clinical studies. A total of 1774 patients/subjects received PEP005 Gel across the 25 completed studies in the clinical development programme. The safety overview provided focused on the 13 studies in which patients received PEP005 Gel across a selected area of skin (i.e., field) for treatment of SK lesions. Within this group of patients, 1165 received PEP005 Gel and 632 received vehicle gel. Long-term safety from 3 observational studies was also presented. In addition, a further 7 studies provided additional safety information. Of these studies, three assessed safety in healthy volunteers (PEP005-005, PEP005-023, and PEP005-024), and four provided safety data in patients receiving treatment for non-malignant skin cancer (NMSC) (PEP005-002, PEP005-003, PEP005-008 and PEP005-009).
- Of the supporting studies in healthy volunteers, **PEP005-005** was a randomized, controlled study to evaluate the sensitizing potential of PEP005 Topical Gel (0.01% concentration) using a repeat insult patch test design. A total of 238 subjects were enrolled. There was no evidence of a sensitization potential or significant irritation following repeated applications of PEP005 Topical Gel (0.01% concentration). **PEP005-023** was a 4-day, randomized, controlled, open application study to evaluate the photo-irritation potential of PEP005 (ingenol mebutate) Gel, 0.01%, using a phototoxicity test design. A total of 34 subjects were enrolled. There were no statistically significant differences between these irradiated treatment areas with respect to signs of photo-irritation. There was no significant irritation observed at the non-irradiated areas treated with the study medication or vehicle, and there was no statistically significant difference in signs of the photo-irritation between non-irradiated treatment areas. **PEP005-024** was a randomized, controlled study to evaluate the photoallergic potential of PEP005 (ingenol mebutate) Gel, 0.01% in healthy volunteers using an open application photoallergic test design. A total of 60 subjects were enrolled. Neither PEP005 Gel 0.01% nor vehicle showed any potential for photosensitization.
- Of the supporting studies in patients receiving treatment for non-malignant skin cancer (NMSC), **PEP005-002** was a multi-centre, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 Topical Gel, 0.0025%, 0.01%, and 0.05%, with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications

to nodular basal cell carcinoma. A total of 58 patients were enrolled. The study was not statistically powered to conduct formal hypothesis/inferential testing. No statistically significant differences were observed among treatment groups. **PEP005-003** was a multi-centre, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to superficial basal cell carcinoma. The study was not statistically powered to conduct formal hypothesis/inferential testing. Overall, the incidence of AEs was low. No patients enrolled in this study had any serious adverse events (SAEs). Of the 60 patients enrolled in this study, four patients had a wound infection and three patients experienced a fall. **PEP005-008** was a multi-centre, open-label study to determine the safety and efficacy of PEP005 0.05% Topical Gel in patients with cutaneous Squamous Cell Carcinoma in situ (SCCIS, Bowen's Disease). A total of 34 subjects were screened and 25 were enrolled in the study. Safety parameters were assessed using summary statistics. All 25 subjects experienced at least one expected LSR greater than baseline within the first week after receiving PEP005 0.05% Topical Gel. Of these, the most frequently reported responses were erythema (25 / 25; 100%), skin desquamation (20 / 25; 80%) and swelling (14 / 25; 56%). **PEP005-009** was an open-label, multicentre, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel given as either a single application (on Day 1) or as two applications (on Day 1 and Day 8) to a superficial basal cell carcinoma (sBCC) on the trunk. The most common treatment-related AEs among 47 patients treated at the 0.25% concentration were application-site reactions (36% of patients in Arm 1 and 50% in Arm 2); these included pruritus, irritation and, less frequently, pain. Other possibly treatment-related AEs in the overall study population were limited to influenza and arthralgia in one patient each.

- From the overall safety database (across all SK field treatment studies), 42.5% of PEP005 Gel-treated patients had an AE compared with 24.2% of vehicle-treated patients. For PEP005 Gel-treated patients, the most frequently reported AEs considered related to study medication included application site pruritus (10.7%), application site pain (7.8%), and application site irritation (7.0%). Differences were noted with respect to the incidence of treatment-related AEs between treatment locations. In the controlled Phase III studies, patients treated with PEP005 Gel on the face or scalp had a higher incidence of application site pain than patients treated on the trunk or extremities (13.9% vs. 1.8%, respectively). Similarly, patients treated on the face or scalp had eye-associated disorders, such as eyelid oedema (1.1%) and periorbital oedema (2.6%), whereas patients treated on the trunk or extremities had no reports of these events. The majority of patients had an AE with maximum severity of mild or moderate intensity. Severe AEs were reported by 3.2% of PEP005 Gel-treated patients and 1.6% of vehicle-treated patients.
- From the overall safety database (across all SK field treatment studies), SAEs were identified for 4.2% of patients in the PEP005 Gel group and 3.6% of patients in the vehicle group. Of these SAEs, BCC (occurring in 1.5% of PEP005 Gel-treated patients and 1.1% of vehicle-treated patients) and SCC (0.9% of PEP005 Gel-treated patients and 0.8% of vehicle-treated patients) were the most frequently reported for both treatment groups . Three patients (all treated with PEP005 Gel, 0.05%) had an SAE that was assessed as treatment-related; 1 patient had Bowen's disease, graded as mild and 2 patients had SCC, 1 graded as mild and the other graded as moderate.
- Across all studies, there was one death, which occurred in a patient who received PEP005 Gel, 0.005% in study PEP005-015. The patient, a [information redacted] White male, died of coronary artery atherosclerosis and hypertension approximately 4 months after receiving study treatment. There were no safety issues identified with regard to abnormal laboratory findings. No significant safety issues were identified as a result of discontinuations.

- Safety results from pivotal studies were consistent with the overall safety database, and did not raise any significant safety issues.
- Long-term safety was assessed in 3 prospective, longitudinal, observational studies (PEP005-030, PEP005-031, and PEP005-032) that were designed to evaluate lesion recurrence and safety within the selected treatment area over a 12-month follow-up period in patients who had achieved complete clearance of AK lesions in studies PEP005-016, PEP005- 020, PEP005-025, and PEP005-028. A total of 198 patients had demonstrated complete clearance of AK lesions (following treatment with PEP005 Gel [184 patients] or vehicle [14 patients]) at the Day 57 visit of the prior study and were enrolled in the long-term, follow-up studies. During follow-up, no patient received PEP005 Gel, and 14 patients prematurely discontinued due to: withdrawal of consent (9 patients), protocol violation (2 patients), lost to follow-up (1 patient), investigator decision (1 patient), and inability to return to the study site for the 12-month visit (1 patient). Over 12 months of follow-up, 3 of the 198 patients had an AE within the selected treatment area that consisted of a mild sun burn, a moderate haematoma, and a mild rash. All 3 AEs occurred approximately 8 to 9 months after the start of follow-up; all events resolved within 2 weeks of onset, and all were considered not related to the study drug received during the prior study.

8. Summary and discussion

8.1. Clinical aspects

8.1.1. Pharmacokinetics

Ingenol mebutate, at the concentrations applied topically for treatment of SK lesions, has no detectable systemic absorption. This is supported by the human PK profile from allometric scaling, as well as some limited PK data obtained from subjects in 4 clinical studies.

8.1.2. Pharmacodynamics

No clinical studies on human pharmacodynamics were conducted. The mechanism of action in SK is not fully understood, but appears to be a combination of induction of local lesion cell death and promotion of an inflammatory response with neutrophils and other immuno-competent cells.

8.1.3. Clinical efficacy

8.1.3.1. *Dose-response studies and main clinical studies*

Information on clinical efficacy was provided for the 2 specific indications, the treatment of solar (actinic) keratoses (SK) on the face and scalp (0.015% Picato Gel), and for the treatment of SK on the body (non-head regions) (0.05% Picato Gel). For the first indication, PEP005-015, PEP005-016 and PEP005-025 were randomised, double-blind, vehicle-controlled, parallel-group studies, and were the pivotal studies. PEP005-015 was a dose-ranging study that included the proposed dosage regimen treatment on head locations. PEP005-016 and PEP005-025 were Phase III studies that evaluated the proposed dosage regimen of Picato Gel for treatment of head locations. For the second indication, PEP005-014 and PEP005-028 were well-controlled Phase III studies that evaluated the proposed dosage regimen application of Picato Gel for treatment of non-head locations, and should be regarded as the pivotal studies for this indication. Additionally, PEP005-006 was a Phase II, randomised, double-blind, double dummy, vehicle-controlled sequential cohort study which provided dose-ranging information for the second indication, although it included subjects with both face and scalp as well as body (non-head regions) SK.

For the pivotal studies, a study design using an active comparator was not employed because of the potential to introduce bias with regard to the selection and timing of study endpoints. This was reasonable, as any available active comparator used in the same patient population represent different modalities of treatment. As a result, efficacy endpoints would have been measured at different times during a comparator trial. As an example, Imiquimod is approved for treatment on the face and scalp, and is available in two strengths. The first is a 5% cream (Aldara™) which in Australia is approved for cyclic treatment; 3 times per week for 4 weeks. After a 4-week no-treatment period another 4-week course can be applied if required. A continuous treatment period of 3 times per week for 16 weeks is also approved in Australia All pivotal studies were vehicle-controlled.

For the pivotal studies, the majority of SKs were diagnosed clinically, not histologically. In a study where 271 lesions were biopsied to correlate SK and SCC, clinical diagnosis and histopathologic findings agreed in 91% of the biopsies. Punch biopsies of 220 clinically diagnosed untreated AKs were performed at baseline plus 51 lesions unresponsive to treatment (total, 271). Clinical diagnosis and histopathologic findings agreed in 91% (246/271) of the lesions biopsied. The results from the biopsied lesions were: (1) benign changes 4% (11/271) and (2) occult cutaneous malignancy in 5% (14/271) of the cases, 12 squamous cell carcinomas and 2 basal cell carcinomas. Histological data were evaluated in a Phase I, lesion-specific study (PEP005-001). While only small numbers were involved, it did appear to support histological confirmation of clearance.

For the pivotal studies, the comparative efficacy analyses for head and non-head locations used the same efficacy endpoints. For the combined studies populations, the primary efficacy endpoint was complete clearance, defined as the proportion of patients at Day 57 with no clinically visible SK lesions in the selected treatment area. For the head location, this endpoint was pre-specified as the primary endpoint in the two adequate and well-controlled Phase III studies (PEP005-016 and PEP005-025) and the Phase II dose-ranging study (PEP005-015). For the non-head location, this endpoint was pre-specified as the primary endpoint in the two adequate and well controlled Phase III studies (PEP005-014 and PEP005-028) but was a secondary endpoint in the Phase II dose-ranging study (PEP005-006). The secondary endpoint was partial clearance rate, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of clinically visible SK lesions identified at baseline in the selected treatment area. Percent reduction from baseline in the total number of SK lesions at Day 57 was an additional endpoint. These efficacy endpoints were clinically appropriate. All pivotal studies were adequately powered to produce statistically significant results.

For the head locations, results of the primary efficacy analyses were statistically significant for both pivotal studies. At Day 57, 37% and 47% of the PEP005 Gel-treated patients achieved complete clearance compared to 2% and 5% of vehicle gel-treated patients in Study PEP005-016 and PEP005-025, respectively (Study PEP005-016, $p < 0.001$; Study PEP005-025, $p < 0.001$). Findings from the secondary analysis were consistent between the studies; 60% and 68% of the PEP005 Gel-treated patients achieved partial clearance compared to 7% and 8% of vehicle gel-treated patients in Study PEP005-016 and PEP005-025, respectively (Study PEP005-016, $p < 0.001$; Study PEP005-025, $p < 0.001$). The additional efficacy endpoint of percent reduction from baseline in the number of SK lesions was also positive and consistent across the two studies (median of 83% and 87% in the PEP005 Gel groups for PEP005-016 and PEP005-025, respectively versus 0% in the vehicle gel group for each study).

For the non-head locations, results of the primary efficacy analyses were statistically significant for both controlled studies. At Day 57, 28% and 42% of the PEP005 Gel-treated patients achieved complete clearance compared to 5% in each of the vehicle gel groups in Study PEP005-014 and PEP005-028, respectively (Study PEP005-014, $p < 0.001$; Study PEP005-028, $p < 0.001$). Findings from the secondary analysis were consistent between the studies; 44% and 55% of the PEP005 Gel-treated patients achieved partial clearance compared to 7% in each of

the vehicle gel groups in Study PEP005-014 and PEP005-028, respectively (Study PEP005-014, $p < 0.001$; Study PEP005-028, $p < 0.001$). The additional efficacy endpoint of percent reduction from baseline in the number of SK lesions was also positive and consistent across the two studies (median of 69% and 75% in the PEP005 Gel groups for PEP005-014 and PEP005-028, respectively versus 0% in the vehicle gel group for each study).

8.1.3.2. *Clinical studies in special populations*

Not applicable.

8.1.3.3. *Analysis performed across trials (pooled analyses and meta-analysis)*

For the head and scalp indication, data were pooled across studies and referred to as "combined studies populations". Two combined studies populations were presented. One combined studies population pooled data from PEP005-016 and PEP005-025 and another pooled data PEP005-016, PEP005-025, and PEP005-015. For the trunk and extremities indication, data were pooled across studies and referred to as "combined studies populations". Two combined studies populations were presented. One combined studies population pooled data from PEP005-014 and PEP005-028 and another pooled data from PEP005-014, PEP005-028, and PEP005-006.

For the combined head and scalp data, 42% of PEP005 Gel patients achieved complete clearance compared with 4% of vehicle gel patients ($p < 0.001$). In addition, 64% of PEP005 Gel patients achieved partial clearance compared to 7% of vehicle gel patients ($p < 0.001$). For the combined trunk and extremities data, 34% of PEP005 Gel patients achieved complete clearance compared with 5% of vehicle gel patients ($p < 0.001$). In addition, 49% of PEP005 Gel patients achieved partial clearance compared to 7% of vehicle gel patients ($p < 0.001$).

8.1.3.4. *Supportive studies*

Three clinical studies provided information on long-term efficacy. PEP005-030 was a long-term follow-up study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025 for the head and scalp indication. Two trials (PEP005-031 and PEP005-032) were long-term follow-up studies in patients who achieved complete clearance at Day 57 in previous trials for the trunk and extremities indication. No study medication was administered during these studies. In PEP005-030 at 12 months of follow-up, 54% of patients who had been treated with PEP005 Gel in the previous Phase III studies (N=108), 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 III studies), the mean lesion-based recurrence rate was 13%. For the combined PEP005-031 and PEP005-032 at 12 months of follow-up, 56% of patients who had been treated with PEP005 Gel in the previous Phase III studies (N=76), 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 III studies), the mean lesion-based recurrence rate was 13%. A further 9 clinical studies provided supporting information on efficacy. These studies were PEP005-007, PEP005-020, PEP005-004, PEP005-017, PEP005-018, PEP005-013, PEP005-022, AGN204332-004 and PEP005-001. These studies were either open-label, involved small numbers, or had limited statistical power.

8.1.3.5. *Clinical safety*

8.1.3.5.1. Patient exposure

A total of 1774 patients/subjects received PEP005 Gel across the 25 completed studies in the clinical development programme. The safety overview provided focused on the 13 studies in which patients received PEP005 Gel across a selected area of skin (i.e., field) for treatment of SK lesions. Within this group of patients, 1165 received PEP005 Gel and 632 received vehicle gel.

8.1.3.5.2. Adverse events

A total of 42.5% of PEP005 Gel-treated patients had an AE compared with 24.2% of vehicle-treated patients. For PEP005 Gel-treated patients, the most frequently reported AEs considered related to study medication included application site pruritus (10.7%), application site pain (7.8%), and application site irritation (7.0%). Differences were noted with respect to the incidence of treatment-related AEs between treatment locations. In the controlled Phase III studies, patients treated with PEP005 Gel on the face or scalp had a higher incidence of application site pain than patients treated on the trunk or extremities (13.9% vs. 1.8%, respectively). Similarly, patients treated on the face or scalp had eye-associated disorders, such as eyelid oedema (1.1%) and periorbital oedema (2.6%), whereas patients treated on the trunk or extremities had no reports of these events.

The majority of patients had an AE with maximum severity of mild or moderate intensity. Severe AEs were reported by 3.2% of PEP005 Gel-treated patients and 1.6% of vehicle-treated patients. Severe events occurred at a higher frequency for patients treated with PEP005 Gel compared to vehicle in the SOC of general disorders and administrative site conditions, with application site reactions (e.g., irritation, pain and pruritus) attributed for this difference between treatment groups.

8.1.3.5.3. Serious adverse events and deaths

SAEs were identified (by both the investigator and Applicant) for 4.2% of patients in the PEP005 Gel group and 3.6% of patients in the vehicle group. Of these SAEs, BCC (occurring in 1.5% of PEP005 Gel-treated patients and 1.1% of vehicle-treated patients) and SCC (0.9% of PEP005 Gel-treated patients and 0.8% of vehicle-treated patients) were the most frequently reported for both treatment groups. Across all studies, there was one death, which occurred in a patient who received PEP005 Gel, 0.005% in study PEP005-015. The investigator judged the death as not related to study medication.

8.1.3.5.4. Laboratory findings

There were no meaningful shifts or trends in any of the clinical laboratory parameters.

8.1.3.5.5. Safety in special populations

Not applicable.

8.1.3.5.6. Immunological events

Not applicable.

8.1.3.5.7. Safety related to drug-drug interactions and other interactions

Not applicable.

8.1.3.5.8. Discontinuation due to adverse events

In the 13 studies that evaluated field treatment of PEP005 Gel for SK lesions, a total of 3 patients (1 treated with PEP005 Gel and 2 treated with vehicle) discontinued from the study due to one or more AEs. In the 13 SK field treatment studies, a total of 37 patients (37 treated with PEP005 Gel and 0 treated with vehicle) discontinued study medication due to one or more AEs. No significant safety issues were identified as a result of these discontinuations.

9. First round benefit-risk assessment

9.1. Benefits

From the clinical study information provided, the complete clearance rates of PEP005 Gel, 0.015% on head locations were 37% and 47%, and for PEP005 Gel, 0.05% on non-head locations, the complete clearance rates were 28% and 42%. These results were statistically significant in comparison to vehicle gel ($p < 0.001$, for each study and for the pooled Phase 3 data for each location [head and non-head]). These results appear comparable with currently marketed products (figures provided by the applicant were 15-58% for 5-FU; 34-47% for diclofenac; and 26-46% for imiquimod). A table summarising results for Aldara (imiquimod) appears below.

Table 77. Trials of topical treatments for Actinic Keratoses

*Trials**	*Treatment regimen*	*No. of participants*	*Complete response (%)*	*Partial response† (%)*
Diclofenac 3% (Solaraze) in hyaluronan 2.5% gel				
Wolf, et al., 2001[38]	Twice daily for 90 days	120	Treatment: 47.0 Vehicle: 19.0	—
Imiquimod 5% cream (Aldara)				
Korman, et al., 2005[35]	Once daily, three times per week, for 16 weeks	492	Treatment: 48.3 Vehicle: 7.2	Treatment: 64.0 Vehicle: 13.6
Lebwohl, et al., 2004[33]	Once daily, two times per week, for 16 weeks	436	Treatment: 45.1 Vehicle: 3.2 (95% CI, 34.9 to 49)‡	Treatment: 59.1 Vehicle: 11.8 (95% CI, 39.5 to 55.1)‡
Szeimies, et al., 2004[34]	Once daily, three times per week, for 16 weeks	286	Treatment: 57.1 Vehicle: 2.2	Treatment: 72.1 Vehicle: 4.3

CI = confidence interval.

**—Randomized, double-blind, vehicle-controlled, phase III trials.*

†—*75 percent reduction in actinic keratoses.*

‡—*CIs are for the treatment group minus the vehicle group.*

(McIntyre WJ et al. Treatment options for actinic keratoses. *Am Fam Physician* 2007;76(5):667-71)

PEP005 Gel treatment, however, is efficacious after being applied for a substantially shorter duration. For head (face and scalp), PEP005 Gel, 0.015% is applied for three days and for non-head (trunk and extremities), PEP005 Gel, 0.05% is applied for only two days. In contrast, the applicant noted that other products have longer durations of treatment. Treatment with 5-FU requires at least 3 to 4 weeks diclofenac requires 8 to 12 weeks, and imiquimod requires 4 weeks of treatment with efficacy assessment after the following 4-week off treatment period or 16 weeks of continuous treatment. Longer treatment durations reduce patient compliance. Treatment compliance with the PEP005 Gel dosing regimen in the Phase 3 studies was noted to be 99%. It must be noted, however, that the safety and efficacy of PEP005 Gel treatment was not directly compared with any active comparators.

PEP005 Gel applied topically at the concentrations used for treatment of SK lesions, has no systemic absorption, whereas, the applicant noted that measurable plasma concentrations occur with use of 5-FU, diclofenac, and imiquimod.

A follow-up period of 12 months was selected for each of the long-term studies. At the 12 month follow-up, patient-based recurrence was 54% for head (face and scalp) locations and 56% for non-head (trunk and extremities) locations. The applicant noted that these results are consistent with patient-based recurrence for imiquimod (42-67%). Lesion-based recurrence at 12 month follow-up was 13% for PEP005 Gel treated patients in each location (head and non-

head). These findings are also consistent with lesion-based recurrence of 9% observed for imiquimod.

9.2. Risks

Adequate information was provided to establish a side-effect profile for this product. A total of 43% of patients treated with PEP005 Gel experienced an AE. Most AEs could be attributed to application site reactions and were typically considered related to treatment. Application site pruritus, application site pain, and application site irritation were the most frequently reported. Only 3.2% of PEP005 Gel-treated patients had a severe AE. Discontinuation of treatment due to an AE occurred in only 3% of patients who received PEP005 Gel; discontinuation from the study occurred in 0.1% of patients. Serious AEs occurred at a low incidence (4% of PEP005 Gel patients) and most were unrelated to study medication. One death occurred in a PEP005 Gel-treated patient (due to coronary atherosclerosis and hypertension) and was considered unrelated to study medication. Neoplasms such as BCC and SCC of the skin were infrequent, and occurred at similar incidences for PEP005 Gel and vehicle patients. This profile appeared to compare favourably with currently marketed products. While therapeutic failure could present a possible risk, results from the clinical studies program suggest that this would be comparable to any of the active comparators currently marketed. The nature of the treatment of AK using any medication requires clinical follow-up for monitoring of both therapeutic failure and possible recurrence, especially in chronically solar-damaged skin.

Four studies provided data in patients receiving treatment for non-malignant skin cancer (NMSC) (PEP005-002, PEP005-003, PEP005-008 and PEP005-009). While these studies were included primarily to contribute to the safety database, they did provide some efficacy data on utility in alternative diagnoses. However for the majority of these studies, the analyses were primarily descriptive in nature, and were not statistically powered to conduct formal hypothesis/inferential testing. Conditions treated included nodular BCC, superficial BCC, and SCCIS.

Eye disorders, however, were seen more frequently in patients treated with PEP005 Gel (2.3% vs. 0.3% in vehicle patients). Local skin responses were common with PEP005 Gel treatment; 95% of PEP005 Gel-treated patients showed an increase in LSR scores relative to baseline whereas most patients treated with vehicle showed no change from baseline LSR score. For patients treated on the face or scalp, the maximum LSR score occurred on Day 4, which returned to baseline values (or below) by Day 15. For patients treated on the trunk or extremities, the maximum LSR score occurred between Days 3 and 8, and returned to baseline values (or below) by Day 29. For both treatment locations (face/scalp and trunk/extremities), erythema and flaking/scaling were the most common LSRs, followed by crusting and swelling. Local skin responses on the face and scalp generally were of greater intensity than responses on the trunk and extremities. The majority of patients who received PEP005 Gel showed no signs of hypopigmentation, hyperpigmentation or scarring at baseline or at the end-of-study assessments.

No clinically meaningful changes in laboratory parameters, vital signs, or ECG assessments were seen with PEP005 Gel treatment. Localised application site disorders (pruritus, pain, irritation) and local skin responses, particularly erythema, flaking, and scaling are the main characteristics of the safety profile of PEP005 Gel. These local adverse events are transient, and typically resolve without sequelae within 2-4 weeks of application. Additionally, PEP005 Gel is not systemically absorbed. The applicant noted that comparator products also report local skin responses but these appear more intense and several products recommend “rest-periods” when severe skin reactions are experienced (imiquimod and 5-FU). This is consistent with current clinical experience. No tabular summary comparing adverse event rates based on clinical trial data was provided. The applicant also noted that comparator products also report systemic

absorption when applied topically and systemic adverse events such as flu-like symptoms and fatigue (imiquimod).

The formulation proposed for marketing was used in the pivotal studies (0.015% Picato Gel in studies PEP005-016 and PEP005-025, 0.05% in studies PEP005-014 and PEP005-028). A valid rationale for the lack of active comparators was provided. While the data set provided only shows that Picato Gel is better than placebo, adequate information was provided to suggest that efficacy was comparable to currently available comparators. While a non-inferiority study would be preferred, this risk would be mitigated by adequate post-marketing surveillance. The superiority margins in the pivotal studies were appropriate, and clinically meaningful.

10. First round recommendation regarding authorisation

On the basis of the information provided by the applicant, the application for registration of Picato Gel is supported based on the proposed indications.

11. Clinical questions

Nil.

12. References

Nil

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au