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PEP005 (ingenol mebutate) Gel

2.7.4 Summary of Clinical Safety for Actinic Keratosis

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Clinical Development

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Module 2
Summary of Clinical Safety
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AK	actinic keratosis
AUS	Australia
AV	atrioventricular
BCC	basal cell carcinoma
BMI	body mass index
CI	confidence interval
CPK	creatinine phosphokinase
CSR	clinical study report
CV	coefficient of variation
DBP	diastolic blood pressure
E. peplus	*Euphorbia peplus*
HR	heart rate
I_{kr}	Potassium rectifier current
ITT	intent-to-treat
iv	intravenous
LBBB	left bundle branch block
LLOQ	lower limit of quantification
LSR	local skin response
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NMSC	non-melanoma skin cancer
NOAEL	no-observable-adverse-effect-level
NOEL	no-observable-effect-level
NZ	New Zealand
qd	Once daily

QTcB	The QT interval (in msec) of the ECG corrected for heart rate using Bazett's correction formula: $QTcB = (QT)/(RR)^{1/2}$, where RR interval is the interval between R waves (in msec)
QTcF	The QT interval (in msec) of the ECG corrected for heart rate using Fridericia's correction formula: $QTcF = (QT)/(RR)^{1/3}$, where RR interval is the interval between R waves (in msec)
RBBB	right bundle branch block
RBC	red blood cell (count)
SAE	serious adverse event
SBP	systolic blood pressure
SCC	squamous cell carcinoma
SCCIS	squamous cell carcinoma in situ
SD	standard deviation
SHE	Syrian hamster embryo
US	United States

1 EXPOSURE TO THE DRUG

Ingenol mebutate, the active ingredient in PEP005 Gel, is extracted from the plant *Euphorbia peplus* (*E. peplus*). Historically, the sap from *E. peplus* has been used as a home remedy for a variety of conditions, including warts, corns, waxy growths, skin cancer and solar keratoses. Ingenol mebutate is a pleiotropic effector with a dual mechanism of action involving rapid primary necrosis (24–48 hours), followed by tumor cell-specific immune response characterized by antibody-dependent cellular cytotoxicity that removes residual disease.

The Applicant had evaluated ingenol mebutate (formulated in the PEP005 Gel) in controlled clinical trials for the topical treatment of actinic keratosis (AK). This mechanism of action of ingenol mebutate distinguishes it from current therapeutic options for AK and provides a rationale for substantially shorter durations of treatment (2–3 days) compared to approved topical AK products (2–16 weeks).

No systemic absorption of topical ingenol mebutate was detected in clinical studies (Studies PEP005-004, PEP005-013, PEP005-017). In a maximal use study (PEP005-017), levels of ingenol mebutate and its acyl isomers were below the lower limit of quantification (LLOQ; 0.1 ng/mL) following topical application of PEP005 Gel, 0.05% once daily to a 100 cm^2 area for 2 consecutive days. The human pharmacokinetic (PK) profile of topical PEP005 Gel administration was predicted using allometric scaling from in vivo animal PK and in vitro percutaneous absorption data. Based on the estimated ingenol mebutate assumed absorption rate constant and topical bioavailability, the volume of distribution at steady state, and blood clearance, a minimal topical dose of 2000 µg/kg/day would be required to produce systemic ingenol mebutate concentrations above the LLOQ. This estimated topical dose is 1000-times above the maximum intended clinical dose of 2 µg/kg/day.

The goal of the PEP005 Gel AK development program was to define effective, well-tolerated treatment regimens with favorable safety profiles. Two regimens, used as field therapy and based on anatomic location have been identified:

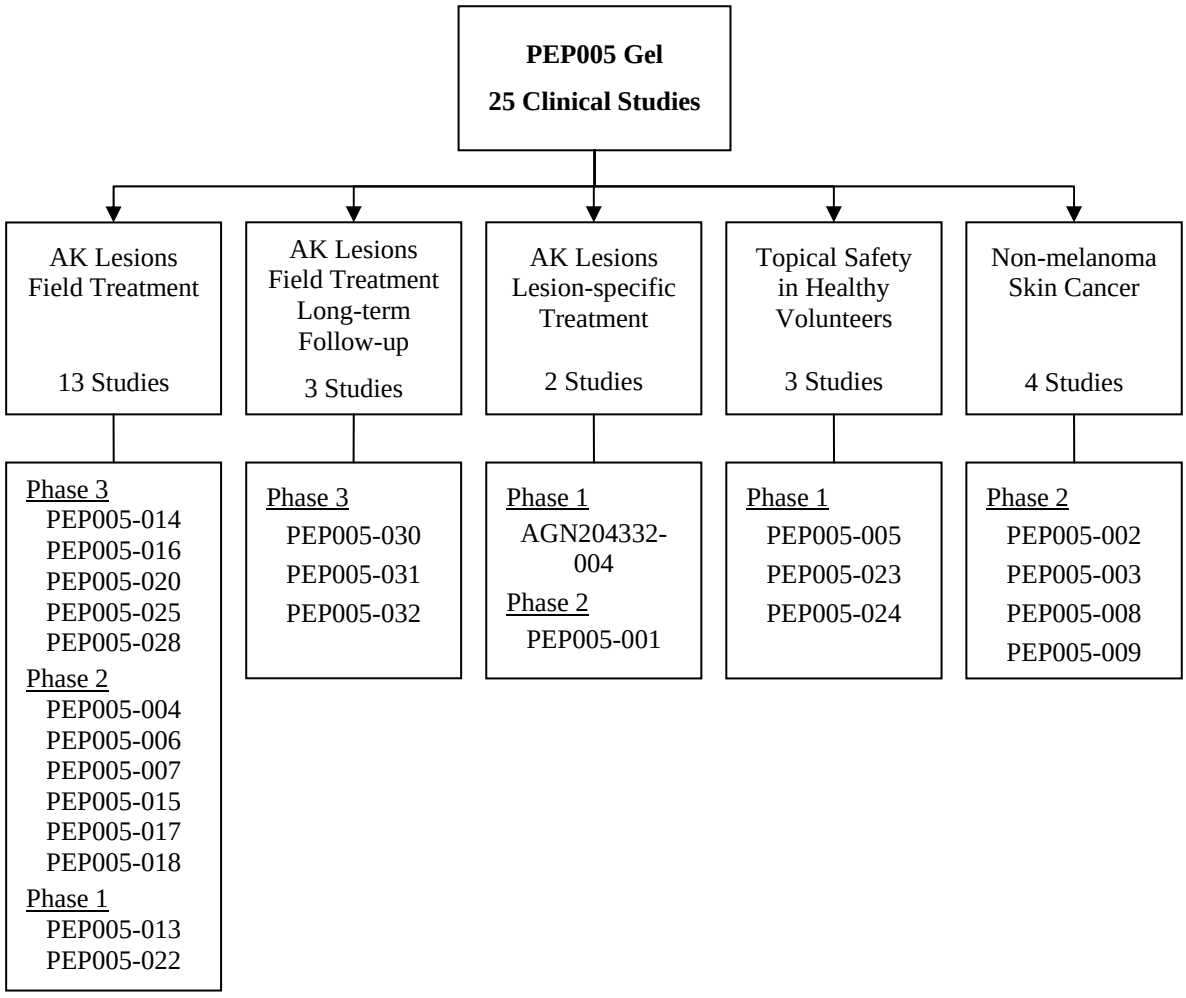
- Face/scalp: PEP005 Gel, 0.015% for 3 consecutive days
- Trunk/Extremities: PEP005 Gel, 0.05% for 2 consecutive days

1.1 OVERALL SAFETY EVAULATION PLAN AND NARRATIVES OF SAFETY STUDIES

1.1.1 Studies in the PEP005 Gel Development Program

To date, 25 clinical studies (Figure 1) have been completed and a total of 1774 patients in the United States, Australia, and New Zealand have received PEP005 Gel. While all these studies contribute to the understanding of the safety of topically administered PEP005 Gel, the focus of this safety summary is on the data obtained for the AK studies, specifically the 13 studies in which patients received treatment across a selected area of skin (i.e., field). Supporting safety information is derived from: 2 studies in which AK patients received treatment of specific lesions; 3 long-term observational safety studies in AK patients who had been treated with PEP005 Gel in four controlled Phase 3 studies; 3 topical safety studies in healthy volunteers that assessed the potential for contact sensitization, phototoxicity, and photoallergy; and 4 studies in patients with non-melanoma skin cancer (NMSC) that evaluated the effectiveness and safety of PEP005 Gel for treatment of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Figure 1 Overview of Completed Clinical Studies for PEP005 Gel



A summary of the number of patients/subjects who received at least one dose of PEP005 Gel and/or vehicle gel in the clinical studies (thereby comprising the safety population) is provided in Table 1.

Table 1 Summary of Number of Patients/Subjects Dosed with PEP005 Gel or Vehicle Gel

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
AK Lesions, Lesion-specific treatment (2 studies)	57	17
Topical Safety, Healthy Volunteers (3 studies)	332	*
NMSC (4 studies)	220	24

*All subjects in the 3 topical safety studies received both PEP005 Gel and vehicle gel.

1.1.2 Development Plan for PEP005 Gel in Actinic Keratosis

The early AK clinical development program focused on the treatment of individual AK lesions (i.e., lesion-specific therapy) (studies AGN 204332-004 and PEP005-001). Once PEP005 Gel was established as having an acceptable safety profile for the treatment of individual AK lesions, subsequent Phase 2 studies demonstrated that PEP005 Gel was well tolerated using field application to treat a 9 cm^2 (PEP005-004) or 25 cm^2 area of skin (studies PEP005-006, PEP005-007, and PEP005-015).

Early AK clinical trials showed that different concentrations of PEP005 Gel were needed to treat AK lesions in different anatomical locations. For field application to AK lesions on the trunk and extremities, the maximum tolerated dose (MTD) of PEP005 Gel was established as 0.05%, administered once daily for 2 consecutive days (PEP005-004); this dose was identified in the first dose-ranging study (PEP005-006) as the appropriate dose for the controlled Phase 3 studies PEP005-014 and PEP005-028. Another Phase 2 study (PEP005-018) established the safety of PEP005 Gel, 0.05%, for treating the dorsal aspect of the hand, further extending the anatomical areas treated with PEP005 Gel. For field application to AK lesions on the face and scalp, the MTD was found to be PEP005 Gel, 0.025% once daily for 2 consecutive days (PEP005-007). Based on data from a second dose-ranging study (PEP005-015), PEP005 Gel, 0.015% once daily for 3 consecutive days, was selected as the dose for the Phase 3 studies PEP005-016 and PEP005-025.

Additional studies supporting maximal use and PK properties of PEP005 Gel include studies PEP005-013, PEP005-022 and PEP005-017. In these studies, PEP005 Gel, 0.05% was applied to areas of skin of up to 100 cm^2 on the dorsal aspect of the forearm. Both the PEP005-013 and the PEP005-017 study evaluated the PK of PEP005 Gel.

The Phase 3 program for PEP005 Gel in AK also included PEP005-020, an open-label safety study for the treatment of AK lesions on the trunk and extremity, conducted to increase the safety data generated on non-head anatomical areas.
Three observational long-term follow-up studies (PEP005-030, PEP005-031 and PEP005-032) were conducted in patients who completed the Phase 3 PEP005 Gel studies and had achieved complete clearance of AK lesions. In these 12-month follow-up studies, patients received no study drug; the objectives were to evaluate safety and AK recurrence within the areas treated with PEP005 Gel during the Phase 3 studies. Safety results from these studies are summarized in Section 2.1.6.
An additional 5 studies involving PEP005 Gel are ongoing or planned. These studies include evaluations of safety and efficacy in patients with seborrhoeic keratosis (PEP005-033) and patients with photo-damaged skin (PEP005-036); an assessment of local tolerability on the finger following exposure to PEP005 Gel and hand washing (LP0041-01); and examinations of the biological effects of PEP005 Gel in patients with AK lesions on the upper extremities (LP0041-02 and LP0041-03).
In this summary of clinical safety, all data from the 25 completed studies are presented along with any serious adverse events (SAEs) reported from the ongoing studies through 31 March 2011.

1.1.3 Summary of All Investigations Pertinent to Safety

1.1.3.1 Tabular Summaries of Clinical Studies

Tabular summaries of the clinical studies are presented and organized as follows:

- Table 2 Summary of Studies in AK Patients Who Received Field Application of Study Medication
- Table 3 Summary of Long-term Follow-up Studies of AK Patients Who Received Field Application of Study Medication
- Table 4 Summary of Lesion-specific Studies
- Table 5 Summary of Topical Safety Studies
- Table 6 Summary of Non-melanoma Skin Cancer Studies
- Table 7 Summary of Ongoing or Planned Studies

Table 2 Summary of Studies in AK Patients Who Received Field Application of Study Medication

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Phase 3 Controlled Studies, Field Application, Actinic Keratosis								
PEP005-014 Completed Study dates: 5 Sep 2008 23 Feb 2009	AK lesions trunk and extremities	US (18) AUS (2)	Double-blind, parallel group, vehicle-controlled, field application (25 cm^2 treatment area)	0.05% qd Vehicle qd	126/122 129/128	158/96 36–88	2 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs, ECGs
PEP005-016 Completed Study dates: 5 Jun 2009 to 10 Sep 2009	AK lesions face and scalp	US (19) AUS (2)	Double-blind, parallel group, vehicle-controlled, field application (25 cm^2 treatment area)	0.015% qd Vehicle qd	135/132 134/127	235/32 37–88	3 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs, ECGs
PEP005-025 Completed Study dates: 1 Jun 2009 to 2 Sep 2009	AK lesions face and scalp	US (19) AUS (2)	Double-blind, parallel group, vehicle-controlled, field application (25 cm^2 treatment area)	0.015% qd Vehicle qd	142/142 136/135	229/49 34–89	3 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs, ECGs
PEP005-028 Completed Study dates: 22 Jul 2009 14 Oct 2009	AK lesions trunk and extremities	US (17)	Double-blind, parallel group, vehicle-controlled, field application (25 cm^2 treatment area)	0.05% qd Vehicle qd	100/98 103/99	127/76 34–89	2 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs, ECGs

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 2 Summary of Studies in AK Patients Who Received Field Application of Study Medication (Cont'd)

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Other Controlled Studies, Field Application, Actinic Keratosis								
PEP005-006 Completed Study dates: 11 Sep 2006 19 Jun 2007	AK lesions face and scalp, trunk and extremities	US (22)	Double-blind, double dummy, parallel group, vehicle-controlled, dose ranging, field application (25 cm^2 treatment area) (Phase 2b study)	2 days 0.05% qd 3 days 0.025% qd 0.05% qd Vehicle qd	 55/54 50/50 57/57 60/59	178/44 43–85	2 D or 3 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs
PEP005-015 Completed Study dates: 24 Jun 2008 20 Oct 2008	AK lesions face and scalp	US (25) AUS (3)	Double-blind, parallel group, dose-ranging, vehicle-controlled, field application (25 cm^2 treatment area) (Phase 2 study)	2 days 0.005% qd 0.01% qd 0.015% qd Vehicle qd 3 days 0.005% qd 0.01% qd 0.015% qd Vehicle qd	 33/32 34/34 33/33 33/31 33/31 34/34 32/32 33/33	236/28 46–91	2 D or 3 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs
PEP005-017 Completed Study dates: 18 Mar 2009 27 May 2009	AK lesions trunk and extremities	US (1)	Double-blind, parallel group, vehicle-controlled, field application (100 cm^2 treatment area) (Phase 2 study)	0.05% qd Vehicle qd	13/13 3/3	6/10 48–79	2 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 2 Summary of Studies in AK Patients Who Received Field Application of Study Medication (Cont'd)

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Phase 3 Uncontrolled Studies, Field Application, Actinic Keratosis								
PEP005-020 Completed Study dates: 8 Jun 2009 2 Sep 2009	AK lesions trunk and extremities	US (8) AUS (3)	Open-label, uncontrolled, single arm, field application (25 cm^2 treatment area) (Phase 3b study)	0.05% qd	102/102	68/34 38–88	2 D	AEs, LSRs, pigmentation and scarring, abnormal proliferation, vital signs
Phase 2 Uncontrolled Studies, Field Application, Actinic Keratosis								
PEP005-004 Completed Study dates: 7 Sep 2005 14 Mar 2006	AK lesions trunk and extremities	US (1)	Open-label, uncontrolled, dose escalation, field application to a single lesion (9 cm^2 treatment area) (Phase 2b study)	0.01% qd 0.025%qd 0.05% qd 0.075% qd	3/3 3/3 10/10 6/6	16/6 64–87	2 D	AEs (including assessments of local skin reactions, scarring, and abnormal proliferation), clinical laboratory assessments, vital signs, determination of MTD
PEP005-007 Completed Study dates: 18 Jan 2007 13 Nov 2007	AK lesions face and scalp	AUS/NZ (9)	Open-label, dose escalation, field application (25 cm^2 treatment area) (Phase 2a study)	2 days 0.0125% qd 0.0175% qd 0.025% qd 3 days 0.0025% qd 0.005% qd 0.0075% qd 0.0125% qd 0.0175% qd 0.025% qd	 3/3 3/3 30/30 6/6 8/8 9/9 11/10 10/9 8/8	65/23 42–89	2 D or 3 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assessments, vital signs, determination of MTD

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 2 Summary of Studies in AK Patients Who Received Field Application of Study Medication (Cont'd)

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Phase 2 Uncontrolled Studies, Field Application, Actinic Keratosis (Cont'd)								
PEP005-018 Completed Study dates: 11 Oct 2007 18 Dec 2007	AK lesions trunk and extremities	US (4)	Open-label, single-arm, uncontrolled, field application, (25 cm^2 treatment area) (Phase 2 study)	0.05% qd	11/11	11/0 57–82	2 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs
Phase 1 Uncontrolled Studies, Field Application, Actinic Keratosis								
PEP005-013 Completed Study dates: 17 Oct 2007 23 Apr 2008	AK lesions trunk and extremities	AUS (1)	Open-label, PK, field application (100 cm^2 treatment area) (Phase 1 study)	0.05% qd	6/6	6/0 56–81	2 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs
PEP005-022 Completed Study dates: 3 Apr 2008 4 Sep 2008	AK lesions trunk and extremities	US (8) AUS (4)	Open-label, assessment of application to treatment areas ranging from 25 to 100 cm^2 (Phase 1 study)	0.05% qd	64/63	64/0 44–85	2 D	AEs, LSR scoring, pigmentation and scarring, abnormal proliferation, clinical laboratory assess-ments, vital signs

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 3 Summary of Long-term Follow-up Studies of AK Patients Who Received Field Application of Study Medication

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Long-term, Observational Studies								
PEP005-030 Completed Study dates: 29 Jul 2009 16 Sep 2010	AK lesions face and scalp	US (38) AUS (4)	Prospective, longitudinal, observational study. Patients received PEP005 Gel or vehicle in study PEP005-016 or PEP005-025 and had complete lesion clearance.	None	117/108	91/26 37–88	NA	AEs within the treatment area
PEP005-031 Completed Study dates: 29 Jul 2009 14 Sep 2010	AK lesions trunk and extremities	US (8) AUS (3)	Prospective, longitudinal, observational study. Patients received PEP005 Gel in study PEP005-020 and had complete lesion clearance.	None	38/34	25/13 38–80	NA	AEs within the treatment area
PEP005-032 Completed Study dates: 24 Sep 2009 11 Oct 2010	AK lesions trunk and extremities	US (15)	Prospective, longitudinal, observational study. Patients received PEP005 Gel or vehicle in study PEP005-028 and had complete lesion clearance.	None	43/42	25/18 44–79	NA	AEs within the treatment area

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 4 Summary of Lesion-specific Studies

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Lesion-specific Treatment Studies								
AGN204332-004 Completed Study dates: 12 Aug 2004 15 Oct 2004	AK lesions trunk and extremities	US (4)	Double-blind, parallel group, vehicle-controlled (Phase 1 study)	0.01% Vehicle	11/11 5/4	14/2 42–82	1 D	AEs, clinical laboratory assessments, vital signs
PEP005-001 Completed Study dates: 17 Mar 2005 14 Oct 2005	AK lesions face, scalp, trunk and extremities	AUS (7)	Double-blind, parallel group, vehicle-controlled, dose ranging (Phase 2a study)	Dosed on Days 1 and 2: 0.0025% 0.01% 0.05% Vehicle Dosed on Days 1 and 8: 0.0025% 0.01% 0.05% Vehicle	 9/8 8/7 9/8 6/6 8/7 8/8 9/7 6/6	52/6 44–86	2 D	AEs (including assessments of local skin reactions and abnormal proliferation), clinical laboratory assessments, vital signs

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 5 Summary of Topical Safety Studies

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Topical Safety Studies								
PEP005-005 Completed Study dates: 3 Jul 2006 7 Oct 2006	Healthy volunteers	US (1)	Double-blind, randomized, vehicle-controlled, within-subject comparison ($4\ cm^2$ treatment area) (Phase 1 study)	0.01% and Vehicle applied to two treatment areas	238/220	42/196 19–65	10 doses of both PEP005 Gel and vehicle over 6–8 weeks	Dermal sensitization (local tolerability), AEs, vital signs
PEP005-023 Completed Study dates: 30 Mar 2009 3 Apr 2009	Healthy volunteers	US (1)	Randomized, within subject comparison ($4\ cm^2$ treatment area) (Phase 1 study)	0.01% and Vehicle applied to two treatment areas (irradiated and non-irradiated) once	34/33	4/30 18–65	1 D	Dermal photoirritation (local tolerability), AEs
PEP005-024 Completed Study dates: 2 Mar 2009 24 Apr 2009	Healthy volunteers	US (1)	Randomized, within subject comparison ($4\ cm^2$ treatment area) (Phase 1 study)	0.01% and Vehicle applied to two treatment areas (irradiated and non-irradiated)	60/55	14/46 19–64	7 doses of both PEP005 Gel and vehicle over 6–8 weeks	Dermal photosensitization, local tolerability, AEs

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 6 Summary of Non-melanoma Skin Cancer Studies

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Other Studies: Non-melanoma Skin Cancer								
PEP005-002 Completed Study dates: 6 Apr 2005 19 May 2006	NMSC nodular BCC on the face, scalp, trunk and extremities	AUS (10)	Double-blind, randomized, vehicle-controlled, parallel group (Phase 2a study)	Dosed on Days 1 and 2: 0.0025% 0.01% 0.05% Vehicle Dosed on Days 1 and 8: 0.0025% 0.01% 0.05% Vehicle	 7/7 8/7 8/8 6/6 7/7 8/8 8/8 6/5	37/21 44–87	2 D	AEs (including local skin reactions, pigmentation and scarring), abnormal proliferation, clinical laboratory assessments, vital signs
PEP005-003 Completed Study dates: 7 Apr 2005 7 Mar 2006	NMSC superficial BCC on the face, scalp, trunk and extremities	AUS (8)	Double-blind, randomized, vehicle-controlled, parallel group (Phase 2a study)	Dosed on Days 1 and 2: 0.0025% 0.01% 0.05% Vehicle Dosed on Days 1 and 8: 0.0025% 0.01% 0.05% Vehicle	 8/8 8/8 8/8 6/6 8/8 8/8 8/8 6/6	44/16 34–86	2 D	AEs (including local skin reactions, pigmentation and scarring), abnormal proliferation, clinical laboratory assessments, vital signs

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 6 Summary of Non-melanoma Skin Cancer Studies (Cont'd)

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
Other Studies: Non-melanoma Skin Cancer (Cont'd)								
PEP005-008 Completed Study dates: 17 May 2006 30 Nov 2006	NMSC SCCIS on the face, trunk, and extremities	AUS (3)	Open-label (Phase 2a study)	0.05% qd	25/25	19/6 54–85	2 D	AEs (including severity of local skin responses, pigmentation and scarring), abnormal proliferation, vital signs
PEP005-009 Completed Study dates: 9 Feb 2007 17 Mar 2010	NMSC superficial BCC on the trunk	US (10)	Open-label, dose escalation (Phase 2 study)	Day 1 0.025% 0.05% 0.075% 0.1% 0.125% 0.15% 0.175% 0.2% 0.225% 0.25% Days 1 and 8: 0.025% 0.05% 0.075% 0.1% 0.125% 0.15% 0.175% 0.2% 0.225% 0.25%	 3/3 3/3 3/3 3/3 3/3 3/3 3/3 3/3 3/3 25/25 3/3 3/3 3/3 3/3 3/3 3/3 3/3 3/3 3/3 22/21	76/25 37–84	1 D or 2 D	AEs (including local skin responses, pigmentation and scarring), clinical laboratory assessments, abnormal proliferation, determination of MTD

[a]The term 'entered' refers to the number of patients randomized (for randomized studies) or treated (for non-randomized studies)

Table 7 Summary of Ongoing or Planned Studies

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
PEP005-033 Ongoing Study dates: 4 Oct 2010 22 Dec 2010	Patients with seborrhoeic keratosis on the trunk and extremities	TBD	Open-label (Phase 2a study)	0.05% qd	24 planned	TBD	3 D	AEs, LSRs, and scarring
PEP005-036 Ongoing Study dates: 11 Oct 2010 20 Jan 2011	Patients with photo-damaged skin on the face	TBD	Single arm, open-label (Phase 2a study)	0.015% qd	24 planned	TBD	3 D	AEs, LSRs, pigmentation and scarring
LP0041-01 Ongoing Study dates: 23 Feb 2011 24 Mar 2011	Healthy subjects	TBD	Randomized, open-label, 2-arm, non-controlled (Phase 1 study)	0.05% qd 0.015% qd	100 planned	TBD	2 D 3 D	AEs, LSRs, adverse drug reactions, reasons for withdrawal from the trial

Table 7 Summary of Ongoing or Planned Studies (Cont'd)

Protocol No. Study status and dates	Population	Locations (No. of Study Centers)	Design; Control Type	PEP005 Gel and Vehicle, Dose & Regimen	No. Patients by dose group; Entered[a]/ Completed	Gender M/F & Age range (years) for the Safety Population	Treatment Duration	Safety Assessments
LP0041-02 Planning phase Estimated to start Q4 2011	Patients with AK lesions on the upper extremities	TBD	Open-label (Phase 2 study)	0.05% qd	Up to 26 planned	TBD	2 D	AEs, LSRs
LP0041-03 Planning phase Estimated to start Q4 2011	Patients with AK lesions on the upper extremities	TBD	Open-label (Phase 2 study)	0.05% qd Vehicle, qd	24 planned	TBD	2 D	AEs, LSRs, pigmentation and scarring

1.1.4 Methods and Definitions

A statistical analysis plan for this safety summary is provided in Module 5.3.5.3.

1.1.5 Analysis Populations

The safety analyses include all patients/subjects who received at least one dose of PEP005 Gel or vehicle gel. All safety data were summarized descriptively by treatment received. During the development program, 3 patients received study medication different from the treatment to which they were randomized; data for these 3 patients were summarized according to the treatment actually received, as follows:

- Patient [redacted] in Study PEP005-016 was randomized to the PEP005 Gel, 0.015% group but actually received vehicle gel; data for this patient were included in the vehicle group for all safety analyses.
- Patient [redacted] in Study PEP005-028 was randomized to the PEP005 Gel, 0.05% group but actually received vehicle gel; data for this patient were included in the vehicle group for all safety analyses.
- Patient [redacted] in Study PEP005-028 was randomized to the vehicle gel group but actually received PEP005 Gel, 0.05%; data for this patient were included in the PEP005 Gel, 0.05% group for all safety analyses.

The focus of the safety analysis is on the AK patients who received field application of study medication. Data summaries within this document generally compare data from the pooled controlled Phase 3 studies for face/scalp treatment locations to data from the pooled controlled Phase 3 studies for trunk/extremity treatment locations to pooled data for the Phase 3 studies of both face/scalp and trunk/extremity locations to pooled data for all 13 studies that utilized the field application strategy in AK patients (Table 8).

Table 8 Studies from which Safety Data were Pooled and Summarized

Controlled Phase 3 Studies			All AK Field Treatment Studies
Face and Scalp	**Trunk and Extremities**	**Face/Scalp and Trunk/Extremities Combined**	**All Locations**
PEP005-016 PEP005-025	PEP005-014 PEP005-028	PEP005-014 PEP005-016 PEP005-025 PEP005-028	PEP005-004 PEP005-006 PEP005-007 PEP005-013 PEP005-014 PEP005-015 PEP005-016 PEP005-017 PEP005-018 PEP005-020 PEP005-022 PEP005-025 PEP005-028

Data summaries were also prepared for pooled data from studies for field treatment of AK lesions on:

- the face and scalp (studies PEP005-006 [scalp], PEP005-007, PEP005-015, PEP005-016, and PEP005-025), and
- the trunk and extremities (PEP005-004, PEP005-006 [non-scalp], PEP005-013, PEP005-014, PEP005-017, PEP005-018, PEP005-020, PEP005-022, and PEP005-028).

These data summaries are included in the Appendix tables.

Safety data from the 9 additional studies (2 lesion-specific AK studies and 7 non-AK studies) in which patients received study medication (Table 9) provide supportive information and are discussed as appropriate. Safety summaries for all these 9 studies are provided in the Appendix tables.

Table 9 Lesion-specific and Non-AK Studies

Lesion-Specific Studies	Topical Safety Studies	NMSC Studies
AGN204332-004 PEP005-001	PEP005-005 PEP005-023 PEP005-024	PEP005-002 PEP005-003 PEP005-008 PEP005-009

Safety data from the three long-term follow-up studies (PEP005-030, PEP005-031, and PEP005-032) are discussed in Section 2.1.6.

1.1.5.1 Adverse Events

An AE was defined as any unfavorable or unintended sign (including abnormal laboratory findings), symptom, or disease that appeared or worsened during the clinical trial, whether or not deemed causally associated with the study medication. All AEs observed by the investigator or professional collaborators or reported spontaneously by the patient or in response to a direct question were evaluated by the investigator and noted as verbatim terms in the case report form (CRF). Verbatim terms were subsequently mapped using a MedDRA thesaurus (version 12.0) to a system organ class (SOC) and preferred term. Any preferred terms that mapped to a different SOC in earlier versions of MedDRA (e.g., for clinical study reports [CSRs] completed before December 2008) were re-mapped to the primary SOC term in the version 12.0 hierarchy. A listing of the recoded terms is provided in Appendix Table 31.
A treatment-emergent AE was defined as an AE that started or worsened with application or after application of the first dose of study medication. Any event identified prior to application of the first dose of study medication was recorded as patient history.
A treatment-related AE was a treatment-emergent AE for which the investigator assigned causality (such as “definite”, “probable”, or “possible”) to the study medication.
The severity of AEs were graded by the investigator based on the following criteria:

- Mild Awareness of a sign or symptom, but easily tolerated
- Moderate Discomfort enough to cause interference with usual activity
- Severe Incapacitating with inability to work or do usual activity
- Not applicable An ‘all or nothing’ finding that cannot be graded

1.1.5.2 Serious Adverse Events

An SAE was characterized as an untoward medical occurrence that: resulted in death, was life-threatening, required hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, caused a congenital anomaly or birth defect, and/or was considered medically significant by the investigator.
Following review of AEs in the clinical database, the Applicant identified and reclassified additional events as serious. All additional events were in the SOC of ‘neoplasms benign, malignant and unspecified (including cysts and polyps)’, with preferred terms of BCC, SCC, malignant melanoma, basosquamous carcinoma, Bowen’s disease, and skin neoplasm (see Section 2.1.3). The Applicant-identified SAEs are only described in this summary document

as well as the appendix tables for integrated analysis of safety (Module 5, Section 5.3.5.3); these additional events are not described in the individual clinical study reports.

1.1.5.3 Local Skin Responses

In very early studies, local skin responses (LSRs) were reported as AEs; subsequently, 8 specific responses of interest were identified and a grading scale for these specific LSRs was established. The original 8 LSRs were: erythema, flaking/scaling, swelling, crusting, erosion/ulceration, vesiculation/pustulation, pigmentation (hypo and hyper), and scarring. These LSRs were assessed within the selected treatment area at the baseline visit and each successive visit through study completion. Skin responses other than these 8 were recorded as AEs. The 8 LSRs were each graded by the investigator on a scale of 0 to 4, then summed to give a composite score with a maximum possible score of 32. This system was used for the following AK studies: PEP005-006, PEP005-007, PEP005-013, and PEP005-018. In subsequent studies, including the controlled Phase 3 studies, pigmentation (hypopigmentation and hyperpigmentation) and scarring were graded separately from the LSRs. A maximum score of 24 was also used when calculating the composite score for these subsequent studies. Consequently, for this safety summary, LSRs included the following 6 responses: erythema, flaking/scaling, swelling, crusting, erosion/ulceration, and vesiculation/pustulation. The grading criteria for the LSRs are summarized in Table 10 and depicted in Attachment 1. A composite LSR score was calculated by summing the scores of each of the 6 individual LSR scores, giving a maximum possible composite score of 24. (For the studies where pigmentation and scarring were included as part of grading LSRs, the composite score was recalculated, excluding the pigmentation and scarring components.)

Table 10 Grading Criteria for Local Skin Responses

Local Skin Response	**Grading Criteria**				
	0	**1**	**2**	**3**	**4**
Erythema	Not present	Slightly pink < 50%	Pink or light red > 50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking / Scaling	Not present	Isolated scale, specific to lesion	Scale < 50%	Scale > 50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting	Crusting < 50%	Crusting > 50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation / Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles < 50%	Transudate or pustules, with or without vesicles > 50%	Transudate or pustules, with or without vesicles extending outside treatment area
Erosion / Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion > 50%	Black eschar or ulceration

1.1.5.4 Pigmentation and Scarring

The treatment area was assessed by a qualified dermatologist at baseline and all subsequent visits (including unscheduled/ post study follow-up visits, as warranted) for pigmentation and scarring. Grading criteria for pigmentation and scarring differed between early studies and later studies (which included the controlled Phase 3 studies). For this safety summary, the scores were simplified to two qualitative descriptors of ‘not present’ or ‘present’ to convey

the absence or presence of hypopigmentation, hyperpigmentation, or scarring at baseline and the end of the study.

1.2 OVERALL EXTENT OF EXPOSURE

1.2.1 Disposition

Across the 13 studies that evaluated field application(s) of study medication for treatment of AK lesions, 1165 patients received PEP005 Gel and 632 patients received vehicle gel (Table 11). The vast majority of patients completed the study through follow-up assessments. Approximately 2% of patients (1.6% treated with PEP005 Gel and 2.5% treated with vehicle gel) terminated early from the study. Reasons for termination were similar between treatment groups and included the patient's withdrawal of consent or decision to terminate (0.4% PEP005 Gel vs. 1.4% vehicle), an abnormal lab test or AE (0.3% PEP005 Gel vs. 0.5% vehicle), a protocol deviation or violation (0.3% PEP005 Gel vs. 0.3% vehicle), or the patient was lost to follow-up (0.3% PEP005 Gel vs. 0% vehicle gel).
A summary of disposition in the other 9 studies in which patients/subjects received PEP005 Gel and/or vehicle gel is presented in Table 12. In general, the reasons for study termination were similar to those in the AK field treatment studies.

Table 11 Disposition of Patients in the AK Field Treatment Studies

	Controlled Phase 3 Studies						All AK Field Treatment Studies	
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]		All Locations[d]	
	0.015% PEP005 Gel	Vehicle	0.05% PEP005 Gel	Vehicle	PEP005 Gel	Vehicle	PEP005 Gel	Vehicle
ITT Population (Randomized)	276	271	226	232	502	503	1172	632
Safety Population (Treated)	274 (99.3%)	271 (100.0%)	225 (99.6%)	232 (100.0%)	499 (99.4%)	503 (100.0%)	1165 (99.4%)	632 (100.0%)
Patients Terminating the Study Early	3 (1.1%)	8 (3.0%)	6 (2.7%)	5 (2.2%)	9 (1.8%)	13 (2.6%)	19 (1.6%)	16 (2.5%)
Reason for Early Termination								
Abnormal Lab Test/Adverse Event	1 (0.4%)	1 (0.4%)	2 (0.9%)	2 (0.9%)	3 (0.6%)	3 (0.6%)	4 (0.3%)	3 (0.5%)
Consent Withdrawn / Subject Decision	2 (0.7%)	6 (2.2%)	0 (0.0%)	1 (0.4%)	2 (0.4%)	7 (1.4%)	5 (0.4%)	9 (1.4%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	3 (0.3%)	0 (0.0%)
No Actinic Keratosis Lesions	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Deviation/Violation	0 (0.0%)	1 (0.4%)	2 (0.9%)	1 (0.4%)	2 (0.4%)	2 (0.4%)	3 (0.3%)	2 (0.3%)
Screening or Inclusion / Exclusion Failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Applicant/Investigator Decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.3%)

Source: [a]Appendix Table 1.1.6; [b]Appendix Table 1.2.10; [c]Appendix Table 1.3.2; [d]Appendix Table 1.3.3

Table 12 Summary of Disposition in the Other Studies

Study	No. of Patients/Subjects in the Safety Population		No. (%) of Patients/Subjects Terminating the Study	
	PEP005 Gel	Vehicle	PEP005 Gel	Vehicle
AK, Lesion Specific Studies				
AGN204332-004[a]	11	5	0/11 (0.0%)	1/5 (20.0%)
PEP005-001[b]	46	12	6/46 (13.0%)	0/12 (0.0%)
Topical Safety Studies				
PEP005-005[c]	238	*	18/238 (7.6%)	*
PEP005-023[d]	34	*	1/34 (2.9%)	*
PEP005-024[e]	60	*	5/60 (8.3%)	*
NMSC Studies				
PEP005-002[f]	46	12	1/46 (2.2%)	1/12 (8.3%)
PEP005-003[g]	48	12	0/48 (0.0%)	0/12 (0.0%)
PEP005-008[h]	25	Not applicable	0/25 (0.0%)	Not applicable
PEP005-009[i]	101	Not applicable	1/101 (1.0%)	Not applicable

*All subjects in the 3 topical safety studies received both PEP005 Gel and vehicle gel.

Source: [a]Appendix Table 1.4.1; [b]Appendix Table 1.4.2; [c]Appendix Table 1.5.1; [d]Appendix Table 1.5.2; [e]Appendix Table 1.5.3; [f]Appendix Table 1.4.3; [g]Appendix Table 1.4.4; [h]Appendix Table 1.4.5; and [i]Appendix Table 1.4.6

1.2.2 Extent of Exposure

The summary of treatment exposure (Table 13) reflects the actual number of days that patients applied study medication to a treatment location. For the controlled Phase 3 studies, depending on the treatment location, patients were to apply PEP005 Gel or vehicle gel for either 2 days (for trunk and extremities locations) or 3 days (for face and scalp locations). Nearly all patients (> 98.9%) in the Phase 3 studies complied with and completed the regimen. Across all AK field treatment studies, most patients had either 2 or 3 days of treatment, and 3.6% of PEP005 Gel-treated patients and 0.2% of vehicle-treated patients had only 1 day of treatment. The face and the arm were the most frequent treatment locations (Table 14). In the controlled Phase 3 studies in which AK lesions on the face and scalp were treated with study drug, the face was the more frequently treated site (for approximately 80% of patients), reflecting the protocol-specified enrollment design (controlling for 80% of patients needing treatment on the face and 20% on the scalp). In the controlled Phase 3 studies that evaluated treatment of AK lesions on the trunk and extremities, the arm was the most frequently treated site (for approximately 63% of patients) followed by the back of the hand (for approximately 24% of patients).

A total of 95 patients/subjects participated in and received PEP005 Gel or vehicle treatment in 2 or more clinical studies (Appendix Table 26). These patients were identified based on birth date, sex, and geographic location of study site, and when available, height and initials. Of these patients, 58 received only PEP005 Gel in the studies in which they participated (Appendix Table 27). Six of the 58 were healthy subjects who participated in studies PEP005-005 (contact sensitization study) and either PEP005-023 (phototoxicity study) or PEP005-024 (photo-sensitization study). Because the dosing regimen in these topical safety studies was not representative of that for field treatment of AK lesions, these 6 subjects were excluded from exposure summaries. The remaining 52 patients had a median cumulative dosing duration of 4 days (range 2–7 days) (Appendix Table 28.1), and the mean – SD PEP005 Gel concentration per dosing day was 0.031% – 0.020% (Appendix Table 28.2). Of these 52 patients, 49 received PEP005 Gel for field treatment of AK lesions after previously receiving PEP005 Gel in an AK or non-AK study (29 received treatment on the face or scalp and 20 on the trunk or extremities). The median cumulative dosing duration for these 49 patients was 4 days (range 2–7 days), and the mean – SD PEP005 Gel concentration per dosing day was 0.029% – 0.016% (Appendix Table 28.2).

Table 13 Summary of Treatment Exposure

Days of Treatment	Controlled Phase 3 Studies						All AK Field Treatment 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)
1	3 (1.1%)	0 (0.0%)	3 (1.3%)	0 (0.0%)	6 (1.2%)	0 (0.0%)	42 (3.6%)	1 (0.2%)
2	2 (0.7%)	0 (0.0%)	222 (98.7%)	232 (100.0%)	224 (44.9%)	232 (46.1%)	648 (55.6%)	268 (42.4%)
3	269 (98.2%)	271 (100.0%)	0 (0.0%)	0 (0.0%)	269 (53.9%)	271 (53.9%)	475 (40.8%)	363 (57.4%)

Note: For the controlled Phase 3 studies, depending on the treatment location, patients were to apply PEP005 Gel or vehicle gel for either 2 days (for trunk and extremities locations) or 3 days (for face and scalp locations).

Source: [a]Appendix Table 2.1.6; [b]Appendix Table 2.2.10; [c]Appendix Table 2.3.2; [d]Appendix Table 2.3.3

Table 14 Summary of Treatment Location

Treatment Location	Controlled Phase 3 Studies						All AK Field Treatment 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)
Arm	0 (0.0%)	0 (0.0%)	141 (62.7%)	149 (64.2%)	141 (28.3%)	149 (29.6%)	403 (34.6%)	190 (30.1%)
Back	0 (0.0%)	0 (0.0%)	4 (1.8%)	3 (1.3%)	4 (0.8%)	3 (0.6%)	7 (0.6%)	3 (0.5%)
Back of Hand	0 (0.0%)	0 (0.0%)	54 (24.0%)	56 (24.1%)	54 (10.8%)	56 (11.1%)	106 (9.1%)	56 (8.9%)
Chest	0 (0.0%)	0 (0.0%)	14 (6.2%)	11 (4.7%)	14 (2.8%)	11 (2.2%)	27 (2.3%)	14 (2.2%)
Face	218 (79.6%)	221 (81.5%)	0 (0.0%)	0 (0.0%)	218 (43.7%)	221 (43.9%)	440 (37.8%)	272 (43.0%)
Face and Scalp*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (1.6%)	0 (0.0%)
Leg	0 (0.0%)	0 (0.0%)	9 (4.0%)	10 (4.3%)	9 (1.8%)	10 (2.0%)	10 (0.9%)	10 (1.6%)
Scalp	56 (20.4%)	50 (18.5%)	0 (0.0%)	0 (0.0%)	56 (11.2%)	50 (9.9%)	145 (12.4%)	82 (13.0%)
Shoulder	0 (0.0%)	0 (0.0%)	3 (1.3%)	3 (1.3%)	3 (0.6%)	3 (0.6%)	8 (0.7%)	5 (0.8%)

*The subjects who received field treatment for AK on both the face and scalp were from Study PEP005-007.
Source: [a]Appendix Table 3.1.6; [b]Appendix Table 3.2.10; [c]Appendix Table 3.3.2; [d]Appendix Table 3.3.3

1.3 DEMOGRAPHIC AND OTHER CHARACTERISTICS OF STUDY POPULATION

Patients in the AK studies who received field application of study medication were predominantly male (79.3% PEP005 Gel vs. 75.2% vehicle) and white (99.7% PEP005 Gel vs. 100.0% vehicle). Patients had a mean age of approximately 66 years (range: 34 to 90 years), with about 20% of patients > 75 years old. The vast majority of patients were located in the United States (82.2% PEP05 Gel vs. 93.4% vehicle), with the remainder located in Australia and New Zealand (17.8% PEP05 Gel vs. 6.6% vehicle). Patients primarily had a Fitzpatrick skin type of I, II, or III (93.6% PEP05 Gel vs. 94.1% vehicle); relatively few patients had a Fitzpatrick skin type of IV or greater (6.4% PEP05 Gel vs. 5.9% vehicle). The demographics of the patients included in the AK studies are summarized in Table 15. The demographics were representative of those observed for the general population of patients diagnosed with AK. Epidemiology surveys have shown that the prevalence of AK increases with age, more men than women are diagnosed with AK, and patients with fair skin, specifically white skin that burns easily are at greater risk for developing AK with sun exposure.[1,2,3] One study noted that AK was rare among the black population (accounting for 0.2% of physician office visits associated with the diagnosis of AK).[3]

At baseline, patients tended to have 4 to 6 AK lesions, consistent with the protocol-specified inclusion criteria of 4 to 8 lesions for the majority of studies involving AK field treatment. The majority of patients (82.5% PEP005 Gel vs. 79.9% vehicle) reported prior cryotherapy treatment. Both imiquimod and 5-fluorouracil had been used to a lesser extent: 15% of PEP005 Gel-treated patients and 16% of placebo-treated patients had prior treatment with imiquimod; and 24.2% of PEP Gel-treated patients and 21.5% of placebo-treated patients reported prior treatment with 5-fluorouracil. Approximately half the patients had a history of skin cancer. Baseline characteristics are summarized in Table 16.

For patients in the controlled Phase 3 studies, gastrointestinal disorders, cardiac disorders, and history of allergy were each reported by, on average, approximately 25–30% of patients; and endocrine disorders were reported by approximately 15% of patients. These data are summarized in Table 17.

Overall, demographics, baseline characteristics, and medical histories were similar between patients treated with PEP005 Gel and vehicle gel.

Table 15 Demographics

	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)
Geographic Location								
United States	253 (92.3%)	251 (92.6%)	209 (92.9%)	219 (94.4%)	462 (92.6%)	470 (93.4%)	958 (82.2%)	590 (93.4%)
Australia/New Zealand	21 (7.7%)	20 (7.4%)	16 (7.1%)	13 (5.6%)	37 (7.4%)	33 (6.6%)	207 (17.8%)	42 (6.6%)
Age (years)								
N	274	271	225	232	499	503	1165	632
Mean (SD)	64.2 (10.7)	64.4 (10.1)	66.4 (10.4)	66.0 (10.2)	65.2 (10.6)	64.9 (10.2)	66.1 (10.3)	65.4 (10.1)
Median	64.0	64.0	67.0	66.0	65.0	65.0	66.0	65.0
Min, Max	34.0, 88.0	40.0, 89.0	43.0, 88.0	34.0, 89.0	34.0, 88.0	34.0, 89.0	34.0, 90.0	34.0, 90.0
Age Category								
< 65 years	142 (51.8%)	141 (52.0%)	94 (41.8%)	100 (43.1%)	236 (47.3%)	241 (47.9%)	509 (43.7%)	293 (46.4%)
≥ 65 and ≤ 75 years	83 (30.3%)	88 (32.5%)	83 (36.9%)	86 (37.1%)	166 (33.3%)	174 (34.6%)	415 (35.6%)	223 (35.3%)
> 75 years	49 (17.9%)	42 (15.5%)	48 (21.3%)	46 (19.8%)	97 (19.4%)	88 (17.5%)	241 (20.7%)	116 (18.4%)
Sex								
Male	231 (84.3%)	233 (86.0%)	144 (64.0%)	141 (60.8%)	375 (75.2%)	374 (74.4%)	924 (79.3%)	475 (75.2%)
Female	43 (15.7%)	38 (14.0%)	81 (36.0%)	91 (39.2%)	124 (24.8%)	129 (25.6%)	241 (20.7%)	157 (24.8%)
Race								
White	274 (100.0%)	271 (100.0%)	225 (100.0%)	232 (100.0%)	499 (100.0%)	503 (100.0%)	1161 (99.7%)	632 (100.0%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.3%)	0 (0.0%)

Source: [a]Appendix Table 3.1.6; [b]Appendix Table 3.2.10; [c]Appendix Table 3.3.2; [d]Appendix Table 3.3.3

Continued

Table 15 Demographics (Cont'd)

	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)
Ethnicity								
Hispanic	1 (0.4%)	3 (1.1%)	3 (1.3%)	2 (0.9%)	4 (0.8%)	5 (1.0%)	9 (0.8%)	5 (0.8%)
Not Hispanic	273 (99.6%)	268 (98.9%)	222 (98.7%)	230 (99.1%)	495 (99.2%)	498 (99.0%)	1150 (98.7%)	627 (99.2%)
Fitzpatrick Skin Type								
I	51 (18.6%)	34 (12.5%)	52 (23.1%)	55 (23.7%)	103 (20.6%)	89 (17.7%)	255 (21.9%)	110 (17.4%)
II	121 (44.2%)	113 (41.7%)	104 (46.2%)	118 (50.9%)	225 (45.1%)	231 (45.9%)	532 (45.7%)	290 (45.9%)
III	83 (30.3%)	111 (41.0%)	52 (23.1%)	48 (20.7%)	135 (27.1%)	159 (31.6%)	303 (26.0%)	195 (30.9%)
IV	19 (6.9%)	13 (4.8%)	15 (6.7%)	11 (4.7%)	34 (6.8%)	24 (4.8%)	71 (6.1%)	36 (5.7%)
V	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
VI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Source: [a]Appendix Table 3.1.6; [b]Appendix Table 3.2.10; [c]Appendix Table 3.3.2; [d]Appendix Table 3.3.3

Table 16 Baseline Characteristics

	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)
Baseline Lesion Count								
1*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	22 (1.9%)	0 (0.0%)
4	48 (17.5%)	57 (21.0%)	65 (28.9%)	63 (27.2%)	113 (22.6%)	120 (23.9%)	246 (21.1%)	148 (23.4%)
5	75 (27.4%)	79 (29.2%)	63 (28.0%)	60 (25.9%)	138 (27.7%)	139 (27.6%)	294 (25.2%)	178 (28.2%)
6	55 (20.1%)	64 (23.6%)	49 (21.8%)	52 (22.4%)	104 (20.8%)	116 (23.1%)	237 (20.3%)	145 (22.9%)
7	52 (19.0%)	37 (13.7%)	23 (10.2%)	29 (12.5%)	75 (15.0%)	66 (13.1%)	165 (14.2%)	84 (13.3%)
8	44 (16.1%)	34 (12.5%)	23 (10.2%)	28 (12.1%)	67 (13.4%)	62 (12.3%)	129 (11.1%)	76 (12.0%)
9**	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	2 (0.4%)	0 (0.0%)	2 (0.2%)	1 (0.2%)
Skin Cancer History								
No	149 (54.4%)	151 (55.7%)	106 (47.1%)	110 (47.4%)	255 (51.1%)	261 (51.9%)	521 (44.7%)	318 (50.3%)
Yes	125 (45.6%)	120 (44.3%)	119 (52.9%)	122 (52.6%)	244 (48.9%)	242 (48.1%)	644 (55.3%)	3147 (49.7%)
Prior Cryotherapy								
No	51 (18.6%)	44 (16.2%)	56 (24.9%)	54 (23.3%)	107 (21.4%)	98 (19.5%)	204 (17.5%)	127 (20.1%)
Yes	223 (81.4%)	227 (83.8%)	169 (75.1%)	178 (76.7%)	392 (78.6%)	405 (80.5%)	961 (82.5%)	505 (79.9%)
Prior Imiquimod								
No	249 (90.9%)	240 (88.6%)	204 (90.7%)	200 (86.2%)	453 (90.8%)	440 (87.5%)	990 (85.0%)	531 (84.0%)
Yes	25 (9.1%)	31 (11.4%)	21 (9.3%)	32 (13.8%)	46 (9.2%)	63 (12.5%)	175 (15.0%)	101 (16.0%)
Prior 5-Fluorouracil								
No	220 (80.3%)	219 (80.8%)	176 (78.2%)	176 (75.9%)	396 (79.4%)	395 (78.5%)	883 (75.8%)	496 (78.5%)
Yes	54 (19.7%)	52 (19.2%)	49 (21.8%)	56 (24.1%)	103 (20.6%)	108 (21.5%)	282 (24.2%)	136 (21.5%)

*All patients with 1 AK lesion at baseline were from Study PEP005-004, for which the inclusion criteria specified that 1 AK lesion be selected for treatment.
**A total of 3 patients (2 treated with PEP005 Gel, 0.05% in Study PEP005-014 and 1 treated with vehicle gel in Study PEP005-006) had 9 AK lesions at baseline, which exceeded the protocol-specified inclusion criteria of 4 to 8 AK lesions.
Source: [a]Appendix Table 3.1.6; [b]Appendix Table 3.2.10; [c]Appendix Table 3.3.2; [d]Appendix Table 3.3.3

Table 17 Medical History for Patients in the Controlled Phase 3 Studies

	Controlled Phase 3 Studies					
	Face and Scalp[a]		Trunk and Extremities[b]		Face/Scalp and Trunk/Extremities Combined[c]	
	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)
History of Gastrointestinal Disorder						
No	208 (75.9%)	195 (72.0%)	162 (72.0%)	154 (66.4%)	370 (74.1%)	349 (69.4%)
Yes	66 (24.1%)	76 (28.0%)	63 (28.0%)	78 (33.6%)	129 (25.9%)	154 (30.6%)
History of Cardiac Disorder						
No	225 (82.1%)	213 (78.6%)	160 (71.1%)	147 (63.4%)	385 (77.2%)	360 (71.6%)
Yes	49 (17.9%)	58 (21.4%)	65 (28.9%)	85 (36.6%)	114 (22.8%)	143 (28.4%)
History of Endocrine Disorder						
No	257 (93.8%)	254 (93.7%)	165 (73.3%)	173 (74.6%)	422 (84.6%)	427 (84.9%)
Yes	17 (6.2%)	17 (6.3%)	60 (26.7%)	59 (25.4%)	77 (15.4%)	76 (15.1%)
History of Allergy						
No	183 (66.8%)	186 (68.6%)	148 (65.8%)	155 (66.8%)	331 (66.3%)	341 (67.8%)
Yes	91 (33.2%)	85 (31.4%)	77 (34.2%)	77 (33.2%)	168 (33.7%)	162 (32.2%)

Source: [a]Appendix Table 3.1.6; [b]Appendix Table 3.2.10; [c]Appendix Table 3.3.2

2 ADVERSE EVENTS

2.1 ANALYSIS OF ADVERSE EVENTS

Across all AK 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 is attributed to a higher rate of application site reactions occurring in patients treated with active rather than vehicle gel. 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). The majority of patients had an AE with maximum severity of mild or moderate intensity; 3.2% of PEP005 Gel-treated patients and 1.6% of vehicle-treated patients had a severe AE. The emergence of an AE resulted in discontinuation of treatment for 3.2% and 0% of PEP005 Gel- and vehicle-treated patients, respectively, and discontinuation from the study for 0.1% and 0.3%, respectively. There was one reported death in a patient who had been treated with PEP005 Gel; the death was attributed to coronary artery atherosclerosis and hypertension, considered unrelated to study medication (Section 2.1.2). Other SAEs were reported for 4.2% of PEP005 Gel-treated patients and 3.6% of vehicle-treated patients; 3 SAEs (all occurring in PEP005 Gel-treated patients and all SCC-type lesions) were considered related to study medication (Section 2.1.3.1). An overview of AEs for the 13 AK field treatment studies is provided in Table 18.

Table 18 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%)

Source: [a]Appendix Table 4.1.6; [b]Appendix Table 4.2.10; [c]Appendix Table 4.3.2; [d]Appendix Table 4.3.3

2.1.1 Common Adverse Events

Treatment-emergent AEs with an incidence of ≥ 1% in any treatment group are summarized in Table 19. Across all field application studies, 42.5% of patients treated with PEP005 Gel and 24.2% of patients treated with vehicle had one or more treatment-emergent AEs. 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. Infections and infestations (including the AEs of application site infection and nasopharyngitis) were reported at marginally higher rates for PEP005 Gel-treated patients than vehicle-treated patients (7.6% for the SOC vs. 5.5% for the SOC, respectively). Infections and infestations are further discussed in Section 2.1.5, along with other AEs within specific SOCs or by selected groupings, including cardiac disorders, eye disorders, and neoplasms.

Table 19 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%)

Source: [a]Appendix Table 5.1.6; [b]Appendix Table 5.2.10; [c]Appendix Table 5.3.2; [d]Appendix Table 5.3.3

Continued

Table 19 Summary of Treatment-emergent Adverse Events with an Incidence of ≥ 1% in Any Group (Cont'd)

	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)
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%)

Source: [a]Appendix Table 5.1.6; [b]Appendix Table 5.2.10; [c]Appendix Table 5.3.2; [d]Appendix Table 5.3.3

2.1.1.1 Treatment-related Adverse Events

Among AK patients who received field application(s) of PEP005 Gel, 26.8% had at least one AE considered by the investigator as related to treatment; in comparison, 3.5% of vehicle-treated patients had an AE considered related to treatment (Table 20). 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%).

Some differences were noted with respect to the incidence of treatment-related AEs between treatment locations. In the controlled Phase 3 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 edema (1.1%) and periorbital edema (2.6%), whereas patients who received PEP005 Gel on the trunk or extremities had no report of these events.

In the 9 other studies in which patients/subjects received study drug (AGN204332-004, PEP005-001, PEP005-002, PEP005-003, PEP005-008, PEP005-009, PEP005-005, PEP005-023, PEP005-024), AEs considered related to study medication were consistent with those reported for patients treated for AK. In the additional 9 studies (lesion-specific and non-AK), application site reactions and skin and subcutaneous disorders were most frequently noted by the investigator as related to PEP005 Gel (Appendix Tables 7.4.1, 7.4.2, 7.4.3, 7.4.4, 7.4.5, 7.4.6, 7.5.1, 7.5.2, and 7.5.3).

Table 20 Summary of Treatment-emergent Adverse Events Considered Related to Study Medication 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	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%)

Source: [a]Appendix Table 7.1.6; [b]Appendix Table 7.2.10; [c]Appendix Table 7.3.2; [d]Appendix Table 7.3.3

2.1.1.2 Adverse Events by Severity

Among AK patients who received field application(s) of study medication, the majority of AEs were mild or moderate: 25.8% of patients treated with PEP005 Gel vs. 17.1% of patients treated with vehicle had a mild AE, and 13.5% of patients treated with PEP005 Gel vs. 5.4% of patients treated with vehicle had a moderate AE (Appendix Table 6.3.3).
Severe AEs were reported by 3.2% of patients treated with PEP005 Gel and 1.6% of patients treated with vehicle (Table 21). 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.
Patients treated with PEP005 Gel had marginally higher incidences of AEs within the SOCs of musculoskeletal and connective tissue disorders, gastrointestinal disorders, infections and infestations, and eye disorders compared with vehicle-treated patients.

- Within the SOC of musculoskeletal and connective tissue disorders, severe AEs for patients treated with PEP005 Gel included muscle spasms (2 patients), back pain, intervertebral disc protrusion, polymyalgia rheumatica, and spinal osteoarthritis (each reported once); and severe AEs for vehicle-treated patients included extremity pain (1 patient) (Appendix Table 6.3.3).
- Severe gastrointestinal disorders for patients treated with PEP005 Gel included diarrhea, vomiting, abdominal distension, toothache, and small intestinal obstruction (1 patient each) (Appendix Table 6.3.3).
- Severe infections and infestations for patients treated with PEP005 Gel included campylobacter infection, cystitis, and epiglottitis (1 patient each) (Appendix Table 6.3.3).
- Severe eye disorders for patients treated with PEP005 Gel included eyelid edema, eye edema, eye pain, and eyelid ptosis (each reported once) (Appendix Table 6.3.3).

Table 21 Summary of Severe Treatment-emergent Adverse Events Reported by ≥ 2 Patients in Either Treatment Arm (All Field 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%)

Source: Appendix Table 6.3.3

Adverse events reported in the other 9 studies in which patients received study medication were predominantly mild or moderate; 13 patients (12 treated with PEP005 Gel and 1 treated with vehicle) in these other studies had a severe AE (Appendix Tables 6.4.1, 6.4.2, 6.4.3, 6.4.4, 6.4.5, 6.4.6, 6.5.1, 6.5.2, and 6.5.3). Severe events included:

- severe application site pain and severe diarrhea (1 patient each, both treated with PEP005 Gel) in study PEP005-001 (Appendix Table 6.4.2)
- severe neoplasm progression (1 patient treated with PEP005 Gel), severe malignant melanoma (reported for 1 patient treated with PEP005 Gel and 1 treated with vehicle), severe erythema, severe skin ulcer, severe application site irritation, and severe animal bite (each reported once for patients treated with PEP005 Gel) in study PEP005-002 (Appendix Table 6.4.3)
- severe skin exfoliation (1 patient treated with PEP005 Gel) in study PEP005-003 (Appendix Table 6.4.4)
- severe gouty arthritis, severe atrial fibrillation, severe upper abdominal pain, severe lymphangitis, severe nausea, severe erosive esophagitis, and severe mesenteric vein

thrombosis, (each reported once in a total of 4 patients, all treated with PEP005 Gel) in study PEP005-009 (Appendix Table 6.4.6)

2.1.1.3 Treatment-related Severe Adverse Events

For the AK population who received field application(s) of study drug, the majority of AEs considered related to study medication were mild. Among patients treated with PEP005 Gel, 17.4% had at least one treatment-related AE that was graded as mild, 7.9% had a related AE graded as moderate, and 1.5% had a severe related AE (Appendix Table 8.3.3). All severe related AEs occurred in patients treated with PEP005 Gel and predominantly involved application site reactions (e.g., application site irritation and pain) (Table 22).

Table 22 Summary of All Severe Treatment-emergent Adverse Events Considered Related to Study Medication (All Field 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%)

Source: Appendix Table 8.3.3

In the 9 additional studies (lesion-specific and non-AK), a total of 5 patients (all treated with PEP005 Gel) had a severe AE considered by the investigator as related to study medication (Appendix Tables 8.4.1, 8.4.2, 8.4.3, 8.4.4, 8.4.5, 8.4.6, 8.5.1, 8.5.2, and 8.5.3). The severe related AEs included:

- severe application site pain (1 patient) in study PEP005-001 (Appendix Table 8.4.2)
- severe erythema, severe skin ulcer, severe application site irritation (each reported once in a total of 2 patients) in study PEP005-002 (Appendix Table 8.4.3)
- severe skin exfoliation (1 patient) in study PEP005-003 (Appendix Table 8.4.4)
- severe lymphangitis (1 patient) in study PEP005-009 (Appendix Table 8.4.6)

2.1.1.4 Analysis of Adverse Events across PEP005 Gel Concentration

For the all AK population, a summary of AEs by dose is included in Appendix Table 5.3.3, and AEs with an incidence of ≥ 1% in the all AK population (N=1165) by PEP005 Gel concentration are summarized in Table 23. The majority of subjects either received a 0.015% or 0.05% concentration of PEP005 Gel, reflecting dosing in the Phase 3 studies for face/scalp and trunk/extremities, respectively. The 6 subjects who received the highest concentration of PEP005 Gel (i.e., > 0.05%) were from study PEP005-004; the actual concentration was 0.075%, which was applied once daily for 2 consecutive days to lesions on the trunk or extremities. This regimen was found to be dose-limiting, and the MTD was established below this concentration (Section 1.1.2).

In general, AEs appeared consistent across the various gel concentrations evaluated; application site disorders were most frequently reported, with no apparent trend with increasing concentration (excluding the highest concentration of 0.075%, described above). Overall, AEs were typically graded as mild or moderate; no more than 4.1% of patients had a severe event, and the frequency of severe events did not increase with increasing gel concentration (Appendix Table 6.3.3). Similarly, the incidence of treatment-related AEs remained fairly constant (ranging from approximately 24% to 31%), with no apparent increase with gel concentration except for concentrations > 0.5% (i.e., 0.075%), for which 5/6 (83.3%) patients had an AE considered related to PEP005 Gel (Appendix Table 7.3.3).

Table 23 Summary of Adverse Events with an Incidence of ≥ 1% for the PEP005 Gel-Treated Patients in the All AK Population by PEP005 Gel Concentration

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%)

Source: Appendix Table 5.3.3

Continued

Table 23 Summary of Adverse Events with an Incidence of ≥ 1% for the PEP005 Gel-Treated Patients in the All AK Population by PEP005 Gel Concentration (Cont'd)

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 Hypertension	2 (1.1%) 2 (1.1%)	2 (0.6%) 2 (0.6%)	3 (2.9%) 2 (2.0%)	7 (1.3%) 6 (1.1%)	0 (0.0%) 0 (0.0%)

Source: Appendix Table 5.3.3

2.1.1.5 Effects of Dosing Regimen and Treatment Location

The effects of concentration are confounded by the dosing regimen (once daily for 2 or 3 consecutive days) and the treatment location. A subgroup analysis of application site pain and application site pruritus (the only 2 AEs in the controlled Phase 3 studies that had a difference in incidence rates between the PEP005 Gel group and the vehicle group of at least 5%) showed that patients treated on the face/scalp with the 0.015% PEP005 Gel for 3 consecutive days had a higher incidence of application site pain than patients treated on the trunk/extremities with the 0.05% PEP005 Gel for 2 consecutive days (Section 2.1.1). There was no relationship observed for application site pruritus.

2.1.1.6 Effect of Multiple Treatments of PEP005 Gel

As was noted in Section 1.2.2, 49 patients received PEP005 Gel for field treatment of AK lesions after previously receiving PEP005 Gel in an AK or non-AK study (29 received treatment on the face or scalp and 20 on the trunk or extremities). Adverse events (Appendix Table 29.1) were examined for these 49 patients. The results showed that patients were not at higher risk for experiencing an AE or application site disorder with multiple treatments of PEP005 Gel (Table 24). Due to the small number of patients who participated in multiple AK field treatment studies and the lack of any observable trends in the incidence of AEs for these patients, the sample sizes for the pooled studies were not adjusted for patients who participated in multiple studies.

Table 24 Adverse Events and Application Site Disorders Reported in Patients Who Received Multiple Treatments of PEP005 Gel: Comparison of Incidence between Earlier and Later Exposure

	Face/Scalp (N=29)		**Trunk/Extremities (N=20)**	
	Later Study		**Later Study**	
Earlier Study	**None Reported**	**At Least 1 Reported**	**None Reported**	**At Least 1 Reported**
Any AE				
None reported	4	8	7	1
At least 1 reported	10	7	3	9
Application Site Disorder				
None reported	15	7	11	1
At least 1 reported	6	1	4	4

Source: Appendix Table 29.2

2.1.1.7 Combined Adverse Events and Local Skin Responses

In order to provide a comprehensive summary of safety following topical administration of PEP005 Gel, treatment-emergent AEs and LSRs observed after the baseline visit from the controlled Phase 3 studies PEP005-014, PEP005-016, PEP005-025, and PEP005-028 were combined in accord with the Guideline on Summary of Product Characteristics (SmPC), dated September 2009.[4] To accomplish this goal, terminology used for LSRs (Table 10) was aligned with that for AEs; as such, each LSR term was mapped to a MedDRA (version 12.0) preferred term as outlined in Table 25.

Table 25 Coding Key Used for Mapping LSR Terms to MedDRA Preferred Terms

LSR Term	MedDRA Preferred Term	Comment
Erythema	Application site erythema	-
Flaking/Scaling	Application site exfoliation	-
Crusting	Application site scab	-
Swelling	Application site swelling	-
Vesiculation/Pustulation	Application site vesicles Application site pustules	LSR Vesicles = Application site vesicle for Grade 1 responses LSR Pustulation = Application site pustules for Grade 2–4 responses
Erosion/Ulceration	Application site erosion Application site ulcer	LSR Erosion = Application site erosion for Grade 1–3 responses LSR Ulceration = Application site ulcer for Grade 4 responses
Pigmentation	Skin hyperpigmentation Skin hypopigmentation	-
Scarring	Application site scar	

Table 26 presents the combined summary of AEs and LSRs with an incidence of ≥ 1%; a complete summary is provided in Appendix Table 5.6. Based on this combined summary, frequently reported events (reported for ≥ 10% of patients) included: application site erythema, application site exfoliation, application site scab, application site swelling, application site pustules, application site erosion, application site vesicles, skin hyperpigmentation, and skin hypopigmentation.
(Note: LSR data are summarized separately in Section 4.3.)

Table 26 Summary of Treatment-emergent Adverse Events and Local Skin Reactions in the Controlled Phase 3 Studies with and Incidence of ≥ 1% in Any Group

System Organ Class **Preferred Term**	**0.015% PEP005 Gel (N=274)**	**0.05% PEP005 Gel (N=225)**	**PEP005 Gel (N=499)**	**Vehicle (N=503)**
Any AE All Systems	273 (99.6%)	224 (99.6%)	497 (99.6%)	396 (78.7%)
General Disorders & Administration Site Conditions	273 (99.6%)	223 (99.1%)	496 (99.4%)	358 (71.2%)
Application Site Exfoliation	266 (97.1%)	222 (98.7%)	488 (97.8%)	331 (65.8%)
Application Site Erythema	272 (99.3%)	220 (97.8%)	492 (98.6%)	286 (56.9%)
Application Site Scab	229 83.6%)	175 (77.8%)	404 (81.0%)	96 (19.1%)
Application Site Swelling	217 (79.2%)	143 (63.6%)	360 (72.1%)	27 (5.4%)
Application Site Erosion	86 (31.4%)	57 (25.3%)	143 (28.7%)	12 (2.4%)
Application Site Vesicles	41 (15.0%)	57 (25.3%)	98 (19.6%)	2 (0.4%)
Application Site Pain	38 (13.9%)	5 (2.2%)	43 (8.6%)	1 (0.2%)
Application Site Pruritus	22 (8.0%)	19 (8.4%)	41 (8.2%)	3 (0.6%)
Application Site Scar	2 (0.7%)	7 (3.1%)	9 (1.8%)	11 (2.2%)
Application Site Irritation	5 (1.8%)	8 (3.6%)	13 (2.6%)	1 (0.2%)
Infections and Infestations	125 (45.6%)	63 (28.0%)	188 (37.7%)	26 (5.2%)
Application Site Pustules	118 (43.1%)	52 (23.1%)	170 (34.1%)	1 (0.2%)
Application Site Infection	7 (2.6%)	0 (0.0%)	7 (1.4%)	1 (0.2%)
Nasopharyngitis	0 (0.0%)	4 (1.8%)	4 (0.8%)	3 (0.6%)
Upper Respiratory Tract Infection	0 (0.0%)	3 (1.3%)	3 (0.6%)	4 (0.8%)
Skin and Subcutaneous Tissue Disorders	72 (26.3%)	52 (23.1%)	124 (24.8%)	94 (18.7%)
Skin Hyperpigmentation	45 (16.4%)	32 (14.2%)	77 (15.4%)	63 (12.5%)
Skin Hypopigmentation	32 (11.7%)	19 (8.4%)	51 (10.2%)	43 (8.5%)
Periorbital Oedema	7 (2.6%)	0 (0.0%)	7 (1.4%)	0 (0.0%)
Injury, Poisoning and Procedural Complications	10 (3.6%)	8 (3.6%)	18 (3.6%)	19 (3.8%)
Back Injury	3 (1.1%)	0 (0.0%)	3 (0.6%)	0 (0.0%)
Contusion	1 (0.4%)	1 (0.4%)	2 (0.4%)	6 (1.2%)

Source: Appendix Table 5.6

Table 26 Summary of Treatment-emergent Adverse Events and Local Skin Reactions in the Controlled Phase 3 Studies with and Incidence of ≥ 1% in Any Group (Cont'd)

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%)

Source: Appendix Table 5.6

2.1.2 Deaths

Across all studies in the development program, only one death (unrelated to study medication) was reported (Appendix Table 13). The patient had received PEP005 Gel, 0.005% in study PEP005-015 (a double-blind, parallel group, dose-ranging, vehicle-controlled study in patients with AK lesions on the face and scalp). A brief narrative for the patient follows (also refer to the CSR for PEP005-015):

- Patient [redacted] enrolled in study PEP005-015 on [redacted] and was randomized to receive PEP005 Gel, 0.005%, applied once daily to AK lesions on the face for 3 consecutive days. The patient was a 58-year-old white male, with a medical history of hypertension, impaired fasting glycemia, insulin resistance, vitamin D deficiency, and right otitis externa. Concomitant medications included irbesartan 300 mg orally, once daily for control of hypertension and over-the-counter supplements (magnesium and glucosamin with chondroitin sulfate) for general health. At screening, the patient had a blood pressure of 132/90 mmHg, a height of 180 cm and a weight of 102 kg. Following randomization, the patient applied the topical study medication from [redacted] to [redacted] 2008 and complied with the per-protocol follow-up visits through the Day 29 visit on [redacted] 2008. Local skin responses observed in the treatment area had peaked at Day 3 and subsequently resolved. The patient had no ongoing AE. On the morning of [redacted] 2008 (4 weeks after study medication treatment), the patient was out for a walk or run and was subsequently found dead on the sidewalk. The cause of death was listed on the death certificate as coronary artery atherosclerosis and hypertension. The investigator judged the event as not related to study medication.

2.1.3 Other Serious Adverse Events

During each study, investigators identified SAEs based on the definition provided in the protocol and summarized in Section 1.1.5.2 of this document. Following review of AEs in the clinical database, the Applicant identified additional events that were reclassified as serious. All additional events were in the SOC of 'neoplasms benign, malignant and unspecified (including cysts and polyps)', and the specific preferred terms were: BCC, SCC, malignant melanoma, basosquamous carcinoma, Bowen's disease, and skin neoplasm (see Table 28 and Table 31).

2.1.3.1 Serious Adverse Events Reported in Studies Evaluating Field Application of Study Medication for Treatment of AK Lesions

Among the patients who received field applications of PEP005 Gel or vehicle for treatment of AK lesions, 4.2% in the PEP005 Gel group and 3.6% in the vehicle group had one or more SAEs; Table 27 presents all SAEs, whether Investigator- or Applicant-identified. 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 SAEs for both treatment groups. All serious events of BCC and approximately half of the reported SCCs were classified as SAEs by the Applicant. Table 28 summarizes the investigator-determined SAEs and the additional Applicant-determined SAEs; this table only shows SAEs within the SOC of 'neoplasms benign, malignant and unspecified (including cysts and polyps)' because this was the only SOC affected by the additional Applicant-determined SAEs.

It should be noted that Table 27 and Table 28 only summarize treatment-emergent SAEs. In study PEP005-015, one patient [redacted] had an SAE of SCC during the screening period (starting on Day −16 and continuing through Day 39). The event was originally reported as an AE by the investigator and graded as mild; the event was subsequently reclassified as an SAE by the Applicant (Appendix Table 14.2). Because this event occurred prior to the patient receiving study medication, it was not included in Table 27 and Table 28.

Table 27 Summary of Serious Adverse Events (Including Both Investigator-determined and Applicant-determined Events)

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)
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%)

Source: [a]Appendix Table 9.1.6; [b]Appendix Table 9.2.10; [c]Appendix Table 9.3.2; [d]Appendix Table 9.3.3

Continued

Table 27 Summary of Serious Adverse Events (Including Both Investigator-determined and Applicant-determined Events) (Cont'd)

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)
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%)

Source: [a]Appendix Table 9.1.6; [b]Appendix Table 9.2.10; [c]Appendix Table 9.3.2; [d]Appendix Table 9.3.3

Table 28 Summary of Investigator-determined and Additional 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%)	--	--

Source: [a]Appendix Table 9.6.1; [b]Appendix Table 9.6.2

The majority of the SAEs were considered unrelated to study medication. Three patients (all treated with PEP005 Gel, 0.05%) had an SAE considered related to treatment (Appendix Tables 14.1 and 14.2). The three related SAEs are described below:

- In Study PEP005-013, Patient [redacted] (treated with daily doses of PEP005 Gel, 0.05% on the forearm on Days 1 and 2) had an SAE of Bowen's disease within the treatment area. The investigator graded the event as mild, considered it possibly related to study drug, and identified it as an SAE. The patient was a 73-year-old Caucasian male with a history of cataracts, asthma, angina, vertebral-basilar ischemia, gastroesophageal reflux disease, arthritis and osteoporosis. The patient had AK since [redacted] on his face, neck, V of chest, trunk and extremities, as well as keratoacanthoma, BCC, SCC, and intra-epidermal carcinoma. On Study Day 57, a punch biopsy of a nodule in the distal part of the treatment area on the right forearm revealed SCC in an intra-epidermal carcinoma. At the time of the event the patient's concomitant medications included salbutamol sulfate, omeprazole, risedronate, diltiazem, perindropil, atorvastatin, ciclesonide, and aspirin. The carcinoma (characterized as Bowen's disease) was adequately excised on Study Day 92, and the patient recovered. (Refer to the CSR for study PEP005-013.)
- In Study PEP005-022, Patient [redacted] (treated with daily doses of PEP005 Gel, 0.05% on Day 1 [25 cm^2 area] and Day 2 [50 cm^2 area]) had an SAE of SCC within the treatment

area. The investigator graded the event as mild, considered it possibly related to study drug, and identified it as an SAE. The patient was a 68-year-old Caucasian male with severe AK at baseline and a history of BCC (9 lesions), SCC (2 lesions), glaucoma, and hypertension. Concomitant medications included oral ramipril and topical latanoprost. A keratotic nodule developed on the right forearm treatment area during follow-up. Macroscopic examination showed a skin ellipse measuring 15 × 7 mm, with a central pale lesion of approximately 5 mm in diameter. An incisional biopsy performed on Day 29 showed well-differentiated SCC, with keratosis, epidermal hyperplasia, and irregular downgrowths of atypical squamous cells with abundant cytoplasm against a background of solar elastosis of the dermis. The lesion was completely excised on Day 39, at which time macroscopic examination showed a skin ellipse of 19 × 6 mm bearing a linear scar of 14 mm. Microscopic examination findings were consistent with a recent surgical site (inflammation, granulation tissue, and foreign body giant cells) and showed no evidence of residual SCC, and the patient recovered. (Refer to the CSR for study PEP005-022.)

- In Study PEP005-020, Patient [redacted] (treated with daily doses of PEP005 Gel, 0.05% on the arm on Days 1 and 2) had an SAE of SCC in the treatment area. The investigator graded the event as moderate in intensity and considered it possibly related to study drug. The Applicant identified the event as an SAE. The patient was a 72-year-old white male with a history of BCC on the face and neck and SCC on the cheek and arm. At the Day 57 visit, an abnormal proliferation was observed; a biopsy was performed the same day, which indicated SCC. On Day 64, the SCC excised, and the event was considered resolved and the patient recovered. (Refer to the CSR for study PEP005-020.)

2.1.3.1.1 Squamous Cell Carcinoma Reported during Studies Evaluating Field Application of Study Medication for Treatment of AK Lesions

As noted in Table 27, an SCC was reported for 11 patients (0.9%) in the PEP005 Gel group and 5 patients (0.8%) in the vehicle gel group during a study that evaluated field application of study medication for treatment of AK lesions. Details regarding these patients, including location of the SCC (i.e., inside vs. outside the treatment area) are provided in Attachment 2. Among these patients, the SCC was determined to be inside or possibly inside the treatment area for 3 patients (0.3%) who received PEP005 Gel and 2 patients (0.3%) who received vehicle gel (Table 29).

Table 29 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%)

Source: [a]Table 27
[b]Attachment 2

2.1.3.2 Serious Adverse Events in Lesion-specific and Non-AK Studies

Across the other 9 studies in which patients/subjects received study drug (i.e., for lesion-specific AK treatment, for assessment of topical safety in healthy volunteers, and for treatment of NMSC), a total of 15 PEP005 Gel-treated patients and 4 vehicle-treated patients had an SAE (Table 30). Patients in the NMSC studies had the highest rate of SAEs (which most frequently involved neoplasms) compared to subjects in the topical safety studies (with no SAEs) or patients in the studies that evaluated lesion-specific AK treatment.

The most frequently reported SAE across the other 9 studies was BCC, which occurred in 8 (0.7%) PEP005 Gel-treated patients and 3 (0.5%) vehicle-treated patients (Table 31). All serious events of BCC were classified as SAEs by the Applicant. A summary of investigator-determined SAEs along with additional Applicant-determined SAEs (which only included events within the SOC of 'neoplasms benign, malignant and unspecified [including cysts and polyps]') is provided in Table 31.

As was noted previously, the summary tables of SAEs only include treatment-emergent SAEs. In study PEP005-001, one patient [redacted] had an SAE of musculoskeletal chest pain during the screening period (starting on Day −24 and ending on Day −23); the event was reported as an SAE by the investigator and graded as moderate (Appendix Table 14.1). Because this event occurred prior to the patient receiving study medication, it was not included in Table 30 and Table 31.

Table 30 Incidence of SAEs in the Lesion-specific and Non-AK Studies (Including Both Investigator-determined and Applicant-determined Events

Population	No. of Patients/Subjects	
	PEP005 Gel (N=609)	Vehicle (n=41)
AK Lesions, Lesion-specific treatment (2 studies) [a, b]	1/57 (1.8%)	0/17 (0.0%)
Topical Safety, Healthy Volunteers (3 studies) [c, d, e]	0/332 (0.0%)	Not applicable*
NMSC (4 studies) [f, g, h, i]	14/220 (6.4%)	4/24 (16.7%)

*All subjects in the 3 topical safety studies received both PEP005 Gel and vehicle gel.

Source: [a]Appendix Table 9.4.1; [b]Appendix Table 9.4.2;
[c]Appendix Table 9.5.1; [d]Appendix Table 9.5.2; [e]Appendix Table 9.5.3;
[f]Appendix Table 9.4.3; [g]Appendix Table 9.4.4; [h]Appendix Table 9.4.5; [i]Appendix Table 9.4.6

Table 31 Summary of Investigator-determined and Additional Applicant-determined SAEs in the Lesion-specific and Non-AK Studies

	Investigator-determined SAEs[a]		Additional Applicant-determined SAEs[b]	
System Organ Class Preferred Term	PEP005 Gel (N=609)	Vehicle (N=41)	PEP005 Gel (N=609)	Vehicle (N=41)
Serious AEs – All Systems	7 (1.1%)	1 (2.4%)	8 (0.7%)	3 (0.5%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts & Polyps)	2 (0.3%)	1 (2.4%)	8 (0.7%)	3 (0.5%)
Basal Cell Carcinoma	--	--	5 (0.4%)	3 (0.5%)
Neoplasm Progression	--	--	2 (0.2%)	0 (0.0%)
Squamous Cell Carcinoma	--	--	1 (0.1%)	0 (0.0%)
Benign Neoplasm of Bladder	1 (0.2%)	0 (0.0%)	--	--
Malignant Melanoma	1 (0.2%)	0 (0.0%)	--	--
Malignant Melanoma Stage IV	0 (0.0%)	1 (2.4%)	--	--
Cardiac Disorders	3 (0.5%)	0 (0.0%)	--	--
Angina Unstable	1 (0.2%)	0 (0.0%)	--	--
Cardiac Failure Chronic	1 (0.2%)	0 (0.0%)	--	--
Myocardial Infarction	1 (0.2%)	0 (0.0%)	--	--
Gastrointestinal Disorders	1 (0.2%)	0 (0.0%)	--	--
Mesenteric Vein Thrombosis	1 (0.2%)	0 (0.0%)	--	--
Injury Poisoning and Procedural Complications	1 (0.2%)	0 (0.0%)	--	--
Animal Bite	1 (0.2%)	0 (0.0%)	--	--

Source: [a]Appendix Table 9.6.3; [b]Appendix Table 9.6.4

While the majority of SAEs in these other 9 studies were considered unrelated to study medication, 2 patients had an SAE considered related (Appendix Table 14.1 and 14.2); these SAEs are briefly described below:

- In study PEP005-002, Patient [redacted] received two doses of PEP005 Gel, 0.01% on Days 1 and 2 for nodular BCC on the face. On Day 57, an abnormal proliferation in the treatment area was noted. The investigator reported a mild, possibly drug-related AE of 'neoplasm progression'. On Day 63 the patient terminated from the study early; on the same day, the lesion was excised. The Applicant identified the event as an SAE.
- In study PEP005-002, Patient [redacted] received two doses of vehicle on Days 1 and 2 to a lesion on the back. On Day 82, the patient had a BCC on the right upper back, which the investigator reported as a moderate, possibly drug-related AE. The BCC was excised on the same day and the event was considered resolved. The Applicant identified the event as an SAE.

2.1.3.3 Serious Adverse Events from Ongoing Studies

Through [redacted] 2011, two SAEs were reported from the ongoing studies (which are outlined in Table 7). Both SAEs were considered not related to study medication and are briefly described below:

- In Study PEP005-033, Patient [redacted] a 77 year-old male, received 3 consecutive daily doses of PEP005 Gel, 0.05% for seborrhoeic keratosis. Approximately 2 weeks after the last dose of study medication, the patient had an SAE of prostate hypertrophy that led to hospitalization for a transurethral resection as treatment for the event. Two days later, the event resolved. The investigator considered the prostate hypertrophy as not related to PEP005 Gel.
- In Study PEP005-036, Patient [redacted] a 64 year-old male, received 3 consecutive daily doses of PEP005 Gel, 0.015% for photo-damaged skin. Approximately 6 weeks after the last dose of study medication, the patient was diagnosed with an SAE of SCC on the lower arm (outside the area that had been treated with PEP005 Gel). The SCC lesion was removed and the event was considered resolved. The investigator considered the event as not related to PEP005 Gel.

2.1.4 Other Significant Adverse Events

2.1.4.1 Adverse Events Leading to Discontinuation

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

or more AEs (Table 32). A total of 37 patients (37 treated with PEP005 Gel and 0 treated with vehicle) discontinued study medication due to one or more AEs (Table 33). Although patients discontinued study medication, most remained in the study for observation of AK lesion disposition and safety assessments through Day 57. Discontinuation of study medication was primarily attributed to application site reactions, notably irritation and pain. AEs that led to discontinuation from the study and those that led to discontinuation of study medications are described in Sections 2.1.4.1.1 and 2.1.4.1.2, respectively.

In the 9 other studies in which patients/subjects received study drug (AGN204332-004, PEP005-001, PEP005-002, PEP005-003, PEP005-008, PEP005-009, PEP005-005, PEP005-023, PEP005-024) one patient/subject discontinued from the study (Appendix Tables 10.4.1, 10.4.2, 10.4.3, 10.4.4, 10.4.5, 10.4.6, 10.5.1, 10.5.2, and 10.5.3) and 4 patients discontinued study medication (Appendix Tables 11.4.1, 11.4.2, 11.4.3, 11.4.4, 11.4.5, 11.4.6, 11.5.1, 11.5.2, and 11.5.3).

2.1.4.1.1 Adverse Events Leading to Discontinuation from the Study

A total of 3 patients (1 treated with PEP005 Gel and 2 treated with vehicle) across the 13 studies that evaluated field treatment of PEP005 Gel for AK lesions had an AE that led to discontinuation from the study (Table 32). The AE that led to study discontinuation in the patient treated with PEP005 Gel was considered related to study; the AEs in the 2 patients treated with vehicle gel were considered unrelated. Information for each of these patients is provided below.

- Patient [redacted] a 61-year-old male, received 3 doses of PEP005 Gel 0.015% in study PEP005-016 (AK lesions face and scalp). Following the first application of study medication (Day 1), the patient experienced severe application site (face) pain that was considered by the investigator as definitely related to study medication. A few days later (on Day 4 of the study), the patient also reported severe eye pain (characterized as both pain and burning) and severe periorbital edema; these events were considered probably related to study medication. All events resolved by Day 11, and the patient was discontinued from the study on Day 29. None of the events were serious.
- Patient [redacted] a 79-year-old male, received 3 doses of vehicle in study PEP005-016 (AK lesions face and scalp). On Day 26 of the study, the patient fell off a ladder and experienced multiple trauma and loss of consciousness; following recovery of these events, the patient developed shortness of breath with lower extremity edema, which led to a diagnosis of acute pulmonary embolism (Day 44). At last contact, the patient was recovering. The events were graded as severe and considered by the investigator as not related to

study medication. The patient was discontinued from the study on Day 29. None of the events were serious.

- Patient [redacted] an 84-year-old male, received vehicle in study PEP005-028 (AK lesions trunk and extremities). During the study, the patient was hospitalized due to a severe MI. The investigator considered the event as not related to study medication. The patient recovered, and was discontinued from the study.

One patient in the 9 additional studies (lesion-specific and non-AK) discontinued from the study due to an AE. Patient [redacted] a 79-year-old female in study PEP005-008, received two doses of PEP005 Gel, 0.05% on Days 1 and 2, respectively. On Day 3, the patient developed diarrhea (moderate in intensity) that resolved on Day 7. The AE was considered by the investigator as possibly related to study medication, and the patient was discontinued from the study (Appendix Tables 10.4.5 and 15).

Table 32 Summary of Adverse Events Leading to Discontinuation from the Study

	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 (N=1165)	Vehicle (N=632)
All Systems	1 (0.4%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.2%)	2 (0.4%)	1 (0.1%)	2 (0.3%)
Eye Disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Eye Pain	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
General Disorders And Administration Site Conditions	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Pain	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Skin And Subcutaneous Tissue Disorders	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Periorbital Oedema	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Cardiac Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Myocardial Infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Injury, Poisoning And Procedural Complications	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
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%)
Nervous System Disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Loss Of Consciousness	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
Respiratory, Thoracic And Mediastinal Disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)
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%)

Source: [a]Appendix Table 10.1.6; [b]Appendix Table 10.2.10; [c]Appendix Table 10.3.2; [d]Appendix Table 10.3.3

2.1.4.1.2 Adverse Events Leading to Discontinuation of Treatment

Across the 13 studies in which AK patients received field application(s) of study medication, 37 (3.2%) patients in the PEP005 Gel groups discontinued study medication due to an AE compared with no patient in the vehicle group (Table 33). The AEs that primarily led to discontinuation of PEP005 Gel dosing were application site irritation and application site pain.

Studies that evaluated PEP005 Gel for treatment of AK lesions on non-head locations (i.e., the trunk and extremities) had an overall lower incidence of discontinuation of study medication due to an AE compared with studies that evaluated PEP005 Gel on head locations (i.e., face and scalp). Of the 561 AK patients who received field treatment on non-head locations, 10 (1.8%) discontinued dosing due to an AE (Appendix Table 11.2.11). In comparison, 27 of the 604 AK patients (4.5%) who received field treatment on head locations discontinued dosing due to an AE (Appendix Table 11.1.7). As the development program progressed and a final concentration and regimen were selected, only 3 of these patients treated on the face and scalp came from the two controlled Phase 3 studies (Studies PEP005-16 and PEP005-25), which assessed a 3-day dosing regimen of PEP005 Gel, 0.015% (Table 33). Ten percent of patients who received higher strengths (i.e., > 0.015%) of PEP005 Gel on head locations discontinued dosing due to an AE, predominantly application site pain and application site irritation (Appendix Table 11.1.7).

In the 9 additional studies (lesion-specific and non-AK) in which patients received study medication, a total of 4 patients discontinued dosing due to:

- application site pain (one patient in study PEP005-001; Appendix Tables 11.4.2),
- erythema and skin exfoliation (both reported for one patient in study PEP005-002; Appendix Table 11.4.3),
- lymphangitis (one patient in study PEP005-009; Appendix Table 11.4.6), and
- pregnancy (one patient in study PEP005-005; Appendix Table 11.5.1).

Table 33 Summary of Adverse Events Leading to Discontinuation of Treatment

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)
All Systems	3 (1.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	37 (3.2%)	0 (0.0%)
General Disorders and Administration Site Conditions	3 (1.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	4 (0.8%)	0 (0.0%)	33 (2.8%)	0 (0.0%)
Application Site Irritation	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	16 (1.4%)	0 (0.0%)
Application Site Pain	2 (0.7%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	16 (1.4%)	0 (0.0%)
Application Site Vesicles	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Application Site Pruritus	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	3 (0.3%)	0 (0.0%)
Application Site Discomfort	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Application Site Swelling	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Application Site Discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Erosion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Erythema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Paraesthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Warmth	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Scab	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Facial 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%)
Eye Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Eyelid Oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Eye Oedema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Eye Swelling	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Eyelid Ptosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

Source: [a]Appendix Table 11.1.6; [b]Appendix Table 11.2.10; [c]Appendix Table 11.3.2; [d]Appendix Table 11.3.3

Continued

Table 33 Summary of Adverse Events Leading to Discontinuation of Treatment (Cont'd)

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)
Infections and Infestations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
Application Site Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Application Site Pustules	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Nasopharyngitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Urinary Tract Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Nervous System 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%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal 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%)
Nasal Congestion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Psychiatric Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Insomnia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

Source: [a]Appendix Table 11.1.6; [b]Appendix Table 11.2.10; [c]Appendix Table 11.3.2; [d]Appendix Table 11.3.3

2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Adverse events within the MedDRA SOCs of infections and infestations, neoplasms, eye disorders, and cardiac disorders were examined; these AEs were selected prospectively by the Applicant because they were considered relevant to the drug, the method of delivery, and drug development considerations. Because skin reactions following PEP005 Gel administration have included pustules, infections were evaluated to assess whether these skin reactions become infectious. Malignancies were examined to assess the incidence of non-melanoma skin cancers inside and adjacent to the AK treatment area. Eye disorders were selected because of the known eye irritation of ingenol mebutate and other related extracts from the plant *E. peplus* [5–12]; topical administration of PEP005 Gel on the face, arm, or back of hand could inadvertently come in contact with the eye and produce local toxicity. Cardiac disorders, including 12-lead ECG data, were examined (despite pre-clinical evidence showing a lack of cardiac toxicity) to ensure that there were no aberrant or adverse cardiac effects in the target patient population, typically ≥ 65 years of age. Each of these types of AEs for the AK population with field application of study medication is discussed in the following sections.

2.1.5.1 Infections and Infestations

Infections and infestations, as defined clinically by the investigators, occurred in 7.6% vs. 5.5% of patients treated with PEP005 Gel vs. vehicle, respectively (Table 34). Among the PEP005 Gel-treated patients, the more commonly reported (≥ 0.5%) infections included nasopharyngitis (1.1%), application site infection (0.9%), upper respiratory tract infection (0.8%), influenza (0.7%), and urinary tract infection (0.5%). In comparison, the more commonly reported infections for vehicle-treated patients were upper respiratory tract infection (1.1%), bronchitis (0.6%), sinusitis (0.6%), gastroenteritis (0.5%), nasopharyngitis (0.5%), and urinary tract infection (0.5%).

In the controlled Phase 3 studies, nasopharyngitis was reported more frequently for patients treated on the trunk or extremities compared to patients treated on the face or scalp. For each treatment location (trunk and extremities versus face and scalp), there were no clinically meaningful differences between PEP005 Gel-treated patients and vehicle-treated patients with respect to nasopharyngitis. For patients treated on trunk or extremity locations, the incidence of nasopharyngitis was 1.8% in PEP005 Gel treatment group and 0.9% for the vehicle group (Appendix Table 5.2.10). In comparison, among patients treated on the face or scalp, no patient treated with PEP005 Gel and 1 patient (0.4%) treated with vehicle reported nasopharyngitis (Appendix Table 5.1.6).

Of the PEP005 Gel-treated patients, 18 (1.5%) had an infection that was considered by the investigator as related to study medication (Appendix Table 7.3.3), which included application site infection (10 [0.9%] patients), application site pustules (3 [0.3%] patients), application site cellulitis (2 [0.2%] patients), folliculitis, impetigo, and influenza (each 1 [0.1%] patient). In comparison, only 1 (0.2%) vehicle-treated patient had a related infection of application site infection.

The majority of infections were graded as either mild or moderate; severe events occurred in 0.3% vs. 0% of patients treated with PEP005 Gel vs. vehicle (Appendix Table 6.3.3). None of the related infections and infestations were graded as severe (Appendix Table 8.3.3). No patient discontinued from the study due to an infection (Appendix Table 10.3.3); however, 4 (0.3%) patients treated with PEP005 Gel discontinued treatment due to application site infection (1 patient), application site pustules (1 patient), nasopharyngitis (1 patient), and urinary tract infection (1 patient) (Appendix Table 11.3.3).

Table 34 Summary of Infections and Infestations

System Organ Class Preferred Term	All Field Application AK Studies PEP005 Gel (N=1165)	 Vehicle (N=632)
Infections and Infestations	88 (7.6%)	35 (5.5%)
Nasopharyngitis	13 (1.1%)	3 (0.5%)
Upper Respiratory Tract Infection	9 (0.8%)	7 (1.1%)
Application Site Infection	10 (0.9%)	1 (0.2%)
Influenza	8 (0.7%)	2 (0.3%)
Urinary Tract Infection	6 (0.5%)	3 (0.5%)
Sinusitis	5 (0.4%)	4 (0.6%)
Bronchitis	2 (0.2%)	4 (0.6%)
Respiratory Tract Infection	4 (0.3%)	0 (0.0%)
Gastroenteritis	2 (0.2%)	3 (0.5%)
Application Site Pustules	3 (0.3%)	0 (0.0%)
Lower Respiratory Tract Infection	3 (0.3%)	0 (0.0%)
Otitis Media	3 (0.3%)	0 (0.0%)
Cellulitis	2 (0.2%)	1 (0.2%)
Gastroenteritis Viral	2 (0.2%)	1 (0.2%)
Pharyngitis	2 (0.2%)	1 (0.2%)
Application Site Cellulitis	2 (0.2%)	0 (0.0%)
Cystitis	2 (0.2%)	0 (0.0%)
Herpes Zoster	2 (0.2%)	0 (0.0%)
Ear Infection	1 (0.1%)	1 (0.2%)
Herpes Simplex	1 (0.1%)	1 (0.2%)
Postoperative Wound Infection	1 (0.1%)	1 (0.2%)
Wound Infection	1 (0.1%)	1 (0.2%)
Abdominal Abscess	1 (0.1%)	0 (0.0%)
Campylobacter Infection	1 (0.1%)	0 (0.0%)
Epiglottitis	1 (0.1%)	0 (0.0%)
Folliculitis	1 (0.1%)	0 (0.0%)
Impetigo	1 (0.1%)	0 (0.0%)
Infection	1 (0.1%)	0 (0.0%)
Intertrigo Candida	1 (0.1%)	0 (0.0%)
Kidney Infection	1 (0.1%)	0 (0.0%)
Otitis Externa	1 (0.1%)	0 (0.0%)
Skin Infection	0 (0.0%)	2 (0.3%)
Staphylococcal Infection	1 (0.1%)	0 (0.0%)
Subcutaneous Abscess	1 (0.1%)	0 (0.0%)
Tinea Cruris	1 (0.1%)	0 (0.0%)
Tooth Abscess	1 (0.1%)	0 (0.0%)
Tooth Infection	1 (0.1%)	0 (0.0%)
Vaginitis Bacterial	1 (0.1%)	0 (0.0%)
Carbuncle	0 (0.0%)	1 (0.2%)
Diverticulitis	0 (0.0%)	1 (0.2%)
Escherichia Infection	0 (0.0%)	1 (0.2%)
Localised Infection	0 (0.0%)	1 (0.2%)
Pneumonia Primary Atypical	0 (0.0%)	1 (0.2%)
Prostate Infection	0 (0.0%)	1 (0.2%)

Source: Appendix Table 5.3.3

2.1.5.2 Neoplasms

Neoplasms were reported for a similar proportion of patients within the treatment groups, 3.0% vs. 2.7% for PEP005 Gel vs. vehicle, respectively (Table 35). Basal cell carcinoma and SCC were the more frequently reported types of neoplasms and occurred with similar frequency between groups (BCC: 1.5% vs. 1.1% for PEP005 Gel vs. vehicle; SCC: 0.9% vs. 0.8% for PEP005 Gel vs. vehicle).

The majority of neoplasms were graded as mild or moderate (Appendix Table 6.3.3). A severe neoplasm was reported for 1 patient treated with PEP005 Gel (a malignant melanoma in study PEP005-025; Appendix Table 6.1.5) and 2 patients treated with vehicle (breast cancer and lymphoma, both in study PEP005-014; Appendix Table 6.2.4).

Four (0.3%) patients in the PEP005 Gel group and no patient in the vehicle group had a total of 5 neoplasms considered related to study medication (Appendix Table 7.3.3); of the 5 neoplasms, 3 (2 SCC and 1 Bowen's disease) represented a non-melanoma skin cancer and 2 of the neoplasms (both keratoacanthoma) were benign. Information regarding the treatment-related neoplasms is provided below:

- Patient [redacted] in Study PEP005-013 had a keratoacanthoma and a Bowen's disease lesion in the treatment area following dosing with PEP005 Gel, 0.05%, observed on Days 14 and 57, respectively (CSR for PEP005-013). The Bowen's disease was reported by the investigator as an SAE and is discussed in Section 2.1.3.
- Patient [redacted] in Study PEP005-013 had a keratoacanthoma develop in the treatment area > 23 days (but < 57 days) following dosing with PEP005 Gel, 0.05% (CSR for PEP005-013).
- Patient [redacted] in Study PEP005-020 had SCC develop in the treatment area 44 days following dosing with PEP005 Gel, 0.05% (CSR for PEP005-020). The event was identified by the Applicant as an SAE and is discussed in Section 2.1.3.
- Patient [redacted] in Study PEP005-022 had SCC develop in the treatment area within 29 days following dosing with PEP005 Gel, 0.05% (CSR for PEP005-022). This event was reported by the investigator as an SAE and is discussed in Section 2.1.3.

No neoplasm led to discontinuation of study medication (Appendix Table 11.3.3) or discontinuation from the study (Appendix Table 10.3.3).

Table 35 Summary of Neoplasms

System Organ Class Preferred Term	All Field Application AK Studies PEP005 Gel (N=1165)	 Vehicle (N=632)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts & Polyps)	35 (3.0%)	17 (2.7%)
Basal Cell Carcinoma	17 (1.5%)	7 (1.1%)
Squamous Cell Carcinoma	11 (0.9%)	5 (0.8%)
Seborrhoeic Keratosis	3 (0.3%)	1 (0.2%)
Keratoacanthoma	3 (0.3%)	0 (0.0%)
Bowen's Disease	2 (0.2%)	0 (0.0%)
Malignant Melanoma	1 (0.1%)	1 (0.2%)
Acanthoma	1 (0.1%)	0 (0.0%)
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%)
Skin Papilloma	0 (0.0%)	1 (0.2%)

Source: Appendix Table 5.3.3

2.1.5.3 Eye Disorders

Eye disorders occurred more frequently in the PEP005 Gel treatment groups than the vehicle groups (Table 36). Eyelid edema, along with periorbital edema (in the SOC of skin and subcutaneous disorders), were the most frequently reported eye-associated events. The majority of eye disorders and periorbital edema were graded as mild or moderate (Appendix Table 6.3.3) and were generally considered related to study treatment (Appendix Table 7.3.3). There were 5 severe related events (all in patients treated with PEP005 Gel); these severe related AEs included periorbital edema, eyelid edema, eye edema, eye pain, and eyelid ptosis (Appendix Table 8.3.3). All severe eye disorders resolved without sequelae.

Only one subject had eye-associated AEs (severe eye pain and severe periorbital edema) that resulted from inadvertent eye exposure following application of PEP005 Gel to the face; both events were considered related to study medication and the patient discontinued from the study (Appendix Table 10.3.3 and Section 2.1.4.1.1).

Table 36 Summary of Eye Disorders

System Organ Class Preferred Term	All Field Application AK Studies PEP005 Gel (N=1165)	 Vehicle (N=632)
Eye Disorders	27 (2.3%)	2 (0.3%)
Eyelid Oedema	9 (0.8%)	0 (0.0%)
Eye Swelling	4 (0.3%)	0 (0.0%)
Conjunctivitis	2 (0.2%)	0 (0.0%)
Eye Oedema	2 (0.2%)	0 (0.0%)
Eye Pain	2 (0.2%)	0 (0.0%)
Lacrimation Increased	2 (0.2%)	0 (0.0%)
Orbital Oedema	2 (0.2%)	0 (0.0%)
Blepharitis	1 (0.1%)	0 (0.0%)
Dry Eye	1 (0.1%)	0 (0.0%)
Eye Haemorrhage	1 (0.1%)	0 (0.0%)
Eyelid Ptosis	1 (0.1%)	0 (0.0%)
Scleral Discolouration	1 (0.1%)	0 (0.0%)
Vision Blurred	1 (0.1%)	0 (0.0%)
Eye Irritation	0 (0.0%)	1 (0.2%)
Visual Impairment	0 (0.0%)	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	56 (4.8%)	14 (2.2%)
Periorbital Oedema	12 (1.0%)	0 (0.0%)

Source: Appendix Table 5.3.3

2.1.5.4 Cardiac Disorders

Cardiac disorders occurred with similar frequency between patients treated with PEP005 Gel (1.7%) and patients treated with vehicle (2.8%). The most frequently reported cardiac disorders were angina pectoris, first degree atrioventricular (AV) block, myocardial infarction (MI), and ventricular extrasystoles; the incidence of each of these events was similar between treatment groups (Table 37). The maximum severity of cardiac disorders was generally mild or moderate; severe cardiac events were experienced by 0.3% of PEP005 Gel-treated patients and 0.6% of vehicle-treated patients (Appendix Table 6.3.3). Cardiac disorders considered by the investigator as related to study treatment were experienced by 0.2% of PEP005 Gel-treated patients and included ventricular extrasystoles and palpitations. In comparison, 0.3% of vehicle-treated patients had a study-drug related cardiac disorder, which included ventricular extrasystoles, left bundle branch block (LBBB), and extrasystoles (Appendix Table 7.3.3). No patient had a severe cardiac event considered related to study medication (Appendix Table 8.3.3). One patient, treated with vehicle, discontinued from the study due to a severe, unrelated MI (see Section 2.1.4.1.1). Electrocardiogram abnormalities that were reported as AEs are discussed in Section 4.2.2. An ECG safety analysis of the data from the

controlled Phase 3 studies showed that PEP005 Gel had no effect on the ECG and cardiac repolarization (see Section 4.2.3 and Combined Cardiac ECG Safety Report).

Table 37 Summary of Cardiac Disorders

System Organ Class Preferred Term	All Field Application AK Studies PEP005 Gel (N=1165)	 Vehicle (N=632)
Cardiac Disorders	20 (1.7%)	18 (2.8%)
Angina Pectoris	4 (0.3%)	2 (0.3%)
Myocardial Infarction	3 (0.3%)	4 (0.6%)
Atrioventricular Block First Degree	3 (0.3%)	2 (0.3%)
Ventricular Extrasystoles	3 (0.3%)	2 (0.3%)
Atrial Fibrillation	2 (0.2%)	2 (0.3%)
Coronary Artery Disease	1 (0.1%)	1 (0.2%)
Extrasystoles	1 (0.1%)	1 (0.2%)
Supraventricular Extrasystoles	1 (0.1%)	1 (0.2%)
Aortic Valve Disease	1 (0.1%)	0 (0.0%)
Atrial Flutter	1 (0.1%)	0 (0.0%)
Bundle Branch Block Right	0 (0.0%)	2 (0.3%)
Cardiac Ventricular Disorder	1 (0.1%)	0 (0.0%)
Palpitations	1 (0.1%)	0 (0.0%)
Acute Coronary Syndrome	0 (0.0%)	1 (0.2%)
Bundle Branch Block Left	0 (0.0%)	1 (0.2%)
Sinus Arrhythmia	0 (0.0%)	1 (0.2%)
Tachycardia	0 (0.0%)	1 (0.2%)
Ventricular Pre-Excitation	0 (0.0%)	1 (0.2%)

Source: Appendix Table 5.3.3

2.1.6 Long-term Adverse Effects

Three prospective, longitudinal, observational studies (designated PEP005-030, PEP005-031, and PEP005-032) were designed to evaluate the recurrence of AK lesions and safety within the selected treatment area for a 12-month follow-up period in patients who achieved complete clearance of AK lesions in studies PEP005-016, PEP005-020, PEP005-025, and PEP005-028. During these 3 observational studies, no patient received PEP005 Gel. The safety findings from these 3 studies are summarized in the following section, and the efficacy findings (i.e., recurrence of AK) are provided in the summary of clinical efficacy (Module 2.7.3).

2.1.6.1 Study Patients

Prior to entering the long-term follow-up studies, all patients had received PEP005 Gel to a 25 cm^2 treatment area on the face or scalp (studies PEP005-016 and PEP005-025), or the

trunk or extremities (studies PEP005-020 and PEP005-028). Originally the long-term follow-up studies were designed to include patients who had completed the Day 57 visit of the study in which they had received PEP005 Gel or vehicle; this criterion was subsequently amended to limit eligibility to patients who had complete clearance of AK lesions at the Day 57 visit. Patients who no longer met the eligibility criterion were withdrawn from the study (which impacted studies PEP005-030 and PEP005-031, but not PEP005-032, as patients had not yet enrolled in that study). While the focus of the long-term studies is on the patients who achieved complete clearance of AK lesions at Day 57, any known safety information from subjects who had originally enrolled in PEP005-030 and PEP005-031 but were subsequently withdrawn because of the change in eligibility, is described in Section 2.1.6.2.

Across the 3 studies, a total of 198 patients (184 treated with PEP005 Gel and 14 treated with vehicle, all of whom had achieved complete clearance of AK lesions in the prior treatment study) enrolled in the long-term follow-up studies. Patients had a mean age that ranged from approximately 61 to 68 years, and the majority were male and white, with Fitzpatrick skin types of I, II, or III. A brief summary of demographics and baseline characteristics for patients followed in studies PEP005-030, PEP005-031, and PEP005-032 is provided in Table 38.

Of the 198 patients enrolled across the 3 studies, 14 patients discontinued early (9 from study PEP005-030, 4 from study PEP005-031, and 1 from study PEP005-032). Reasons for discontinuation from the study included the following: 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) (CSR for PEP005-030 Table 14.1.1.1; CSR for PEP005-031 Table 14.1.1.1; CSR for PEP005-032 Table 14.1.1.1).

Table 38 Summary of Demographics and Baseline Characteristics of Patients in PEP005-030, PEP005-031, and PEP005-032

	PEP005-030[a]		PEP005-031[b]	PEP005-032[c]	
	Treatment Group in PEP005-016 / PEP005-025		Treatment Group in PEP005-020*	Treatment Group in PEP005-028	
	0.015% PEP005 Gel (N=108)	Vehicle (N=9)	0.05% PEP005 Gel (N=38)	0.05% PEP005 Gel (N=38)	Vehicle (N=5)
Age (years), mean (SD)	63.0 (9.9)	61.4 (10.5)	62.3 (10.6)	64.6 (8.6)	67.6 (10.6)
Male, n (%)	83 (76.9)	8 (88.9)	25 (65.8)	22 (57.9)	3 (60.0)
White, n (%)	108 (100.0)	9 (100.0)	37 (97.4)	38 (100.0)	5 (100.0)
Fitzpatrick Skin Type, n (%)					
I	27 (25.0)	1 (11.1)	6 (15.8)	10 (26.3)	0
II	43 (39.8)	5 (55.6)	17 (44.7)	12 (31.6)	3 (60.0)
III	31 (28.7)	3 (33.3)	12 (31.6)	15 (39.5)	2 (40.0)
IV	7 (6.5)	0	3 (7.9)	1 (2.6)	0
V	0	0	0	0	0
VI	0	0	0	0	0
Location of Treatment, n (%)					
Face / Scalp	108 (100.0)	9 (100.0)	NA	NA	NA
Trunk / Extremities	NA	NA	38 (100.0)	38 (100.0)	5 (100.0)

Note: The patients summarized in this table had complete clearance of AK lesions at Day 57 of the study in which they received treatment, PEP005 Gel or vehicle.
*All patients in PEP005-020 received 0.05% PEP005 Gel (none received vehicle).
NA = not applicable
Source: [a]CSR for PEP005-030 Table 14.1.3.1
[b]CSR for PEP005-031 Table 14.1.3.1
[c]CSR for PEP005-032 Table 14.1.3

2.1.6.2 Safety through 12 Months of Follow-up

During follow-up, AEs within the selected treatment area were assessed. Through 12 months of observation, a total of 3 patients who satisfied the amended eligibility criterion regarding complete clearance of AK lesions had an AE in the selected treatment area, as follows:

- Patient [redacted] in study PEP005-030 had received PEP005 Gel, 0.015% on the face in study PEP005-025. On Day 271 of the follow-up study, the patient had an AE of mild sunburn that was considered by the investigator as not related to study drug. The patient used topical aloe vera to treat the AE, and 7 days after onset, the event resolved (CSR for PEP005-030, Section 12.2).

- Patient [redacted] in study PEP005-031 had received PEP005 Gel, 0.05% on the back of the hand in study PEP005-020. On Day 265 of the follow-up study, the patient had an AE of haematoma that was graded as moderate and considered by the investigator as not related to study drug. The event resolved 7 days after onset without intervention (CSR for PEP005-031, Section 12.2).
- Patient [redacted] in study PEP005-032 had received PEP005 Gel, 0.05% on the arm in study PEP005-028. On Day 251 of the follow-up study, the patient had a mild rash on both forearms. The patient received one dose of oral ivermectin as well as topical diflorasone diacetate (twice daily for 4 days). The rash resolved 13 days after onset. The AE was considered by the investigator as not related to study drug (CSR for PEP005-032, Section 12.2).

Among the patients withdrawn from the long-term follow-up studies because of the change in eligibility criteria, only one patient had a reported AE. Patient [redacted] had a BCC, reported on Day 100 of study PEP005-031. The patient had received PEP005 Gel, 0.05%, on the back of the hand in study PEP005-020. The BCC was apparent within the treatment area, was graded as moderate, and considered by the investigator as not related to study medication. No action was taken, and at the time of last contact, there was little or no change in the BCC. This event is listed in the CSR for PEP005-031, Listing 16.2.7.1.2 (note, following review of AEs in the clinical database, the Applicant identified the BCC as an SAE).

2.2 NARRATIVES

Narratives for the investigator-identified SAEs (including the death narrative) are located in the individual clinical study reports. Narratives for the Applicant-determined SAEs are located in Attachment 3.

3 CLINICAL LABORATORY EVALUATIONS

The vast majority of clinical laboratory parameters (hematology and serum chemistry) were within normal limits at the time points measured in the studies (Appendix Table 18.3.3). For purposes of this safety summary, normal is defined as laboratory values ranging from half the lower limit of normal to 2-times the upper limit of normal. 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 (see Appendix Tables 18.1.1 through 18.3.3). There were no meaningful shifts or trends in any of the clinical laboratory parameters.

While laboratory abnormalities were reported as AEs throughout the development program, very few were considered related to study medication. Among the AK patients with field applications of study medication, 3/1165 (0.3%) treated with PEP005 Gel and 2/631 (0.3%) treated with vehicle had a laboratory abnormality reported as a treatment-related AE. These AEs included isolated reports of increased blood creatinine phosphokinase (CPK), abnormal lymphocyte morphology, and protein present in the urine for patients treated with PEP005 Gel, and abnormal liver function test and abnormal lymphocyte morphology for the vehicle-treated patients (Appendix Table 7.3.3).

In the other 9 additional studies (lesion-specific and non-AK) in which patients/subjects received study medication, 3 patients (all received PEP005 Gel) had one or more laboratory abnormalities reported as treatment-related AEs. The events in these patients included: increased blood CPK (1 patient in study PEP005-002; Appendix Table 7.4.3), red blood cells and white blood cells present in urine (1 patient in study PEP005-002; Appendix Table 7.4.3), and increased alanine aminotransferase and increased alkaline phosphatase (1 patient in study PEP005-003; Appendix Table 7.4.4).

Overall, the data show that there was no trend in clinically important laboratory abnormalities.

4 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1 VITAL SIGNS

Vital signs collected throughout the development program included systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Overall, throughout the development program, the vast majority of patients had vital sign values that were normal at baseline and remained normal during the study period (Table 39). For AK patients who received field application of study medication, shifts from normal values to those considered clinically significant occurred in 9–15% of patients, which was generally similar between patients treated with PEP005 Gel and those treated with vehicle. The criteria for a vital sign value to be considered clinically significant were as follows:

- SBP: ≥ 180 mmHg or ≤ 90 mmHg or an increase or decrease of 20 mmHg
- DBP: ≥ 105 mmHg or ≤ 50 mmHg or an increase or decrease of 15 mmHg
- HR: ≥ 120 bpm or ≤ 50 bpm or an increase or decrease of 15 bpm

Hypertension was reported as an AE for 12 (1.0%) of the AK patients who received field applications of PEP005 Gel and for 3 (0.5%) of the AK patients who received vehicle (an additional vehicle-treated patient had an AE of increased blood pressure) (Appendix Table 5.3.3). Hypertension in 2 of the PEP005 Gel-treated patients was considered by the investigator as related to study medication (Appendix Table 7.3.3); the increased blood pressure in the vehicle-treated patient was also considered related to study medication. One patient treated with PEP005 Gel in study PEP005-022 had moderate hypertension that was reported as an SAE (Appendix Table 14.1); this event was considered not related to study medication.

Vital signs in the other 9 studies (lesion-specific and non-AK) showed similar results, with the majority of values remaining normal throughout the studies (Appendix Tables 19.4.1, 19.4.2, 19.4.3, 19.4.4, 19.4.5, 19.4.6, and 19.5.1). While hypertension was reported infrequently in these studies, none of the events was considered related to study medication (Appendix Tables 7.4.1, 7.4.2, 7.4.3, 7.4.4, 7.4.5, 7.4.6, 7.5.1, 7.5.2, and 7.5.3).

No clinically meaningful differences were observed between the treatment groups with respect to vital signs.

Table 39 Clinically Significant Shifts in Vital Signs

Shifts from Baseline → Final Visit	Controlled Phase 3 Studies				Combined Studies for Field Treatment of AK Lesions[c]	
	Face and Scalp[a]		Trunk and Extremities[b]			
	PEP005 Gel (N=274)	Vehicle (N=271)	PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=1165)	Vehicle (N=632)
SBP						
Normal → Normal	235 (85.8%)	235 (86.7%)	192 (85.3%)	200 (86.2%)	983 (84.4%)	546 (86.4%)
Significant → Significant	0 (0.0%)	2 (0.7%)	1 (0.4%)	1 (0.4%)	7 (0.6%)	3 (0.5%)
Normal → Significant	39 (14.2%)	34 (12.5%)	32 (14.2%)	30 (12.9%)	172 (14.8%)	82 (13.0%)
Significant → Normal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (0.3%)	1 (0.2%)
DBP						
Normal → Normal	242 (88.3%)	250 (92.3%)	197 (87.6%)	208 (89.7%)	1023 (87.8%)	571 (90.3%)
Significant → Significant	1 (0.4%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.3%)	3 (0.5%)
Normal → Significant	31 (11.3%)	18 (6.6%)	28 (12.4%)	24 (10.3%)	137 (11.8%)	57 (9.0%)
Significant → Normal	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.2%)
HR						
Normal → Normal	227 (82.8%)	233 (86.0%)	196 (87.1%)	210 (90.5%)	1004 (86.2%)	540 (85.4%)
Significant → Significant	5 (1.8%)	3 (1.1%)	0 (0.0%)	3 (1.3%)	13 (1.1%)	10 (1.6%)
Normal → Significant	38 (13.9%)	33 (12.2%)	27 (12.0%)	18 (7.8%)	132 (11.3%)	76 (12.0%)
Significant → Normal	4 (1.5%)	2 (0.7%)	2 (0.9%)	1 (0.4%)	16 (1.4%)	6 (0.9%)

Source: [a]Appendix Table 19.1.6; [b]Appendix Table 19.2.10; [c]Appendix Table 19.3.3

4.2 ELECTROCARDIOGRAM RESULTS

ECGs were performed in studies PEP005-014, PEP005-028, PEP005-016, and PEP005-025. In each of these studies, two 12-lead surface ECGs were collected at screening (up to 14 days prior to the first dose of study drug) and the day after the last dose of study drug (Day 3 for studies PEP005-014 and PEP005-028, and Day 4 for studies PEP005-016 and PEP005-025). ECGs were transferred electronically to a central ECG laboratory where a cardiologist reviewed and interpreted all ECG tracings. The interpretation was then provided to the site electronically including notification of any ECG abnormalities. ECG intervals and ECG abnormalities that were reported as AEs are summarized in Sections 4.2.1, and 4.2.2, respectively. In addition, results of cardiac safety testing are summarized in Section 4.2.3.

4.2.1 ECG Intervals

ECG intervals were determined from the tracings collected at the screening visit (which provided baseline values) and the Day 3 or 4 visits. ECG intervals included PR, QRS, QT and QTc, using both the Bazett [QTcB] and Fridericia [QTcF] correction formulae. Mean values for each of these parameters at baseline and Day 3/4, as well as change from baseline

values are summarized in Table 40. For each parameter in all 4 studies, mean values at pre- and postdose, and mean changes from baseline were similar between patients treated with PEP005 Gel and those treated with vehicle. All postdose ECG intervals showed minimal changes from predose values; and the direction and magnitude of the changes were generally similar between treatment groups with no apparent trend.

The PR interval showed mean changes ranging from −2.1 to −1.0 msec for patients treated with PEP005 Gel compared with −2.7 to +0.4 msec for patients treated with vehicle. QRS mean changes from baseline ranged from −0.8 to +0.2 msec for patients treated with PEP005 Gel compared to −0.6 to +0.3 msec for patients treated with vehicle. Following treatment, all patients showed a slight mean decrease from baseline in QT values, ranging from −12.2 to −5.7 msec and −9.7 to −7.1 msec for patients treated with PEP005 Gel and vehicle, respectively.

Mean changes in QTc values ranged from −3.7 to +3.8 msec for QTcB and −6.5 to +0.1 msec for QTcF in patients treated with PEP005 Gel compared with −4.7 to +2.0 msec for QTcB and −5.5 to −1.4 msec for QTcF in patients treated with vehicle. Changes in QTcB and QTcF values from baseline to Day 3/4 were categorized as < 30 msec for the vast majority of patients; and no patient dosed with PEP005 Gel and 1 patient dosed with vehicle (in study PEP005-025) had a change of > 60 msec (Appendix Tables 20.1.1, 20.1.2, 20.2.1, and 20.2.2). Absolute QTcB and QTcF values at both baseline and Day 3/4 were ≤ 450 msec for most of the patients across the four studies (PEP005-014, PEP005-028, PEP005-016, and PEP005-025) (Appendix Tables 20.1.1, 20.1.2, 20.2.1, and 20.2.2). Only one patient had an absolute QTc value that was > 500 msec (Appendix Tables 21.2.1 and 21.2.2). Patient [redacted] in study PEP005-028 (randomized to the vehicle group), had baseline QTc values of 531 and 507 msec (QTcB and QTcF, respectively). On Day 3, the QTc values were marginally lower at 505 and 490 msec (QTcB and QTcF, respectively). The cardiologist's review of this patient's ECG indicated that the patient had QTc interval prolongation and LBBB present at baseline that continued through Day 3 (refer to the CSR for PEP005-028).

With respect to ECG intervals, there were no clinically meaningful differences observed between treatment groups.

Table 40 Summary of Selected ECG Intervals from Studies PEP005-016, PEP005-025, PEP005-014, and PEP005-028

ECG Interval Mean – SD	Study PEP005-016[a] (Face and Scalp)		Study PEP005-025[b] (Face and Scalp)		Study PEP004-014[c] (Trunk and Extremities)		Study PEP004-028[d] (Trunk and Extremities)	
	0.015% PEP005 Gel (N=132)	Vehicle (N=135)	0.015% PEP005 Gel (N=142)	Vehicle (N=136)	0.05% PEP005 Gel (N=125)	Vehicle (N=129)	0.05% PEP005 Gel (N=100)	Vehicle (N=103)
PR (msec)								
Baseline	163.8 – 37.7	167.9 – 34.9	169.6 – 33.9	171.4 – 34.2	173.0 – 27.6	168.8 – 27.9	164.7 – 41.0	158.3 – 47.9
Day 3/4	163.1 – 37.6	165.5 – 41.0	168.4 – 32.2	170.8 – 31.3	173.3 – 25.0	166.4 – 27.3	162.1 – 36.3	158.4 – 46.0
Change from Baseline	−1.0 – 11.8	−2.7 – 21.0	−1.5 – 11.9	−0.5 – 14.0	−1.9 – 12.3	−1.5 – 11.5	−2.1 – 19.8	0.4 – 12.6
QRS (msec)								
Baseline	98.6 – 12.8	98.0 – 11.9	98.5 – 12.3	98.8 – 11.7	89.2 – 8.9	86.9 – 9.1	98.6 – 14.7	100.3 – 16.0
Day 3/4	98.9 – 13.9	97.3 – 12.4	97.8 – 12.6	99.0 – 11.8	88.8 – 9.0	86.9 – 10.2	98.3 – 14.0	100.0 – 17.5
Change from Baseline	0.2 – 6.2	−0.6 – 7.4	−0.6 – 6.3	0.3 – 6.0	−0.8 – 6.6	0.2 – 8.5	−0.5 – 6.3	−0.5 – 7.1
QT (msec)								
Baseline	407.5 – 30.7	409.3 – 28.6	413.5 – 31.0	411.9 – 30.1	403.8 – 27.2	400.8 – 29.2	422.2 – 29.4	410.3 – 34.4
Day 3/4	401.3 – 30.3	402.1 – 30.6	405.6 – 28.8	401.9 – 30.4	397.2 – 26.7	394.4 – 25.8	409.9 – 27.8	402.6 – 34.7
Change from Baseline	−5.7 – 20.7	−7.9 – 22.9	−7.9 – 24.1	−9.7 – 21.4	−7.1 – 19.8	−7.1 – 21.0	−12.2 – 21.0	−7.3 – 18.2
QTcB (msec)								
Baseline	422.4 – 20.9	417.9 – 19.7	420.2 – 20.0	416.9 – 19.1	412.7 – 21.3	415.0 – 22.8	426.5 – 20.9	426.9 – 26.6
Day 3/4	420.6 – 20.7	420.5 – 21.0	420.2 – 21.1	418.0 – 20.3	415.5 – 19.1	413.9 – 24.0	423.3 – 20.2	422.2 – 25.0
Change from Baseline	−1.4 – 18.5	2.0 – 17.3	0.2 – 17.5	1.0 – 19.1	3.8 – 16.6	−1.9 – 18.4	−3.7 – 18.2	−4.7 – 17.0
QTcF (msec)								
Baseline	416.8 – 17.6	414.6 – 18.0	417.5 – 18.7	414.8 – 16.9	409.4 – 17.9	409.9 – 20.5	424.5 – 17.1	420.8 – 23.7
Day 3/4	413.5 – 18.0	413.8 – 19.2	414.9 – 18.7	412.0 – 17.6	409.0 – 16.7	407.1 – 19.9	418.3 – 16.7	415.1 – 23.3
Change from Baseline	−3.0 – 16.7	−1.4 – 14.0	−2.6 – 15.5	−2.8 – 15.9	0.1 – 14.2	−3.6 – 16.1	−6.5 – 14.1	−5.5 – 13.9

Source: [a]Appendix Table 20.1.1; [b]Appendix Table 20.1.2; [c]Appendix Table 20.2.1; [d]Appendix Table 20.2.2

4.2.2 ECG Abnormalities Reported as Adverse Events

Across the 4 studies in which ECGs were obtained (PEP005-014, PEP005-028, PEP005-016, and PEP005-025), a total of 29 patients (13 treated with PEP005 Gel and 16 treated with vehicle) had an ECG abnormality that was reported as an AE (Table 41).

For patients treated with the 0.015% PEP005 Gel in studies PEP005-016, and PEP005-025, AEs identified through ECG included QT prolongation (3 patients) and ventricular extrasystoles (1 patient). For vehicle-treated patients in these two studies, the AEs included QT prolongation (3 patients), first degree AV block (2 patients), and atrial fibrillation, LBBB, right bundle branch block (RBBB), ECG ST-T changes, sinus arrhythmia, supraventricular extrasystoles, tachycardia, and ventricular extrasystoles (1 patient each).

In studies PEP005-014 and PEP005-028, where a higher dose of PEP005 Gel (0.05%) was evaluated, all AEs that were derived from ECG abnormalities occurred in study PEP005-014; no ECG abnormality in study PEP005-028 was reported as an AE. The AEs reported for patients who received the 0.05% PEP005 Gel included first degree AV block (3 patients), ECG T wave inversion (2 patients), MI (2 patients), and abnormal QRS axis, abnormal ST segment, decreased T wave amplitude, supraventricular extrasystoles, and ventricular extrasystoles (1 patient each). In comparison, patients in the corresponding vehicle cohort had biphasic T wave (3 patients), MI (3 patients), abnormal ST segment (2 patients), and RBBB, prolonged QRS complex, decreased T wave amplitude, ventricular extrasystoles, and ventricular pre-excitation (1 patient each).

It should be noted that the MIs described above and summarized in Table 41 were all identified on ECG tracings and characterized as old MIs of undetermined age. For the 5 patients in this discussion of ECG abnormalities (2 patients treated with 0.05% PEP005 Gel [Nos. [redacted] and [redacted], and 3 treated with vehicle [Nos. [redacted], and [redacted], all in study PEP005-014), the MIs did not occur while the patients were in the study (refer to the CSR for PEP005-014).

Of the 29 patients with ECG abnormalities reported as AEs, 4 patients (2 treated with PEP005 Gel and 2 treated with vehicle) had an event considered related to study medication (Appendix Tables 7.1.4, 7.1.5, 7.2.4, and 7.2.9):

- Patient [redacted] (PEP005 Gel, 0.015%) in study PEP005-016 had mild ventricular extrasystoles and mild QT prolongation observed on the Day 4 ECG tracing; both events were considered by the investigator as possibly related to study drug. By the Day 57 visit, the events had resolved without intervention.

- Patient [redacted] PEP005 Gel, 0.015%) in study PEP005-025 had mild QT prolongation on Day 4 that was considered possibly related to study medication. By Day 16, the patient had recovered without intervention.
- Patient [redacted] vehicle) in study PEP005-016 had mild LBBB and mild ventricular extrasystoles, both observed on the Day 4 ECG tracing and considered possibly related to study medication. The events had resolved by the Day 57 visit without intervention.
- Patient [redacted] (vehicle) n study PEP005-025 had mild QT prolongation on Day 4, considered possibly related to study drug; the patient had recovered by Day 57 without intervention.

Table 41 ECG Abnormalities Reported as Adverse Events

AE Preferred Term	Study PEP005-016[a] (Face and Scalp)		Study PEP005-025[b] (Face and Scalp)		Study PEP004-014[c] (Trunk and Extremities)		Study PEP004-028[d] (Trunk and Extremities)	
	0.015% PEP005 Gel (N=132)	Vehicle (N=135)	0.015% PEP005 Gel (N=142)	Vehicle (N=136)	0.05% PEP005 Gel (N=125)	Vehicle (N=129)	0.05% PEP005 Gel (N=100)	Vehicle (N=103)
Any ECG abnormality reported as an AE	2 (1.5%)	3 (2.2%)	1 (0.7%)	6 (4.4%)	10 (8.0%)	7 (5.4%)	0 (0.0%)	0 (0.0%)
Atrial Fibrillation	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atrioventricular Block First Degree	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	3 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bundle Branch Block Left	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bundle Branch Block Right	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
ECG QRS Axis Abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECG QRS Complex Prolonged	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
ECG QT Prolonged	2 (1.5%)	0 (0.0%)	1 (0.7%)	3 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECG ST Segment Abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	2 (1.6%)	0 (0.0%)	0 (0.0%)
ECG ST-T changes	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ECG T Wave Amplitude Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
ECG T Wave Biphasic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
ECG T Wave Inversion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myocardial Infarction*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Sinus Arrhythmia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Supraventricular Extrasystoles	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachycardia	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ventricular Extrasystoles	1 (0.8%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Ventricular Pre-Excitation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)

*The MIs noted in this table did not occur during the study, but were found on ECG tracings and characterized as old MIs of an undetermined age (see CSR for PEP005-014).
Source: [a]Appendix Table 5.1.4 and CSR for Study PEP005-016; [b]Appendix Table 5.1.5 and CSR for Study PEP005-025; [c]Appendix Table 5.2.4 and CSR for Study PEP005-014; [d]Appendix Table 5.2.9 and CSR for Study PEP005-028

4.2.3 Cardiac Safety Testing

ECG safety analyses were performed using data obtained from all enrolled patients in studies PEP005-014, PEP005-028, PEP005-016, and PEP005-025 with at least one available pre-treatment ECG and at least one post-treatment ECG. The following analyses were performed: a central tendency analysis, an outlier analysis, and a morphological analysis. The results showed that patients treated with PEP005 Gel had no clinically relevant signal of any changes in heart rate, AV conduction, cardiac depolarization, or cardiac wave form morphology or new rhythms. The data from the central tendency and outlier analyses demonstrated no clear signal of any effect on cardiac repolarization.
A complete report describing the ECG safety analyses is provided in Module 5, Section 5.3.5.3.

4.3 LOCAL SKIN RESPONSE

At baseline and each subsequent study visit the treatment area was assessed for the following LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration. Each of the six LSRs was graded from 0–4 (see Section 1.1.5.3), then summed to give a composite LSR score that ranged from 0–24.

4.3.1 Composite LSR Scores

Baseline assessments of erythema, flaking/scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration resulted in assignment of a non-zero LSR score for the majority of patients, reflecting presence of localized irritation at the lesion site, predominantly attributed to erythema and flaking/scaling. Following application of study medication, most 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; approximately 95% vs. 36% of AK patients who received field applications of PEP005 Gel vs. vehicle, respectively, had a post-treatment increase in LSR score (Appendix Table 22.3.3).
For AK patients with field application of study medications, the mean (– SD) of the maximum composite LSR scores for patients treated with PEP005 Gel (regardless of treatment location, concentration or dosing regimen) was 7.8 (– 3.8); in contrast, this score for vehicle-treated patients was 1.8 (– 1.5) (Appendix Table 22.3.3). For the majority of the AK patients, the maximum LSR score occurred on Days 3 and 4, with the score returning to baseline values (or below) by Day 29 (Appendix Table 22.3.3).

For patients in the controlled phase 3 studies, the mean (– SD) of the maximum composite LSR score for PEP005 Gel-treated patients was 8.1 (– 4.0), and that for vehicle-treated patients was 1.7 (– 1.6) (Appendix Table 22.3.2). Local skin responses differed between treatment locations, with PEP005 Gel-treated areas on the face and scalp having a generally greater intensity than responses on the trunk and extremities. Patients treated on the face or scalp in the controlled Phase 3 studies received PEP005 Gel, 0.015% for 3 consecutive days. In this population, the mean (– SD) maximum composite LSR score was 9.1 (– 4.1), with the majority of patients having a maximum score on Day 4 (Table 42). In contrast, patients treated on the trunk or extremities in the controlled Phase 3 studies received PEP005 Gel, 0.05% for 2 consecutive days and had a mean (– SD) maximum composite LSR score of 6.8 (– 3.5), with the majority of patients having a maximum score on Days 3 or 8 (Table 42). Figure 2 shows the mean composite LSR score on each observation day for patients treated on the face/scalp or trunk/extremities with PEP005 Gel or vehicle; the figure shows that the mean composite LSR score for patients treated on the face/scalp occurs earlier and resolves sooner than that for patients treated on the trunk/extremities.

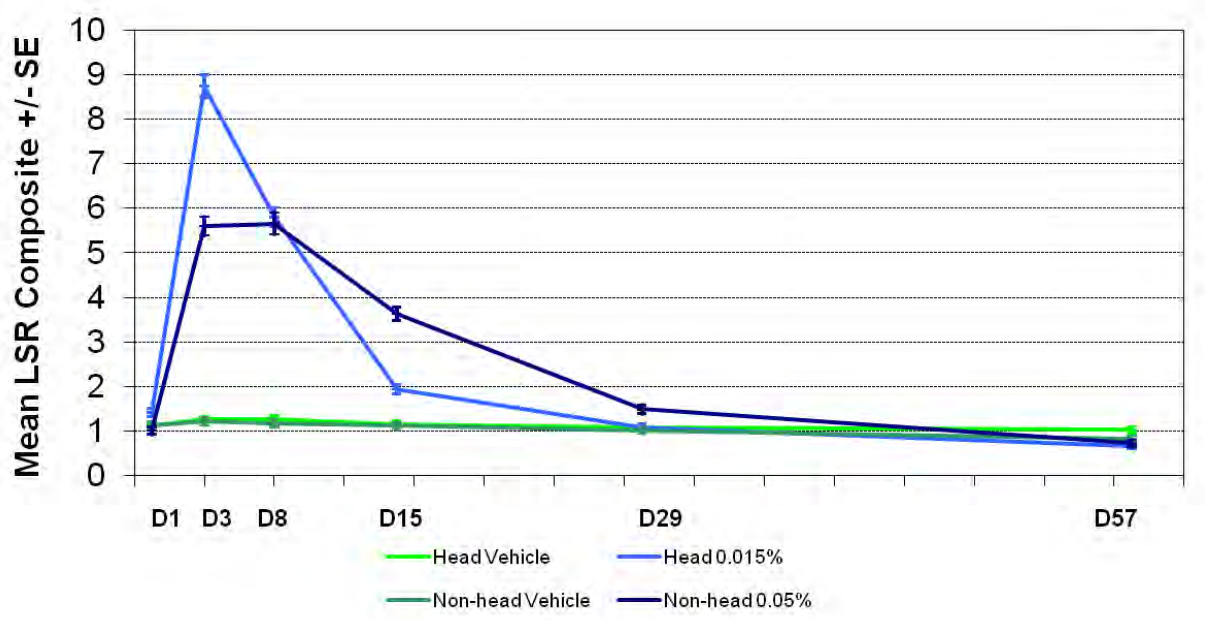
Table 42 Summary of Local Skin Response (Composite Score) for the Controlled Phase 3 Studies by Treatment Location

Summary of LSR Composite Score	Controlled Phase 3 Studies			
	Face/Scalp[a]		Trunk/Extremities[b]	
	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)
Baseline score, mean (SD)	1.4 (1.5)	1.1 (1.2)	1.0 (1.2)	1.1 (1.3)
Maximum score post baseline, mean (SD)*	9.1 (4.1)	1.8 (1.6)	6.8 (3.5)	1.6 (1.5)
Patients with a score > 0, n (%)	272 (99.3%)	199 (73.4%)	223 (99.1%)	158 (68.1%)
Patients with a score > baseline, n (%)	268 (97.8%)	97 (35.8%)	217 (96.4%)	72 (31.0%)
Study day of maximum score, n (%)				
No scores > baseline	5 (1.8%)	174 (64.2%)	8 (3.6%)	160 (69.0%)
Day 3/4	224 (81.8%)	34 (12.5%)	124 (55.1%)	32 (13.8%)
Day 8	39 (14.2%)	22 (8.1%)	73 (32.4%)	19 (8.2%)
Day 15	4 (1.5%)	18 (6.6%)	19 (8.4%)	11 (4.7%)
Day 29	0 (0.0%)	17 (6.3%)	0 (0.0%)	9 (3.9%)
Day 57	1 (0.4%)	6 (2.2%)	1 (0.4%)	1 (0.4%)
Study day of score < baseline, n (%)				
All scores > baseline	16 (5.8%)	23 (8.5%)	34 (15.1%)	12 (5.2%)
Day 3/4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 8	20 (7.3%)	20 (7.4%)	6 (2.7%)	19 (8.2%)
Day 15	118 (43.1%)	15 (5.5%)	22 (9.8%)	13 (5.6%)
Day 29	77 (28.1%)	15 (5.5%)	89 (39.6%)	12 (5.2%)
Day 57	37 (13.5%)	24 (8.9%)	66 (29.3%)	16 (6.9%)

*Note: the maximum composite LSR score is independent of time, it reflects the highest score at any time post baseline.

Source: [a]Appendix Table 22.1.6; [b]Appendix Table 22.2.10

Figure 2 Mean Composite LSR Score on Each Observation Day



Source: Appendix Tables 22.6.1 and 22.6.2

4.3.1.1 Evaluation of Treatment Regimen and Mean Maximum LSR Composite Score

A subgroup analysis of the change in mean maximum LSR composite score (indicative of intensity of specific local skin responses [Table 10]) showed that patients dosed with the 0.015% PEP005 Gel for 3 days on the face/scalp had a significantly greater change in the mean maximum LSR composite score (indicating greater intensity) than patients dosed with 0.05% PEP005 Gel for 2 days on trunk/extremity locations (Section 5.2).

4.3.1.2 Evaluation of Multiple Treatments of PEP005 Gel on Maximum LSR Composite Scores

As was noted in Section 1.2.2, 49 patients received PEP005 Gel for field treatment of AK lesions after previously receiving PEP005 Gel in an AK or non-AK study (29 received treatment on the face or scalp and 20 on the trunk or extremities). Maximum composite LSR scores (Appendix Table 30.1) were examined for these 49 patients. A within patient analysis of LSRs (Table 43) had too few patients for meaningful interpretation. Due to the small number of patients who participated in multiple AK field treatment studies and the limited information on the occurrence of LSRs for these patients, the sample sizes for the pooled studies were not adjusted for patients who participated in multiple studies.

Table 43 Maximum Composite LSR Scores for Earlier and Later Exposure to PEP005 Gel

Maximum Composite LSR Score, Mean ± SD	Treatment Location (First → Second Study)			
	Head → Head (N=8)	Non-head → Non-head (N=10)	Head → Non-head (N=5)	Non-head → Head (N=4[a])
Earlier study	8.63 ± 2.72	7.40 ± 2.50	9.80 ± 4.66	7.00 ± 4.97
Later study	8.38 ± 5.40	5.20 ± 3.01	6.80 ± 2.17	7.25 ± 2.22
Difference[b]	−0.25 ± 4.77	−2.20 ± 2.74	−3.00 ± 3.39	0.25 ± 4.11

[a]One patient was missing the maximum composite LSR score in the earlier study

[b]Difference = later − earlier

Source: Appendix Table 30.2

4.3.2 Individual Local Skin Responses

For both treatment locations (face/scalp and trunk/extremities), erythema and flaking/scaling were the most common LSRs, followed by crusting and swelling. Erythema and flaking/scaling were present to some extent prior to application of study medication; and these persisted with vehicle treatment and worsened following PEP005 Gel treatment (Appendix Tables 22.1.6 and 22.2.10). Grade 4 responses (i.e., extending beyond the treatment area) were observed more frequently for erythema than the other LSRs, independent of treatment location.

For approximately 70% of patients treated with 0.015% PEP005 Gel on the face or scalp in the controlled Phase 3 studies, erythema reached a maximum grade of 3 (red skin, restricted to the treatment area) or 4 (red skin, extending outside treatment area) (Table 44). In contrast, approximately 86% of the corresponding vehicle-treated patients had a maximum post baseline erythema grade of 0 (not present) or 1 (slightly pink skin limited to < 50% of the treatment area). For patients treated with 0.05% PEP005 Gel on the trunk or extremities (0.05% for 2 consecutive days), erythema tended to be less intense than that observed on the face/scalp; the majority (approximately 56%) of patients treated on trunk or extremity locations had erythema scores of 1 or 2 (pink or light red skin covering > 50% of the treatment area).

For flaking/scaling, the majority of PEP005 Gel-treated patients (independent of location) had maximum post baseline scores of either 1 or 2, and approximately one-third of patients had scores of 3; vehicle-treated subjects had maximum post baseline scores of 0 or 1 (Table 44). Crusting showed a similar trend with maximum post baseline scores of 1 or 2 for the majority of PEP005 Gel-treated patients, whereas the majority of vehicle treated patients had a score of 0. Maximum post baseline scores for swelling and vesiculation/pustulation were 0 or 1 for the majority of PEP005 Gel-treated patients and 0 for the majority of vehicle-treated patients.

For patients treated with 0.015% PEP005 Gel on the face or scalp, maximum post baseline scores for each LSR (except flaking/scaling) were observed on Day 4 (the day following the last dose of study medication); flaking/scaling peaked between Days 4 and 8. Resolution to baseline (or below) values generally occurred by Day 8 for swelling, vesiculation/pustulation, and erosion/ulceration and by Day 15 for erythema, flaking/scaling, and crusting (Appendix Table 22.3.2).

For patients treated with 0.05% PEP005 Gel on the trunk or extremities, maximum post baseline scores occurred on Day 3 (the day following the last dose of study medication) for erythema, swelling, and vesiculation/pustulation. Maximum post baseline scores occurred on Day 8 for flaking/scaling, crusting, and erosion/ulceration. Resolution to baseline (or below) values occurred by Day 8 for swelling and vesiculation/pustulation, by Day 15 for erosion/ulceration, and by Day 29 for erythema, flaking/scaling, and crusting (Appendix Table 22.3.2).

Table 44 Summary of Maximum Score of Each Local Skin Response Post Baseline for the Controlled Phase 3 Studies by Treatment Location

Local Skin Response	Maximum Grade Post Baseline*	Controlled Phase 3 Studies			
		Face/Scalp[a]		Trunk/Extremities[b]	
		0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)
Erythema	0	1 (0.4%)	105 (38.7%)	5 (2.2%)	112 (48.3%)
	1	25 (9.1%)	127 (46.9%)	31 (13.8%)	102 (44.0%)
	2	56 (20.4%)	33 (12.2%)	94 (41.8%)	16 (6.9%)
	3	125 (45.6%)	6 (2.2%)	61 (27.1%)	2 (0.9%)
	4	66 (24.1%)	0 (0.0%)	34 (15.1%)	0 (0.0%)
	Any grade > 0	272 (99.3%)	166 (61.3%)	220 (97.8%)	120 (51.7%)
Flaking/Scaling	0	7 (2.6%)	89 (32.8%)	3 (1.3%)	83 (35.8%)
	1	52 (19.0%)	142 (52.4%)	52 (23.1%)	131 (56.5%)
	2	91 (33.2%)	36 (13.3%)	86 (38.2%)	15 (6.5%)
	3	98 (35.8%)	4 (1.5%)	66 (29.3%)	3 (1.3%)
	4	25 (9.1%)	0 (0.0%)	18 (8.0%)	0 (0.0%)
	Any grade > 0	266 (97.1%)	182 (67.2%)	222 (98.7%)	149 (64.2%)
Crusting	0	44 (16.1%)	219 (80.8%)	50 (22.2%)	188 (81.0%)
	1	85 (31.0%)	47 (17.3%)	105 (46.7%)	38 (16.4%)
	2	64 (23.4%)	5 (1.8%)	39 (17.3%)	4 (1.7%)
	3	64 (23.4%)	0 (0.0%)	23 (10.2%)	2 (0.9%)
	4	16 (5.8%)	0 (0.0%)	8 (3.6%)	0 (0.0%)
	Any grade > 0	229 (83.6%)	52 (19.2%)	175 (77.8%)	44 (19.0%)
Swelling	0	56 (20.4%)	257 (94.8%)	82 (36.4%)	219 (94.4%)
	1	88 (32.1%)	12 (4.4%)	65 (28.9%)	13 (5.6%)
	2	67 (24.5%)	2 (0.7%)	51 (22.7%)	0 (0.0%)
	3	48 (17.5%)	0 (0.0%)	20 (8.9%)	0 (0.0%)
	4	14 (5.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)
	Any grade > 0	217 (79.2%)	14 (5.2%)	143 (63.6%)	13 (5.6%)
Vesiculation/Pustulation	0	119 (43.4%)	270 (99.6%)	127 (56.4%)	230 (99.1%)
	1	36 (13.1%)	1 (0.4%)	46 (20.4%)	1 (0.4%)
	2	53 (19.3%)	0 (0.0%)	30 (13.3%)	1 (0.4%)
	3	50 (18.2%)	0 (0.0%)	19 (8.4%)	0 (0.0%)
	4	15 (5.5%)	0 (0.0%)	3 (1.3%)	0 (0.0%)
	Any grade > 0	154 (56.2%)	1 (0.4%)	98 (43.6%)	2 (0.9%)
Erosion/Ulceration	0	186 (67.9%)	267 (98.5%)	167 (74.2%)	226 (97.4%)
	1	55 (20.1%)	4 (1.5%)	37 (16.4%)	6 (2.6%)
	2	26 (9.5%)	0 (0.0%)	15 (6.7%)	0 (0.0%)
	3	5 (1.8%)	0 (0.0%)	4 (1.8%)	0 (0.0%)
	4	1 (0.4%)	0 (0.0%)	2 (0.9%)	0 (0.0%)
	Any grade > 0	87 (31.8%)	4 (1.5%)	58 (25.8%)	6 (2.6%)

*For grade definitions, see Table 10

Source: [a]Appendix Table 22.1.6; [b]Appendix Table 22.2.10

4.3.3 Evaluation of Local Skin Response and Efficacy

Post hoc analyses were performed to investigate whether there was an association between LSR (maximum values of the composite LSR score, erythema, swelling, crusting, flaking/scaling, vesiculation/pustulation, and erosion/ulceration) and efficacy (complete or partial clearance of AK lesions and percent reduction in AK lesion count). For these analyses, two populations were examined: (1) the PEP005 Gel-treated patients in the pooled Phase 3 studies (PEP005-016, PEP005-025, PEP005-014, and PEP005-028) and (2) the PEP005 Gel-treated patients in the pooled Phase 2 and 3 studies (PEP005-016, PEP005-025, PEP005-015, PEP005-014, PEP005-028, and PEP005-006). For all analyses, the face/scalp studies were analyzed separately from the trunk/extremities studies due to the observed differences in LSRs between the two anatomical locations.

The results of these analyses showed that:

- There were consistent, significant positive associations for maximum composite LSR score and maximum erythema score with complete clearance, partial clearance, and percent reduction in AK lesion count. This association was apparent for patients treated on face or scalp and trunk or extremity locations.
- The association was generally stronger for patients treated on face or scalp locations than trunk or extremity locations.
- Patients treated on the face or scalp with a maximum composite LSR score of ≥ 10 had a complete clearance rate of 54% versus 35% for patients with a score < 10. Patients treated on the trunk or extremities with a maximum composite score of ≥ 6 had a complete clearance rate of 41% versus 26% for patients with a score < 6.
- The association of maximum swelling score with complete clearance was significant for patients treated on face or scalp locations.
- The maximum erosion and vesiculation scores showed a trend for association with complete clearance that was sometimes statistically significant. The maximum flaking and crusting scores did not seem to be associated with achieving complete clearance.

A more complete presentation of the results of these post hoc analyses is presented in the summary of clinical efficacy (Module 2.7.3, Section 3.3.2, both head [face and scalp] and non-head [trunk and extremities] treatment locations).

4.4 PIGMENTATION AND SCARRING

At baseline and each clinic visit, the treatment area was assessed for hypo- and hyperpigmentation and scarring. The results are summarized here as the presence or absence of pigmentation or scarring at baseline versus at the end-of-study visit (Table 45).

The majority of patients who received field application of study medication for the treatment of AK lesions showed no hypopigmentation, hyperpigmentation, or scarring at baseline or the end-of-study assessments. Generally, hypopigmentation, hyperpigmentation, or scarring that was present at baseline remained unchanged at the end of the study. However, any shift that occurred for these parameters (especially for pigmentation) were more likely indicative of an improvement, with 8.0% and 7.8% of PEP005 Gel-treated patients having hypo- or hyper-pigmentation (respectively) at baseline that was absent at the end of the study. While vehicle-treated patients showed a similar trend, the proportion of these patients was smaller than for PEP005 Gel-treated patients: 3.5% and 4.4% of vehicle-treated patients had hypo- or hyperpigmentation (respectively) at baseline that was absent at the end of the study. A small percentage of patients had no pigmentation or scarring observed at baseline but showed pigmentation or scarring at the end of the study. The incidence of this type of shift was similar between treatment groups for scarring (0.2% in each of the PEP005 Gel and vehicle groups) and slightly higher for PEP005 Gel-treated patients than vehicle-treated patients for both hypopigmentation (2.2% vs.0.5%, PEP005 Gel vs. vehicle, respectively) and hyperpigmentation (1.5% vs.0.9%, PEP005 Gel vs. vehicle, respectively).

Table 45 Incidence of Patients with Hypopigmentation, Hyperpigmentation, and Scarring at Baseline versus at Study Completion

Parameter **Baseline → End of Study**	**PEP005 Gel** **(N = 1165)**	**Vehicle** **(N = 632)**
Hypopigmentation		
Not present → Not present	924 (79.3%)	566 (89.6%)
Present → Present	114 (9.8%)	38 (6.0%)
Not present → Present	26 (2.2%)	3 (0.5%)
Present → Not present	93 (8.0%)	22 (3.5%)
Missing assessment	8 (0.7%)	3 (0.5%)
Hyperpigmentation		
Not present → Not present	914 (78.5%)	545 (86.2%)
Present → Present	135 (11.6%)	50 (7.9%)
Not present → Present	18 (1.5%)	6 (0.9%)
Present → Not present	91 (7.8%)	28 (4.4%)
Missing assessment	7 (0.6%)	3 (0.5%)
Scarring		
Not present → Not present	1091 (93.6%)	607 (96.0%)
Present → Present	30 (2.6%)	13 (2.1%)
Not present → Present	2 (0.2%)	1 (0.2%)
Present → Not present	35 (3.0%)	8 (1.3%)
Missing assessment	7 (0.6%)	3 (0.5%)

Source: Appendix Table 24.3.3

4.5 ABNORMAL PROLIFERATION

For several of the studies, dermatologic examinations of the selected treatment area were performed, which included evaluation for the presence of abnormal proliferation. If clinically warranted based on the findings of the examination, lesions were biopsied or excised per standard of care, and the results reported as an AE or SAE, as appropriate.

An abnormal proliferation within the treatment area was recorded for a total of 18 patients: 14 patients treated with PEP005 Gel and 4 treated with vehicle (Appendix Table 25). Information regarding the 18 patients is summarized in Sections 4.5.1 (for AK field treatment studies) and 4.5.2 (for non-AK studies); further information can be found in corresponding CSRs.

It should be noted that for the AK treatment studies, examinations of the treatment area for abnormal proliferations were performed in conjunction with assessments of LSRs; observations of abnormal proliferation could have been confounded, depending on the intensity of the LSR. As such, several of the reports of abnormal proliferation were not associated with a

specific lesion, may not have had a follow-up procedure, and were not apparent at subsequent examinations.

4.5.1 Abnormal Proliferation in AK Field Treatment Studies

- PEP005-006 Patient [redacted] was treated with PEP005 Gel, 0.05% on Days 1, 2, and 3 for AK lesions and was noted to have abnormal proliferation in the treatment area on Day 3 of the study. No biopsy or excision was performed, and no associated AE was reported. At subsequent observations of the treatment area, no abnormal proliferation was observed.

  Patient [redacted] was treated with PEP005 Gel, 0.025% on Days 1 and 2 for AK lesions and had an abnormal proliferation noted on Days 8, 16 and 30. A biopsy was performed on Day 16, the results of which indicated SCC. The finding was reported as a moderate AE, not related to study medication. The SCC was excised on Day 30, and the event was considered resolved.

  Patient [redacted] received vehicle treatment for AK lesions and had an abnormal proliferation on Day 31. A biopsy was performed the same day, and the results indicated BCC. The finding was reported as a moderate AE, not related to study medication.

- PEP005-013 Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for AK lesions on the arm. The patient had an abnormal proliferation noted on Days 15, 22, 57 and 92. A punch biopsy on Day 15 indicated keratoacanthoma, reported as AE and considered definitely related to study medication. On Day 22 the patient had cryotherapy of solar keratoses and seborrheic keratoses. On Day 57 a punch biopsy indicated SCC, which was excised on Day 92. The SCC (Bowen's disease) was reported as a possibly drug-related AE.

  Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for AK lesions on the arm. On Day 36 the patient had an abnormal proliferation that was biopsied; the biopsy cleared the lesion.

- PEP005-014 Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for AK lesions. The patient had an abnormal proliferation on Day 27, which was biopsied and revealed chronic eczematous dermatitis associated with focal AK. The finding was reported as a mild AE, considered probably related to study medication; the event was ongoing at last contact.
- PEP005-016 Patient [redacted] received PEP005 Gel, 0.015% on Days 1, 2, and 3 for AK lesions on the scalp. Following treatment, the patient had Grade 4 LSRs, which included erythema, swelling, and vesiculation/pustulation (the pustules prompted a skin culture). On Day 8, the investigator noted a suspected abnormal proliferation. With improvement in LSR and negative culture results, the investigator had no further suspicion of abnormal proliferation, and no follow-up was considered warranted.
- PEP005-020 Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for AK lesions on the back of the hand and had an abnormal proliferation at the treatment site on Day 57, which was biopsied the same day. Results of the biopsy showed hypertrophic solar keratosis. The investigator considered that the finding was normal and no further action was taken.

  Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for AK lesions on the arm and had an abnormal proliferation at the treatment site on Day 57, which was biopsied the same day. Results of the biopsy indicated SCC. The finding was reported as a moderate AE, possibly related to study medication. On Day 64, the SCC was excised, and the event was considered resolved.
- PEP005-022 Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for treatment of AK lesions on the arm. On Day 29, the patient had a keratotic nodule in the treatment area. An incisional biopsy was performed, which showed well-differentiated SCC; the lesion was completely excised on Day 39. The SCC was considered by the investigator as possibly related to treatment.

- PEP005-025 Patient [redacted] received vehicle for AK lesions and had an abnormal proliferation on Day 58, which was diagnosed as basosquamous carcinoma and reported as a mild AE, not related to study drug. Approximately 6 weeks later, the abnormal proliferation was excised and the AE was considered resolved.
- PEP005-028 Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for AK lesions on the arm. On Day 56, the patient had a lesion biopsied in the treatment area that revealed pale cell acanthoma. The finding was recorded as an AE.

  Patient [redacted] received vehicle for AK lesions and had an abnormal proliferation on Day 29 that was absent at subsequent observations. No biopsy or other procedure performed, and no AE was reported.

  Patient [redacted] received vehicle for AK lesions and had an abnormal proliferation on Day 8 that was absent at subsequent observations. The patient had no biopsy or other procedure performed, and no AE was reported.

4.5.2 Abnormal Proliferation in Non-AK Studies

- PEP005-002 Patient [redacted] received PEP005 Gel, 0.0025% on Days 1 and 8 for nodular BCC on the arm. On Day 59, an abnormal proliferation of the study lesion was noted, which was reported as an unrelated severe AE of 'neoplasm progression'. No corrective therapy was noted.

  Patient [redacted] received PEP005 Gel, 0.05% on Days 1 and 2 for nodular BCC on the chest. On Day 8, an abnormal proliferation within the treatment area was noted; no biopsy/excision was performed, and no AE was reported. At all subsequent observations, the investigator reported an absence of abnormal proliferation.

  Patient [redacted] received PEP005 Gel, 0.01% on Days 1 and 2 for nodular BCC on the face. On Day 57, an abnormal proliferation in the treatment area was noted. A mild AE of 'neoplasm progression' was reported and considered possibly related to study drug. On Day 63 the

patient terminated from the study early; on the same day, the lesion was excised.

- PEP005-003 Patient [redacted] was treated with PEP005 Gel, 0.05% on Days 1 and 8 for treatment of SCC and was noted to have abnormal proliferation in the treatment area on Day 15. No biopsy was performed, and no AE was reported. At subsequent observations, the investigator noted there was no abnormal proliferation.

4.6 TOPICAL SAFETY

4.6.1 Skin Sensitization Potential of PEP005 Gel

In study PEP005-005, a repeat insult test design was used to examine the potential of PEP005 Gel to induce skin sensitization in healthy volunteers (N = 238). Subjects received open-label treatment to a 4 cm^2 area on the infrascapular region of the back. Treatment consisted of PEP005 Gel, 0.01%, and vehicle gel control, administered 3 times weekly for 3 weeks during the induction phase (9 applications), and once during the challenge phase (i.e., 10 applications in total). A visual scale was used to assess the degree of erythema, edema and other signs of cutaneous irritation at the application sites.

The study population consisted of 196 (82%) females and 42 (18%) males, of which 165 (69%) were Caucasian, 49 (21%) were Hispanic, 21 (9%) were African-American, 2 (0.8%) were Asian and 1 (0.4%) was classified as 'Other'. Subjects ranged in age from 19-65 years (with a mean of 43.7 years). Fitzpatrick skin types were recorded as Type I (n = 5), Type II (n = 37), Type III (n = 122) and Type IV (n = 74).

Following induction treatment, there was a 10–14-day rest period, after which subjects received a single challenge of PEP005 Gel, 0.01%, applied to a naïve site on the back. Observations at the naïve site during challenge and the patterns of reactivity during the induction period provided the basis for the interpretation of contact sensitization. During the induction phase, 20 subjects experienced minimal erythema at the PEP005 Gel application site. In 15 of these subjects, erythema resolved before the end of the induction phase. No reactions were observed after application of the vehicle gel control. Mean and total cumulative irritation scores were significantly increased following treatment with PEP005 Gel, 0.01%, compared to vehicle gel control. Although significant irritation reactions (erythema, damage to the epidermis; i.e., oozing, crusting and/or superficial erosion) were observed at challenge in two subjects, there were no reactions indicative of a possible sensitization response.

4.6.2 Phototoxicity Potential of PEP005 Gel

Study PEP005-023 was designed to determine the irritation potential of PEP005 Gel, 0.01% in combination with UV light (16 J/cm^2) exposure. Each subject received two applications of PEP005 Gel and vehicle gel; one application site for each treatment was irradiated and the other remained non-irradiated. A fifth area was untreated and irradiated, serving as a control. Irritation at the five areas were scored and compared. The study population consisted of 30 (88%) females and 4 (12%) males, all of whom were Caucasian. Subjects ranged in age from 18–65 years (with a mean of 45 years).

Mild erythema was observed at all areas that were irradiation with 16 J/cm^2 of UVA light. Areas treated with either PEP005 Gel, 0.01% or vehicle showed no significant irritation following irradiation and had mean irritation scores of 0.20 and 0.17, respectively. Treated areas that had not been irradiated had mean irritation scores of 0.02 and 0.00, respectively. The untreated, irradiated control area had a mean irritation score of 0.21.

Comparison of scores showed a statistically significant difference between the irradiated and non-irradiated treatment areas for both PEP005 Gel, 0.01%, and the vehicle gel ($p < 0.001$). The irritation was mild in nature, and no reactions were at a level to suggest photoirritation. Moreover, there was no statistically significant difference between the irradiated PEP005 Gel, 0.01%, and untreated, irradiated treatment areas ($p = 0.769$), or between the irradiated vehicle and untreated irradiated treatment areas ($p = 0.380$). There were no statistically significant difference between the irradiated PEP005 Gel, 0.01%, treatment area and the irradiated vehicle treatment area ($p = 0.558$); between the irradiated PEP005 Gel, 0.01%, treatment area and the untreated irradiated treatment area ($p = 0.769$); or between the irradiated vehicle treatment area and the untreated irradiated treatment area ($p = 0.380$). No subjects met the pre-specified criteria for a reaction indicative of phototoxicity.

4.6.3 Photosensitization Potential of PEP005 Gel

Study PEP005-024 was designed to assess the photosensitization potential of PEP005 Gel, 0.01%, in combination with UV light (6 J/cm^2) exposure. Each subject received seven applications of the study medication; one set of applications was irradiated and the other remained non-irradiated. A separate untreated area was irradiated and served as a control. Irritation at the irradiated and non-irradiated treatment areas were scored and compared. The study population consisted of 46 (77%) females and 14 (23%) males, all of whom were Caucasian. Subjects ranged in age from 19–64 years (with a mean age of 47 years).

Mild erythema was observed at all areas that were irradiated with 6 J/cm^2 of UVA light. There was no significant irritation in response to PEP005 Gel, 0.01%, or the vehicle gel at the

irradiated treatment areas (which had a mean irritation score of 0.47 and 0.39, respectively) or at the non-irradiated treatment areas (mean irritation score of 0.11 and 0.00, respectively). There was a statistically significant difference between the irradiated PEP005 Gel, 0.01%, treatment area and the irradiated vehicle treatment area ($p = 0.035$); between the non-irradiated treatment areas of PEP005 Gel, 0.01%, and the vehicle ($p = 0.003$), between the irradiated and non-irradiated treatment areas of PEP005 Gel ($p < 0.001$); and between the irradiated and non-irradiated treatment areas of the vehicle ($p < 0.001$).
No evidence of photosensitization was found for PEP005 Gel, 0.01%, or the vehicle gel. Under both irradiated and non-irradiated conditions, neither PEP005 Gel, 0.01%, nor the vehicle gel were associated with more than mild erythema during challenge, and this was unchanged or resolved by the 72-hour reading.

5 SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1 ANALYSIS OF ADVERSE EVENTS BASED ON INTRINSIC AND EXTRINSIC FACTORS

Subgroup analyses of two AEs (application site pain and application site pruritus) were performed to assess the relationship between the event and the following demographic and baseline characteristics: geographic location, age category, sex, race, Fitzpatrick skin type, treatment location, histories of cardiovascular disorders, endocrine disorders, allergy or immunologic disorders, gastrointestinal disorders, concentration, regimen (i.e., number of dosing days), prior cryotherapy, or prior therapy with either imiquimod or 5-fluorouracil. The two AEs were chosen based on a difference in incidence rates between the PEP005 Gel group and the vehicle group of at least 5% for the controlled Phase 3 studies for face/scalp and trunk/extremities combined. The results of these analyses showed that:

- For the face/scalp controlled Phase 3 studies (PEP005-016 and PEP005-025), there was no apparent relationship between any of the demographic and baseline characteristics and the AEs of application site pain or application site pruritus, based on incidence within each subgroup and 95% confidence interval (CI) (Appendix Table 12.1.1).
- For the trunk/extremities controlled Phase 3 studies (PEP005-014 and PEP005-028), there was no relationship between any of the demographic and baseline characteristics and the AEs of application site pain or application site pruritus, based on incidence within each subgroup and 95% CI (Appendix Tables 12.2.1).
- Analysis of the pooled data from all four Phase 3 studies showed that patients treated on the face or scalp with 0.015% PEP005 Gel for 3 days had a higher incidence of application site pain (13.9%, 95% CI = 10.0, 18.5) than patients treated on the trunk or extremities with 0.05% PEP005 Gel for 2 days (2.2%, 95% CI = 0.7, 5.1); this effect was not observed for application site pruritus (Appendix Table 12.3.1).

5.2 ANALYSES OF CHANGE FROM BASELINE IN MEAN MAXIMUM LSR COMPOSITE SCORE BASED ON INTRINSIC AND EXTRINSIC FACTORS

Subgroup analyses of the mean maximum composite score from baseline for the LSR composite score were performed to assess whether there was a relationship between post-dose composite LSR score and the following demographic and baseline characteristics: geographic location, age category, sex, race, Fitzpatrick skin type, treatment location, histories of cardiovascular disorders, endocrine disorders, allergy/immunologic disorders, gastrointestinal

disorders, concentration of PEP005 Gel, dosing regimen (i.e., number of dosing days), prior cryotherapy, or prior therapy with either imiquimod or 5-fluorouracil. The results of these analyses showed that:

- For the face/scalp controlled Phase 3 studies (PEP005-016 and PEP005-025), there was no apparent relationship between any of the demographic and baseline characteristics and the change in mean maximum composite LSR score, based on the mean response within each subgroup and 95% CI (Appendix Table 23.1.1).
- For the trunk/extremity controlled Phase 3 studies (PEP005-014 and PEP005-028), there was no apparent relationship between any of the demographic and baseline characteristics and the change in mean maximum composite LSR score, based on the mean response within each subgroup and 95% CI (Appendix Table 23.2.1).
- In a combined analysis of the four Phase 3 studies (PEP005-016, PEP005-025, PEP005-014, and PEP005-028), patients who received the 0.015% PEP005 Gel for 3 days on the face or scalp had a greater change in the mean maximum LSR composite score following dosing (mean [SD] = 9.1 [4.1], 95% CI = 8.6, 9.6) than patients dosed with 0.05% PEP005 Gel for 2 days on trunk and extremity locations (mean [SD] = 6.8 [3.5], 95% CI = 6.3, 7.2) (Appendix Table 23.3.1).

5.3 DRUG INTERACTIONS

Pre-clinical and clinical pharmacokinetic studies have demonstrated that ingenol mebutate administered topically according to the proposed dosing regimen (0.015% x 3 days for lesions on the face and scalp and 0.05% x 2 days for lesions on the trunk and extremities) has no systemic absorption. In vivo studies showed no direct or mechanism-based inhibition or induction of human CYP isoforms, suggesting that a pharmacokinetic drug interaction following topical administration of PEP005 Gel is negligible. Based on these findings, no clinical drug interaction studies have been performed.

5.4 USE IN PREGNANCY AND LACTATION

Women of child-bearing potential who enrolled in any of the clinical studies were required to use an effective form of birth control, and women who were lactating were excluded from the studies. Across the 25 clinical studies in which patients/subjects received PEP005 Gel, there was one reported pregnancy. In Study PEP005-005 (which evaluated the sensitizing potential of PEP005 Gel in healthy volunteers), a 21-year-old female volunteer received PEP005 Gel during the induction phase of the study, but had a positive pregnancy test prior to the challenge phase and was discontinued from any further treatment. Later attempts to contact the

subject were unsuccessful; the subject was lost to follow-up, and the outcome of the pregnancy is unknown.
Pre-clinical developmental toxicity studies in rats and rabbits did not demonstrate any significant reproductive toxicity potential following iv administration; and based on these studies, ingenol mebutate is not considered to be a reproductive toxicant.
Following dermal application, no quantifiable levels of ingenol mebutate were detected. This lack of systemic exposure suggests no appreciable risk to humans receiving therapeutic doses of PEP005 Gel. However, in the absence of clinical experience in pregnant or lactating women, caution is advised when prescribing to these patients.

5.5 OVERDOSE

Topical overdosing of PEP005 Gel could result in an increased incidence of severity of local skin reactions.
There has been no experience of overdose with PEP005 Gel. No incidents of accidental oral ingestion have been reported

5.6 DRUG ABUSE

PEP005 Gel has no potential for abuse.

5.7 WITHDRAWAL AND REBOUND

There were no withdrawal or rebound effects reported in clinical trials and none would be expected with PEP005 Gel treatment.

5.8 EFFECTS ON ABILITY TO DRIVE OR OPERATE MACHINERY OR IMPAIRMENT OF MENTAL ABILITY

There are no expected effects on the ability to drive or operate machinery and no impairment on mental ability.

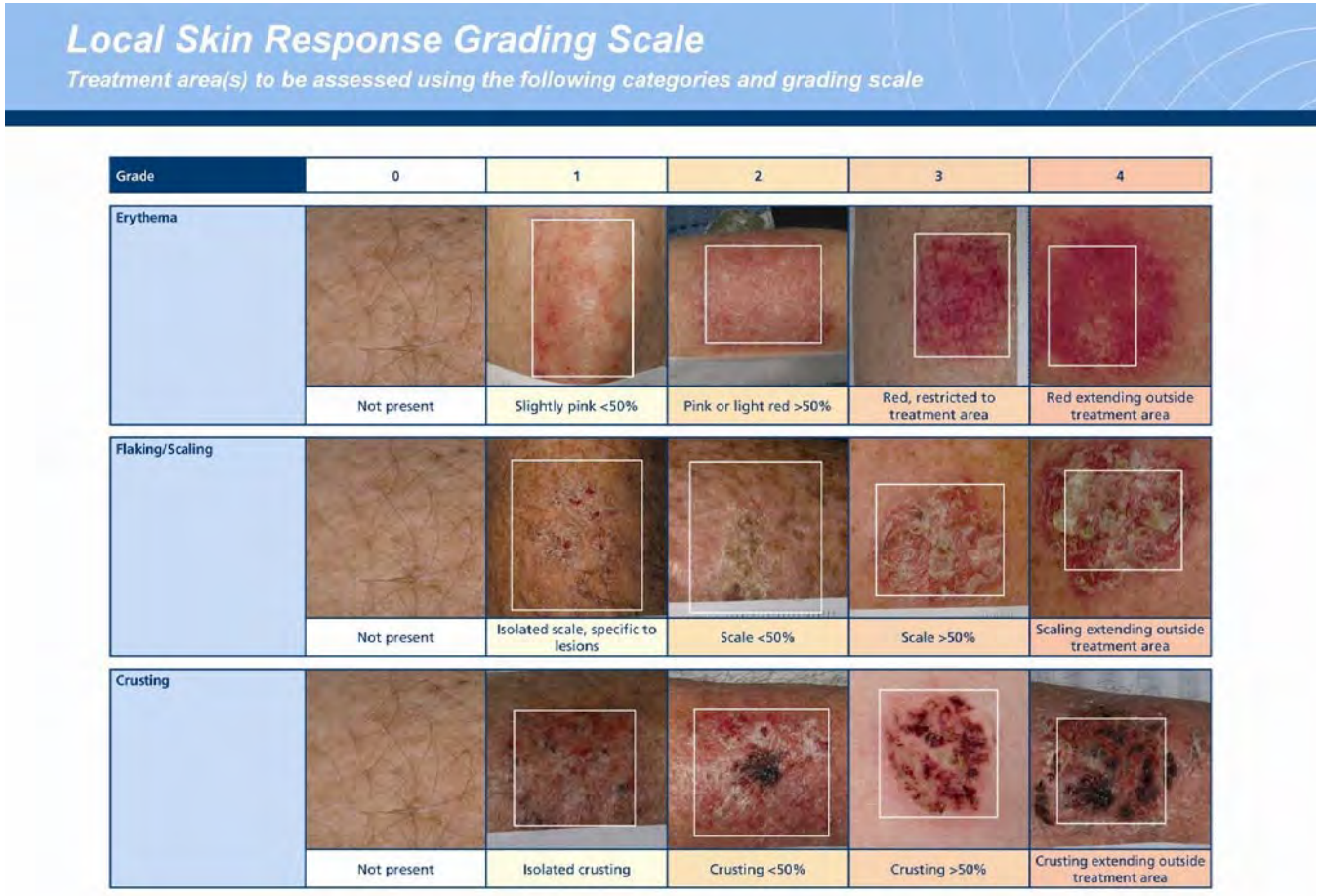
6 POSTMARKETING DATA

As of the date of this document, PEP005 (ingenol mebutate) Gel is not marketed in any country; postmarketing data are therefore not available.

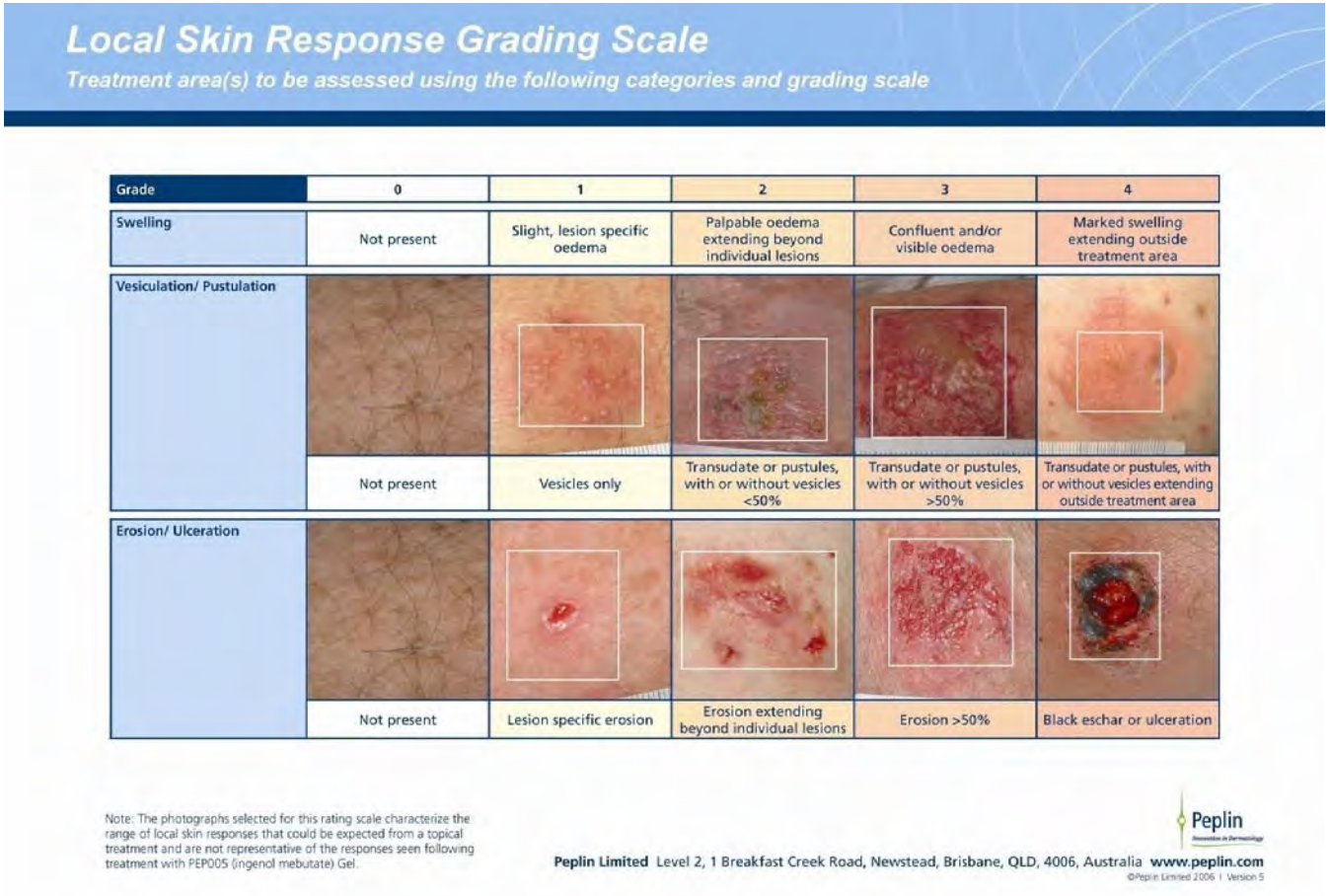
REFERENCES

1. Engel A, Johnson ML, Haynes SG. Health effects of sunlight exposure in the United States. Arch Dermatol. 1988;124:72-9.
2. Gupta AK, Cooper EA, Feldman SR, and Fleischer AB. A survey of office visits for actinic keratosis as reported by NAMCS, 1990-1999. *Cutis*. 2002;70(2 Suppl):8-13.
3. Smith ES, Feldman SR, Fleischer AB, Leshin B, McMichael A. Characteristics of office-based visits for skin cancer. *Dermatol Surg*. 1998;24:981-5.
4. European Commission. EU Legislation – Eudralex – Volume 2C – Regulatory Guidelines. http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm Guideline on Summary of Product Characteristics – SmPC (September 2009). Accessed 12 May 2011.
5. Eke T, Al-Husainy S, Raynor M. The spectrum of ocular inflammation caused by *Euphorbia* plant sap. *Arch Ophthalmol*. 2000;118:13-16.
6. Merani R, Sa-Ngiampornpanit T, Kerdraon Y, Billson F, McClellan K. *Euphorbia lactea* sap keratouveitis: Case report and review of the literature. *Cornea*. 2007;26:749-52.
7. Biedner BZ, Sachs U, Witztum A. *Euphorbia peplus* latex keratoconjunctivitis. *Ann Ophthalmol*. 1981;13:739-40.
8. Eke T. Acute kerato-uveitis associated with topical self-administration of the sap of the Petty Spurge (*Euphorbia peplus*). *Eye* 1994;8:694-6.
9. Duke-Elder S. *System of Ophthalmology*. Vol 14. London, UK; Kimpton; 1972;1185.
10. Grant WM, Schuman JS. *Toxicology of the Eye*. 4th ed. Springfield IL; CC Thomas; 1993;680-2.
11. Morris B, Richardson EK, Adams A, Chohan A. Green fingers, red eyes! Ocular hazards of gardening. *Emerg Med J*. 2006;23:584.
12. Basak SK, Bakshi PK, Basu S, Basak S. Keratouveitis caused by *Euphorbia* plant sap. Indian *J Ophthalmol*. 2009;57:311-13.

Attachment 1 Local Skin Response Grading Scale



Attachment 1 Local Skin Response Grading Scale (Cont'd)



Attachment 2 Listing of Patients with Squamous Cell Carcinoma[a] in All Field Application AK Studies

Study-Site-Subject Number	Treatment group	Location of treatment area	AE Verbatim Term	Location of AE compared to treatment area[b]
PEP005-006-101-01048	Vehicle Gel, Days 1, 2, 3	Arm, right	0.8 cm lesions right lower arm biopsy-SCC	Possibly inside treatment area
PEP005-006-105-01029	Vehicle Gel, Days 1, 2, 3	Arm, right	SCC left lower lateral forehead SCC left radial wrist ulnar Superficial SCC left radial wrist Superficial SCC mid right hand	Outside treatment area Outside treatment area Outside treatment area Outside treatment area
PEP005-006-105-02082	0.05% PEP005 Gel, Days 2, 3	Arm, left	Suspicious lesion left upper forehead (SCC)	Outside treatment area
PEP005-006-107-01010	0.025% PEP005 Gel, Days 1, 2, 3	Scalp, right	SCC of scalp	Possibly inside treatment area
PEP005-006-108-02085	0.05% PEP005 Gel, Days 1, 2, 3	Arm, right	SCC of the skin left posterior thigh	Outside treatment area
PEP005-006-128-01083	0.025% PEP005 Gel, Days 1, 2, 3	Arm, right	Dome shaped erythematous nodule with central keratotic plug left leg (SCC) SCC left leg	Outside treatment area Outside treatment area
PEP005-007-052-05204	0.025% PEP005 Gel, Days 1, 2	Face	SCC left side of neck	Outside treatment area
PEP005-014-066-66007	Vehicle Gel, Days 1, 2	Arm, left	SCC left forearm	Inside treatment area (CRF)
PEP005-018-107-10703	0.05% PEP005 Gel, Days 1, 2	Back of hand, left	SCC right chest	Outside treatment area (CRF)

a Treatment emergent AEs with a MedDRA Preferred Term of Squamous Cell Carcinoma

b Information based on either tick-box in CRF (PEP005-014, PEP005-018, PEP005-020, PEP005-022 and PEP005-028) or comparison of location of AE as stated in verbatim term and location of treatment area, where the CRF did not include this tick-box (PEP005-006 and PEP005-007).

Source: Clinical Study Reports for studies PEP005-006 Listings 16.2.17 and 16.2.25.1, PEP005-007 Listings 16.2.16 and 16.2.23.1, PEP005-014 Listings 16.2.6.1 and 16.2.7, PEP005-018 Listings 16.2.16 and 16.2.23, PEP005-020 Listings 16.2.6 and 16.2.7.1, PEP005-022 Listings 16.2.14 and 16.2.22, and PEP005-028 Listings 16.2.6 and 16.2.7.1

Attachment 2 Listing of Patients with Squamous Cell Carcinoma[a] in All Field Application AK Studies (Cont'd)

Study-Site-Subject Number	Treatment group	Location of treatment area	AE Verbatim Term	Location of AE compared to treatment area[b]
PEP005-020-086-00206	0.05% PEP005 Gel, Days 1, 2	Back of hand, right	SCC left Forearm	Outside treatment area (CRF)
PEP005-020-088-00209	0.05% PEP005 Gel, Days 1, 2	Arm, left	SCC	Inside treatment area (CRF)
PEP005-022-012-01203	0.05% PEP005 Gel, Days 1, 2 (25 cm^2, 50 cm^2)	Extensor forearm, right and left	SCC right forearm	Inside treatment area (CRF)
PEP005-022-143-14306	0.05% PEP005 Gel, Days 1, 2 (100 cm^2)	Extensor forearm, right	SCC	Outside treatment area (CRF)
PEP005-028-061-00001	Vehicle Gel, Days 1, 2	Arm, left	SCC left lateral hand SCC left medial hand SCC right volar forearm	Outside treatment area (CRF) Outside treatment area (CRF) Outside treatment area (CRF)
PEP005-028-067-00004	Vehicle Gel, Days 1, 2	Back of hand, left	SCC mid lower lip	Outside treatment area (CRF)
PEP005-028-067-00009	0.05% PEP005 Gel, Days 1, 2	Back of hand, left	SCC right calf	Outside treatment area (CRF)

a Treatment emergent AEs with a MedDRA Preferred Term of Squamous Cell Carcinoma

b Information based on either tick-box in CRF (PEP005-014, PEP005-018, PEP005-020, PEP005-022 and PEP005-028) or comparison of location of AE as stated in verbatim term and location of treatment area, where the CRF did not include this tick-box (PEP005-006 and PEP005-007).

Source: Clinical Study Reports for studies PEP005-006 Listings 16.2.17 and 16.2.25.1, PEP005-007 Listings 16.2.16 and 16.2.23.1, PEP005-014 Listings 16.2.6.1 and 16.2.7, PEP005-018 Listings 16.2.16 and 16.2.23, PEP005-020 Listings 16.2.6 and 16.2.7.1, PEP005-022 Listings 16.2.14 and 16.2.22, and PEP005-028 Listings 16.2.6 and 16.2.7.1

Attachment 3 Narratives for Sponsor-determined Serious Adverse Events

Patient PEP005 [redacted] This case concerns a 62-year-old female patient, who participated in study PEP005-002. The patient was administered 0.01% PEP005 Gel topically on the chest, on [redacted] and [redacted]
Reportedly the patient experienced BCC on the [redacted] 2005. The BCC was 14 cm (R) T3, location was unknown and it was assessed as moderate by the investigator. The event resolved on [redacted] 2005.
The patient's medical history included dry eyes since [redacted] gastric reflux since [redacted] headaches since [redacted] morphine allergy since [redacted] osteoarthritis fingers since [redacted] pancreatitis since [redacted] tinnitus since [redacted] urinary tract infection since [redacted] and ongoing.
Past history included cholecystectomy in [redacted] and pleurisy in [redacted]
Concomitant medication included: mebeverine due to post cholecystectomy, paracetamol due to headaches, pancreatin due to post cholecystectomy and propylene glycol due to dry eyes.
The investigator initially reported the BCC as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor assessed the BCC as not related to study medication based on previous results from preclinical and clinical trials with topical treatment of PEP005 Gel, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005- This case concerns a 53-year-old female patient, who participated in study PEP005-002. The patient was administered vehicle gel (no drug), topically on the back on Days 1 and 2 2005 and 2005).
Reportedly the patient experienced BCC on 2006 (approximately 2 months after therapy start). The BCC was located inside or close to the treatment area (on the right upper back), and was assessed as moderate by investigator. The event resolved on 2006.
The patient's medical history included sulphur allergy since seborrhoea dermatitis since hypercholesterolaemia since and asthma since , all ongoing. Past medical history included AKs and SBCC on multiple locations, dates and outcome unknown and NBCCs in on multiple locations and outcome unknown. Concomitant medications included ezetimibe and atorvastatin due to hypercholesterolaemia, fluticasone/salmeterol due to asthma and calcium, fish oil and vitamin for health supplement.
The investigator initially reported the event as non-serious and possibly related to treatment with the vehicle gel. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is possibly related to the vehicle gel (no drug). As the reaction occurred inside or close to the treatment area, it cannot be excluded that the vehicle gel contributed to its occurrence.
No further information is available.

Patient PEP005- This case concerns a 69-year-old male patient, who participated in study PEP005-002. The patient was administered vehicle gel, topically on the leg on Days 1 2005) and 8 2005).

Reportedly the patient experienced BCC on the 2005 (approximately 2 months after therapy start). The BCC was on an unknown location, and was assessed as mild by the investigator. The event was reported as resolved on the 2005.

The patient's medical history included tinnitus since and on-going. Past medical history included pneumonia in and resolved, NBCCs on multiple locations in and outcome unknown and AK, SCCs and SBCCs all on multiple locations, dates and outcome unknown.

There was no concomitant medication to be reported.

The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.

No further information is available.

Patient PEP005 [redacted] This case concerns a 69-year-old male patient, who participated in study PEP005-002. The patient was administered PEP005 Gel, 0.0025%, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2005) and 8 [redacted] 2005).
Reportedly the patient experienced neoplasm progression on the [redacted] 2005 (1 month after therapy start). The neoplasm progression was inside the treatment area, and was assessed as severe by the investigator. The event was reported as resolved on the [redacted] 2005.
The patient's medical history included asthma since [redacted] gastric reflux since [redacted] hypertension since [redacted] and hypercholesteremia since [redacted] all on-going. Past medical history included prostatic carcinoma in [redacted] and resolved, NBCCs on multiple locations in [redacted] and outcome unknown, AKs, SBCCs and SCCs on multiple locations with dates and outcome unknown. Concomitant medication included: cyproterone acetate due to prostatic carcinoma, atorvastatin due to hypercholesteremia, atropine/diphenoxylate due to diarrhea, budesonide due to asthma, pantoprazole due to gastric reflux and ramipril due to hypertension.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of Ingenol mebutate.
No further information is available.

Patient PEP005-014 [redacted] This case concerns a 66-year-old male patient, who participated in study PEP005-014. The patient was administered vehicle gel, topically on the arm. Study medication was to be applied on Days 1 [redacted]2008) and 2 [redacted]/2008).
Reportedly the patient experienced BCC on the [redacted]2008 (12 days after therapy start). The BCC was located on the left cheek, outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the [redacted]2008.
In addition to the event the patient experienced AK on the [redacted]2009 (2 months after therapy start). This event was unresolved with little or no change on the last follow-up.
The patient's medical history included intermittent sinus infections since [redacted] type II diabetes since [redacted], acid reflux since [redacted] pituitary gland tumor since [redacted] hypercholesterolemia and hypertension since [redacted] and sleep apnea since [redacted] all on-going. Past medical history included bulging disc in [redacted] back surgery-bulging disc in [redacted], trigger finger release in [redacted] and staph infection of the right hand in [redacted].Concomitant medication included: alendronate and acetylsalicylic acid due to preventative treatment, cabergoline due to pituitary tumor, valsartan and hydrochlorothiazide due to hypertension, glimepiride, metformin and insulin due to type II diabetes, omeprazole due to acid reflux, simvastatin due to hypercholesterolemia and fish oil, multivitamin and vitamin D due to general health.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-014 [redacted] This case concerns a 43-year-old male patient, who participated in the PEP005-014 study. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand. Study medication was to be applied on Days 1 [redacted] 2008) and 2 [redacted] 2008).

Reportedly the patient experienced BCC on the [redacted] 2008 (1 month after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.

The patient's medical history included depression since [redacted] and scar in the left clavicular area since [redacted] both on-going. Past medical history included BCC on back in [redacted] BCC on left upper back in [redacted] and melanoma in situ in the left clavicular area in [redacted] Concomitant medication included: fluoxetine due to depression and lidocaine with epinephrine due to electrodessication and curettage depression.

The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from controlled preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-014 [redacted] This case concerns a 78-year-old male patient, who participated in the PEP005- 014 study. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2008) and 2 ([redacted] /2008). Reportedly the patient experienced BCC on multiple locations on the [redacted] 2009 (2 months after therapy start). The BCCs were located outside the treatment area and were assessed as mild by the investigator. The events were unresolved with little or no change on the last follow-up.

The patient's medical history included gout since [redacted] hypertension since [redacted] hypothyroidism since [redacted] seborrheic keratosis since [redacted] solar lentigo since [redacted] BCC on left forearm since [redacted] and lichen planus like keratosis since [redacted] all on-going. Past medical history included multiple BCCs on different locations in [redacted] and [redacted] malignant melanoma in [redacted] and SCC in [redacted] Concomitant medication included: allopurinol due to gout, valsartan due to hypertension and levothyroxine due to hypothyroidism.

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from controlled preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-014 [redacted] This case concerns a 76-year-old female patient, who participated in study PEP005- 014. The patient was administered PEP005 Gel, 0.05%, topically on the leg. Study medication was to be applied on days 1 [redacted] 2008) and 2 [redacted] 2008). Reportedly the patient had a skin neoplasm on [redacted] /2009 (2 months after therapy start). The skin neoplasm was located outside the treatment area, and was assessed as mild by the investigator. The event was unresolved with little or no change on the last follow-up.
Prior to the event, the patient had abnormal lymphocyte morphology on [redacted] 2008 (3 days after therapy start) and purpurea on the [redacted] 2009 (2 months after therapy start).
The patient's medical history included broken finger right hand (date unknown), allergy to penicillin and sulfa drugs since [redacted] decreased vision since [redacted] hysterectomy in [redacted] breast cancer in [redacted] mastectomy of the right breast in [redacted] scar on abdomen and chest (dates unknown) and stomach ulcer since [redacted] hypothyroidism since [redacted] headaches since [redacted] frequent bladder infections since [redacted] restless leg syndrome since 2007, arthritis since [redacted] diarrhea since [redacted] hypertension since [redacted] and overactive bladder since [redacted] all ongoing. Past medical history included SCC on chest in [redacted] brain aneurism with associated surgical procedure in [redacted] and SCC on right posterior neck in 2008. Concomitant medication included: nizatidine for ulcer, celecoxib for arthritis, ciprofloxacin and metronidazole for diarrhea, carvedilol for hypertension, cranberry capsules for frequent bladder infections, darifenacin for overactive bladder, pramipexole and alprazolam for restless leg syndrome, levothyroxine for hypothyroidism, and ginko biloba, calcium, vitamin B12 and vitamin E for dietary supplements.
The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review. The sponsor's causality assessment of the case is not related, based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-014 [redacted] This case concerns an 83-year-old male patient, who participated in study PEP005- 014. The patient was administered vehicle gel, topically on the arm. Study medication was to be applied on Days 1 [redacted]2008) and 2 [redacted]2008).
Reportedly the patient experienced SCC on the [redacted]/2008 (2 months after therapy start).
The SCC was located inside the treatment area, and was assessed as mild by the investigator.
The event was reported as recovered on the [redacted]/2008.
The patient's medical history included BCC on left cheek since [redacted] SCC on right cheek since [redacted] hypertension since [redacted] SCC on ear since [redacted] BCC on ear and cheek since [redacted] BCC on forehead since [redacted] left anterior fascicular block since [redacted] and left axis deviation since [redacted] all on-going.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-014 [redacted] This case concerns an 81-year-old male patient, who participated in the PEP005- 014 study. The patient was administered vehicle gel, topically on the chest. Study medication was to be applied on Days 1 [redacted]/2008) and 2 [redacted] 2008). Reportedly the patient experienced BCC on the [redacted]/2008 (2 months after therapy start). The BCC was located outside the treatment area, and was assessed as moderate by the investigator. The event was unresolved with little or no change on the last follow-up.
Prior to the event the patient experienced staphylococcal skin infection inside the treatment area on the [redacted] 2008 (three weeks after therapy start).
The patient's medical history included insomnia since [redacted] first degree AV-block on ECG since [redacted] and left superior axis deviation since [redacted] all on-going. Past medical history included bowel cancer in [redacted] recurrent depressive episodes since [redacted] multiple IECs in [redacted] multiple BCCs in [redacted] multiple SCCs in [redacted] osteoarthritis in [redacted] asbestos plaques on lungs in [redacted] and headaches in [redacted]
Concomitant medication included: sodium chloride injection, due to staph infection in treatment area and zolpidem due to insomnia.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-015-19 [redacted] This case concerns a 67-year-old male patient, who participated in study PEP005-015. The patient was administered vehicle gel, topically on the face. Study medication was to be applied on Days 1 [redacted] 2008) and 2 [redacted] 2008).
Reportedly the patient experienced SCC on [redacted] 2008 (2 weeks before therapy start). The SCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.
The patient's medical history included hypertension since [redacted] gout since [redacted] hyperlipidemia since [redacted] and eczema since [redacted], all on-going. Past medical history included BCC in [redacted] and [redacted] melanoma in [redacted] and multiple SCCs in [redacted] and [redacted] Concomitant medication included: allopurinol due to gout, acetylsalicylic acid due to prophylaxis, amoxicillin due to tooth extraction, amlodipine and atorvastatin due to hypertension/hyperlipidemia, hydrochlorothiazide and lisinopril due to hypertension and multivitamins with minerals due to dietary supplement.
The investigator initially reported the SCC as a non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation and the event started prior to treatment.
No further information is available.

Patient PEP005-015 [redacted] This case concerns a 66-year-old male patient, who participated in study PEP005-015. The patient was administered PEP005 Gel, 0.015%, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted] 2008 and the last dose was applied on [redacted] 2008.
Reportedly the patient experienced BCC on the [redacted] 2008(approximately 2 months after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.
Prior to the event, the patient experienced muscle strain and acid reflux on the [redacted] 2008 (2 weeks after therapy start).
The patient's medical history included seasonal allergic rhinitis since [redacted] hypercholesterolemia and hypertension since [redacted] and plantar fasciitis since [redacted] all on-going. Concomitant medication included: celecoxib due to muscle strain, rosuvastatin due to hypercholesterolemia, valsartan and hydrochlorothiazide due to hypertension, ibuprofen due to plantar fasciitis, amlodipine due to hypertension and lansoprazole due to acid reflux.
The investigator initially reported the BCC as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of Ingenol mebutate.
No further information is available.

Patient PEP005-016-03 [redacted] This case concerns a 61-year-old male patient, who participated in study PEP005-016. The patient was administered vehicle gel, topically on the scalp. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted] 2009 and the last dose was applied on [redacted] 2009.

Reportedly the patient experienced malignant melanoma on the [redacted] 2009 (20 days after therapy start). The malignant melanoma was located outside the treatment area, and was assessed as moderate by the investigator. The event was reported as resolved on the last follow-up.

The patient's medical history included high triglycerides since [redacted] and on-going. Concomitant medication included: gemfibrozil due to high triglycerides and atorvastatin due to high triglycerides.

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.

No further information is available.

Patient PEP005-016-16 [redacted] This case concerns a 60-year-old male patient, who participated in study PEP005-016. The patient was administered PEP005 Gel, 0.015%, topically on the face. Study medication was to be applied on days 1, 2 and 3; the first dose was applied on [redacted] 2009 and the last dose was applied on [redacted] 2009.
Reportedly the patient experienced BCC on the [redacted] 2009(approximately two months after therapy start). The BCC was located outside the treatment area, and was assessed as moderate by the investigator. The event was reported as resolved on the last follow-up.
The patient's medical history included acid reflux since [redacted] type II diabetes and hypertension since [redacted] and hypercholesterolemia since [redacted] all on-going. Past medical history included BCC in [redacted] and [redacted] and squamous cell carcinoma in [redacted] Concomitant medication included: acetylsalicylic acid due to cardiac prophylaxis, lisinopril due to hypertension, metformin, due to type II diabetes, omeprazole due to acid reflux and simvastatin due to hypercholesterolemia.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005 [redacted] This case concerns a 74-year-old male patient, who participated in study PEP005-018. The patient was administered PEP005 Gel, 0.05%, topically on the back of the hand. Study medication was to be applied on Days 1 ([redacted]2007) and 2 [redacted]2007).

Reportedly the patient experienced BCC on the [redacted]2007 (one week after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.

The patient's medical history included acid reflux since [redacted], hearing loss and hypertension since [redacted] diabetes since [redacted] dysplatic nevus in mid low back since [redacted] and SCCs located on left infraorbital and left posterior arm since [redacted] all on-going. Other medical history included BCC on nose in [redacted] barrett esophagus in [redacted] and thyroid cancer in [redacted]

Concomitant medication included: glipizide due to diabetes, lisinopril due to hypertension, metoprolol due to hypertension, metformin due to diabetes, omeprazole due to acid reflux, levothyroxine due to thyroidectomy and vitamins and calcium due to health maintenance.

The investigator initially reported the event as a non-serious and not related event to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005 [redacted] This case concerns a 71-year-old male patient, who participated in study PEP005-018. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand. Study medication was to be applied on Days 1 [redacted] 2007) and 2 [redacted] 2007).

Reportedly the patient experienced SCC on the [redacted] 2007(1 week after therapy start). The SCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.

In addition to the event the patient experienced skin exfoliation and skin lesion on the rim and behind the left ear on the [redacted] 2007 (2 months after therapy start).

The Investigator initially reported the event as serious and not related to treatment with PEP005.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-020 [redacted] This case concerns an 80-year-old male patient, who participated in study PEP005-020. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] 2009).

Reportedly the patient experienced BCC on [redacted] 2009 (3 weeks after therapy start). The BCC was located outside the treatment area, and was assessed as moderate by the investigator. The event was reported as resolved on the last follow-up. Prior to the event the patient experienced application site pain on [redacted] 2009 (3 days after therapy start).

The patient's medical history included food allergy (shrimp) since [redacted] environmental allergies since [redacted] rosacea since [redacted] gastroesophageal reflux disease (GERD) since [redacted] hyperlipidemia since [redacted] hypertension since [redacted] and onychodystrophy since [redacted] all ongoing. Other medical history included bilateral hernia repair in [redacted] mastoidectomy of right ear in [redacted] bilateral eczema on hands in [redacted] seborrheic dermatitis in [redacted] SCCs in [redacted] and [redacted] cerebral vascular accident in [redacted] BCCs in [redacted] and [redacted] keratoacanthoma in [redacted] bilateral cataract surgery in [redacted] and malignant melanoma in [redacted]

Concomitant medication included: acetylsalicylic acid due to prophylaxis, rosuvastatin for hyperlipidemia, lisinopril and metoprolol for hypertension, lansoprazole for GERD, acetaminophen and hydrocodone/acetaminophen for pain at the treatment site and multivitamins and minerals for general health maintenance.

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review. The sponsor's causality assessment of the case is not related, based on previous results from preclinical and clinical trials with ingenol mebutate, where it was demonstrated that, at concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-020 [redacted] This case concerns an 80-year-old male patient, who participated in study PEP005-020. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted]/2009).

Reportedly the patient experienced BCC on [redacted] 2009 (2.5 months after therapy start). The BCC was located outside the treatment area, and was assessed as not accessible by the investigator. The event was reported as resolved on the last follow-up.

The patient's medical history included coronary artery disease, atrial fibrillation and high cholesterol since [redacted] and on-going. Past medical history included myocardial infarction in [redacted] and melanoma in [redacted] Concomitant medication included: warfarin, digoxin, isosorbide dinitrate and metoprolol due to coronary artery disease and atorvastatin and ezetimibe due to high cholesterol.

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-020 [redacted] This case concerns a 63-year-old female patient, who participated in study PEP005-020. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] 2009). Reportedly the patient experienced BCC on [redacted] 2009 (1 month after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.

The patient's medical history included postmenopausal since [redacted] and on-going. Other medical history included multiple BCCs in [redacted] and [redacted] SCC in [redacted] and porokeratosis in [redacted]

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-020 [redacted] This case concerns an 84-year-old female patient, who participated in study PEP005-020. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand. Study medication was to be applied on Days 1 [redacted]2009) and 2 [redacted]2009).

Reportedly the patient experienced SCC on [redacted] 2009 (3 weeks after therapy start). The SCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.

The patient's medical history included postmenopausal since [redacted] anxiety since [redacted] hypertension since [redacted] and peripheral vascular disease since [redacted] all ongoing. Concomitant medication included: amlodipine, irbesartan and metoprolol due to hypertension, acetylsalicylic acid due to peripheral vascular disease and escitalopram due to anxiety.

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-020 [redacted] This case concerns a 72-year-old male patient, who participated in study PEP005-020 study. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 [redacted]/2009) and 2 ([redacted]/2009). Reportedly the patient experienced SCC on [redacted]2009 (44 days after therapy start). The SCC was located inside the treatment area, and was assessed as moderate by investigator. The event resolved on the [redacted]2009.

The patient's medical history included hypertension since [redacted] ischaemic heart disease since [redacted] high cholesterol since [redacted] and gout since [redacted] all on-going. Past medical history included dysplastic naevus in [redacted] angioplasty in [redacted] multiple BCCs in [redacted] multiple SCCs in [redacted] BCC in [redacted] and SCC in [redacted]

Concomitant medication included: acetylsalicylic acid due to ischaemic heart disease, colchicine due to gout, enalapril due to hypertension and simvastatin due to high cholesterol.

The investigator initially reported the event as a non-serious and possibly related event to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is possibly related. As the reaction occurred inside the treatment area, it cannot be excluded that the drug has contributed to its occurrence.

No further information is available.

Patient PEP005-022 [redacted] This case concerns a 71-year-old male patient, who participated in study PEP005-022. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2008) and 2 [redacted] 2008).
Reportedly the patient experienced SCC on [redacted] 2008 (49 days after therapy start). The SCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as unresolved with little or no change on the last follow-up.
The patient's medical history included non-insulin dependent diabetes, hypercholesterolemia and hypertension since [redacted] all on-going. Other medical history included arthritis in [redacted]
Concomitant medication included: hydrochlorothiazide due to hypertension, simvastatin due to hypercholesterolemia and metformin due to diabetes.
The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-025 [redacted] This case concerns a 59-year-old female patient, who participated in study PEP005-025. The patient was administered PEP005 Gel, 0.015%, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted]/2009 and the last dose was applied on [redacted] 2009.
Reportedly the patient experienced BCC on the [redacted]/2009 (2 months after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.
Prior to the event, the patient experienced intertriga candida on the right breast and sciatica in left leg, both of the events occurred on the [redacted] 2009 (1 month after therapy start).
The patient's medical history included hysterectomy in [redacted] allergy to levaquin since [redacted] and ongoing and hypertension since [redacted] and on-going. Concomitant medication included: zinc oxide and naftifine HCl due to intertrigo candida.
The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-025 [redacted] This case concerns a 68-year-old male patient, who participated in study PEP005-025. The patient was administered vehicle gel, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted] 2009 and the last dose was applied on [redacted] 2009.
Reportedly the patient experienced BCC on [redacted] 2009 (5 days after therapy start). The basal cell carcinoma was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.
The patient's medical history included diabetes mellitus type II since [redacted] hypercholesterolemia since [redacted] hypertension since [redacted] and atrial fibrillation since [redacted] all on-going.
Concomitant medication included: glimepiride and metformin due to diabetes, metoprolol and dofetilide due to hypertension, simvastatin due to hypercholesterolemia and warfarin due to atrial fibrillation.
The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-025 [redacted] This case concerns a 71-year-old male patient, who participated in study PEP005-025. The patient was administered PEP005 Gel, 0.015%, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted] 2009 and the last dose was applied on [redacted] 2009.

Reportedly the patient experienced two cancer events. The first was BCC on [redacted] /2009 (2 weeks after therapy start) located outside the treatment area, which was assessed as mild by the investigator. The event was reported as resolved on the [redacted] 2009. The patient also experienced malignant melanoma on [redacted] 2009 (3 weeks after therapy start). The malignant melanoma was located outside the treatment area, and was assessed as severe by the investigator. The event was reported as unresolved with little or no change at follow-up.

The patient's medical history included hypertension and hypercholesterolemia since [redacted] sleep apnea since [redacted] aphasia since [redacted] diabetes since [redacted] anxiety since [redacted] and arthritis since [redacted] all on-going. Past medical history included stroke in [redacted] seizure in [redacted] and cataracts and removal in [redacted] Concomitant medication included: pioglitazone hydrochloride and insulin glargine due to diabetes, acetylsalicylic acid/extended-release dipyridamole due to stroke prophylaxis, triamterene/hydrochlorothiazide, losartan and lisinopril due to hypertension, propoxyphene napsylate/cetaminophen and tramadol due to arthritis, atorvastatin due to hypercholesterolemia, phenytoin due to seizure prophylaxis and venlafaxine due to anxiety.

The investigator initially reported both events as non-serious and not related to the treatment with PEP005. The sponsor upgraded the events to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-025- This case concerns a 56-year-old male patient, who participated in study PEP005-025. The patient was administered vehicle gel, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on 2009 and the last dose was applied on 2009.
Reportedly the patient experienced basosquamous carcinoma on 2009 (2 months after therapy start). The basosquamous carcinoma was located inside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the last follow-up.
The patient's medical history included blindness on right eye since Past medical history included lung cancer in BCC in SCC in and intra epidermal carcinoma in
The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-028 [redacted] This case concerns a 74-year-old male patient, who participated in the PEP005-028 study. The patient was administered vehicle gel, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] 2009).
Reportedly the patient experienced SCCs on multiple locations on [redacted] 2009 (1 month after therapy start). The SCCs were located outside the treatment area, and were assessed as mild by the investigator. The event was reported as resolved on [redacted] 2009.
The patient also experienced skin papilloma on [redacted] 2009 (6 weeks after therapy start).
The patient's medical history included herniorrhaphy rating in [redacted] and [redacted] appendectomy in [redacted] TURP in [redacted] allergy: amlodipine basylate since [redacted] and ongoing, hypertension since [redacted] and ongoing, allergy: oxaprozin since [redacted] and ongoing, seborrheic keratosis in [redacted] bullous dermatosis and dermatitis in [redacted] arthropod assault ongoing since [redacted] epidermal inclusion cyst ongoing since [redacted] blisters (psuedo porphyria) in [redacted] hemorrhoidectomy in [redacted] SCC in [redacted] and [redacted] acid reflux ongoing since [redacted] epidermal hyperpigmentation ongoing since [redacted] gout ongoing since [redacted] melanoma in situ mohs in [redacted] SCC (recurrent) mohs in [redacted] verruca (wart) in [redacted] atypical squamous proliferation in [redacted] hypercholesterolemia ongoing since [redacted] CVA in [redacted] MI in [redacted] arthritis since [redacted] pacemaker since [redacted] and enlarged prostate since [redacted] Concomitant medication included: acetylsalicylic acid for prophylaxis, irbesartan and enalapril for hypertension, dutasteride for enlarged prostate, colchicine and febuxostat for uric acid, furosemide for diuresis, hydrocortisone for facial dermatosis, esomeprazole for acid reflux, niacin and pravastatin for hypercholesterolemia, and multivitamins/minerals, fish oil, glucosamine/chondroitin and potassium for general health.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-028 [redacted] This case concerns a 72-year-old male patient, who participated in the PEP005-028 study. The patient was administered vehicle gel, topically on the shoulder. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] 2009).
Reportedly the patient experienced BCC on [redacted] 2009 (3 weeks after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as unresolved with little or no change on the last follow-up.
The patient's medical history included dentures since [redacted] hypothyroidism since [redacted] morphine allergy since [redacted], hearing aids since [redacted] gout since [redacted] benign prostatic hypertrophy since [redacted] and seborrheic dermatitis since [redacted] all ongoing.
Past medical history included MI in [redacted] coronary artery bypass in [redacted] and [redacted] cancer (unknown) in [redacted] and [redacted] BCC in [redacted] seborrheic keratosis in [redacted] and BCC (MOHS) in [redacted]
Concomitant medication included: allopurinol due to gout, acetylsalicylic acid due to MI prevention, atenolol due to cardiovascular event precaution post MI, ascorbic acid, fish oil, folic acid, vitamin B12 and glucosamine due to health supplement, ketoconazole due to seborrheic dermatitis and levothyroxine due to hypothyroidism.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-028 [redacted] This case concerns a 77-year-old male patient, who participated in the PEP005-028 study. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 [redacted]/2009) and 2 [redacted] 2009). Reportedly the patient experienced BCC on [redacted] 2009 (51 days after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was reported as resolved on the [redacted] 2009.
The patient's medical history included seasonal allergies since [redacted] diabetes mellitus since [redacted] benign prostatic hypertrophy since [redacted] chronic prostatitis since [redacted] hypercholesterolemia since [redacted] and hypertension since [redacted] all ongoing.
Concomitant medication included: quinapril and hydrochlorothiazide due to hypertension, acetylsalicylic acid due to CAD prevention, dutasteride due to benign prostatic hyperplasia, diphenhydramine due to seasonal allergies, insulin lispro and insulin glargine due to diabetes mellitus, sulfamethoxazole trimethoprim due to chronic prostatitis, simvastatin due to hypercholesterolemia and multivitamin due to health supplement.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-028 [redacted] This case concerns a 74-year-old male patient, who participated in the PEP005-028 study. The patient was administered vehicle gel, topically on the back of hand. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] /2009). Reportedly the patient experienced SCC on the [redacted] 2009 (6 weeks after therapy start). The SCC was located outside the treatment area, and was assessed as moderate by the investigator. The event was unresolved with little or no change on the last follow-up.
The patient's medical history included myopia since [redacted] hypertension since [redacted] hypercholesterolemia since [redacted] and benign prostatic hyperplasia since [redacted] all ongoing. Past medical history included hemangioma in [redacted] EIC in [redacted] multiple BCCs in [redacted] and [redacted] SBCC in [redacted] multiple SCCs in [redacted] and [redacted] invasive SCC in [redacted] and [redacted] fibrosing BCC in [redacted] sclerosing BCC in [redacted] infiltrative BCC in [redacted] and subacute dermatitis in [redacted] Other medical history included participation in investigational drug studies; imiquimod vs. placebo and 5-fluoracil vs. placebo.
Concomitant medication included: acetylsalicylic acid due to stroke prophylaxis, carvedilol and hydrochlorothiazide due to hypertension and atorvastatin and niacin due to hypercholesterolemia.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-028 [redacted] This case concerns an 85-year-old female patient, who participated in the PEP005-028 study. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] /2009).

Reportedly the patient experienced SCC on [redacted] /2009 (2 weeks after therapy start). The SCC was located outside the treatment area, and was assessed as moderate by the investigator. The event was unresolved with little or no change at follow-up. Prior to the event the patient experienced AK on [redacted] 2009 (2 weeks after therapy start). The patient's medical history included farsightedness since [redacted] hyperlipidemia since [redacted], hard of hearing since [redacted] postmenopausal since [redacted] bilateral cataracts since [redacted] essential thrombocytosis since [redacted] hypertension since [redacted] osteoarthritis (bilateral fingers and back) since [redacted] acid reflux since [redacted] insomnia since [redacted] onychomycosis since [redacted] and sciatica in back since [redacted] all ongoing. Past medical history included paronychia in [redacted] SCC in [redacted] nummular dermatitis in [redacted] keratoacanthoma in [redacted] keratoacanthoma type SCC with stasis dermatitis in [redacted] and minor tremors in [redacted] Concomitant medication included: naproxen and acetaminophen for arthritis pain, acetylsalicylic acid for stroke prophylaxis, glucosamine for arthritis, hydroxyurea for essential thrombocytosis, lovastatin for hypercholesterolemia, omeprazole for acid reflux, triamterene/ hydrochlorothiazide for hypertension, acetaminophen and diphenhydramine for insomnia, and ascorbic acid for nutritional supplement.

The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-028-[redacted] This case concerns a 58-year-old male patient, who participated in the PEP005-028 study. The patient was administered vehicle gel, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2009) and 2 [redacted] 2009).
Reportedly the patient experienced BCC on [redacted] 2009 (2 months after therapy start). The BCC was located outside the treatment area, and was assessed as mild by the investigator. The event was unresolved with little or no change on the last follow-up.
The patient's medical history included diabetes type II since [redacted] hypercholesterolemia since [redacted] hypertension since [redacted] muscle spasm since [redacted] and obesity since [redacted] all ongoing.
Concomitant medication included: losartan and hydrochlorothiazide due to hypertension, simvastatin due to hypercholesterolemia, metformin due to diabetes type II and diclofenac and cyclobenzaprine due to muscle spasm.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive any PEP005 formulation.
No further information is available.

Patient PEP005-020 [redacted] This case concerns a 71-year-old male patient, who participated in the PEP005-031 study. The patient was administered PEP005 Gel, 0.05%, topically on the back of hand, applied on Days 1 [redacted] 2009) and 2 [redacted] 2009).
Reportedly the patient experienced BCC on the [redacted] 2009 (three months after therapy start). The BCC was located inside the treatment area, and was assessed as moderate by the investigator. The event was unresolved with little or no change on the last follow-up.
The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-003 This case concerns a 36-year-old male patient, who participated in the PEP005-003 study. The patient was administered vehicle gel, topically on the Shoulder. Study medication was to be applied on Days 1 /2005) and 8 2005). Reportedly the patient experienced BCC on the 2006 (three months after therapy start). The BCC was assessed as mild by the investigator. The event was unresolved at last follow-up.

The patient's medical history included multiple AK, SBCC and SCC on the face, trunk and extremities since and ongoing. Concomitant medication included: 1% xylocaine and adrenaline - due to excision of BCC, Celebrex – due to torn medial meniscus of the left knee, paracetamol – pain management for excision of BCC and 1% xylocaine and adrenaline as local anaesthetic.

The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive and PEP005 formulation.

No further information is available.

Patient PEP005-006 [redacted] This case concerns an 80-year-old male patient, who participated in the PEP005-006 study. The patient was administered vehicle gel, topically on the Scalp. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted] 2006 and the last dose was applied on [redacted] 2006.
Reportedly the patient experienced BCC on [redacted] 2007 (2 months after therapy start). The BCC was located on the left side of the nose and was assessed as mild by the investigator. The outcome of the event was unknown at last follow-up.
The patient's medical history included BCC in [redacted] depression in [redacted] merkel cell carcinoma in [redacted] neuroendocrine carcinoma in [redacted] rosacea on the nose since [redacted] and ongoing, SCC in [redacted] and in [redacted] and SCC in situ in [redacted] Concomitant medication included: tetracycline, due to rosacea and treatment is ongoing.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive and PEP005 formulation.
No further information is available.

Patient PEP005-006 This case concerns a 61-year-old male patient, who participated in the PEP005-006 study. The patient was administered vehicle gel, topically on the arm. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on 2006 and the last dose was applied on 2006.

Reportedly the patient experienced BCC on the 2006 (one month after therapy start). The BCC was located at an unknown location, and was assessed as moderate by the investigator. The event outcome was not reported on the last follow-up.

The patient's medical history included: anxiety since and ongoing, arthritis since and ongoing, coronary artery disease since and ongoing, dementia since and ongoing, follicular cyst on the nose since with unknown outcome, GERD since and ongoing, hyperlipidemia since and ongoing, hypertension since and ongoing, insomnia since and ongoing, migraines since and ongoing, seizures since and ongoing, squamous cell carcinoma on multiple location on the arm since with outcome unknown.

Concomitant medication included: donepezil HCL due to dementia in celecoxib due to arthritis in rosuvastatin calcium due to hyperlipidemia in terazosin HCL due to hypertension in lamotrigine due to seizures in eszopiclone due to insomnia in esomeprazole magnesium due to GERD in niacin due to hyperlipidemia in and galantamine and mirtazapine due to dementia in

The investigator initially reported the event as non-serious and not related to the treatment with vehicle. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related. This is based on the fact that the patient did not receive and formulation of PEP005.

No further information is available.

Patient PEP005-006 This case concerns a 79-year-old Female patient, who participated in the PEP005-006 study. The patient was administered PEP005 Gel, 0.025%, topically on the arm. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on 2006 and the last dose was applied on 2006.

Reportedly the patient experienced dome shaped erythematous nodule with central keratotic plug on the left leg (SCC) on 2006 (approximately 2 months after therapy start). The SCC was located on the left leg outside the treatment area and was assessed as moderate by the investigator. The event was reported as little or no change at last follow-up. The patient also experienced SCC on 2007 (approximately 3 months after therapy start). The SCC was located on the left leg, outside the treatment area and was assessed as moderate by the investigator. It was not reported if this lesion was the same one reported on /2006. The event was reported as recovered at last follow-up.

Prior to the event the patient experienced pruritus at application site on 2006 (during therapy). The pruritus at application site was assessed as moderate by the investigator. The event was reported as recovered at last follow-up.

The patient's medical history included: basal cell on the nose in and on the temple in with unknown outcome, bilateral cataracts in with unknown outcome, degenerative joint disease in and ongoing, intermittent vertigo in with unknown outcome, kerato canthoma on the right arm in with unknown outcome, microscopic hematuria in with unknown outcome, osteoarthritis in and ongoing, osteoporosis in and ongoing and seborrheic keratosis on the temple and the breast in with an unknown outcome.

Concomitant medication include: calcium due to health maintenance, folic acid due to health maintenance, alendronate sodium due to osteoporosis and multivitamins due to health maintenance.

The investigator initially reported the first event as non-serious and not related, and the second event as serious and not related to the treatment with PEP005. The sponsor upgraded the first event to serious due to medical significance after data review, and assesses both events as serious.

The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-006 This case concerns a 70-year-old male patient, who participated in the PEP005-006 study. The patient was administered PEP005 Gel, 0.05%, topically on the arm. The patient received a vehicle treatment on Day 1 (2006) and PEP005 Gel on Days 2 2006) and 3 2006).
Reportedly the patient experienced BCC on 2006(same month as therapy start). The BCC was located at an unknown location, and was assessed as moderate by the investigator. The event was reported as recovered at last follow-up.
The patient's medical history included: erectile dysfunction in 2001 and ongoing, and glaucoma in and ongoing. Concomitant medication include: sildenafil due to erectile dysfunction and latanoprost due to glaucoma.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-007 This case concerns an 80-year-old male patient, who participated in the PEP005-007 study. The patient was administered PEP005 Gel, 0.025%, topically on the face. Study medication was to be applied on Days 1 2007) and 2 2007). Reportedly the patient experienced BCC on 2007(2 months after therapy start). The BCC was located on the right side of the neck outside the treatment area, and was assessed as moderate by the investigator. The event was reported as recovered at last follow-up.
Prior to the event, the patient experienced swelling in the right eye on the /2007 (the day after last treatment). The swelling in the eye was assessed as moderate by the investigator. The event was reported as recovered at last follow-up.
The patient's medical history included: multiple BCC in with unknown outcomes, enlarged prostate in with unknown outcome, multiple SCC in with unknown outcomes, a slight stroke in with unknown outcome and vertigo in and ongoing.
Concomitant medication include: prochlorperazine due to vertigo and warfarin due to stroke.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-007 [redacted] This case concerns a 66-year-old male patient, who participated in the PEP005-007 study. The patient was administered PEP005 Gel, 0.0075%, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on [redacted] 2007 and the last dose was applied on [redacted] /2007.
Reportedly the patient experienced Bowen's disease at an unknown date, the event ended [redacted] 2007. Bowen's disease was reported to be located inside the treatment area, and was assessed as mild by the investigator. The event was reported as recovered at last follow-up.
The patient's medical history included: a right inguinal hernia since [redacted] and ongoing, BCCs' in multiple locations since [redacted] with unknown outcome, cholecystitis since [redacted] with unknown outcome, epidermal cyst in the right thigh since [redacted] with unknown outcome, a hiatus hernia since [redacted] and ongoing, hypotension since [redacted] and ongoing, IEC on the right forearm in [redacted] with unknown outcome, ischemic heart disease since [redacted] and ongoing, rosacea on the face since [redacted] and ongoing, SCC on the right thigh in [redacted] with unknown outcome, seborrhoeic keratoses at various locations since [redacted] and ongoing and traumatic brain injury since [redacted] and ongoing. Concomitant medication include: acetylsalicylic acid, isosorbide mononitrate, clopidogrel hydrogen, isosorbide-5-mononitrate and simvastatin due to ischemic heart disease, citalopram and pericyazine due to traumatic brain injury.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-007 This case concerns an 86-year-old male patient, who participated in the PEP005-007 study. The patient was administered PEP005 Gel, 0.0050% topically on the face. Study medication was to be applied on Days 1, 2 and 3; the first dose was applied on 2007 and the last dose was applied on 2007.
Reportedly the patient experienced BCC on the 2007 (2 months after therapy start). The BCC was located at the left upper back, outside the treatment area and was assessed as moderate by the investigator. The event was reported recovered at last follow-up.
Prior to the event the patient experienced urinary tract infections on the /2007, the /2007 and the 2007 (during treatment, and approximately a month after therapy start). The urinary tract infections were assessed as mild by the investigator. The events from the 2007 and the 2007 were reported as recovered while the event from the 2007 was reported as recovering at last follow-up.
The patient's medical history included: atrial fibrillation since and ongoing, fibroxanthoma in the scalp in with an unknown outcome, melanoma in the left postauricular in with an unknown outcome, multiple BCCs in with an unknown outcome, multiple SCCs in with an unknown outcome, recurrent UTIs since and ongoing and reflux since and ongoing. Concomitant medication include: acetylsalicylic acid and warfarin due to atrial fibrillation, omeprazole due to reflux, trimethoprim due to UTIs.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-007 This case concerns a 69-year-old Female patient, who participated in the PEP005-007 study. The patient was administered PEP005 Gel, 0.0175%, topically on the face. Study medication was to be applied on Days 1, 2 and 3; the patient received two doses of treatment medication for a total of two days. The first dose was applied on 2007 and the last dose was applied on 2007.
Reportedly the patient experienced superficial BCC on multiple locations on 2007 (2 months after therapy start). The BCC was located on the left posterior shoulder and on the left and right upper back, outside the treatment area and was assessed as moderate by the investigator. The event was reported as recovered at last follow-up.
Prior to the event the patient experienced discomfort in the treatment area and insomnia on the 2007 (during therapy). The events were assessed as moderate by the investigator. The events were reported as recovered at last follow-up.
The patient's medical history included: arthritis since and ongoing, multiple BCCs in with an unknown outcome, gout since and ongoing, hypertension since and ongoing, mild depression since and ongoing, psoriasis since and ongoing, SCC in the right temple in with an unknown outcome. Concomitant medication include: allopurinol due to gout, metoprolol tartrate due to hypertension, diclofenac due to arthritis, dothiepin due to depression, cilazapril due to hypertension, joint care supplement due to arthritis, multivitamin due to general wellbeing.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-009 This case concerns a 48-year-old female patient, who participated in the PEP005-009 study. The patient was administered PEP005 Gel, 0.15%, topically on the chest. Study medication was to be applied on Day 1 2008).
Reportedly the patient experienced BCC on 2008 (approximately 3 months after therapy start). The BCC was located on the upper left arm, outside the treatment area and was assessed as mild by the investigator. The event was reported as recovered at last follow-up.
Prior to the event, the patient experienced application site itching and burning on /2008 (during therapy period). The events were assessed as mild by the investigator and related to study treatment. The event was reported as recovered at last follow-up. On /2008 (approximately 1 month after therapy start) the patient experienced heat rash, assessed by the investigator as mild and not related to study treatment. The event was reported as recovered at last follow-up.
The patient's medical history included: AK in multiple locations ongoing since angiomas in the upper back region in with unknown outcome, compound nevus in multiple locations in and with unknown outcome, depression ongoing since heel spurs in with unknown outcome, hemangiomas in the chest and back ongoing since hemorrhoids ongoing since hypothyroidism ongoing since inter dermal nevus on the right shoulder and right clavicle ongoing since lentigos on the back, chest and upper extremities ongoing since melanoma back and right lower abdomen in with unknown outcome, and menopause since
Concomitant medication included gold bond powder for heat rash to
The investigator initially reported the BCC as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-009 This case concerns a 54-year-old male patient, who participated in the PEP005-009 study. The patient was administered PEP005 Gel, 0.25%, topically on the back. Study medication was to be applied on Day 1 (/2009).
Reportedly the patient experienced BCC on 2009 (approximately 3 months after therapy start). The BCC was located on the right upper lateral forehead, outside the treatment area and the severity of the event was not assessed. The event was reported as recovered at last follow-up.
Prior to the event the patient experienced mild itching in treatment area (application site reaction) on the 2009 (during therapy period). The event was assessed as mild by the investigator and related to the treatment with PEP005. The event was reported as recovered at last follow-up. On the 2009 (one day after therapy) the patient experienced skin abrasion on back. This event was assessed as mild by the investigator and not related to the treatment with PEP005. The event was reported as recovered at last follow-up. On 2009 (approximately 1 month after therapy start) the patient experienced anal fissure. This event was assessed as moderate by the investigator and not related to the treatment with PEP005. The event was reported as recovered at last follow-up.
The patient's medical history included AK on the forehead since and ongoing, allergy (seasonal) since and ongoing, gerd gastroesophageal reflux disease since and ongoing, hemangioma on the abdomen since and ongoing, intradermal nevus on the right shoulder since and ongoing, joint pain since and ongoing, lentigos in multiple locations since and ongoing, nodular BCC in the left dorsal forearm in with unknown outcome, seborrheic keratoses on the back and chest since and ongoing and squamous cell carcinoma in situ on the right superior helix in with unknown outcome.
Concomitant medication included: naproxen due to joint pain, loratadine due to seasonal allergy, glucosamine as supplement, omeprazole due to gerd and bisacodyl due to an anal fissure.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-013 This case concerns a 66-year-old male patient, who participated in the PEP005-013 study. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 (2007) and 2 2007). Reportedly the patient experienced BCC on 2007 (within 1 month after therapy start). The BCC was located on the nose, outside the treatment are; and was assessed as mild by the investigator. The event was reported recovered at last follow-up.
The patient's medical history included BCCs in various locations in with unknown outcome, COPD since and ongoing, IECs in various locations in with unknown outcome, osteoporosis since and ongoing and seborrhoeic keratosis in various locations and ongoing. Concomitant medication included: alendronate due to osteoporosis and tiotropium bromide due to COPD.
The investigator initially reported the event as non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-002 This case concerns a 62-year-old female patient, who participated in the PEP005-002 study. The patient was administered PEP005 Gel, 0.01%, topically on the face. Study medication was to be applied on Days 1 2006) and 2 2006).
Reportedly the patient experienced BCC (unknown period after therapy start). The BCC was located in the chin. Proximity to the treatment area is unknown, and was assessed as mild by the investigator. The outcome of the event is unknown.
Prior to the event the patient experienced a urinary tract infection and solar keratosis on the nose. The date and outcome of these events are unknown.
The patient's medical history included hypertension (continuous since , hysteroscopy (resolved in , laparoscopy (resolved in and a prior melanoma in with an unknown outcome and duration. Concomitant medication included: cefalexin - due to urinary tract infection, atenolol – due to hypertension and Xylocaine 1 % with adrenaline (2 doses) used as a local anaesthetic.
The investigator initially reported the event as a non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-002[redacted]: This case concerns a 54-year-old male patient, who participated in the PEP005-002 study. The patient was administered PEP005 Gel, 0.0025%, topically on the back. Study medication was to be applied on Days 1 [redacted]/2005) and 8 ([redacted]2005). Reportedly the patient experienced BCC on the [redacted]2006 (5 months after therapy start). The BCC was assessed as mild by investigator. The event resolved on the [redacted]2006.
The patient's medical history included hypercholesterolemia since [redacted] and ongoing. Furthermore on screening the [redacted] the patient expressed multiple NBCC on the face, trunk and extremities. Past medical history included multiple AKs, SBCCs and SCCs, dates unknown. Concomitant medication included: atorvastatin calcium, due to hypercholesterolemia.
The investigator initially reported the event as a non-serious and not related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.
The sponsor's causality assessment of the case is not related. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.
No further information is available.

Patient PEP005-002 This case concerns a 77-year-old female patient, who participated in the PEP005-002 study. The patient was administered PEP005 Gel, 0.01% on Days 1 2005) and 2 2005), topically on the face.
Reportedly the patient experienced neoplasm progression on the 2005 (56 days after therapy start). Furthermore the patient experienced bleeding from the reported neoplasm as well as folliculitis 10mm fro reported neoplasm. The neoplasm progression was located inside the treatment area, and was assessed as mild by investigator. The event was unresolved at last follow-up.
Prior to the event the patient experienced application site pain assessed as mild, start date, end date or outcome are unknown.
The patient's medical history included reflux oesophagitis since and osteoporosis since both ongoing. Past medical history included NBCCs in and AKs in
Concomitant medication included: alendronate sodium, due to osteoporosis and esomeprazole magnesium, due to reflux oesophagitis.
The investigator initially reported the event as a non-serious and possibly related to the treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review. The sponsor's causality assessment of the case is possibly related. As the event occured within the treatment area, it can not be excluded that the drug was not related
No further information is available.

Patient PEP005-002 This case concerns a 76 -year-old female patient, who participated in the PEP005-002 study. The patient was administered PEP005 Gel, 0.01 %, topically on the arm. Study medication was to be applied on Days 1 2005) and 2 (2005). Reportedly the patient experienced SCC of the skin on the 2005 (2.5 months after therapy start). The SCC was located on the forearm, not further specified whether located inside or outside the treatment area, and was assessed as mild by investigator. The event resolved on the 2005.

The patient's medical history included hypercholesteremia, hypertension, non-insulin dependent diabetes, osteoarthritis and reflux since and ongoing. Furthermore it included sinusitis since and torn cruciate ligament on the right knee since June and ongoing. Past medical history included AKs, NBCCs in SBCCs and SCCs.

Concomitant medication included: acular eye drops due to sinusitis, avapro HCT due to hypertension, gliclazide due to non-insulin dependent diabetes, aluminum hydroxide and magnesium carbonate due to Hiatus hernia, atorvastatin due to hypercholesteremia, neosporin due to sinusitis, acetaminophen due to osteoarthritis, and eye drops due to sinusitis.

The investigator initially reported the event as non-serious and not related to treatment with PEP005. The sponsor upgraded the event to serious due to medical significance after data review.

The sponsor's causality assessment of the case is not related event. This is based on previous results from preclinical and clinical trials with topical treatment of ingenol mebutate, where it was demonstrated that, at the concentrations applied topically for treatment of AK lesions, there was no systemic absorption of ingenol mebutate.

No further information is available.

Patient PEP005-022 [redacted] This case concerns a 68-year-old male patient, who participated in the PEP005-022 study. The patient was administered PEP005 Gel, 0.05%, topically on the arm. Study medication was to be applied on Days 1 [redacted] 2008) and 2 [redacted] 2008). Reportedly the patient experienced SCC on [redacted] 2008 (29 days after therapy start). It was not reported whether this lesion was a progression of the prior hyperkeratosis. The SCC was located inside the treatment area, and was assessed as mild by investigator. The event resolved on the [redacted] 2008.
Prior to the event the patient experienced hyperkeratosis on the forearm on the [redacted] 2008 (26 days after therapy start). The hyperkeratosis was located inside the treatment area, and was assessed as mild by investigator. The event resolved on the [redacted] 2008.
Furthermore the patient experienced BCC on the [redacted] 2008 (51 days after therapy start). The BCC was located outside the treatment area, and was assessed as mild by investigator. The event resolved on the [redacted] 2008.
The patient's medical history included glaucoma since [redacted] and hypertension since [redacted] both ongoing. Past medical history included BCCs on different locations in [redacted] and [redacted] Also, it included two SCCs in [redacted] and [redacted] on different locations. Concomitant medication included: latanoprost, due to glaucoma and ramipril, due to hypertension.
The investigator initially reported the SCC as a serious and possibly related event to the treatment with PEP005. The investigator's report on the BCC was as non-serious and not related to treatment. The sponsor upgraded the BCC to serious due to medical significance after data review. The sponsor's causality assessment of the case is possibly related. As the event occured within the treatment area, it can not be excluded that the drug was not related
No further information is available.