CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	DDDP/ODE III/OND/CDER
Reviewer Name(s)	Joanna W. Ku, MD
Through CDTL	Jill A. Lindstrom, MD
Review Completion Date	November 1, 2011
Established Name	Ingenol mebutate gel, 0.015% and 0.05%
(Proposed) Trade Name	Picato Gel
Therapeutic Class	Actinic keratosis product
Applicant	LEO Pharma A/S
Formulation(s)	Topical gel
Dosing Regimen	Face and scalp: 0.05% once daily for 3 consecutive days Trunk and extremities: 0.015% once daily for 2 consecutive days
Indication(s)	Topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities
Intended Population(s)	Adults 18 years and older

Template Version: March 6, 200

List of Abbreviations and Definitions of Terms

AE	adverse event
AK	actinic keratosis
AV	atrioventricular
BCC	basal cell carcinoma
BMI	body mass index
CI	confidence interval
CRO	contract research organization
CSR	clinical study report
E. peplus	*Euphorbia peplus*
HR	heart rate
Head	face/scalp
ITT	intent-to-treat
IV	intravenous
IR	Information Request
LLOQ/LOQ	lower limit of quantification
LOCF	last observation carried forward
LSR(s)	local skin reaction(s)
MedDRA	Medical Dictionary for Regulatory Activities
NMSC(s)	non-melanoma skin cancer(s)
NOAEL	no-observable-adverse-effect-level
Non-head	trunk/extremities
NOEL	no-observable-effect-level
PEP005 Gel	Ingenol mebutate, or PICATO™ Gel
PK	pharmacokinetics
QD	Once daily
SAE	serious adverse event
SOC	system organ class
SBP	systolic blood pressure
SCC	squamous cell carcinoma
SD	standard deviation
SHE	Syrian hamster embryo

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended action is approval.

1.2 Risk Benefit Assessment

The Applicant has provided sufficient evidence for approval. The drug substance, ingenol mebutate, is a small molecule and a new molecular entity that is extracted and purified from the plant *Euphorbia peplus.* The drug product, PEP005 Gel, is a topical gel for the treatment of actinic keratosis (AK):

- On the face and scalp: Apply gel 0.015% to the affected area once daily for 3 consecutive days;

- On the trunk and extremities: Apply gel 0.05% to the affected area once daily for 2 consecutive days.

The agreed upon primary endpoint was the rate of 'complete clearance,' defined as the proportion (%) of subjects at Day 57 after treatment with no clinically visible AK lesions in the 'selected treatment area.' 'Selected treatment area' was defined as a continuous 25 cm^2 treatment area of skin with 4 to 8 clinically typical, visible, and discrete AK lesions. 'Recurrence' was defined as any (>0) number of clinically visible AK lesions 12 months after complete clearance in the selected treatment area at Day 57.

The clinical program consisted of 25 clinical trials/studies (Figure 1), in which a total of 1774 subjects received at least 1 dose of PEP005 Gel and 673 received Vehicle. The program consisted of:

1. Four Phase 3 vehicle-controlled pivotal trials: two trials in which subjects received field treatment (i.e., treatment across a selected area of skin) of AKs on the face or scalp, and two trials in which subjects received field treatment of AKs on the trunk or extremities
2. Three 12-month observational extension studies, in which Phase 3 subjects with 'complete clearance' at Day 57 in the pivotal trials were not retreated but followed for 12 months for monitoring of recurrence of AK lesions and local skin safety in the previously treated area
3. Eleven other AK trials: two trials in which subjects received AK lesion-specific treatment, and nine trials in which subject received AK field treatment
4. Three dermal safety trials in healthy adult volunteers, in which subjects received treatment to study drug's effects on skin contact sensitization, phototoxicity, and photoallergenicity

5. Four Phase 2 trials, in which subjects received treatment to study the effects of the drug on basal cell carcinoma or squamous cell carcinoma *in situ*

Four adequate and well controlled Phase 3 pivotal vehicle-controlled trials were conducted, in the United States (majority) and Australia. Subject demographics were 100% Caucasian and approximately 60% male; the mean age was approximately 60.

The pivotal trials were:

- **Study 016 and Study 025 (on the face/scalp)** conducted in a total of 545 subjects who were randomized 1:1 to PEP005 Gel: Vehicle
- **Study 014 and Study 028 (on the trunk/extremities)** conducted in a total of 457 subjects who were randomized 1:1 to PEP005 Gel: vehicle

PEP005 Gel when applied as indicated was shown to be statistically superior to vehicle gel based on the intent to treat (ITT) population at significance level of 0.05.

- In the face/scalp population, complete clearance at Day 57 was observed in 37% of PEP005 Gel treated subjects and 2% of vehicle subjects ($p<0.001$) (Study 016); and, 47% of PEP005 Gel treated subjects and 5% of vehicle subjects ($p<0.001$) (Study 025)

- In the trunk/extremities population, complete clearance at Day 57 was observed in 28% of PEP005 Gel treated subject and 5% of vehicle subject ($p<0.001$) (Study 014); and, 42% of PEP005 Gel treated subject and 5% of vehicle subjects ($p<0.001$) (Study 028).

About half of the successfully treated subjects experienced 'recurrence' of at least one AK lesion in the treated area. Recurrence rate at Month 12 was 54% for the 108 face/scalp subjects studied, and 58% for the 38 trunk/extremities subjects studied.

The physiologic effect of the drug appears to involve induction of cell necrosis. The mechanism of action by which the drug induces cell death is unknown. Clinical trials conducted under 'maximal use conditions' demonstrated that treatment of a 100 cm^2 area of skin with PEP005 Gel, 0.05% once daily for 2 consecutive days resulted in minimal systemic exposure of PEP005 Gel or its acyl isomers. The blood level of the drug, and its acyl isomers were below the LOQ (0.1 ng/mL) in all the samples collected.

Drug adverse reactions observed included:

1. Ocular and peri-ocular disorders, including severe reactions of eye pain, eyelid edema, eyelid ptosis, and periorbital edema. These were most likely due to contact irritation/dermatitis

2. Local skin reactions, including erythema, scaling/flaking, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, and other application site reactions such as application site pain and application site infections.

The majority of adverse reactions resolved spontaneously, and reactions that required treatment were treated successfully with concomitant medications, and resulted in no serious medical outcomes or permanent side effects. Benefits appear to outweigh risks. If approved, PEP005 Gel could offer an additional therapeutic option for actinic keratosis with a shorter duration of treatment course than that of currently available topical products. No comparative trials have been conducted.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

None recommended.

1.4 Recommendations for Postmarket Requirements (PMRs) and Commitments (PMCs)

None recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Ingenol mebutate (proposed tradename, PICATO Gel®[1]; investigational drug name, PEP005 Gel) is a small molecule and a new molecular entity, and is an ingenol derivative extracted from the sap of the plant *Euphorbia peplus*. The extract of this plant has been used in the homeopathic setting as an herbal remedy to treat various skin conditions. The Applicant's proposed pharmacologic class is (b) (4) cell death inducer (b) (4) The drug product is a clear colorless gel intended for topical administration. The proposed indication is for the tropical treatment of actinic keratosis (AK) on the face and scalp, and on the trunk and extremities. The proposed dosage and administration is:

1 FDA Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Risk Management finds the proposed proprietary name PICATO acceptable for this product.

- On the face and scalp: Apply gel 0.015% to the affected area once daily for 3 consecutive days

- On the trunk and extremities: Apply gel 0.05% to the affected area once daily for 2 consecutive days

2.2 Tables of Currently Available Treatments for Proposed Indications

Current treatments for AKs include excisional surgery; laser, chemical peels and dermabrasion; systemic retinoids; photodynamic therapy (red or blue light used in combination with photosensitizing cream (5-aminolaevulinic acid, methyl 5-aminolaevulinate); cryotherapy; and, topical products. Topical products that are approved for the indication include 5-fluorouracil (5-FU) cream, imiquimod cream, diclofenac gel, aminolevulinic acid solution, methyl-aminolevulinic cream, and salicylic acid ointment (Table 1).

Table 1 FDA approved and currently available topical treatment for AK related indications

Application	**Drug**	**Dosage Form Route of Administration**	**Indication**
NDA 020723 NDA 022483 NDA 201153	Imiquimod (ALDARA® ZYCLARA®)	Cream 5% topical Cream 3.75% topical	Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults
NDA 020985	5-Fluorouracil (CARAC®)	Cream 0.5% topical	Topical treatment of multiple actinic or solar keratoses of the face and anterior scalp
NDA 016831	5-Fluorouracil (EFUDEX®)	Solution 2% topical Solution 5% topical Cream 5% topical	Treatment of multiple actinic or solar keratoses
NDA 016988	5-Fluorouracil (FLUOROPLEX®)	Cream 1% topical	Topical treatment of multiple actinic (solar) keratoses
NDA 021005	Diclofenac (SOLARAZE®)	Gel 3% topical	Topical treatment of actinic keratoses (AK). Sun avoidance is indicated during therapy
NDA 021415	Methyl aminolevulinate HCL (METVIXIA®)	Cream 16.8% topical	Treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation in the physician's office when other therapies are considered medically less appropriate
NDA 020965	Aminolevulinic acid HCL (LEVULAN KERASTICK®)	Solution 20% topical	Treatment of minimally to moderately thick actinic keratoses of the face or scalp

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is not approved for marketing as drug product in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The natural history of actinic keratosis (solar keratosis) can be described as continual flux with new lesions appearing and some old lesions remitting with the incidence and remission rates in part dictated by solar exposure. Actinic keratoses (AKs) may progress to squamous cell cancers (SCCs). Areas of the skin that are prone to AKs and SCCs are those that are prone to increased sun exposure (face, scalp, backs of hands and forearms). AKs occur most frequently in the elderly, especially in men, who are also at highest risk for death or disfigurement from SCCs. Most patients present with multiple AKs, although single lesions do occur. In one report, the yearly rate of progression of an AK to an invasive SCC in an average-risk person in Australia was between 8 and 24 per 10,000; in another report, the rate was 12% over 5 years. Over the course of a year, 20 to 25% of AKs can regress spontaneously without treatment.[2] In the United States, destruction of AKs is the most commonly performed outpatient dermatologic procedure. Treatment of actinic keratosis is the subject of a commissioned report by the Agency for Healthcare Research and Quality (AHRQ). Important safety issues with the related drugs are summarized in Table 2.

Table 2 Warnings and contraindications in labeling (paraphrased) for approved and available AK topical products

Aldara® (imiquimod cream)	Local skin reactions (e.g. skin weeping or erosion), systemic reactions flu-like signs and symptoms (may include malaise, fever, nausea, myalgia and rigors).
Carac® (fluorouracil cream)	Local inflammation and ulceration; potential for delayed hypersensitivity; symptoms of dihydropyrimidine dehydrogenase (DPD) deficiency, which may include systemic toxicity such as stomatitis, diarrhea, neutropenia, and neurotoxicity.
Efudex® (fluorouracil topical solution and cream)	Local inflammation; symptoms of DPD deficiency. Teratogenic. Contraindicated in women who are or may become pregnant during therapy.

2 Helfand M, Gorman A, Mahon S, et al. Actinic Keratoses Final Report Submitted to the Agency for Healthcare Research and Quality (AHRQ). Oregon Health & Science University Evidence-based Practice Center, May 2001.

Fluoroplex® (fluorouracil)	An increased in the incidence of inflammatory reactions in the adjacent normal skin if an occlusive dressing is used. Potential for delayed hypersensitivity. Teratogenic. Contraindicated in women who are or may become pregnant.
Metvixia® (methyl aminolevulinate cream, in combination with Aktilite CL lamp red light)	Photosensitivity; hypersensitivity; irritation to mucous membrane. Contraindicated in patients with allergies to porphyrins, and peanut and/or almond oil.
Levulan® (aminolevulinic acid HCL topical solution, in combination with BLU-U Blue Light Photodynamic Therapy	Photosensitivity; irritation to the eyes or mucous membrane. Contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, or porphyrins.
Solaraze® (diclofenac gel)	Local dermal adverse reactions; as with other NSAIDS, anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Diclofenac should be given with caution to patients with the aspirin triad.
Zyclara® (imiquimod cream)	Local skin reactions; flu-like signs and symptoms which may include fatigue, nausea, fever, myalgia, malaise, and chills; lymphadenopathy.

All topical AK treatments can cause local skin reactions at the treatment area. There are no comparative data on the effect of different management strategies or different methods of removal of AKs, and on incidence, morbidity, or mortality from invasive SCC.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The commercial IND was filed under IND 70114 on June 28, 2004. Highlights of the clinical discussion include the following:

1. Pre-IND meeting (October 28, 2003)
   FDA stated that the clinical endpoint for treatment of AK is "% of subjects with complete clearance of AK lesions at a pre-specified time-point."

2. Guidance meeting (March 7, 2005)
   FDA stated the clinical development program should address recurrence and durability of effect. AK is considered to be a chronic indication both clinically and for regulatory purposes.

3. Special Protocol Assessment (SPA) response letter (June 2, 2008)
   Regarding Applicant's proposed Phase 3 trial in the AKs in the trunk/extremities regions (Study PEP005-014), FDA stated that agreement was reached on the general study design: the selected treatment area was to be 25 cm^2 ('4 to 8 clinically typical, visible, and discrete AK lesions within a continuous 25 cm^2 treatment area on non-head locations'); the dose regimen was to be once daily for 2 consecutive days; the primary efficacy endpoint was to be "complete clearance rate of AK lesions defined as the proportions of patients at the Day 57 visit with no clinically visible AK lesions in the selected treatment area;" the secondary efficacy endpoint was to be "partial clearance rate of AK lesions, defined as the proportion of patients at the Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at Baseline in the selected treatment area."

4. End of Phase 2 meeting (June 3, 2009)
   FDA stated that while complete clearance of AK would be a meaningful endpoint for labeling, it is not clear that partial clearing (e.g., 75%) is clinically meaningful. For example, a 75% or greater reduction in the number of AK lesions could still leave the largest AK lesion unaffected and the lesion could progress into a squamous cell carcinoma. Also, given that AK lesions can spontaneously and recur, it will be important to follow longer term outcomes following treatment. Lesions that appear or lesions that remain refractory should be fully investigated including biopsy and measurement for size and thickness. FDA reiterated that all subjects should be followed for at least 1 year after the primary efficacy time point, to obtain recurrence and safety data, as this information is clinically important and necessary for public health. FDA considered the head vs. non-head regions to be two separate indications.

5. Guidance meeting (September 16, 2009)
   FDA stated that for examination of recurrence, only subjects who had complete clearance of AK (lesion count of zero) at the end of the pivotal study need to be followed, because the information that is needed is on occurrence rate in subjects who had complete clearance. FDA stated: "Please enroll only patients who had complete clearance of AKs (lesion count of 0) at the end of the pivotal studies because the information that we need is on recurrence in patients who had complete clearance." As treatment in other areas may mask the true incidence of AK lesions, FDA recommended that subjects be prohibited from receiving treatment such as 5-FU, imiquimod in contiguous/nearby sites, or receiving any systemic agents that may mask the true incidence of AKs in the original targeted field.

2.6 Other Relevant Background Information

PEP005 Gel was developed by Peplin Inc. from inception through Phase 3 clinical trials. Peplin was acquired by LEO Pharma A/S in November 2009. LEO Pharma A/S is the

application (the Applicant) of this NDA. The drug was referred to as 'PEP005 Gel' in drug development.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality and integrity of the submission appear acceptable.

3.2 Compliance with Good Clinical Practices (GCP)

Division of Scientific Investigation (DSI) clinical audit sites were selected base on high enrollment and large treatment effects.

Table 3 Clinical sites inspected for DSI clinical audits

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 06: Karl G. Heine, MD Solutions…A Clinical Trials Company, LLC 880 Seven Hills Drive, Suite 150 Henderson, NV 89052-4380 Phone: (702) 285-6081 Fax: (7002) 456-0088	PEP005-025	N=16	Topical treatment of actinic keratosis on the face and scalp (Head)
Site 62: Suzanne Bruce, MD Suzanne Bruce and Associates, PA The Center for Skin Research 1900 St. James Place, Suite 650 Houston, TX 77056 Phone: (713) 985-0210	PEP005-028	N=16	Topical treatment of actinic keratosis on the trunk and extremities (non-Head)

At Dr. Heine's site (Site 06), 23 subjects were screened, 16 subjects completed the study, and 8 subjects' records were inspected. Two protocol violations/deviations of clinical interest were noted. 1) There was a failure to adhere and/or institute proper photograph procedures, and to make correct anatomical land markings in tracing transparencies. 2) The site's staff believed that they (investigator, study personnel) knew of the treatment assignment based on the occurrence of local skin reactions.

The findings should not impede our ability to accept the overall data quality and study conclusions. 1. The protocol violations regarding to poor tracing and photo documentation were not repeated at the other inspected site (Dr. Bruce's site, Site 62); there was no evidence to suggest a program wide problem. 2. Photographs were used for visual documentation purposes. As specified by the study protocol, the photographs

were used only as aids 'to support the investigator's assessment of the treatment area.'
3. Given the robustness of efficacy findings throughout different sites, and most compellingly, the primary efficacy endpoint was based on an objective count of complete clearance (zero lesion count) in the treated area, the efficacy assessment was likely independent of investigator's bias, and the results were reliable. A stronger study design would have been to incorporate the use of a blinded assessor, who, ideally, should not have had clinical contact with the subjects and therefore knowledge of the local skin reactions prior to the efficacy assessments.

3.3 Financial Disclosures

FDA Form 3454 was submitted to the NDA, which certified that based on the Applicant's knowledge, the listed clinical Investigators 1) did not participate in any financial arrangement with the Applicant of a covered study whereby the value of compensation to the investigator or conducting the study could be affected by the outcome of the study; 2) had no proprietary interest in this product or significant equity interest in the Applicant of the covered study; and 3) was not the recipient of significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

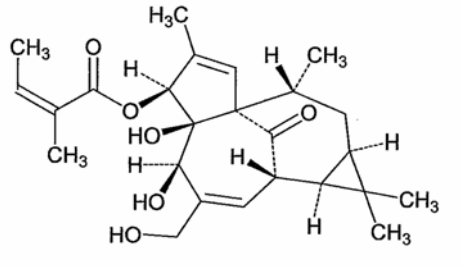
4.1 Chemistry Manufacturing and Controls (CMC)

Please see Dr. Nina Ni's CMC review for details. This reviewer concurs with the labeling language recommended by the CMC review team:

11 DESCRPTION
PICATO (ingenol mebutate) Gel, 0.015% or 0.05% is a clear colorless gel for topical administration, which contains the active substance ingenol mebutate, a cell death inducer.

The chemical name of ingenol mebutate is:
2-Butenoic acid, 2-methyl-, (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-1a,2,5,5a,6,9,10,10a-octahydro-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1*H*-2,8a-methanocyclopenta [*a*]cyclopropa[*e*]cyclodecen-6-yl ester, (2Z) –or (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1*H* 2,8a-methanocyclopenta[*a*]cyclopropa[*e*]cyclodecen-6-yl (2Z) 2 methylbut-2-enoate.

The molecular formula is $C_{25}H_{34}O_6$ and molecular weight is 430.5. Ingenol mebutate is represented by the following structural formula:



Ingenol mebutate is a white to pale yellow crystalline powder. PICATO Gel 0.015% and 0.05% contains 150 mcg and 500 mcg of ingenol mebutate, respectively in each gram of gel consisting of isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, benzyl alcohol, and purified water.

PICATO Gel is clear colorless gel and supplied in unit dose laminate tubes containing a nominal fill weight of 0.47 g with a deliverable weight of 0.25 g. The tubes should be discarded after single use.

16 HOW SUPPLIED/STORAGE AND HANDLING
PICATO Gel is clear colorless gel and supplied in unit dose laminate tubes containing a nominal fill weight of 0.47 g, with a deliverable weight of 0.25 g. The tubes should be discarded after single use.

PICATO Gel is available in 2 dosage strengths: 0.015% and 0.05%.

Dosage Strength	Number of unit dose tubes per carton	NDC#
0.015 %	3	50222-502-47
0.05 %	2	50222-503-47

PICATO Gel should be stored in a refrigerator at 36ºF – 46ºF (2ºC – 8ºC); excursions permitted between 32ºF – 59ºF (0ºC – 15ºC) (see USP for controlled cold temperature). Protect from freezing. Keep out of reach of children.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Please see Dr. Jiaqin Yao's pharmacology-toxicology review for details. There is no disease animal model for AK. The local activity of PEP005 Gel appears to involve induction of cell necrosis. The exact mechanism by which the drug induces cell necrosis is unknown. Local irritation including erythema and edema at the treatment sites was noted in rats, rabbits, or minipigs after topical treatment with the gel. Treatment related dermatitis, acanthosis, parakeratosis, scab formation, and

ulceration/erosion were also observed and the effects increased in severity with increased dose and duration of treatment. This reviewer concurs with labeling recommendations by the pharmacology-toxicology team:

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of PICATO Gel or ingenol mebutate. The effects of ingenol mebutate on fertility have not been evaluated.

Ingenol mebutate was negative in the Ames test, in vitro mouse lymphoma assay, and in vivo rat micronucleus test, but positive in the Syrian hamster embryo (SHE) cell transformation assay.

4.4 Clinical Pharmacology

Please see Dr. Abimbola Adebowale's clinical pharmacology review for details. PK data demonstrated that treatment of a 100 cm^2 area of skin with 0.05% PEP005 Gel, applied once daily to the dorsal forearm for 2 consecutive days did not demonstrate systemic absorption of PEP005 or its metabolites, i.e., levels of ingenol mebutate and its acyl isomers were below the lower limit of quantification (LLOQ 0.1 ng/mL) in samples from all subjects.

4.4.1 Mechanism of Action

The mechanism of action by which the drug induces cell death is unknown.

4.4.2 Pharmacodynamics (PD)

The pharmacodynamics of the drug is unknown.

4.4.3 Pharmacokinetics (PK)

This reviewer concurs with the recommended labeling language by the clinical pharmacology team:

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The mechanism of action by which TRADEMARK Gel induces cell death in the treatment of actinic keratosis is unknown.

12.2 Pharmacodynamics
The pharmacodynamics of TRADEMARK Gel is unknown.

12.3 Pharmacokinetics

Absorption
The systemic exposure to PICATO Gel 0.05% was assessed in two studies in a total of 16 subjects with AK, following application of approximately 1 mL of PICATO Gel, 0.05% to an area of 100 cm^2 of the dorsal forearm once daily for two consecutive days. In these studies, the blood levels of ingenol mebutate and two of its metabolites (acyl isomers of ingenol mebutate) were measured. Blood levels of ingenol mebutate and the two metabolites were below the lower limit of quantification (<0.1 ng/mL) in all the blood samples of the subjects evaluated.

Drug Interactions
In vitro studies demonstrated that [^{3}H]-Ingenol mebutate undergoes extensive metabolism in human hepatocytes.

In vitro studies to assess the potential of ingenol mebutate to inhibit or induce human cytochrome P450 (CYP) enzymes demonstrated that ingenol mebutate does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 or induce CYP 1A2, 2C9, and 3A4. The estimated expected systemic exposure (< 0.1 ng/mL) following topical application of PICATO Gel, 0.05 % to AK subjects in the pharmacokinetic studies described above is negligible compared to the concentrations of ingenol mebutate evaluated in the in vitro studies.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program consisted of 25 trials/studies, in which a total of 1774 subjects were treated with at least 1 dose of PEP005 Gel and 673 subjects were treated with at least 1 dose of vehicle.

The clinical development program included:

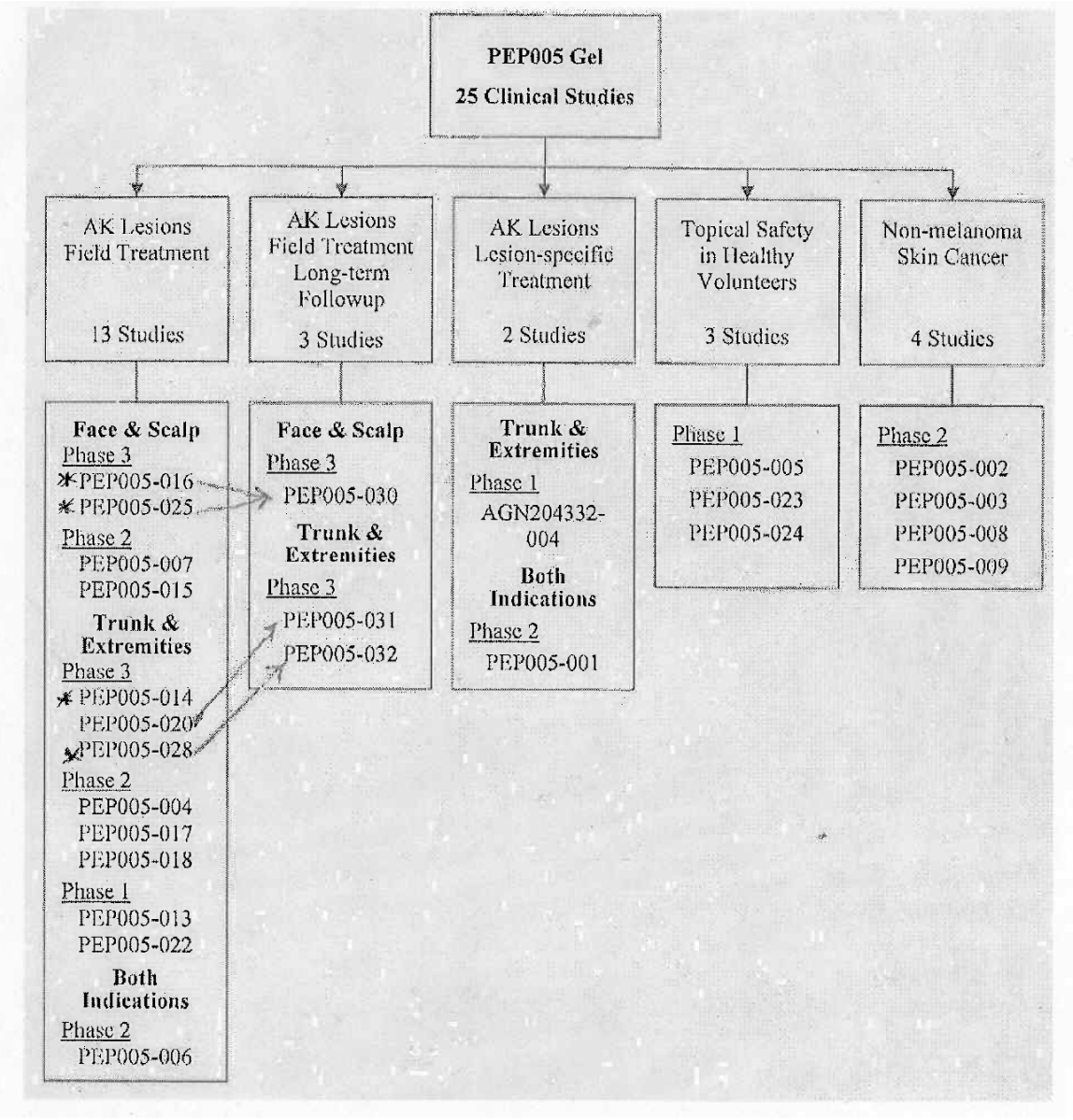
- 18 AK trials - including 3 prospective, longitudinal, observational extension studies on AK recurrence, and AEs in the treated area in Phase 3 subjects who demonstrated complete clearance at Day 57 in the feeder trials
- 3 topical safety trials in healthy volunteers (for skin contact sensitization, phototoxicity, and photoallergenicity)
- 4 non-melanoma skin cancer trials, in studying the effects of the drug on basal cell carcinoma and squamous cell carcinoma *in situ*

The 18 AK trials included:

- 13 field treatment AK trials (including field treatment of a 25 cm^2 skin area that contained 4-8 AK lesions)
- 2 lesion-specific treatment AK trials

- 3 observational extension studies of recurrence of AKs, and AEs in the treated area, in subjects who demonstrated complete clearance at Day 57 in Phase 3 trials.

Figure 1 Overview of PEP005 Gel Clinical Development Program (modified from the Applicant's submission)



* Asterisks mark the pivotal trials; arrows mark the feeder trials to the extension studies

The Phase 3 pivotal trials were:

Study PEP005-016 and PEP005-025 (**Study 016, 025) - face/scalp (head)**
Study PEP005-014 and Study 005-028 (**Study 014, 028) –trunk/extremities (non-head)**

Subjects from Study 016 and Study 025 were followed in the extension Study PEP005-030 (Study 030). Subjects from Study 028 were followed in the extension Study PEP005-032 (Study 032). Subjects from Study 014 were not followed in an extension study. The pivotal trials and the extension studies are listed in Table 4. A complete listing of the clinical trials and studies can be found in Appendix, Table 39. The to-be-marketed formulation was used in all Phase 3 clinical trials and pivotal clinical PK trials.

Table 4 Listings of Phase 3 vehicle controlled pivotal clinical trials and the observational extension studies (table modified from the Applicant's submission)

Type of Study	**Study ID**	**Objectives**	**Study Design**	**Number of subjects (safety population)**	**Test product(s) Dosage, Route, Duration of treatment**
Phase 3 pivotal trials **(face/scalp)**					
Efficacy	PEP005-016 (**Study 016**)	Efficacy, safety	Randomized, Vehicle controlled	N=267 total N=132 PEP005 Gel, N=135 vehicle	0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application 3 days (25 cm^2 treatment area)
Efficacy	PEP005-025 (**Study 025**)	Efficacy, safety	Randomized, Vehicle controlled	N=278 total N=142 PEP005 Gel, N=136 vehicle	0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application 3 days (25 cm^2 treatment area)
Phase 3 pivotal trials **(trunk/extremities)**					
Efficacy	PEP005-014 (**Study 014**)	Efficacy, safety	Randomized, Vehicle controlled	N=254 N=125 PEP005 Gel N=129 vehicle	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application 2 Days (25 cm^2 treatment area)
Efficacy	PEP005-028 (**Study 028**)	Efficacy, safety	Randomized, Vehicle controlled	N=203 N=100 PEP005 Gel N=103 vehicle	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application 2 Days (25 cm^2 treatment area)

Type of Study	**Study ID**	**Objectives**	**Study Design**	**Number of subjects (safety population)**	**Test product(s) Dosage, Route, Duration of treatment**
One-year observational extension study of responders in Phase 3 pivotal trials **(face/scalp)**					
Safety	PEP005-030 (**Study 030**)	12 month follow-up of safety in treatment area and AK recurrence	Prospective, longitudinal, observational	N=117 Previously treated with: PEP005 Gel N=108; vehicle N=9	None; subjects had received PEP005 Gel or vehicle in study PEP005-016 or PEP005-025
One-year observational study of responders in Phase 3 pivotal trial **(trunk/extremities)**					
Safety	PEP005-032 (**Study 032**)	12 month follow-up of safety in treatment area and AK recurrence	Prospective, longitudinal, observational	N=43 Previously treated with PEP005 Gel N=38; vehicle N=5	None; subjects had received PEP005 Gel or vehicle in study PEP005-028

5.2 Review Strategy

Review of efficacy was conducted by this reviewer in conjunction with the Division of Biometrics III (DBIII) reviewers Dr. Carin Kim and Dr. Yuqing Tang. Efficacy was based on the four Phase 3 vehicle controlled pivotal trials; recurrence rate was based on the two extension studies.

Review of safety was conducted by this reviewer. Safety was based on the pivotal trials and the extension studies. Data from the other trials in the development program were used as supporting evidence. Raw datasets were reviewed in conjunction with the Applicant's clinical study reports (CSRs) and the Integrated Summary of Safety (ISS).

5.3 Discussion of Individual Studies/Clinical Trials

The design of the Phase 3 pivotal trials and the 12-month observational extension studies are as follows.

Pivotal trials (face/scalp)

PEP005-016 (Study 016)

- Study design

Study 016 was a multicenter (United States and Australia), randomized, parallel group, double blind, vehicle controlled study to evaluate the efficacy and safety of PEP005 Gel, 0.015%, in adult subjects 18 years and older, for the treatment of AKs on the face or scalp.

- Objectives

The objectives were to evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel, when administered once daily for 3 consecutive days to a contiguous 25 cm^2 area of skin on the face or scalp.

- Eligibility criteria

Subjects were included if they had 4 to 8 clinically typical, visible and discrete AK lesions within a contiguous 25 cm^2 treatment area on the head region (face or scalp). Subjects were excluded if they had cosmetic or therapeutic procedures (e.g., use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing) within 2 weeks and within 2 cm of the selected treatment area; treatment with immunomodulators, or interferon/interferon inducers or systemic medications that suppress the immune system within 4 weeks; treatment with 5-FU, imiquimod, diclofenac, or photodynamic therapy, within 8 weeks and within 2 cm of the selected treatment area. Female subjects must be of either non-childbearing potential or childbearing potential providing negative serum and urine pregnancy test and using effective contraception.

- Study procedures

Study medication was applied at home. For a list of prohibited medications see Appendix, Table 40. Follow up clinic visits for safety assessments were made on Days 4, 8, 15, 29 and 57, including AEs, and focused skin exams for local skin reactions (Table 5, Schedule of Assessments). Subjects were randomized centrally to treatment in a 1:1 ratio. Enrollment aimed for approximately 20% of subjects to be treated on the scalp and 80% on the face. Efficacy assessment was determined at Day 57. Post-study follow-up visits (after Day 57) were required, every 7 to 28 days for all patients with unresolved treatment-related adverse events (AEs), local skin reactions (LSRs), pigmentation and/or scarring at Day 57. LSRs were assessed actively using a grading scale.

Table 5 Schedule of Assessments for Study PEP005-016 (Study 016) (copied electronically from the Applicant's submission)

Visit	Screening	Baseline Day 1	Treatment Days 1,2,3	Follow-up Day 4	Follow-up Day 8	Follow-up Day 15, 29	Day 57 (Early Term)	Unscheduled/ Post-Study Follow-up
Visit Window	**-14 to 1**	**none**	**none**	**none**	**± 2 days**	**± 2 days**	**± 2 days**	**not applicable**
Informed Consent	X							
Medical/Surgical Hx	X							
AK Treatment History	X							
Con. Medications	X	X		X	X	X	X	X
Physical Exam	X						X	X[3]
Vital Signs	X	X		X	X	X	X	X
Height/Weight	X						X (weight only)	
Fitzpatrick Scale	X							
Patient Eligibilit	X	X						
Non-Fasting Labs	X			X	X		X[1]	X[3]
Serum Pregnancy (WOCBP)	X				X		X [1]	
Serum FSH (WONCBP)	X							
Urine Pregnancy (WOCBP)		X						
Electrocardiogram	X			X			X[2]	
Study Medication Dispensing		X						
Study Medication Administration			X					
Study Medication Compliance				X				
Expanded Dermatologic Exam	X							
Focused Dermatologic Examination		X		X	X	X	X	X
Clinical AK Lesion Assessment		X					X	
LSR, Pigmentation and Scarring		X		X	X	X	X	X
Photographs	X	X		X	X	X	X	X
Skindex-16		X			X	X (Day 29 only)	X	

Visit	Screening	Baseline Day 1	Treatment Days 1,2,3	Follow-up Day 4	Follow-up Day 8	Follow-up Day 15, 29	Day 57 (Early Term)	Unscheduled/ Post-Study Follow-up
Visit Window	**-14 to 1**	**none**	**none**	**none**	**± 2 days**	**± 2 days**	**± 2 days**	**not applicable**
TSQM							X	
Adverse Events		X		X	X	X	X	X
SAEs	X	X		X	X	X	X	X

[1] Early term prior to Day 8
[2] Early term prior to Day 4
[3] If required

- Data analysis

Primary efficacy endpoint was complete clearance rate of AK lesions at the Day 57 visit with no clinically visible AK lesions in the selected treatment area (i.e., proportion of subjects who had complete clearance of AKs at Day 57 in the treated skin area). Secondary efficacy endpoint was partial clearance rate of AK lesions at the Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at Baseline, in the selected treatment area. The primary efficacy analysis was based on the intent-to-treat (ITT) population; missing values were imputed using last observation carried forward (LOCF). Safety analysis was based on the safety population, which was defined as all randomized subjects who received at least one dose of study medication and had at least one post baseline evaluation.

PEP005-025 (Study 025)

Study 025 was the second pivotal trial for the face/scalp indication. The study design was similar to that of Study 016.

12-month extension study for AKs recurrence and local safety (face/scalp)

PEP005-030 (Study 030)[3]

- Study design

Study 030 was a 12-month prospective, longitudinal, observational, follow-up study of subjects with AKs on the head region (face/scalp) who demonstrated complete AK clearance by Day 57 in Study 016 and 025. Subjects were not re-treated. Double blind was maintained to the treatment assignment (PEP005 Gel or vehicle gel) in Study 016 and 025.

- Objectives

The primary objectives were to determine recurrence of AK lesions in the treatment area, and to study adverse events in the treatment area.

- Eligibility criteria

The original inclusion criteria allowed enrollment of *all* subjects who completed the Day 57 visit in either study PEP005-016 or PEP005-025. An amendment of the protocol limited enrollment to only those subjects who demonstrated complete clearance of AK lesions (lesion count = 0) at Day 57.

- Study procedure

No subject was re-treated with the study drug. Subjects were prohibited from receiving field treatment or treatment that might mask the incidence of AK lesion recurrence (e.g.,

3 Information presented is based on the final Clinical Study Report, submitted in the 120 Day Safety Update, (July 25, 2011). The study procedures and data analysis plan in the CSR appear to be different (e.g., fewer planned analyses) from those listed in the original study protocol submitted to the NDA on March 31, 2011.

5-FU, imiquimod) inside, or within 2 cm of the selected treatment area at anytime during the study. Isolated lesion treatment, such as cryotherapy or biopsy, was allowed for treatment of AK lesions emerging in the selected treatment area. Clinic visits occurred at Month 3, 6, 9 and 12 after the Day 57 visit of the feeder trial. The number of AK lesions, in the selected treatment area, was counted at each visit. Information regarding intercurrent disorders, therapeutics that could have resulted in immunosuppression and treatment with agents known to alter AK was collected. Information on AEs in the treated area was collected.

Table 6 Schedule of visits and procedures (copied electronically from the Applicant's submission)

Visit	Enrollment/Day 57 previous Peplin AK study	3, 6 , 9 Month Follow-up	12 Month Follow-up	Early Termination
Visit Window	**+ 4 weeks**	**± 2 weeks**	**± 2 weeks**	**Not Applicable**
Informed Consent & authorization	X			
Patient Eligibility	X			
Document selected treatment area	X			
AK lesion count in the selected treatment area	X	X	X	X
Adverse events in the selected treatment area	X	X	X	X
Photographs of selected treatment area	X	X	X	X
Concomitant medications, treatments, procedures	X	X	X	X
Study exit			X	X[1]

[1] Patients no longer eligible for this study will be early terminated from study participation

- Data analysis

The efficacy analysis included a descriptive summary of recurrence rate. If the subject received lesion-specific treatment (i.e., cryotherapy or biopsy) for a lesion that appeared in the selected treatment area, the treated lesion was considered a recurrence. The safety analysis consisted of a descriptive summary of AEs in the treatment area.[4]

Pivotal trials (trunk/extremities)

PEP005-014 (Study 014)

Study 014 was a Phase 3 vehicle controlled pivotal trial conducted in the trunk/extremities; the study design was similar to that of the face/scalp pivotal trials

4 Local skin reactions (LSRs) were not assessed actively in the extension study because the Applicant did not anticipate that LSRs would be present in the extension study based on the observation that LSRs generally resolved in subjects treated with PEP005 Gel by the end of the study (Day 57) in the pivotal trials.

(Study 016, 025). Active treatment was PEP005 Gel at 0.05% concentration and treatment duration was once daily for 2 consecutive days. The study drug was applied to a 25 cm^2 contiguous actinic keratosis (AK) treatment area on the trunk/extremities.

PEP005-028 (Study 028)
Study 028 was the second pivotal trial for the trunk/extremities indication. The study design was similar to that of Study 014.

12-month extension study for AKs recurrence and local safety (trunk/extremities)

Study PEP005-032 (Study 032)
Study 032 was similar in study design as that of the extension study for the face/scalp indication, Study 030. Study 032 was a 12 month, long-term follow-up study of subjects with AKs on trunk/extremities. The objectives were to monitor recurrence of AKs, and local safety in the treatment area in subjects in Study 028 who demonstrated complete clearance at Day 57.

6 Review of Efficacy

Efficacy Summary

Four pivotal clinical trials have been conducted in support of this NDA filing: Study 016 and Study 025 for the face/scalp, and Study 014 and Study 028 for the trunk/extremities. The Applicant is seeking approval for PEP005 Gel, 0.015% and 0.05%, for the topical treatment of AKs on the face and scalp, and on the trunk and extremities, respectively. Both concentrations of PEP005 Gel when applied for treatment of AK were shown to be statistically superior to vehicle gel.

Actinic keratosis of the face and scalp:
PEP005 Gel, 0.015% was statistically superior to vehicle gel in two clinical trials (Study 016 and Study 025) in the treatment of AK on head (face/scalp) locations. The primary efficacy endpoint was the complete clearance rate of AK lesions; defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the selected treatment area. In the two double-blind, vehicle-controlled, clinical trials (Study 016 and 025), 547 adult subjects with AK on the face or scalp were randomized to treatment with either PEP005 Gel 0.015% or vehicle gel for 3 consecutive days, followed by an 8 week follow-up period. The trials enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm^2 contiguous treatment area. Hypertrophic and hyperkeratotic lesions were excluded from treatment. On each scheduled dosing day, the study gel was applied to the entire treatment area. A total of 536 subjects (98%) completed these studies. Study subjects ranged from 34 to 89 years of age (mean 64 years) and 94 % had Fitzpatrick skin type I, II, or III. Approximately 85% of subjects were male, and all PEP005 Gel-treated subjects were Caucasian.

Efficacy was assessed at Day 57. Complete clearance rate was defined as the proportion of subjects with no (zero) clinically visible AK lesions in the treatment area.

Efficacy results are as follows. Partial clearance rate was defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions at Baseline in the selected treatment area.

Number and Percent of Subjects Achieving Complete and Partial Clearance at Day 57 in Each Study

	Study 016		Study 025	
	PICATO® Gel 0.015% (N=135)	Vehicle (N=134)	PICATO® Gel 0.015% (N=142)	Vehicle (N=136)
Complete Clearance Rate	50 (37%)	3 (2%)	67 (47%)	7 (5%)
Partial Clearance Rate (≥75%)	81 (60%)	9 (7%)	96 (68%)	11 (8%)

Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by Study

	Study 016		Study 025	
	PEP005 Gel 0.015% (N=135)	Vehicle (N=134)	PEP005 Gel 0.015% (N=142)	Vehicle (N=136)
Scalp	4/26 (15%)	0/25 (0%)	9/31 (29%)	1/25 (4%)
Face	46/109 (42%)	3/109 (2%)	58/111 (52%)	6/111 (5%)

Subjects who achieved complete clearance at Day 57 in Study 016 and Study 025 entered a 12-month follow-up study (Study 030). Of the 108 PEP005 Gel-treated subjects who achieved complete clearance in Study 016 and Study 025, 58 subjects (54%) had a recurrence within 12 months where recurrence was defined as any identified AK lesion in the previously treated area for subjects who achieved complete clearance at Day 57.

Actinic keratosis of the trunk and extremities:

PEP005 Gel, 0.05% was statistically superior to vehicle gel in 2 trials (Study 014 and Study 028) in the treatment of AK on non-head (trunk/extremities) locations. The primary efficacy endpoint was the complete clearance rate of AK lesions; defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the selected treatment area. Most of the non-head treatment locations studied was on the arm, back of hand, with a small number of subjects with AK lesions on the chest, shoulder, back or leg. In the 2 double-blind, vehicle-controlled clinical trials (Study 014 and 028), 458 adult subjects with AK on the trunk or extremities were randomized to treatment with either PICATO Gel 0.05% or vehicle gel for 2 consecutive days, followed by an 8 week follow-up period. The trials enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm^2 contiguous treatment area. Hypertrophic and hyperkeratotic lesions were excluded from treatment. On each scheduled dosing day, the study gel

was applied to the entire treatment area. A total of 447 subjects (98 %) completed these studies. Study subjects ranged from 34 to 89 years of age (mean 66 years) and 94 % had Fitzpatrick skin type I, II, or III. Approximately 62% of subjects were male, and all PICATO-treated subjects were Caucasian.

Efficacy was assessed at Day 57. Complete clearance rate was defined as the proportion of subjects with no (zero) clinically visible AK lesions in the treatment area. Partial clearance rate was defined as the proportion of subjects with 75% or greater reduction in the number of AK lesions at Baseline in the selected treatment area.

Number and Percent of Subjects Achieving Complete and Partial Clearance at Day 57 in Each Study

	Study 014		Study 028	
	PICATO® Gel 0.05% (N=126)	**Vehicle (N=129)**	**PICATO® Gel 0.05% (N=100)**	**Vehicle (N=103)**
Complete Clearance Rate	35 (28%)	6 (5%)	42 (42%)	5 (5%)
Partial Clearance Rate (≥ 75%)	56 (44 %)	9 (7 %)	55 (55 %)	7 (7 %)

Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by Study

	Study 014		Study 028	
	PICATO Gel 0.05% (N=126)	**Vehicle (N=129)**	**PICATO Gel 0.05% (N=100)**	**Vehicle (N=103)**
Arm	22/84 (26 %)	4/82 (5 %)	27/59 (46 %)	3/67 (5 %)
Back of Hand	4/25 (16 %)	0/29 (0%)	6/28 (21 %)	0/27 (0 %)
Chest	8/9 (89 %)	1/8 (13 %)	3/5 (60 %)	1/3 (33 %)
Other [a]	1/8 (13 %)	1/10 (10 %)	6/8 (75 %)	1/6 (17 %)

[a]Other includes shoulder, back, leg.

Subjects who achieved complete clearance at Day 57 in Study 028 entered a 12-month follow-up period. Of the 38 PEP005 Gel-treated subjects who achieved complete clearance in Study 028, 22 subjects (58%) had a recurrence within 12 months where recurrence was defined as any identified AK lesion in the previously treated area for subjects who achieved complete clearance at Day 57 of Study 028.

Labeling should include a description of the efficacy trials by design, study population, and subject disposition. Data on primary efficacy endpoint by indication and by

anatomical subgroups, as well as by 12 month recurrence data should be presented. Consideration may be given to include partial clearance data.

Efficacy in treatment-resistant lesions and efficacy in more than one cycle treatment have not been evaluated. If approved, PEP005 Gel could offer a treatment option that is shorter in duration, 2 to 3 days in a treatment cycle, compared with other topical agents in the treatment armamentarium. Comparative efficacy has not been evaluated.

6.1 Indication

6.1.1 Methods

Efficacy analysis was conducted in conjunction with Carin Kim, Ph.D. and Yuqing Tang, Ph.D., FDA statistical reviewers. Please see Dr. Kim and Dr. Tang's statistical reviews for details.

6.1.2 Demographics

Head (face/scalp) indication

For both trials, majority (>90%) of the study populations were located the United States, and the rest from Australia. Study populations were fairly evenly balanced between treatment arms in terms of age. More male subjects than female subjects enrolled. All subjects were Caucasian.

Table 7 Subject demographics in individual Phase 3 trials (face/scalp indication) (copied electronically from Dr. Tang's review)

	Study 16	
	Pep005 Gel 0.015% N=135	Vehicle Gel N=134
Age (yrs)		
Mean (Std)	64 (10.5)	63 (9.9)
Median	64	63
Min, Max	38, 88	41, 85
Gender		
Male	116/135 (86%)	120/134 (90%)
Female	19/135 (14%)	14/134 (10%)
	Study 25	
	Pep005 Gel 0.015% N=142	Vehicle Gel N=136
Age (yrs)		
Mean (Std)	65 (11.2)	65 (10.2)
Median	64	66
Min, Max	35, 88	46, 90
Gender		
Male	117/142 (82%)	112/136 (82%)
Female	25/142 (18%)	24/136 (18%)

In addition, baseline disease characteristics were similar between the treatment groups, in Fitzpatrick skin type (approximately 93% were of type I, II, III), history of skin cancer (approximately 46% of the subjects), and prior therapy in the use of cryotherapy (approximately 81%), imiquimod (approximately 9%), and 5-FU (approximately 20%).

Non-head (trunk/extremities) indication

For both trials, majority (>90%) of the study populations were located the United States, and the rest from Australia. Study populations were fairly evenly balanced between treatment arms in terms of age. More male subjects than female subjects enrolled. All subjects were Caucasian.

Table 8 Subject demographics in individual Phase 3 trials (trunk/extremities indication) (copied electronically from Dr. Kim's review)

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

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

In addition, baseline disease characteristics were similar between the treatment groups, in Fitzpatrick skin type (approximately 93% were of type I, II, III), history of skin cancer (approximately 54% of the subjects), and prior therapy in the use of cryotherapy (approximately 75%), imiquimod (approximately 9%), and 5-FU (approximately 24%).

6.1.3 Subject Disposition

Head (face/scalp) indication
For the Phase 3 population (Study 016, 025), 547 subjects were included in the study population. A high percentage of randomized patients completed the study as specified in the protocol at Day 57 (96% and 99%, respectively). Subject disposition by trials is as follows.

Table 9 Subject disposition in Phase 3 trials (face/scalp indication) (copied electronically from Dr. Tang's review)

	Study 16	
	Pep005 Gel 0.015% N=135	Vehicle Gel N=134
Discontinued Subjects	3/135 (2.2%)	7/134 (5.2%)
Adverse Events	1/135 (0.7%)	1/134 (0.7%)
Subject Withdrew	2/135 (1.5%)	5/134 (3.7%)
Protocol Violation	7/134 (5.2%)	1/134 (0.7%)
	Study 25	
	Pep005 Gel 0.015% N=142	Vehicle Gel N=136
Discontinued Subjects	0/142 (0%)	1/136 (0.7%)
Subject Withdrew	0/142 (0%)	1/136 (0.7%)

Non-head (trunk/extremities) indication

For the Phase 3 population (Study 014, 028), 458 subjects were included in the study population. A high percentage of randomized patients completed the study as specified in the protocol at Day 57 (98% and 97%, respectively). Subject disposition by trials is as follows.

Table 10 Subject disposition in Phase 3 trials (trunk/extremities indication) (copied electronically from Dr. Kim's review)

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

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

6.1.4 Analysis of Primary Endpoint(s)

Complete clearance has been used as primary endpoint in other US approved products.

Head (face/scalp) Indication

Complete clearance rate for the pivotal trials are presented below. Response rate was similar in the two trials (Table 11).

Table 11 Efficacy results for the individual Phase 3 trials (face/scalp indication) (Study 016, 025) (copied electronically from Dr. Tang's review)

	Study 16					
	Pep005 Gel 0.015%		Vehicle Gel		P-value	
	ITT [a] N=135	PP [b] N=121	ITT [a] N=134	PP [b] N=125	ITT [a]	PP [b]
Complete Clearance	50 (37%)	44 (36.4%)	3 (2.2%)	3 (2.4%)	<0.0001 [a] <0.0001 [b]	<0.0001 [a] <0.0001 [b]
	Study 25					
	Pep005 Gel 0.015%		Vehicle Gel		P-value	
	ITT [a] N=142	PP [b] N=136	ITT [a] N=136	PP [b] N=130	ITT [a]	PP [b]
Complete Clearance Rate	67 (47.2%)	64 (47.1%)	7 (5.2%)	7 (5.4%)	<0.0001 [a] <0.0001 [a]	<0.0001 [b] <0.0001 [b]

[a] P-value is obtained from the CMH test controlling for site.
[b] P-value is obtained from the CMH test controlling for both site and location (scalp or face).

Response rates by anatomical locations were similar in the two trials. Majority of the subjects were treated for AKs on the face. The response rate was higher in treatment of the face region than on the scalp. The difference in treatment effect may be due to differences in the characteristics of the skin and AK lesions on different skin, and in sun and other environmental exposures.

Table 12 Number and percent of subjects achieving complete clearance at Day 57 by anatomical location and by study (copied electronically from Dr. Tang's review)

Number and Percent of Subjects Achieving Complete Clearance at Day 57 by Anatomical Location and by Study				
	Study 016		**Study 025**	
	PICATO Gel 0.015% (N=135)	**Vehicle (N=134)**	**PICATO Gel 0.015% (N=142)**	**Vehicle (N=136)**
Scalp	4/26 (15%)	0/25 (0%)	9/31 (29%)	1/25 (4%)
Face	46/109 (42%)	3/109 (2%)	58/111 (52%)	6/111 (5%)

Non-head (trunk/extremities) indication

Complete clearance rate for the pivotal trials are presented below (Figure 2). Response rate was similar in the two trials. Majority of the subjects were treated for AKs on the arm; however, response rate was higher in subjects treated for lesions on the chest. The difference in treatment effects may be due to differences in the characteristics of the skin and AK lesions on different skin, and in sun and other environmental exposures.

Figure 2 Efficacy results for individual Phase 3 trials (trunk/extremities indication) (Study 014, 028) (copied electronically from Dr. Kim's review)

Complete Clearance (ITT, LOCF) - Study 014

	Study 014		
	PEP005 (N=126)	**Vehicle (N=129)**	**p-value**
Complete Clearance[(1)]	35/126 (27.8%)	6/129 (4.7%)	<0.0001
Reviewer's analysis[(2)]	35/126 (27.8%)	6/129 (4.7%)	<0.001
Arm	22/84 (26.2%)	4/82 (4.9%)	-
Back of hand	4/25 (16.0%)	0/29 (0%)	-
Chest	8/9 (88.9%)	1/8 (12.5%)	-
Other[(3)]	1/8 (12.5%)	1/10 (10.0%)	-

(1) Complete Clearance is defined as the proportion of subjects with no clinically vis ble AK lesions in the selected treatment area at Day 57. P-value is calculated from a CMH test stratified by anatomical location (protocol-specified method).
(2) P-value is calculated from CMH test stratified by sites (sensitivity analysis).
(3) Other includes shoulder, back, leg.
Source: Applicant's Study Report Table 12.

Complete Clearance (ITT, LOCF) - Study 028

	Study 028		
	PEP005 (N=100)	**Vehicle (N=103)**	**p-value**
Complete Clearance[(1)]	42/100 (42.0%)	5/103 (4.9%)	<0.001
Arm	27/59 (45.8%)	3/67 (4.5%)	-
Back of hand	6/28 (21.4%)	0/27 (0%)	-
Chest	3/5 (60.0%)	1/3 (33.3%)	-
Other[(2)]	6/8 (75.0%)	1/6 (16.7%)	-

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

6.1.5 Analysis of Secondary Endpoints(s)

Agreement was reached in the Special Protocol Assessment (June 2, 2008) that secondary efficacy endpoint was "partial clearance rate of AK lesions defined as the proportion of patients at Day 57 visit with a 75% or greater reduction in the number of AK lesions identified at Baseline, in the selected treatment area." In the face/scalp trials partial clearance was 60% and 7% in PEP005 Gel subjects and vehicle, respectively (Study 016); and 68% and 8% (Study 025). In the trunk/extremities trials, the partial clearance rate was 44% and 7% in PEP005 Gel subjects and vehicle, respectively (Study 014), and 55% and 7% (Study 028). The response rate of partial clearance rate was higher than complete clearance in all pivotal trials. Partial clearance could add additional information but it is not critical. The Division stated in the End of Phase 2 Meeting (June 3, 2009), "We agree that complete clearance of AK would be a meaningful endpoint for labeling. However, it is not clear that partial clearing (e.g., 75%) is clinically meaningful. For example, a 75% or greater reduction in the number of AK lesions could still leave the largest AK lesion in the treatment area unaffected, and the lesion could progress into a squamous cell carcinoma."

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Because AK is not a disease routinely found in the pediatric subpopulation, exemption from the requirements of the Pediatric Research Equity Act (PREA) of 2007 (21 U.S.C. 355c) was granted by FDA.

No overall differences in effectiveness were observed between subjects over the age of 65 and younger subjects.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Recurrence data is of clinical usefulness and should be included in labeling. AKs recurrence after complete clearance was studied in the two 12-month observational follow up studies. Subjects received one treatment cycle during the pivotal trials (i.e., 2 days for face/scalp treatment, and 3 days for trunk/extremities treatment). No additional treatment was administered in the extension studies.

Head (face and scalp) indication - Study 030 (feeder trials: Study 016, 025):
The population of interest was subjects with complete clearance at Day 57 (AK lesion count of zero in the treated area) in the feeder pivotal trials. For this population, a total of 108 subjects from the previous PEP005 Gel treatment groups and 9 subjects from the previous vehicle gel groups from Study 016 and 025 were enrolled. Eight subjects (7%) in the previous PEP005 Gel group and one subject (11%) in the previous vehicle group prematurely discontinued. At 12 month follow up, 54% of subjects (n=58/108) who had been successfully treated (complete clearance at Day 57) in the previous Phase 3 face/scalp trials, had at least 1 new or recurrent AK lesion in the previously treated area.

Non-head (trunk/extremities) indication - Study 032 (feeder trial Study 028):
The population of interest was subjects with complete clearance at Day 57 (AK lesion count of zero in the treated area) of the previous trial. For this population, a total of 38 subjects from the previous PEP005 Gel treatment group and 5 subjects from the previous vehicle gel group from study PEP005-028 were enrolled. One (3%) PEP005 Gel-treated patient prematurely discontinued. At 12 months of follow-up, 58% (n=22/38) of subjects who had been treated with PEP005 Gel in the previous Phase 3 trunk/extremities trial, had at least one new or recurrent AK lesion in the previously treated area.

6.1.10 Additional Efficacy Issues/Analyses

Efficacy in treatment resistant AK lesions has not been studied. Efficacy in repeat/multiple cycle treatment has not been studied. Recurrence was based on the lesion count in the treatment area, and not on whether any particular AK lesions recurred after treatment (lesions were not mapped). Comparative efficacy has not been studied. In the absence of comparative data, any comparative statements should be made with caution. PEP005 Gel required a shorter course of treatment (2-3 days), compared with the 5-FU products (~2 to 6 weeks); diclofenac (60-90 days); and, imiquimod: Aldara® (16 weeks) and Zyclara® (two 2-week treatment cycles separated by a 2 week no-treatment period). Definition for 'complete clearance,' in the CLINICAL STUDIES sections of labeling should be noted. For example, for PEP005 Gel the drug was applied to a field treatment area of a specific size, and complete clearance was

based on lesion clearance in the field treatment of the 25 cm^2 area, whereas for Carac® the drug was applied to the entire face/anterior bald scalp, and complete clearance was determined on lesion clearance in the entire anatomical area.

7 Review of Safety

Safety Summary

Maximum use PK data demonstrated that levels of ingenol and its acyl isomers were below the lower limit of quantification[5] following application of PEP005 Gel, 0.05% once daily to a 100 cm^2 area on the dorsal forearm for 2 consecutive days. No systemic absorption of topical drug was detected in the PK trials (Study 004, 013, 017).

Drug adverse reactions included:

- Ocular and peri-ocular disorders (including severe reactions of eye pain, eyelid edema, eyelid ptosis, and periorbital edema), which were most likely due to contact irritation/dermatitis

- Local skin reactions (include severe reactions of erythema, scaling/flaking, crusting, swelling, vesiculation/pustulation, and erosion/ulceration), and other application site reactions (including application site pain and application site infections)

The safety profile appears acceptable in the benefit/risk profile. The vast majority of adverse reactions were self limiting. Adverse reactions that required treatment were treated successfully with concomitant medications, and resulted in no serious medical outcomes or permanent side effects. Study drop out and discontinuation were low. .

Repeat/multiple cycle use safety has not been studied. Treatment resistant AKs and recurrent AKs were not routinely biopsied for histopathology. Comparative safety has not been studied.

7.1 Methods

The Applicant proposed two indications of treatment of AKs on the face and scalp, and on the trunk and extremities.

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

The data source was from the 25 clinical trials/studies that the Applicant conducted and submitted to the NDA. The data source used in the safety assessment appears adequate, and the Applicant's methods appear appropriate. The applicant's overall

5 LLOQ= 0.1 ng/mL

categorization of data, i.e., whether the safety data were appropriately coded, appears generally acceptable.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.1 Tables of Studies/Clinical Trials. The safety review relied upon data obtained from the four Phase 3, vehicle controlled trials: (Study 016, 025, 014,028). Supporting safety information was derived from the rest of the trials/studies in the development program.

7.1.2 Categorization of Adverse Events

The integrated analysis of the Integrated Summary of Safety (ISS) used the Medical Dictionary for Regulatory Activities (MedDRA) coding of preferred terms. Adverse events (AEs), including listing of the investigator and subject's verbatim/reported terms preferred terms, were provided as complete listings in an electronic format to the NDA submission. The overall categorization of AEs appears appropriate.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant used various pooling strategies, including pooling data across the following:

- 13 AK field treatment trials
- Phase 3 vehicle controlled trials by indication – face/scalp, trunk/extremities
- other trials – AK lesion-specific treatment trials, dermal safety trials in healthy subjects, and non melanoma treatment trials

Notwithstanding the inherent limitations in pooling data across trials of different study designs/populations, the advantage was it increased the sample size. For example, pooling the 13 AK field treatment trials increased the number of PEP005 Gel subjects to N=1165 (N=632 of vehicle subjects). Such pooling strategy allowed a 'first look' exploration and estimation of event rates in a relatively large sample size. From this larger database if a safety signal emerged, additional analyses could be conducted in the Phase 3 vehicle controlled trials (pivotal trials data were examined independently of other pooling strategies as well). Pooling data across all other trials (AK lesion specific, dermal safety in healthy subjects, and non-AK, NMSC trials) provided supportive evidence. Thus the overall pooling strategy was screen broadly for adverse events to reveal the common adverse reactions profile, and to detect some of the less common and more serious adverse reactions associated with drug use. Whether an adverse reaction was consistent across studies/clinical trials was a critical consideration. If a signal was found across different pooling strategies, including in the vehicle-controlled trials, a stronger case could be made for a casual relationship.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 13 Number of subjects dosed with PEP005 Gel or vehicle

Population	**No. (N) of subjects who received at least one dose of study medication**	
	PEP005 Gel	**Vehicle Gel**
AK lesions, field treatment (13 trials)	1165	632
AK lesions, field treatment Phase 3 pivotal vehicle controlled trials-face/scalp (2 trials)	274	271
AK lesions, field treatment Phase 3 pivotal vehicle controlled trial-trunk/extremities (2 trials)	225	232
AK lesions, lesion specific treatment (2 trials)	57	17
Topical safety, healthy volunteers (3 trials)	332	*
NMSC (4 trials)	220	24

* All subjects in the dermal safety trials received both PEP005 Gel and vehicle gel

The overall exposure at proposed doses/durations for indication was adequate. Adequate numbers of subjects with pertinent risk factors were exposed to the drug. Doses and durations of exposure were adequate to assess safety for the intended use. Design of the studies/clinical trials was adequate to answer critical questions for the drug. Potential class effects of local skin reactions were adequately assessed.

There were no subjects that were excluded from the clinical study program to limit the relevance of safety assessment, except for females of childbearing potential who were required to have a negative pregnancy test and to use contraception. Labeling should reflect that there are no adequate and well controlled studies of PEP005 Gel in pregnant women, and that the drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. See Section 7.6.2.

7.2.2 Explorations for Dose Response

Dose ranging testing in Phase 2 suggested that at higher concentration tested more subjects showed peri-lesional and full treatment area involvement of the local skin reactions.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing of clinical trial subjects, including efforts to elicit adverse event (AE) data and monitor laboratory parameters, vital signs, and ECGs were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Routine testing was adequate. Please see Section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Local skin irritation/reactions have been reported for all currently approved and available topical treatments. The Applicant used an active assessment and a prospectively defined grading system to evaluate PEP005 Gel associated local skin reactions (LSRs). See Section 7.3.5.

7.3 Major Safety Results

7.3.1 Deaths

One death was reported in the clinical development program. Subject 27-002 received PEP005 Gel 0.005% applied once daily to AK lesions on the face for 3 consecutive days in Study 015, a double-blind, dose-ranging, vehicle-controlled Phase 2 trial. The subject was a 58 year-old Caucasian male, with a history of hypertension, impaired fasting hyperglycemia, and insulin resistance. Concomitant medications included irbesartan 300 mg once a day for hypertension and over-the-counter magnesium and glucosamine with chondroitin sulfate. At screening, the subject had a blood pressure of 132/90 mmHg, a height of 180 cm, and a weight of 102 kg (BMI of 31). Local skin reactions were observed in the treatment area and peaked at Day 3, subsequently resolving. On the morning of the event day -- 4 weeks after the study medication treatment – the subject was out for a walk or a run and was subsequently found dead on the sidewalk. The cause of death listed on the certificate was coronary artery atherosclerosis and hypertension.

In field application AK trials (PEP005 N=1165, and Vehicle N=632) there was no apparent trend toward an increased cardiac risk. Data for incidence of AEs reported under the system organ class (SOC) CARDIAC DISORDERS in the 13 pooled AK treatment trials is shown in Table 14.

Table 14 Summary of cardiac disorders (copied electronically from the Applicant's submission)

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%)

In addition, in the Phase 3 vehicle-controlled pivotal trials, incidence of AEs reported under the SOC of CARDIAC DISORDERS did not suggest any significant cardiac findings.

Table 15 Incidence of AEs in the system organ class of CARDIAC DISORDERS in Phase 3 vehicle-controlled face/scalp trials (pooled data Study 016, 025, reviewer's analysis)

Adverse event (preferred term)	**0.015% PEP005 Gel subjects (N=274)**	**VEHICLE GEL subjects (N=271)**
MYOCARDIAL INFARCTION	1 (0.4%)	0 (0%)
ATRIAL FIBRILLATION	0 (0%)	1 (0.4%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0 (0%)	2 (0.7%)
BUNDLE BRANCH BLOCK LEFT	0 (0%)	1 (0.4%)
BUNDLE BRANCH BLOCK RIGHT	0 (0%)	1 (0.4%)
SINUS ARRHYTHMIA	0 (0%)	1 (0.4%)
SUPRAVENTRICULAR EXTRASYSTOLES	0 (0%)	1 (0.4%)
TACHYCARDIA	0 (0%)	1 (0.4%)
VENTRICULAR EXTRASYSTOLES	1 (0.4%)	1 (0.4%)

Table 16 Incidence of AEs in the system organ class of CARDIAC DISORDERS (SOC) in Phase 3 vehicle-controlled trunk/extremities trials (pooled data Study 014, 028, reviewer's analysis)

Adverse event (preferred term)	**0.05% PEP005 Gel subjects (N=225)**	**VEHICLE Gel subjects (N=232)**
ATRIOVENTRICULAR BLOCK FIRST DEGREE	3 (1.3%)	0 (0%)
SUPRAVENTRICULAR EXTRASYSTOLES	1 (0.4%)	0 (0%)
ANGINA PECTORIS	0 (0%)	1 (0.4%)
BUNDLE BRANCH BLOCK RIGHT	0 (0%)	1 (0.4%)
CORONARY ARTERY DISEASE	0 (0%)	1 (0.4%)
MYOCARDIAL INFARCTION	2 (0.9%)	4 (1.7%)
VENTRICULAR EXTRASYSTOLES	1 (0.4%)	1 (0.4%)
VENTRICULAR PRE-EXCITATION	0 (0%)	1 (0.4%)

EKG-related AEs reported in the vehicle-controlled pivotal trials (Table 15, Table 16) were nonspecific in nature. Majority of the EKG related AEs were recorded on the 4th day of study period, likely because EKGs were collected on the 4th day of the study per study protocol. The fatal event, possibly sudden cardiac death, was likely not related to PEP005 Gel treatment based on the overall clinical picture: i) isolated incidence, ii) short duration of treatment (3 days), iii) negligible systemic absorption of the drug; iv) long interval delay between treatment and event (4 weeks), v) presence of multiple cardiovascular risk factors (male gender, age, hypertension, obesity), vi) high background rate of atherosclerotic heart disease in the study population of predominantly older Caucasian men, and vi) lack of a cardiac safety signal in the pooled databases, including in the vehicle-controlled trials.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

Per US regulation, 'serious adverse drug experience' is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Per PEP005 Gel study protocols, serious adverse events were to be identified by the investigator as those that resulted in death, were 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 were considered medically significant.

Following a review of the investigator's coding of SAEs, the Applicant identified additional adverse events that were serious that were not identified as SAEs by the investigator. These additional Applicant-identified events were in the system organ class (SOC) of 'NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)', with preferred terms of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma, basosquamous carcinoma, Bowen's disease, and skin neoplasm.

Skin cancers are clinically grouped into melanomas and nonmelanoma skin cancers (NMSCs). Melanomas have a significantly higher propensity for metastasis, which cause significantly greater mortality and morbidity, whereas nonmelanomas, which include BCCs and SCCs, with rare exceptions, do not metastasize and are highly curable if treated early. NMSCs constitute majority of the skin cancers in the US, and tend to develop on sun exposed areas of the body. Thus NMSCs are common in patients with AKs, which also tend to occur in sun exposed areas. Although most NMSCs are non serious, occasionally, NMSCs may be serious, or SAEs, for example, when an NMSC becomes invasive and invade into vital structures or when it metastasizes. Thus whether a NMSC is coded as an SAE is determined on a case by case basis and is subject to clinical judgment. This could partially explain the discrepancy in the SAE coding outcomes between the investigator and the Applicant's. However, the fact that the Applicant identified additional cases of SAEs raises concerns about whether the investigator had appropriately designated all SAEs.

Table 17 presents SAEs, whether investigator- or Applicant-identified, in the 13 field application AK trials. The overall incidence of SAEs was low. Rates were generally similar between treatment groups. SAEs occurred in 4.2% of the subjects in the PEP005 Gel group and 3.6% in the vehicle group. BCC and SCC were the most frequently reported SAEs for both treatment groups. Serious BCCs occurred in 1.5% of PEP005 Gel-treated patients and in 1.1% of vehicle-treated patients. Serious SCC occurred in 0.9% of PEP005 Gel-treated patients and in 0.8% of vehicle-treated patients. See Section 7.3.5 for additional discussions on BCCs and SCCs.

Table 17 Summary of Serious Adverse Events (SAEs), including both investigator-determined and Applicant-determined events (copied electronically from the Applicant's submission)

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

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

Although certain SOCs in the SAE analysis had a higher rate in the PEP005 Gel group, the differences compared to vehicle was small. More importantly there was no trend of clinical significance in specific SAEs by AE preferred terms. For example, although as a class the system organ class (SOC) GASTROINTESTINAL DISORDERS had a higher overall incidence rate in the PEP005 Gel group (0.3% vs. 0.0), by preferred terms this consisted of 1 case of abdominal pain, 1 case of gastroesophageal reflux disease, 1 case of pancreatitis, and 1 case of small intestinal obstructions. Thus, no conclusions could be drawn about the causal relationship between the drug and any particular SAEs (by preferred term) in the gastrointestinal system. A list of all SAEs in Phase 2 and 3 trials is provided in Appendix, Table 41.

Three SAEs listed in Table 17 were considered possibly related to the study drug by the investigator/Applicant.

1. In Study PEP005-013, Subject 0901 (treated with daily doses of PEP005 Gel, 0.05% on the forearm on Days 1 and 2) had an SAE of Bowen's disease (squamous cell carcinoma) 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 subject was a 73-year-old Caucasian male with a history of AK since 1954 on his face, neck, V of chest, trunk and extremities, as well as keratoacanthoma, BCC, SCC, and intra-epidermal carci-noma. 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. The carcinoma (characterized as Bowen's disease) was adequately excised on Study Day 92, and the subject recovered.

2. In Study PEP005-022, Subject 01203 (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 subject was a 68-year-old Caucasian male with severe AK at baseline and a history of BCC (9 lesions) and SCC (2 lesions). A keratotic nodule developed on the right forearm treatment area during followup. 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 subject recovered.
3. In Study PEP005-020, Subject 88/209 (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 did not identify this as an SAE, graded the event as moderate in intensity and considered it possibly related to study drug. The Applicant

identified the event as an SAE. The subject 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 subject recovered.

Although the SAEs were considered possibly drug related (probably because they occurred in the treatment are), the rate of SCCs (including both SAEs and non-SAEs) was similar between the treatment groups in the Phase 3 vehicle-controlled trials (see Section 7.3.5). Further, it is not known whether the SCCs were mapped to normal skin, AKs, or subclinical SCCs at Baseline. A causal relationship could not be established between PEP005 Gel and these SAEs based on the available data.

7.3.3 Dropouts and/or Discontinuations

The topics of dropout from the study and discontinuation from the study medication are discussed next. Complete listing of AEs that led to treatment discontinuation can be found in Appendix, Table 42. The low study drop out and medication discontinuation rate suggested that PEP005 Gel was generally tolerated.

Dropouts from the study

In the 13 field application AK trials (PEP005 treated N=1165; vehicle N=632), 3 subjects (1 treated with PEP005 Gel and 2 treated with vehicle) discontinued from the study due to 1 or more AEs. AEs that led to dropout in the PEP005 Gel subject were 1) eye pain, 2) application site pain, and 3) periorbital edema. All the events were graded severe in intensity and occurred in 1 subject (incidence 0.1%, N=1/1165). Subject 14/017 was a 61-year-old male, who received 3 doses of PEP005 Gel 0.015% in Study 016 (1 of the 2 pivotal vehicle-controlled trials in the face/scalp). Following the first application of study medication (Day 1), he experienced severe application site pain on the face that was considered by the investigator as definitely related to study medication. A few days later (on Day 4 of the study), the subject reported severe eye pain (characterized as both pain and burning) and severe periorbital edema; these events were considered probably related to study medication. The eye pain occurred outside the treatment area. All events resolved by Day 11; the subject was discontinued from the study on Day 29.

In the Phase 3 vehicle-controlled trials, study dropout rate was 1/274 subjects (0.4%) in the PEP005 Gel group in the face/scalp pooled population (subject referenced above), and 0/274 (0.0%) PEP005 Gel group in the trunk/extremities pooled population.

In the 9 additional studies (lesion-specific AK treatment trials and non-AK trials), 1 subject may have discontinued from the study due to an AE. Subject 07/0102 was a 79-year-old female in study PEP005-008, who received 2 doses of PEP005 Gel, 0.05% on Days 1 and 2, respectively. On Day 3, she developed diarrhea (moderate in intensity) that resolved on Day 7. The AE was considered by the investigator as

possibly related to study medication. The subject may have dropped out of the study and/or discontinued the study medication.[6]

Discontinuations from the study medication

Across the 13 field application AK trials (PEP005 Gel treated N=1165; vehicle N=632), 37 (3.2%) subjects in the PEP005 Gel groups discontinued study medication due to an AE, compared to 0 (0%) subject in the vehicle group. Although subjects discontinued study medication, which was administered mostly over 2-3 days, most remained in the study for observation through Day 57.

As final concentration and regimen were selected based on tolerability, fewer subjects discontinued from the study medication in the later trials. In the pivotal vehicle controlled trials, 3 subjects (N=3/274, 1.1%) treated with PEP005 Gel from the face/scalp trials (Studies 016 and 025), and 1 subject (N=1/225, 0.4%) from the trunk/extremities trials (Studies 014 and 028) discontinued the study medication. AEs that led to the medication discontinuations in the pivotal trials were the following:

- In the face/scalp pivotal trials: application site Irritation, application site pain, and application site pruritus
- In the trunk/extremities pivotal trials: application site pain

In the 9 additional trials (lesion-specific AK treatment trials and non-AK trials) in which subjects received PEP005 Gel, a total of 4 subjects discontinued dosing due to: application site pain (1 subject in study PEP005-001), erythema and skin exfoliation (both reported for 1 subject in study PEP005-002)[7], lymphangitis (1 subject in study PEP005-009)[8], and pregnancy (1 subject in study PEP005-005).

7.3.4 Significant Adverse Events

AEs that were graded severe in intensity, regardless whether considered drug related by the investigator or considered serious adverse events (SAEs) are presented below. In the field treatment AK trials (N= 1797: PEP005 Gel N=1165; vehicle N=632), AEs that were graded severe were reported by 3.2% of subjects treated with PEP005 and 1.6% of subjects treated with vehicle. Table 18 below lists severe AEs that occurred at higher incidence rate in the PEP005 treated subjects than vehicle.

6 There was some discrepancy in this subject's record.
7 Erythema and skin foliation occurred in 1 subject treated with 0.05% PEP005 Gel for 2 days (Day 1, 8) for treatment of nodular basal cell carcinoma.
8 Lymphangitis (under the SOC of INFECTIONS AND INFESTATIONS) occurred in 1 subject treated with 0.25% PEP005 Gel for 2 days (Day 1, 8) for treatment of superficial basal cell carcinoma.

Table 18 Severe adverse events occurring at higher incidence in the PEP005 Gel treatment group (field application AK trials, reviewer's analysis modified from the Applicant's table[9])

	All Field Application AK trials	
Severe adverse event System Organ Class (SOC) (preferred term)	**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 pruritus	2 (0.2%)	0 (0.0%)
Application Site pain	5 (0.4%)	0 (0.0%)
Application Site irritation	5 (0.4%)	0 (0.0%)
Application Site swelling	1 (0.1%)	0 (0.0%)
Application Site erosion	1 (0.1%)	0 (0.0%)
Application Site scab	1 (0.1%)	0 (0.0%)
Application Site oedema	1 (0.1%)	0 (0.0%)
Death	1 (0.1%)	0 (0.0%)
Infections and Infestations	3 (0.3%)	0 (0.0%)
Cystitis	1 (0.1%)	0 (0.0%)
Campylobacter Infection	1 (0.1%)	0 (0.0%)
Epiglottis	1 (0.1%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	1 (0.1%)	2 (0.3%)
Periorbital Oedema	1 (0.1%)	0 (0.0%)
Injury, Poisoning, and Procedural Complications	3 (0.3%)	2 (0.3%)
Meniscus lesion	1 (0.1%)	0 (0.0%)
Cervical vertebral fracture	1 (0.1%)	0 (0.0%)
Neoplasms Benign, Malignant and Unspecified	1 (0.1%)	2 (0.3%)
Malignant Melanoma	1 (0.1%)	0 (0.0%)
Nervous System Disorders	1 (0.1%)	0 (0.0%)
Headache	1 (0.1%)	0 (0.0%)
Investigation	1 (0.1%)	0 (0.0%)
Treponin Increased	1 (0.1%)	0 (0.0%)
Musculoskeletal and Connective Tissue Disorders	6 (0.5%)	1 (0.2%)
Back pain	1 (0.1%)	0 (0.0%)
Muscle spasms	2 (0.2%)	0 (0.0%)
Intervertebral Disc Protrusion	1 (0.1%)	0 (0.0%)
Polymyalgia Rheumatica	1 (0.1%)	0 (0.0%)
Spinal Osteoarthritis	1 (0.1%)	0 (0.0%)
Gastrointestinal Disorders	4 (0.3%)	0 (0.0%)
Diarrhea	1 (0.1%)	0 (0.0%)
Vomiting	1 (0.1%)	0 (0.0%)
Abdominal Distension	1 (0.1%)	0 (0.0%)
Tooth Ache	1 (0.1%)	0 (0.0%)
Small Intestinal Obstruction	1 (0.1%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.2%)	1 (0.2%)
Chronic Obstructive Pulmonary Disease	1 (0.1%)	0 (0.0%)
Hypoxia	1 (0.1%)	0 (0.0%)

9 Table 18 was generated using data from the source Table 6.3.3 in the ISS, and is a modified version of the Applicant's Table 20 (ISS). Whereas the Applicant's Table 20 captures severe AEs reported by 2 or more subjects in at least 1 of the 2 treatment arms, Table 18 below lists all severe AEs that occurred at a higher incidence rate in the PEP005 treated group, even if it occurred in only 1 subject in the PEP005 Gel arm.

Cardiac Disorders	4 (0.3%)	4 (0.6%)
Angina Pectoris	2 (0.2%)	1 (0.2%)
Aortic Valve Disease	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%)
Vascular Disorders	1 (0.1%)	0 (0.0%)
Aortic Aneurysm	1 (0.1%)	0 (0.0%)

Data for severe AEs in the Phase 3 vehicle-controlled trials are as follows.

Table 19 Severe AEs occurring at higher incidence in PEP005 treated subjects than vehicle (face/scalp Study 016, 025, reviewer's analysis)

Severe adverse event (preferred term)	**0.015% PEP005 Gel subjects (N=274)**	**VEHICLE subjects (N=271)**
APPLICATION SITE PAIN	4 (1.5%)	0 (0%)
CAMPYLOBACTER INFECTION	1 (0.4%)	0 (0%)
EYE PAIN	1 (0.4%)	0 (0%)
HYPOXIA	1 (0.4%)	0 (0%)
MALIGNANT MELANOMA	1 (0.4%)	0 (0%)
MENISCUS LESION	1 (0.4%)	0 (0%)
MYOCARDIAL INFARCTION	1 (0.4%)	0 (0%)
PERIORBITAL OEDEMA	1 (0.4%)	0 (0%)
SMALL INTESTINAL OBSTRUCTION	1 (0.4%)	0 (0%)

Table 20 Severe AEs occurring at higher incidence in PEP005 treated subjects than vehicle (trunk/extremities Study 014, 028, reviewer's analysis)

Severe adverse event (preferred term)	**0.05% PEP005 Gel subjects (N=225)**	**VEHICLE subjects (N=232)**
ABDOMINAL DISTENSION	1 (0.4%)	0 (0%)
CERVICAL VERTEBRAL FRACTURE	1 (0.4%)	0 (0%)
EPIGLOTTITIS	1 (0.4%)	0 (0%)
INTERVERTEBRAL DISC PROTRUSION	1 (0.4%)	0 (0%)
MUSCLE SPASMS	1 (0.4%)	0 (0%)
SPINAL OSTEOARTHRITIS	1 (0.4%)	0 (0%)
TROPONIN INCREASED	1 (0.4%)	0 (0%)

Although there were severe AEs that had a higher incidence rate in the PEP005 Gel treated group, it is difficult to attribute non local AEs to the study drug due to its limited systemic exposure.

7.3.5 Submission Specific Primary Safety Concerns

Specific safety concerns for this topical product are 1) ocular and peri-ocular disorders, and 2) local skin reactions/application site reactions, including application site infections. Nonmelanoma skin cancer is also discussed next.

1. Skin neoplasms: NMSC (BCC and SCC)

Refer also to Section 7.3.2 above for NMSC as SAEs.

As displayed in
Table 21 below, in the pooled 13 field application AK trials, neoplasms of all types, reported as system organ class (SOC) were 3.0% and 2.7% in the PEP005 Gel and vehicle subjects. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were the more frequently reported types of neoplasms and occurred in a slightly higher frequency in the PEP005 group (BCC: 1.5% and 1.1% for PEP005 Gel and vehicle. SCC: 0.9% and 0.8% for PEP005 Gel and vehicle).

Table 21 Summary of neoplasms in field application AK trials (copied electronically from the Applicant's submission)

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%)

To supplement this data, the ADAE dataset, which provides a listing of AEs from all trials in the clinical development program, was reviewed to study whether the lesions occurred inside or outside the treatment area. This was of interest because the drug was expected to exert only local effect (inside the treatment area) due to its limited systemic exposure. Table 22 and Table 23 below display the findings for BCC and SCC. A total of 36 AEs of BCC were identified, and of these, 16 cases did not have a location designation, and the remaining 17 cases were identified as occurring outside the treatment area.

Table 22 Basal cell carcinoma in the clinical development program (reviewer's analysis)

STUDY ID	SUBJECT ID	AE (PREFERRED TERM)	LOCATION	TREATMENT	AE START DAY IN STUDY DAY
PEP005-002	PEP005-0022221	Basal Cell Carcinoma		0.0025% PEP005 Gel, Days 1, 8	
PEP005-007	PEP005-007505007	Basal Cell Carcinoma		0.0050% PEP005 Gel, Days 1, 2, 3	57
PEP005-002	PEP005-0021229	Basal Cell Carcinoma		0.01% PEP005 Gel, Days 1, 2	
PEP005-002	PEP005-0022202	Basal Cell Carcinoma		0.01% PEP005 Gel, Days 1, 8	
PEP005-007	PEP005-007505012	Basal Cell Carcinoma		0.0175% PEP005 Gel, Days 1, 2, 3	57
PEP005-007	PEP005-007505012	Basal Cell Carcinoma		0.0175% PEP005 Gel, Days 1, 2, 3	57
PEP005-007	PEP005-007505012	Basal Cell Carcinoma		0.0175% PEP005 Gel, Days 1, 2, 3	57
PEP005-007	PEP005-007040408	Basal Cell Carcinoma		0.025% PEP005 Gel, Days 1, 2	57
PEP005-006	PEP005-0061035	Basal Cell Carcinoma		0.05% PEP005 Gel, Days 2, 3	29
PEP005-009	PEP005-00912602	Basal Cell Carcinoma		0.15% PEP005 Gel, Day 1	84
PEP005-009	PEP005-00912631	Basal Cell Carcinoma		0.25% PEP005 Gel, Day 1	86
PEP005-002	PEP005-0021219	Basal Cell Carcinoma		Vehicle Gel, Days 1, 2	
PEP005-006	PEP005-0061098	Basal Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	57
PEP005-006	PEP005-0061049	Basal Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	31
PEP005-002	PEP005-0022209	Basal Cell Carcinoma		Vehicle Gel, Days 1, 8	
PEP005-003	PEP005-0032122	Basal Cell Carcinoma		Vehicle Gel, Days 1, 8	104
PEP005-015	PEP005-015-21-016	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.015% PEP005 Gel, Days 1, 2, 3	57
PEP005-016	PEP005-016-16-015	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.015% PEP005 Gel, Days 1, 2, 3	50
PEP005-025	PEP005-025-01-017	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.015% PEP005 Gel, Days 1, 2, 3	57
PEP005-025	PEP005-025-04-021	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.015% PEP005 Gel, Days 1, 2, 3	48
PEP005-013	PEP005-0130902	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	
PEP005-014	PEP005-014-52004	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	29
PEP005-014	PEP005-014-59008	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	57
PEP005-014	PEP005-014-59008	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	57
PEP005-014	PEP005-014-59008	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	57
PEP005-018	PEP005-01810702	Basal Cell Carcinoma	OUTSIDE	0.05% PEP005 Gel,	8

STUDY ID	SUBJECT ID	AE (PREFERRED TERM)	LOCATION	TREATMENT	AE START DAY IN STUDY DAY
			TREATMENT AREA	Days 1, 2	
PEP005-020	PEP005-020-78-202	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	22
PEP005-020	PEP005-020-80-204	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	79
PEP005-020	PEP005-020-86-204	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	29
PEP005-028	PEP005-028-64-005	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	51
PEP005-022	PEP005-022-01203	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2 (25 cm^2, 50 cm^2)	51
PEP005-014	PEP005-014-50018	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	12
PEP005-014	PEP005-014-70001	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	57
PEP005-028	PEP005-028-61-002	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	22
PEP005-028	PEP005-028-68-002	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	57
PEP005-025	PEP005-025-02-017	Basal Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2, 3	5

In the same database, as displayed in Table 23 below, a total of 31 cases of AEs of squamous cell carcinoma and Bowen's disease (and other AEs that may be related, including 'neoplasm skin,' 'neoplasm progression,' and 'basosquamous carcinoma') were identified. Of these, 16 cases did not have a location designation. Of the 15 AEs that had a location designation, 4 occurred inside the treatment area, and 10 outside treatment area. Of the four AEs that occurred inside the treatment area, two occurred in the PEP005 Gel treatment subjects, and two in the vehicle.

Table 23 Squamous cell carcinoma and related disorders in the clinical development program (reviewer's analysis)

STUDY ID	SUBJECT ID	AE PREFERRED TERM	LOCATION	TREATMENT	AE START DAY IN STUDY DAY
PEP005-002	PEP005-0022213	Neoplasm Progression		0.0025% PEP005 Gel, Days 1, 8	
PEP005-007	PEP005-007111106	Bowen's Disease		0.0075% PEP005 Gel, Days 1, 2, 3	
PEP005-002	PEP005-0021213	Squamous Cell Carcinoma		0.01% PEP005 Gel, Days 1, 2	
PEP005-002	PEP005-0021203	Neoplasm Progression		0.01% PEP005 Gel, Days 1, 2	
PEP005-002	PEP005-0021203	Neoplasm Progression		0.01% PEP005 Gel, Days 1, 2	
PEP005-007	PEP005-007525204	Squamous Cell Carcinoma		0.025% PEP005 Gel, Days 1, 2	36
PEP005-006	PEP005-0061010	Squamous Cell Carcinoma		0.025% PEP005 Gel, Days 1, 2, 3	16
PEP005-006	PEP005-0061083	Squamous Cell Carcinoma		0.025% PEP005 Gel, Days 1, 2, 3	52
PEP005-006	PEP005-0061083	Squamous Cell Carcinoma		0.025% PEP005 Gel, Days 1, 2, 3	78
PEP005-006	PEP005-0062085	Squamous Cell Carcinoma		0.05% PEP005 Gel, Days 1, 2, 3	8
PEP005-006	PEP005-0062082	Squamous Cell Carcinoma		0.05% PEP005 Gel, Days 2, 3	15
PEP005-006	PEP005-0061048	Squamous Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	60
PEP005-006	PEP005-0061029	Squamous Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	30
PEP005-006	PEP005-0061029	Squamous Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	30
PEP005-006	PEP005-0061029	Squamous Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	30
PEP005-006	PEP005-0061029	Squamous Cell Carcinoma		Vehicle Gel, Days 1, 2, 3	30
PEP005-013	PEP005-0130901	Bowen's Disease	INSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	57
PEP005-020	PEP005-020-88-209	Squamous Cell Carcinoma	INSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	44
PEP005-022	PEP005-022-01203	Squamous Cell Carcinoma	INSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2 (25 cm2, 50 cm2)	29
PEP005-014	PEP005-014-66007	Squamous Cell Carcinoma	INSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	58
PEP005-025	PEP005-025-20-005	Basosquamous Carcinoma	INSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2, 3	58
PEP005-014	PEP005-014-63013	Neoplasm Skin	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	57
PEP005-018	PEP005-01810703	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	7
PEP005-020	PEP005-020-86-206	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	22
PEP005-028	PEP005-028-67-009	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2	15

STUDY ID	SUBJECT ID	AE PREFERRED TERM	LOCATION	TREATMENT	AE START DAY IN STUDY DAY
PEP005-022	PEP005-022-14306	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	0.05% PEP005 Gel, Days 1, 2 (100 cm^2)	49
PEP005-015	PEP005-015-19-004	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	-16
PEP005-028	PEP005-028-61-001	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	29
PEP005-028	PEP005-028-61-001	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	29
PEP005-028	PEP005-028-61-001	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	29
PEP005-028	PEP005-028-67-004	Squamous Cell Carcinoma	OUTSIDE TREATMENT AREA	Vehicle Gel, Days 1, 2	45

Although a higher incidence of BCC and SCC was observed in the PEP005 Gel treatment group in the pooled AK field treatment population (Table 21 Summary of neoplasms in field application AK trials (copied electronically from the Applicant's submission), the trend was not observed in Phase 3 vehicle controlled population. Table 24 and Table 25 below display data in the Phase 3 vehicle-controlled trials. Higher incidence of BCC in the PEP005 Gel group (1.1% of subjects treated with PEP005 Gel, and 0.4% of subjects treated with vehicle) was observed in the face/scalp subjects, but not in the trunk/extremities subjects (1.3% PEP005 Gel, 1.7% vehicle). Incidence of both BCC and SCC were actually higher in the vehicle group than PEP005 Gel in the trunk/extremities population (BCC: 1.3% vs. 1.7% for PEP005 Gel vs. vehicle; SCC: 0.4 vs. 0.9% for PEP005 Gel vs. vehicle). In the Phase 3 trials, all lesions of interest (BCC and SCC in the PEP005 Gel group) occurred outside the treatment area, and were observed before Day 57 of the study period.

Table 24 Incidence of neoplasms in the face/scalp vehicle-controlled pivotal trials (Study 016, 025, reviewer's analysis)

Adverse event (preferred term)	0.015% PEP005 GEL subjects (N=274)	VEHICLE GEL subjects (N=271)
BASAL CELL CARCINOMA	3 (1.1%)	1 (0.4%)
SEBORRHOEIC KERATOSIS	1 (0.4%)[1]	0 (0.0%)
BASOSQUAMOUS CARCINOMA	0 (0.0%)	1 (0.4%)[2]
MALIGNANT MELANOMA	1 (0.4%)	1 (0.4%)

All occurred outside the treatment area, except for 1, 2, that occurred inside the treatment area

Table 25 Incidence of neoplasms in the trunk/extremities vehicle-controlled pivotal trials (Study 014, 028, reviewer's analysis)

Adverse event (preferred term)	**0.05% PEP005 GEL subjects (N=225)**	**VEHICLE GEL subjects (N=232)**
ACANTHOMA	1 (0.4%)[1]	0 (0.0%)
NEOPLASM SKIN	1 (0.4%)	0 (0.0%)
BASAL CELL CARCINOMA	3 (1.3%)	4 (1.7%)
BREAST CANCER	0 (0.0%)	1 (0.4%)
CYST	0 (0.0%)	1 (0.4%)
LYMPHOMA	0 (0.0%)	1 (0.4%)
SEBORRHOEIC KERATOSIS	0 (0.0%)	1 (0.4%)
SQUAMOUS CELL CARCINOMA	1 (0.4%)	2 (0.9%)
SQUAMOUS CELL CARCINOMA OF SKIN	0 (0.0%)	1 (0.4%)[2]

All occurred outside the treatment area, except for 1, 2, that occurred inside the treatment area

Animal carcinogenicity data were that PEP005 Gel was **negative** in the Ames test, in the *in vitro* mouse lymphoma assay, and in the *in vivo* rat micronucleus assay, but **positive** in the *in vitro* Syrian hamster embryo (SHE) cell assay.[10] A few tumors were noted in the intravenous 6 month rat toxicity study conducted with PEP005 Gel but it is not clear that the tumors noted in this study were treatment related because the increase in tumor incidence was very small and not statistically significant. Dr. Yao (FDA pharmacology-toxicology reviewer) felt that based on available pre-clinical data, mutagenic potential for PEP005 Gel is possible but likely low given that the product is used only for 2-3 days. Thus far the Applicant has not been required by the Agency to conduct animal carcinogenic studies mainly due to limited duration of clinical use (2 to 3 days). However Dr. Yao recommended that if the clinical conditions of use should change (e.g., longer treatment duration) the need for animal carcinogenicity studies should be re-evaluated.

Taken together, available clinical and pre-clinical evidence suggest that the potential of risk for local skin carcinogenicity is possible but low. The clinical evidence for BCC appears to be stronger than SCC, based on the vehicle-controlled data. The following factors have been considered in determining whether a causal relationship exists. Arguing for a causal relationship between PEP005 Gel and BCC was the repeat trend of higher incidence rate observed: incidence of BCC was higher in the PEP005 Gel group than vehicle in the pooled 13 AK field treatment trials (BCC: 1.5% vs. 1.1% for PEP005 Gel vs. vehicle), and in the pooled vehicle-controlled face/scalp pivotal trials (BCC: 1.1% vs. 0.4% for PEP005 Gel vs. vehicle). Note that the vehicle controlled design of the pivotal trials is important in evaluating an AE for which there is a high background rate in the study population. And, it is known that the drug can cause local skin irritation/cell necrosis/cell death; thus, the drug could alter the local skin environment and could affect cancer potentials through a mechanism that has yet been

10 Following a 24-hour or 7-day treatment period, renal tubular adenoma was seen in one out of 4 males and one out of 6 females intravenously receiving 15 µg/kg/day ingenol mebutate twice weekly for 6 months. Pituitary adenoma was also present in the female with the renal adenoma. Thyroid follicular cell carcinoma was observed in one out of 3 males receiving 15 µg/kg/day ingenol mebutate twice weekly for 6 months followed by a 28-day recovery period. See Dr. Yao's review for details.

characterized. However, both the location of cancers and time to onset argue against causality. In the Phase 3 vehicle controlled trials, all cases of BCCs occurred outside the treatment area. In the total pooled trials of the clinical development program, all documented (for location) cases of BCCs occurred outside the treatment area. It is highly unlikely that a drug with limited systemic exposure could cause an AE at a remote anatomical site on the skin. Further, time to onset was too short. BCCs account for approximately 1 million cases in the US. The typical doubling time, based on the known natural history of BCCs, is approximately 1½ years - whereas in the clinical development, almost all cases were observed before Day 57. Therefore based on the observed time to event, the cases were likely not related to drug treatment; however, this predicates on the assumption that drug-induced BCCs do not have a different time course than that of spontaneously occurring BCCs, i.e., they are not more aggressive, and do not have a shorter doubling time than that of spontaneously occurring BCCs. Arguing against a causal relationship is also the incidence rate in vehicle-controlled trials of the trunk/extremities: the rate of BCC was higher in the vehicle group in the pooled Phase 3 population (1.4% in PEP005 Gel and 1.3% in vehicle). And finally, it should be noted that Phase 2 and 3 trials were not designed to answer this specific question about whether a causal relationship between BCC and the drug exists. The Applicant's conclusion is that neoplasms were reported for a similar proportion of subjects within the treatment groups. This reviewer believes there is insufficient data to conclude a causal relationship exists between PEP005 Gel and NMSC. The signal is equivocal at best, and the strength of evidence is not sufficient to conclude a causal relationship. BCCs occur most frequently in sun-exposed areas, such as the head and neck, and generally do not metastasize. If detected and treated early, the skin cancer is highly curable. They are rarely a threat to one's life expectancy. However, they can metastasize, and can be destructive, e.g., destroy tissues that are adjacent to it. When this occurs on the face, for example, it can be functionally and cosmetically impairing. Thus this issue about causality should not be dismissed without careful consideration.

2. Ocular and peri-ocular disorders

Animal ocular irritation studies have not been conducted because PEP005 Gel is a known ocular irritant. The Applicant provided the following literature review on published case reports of accidental or deliberate exposure in humans to the raw material of the plant, i.e., to the sap of *Euphorbia* species.[11,12] The plant genus Euphorbia consists of > 2000 species, many of which secrete a white, gummy latex sap with contact irritant properties.[13, 14, 15] *Euphorbia* ocular toxicity is characterized by acute

11 Eke T, Al-Husainy S, Raynor M. The spectrum of ocular inflammation caused by Euphorbia plant sap. Arch Ophthalmol 2000;118:13-16

12 Merani R, Sa-ngiampornpanit T, Kerdraon Y, et al. Euphorbia lactea sap keratouveitis: Case report and review of the literature. Cornea 2007:26:749-752

13 Biedner BZ, Sachs U, Witztum A. Euphorbia peplus latex keratoconjunctivitis. Ann Ophthalmol 1981;13:739-740

pain, conjunctival injection, epithelial ulceration, corneal edema, epiphora, lid swelling, photophobia, chemosis and anterior chamber inflammation.[16] Ocular injury symptoms generally occur immediately and may increase in intensity over 1 to 3 days.[17,18] The clinical course and outcome depend on the species, dose, time between exposure and irrigation, and host factors. In severe cases, corneal ulceration and blindness can result.[19] Clinicians managing keratopathy caused by exposure to raw plant material from *Euphorbia* species should be aware of the danger of sight-threatening infection and uveitis, particularly during the first few days (see footnote reference Eke et al, 2000). With early treatment and appropriate management, complete resolution may be achieved within 1 to 2 weeks.

The Applicant has received 1 report of ocular exposure to *E. peplus* sap in a 64-year-old commercial grower who experienced pain and burning in the affected eye within 5 minutes of exposure. Subsequent blurred vision and eyelid swelling occurred, despite extensive ocular flushing with water shortly after the accidental exposure. The patient self-treated by bathing the eye with black tea and applied naphazoline hydrochloride eye drops, which provided no relief. A codeine-paracetamol preparation was prescribed by a local pharmacist. The man reported that light exposure increased the level of pain and decreased vision in the affected eye; ophthalmic investigation on the day of the exposure revealed a deep corneal abrasion. The eye was treated with chloramphenicol and the patient was prescribed ibuprofen for pain. Within 2 days, the pain decreased, the corneal abrasion had improved, and margin sharpness had increased. All signs and symptoms were resolved within 6 days of the accident. Note that all of the above cases describe ocular toxicity associated with exposure to the plant sap - not to the drug product PEP005 Gel, or the drug substance, ingenol mebutate.

Ocular and peri-ocular toxicity to PEP005 Gel is presented next. In the 13 AK field treatment trials, ocular and peri-ocular disorders occurred more frequently in the PEP005 Gel treatment groups than in vehicle. Eyelid edema (in the SOC of EYE DISORDERS) and periorbital edema (SOC of SKIN AND SUBCUTANEOUS DISORDERS) were the most frequently reported eye related disorders

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14 Eke T. Acute kerato-uveitis associated with topical self-administration of the sap of the petty spurge (Euphorbia peplus). Eye 1994;8:694-696

15 Eke T, Al-Husainy S, Raynor M. The spectrum of ocular inflammation caused by Euphorbia plant sap. Arch Ophthalmol 2000;118:13-16

16 Merani R, Sa-ngiampornpanit T, Kerdraon Y, Billson F, McClellan K. Euphorbia lactea sap keratouveitis: Case report and review of the literature. Cornea 2007:26:749-752

17 Duke-Elder S. System of ophthalmology, Vol 14. London, UK: Kimpton, 1972; 1185.

18 Grant WM, Schuman JS. Toxicology of the Eye. 4th Ed. Springfield Ill: CC Thomas, 1993; 680-682.

19 Morris B, Richardson EK, Adams, A, Chohan A. Green fingers, red eyes! Ocular hazards of gardening. Emerg Med J. 2006:23:584

Table 26).

Table 26 Summary of eye related disorders (copied electronically from the Applicant's submission)

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%)

Most of the events listed in Table 26 were considered related to study treatment, and were graded as mild or moderate. Five events were graded severe: severe periorbital edema, severe eyelid edema, severe eye edema, severe eye pain, and severe eyelid ptosis. A total of 3 subjects experienced at least one of these severe AEs (Table 27). Subject PEP005-015-27-022 experienced severe eye pain and severe periorbital edema that resulted from documented inadvertent eye exposure following application of PEP005 Gel to the face and the subject discontinued from the study because of the events. All the severe AEs resolved without sequelae.

Table 27 Severe eye disorders in field application AK trials (reviewer's analysis)

Study	Subject ID	AE Preferred term (Reported term)	Start of AE (Study day)	End of AE (Study day)	Action taken with study treatment	Study drug treatment Location of treatment and AE	Severity of AE
015	PEP005-015-07-002	EYE EDEMA (Drug reaction – edema bilateral eyes)	1	28	DRUG DISCONTINUED	0.015% PEP005 Gel, Days 1, 2, 3 (Face, outside treatment area)	SEVERE
015	PEP005-015-27-022	EYELID OEDEMA (Swelling upper eye lid)	2	10	DRUG DISCONTINUED	0.015% PEP005 Gel, Days 1, 2, 3 (Face; inadvertent eye exposure)	SEVERE
015	PEP005-015-27-022	EYELID PTOSIS (Ptosis)	2	10	DRUG DISCONTINUED	0.015% PEP005 Gel, Days 1, 2, 3 (Face; inadvertent eye exposure)	SEVERE
016	PEP005-016-14-017	PERIORBITAL OEDEMA (periorbital edema)	4	6	NONE	0.015% PEP005 Gel, Days 1, 2, 3 (Face, outside treatment area)	SEVERE
016	PEP005-016-14-017	EYE PAIN (Eye pain)	4	11	NONE	0.015% PEP005 Gel, Days 1, 2, 3 (Face, outside treatment area)	SEVERE

An Information Request was sent to the Applicant to obtain clinical narratives on subjects who experienced the following ocular AEs (listed in Table 26), which are of special clinical interest due to their potential serious nature: diplopia, eye hemorrhage, scleral discoloration, blurry vision, and visual disturbance. Of these, visual disturbance occurred in a vehicle treated subject. The narratives for the AEs that occurred in the PEP005 Gel group are summarized below.

- Diplopia

SUBJECT001-10-004: This case concerns a 73 -year-old female subject, who participated in the PEP005-001 study. The subject was administered PEP005 Gel, 0.05 %, topically to individual AK lesions, all located on the shoulder. Study medication was to be applied on Days 1 and 2 of the study. The subject received both applications of the study medication. The first dose was applied on 28-APR-2005 and the last dose was applied on 29-APR-2005.

The subject experienced diplopia on 03-MAY-2005 (5 days after first application). This event was located outside the treatment area, and was assessed as mild by the investigator. The event resolved on 08-May-2005 (10 days after last application), and no treatment was considered necessary by investigator for the AE.

The subject's medical history included asthma, hypertension, chronic low back pain, L5/S1 laminectomy, osteoporosis, thoracic spine crush fracture, ischemic heart disease, reflux esophagitis, pulmonary embolism, and osteoarthritis knee. Concomitant medications included: ipratropium bromide, salbutamol, morphine sulphate, acetylsalicylic acid, glyceryl trinitrate spray, diltiazem hydrochloride , naproxen sodium, glyceryl trinitrate patch, pantoprazole sodium, salicylic acid 3%, vioform+hydrocortisone, budesonide w/formoterol fumerate, ciprofloxacin and flucloxallin. The Investigator reported the event as a non-serious event, and not related to the treatment with PEP005 Gel.

- Eye hemorrhage

SUBJECT 015-09-007: This case concerns a 49 -year-old male subject, who participated in the PEP005-015 study. The subject was administered PEP005 Gel, 0.015%, topically to a 25 cm^2 area of skin located on the face on Days 1, 2 and 3 of the study. The first dose was applied on 29-Jul-2008 and the last dose was applied on 31-Jul-2008.

The subject experienced broken blood vessels in the right eye (eye hemorrhage) on 30-Jul- 2008 (2 days after first application). This event was located outside the treatment area, and was assessed as moderate by investigator. The patient recovered without treatment and the event had an outcome of resolved on 10-Aug-2008 (12 days after first application).

The patient's medical history included back pain since 1978 and there were no concomitant medications administered during study participation. The Investigator reported the event as a non-serious event, and not related to the treatment with PEP005 Gel.

- Scleral discoloration

SUBJECT025-12-011: This case concerns a 57-year-old male subject, who participated in the PEP005-025 study. The subject was administered PEP005 Gel, 0.015 %, topically to a 25cm^2 area of skin located on the face. Study medication was to be applied on Days 1, 2 and 3 of the study. The subject received all three applications of study medication. The first dose was applied on 23-Jun-2009 and the last dose was applied on 25-Jun-2009.

The subject experienced scleral lentigo in the right eye (scleral discoloration) on 20-Aug-2009 (approximately 1 month after first dose). This event was located outside the treatment area, and was assessed as mild by investigator. The event had an outcome of unresolved and was ongoing with little or no change at last follow up (20-Aug-2009). The subject did not recover from this event.

The patient's medical history included drug hypersensitivity to sulfa, seasonal allergies, irregular bowel movements, dyspepsia, gastroesophageal reflux, tension headache and sagittal jaw reconstruction. Concomitant medications included: acetylsalicylic acid, ranitidine, multivitamins, and ibuprofen. The Investigator

reported the event as non serious event, and not related to the treatment with PEP005 Gel.

- Blurred vision

SUBJECT015-16-023: This case concerns an 82 -year-old male subject, who participated in the PEP005-015 study. The subject was administered PEP005 Gel, 0.015%, topically to a 25 cm^2 area of skin located on the face. Study medication was to be applied on Days 1, 2 and 3 of the study. The subject received all 3 applications of study medication. The first dose was applied on 31-Jul-2008 and the last dose was applied on 02-Aug-2008.

The subject experienced blurred vision in the left eye on 03-Aug-2008 (3 days after the first dose). This event was outside the treatment area and was assessed as moderate by investigator. The subject did not require treatment and the event had an outcome of resolved on 05-Aug-2008 (5 days after the first dose).

The patient's history included myopia, atrial fibrillation, hypercholesterolemia, torn meniscus, appendectomy, meniscus repair (unknown) and previous treatment for actinic keratosis. Concomitant medications included: flecainide acetate, multivitamin, glucosamine, calcium, acetylsalicylic acid and ascorbic acid.

The Investigator reported the event as a non-serious and probably related to the treatment with PEP005 Gel. The Applicant's causality assessment of the case is a non-serious and probably not related event. Confounding factors include past medical history of atrial fibrillation treated with Flecainid [sic]. Blurred vision is stated as a very common adverse drug reaction in the safety information for Flecainid [sic].

Diplopia, eye hemorrhage, sclera discoloration and blurred vision were of interest because they could have potentially serious/significant clinical outcomes. Except for scleral discoloration, the events occurred within days after drug application so a temporal relationship was possible. All were isolated cases, and except for scleral discoloration, resolved without treatment.

There were no AEs that resulted in permanent visual loss or other catastrophic medical consequences, though in a minority of cases a medication was prescribed. A total of 51 AE terms (from the ocular or peri-ocular region) were identified in 42 subjects from all trials conducted with PEP005 Gel (lesion specific and field treatment AK trials, BCC trials, and topical safety trials). In 3 subjects, the event occurred inside the treatment area; in 8 subjects it was not possible to exclude that the event occurred inside the treatment area; and, in the remaining 32 subjects, the event occurred outside the treatment area. Based on the verbatim (reported) terms, the Applicant identified 25 events that were unilaterally located, 16 events that were bilaterally located and 2 events that were unknown. Ophthalmological care was provided for 10 subjects with ocular/peri-ocular region AEs. Treatments administered were of relatively benign nature, and included acetaminophen, ibuprofen diphenhydramine, steroids, and antibiotics. There was no evidence for neurologic involvement.

Phase 3 vehicle controlled data are as follows:

Table 28 Ocular and peri-ocular disorders in Phase 3 vehicle controlled face/scalp trials (Study 016, 025, reviewer's analysis)

	Face/Scalp	
Adverse event (preferred term)	**Subjects (PEP005 GEL, 0.015%) N=274**	**Subjects (VEHICLE GEL) N=271**
PERIORBITAL OEDEMA	7 (2.6%)	0 (0%)
EYELID OEDEMA	3 (1.1%)	0 (0%)
EYE PAIN	2 (0.7%)	0 (0%)
CONJUNCTIVITIS	1 (0.4%)	0 (0%)
EYE OEDEMA	1 (0.4%)	0 (0%)
EYE IRRITATION	0 (0%)	1 (0.4%)
VISUAL DISTURBANCE	0 (0%)	1 (0.4%)

Table 29 Ocular and peri-ocular disorders in Phase 3 vehicle controlled trunk/extremities trials (Study 014, 028, reviewer's analysis)

	Trunk/Extremities	
Adverse event (preferred term)	**Subjects (PEP005 GEL, 0.05%) N=225**	**Subjects (VEHICLE GEL) N=232**
CONJUNCTIVITIS	1 (0.4%)	0 (0%)

There was a higher incidence of ocular and peri-ocular disorders in the PEP005 Gel treated subjects; and, there were more events in the face/scalp population, which is consistent with the assumption that the events were caused by direct contact with the drug. Given limited systemic absorption the mechanism was most likely due to contact dermatitis/direct contact with the eye and the surrounding areas.

Subjects in the pivotal vehicle controlled trials applied the topical drug gel at home and were instructed to take precautions. Per study protocol, subjects were instructed to wear a finger cot for drug application. Study medication was not to be applied immediately following a shower or less than two hours before going to bed. The treatment area was to dry for 15 minutes before any further activity. For 6 hours after medication application, the subject was to avoid touching or washing the treatment area, or engaging in activities that cause excessive sweating. When washing the area after the 6 hour wait period, the area was to be washed gently using a mild, non-abrasive, non-medicated soap. The treatment area was not to be covered with tight clothing. Caution was given that the drug is a "severe eye irritant" and that contact with eyes should be avoided, and if contact were to occur, the subject was to rinse the eyes thoroughly with plenty of water and proceed immediately to the nearest Emergency

Room or Urgent Care Center for treatment. Despite these warnings and precautions, ocular and peri-ocular related AEs occurred.

Cases of ocular/peri-ocular AEs occurred without documentation of exposure. It is likely that the subject did not recall inadvertent eye contact either at the time of the application or later. Therefore warnings should include precautions taken to avoid transfer either at the time of application or later after the drug has been applied to the skin (such as transfer by clothing, jewelry, hair). For the WARNGINGS AND PRECUATION section of product labeling, severe adverse reactions should be listed (reference based on Table 27). The AE regulatory dictionary term 'eye edema'[20] recorded in clinical trial is of little use to prescribers and it is recommended that this term not be included in the label listing; the other terms listed already adequately convey the types of reactions that occurred. For the ADVERSE REACTIONS section, the adverse event term 'periorbital edema' could be captured in the 'common adverse reactions' table that includes adverse reactions occurring in ≥ 2% of subjects treated with PEP005 Gel and at higher frequency than vehicle (see Section 7.4.1 for the recommended table). Other reactions found in

Table 28 and Table 29 of this review could be listed without incidence rate but in order of frequency, under the description, 'less common adverse reactions.' Recommended language is as follows: (deletion in ~~double strikethrough~~; addition in **bold**).

5 WARNINGS AND PRECAUTIONS
5.1 Eye Exposure

(b) (4) **Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, periorbital edema can occur after eye exposure of TRADEMARK Gel *[see Adverse Reactions (6)].* Patients should wash hands well after applying TRADEMARK Gel, and avoid transfer of the drug to the eye during and after application [see Instruction for use (17.1)].** If accidental exposure occurs, the eyes should be flushed immediately with large amounts of water, and the patient should seek medical care as soon as possible *[see Adverse Reactions (6)].*

20 Based on the reported/verbatim term: "drug reaction – edema bilateral eyes"

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience

Table X Adverse reactions occurring in ≥ 2% of subjects treated with TRADEMARK Gel and at higher frequency than vehicle (face/scalp trials)

	Face/Scalp	
Adverse Reactions	**TRADEMARK Gel, 0.015% (N=274)**	**VEHICLE (N=271)**
Application Site Pain	**42 (15%)**	**1 (0%)**
Application Site Pruritus	**22 (8%)**	**3 (1%)**
Application Site Infection	**7 (3%)**	**0 (0%)**
Periorbital Edema	**7 (3%)**	**0 (0%)**
Headache	**6 (2%)**	**3 (1%)**

Less common adverse reactions in subjects treated with TRADEMARK Gel included: eyelid edema, eye pain, conjunctivitis.

3. Application site infections

There was a small difference between PEP005 Gel treated subjects and vehicle-treated subjects with respect to AEs by the SOC INFECTIONS AND INFESTATIONS. Table 30 and Table 31 below display the Phase 3 vehicle controlled data. In the face/scalp trials (Study 016, 025) the % of subject who experienced at least 1 AE in the SOC of INFECTIONS AND INFESTATIONS was 0.07% (N=20/274) in the PEP005 Gel treated subjects, and 0.04% (N=12/271) in vehicle. In the trunk/extremities trials (Study 014, and 028), the incidence was 0.07% (N=15/225) in the PEP005 Gel treated subjects, and 0.06% (N=15/232) in the vehicle. In the face/scalp population, application site infection occurred in 2.6% of subjects, compared with 0% in the vehicle.

Table 30 AEs in the SOC of INFECTIONS AND INFESTATIONS that occurred at higher incidence in PEP005 Gel group than vehicle in the Phase 3 vehicle controlled face/scalp trials (Study 016, 025, reviewer's analysis)

AE (Preferred term)	N of subject (PEP005 GEL, 0.015%) N=274	N of subject (VEHICLE GEL) N=271
APPLICATION SITE INFECTION	7 (2.6%)	0 (0%)
GASTROENTERITIS VIRAL	2 (0.7%)	1 (0.4%)
INFLUENZA	2 (0.7%)	0 (0%)
ABDOMINAL ABSCESS	1 (0.4%)	0 (0%)
CAMPYLOBACTER INFECTION	1 (0.4%)	0 (0%)
GASTROENTERITIS	1 (0.4%)	0 (0%)
INTERTRIGO CANDIDA	1 (0.4%)	0 (0%)
LOWER RESPIRATORY TRACT INFECTION	1 (0.4%)	0 (0%)
RESPIRATORY TRACT INFECTION	1 (0.4%)	0 (0%)
TOOTH INFECTION	1 (0.4%)	0 (0%)
VAGINITIS BACTERIAL	1 (0.4%)	0 (0%)

Table 31 AEs in the SOC of INFECTIONS AND INFESTATIONS that occurred at higher incidence in PEP005 Gel group than vehicle in the Phase 3 vehicle-controlled trunk/extremities trials (Study 014, 028, reviewer's analysis)

AE (Preferred term)	N of subject (PEP005 GEL, 0.015%) N=225	N of subject (VEHICLE GEL) N=232
NASOPHARYNGITIS	4 (1.8%)	2 (0.9%)
CELLULITIS	1 (0.4%)	0 (0%)
CYSTITIS	1 (0.4%)	0 (0%)
EPIGLOTTITIS	1 (0.4%)	0 (0%)
OTITIS MEDIA ACUTE	1 (0.4%)	0 (0%)
STAPHYLOCOCCAL INFECTION	1 (0.4%)	0 (0%)
TINEA CRURIS	1 (0.4%)	0 (0%)
TOOTH ABSCESS	1 (0.4%)	0 (0%)

The Applicant was requested to provide clinical narratives for subjects in the clinical development program who had an AE by the preferred term, 'application site infection.' A total of 11 subjects were identified; 1 subject was treated with vehicle; 10 were treated with PEP005 Gel. In the PEP005 Gel group, 1 subject was treated with 0.025% Gel for 3 days on the back; 1 subject was treated with 0.015% Gel for 3 days on the scalp; 1 subject was treated with 0.015% Gel for 3 days on the chest; and, the remaining 7 subjects were treated with 0.015% Gel for 3 days on the face. Majority of the application site infections occurred on the face. All 10 cases were considered mild by the investigator, and 7 cases resolved without treatment. Three subjects were prescribed oral antibiotics (two subjects were treated empirically without culture testing; one subject had a positive culture for *staphylococcus aureus).* Cultures were obtained in 7 of the 10 cases. Majority (5 cases out of the 7) were positive for *staphylococcus aureus*. The remaining cases were culture positive for *enterobacter cloacae/pseudomonas aeruginosa* (1 case), and *citrobacter koseri* (1 case); these did not require treatment. So in summary in the development program the occurrence of application site infection was relatively infrequent and the outcomes were fairly benign. The higher incidence of Application Site Infection on the face could be captured in the 'common adverse reactions' table, under Adverse Reactions occurring in ≥2% of

Subjects with TRADEMARK Gel and at Higher Frequency than Vehicle (Face/Trial Trials). See Section 7.4.1 for the proposed table, also shown below.

Table X Adverse reactions occurring in ≥ 2% of subjects treated with TRADEMARK Gel and at higher frequency than vehicle (face/scalp trials)

	Face/Scalp	
Adverse Reactions	**TRADEMARK Gel, 0.015% (N=274)**	**VEHICLE (N=271)**
Application Site Pain	**42 (15%)**	**1 (0%)**
Application Site Pruritus	**22 (8%)**	**3 (1%)**
Application Site Infection	**7 (3%)**	**0 (0%)**
Periorbital Edema	**7 (3%)**	**0 (0%)**
Headache	**6 (2%)**	**3 (1%)**

4. Local skin reactions (LSRs)

In earlier trials in the development program, the Applicant identified eight 'local skin responses' (LSRs) that were commonly reported as AEs. These local skin reactions were assessed within the selected treatment area at the Baseline and each successive visit. Application site reactions other than these eight were recorded as AEs. Thus 'local skin reactions/responses' (LSRs) are a subset of all application site reactions. A grading system was established based on the eight selected LSRs: 1) erythema, 2) flaking/scaling, 3) swelling, 4) crusting, 5) erosion/ulceration, 6) vesiculation/postulation, 7) pigmentation (hypo and hyper), 8) scarring. 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 (8 X 4 = 32). This system was used for the Phase 1 and 2 AK field treatment trials PEP005-006, PEP005-007, PEP005-013, and PEP005-018.

In subsequent trials, including the vehicle-controlled Phase 3 trials, pigmentation and scarring were removed from the LSRs and were graded to the description of 'present' or 'not present.'[21] The remaining six LSRs were included in the grading scale, with the maximum score of 24 (6 x 4 = 24). The Applicant's proposed labeling for 'local skin reactions' is based on this revised grading scale. Criteria for the LSR Scale are listed in Table 32 and the accompanying photo guide.

21 Hyper/hypopigmentation and scarring were reviewed separately - no significant trend was observed.

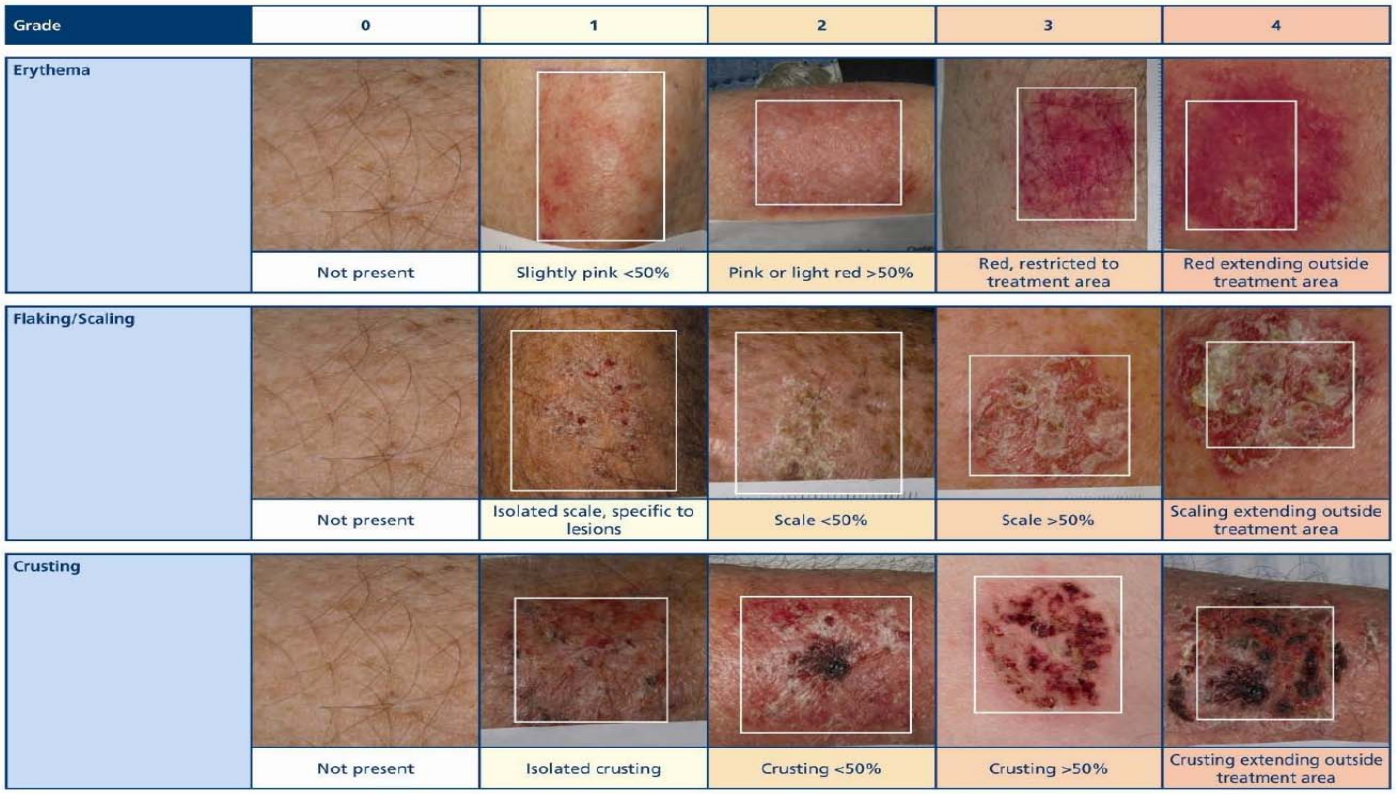
1. erythema
2. flaking/scaling
3. swelling
4. crusting
5. erosion/ulceration
6. vesiculation/postulation

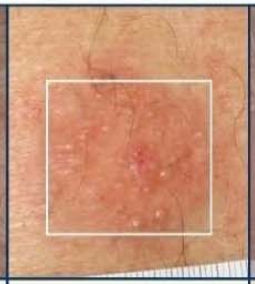
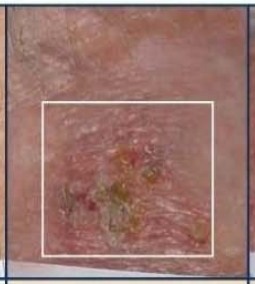
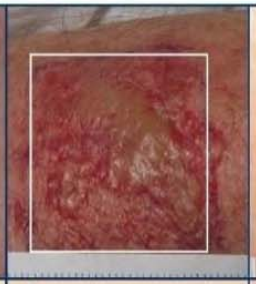
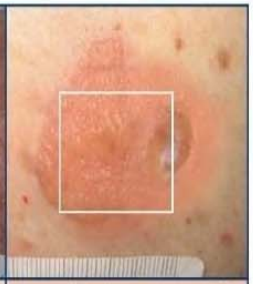
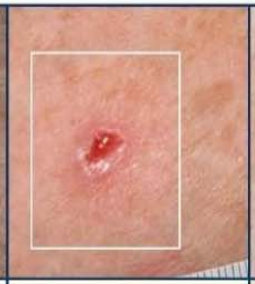
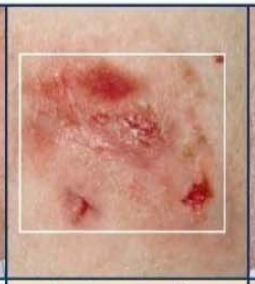
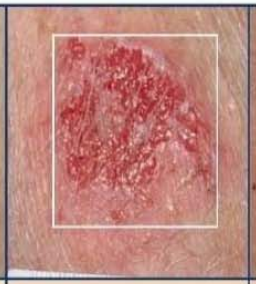
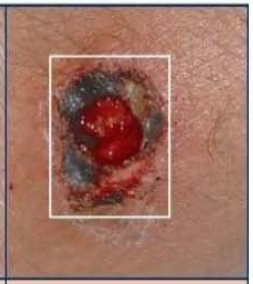
Table 32 Grading Criteria/scale for Local Skin Reactions in Phase 3 trials (copied electronically from the Applicant's submission)

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

Local Skin Response Grading Scale

Treatment area(s) to be assessed using the following categories and grading scale



Grade	0	1	2	3	4
Swelling	Not present	Slight, lesion specific oedema	Palpable oedema extending beyond individual lesions	Confluent and/or visible oedema	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

The Applicant's method of using a separate, active assessment had the disadvantage of diluting the LSRs in the overall AE incidence rate by AE preferred terms. For example, in the table, 'Summary of Treatment-emergent Adverse Events considered related to Study Medication with an incidence of ≥ 1% in Any Group' (Table 19, ISS) – the incidence of the AE application site reaction was '0.0%' in both PEP005 Gel and vehicle groups in the Phase 3 trials. This is because LSRs were not collected as AEs; they were assessed separately as LSRs. In actuality the incidence of application site reaction was not zero. Nonetheless the Applicant's approach is acceptable. The Applicant collected LSRs data, and adequately captured the variety, frequency, and severity of the reactions. A separate assessment for LSRs could in fact highlight their importance, and this reviewer finds the photograph scale guide very useful.

Medical treatment for application site reactions were relative infrequent and minor. In the 1774 subjects who were treated with PEP005 Gel in the development program, 26 subjects received treatment for AEs related to the study drug in the treatment area. All subjects, except one in the BCC trial, were enrolled in the AK trials. The most frequent treatments were analgesics for application site pain (9 subjects), antibiotics (9 subjects) for application site skin infection, and topical steroids (4 subjects) and oral steroids (1 subject) for edema.

In the following section, LSR scores are discussed by composite scores (sum of scores across all variable categories), and by individual maximum scores.

Composite LSR scores

Majority of the subjects in all treatment groups had a non-zero (> 0) score at the treatment site at Baseline, predominantly attributed to erythema and flaking/scaling. In Phase 3 trials, following application of study medication almost all PEP005 Gel-treated subjects (>96%) showed an increase in LSR score relative to Baseline, compared to ~ 30% of the vehicle subjects.

For the majority of subjects, the maximum composite LSR score occurred on Days 3 and 4, with the score returning to Baseline value or below by Day 29 (~ 1 month). In the vehicle controlled Phase 3 trials, subjects treated on the face/scalp experienced LSRs of greater intensity than the trunk/extremities subjects. Maximum composite LSR score was 9.1 in the face/scalp subjects, compared with 6.8 in the trunk/extremities subjects (Table 33).

Table 33 Summary of local skin reactions (composite score) for the controlled Phase 3 trails by indication (copied electronically from the Applicant's submission)

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.

The composite score conveys a general impression of the total degree of LSRs but is not clinically informative for the prescriber or the patient for the specific types or severity of local skin reactions. For example, a composite score of 12 would be uninformative to the typical patient who is deciding to use the drug. For labeling it is more informative to list individual LSR scores, discussed below.

Individual LSR scores (by maximum grade post Baseline)

For both treatment locations (face/scalp and trunk/extremities), erythema and flaking/scaling were the most common LSRs, followed by crusting and swelling. Grade 4 reactions were observed more frequently in the PEP005 Gel group compared with vehicle. Grade 4 reactions were observed more frequently in subjects treated on the face/scalp. Majority of the PEP-005 Gel treated subjects experienced erythema, flaking/scaling, crusting, and/or swelling (any Grade >0). A significant percentage of subjects also experienced (any Grade >0) vesiculation/pustulation, and/or erosion/ulceration (Table 34).

Local skin responses typically occurred within 1 day of treatment initiation, peaked in intensity up to 1 week following completion of treatment, and resolved within 2 weeks for areas treated on the face and scalp and within 4 weeks for areas treated on the trunk and extremities. Additionally, across all LSR categories (erythema, flaking/scaling, etc.) the percentage of PEP005 Gel treated subjects who had Grade 0 response (no reactions) at Day 57 was higher or equal to at Baseline (data not shown).

Table 34 Summary of maximum score of each local skin reactions post Baseline for the controlled Phase 3 trials by indication (copied electronically from the Applicant's submission)

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%)

LSRs at Day 57 and Month 12

The LSRs profile at Day 57 appears acceptable. LSRs were assessed at Days 3/4, Day 8, Day 15, Day 29, and Day 57 in the Phase 3 trials. As shown in Table 35, at Day 57 in the Phase 3 trials the most common remaining LSRs were erythema, and

flaking/scaling, and to less extent, crusting. Rates were lower in the PEP005 Gel treated groups than vehicle. Most of the reactions were of Grade 1 or 2. There were no Grade 4 reactions of crusting, swelling, vesiculation/pustulation, or erosion/ulceration. There was 1 case of Grade 4 erythema, and 1 case of Grade 4 flaking/scaling, in the trunk/extremities PEP005 Gel treated group (Table 35).

Table 35 Local skin reactions at Day 57 or end of treatment controlled Phase 3 trials for field treatment of AK lesions (copied electronically from the Applicant's submission)

		Face/Scalp		Trunk/Extremities	
Local Skin Response	Day 57/ End of treatment Score	PEP005 Gel 0.015% (N=274)	Vehicle Gel (N=271)	PEP005 Gel 0.05% (N=225)	Vehicle Gel (N=232)
ERYTHEMA	Grade 0	201 (73%)	173 (64%)	157 (70%)	158 (68%)
	Grade 1	63 (23%)	90 (33%)	64 (28%)	70 (30%)
	Grade 2	8 (3%)	5 (2%)	2 (1%)	4 (2%)
	Grade 3	1 (0%)	3 (1%)	1 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	1 (0%)	0 (0%)
FLAKING/SCALING	Grade 0	190 (69%)	137 (51%)	154 (68%)	133 (57%)
	Grade 1	83 (30%)	126 (46%)	68 (30%)	97 (42%)
	Grade 2	0 (0%)	5 (2%)	1 (0%)	1 (0%)
	Grade 3	0 (0%)	3 (1%)	1 (0%)	1 (0%)
	Grade 4	0 (0%)	0 (0%)	1 (0%)	0 (0%)
CRUSTING	Grade 0	257 (94%)	252 (93%)	215 (96%)	218 (94%)
	Grade 1	16 (6%)	18 (7%)	8 (4%)	13 (6%)
	Grade 2	0 (0%)	1 (0%)	2 (1%)	0 (0%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	1 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SWELLING	Grade 0	271 (99%)	269 (99%)	222 (99%)	232 (100%)
	Grade 1	2 (1%)	1 (0%)	2 (1%)	0 (0%)
	Grade 2	0 (0%)	1 (0%)	1 (0%)	0 (0%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
VESICULATION/PUSTULATION	Grade 0	273 (100%)	270 (100%)	225 (100%)	232 (100%)
	Grade 1	0 (0%)	1 (0%)	0 (0%)	0 (0%)
	Grade 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
EROSION/ULCERATION	Grade 0	273 (100%)	270 (100%)	225 (100%)	232 (100%)
	Grade 1	0 (0%)	1 (0%)	0 (0%)	0 (0%)
	Grade 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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The LSRs profile at Month 12 appears acceptable. Subjects who had complete clearance of AK lesions (treatment success) at Day 57 in the feeder Phase 3 trials were eligible for enrollment in the 12 months extension studies (Study 030, 032) for studying the recurrence of AKs and AEs in the previously treated area. In the 12 month extension studies, local safety (AEs in the previously treated area) was collected at 3, 6, 9, and 12 Month. Subjects were not re-treated with PEP005 Gel treatment during the 12 month period (the 12 month local skin safety data was based on a single cycle treatment, i.e., 2 days for the face/scalp subjects and 3 days for the trunk/extremities subjects, in the pivotal trials). The face/scalp study (030) enrolled a population of 108 subjects from the previous PEP005 Gel treatment group and 9 subjects from the previous vehicle gel groups from the pivotal trials (Study 016, 025). One local AE was

reported in one subject: on Day 271 of the followup-up study: the subject had an AE of mild sunburn, aloe vera was applied, and the event resolved 7 days after its onset. The trunk/extremities study (032) enrolled a population of 38 subjects from the previous PEP005 Gel treatment group and 5 subjects form the previous vehicle gel group from the pivotal trial (Study 028). One subject experienced one local AE; on Day 251 of the follow-up study, the subject had a mild rash on both forearms and received one dose of oral ivermectin as well as topical diflorasone, and the rash resolved 13 days after onset. No other AEs were observed or reported in the treatment area.

Labeling of the WARNINGS AND PRECAUTIONS and the ADVERSE REACTIONS sections should include a discussion on the LSRs. Since the WARNINGS AND PRECAUTIONS section is intended to describe clinically significant adverse reactions, LSRs that are relatively common and benign conditions (i.e., flaking/scaling) could be omitted from the section, but the more deleterious/undesirable reactions such as swelling, vesiculation/pustulation, and erosions should be included. (A full listing of the reactions evaluated in the LSR grading scale should be included in the ADVERSE REACTIONS section.) It is reasonable to include the Applicant's proposed language on precautions that could mitigate or prevent LSRs, i.e., waiting until the skin is healed from any previous surgical treatment. In addition, the Applicant proposed a table similar to Table 34 for inclusion in the ADVERSE REACTIONS section. This reviewer finds the table difficult to read and the Grade 4 LSRs not highlighted. It is recommended to include only 'any grade' LSRs and Grade 4 LSRs in a table (one for each indication) that can more effectively convey the most important findings. Recommended language follows (deletion in ~~double strikethrough~~; addition in **bold**):

5 WARNINGS AND PRECAUTIONS
5.~~2~~**3** Local Skin **Reactions** (b) (4)

Severe skin reactions in the treated area, including (b) (4) (b) (4) erythema, (b) (4) crusting, **swelling, vesiculation/pustulation, and erosion/ulceration,** can occur after topical application of TRADEMARK Gel [*see Adverse Reactions (6)*]. (b) (4)

Administration of TRADEMARK Gel is not recommended until the skin is healed from any previous drug or surgical treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical **trials** (b) (4) are conducted under widely varying conditions, adverse reaction rates observed in the clinical **trials** (b) (4) of a drug cannot be directly compared to rates in the clinical **trials** (b) (4) of another drug and may not reflect the rates observed in **clinical** practice.

(b) (4)

The data described below reflect exposure to TRADEMARK Gel in **499 subjects with actinic keratosis, including 274 subjects exposed to PICATO Gel field treatment (skin area of 25 cm^2 in the face or scalp regions) at concentration of 0.015% once daily for 3 consecutive days, and 225 subjects exposed to PICATO Gel field treatment (skin area of 25 cm^2 in the trunk or extremities regions) at concentration of 0.05% once daily for 2 consecutive days.** (b) (4)

(b) (4) **L**ocal skin **reactions,** (b) (4) **including** ~~(~~erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, **and** erosion/ulceration~~),~~ were assessed within the selected treatment area and graded by the investigator on a scale of 0 to 4. A grade of 0 represented no reaction present in the treated area, and a grade of 4 indicated a marked and **severe** (b) (4) skin reaction that extended beyond the treated area.

(b) (4)

(b) (4)

Table X Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (face/scalp trials)

(b) (4)

Table X Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (trunk/extremities trials)

(b) (4)

(b) (4)

(b) (4) =Local skin **reactions**= (b) (4) (b) (4) =typically occur within (b) (4) **1** day of treatment initiation, (b) (4) peak**ed** in intensity up to (b) (4) **1** week following completion of treatment, **and** (b) (4) resolv**ed** within 2 weeks for areas treated on the face and scalp and within 4 weeks for areas treated on the trunk and extremities.

(b) (4)

A total of **108 subjects treated with TRADEMARK Gel on the face/scalp and 38 subjects treated on the trunk/extremities were followed for 12 months.** (b) (4) Results from these studies did not change the safety profile of TRADEMARK Gel.

(b) (4)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant proposed the following table (

Table 36) for labeling to describe common adverse reactions:

Table 36 Adverse reactions occurring in ≥ 1% of subjects treated with TRADEMARK Gel and at higher frequency than vehicle (copied electronically from the proposed labeling)

22 The Applicant's proposed language regarding the 12 month followup studies is based on the 120-Day Safety Update, submission dated July 25, 2011

(b) (4)

Table 36 is based on pooled data from the Phase 3 vehicle controlled trials for both indications. This approach does not differentiate safety profiles for the two distinct anatomic regions. For example, eye related AEs occurred more frequently in the face/scalp treatment population. There may be different cosmetic considerations for the face/scalp indication. To describe adverse reactions occurring in ≥ 1% of subjects treated with TRADEMARK Gel and at higher frequency than vehicle by indication, Table 37 and Table 38 are constructed.[23]

Table 37 Adverse reactions occurring in ≥ 1% of subjects treated with PEP005 Gel and at higher frequency than vehicle in Phase 3 trials (face/scalp) (reviewer's analysis)

Adverse reactions (preferred term)	**N (PEP005 Gel, 0.015%) (N=274)**	**N (VEHICLE) (N=271)**
APPLICATION SITE PAIN	42 (15%)	1 (0%)
APPLICATION SITE PRURITUS	22 (8%)	3 (1%)
APPLICATION SITE INFECTION	7 (3%)	0 (0%)
PERIORBITAL OEDEMA	7 (3%)	0 (0%)
HEADACHE	6 (2%)	3 (1%)
BASAL CELL CARCINOMA	3 (1%)	1 (0%)
BACK INJURY	3 (1%)	0 (0%)
EYELID OEDEMA	3 (1%)	0 (0%)
INSOMNIA	3 (1%)	0 (0%)
GASTROENTERITIS VIRAL	2 (1%)	1 (0%)
HYPERTENSION	2 (1%)	1 (0%)
APPLICATION SITE DISCHARGE	2 (1%)	0 (0%)
APPLICATION SITE PARAESTHESIA	2 (1%)	0 (0%)
ARTHRALGIA	2 (1%)	0 (0%)
CONSTIPATION	2 (1%)	0 (0%)
EYE PAIN	2 (1%)	0 (0%)
INFLUENZA	2 (1%)	0 (0%)

Table 38 Adverse reactions occurring in ≥ 1% of subjects treated with PEP005 Gel and at higher frequency than vehicle in Phase 3 trials (trunk/extremities) (reviewer's analysis)

Adverse reactions (preferred term)	**N (PEP005 Gel, 0.05%) (N=225)**	**N (VEHICLE) (N=232)**
APPLICATION SITE PRURITUS	18 (8%)	0 (0%)
APPLICATION SITE IRRITATION	8 (4%)	1 (0%)
NASOPHARYNGITIS	4 (2%)	2 (1%)

23 Percentage rounded to the nearest integers.

APPLICATION SITE PAIN	5 (2%)	0 (0%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	3 (1%)	0 (0%)
APPLICATION SITE PARAESTHESIA	2 (1%)	0 (0%)
APPLICATION SITE WARMTH	2 (1%)	0 (0%)
CHEST PAIN	2 (1%)	1 (0%)
EAR PAIN	2 (1%)	1 (0%)
ELECTROCARDIOGRAM T WAVE INVERSION	2 (1%)	0 (0%)
ERYTHEMA	2 (1%)	0 (0%)
EXCORIATION	2 (1%)	0 (0%)
PRURITUS	2 (1%)	0 (0%)

For labeling to inform about 'common' adverse reactions, this reviewer recommends a cut off rate of ≥ 2% be used, and that adverse reactions be presented by indication. Recommended language follows (deletion in ~~double strikethrough~~; addition in **bold**):

(b) (4)

Table X Adverse reactions occurring in ≥ 2% of subjects treated with TRADEMARK Gel and at higher frequency than vehicle (face/scalp trials)

	Face/Scalp	
Adverse Reactions	**PICATO Gel, 0.015% (N=274)**	**VEHICLE (N=271)**
Application Site Pain	**42 (15%)**	**1 (0%)**
Application Site Pruritus	**22 (8%)**	**3 (1%)**
Application Site Infection	**7 (3%)**	**0 (0%)**
Periorbital Edema	**7 (3%)**	**0 (0%)**
Headache	**6 (2%)**	**3 (1%)**

Table X Adverse reactions occurring in ≥ 2% of subjects treated with TRADEMARK Gel and at higher frequency than vehicle (trunk/extremities trials)

	TRUNK/EXTREMITIES	
ADVERSE REACTIONS	**PICATO Gel, 0.05% (N=225)**	**VEHICLE (N=232)**
Application Site Pruritus	**18 (8%)**	**0 (0%)**
Application Site Irritation	**8 (4%)**	**1 (0%)**
Nasopharyngitis	**4 (2%)**	**2 (1%)**
Application Site Pain	**5 (2%)**	**0 (0%)**

7.4.2 Laboratory Finding

There was no trend in clinically significant laboratory findings.

7.4.3 Vital Signs

There was no trend in clinically significant vital signs findings.

7.4.4 Electrocardiograms (EKGs)

There were no significant EKG abnormalities that changed the safety profile of the drug. Per Phase 3 study protocols, EKGs were obtained at Screening, on Day 4, and at any Unscheduled Visit. EKGs were sent to a central site, and measured and interpreted by US Board cardiologists; it was not specified whether the cardiologists were blinded to treatment assignments. The interpretation was then provided to the study site electronically including notification of any electrocardiographic abnormalities. The investigator reviewed and signed the interpretation.

The Applicant did not conduct a 'Thorough QT/Qtc Study (TQT).' In lieu, they performed EKG analysis throughout Phase 2-3, and submitted a "Combined Cardiac ECG Safety Report." Dr. Monica Fiszman, reviewer in the Division of Cardio-renal Products QT Interdisciplinary Review Team, was consulted regarding whether a TQT was required. She concurred that a TQT study was not needed because 1) the systemic exposure of the drug is within subnanomolar range,[24] and 2) the drug exhibited neither non-clinical effects consistent with QTc Prolongation nor clinically relevant Qtc prolongation effects in the clinical development. She recommended that the Applicant perform routine safety EKG monitoring, as clinically indicated, in ongoing and future clinical studies/trials.

24 The drug can be detected in human blood using an assay with the limit of detection of 0.1 ng/mL. Therefore, the estimated total exposure for the drug is less than 0.23nM.

7.4.5 Special Safety Studies/Clinical Trials

Three topical dermal safety trials in adult healthy volunteers were conducted. PEP005 Gel is a known skin irritant, and therefore occlusion was not used, which the Division stated may be an acceptable approach (April 10, 2005 Pre-Phase 2 Guidance Meeting). A lower concentration of the drug was used (0.01% Gel was used in the dermal safety trials, compared with the indications for use: 0.015% Gel on the face/scalp and 0.05% Gel on the trunk/extremities). The design and results of the dermal safety trials are as follows.

1. Study PEP005-024: photoallergenicity (photosensitization)

N=55 healthy subjects completed the trial. The trial design was a single-center, randomized, within-subject comparison study. Evaluators were blinded to treatment assignment. Minimal erythemal dose (MED) was determined for each subject. In the induction phase, subjects were treated with PEP005 Gel 0.01% and vehicle gel to cover a 4 cm^2 area of the skin, 2 times a week for 3 weeks; the treatment sites were irradiated with 2 times the subject's MED approximately 24 hours after each application. After a rest period of approximately 10-14 days, in the challenge phase naïve treatment sites were treated with PEP005 Gel and Vehicle. These sites and an untreated site, were irradiated with 6 J/cm^2 of UVA (320-400 nm) using a filtered light source and ½ (0.5X) MED of UVA/UVB (290-400 nm) 24 hours after application. If a cutaneous response indicating possible photosensitization was observed a re-challenge was to occur. For local tolerability, mean scores showed moderate erythema at the treatment areas irradiated after the application of PEP005 Gel and vehicle. Non-irradiated treatment areas showed mild irritation for PEP005 Gel and no irritation to vehicle. PEP005 Gel and vehicle under both irradiated and non-irradiated conditions had no more than mild erythema during challenge which either remained the same or resolved by 72-hour reading. Under the testing conditions the potential for photosensitization was not apparent.

2. Study PEP005-023: Phototoxicity (photoirritation)

N=33 healthy subjects completed the trial. This was a single-center, randomized, within-subject comparison study of PEP005 Gel and vehicle. Evaluators were blinded to treatment assignment. The MED was determined for each subject. Each subject was treated with PEP005 Gel (0.01%) and vehicle applied to cover a 4 cm^2 area of skin, followed by irradiation with 16 J/cm2 of UVA light 24 hours later, including an untreated area. Mild erythema was observed at all the irradiated treatment areas, whether treated with the study medication, the reference product (vehicle), or untreated. There were no significant differences between these irradiated treatment areas with respect to signs of photoirritation. There was no significant irritation observed at the non-irradiated areas treated with the study medication or vehicle, and there was no significant difference in signs of the photoirritation between non-irradiated treatment areas. Irradiated treatment areas showed significantly more photoirritation than non-irradiated treatment areas.

There were no adverse events during the study. Based on the testing conditions the potential for phototoxicity was not apparent.

3. Study PEP005-005: Skin irritation and sensitization

N= 220 healthy subjects completed sensitization analysis and 226 for irritation analysis. This was a single center, double blind, randomized, vehicle controlled, within subject comparison study. A positive control was not used. PEP005 Gel (0.01%) and vehicle were applied to cover a 4 cm^2 area of skin, under open-conditions (duration of application unspecified), 3 times a week for 3 weeks during the induction phase, followed by the rest phase of 2 weeks during which there was no study drug application. During the challenge phase, PEP005 Gel and vehicle were reapplied, to a naïve skin area and remained on the skin for 48 hours. There were no reactions greater than minimal erythema at any time during induction. Twenty (20) subjects had minimal erythema at the investigational product site. For 15 of those subjects the reaction resolved prior to the end of induction. There were no reactions at the vehicle control site. Two subjects (Nos. 81 and 85) experienced significant irritation, at challenge. Subject 81 had a minimal or doubtful response at the first challenge reading that increased to erythema with damage to the epidermis at the 24-hour challenge reading and was sustained through the 72-hour reading. The subject returned for a follow-up visit 2 days after the 72-hour challenge evaluation, and the irritation had resolved. Subject No. 85 had erythema with damage to the epidermis, i.e., oozing, crusting and/or superficial erosions at all 4 challenge readings. The subject was advised to return for a follow up visit 2 days after the 72 hour evaluation, but did not return. Both subjects had experienced mild erythema during the induction period. Under the conditions studied the potential for skin sensitization appeared low.

7.4.6 Immunogenicity

PEP005 Gel is a small molecule and immunogenicity is not expected and testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.3.5 for dose dependency in regards to LSRs.

7.5.2 Time Dependency for Adverse Events

See Section 7.3.5 for time sequence of LSRs.

7.5.3 Drug-Demographic Interactions

There were no safety issues pertaining to drug-demographic interactions.

7.5.4 Drug-Disease Interactions

There are no known comorbidities that affect the adverse reaction profile of the drug.

7.5.5 Drug-Drug Interactions

No formal drug-drug interactions trials were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No formal clinical trials in human carcinogenicity were conducted.

7.6.2 Human Reproduction and Pregnancy Data

Women of child-bearing potential who enrolled in any of the clinical trials 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 subjects received PEP005 Gel, there was 1 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.

The drug has minimal systemic absorption and the areas treated are unlikely near breastfeeding areas; section on NURSING MOTHERS may be omitted. This reviewer concurs with labeling language recommended by the pharmacology and toxicology review team:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies of TRADEMARK Gel in pregnant women. TRADEMARK Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted with ingenol mebutate in rats and rabbits. Intravenous doses of 1.5, 3, and 5 µg/kg/day (9, 18, and 30 µg/m^2/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6 – 16) to pregnant female rats. No treatment related effects on embryofetal toxicity or teratogenicity were noted at doses up to 5 µg/kg/day (30

µg/m^2/day). Intravenous doses of 1, 2, and 4 µg/kg/day (12, 24, and 48 µg/m^2/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. An increase in embryo-fetal mortality was noted at 4 µg/kg/day (48 µg/m^2/day). An increased incidence of fetal visceral and skeletal variations was noted in all three ingenol mebutate dose groups. The clinical relevance of these findings is unclear since systemic exposure of ingenol mebutate was not detected in subjects with actinic keratosis treated with TRADEMARK Gel, 0.05% applied to a 100 cm^2 treatment area *[see Clinical Pharmacology (12.3)]*

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric subjects were not evaluated; the intended population is in adults 18 years or older. The product is not likely used in the pediatric population as AK mainly affects adults.

The drug Recommended labeling language is as follows *(deletion in ~~double strikethrough~~; addition in **bold**)*:

8.4 Pediatric Use
Actinic keratosis is not a condition generally seen within the pediatric population.

The safety and **effectiveness** (b) (4) of TRADEMARK Gel for actinic keratosis in patients less than 18 years of age have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no withdrawal effect reported in clinical trials. It is not expected that PEP005 Gel would pose drug abuse, withdrawal/rebound potentials.

Recommended labeling language is as follows *(deletion in ~~double strikethrough~~; addition in **bold**)*:

10 OVERDOSAGE
Topical overdosing of PICATO Gel could result in an increased incidence of local skin reactions. (b) (4)

7.7 Additional Submissions / Safety Issues

PEP005 Gel did not appear to cause local skin reactions to the index finger used to apply the drug in the clinical trial (LP0041-01) conducted. It is reasonable not to require the use of fingercot in clinical use. In Phase 2 and 3 trials, subjects were instructed to wear glove/finger cot when applying the investigational product. To help answer the

question of whether a finger cot is indicated for the application of the Gel, the Applicant conducted Study LP0041-01, a single center, randomized, open label, 2-arm, non-controlled trial in which healthy subjects where randomized to either the gel 0.05% topical exposure once daily for 2 days, or 0.015% topical exposure once daily for 3 days. The subject squeezed the content of one unit-dose tube onto the dominant index finger and then applied the gel to an external test surface area of 25 cm^2. Immediately after exposure the subject washed his/her hands with soap and water. The surface at and around the dominant index finger was assessed for local skin reactions and AEs, at 1 hour after exposure on study treatment days, 1 day after final treatment, and approximately 1 week after final treatment. Other AEs not related to the dominant index fingers were collected by the investigator's questioning: "How have you felt since I saw you last?" at followup visits. A total of 100 subjects were enrolled, with 1:1 randomization.

When no glove or finger cot was used to apply the gel and hands were washed immediately after exposure, no LSRs occurred on the palmar surface of the finger. Five treatment emergent AEs occurred in 5 subjects (10%) in the PEP005 Gel 0.05% arm, including nasopharyngitis, urinary tract infection, lip pain, cough, and Raynaud's phenomenon. Five treatment emergent AEs occurred in 3 subjects (6%) in the PEP005 Gel 0.015% arm, including blister (right middle finger), skin discoloration, scratch (left hand), muscle spasms (right hip), and paraesthesia (tingling on left leg). Of these, two were cutaneous AEs (blister and skin discoloration). Skin discoloration (described below) occurred on the exposed area.

Two treatment-emergent AEs were considered by the investigator to be related to trial medication. One PEP005 Gel 0.015% subject experienced skin discoloration (darkening of skin) (considered mild in nature and probably related to trial medication). The subject was writing during the 1-hour period between exposure and the post-exposure LSR assessment. It was noted by the investigator that writing appeared to have caused the darkening of distal right index finger. This event was the only cutaneous AE that occurred in the exposed area. The event was resolved without sequelae the following day prior to the next exposure. The subject completed all 3 exposures in the Treatment Phase. No recurrence of the skin discoloration was observed after the second or third exposures. The other treatment-related event was Raynaud's phenomenon reaction (considered mild and possibly related to trial medication) in a subject exposed to PEP005 Gel 0.05% who had been diagnosed with Raynaud's phenomenon in 2010. During the 1-hour period between exposure and the post-exposure LSR assessment, the subject reported having swollen hands at home before coming to the clinic visit. She also reported exercising 45 minutes prior to the visit and ballroom dancing the evening before. The event resolved without sequelae later the same day after the subject left the clinic. No other safety concerns were reported during the conduct of this trial.

6 Postmarket Experience

There is no postmarket experience.

9 Appendices

9.1 Literature Review/References

The literature search provided by the Applicant is adequate.

9.2 Labeling Recommendations

Topic specific labeling recommendations have been incorporated in the rest of the review. The remaining recommendations are discussed below.

1. Although field treatment was applied in the pivotal trials, prescribers should have the latitude to choose lesion specific treatment for their patients, given the high incidence of local skin reactions, which not only occurred in the AK lesions but extended to inter-lesional areas in the entire treatment area. Therefore, the recommended language for DOSAGE AND ADMINISTRATION is left purposely open, to convey that the drug may be applied to the affected area, up to one continuous field treatment. It is not prescriptive that a defined 25 cm^2 area be treated.

2. (b) (4)

3. DOSAGE AND ADMINISTRATION should include instructions on allowing the area to dry for 15 minutes, and washing the treated area with a mild soap and water after 6 hours of applying PEP005 Gel. These instructions were given in the pivotal trials, and would help to minimize the exposure to the eye and the risk for local skin reactions.

4. The local activity of PEP005 Gel appears to involve induction of cell necrosis, although the exact mechanism of cell necrosis induced by the drug substance is unknown. The pharmacology/toxicology review team felt that the **pharmacologic class** of the drug could be 'cell death inducer' based on the observed physiologic effects; however, whether an **established pharmacologic class** should be designated should be decided based on clinical judgment. In a guidance document addressing this issue regarding the established

pharmacological class[25], the Agency stated that the while determination of pharmacologic class can based on mechanism of action, physiologic effect, or chemical structure, the established pharmacologic class is a term or phrase that is scientifically valid and clinically meaningful according to the following definitions:

- A *scientifically valid* pharmacologic class is supported by documented and submitted empiric evidence showing that the drug's pharmacologic class is known, not theoretical, and relevant and specific to the indication

- A *clinically meaningful* pharmacologic class term or phrase enhances the ability of professionals to understand physiologic effects related to the indication or to anticipate undesirable effects that may be associated with the drug or pharmacologic class

The Guidance discusses that knowing the established pharmacologic class can provide prescribers with important information about what to expect from the drug and how it relates to the other therapeutic options. Such information can also help reduce the risk of duplicative therapy and drug interactions, as well as provide important treatment information in cases of drug overdose. Given that the exact mechanism of the drug is unknown, and that the term 'cell death inducer' is not only non-specific but also non-existent in other labels for topical AK agents, it is unlikely that the clinical utilities as discussed in the Guidance could be achieved. It is also unlikely that an established pharmacologic class designation of 'cell death inducer' would add any useful information that prescribers could not gather from the label otherwise. It does not appear that such a designation would make it easier for heath care professionals to access, read, and use, make prescribing decisions. This could change when additional information about the drug or other drugs in the same class becomes available. But for the time being the recommendation is not to list an established pharmacologic class in labeling.

This reviewer recommends the following labeling language (addition in **bold**; deletion in ~~double strikethrough~~):

1 INDICATIONS AND USAGE
TRADEMARK Gel is indicated for the topical treatment of actinic keratosis on the face and scalp and on the trunk and extremities

2 DOSAGE AND ADMINISTRATION
For topical use only; **TRADEMARK Gel is not for oral, ophthalmic, or intravaginal use.**

25 Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products—Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information, Good Review Practice (October 2009 Labeling, FDA)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not required.

9.4 Additional Tables

Table 39 Listings of the clinical trials and studies submitted to the NDA (modified from the Applicant's submission)

Type of Study	**Study ID**	**Objectives**	**Study Design**	**Number of subjects Diagnosis**	**Test product(s) Dosage, Route, Duration of treatment**
Phase 3 pivotal trials (face/scalp)					
Efficacy	PEP005-016	Efficacy, safety	Randomized, Vehicle controlled	N=269 (N=135 PEP005 Gel, N= 134 vehicle) AK lesions face/scalp	0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application 3 days Field application (25 cm^2 treatment area)
Efficacy	PEP005-025	Efficacy, safety	Randomized, Vehicle controlled	N=278 (N=142 PEP005 Gel, N=136 vehicle) AK lesions face/scalp	0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application 3 days Field application (25 cm^2 treatment area)
Phase 3 pivotal trials (trunk/extremities)					
Efficacy	PEP005-014	Efficacy, safety	Randomized, Vehicle controlled	N=255 (N=126 PEP005 Gel N=129 vehicle) AK lesions trunk/extremities	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application 2 Days (25 cm^2 treatment area)
Efficacy	PEP005-028	Efficacy, safety	Randomized, Vehicle controlled	N=203 (N=100 PEP005 Gel	0.05% PEP005 Gel, qd Vehicle Gel, qd

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
				N=103 vehicle) AK lesions trunk/extremities	Topical field application 2 Days (25 cm^2 treatment area)
One-year follow up study for responders in Phase 3 pivotal trials (face/scalp)					
Safety	PEP005-030 *(Ongoing)	12 month follow-up of safety in treatment area	Prospective, longitudinal, observational	N=117 AK lesions face/scalp	None Patients had received PEP005 Gel or vehicle in study PEP005-016 or PEP005-025
One-year follow up study for responders in Phase 3 pivotal trial (trunk/extremities)					
Safety	PEP005-032 *(Ongoing)	12 month follow-up of safety in treatment area	Prospective, longitudinal, observational	N=43 AK lesions trunk/extremities	None Patients had received PEP005 Gel or vehicle in study PEP005-028
Phase 2/3 open label field treatment trials (trunk/extremities)					
Safety	PEP005-018	Safety, efficacy	OL	N=11 AK lesions trunk/extremities	0.05%, qd 2 Days Topical field application (25 cm^2 treatment area)
Safety	PEP005-020	Safety, efficacy	OL	N=102 AK lesions trunk/extremities	0.05% PEP005 Gel, qd 2 Days Topical field application (25 cm^2 treatment area)

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
Safety	PEP005-022	Safety	OL	N=74 AK lesions trunk/extremities	0.05% PEP005 Gel, qd 2 Days Topical field application, treatment areas ranging from 25–100 cm^2
One-year follow up study for recurrence of responders in Phase 2/3 (trunk/extremities)					
Safety	PEP005-031 *(Ongoing)	Long-term safety in treatment area	Prospective, longitudinal, observational	N=38 AK lesions trunk/extremities	None Patients had received PEP005 Gel or vehicle in study PEP005-020
Phase 2 dosing ranging field treatment trials (face/scalp and trunk/extremities)					
Safety	PEP005-006	Safety, efficacy dose ranging	Randomized, Vehicle controlled	N=222 (N=162 PEP005, N= 60 vehicle) AK lesions scalp only, not face trunk/extremities	0.025% or 0.05% PEP005 Gel, qd Vehicle Gel, qd 2 days or 3 days 2 days 0.05% qd (N=55) 3 days 0.025% qd (N=50) 0.05% qd (N=57) Vehicle qd (N=60) Topical field application (25 cm^2 treatment area)

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
Phase 2 dose ranging field treatment trials (face/scalp)					
Safety	PEP005-007	Safety, efficacy dose ranging	OL	N=94 AK lesions face/scalp	0.0025%, 0.005%, 0.0075%, 0.0125%, 0.0175%, or 0.025% PEP005 Gel, qd 2 Days or 3 Days Topical field application (25 cm^2 treatment area)
Safety	PEP005-015	Safety, efficacy dose ranging	Randomized, Vehicle controlled	N=265 (N=199 PEP005 Gel N=66 vehicle) AK lesions face/scalp	0.005%, 0.01%, or 0.015% PEP005 Gel, qd Vehicle Gel, qd 2 Days or 3 Days 2 days 0.005% qd (N=33) 0.01% qd (N= 34) 0.015% qd (N= 33) Vehicle qd (N= 33) 3 days 0.005% qd (N= 33) 0.01% qd (N= 34) 0.015% qd (N= 32) Vehicle qd (N= 33) Topical field application (25 cm^2 treatment area)

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
Phase 2 dose ranging field treatment trials (trunk/extremities)					
Safety	PEP005-004	Determine MTD, safety, efficacy	OL	N=22 AK lesions trunk/extremities	0.01%, 0.025%, 0.05%, 0.075% PEP005 Gel, qd 2 Days 0.01% qd (N= 3) 0.025%qd (N= 3) 0.05% qd (N= 10) 0.075% qd (N= 6) Topical field application (9 cm^2 treatment area)
AK lesion specific treatment trials					
Safety	AGN-204332-004	Pilot safety	Randomized, Vehicle controlled	(N=16 N=11 PEP005 Gel N=5 vehicle) AK lesions trunk/extremities	0.01% PEP005 Gel, qd Vehicle Gel, qd 1 Day Lesion-specific topical Application
Safety	PEP005-001	Safety, efficacy	Randomized, Vehicle controlled	N=63 (N=51 PEP005 Gel N=12 vehicle)	0.0025%, 0.01%, or 0.05% PEP005 Gel, qd Vehicle Gel, qd

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
				AK lesions face/scalp trunk/extremities	Lesion-specific topical application on Day 1 and Day 2 or 8 2 Days
PK trials (trunk/extremities)					
PK	PEP005-017	PK, safety, efficacy	Randomized, Vehicle controlled	N=16 (N=13 PEP005, N=3 vehicle) AK lesions trunk/extremities	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical 2 days Field application (100 cm^2 treatment area)
PK	PEP005-013	PK safety	OL	N=8 AK lesions trunk/extremities	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical 2 days Field application (100 cm^2 treatment area)
Non-melanoma skin cancer (basal cell carcinoma and squamous cell in-situ) trials					
Safety	PEP005-002	Safety, efficacy	Randomized, Vehicle-controlled	N=58 (N=46 PEP005, N=12 vehicle) Nodular BCC on face/scalp and trunk/extremities	0.0025%, 0.01%, 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical application on Day 1 and Day 2 or 8 Dosed on

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
					Days 1 and 2: 0.0025% (N=7) 0.01% (N=8) 0.05% (N=8) Vehicle Dosed on Days 1 and 8: 0.0025% (N=7) 0.01% (N=8) 0.05% (N=8) Vehicle (N=6) 2 Days
Safety	PEP005-003	Safety, efficacy	Randomized, Vehicle-controlled	N=60 (N=48 PEP005, N=12 vehicle) Superficial BCC on face/scalp and trunk/extremities	0.0025%, 0.01%, 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical application on Day 1 and Day 2 or 8 Dosed on Days 1 and 2: 0.0025% (N=8) 0.01% (N=8) 0.05% (N=8) Vehicle Dosed on Days 1 and 8: 0.0025% (N=8) 0.01% (N=8) 0.05% (N=8) Vehicle (N=6) 2 Days

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
Efficacy	PEP005-008	Efficacy, safety	OL	N=25 SCCIS on the Face only, not scalp trunk/extremities	0.05% PEP005 Gel, qd Topical application 2 Days
Safety	PEP005-009	Determine MTD, safety, efficacy	OL	N=101 NMSC superficial BCC on the trunk	0.025%, 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, 0.175%, 0.2%, 0.225% or 0.25% PEP005 Gel Topical application on Day 1 or Days 1 and 8 Day 1 0.025% (N=3) 0.05% (N=3) 0.075% (N=3) 0.1% (N=3) 0.125% (N=3) 0.15% (N=3) 0.175% (N=3) 0.2% (N=3) 0.225% (N=3) 0.25% (N=3) Days 1 and 8: 0.025% (N=3) 0.05% (N=25) 0.075% (N=3) 0.1% (N=3)

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
					0.125% (N=3) 0.15% (N=3) 0.175% (N=3) 0.2% (N=3) 0.225% (N=3) 0.25% (N= 22) 1 Day or 2 Days
Topical safety trials in healthy volunteers					
Safety	PEP005-005	Dermal sensitization	Double-blind, randomized, vehicle controlled, within subject comparison (4 cm^2 treatment area)	N=238 Healthy subjects	0.01% PEP005 Gel Vehicle Gel Topical application (4 cm^2 treatment area) 0.01% and Vehicle applied to two treatment areas 10 doses of both PEP005 Gel and vehicle over 6–8 weeks
Safety	PEP005-023	Dermal photo-irritation	Randomized, Within subject comparison to vehicle	N=34 Healthy subjects	0.01% PEP005 Gel Vehicle Gel Topical application (two 4 cm^2 treatment areas) 1 Day
Safety	PEP005-024	Dermal photo-sensitization	Randomized within subject comparison to vehicle	N=60 Healthy subjects	0.01% PEP005 Gel Vehicle Gel Topical application (two

Type of Study	Study ID	Objectives	Study Design	Number of subjects Diagnosis	Test product(s) Dosage, Route, Duration of treatment
					4 cm^2 treatment areas) 7 doses of both PEP005 Gel and vehicle over 6–8 weeks

Table 40 Prohibited treatments and procedures in Study 016 (copied electronically from the Applicant's submission)

Prohibited Treatments	Location	Exclusion Period restrictions
Cosmetic procedures (e.g., use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing)	within 10 cm of the selected treatment area	Anytime during the study
Acid-containing therapeutic products (e.g., salicylic acid or fruit acids, such as α and β hydroxy acids and glycolic acids), topical retinoids or light chemical peels	within 2 cm of the selected treatment area	Anytime during the study
Medicated/ therapeutic topical salves (non-medicated/non-irritant salves are acceptable)	within 2 cm of the selected treatment area	*may be used with discretion after Day 15*
Any medications or treatments that might influence the intended effects or mask the side effects of treatment, such as topical corticosteroids	within 2 cm of the selected treatment area	*may be used with discretion after Day 15*
Artificial tanners	within 5 cm of the selected treatment area	Anytime during the study
Psoralen plus UVA (PUVA) or the use of UVB therapy	anywhere	Anytime during the study
5-FU, imiquimod, diclofenac or photodynamic therapy	anywhere	Anytime during the study
Immuno-modulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine, chlorambucil, methotrexate, podophyllin, camptothecin) or interferon/ interferon inducers	excluded	Anytime during the study
Medications that suppress the immune system (e.g., cyclosporine, prednisone, methotrexate, alefacept, infliximab)	excluded	Anytime during the study
Systemic retinoids (e.g., isotretinoin, acitretin, bexarotene)	excluded	Anytime during the study
Excessive or prolonged exposure to ultraviolet light (e.g., sunlight, tanning booths)	excluded	Anytime during the study
During the study, patients must not receive any other investigational drugs, agents or devices or any chemotherapy for cancer treatment or any medications or treatments that might influence the intended effects or mask the side effects of study medication.	excluded	Anytime during the study
Elective surgical procedures.		*defer until after Day 15, with discretion*

Table 41 Serious adverse events (SAEs) identified by the investigator or Applicant in Phase 2 and 3 trials

STUDY	SITE	SUBJECT	AGE	SEX	TREATMENT	STUDY DAY OF ONSET	ADVERSE EVENT (AE) SYSTEM ORGAN CLASS	AE (PREFERRED TERM)	AE (REPORTED TERM)	TREATMENT LOCATION	DISCONTINUE
028	074	028-074-00002	61	MALE	0.05% PEP005 Gel, Days 1, 2	34	GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	ABDOMINAL PAIN RESULTING IN HOSPITALIZATION	Arm	No
006	131	006-131-02117	67	MALE	Vehicle Gel, Days 1, 2, 3	18	CARDIAC DISORDERS	ACUTE CORONARY SYNDROME	ACUTE CORONARY SYNDROME	Arm	No
006	126	006-126-01052	72	MALE	0.025% PEP005 Gel, Days 1, 2, 3	27	CARDIAC DISORDERS	ANGINA PECTORIS	ANGINA PECTORIS	Arm	No
014	060	014-060-60026	50	FEMALE	Vehicle Gel, Days 1, 2	52	CARDIAC DISORDERS	ANGINA PECTORIS	ANGINA PECTORIS	Arm	No
028	079	028-079-00010	73	MALE	0.05% PEP005 Gel, Days 1, 2	41	CARDIAC DISORDERS	ANGINA PECTORIS	CHEST PAIN	Back of Hand	No
028	079	028-079-00014	67	MALE	Vehicle Gel, Days 1, 2	49	CARDIAC DISORDERS	ANGINA PECTORIS	CHEST PAIN	Arm	No
006	131	006-131-01024	77	MALE	0.025% PEP005 Gel, Days 1, 2, 3	46	VASCULAR DISORDERS	AORTIC ANEURYSM	ASCENDING AORTIC ANEURYSM	Arm	No
006	127	006-127-01062	63	MALE	Vehicle Gel, Days 1, 2, 3	21	CARDIAC DISORDERS	ATRIAL FIBRILLATION	ATRIAL FIBRILLATION	Chest	No
006	127	006-127-01062	63	MALE	Vehicle Gel, Days 1, 2, 3	14	CARDIAC DISORDERS	ATRIAL FIBRILLATION	NEW ONSET ATRIAL FIBRILLATION	Chest	No
020	070	020-070-00202	61	MALE	0.05% PEP005 Gel, Days 1, 2	43	CARDIAC DISORDERS	ATRIAL FIBRILLATION	WORSENING OF RECURRENT ATRIAL FIBRILLATION	Arm	No
014	059	014-059-59018	65	FEMALE	Vehicle Gel, Days 1, 2	14	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	BREAST CANCER	BREAST CANCER	Arm	No
016	005	016-005-00003	86	MALE	0.015% PEP005 Gel, Days 1, 2, 3	16	INFECTIONS AND INFESTATIONS	CAMPYLOBACTER INFECTION	CAMPYLOBACTER	Scalp	No
014	050	014-050-50024	88	MALE	0.05% PEP005 Gel, Days 1, 2	59	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	CERVICAL VERTEBRAL FRACTURE	FRACTURED C4 & C5 SECONDARY TO FALL	Arm	No
006	129	006-129-01114	76	MALE	0.05% PEP005 Gel, Days 2, 3	51	CARDIAC DISORDERS	CORONARY ARTERY DISEASE	CORONARY ARTERY DISEASE	Scalp	No
015	027	015-027-00002	58	MALE	0.005% PEP005 Gel, Days 1, 2, 3	36	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	DEATH	SUDDEN DEATH - CORONARY ARTERY ATHEROSCLEROSIS,	Face	No

STUDY	SITE	SUBJECT	AGE	SEX	TREATMENT	STUDY DAY OF ONSET	ADVERSE EVENT (AE) SYSTEM ORGAN CLASS	AE (PREFERRED TERM)	AE (REPORTED TERM)	TREATMENT LOCATION	DISCONTINUE
									HYPERTENSION		
015	021	015-021-00016	66	MALE	0.015% PEP005 Gel, Days 1, 2, 3	14	GASTROINTESTINAL DISORDERS	GASTROOESOPHAGEAL REFLUX DISEASE	ACID REFLUX	Face	No
025	004	025-004-00007	82	MALE	0.015% PEP005 Gel, Days 1, 2, 3	19	SURGICAL AND MEDICAL PROCEDURES	HIP ARTHROPLASTY	HIP REPLACEMENT	Face	No
016	016	016-016-00001	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	43	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	HYPOXIA	HYPOXIA	Scalp	No
016	006	016-006-00010	79	MALE	Vehicle Gel, Days 1, 2, 3	26	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	INJURY	MULTIPLE TRAUMA	Face	Yes
014	067	014-067-67004	79	MALE	Vehicle Gel, Days 1, 2	1	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	LYMPHOMA	NECK LYMPHOMA	Arm	No
016	016	016-016-00001	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	42	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	MENISCUS LESION	LATERAL MENISCUS TEAR DUE TO WORK INJURY	Scalp	No
020	078	020-078-00212	54	FEMALE	0.05% PEP005 Gel, Days 1, 2	8	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MUSCLE SPASMS	SEVERE MUSCLE CRAMPING	Back of Hand	No
015	021	015-021-00016	66	MALE	0.015% PEP005 Gel, Days 1, 2, 3	14	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	MUSCLE STRAIN	MUSCLE STRAIN	Face	No
020	088	020-088-00204	83	MALE	0.05% PEP005 Gel, Days 1, 2	46	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MUSCULAR WEAKNESS	REDUCED MOBILITY SECONDARY TO MUSCLE WEAKNESS	Back of Hand	No
025	004	025-004-00007	82	MALE	0.015% PEP005 Gel, Days 1, 2, 3	22	CARDIAC DISORDERS	MYOCARDIAL INFARCTION	MYOCARDIAL INFARCTION	Face	No
028	079	028-079-00023	84	MALE	Vehicle Gel, Days 1, 2		CARDIAC DISORDERS	MYOCARDIAL INFARCTION	HEART ATTACK	Back of Hand	Yes
016	006	016-006-00010	79	MALE	Vehicle Gel, Days 1, 2, 3	44	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY EMBOLISM	PULMONARY EMBOLISM	Face	Yes
016	005	016-005-00003	86	MALE	0.015% PEP005 Gel, Days 1, 2, 3	16	GASTROINTESTINAL DISORDERS	SMALL INTESTINAL OBSTRUCTION	SMALL BOWEL OBSTRUCTION	Scalp	No
006	128	006-128-	79	FEMALE	0.025%	78	NEOPLASMS BENIGN,	SQUAMOUS CELL	SQUAMOUS CELL	Arm	No

STUDY	SITE	SUBJECT	AGE	SEX	TREATMENT	STUDY DAY OF ONSET	ADVERSE EVENT (AE) SYSTEM ORGAN CLASS	AE (PREFERRED TERM)	AE (REPORTED TERM)	TREATMENT LOCATION	DISCONTINUE
		01083			PEP005 Gel, Days 1, 2, 3		MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	CARCINOMA	CARCINOMA LEFT LEG		
006	107	006-107-01010	63	MALE	0.025% PEP005 Gel, Days 1, 2, 3	16	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SQUAMOUS CELL CARCINOMA OF SCALP	Scalp	No
006	108	006-108-02085	82	FEMALE	0.05% PEP005 Gel, Days 1, 2, 3	8	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SQUAMOUS CELL CARCINOMA OF THE SKIN L POSTERIOR THIGH	Arm	No
006	105	006-105-02082	74	MALE	0.05% PEP005 Gel, Days 2, 3	15	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SUSPICIOUS LESION LEFT UPPER FOREHEAD (SQUAMOUS CELL CARCINOMA)	Arm	No
006	101	006-101-01048	81	FEMALE	Vehicle Gel, Days 1, 2, 3	60	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	.8 CM LESIONS RT LOWER ARM BIOPSY-SCC	Arm	No
006	105	006-105-01029	67	MALE	Vehicle Gel, Days 1, 2, 3	30	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SQUAMOUS CELL CARCINOMA LEFT LOWER LATERAL FOREHEAD	Arm	No
006	105	006-105-01029	67	MALE	Vehicle Gel, Days 1, 2, 3	30	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SQUAMOUS CELL CARCINOMA LEFT RADIAL WRIST ULNAR	Arm	No
006	105	006-105-01029	67	MALE	Vehicle Gel, Days 1, 2, 3	30	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SUPERFICIAL SQUAMOUS CELL CARCINOMA LEFT RADIAL WRIST	Arm	No
006	105	006-105-01029	67	MALE	Vehicle Gel, Days 1, 2, 3	30	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SUPERFICIAL SQUAMOUS CELL CARCINOMA MID RIGHT HAND	Arm	No
018	107	018-107-10703	71	MALE	0.05% PEP005 Gel, Days 1, 2	7	NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	SQUAMOUS CELL CARCINOMA	SCC RT CHEST	Back of Hand	No
006	137	006-137-01069	58	MALE	0.025% PEP005 Gel, Days 1, 2, 3	25	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	UPPER LIMB FRACTURE	BROKEN LEFT ARM	Arm	No
016	011	016-011-	73	MALE	Vehicle Gel,	4	INJURY, POISONING	VASCULAR	PSEUDOANEURYSM	Face	No

00011	Days 1, 2, 3	AND PROCEDURAL COMPLICATIONS	PSEUDOANEURYSM	RIGHT ANTECUBITAL FOSSA

Table 42 AEs that led to medication discontinuation (from PEP005 Gel treatment) in Phase 2 and 3 trials

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
001	001-003-02014	84	FEMALE	0.01% PEP005 Gel, Days 1, 8	*	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN AT SITE OF APPLICATION OF STUDY GEL FOR LESIONS 1, 3, 4	NO	Face	DISCONTINUED
002	002-011-01203	77	FEMALE	0.01% PEP005 Gel, Days 1, 2		GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE BLEEDING	BLEEDING FROM TARGET TUMOUR	NO	Face	NONE
002	002-011-01203	77	FEMALE	0.01% PEP005 Gel, Days 1, 2		GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN TREATMENT AREA	NO	Face	NONE
002	002-011-01203	77	FEMALE	0.01% PEP005 Gel, Days 1, 2		INFECTIONS AND INFESTATIONS	FOLLICULITIS	FOLLICULITIS 10MM FROM TARGET TUMOUR	NO	Face	NONE
002	002-011-01203	77	FEMALE	0.01% PEP005 Gel, Days 1, 2		NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	NEOPLASM PROGRESSION	ABNORMAL TUMOUR PROLIFERATION (TUMOUR ENLARGING) OF THE STUDY LESION	YES	Face	NONE
002	002-011-01203	77	FEMALE	0.01% PEP005 Gel, Days 1, 2		NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	NEOPLASM PROGRESSION	ABNORMAL TUMOUR PROLIFERATION (TUMOUR ENLARGING) OF THE STUDY LESION	YES	Face	NONE
002	002-009-01228	78	FEMALE	0.05% PEP005 Gel, Days 1, 2		SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ERYTHEMA	ERYTHEMA OUTSIDE TREATMENT AREA	NO	Back	DISCONTINUED
002	002-009-01228	78	FEMALE	0.05% PEP005 Gel, Days 1, 2		SKIN AND SUBCUTANEOUS TISSUE DISORDERS	SKIN EXFOLIATION	FLAKY/DRY/SCALE OUTSIDE TREATMENT AREA	NO	Back	DISCONTINUED
005	005-001-00037	21	FEMALE	0.01% PEP005 Gel, 9 Days	36	PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	PREGNANCY		NO		STUDY PRODUCT DISCONTINUED
006	006-101-01046	69	MALE	0.025% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN OF BURNING SENSATION AT TREATMENT AREA	NO	Arm	DOSE DISCONTINUED
006	006-126-	73	MALE	0.025%	3	GENERAL DISORDERS	APPLICATION	PAIN AT	NO	Chest	DOSE

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
	01005			PEP005 Gel, Days 1, 2, 3		AND ADMINISTRATION SITE CONDITIONS	SITE PAIN	TREATMENT SITE			DISCONTINUED
006	006-101-01097	70	MALE	0.025% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING AT TREATMENT SITE ON SCALP	NO	Scalp	DOSE DISCONTINUED
006	006-101-01097	70	MALE	0.025% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN AT TREATMENT SITE ON SCALP	NO	Scalp	DOSE DISCONTINUED
006	006-107-01010	63	MALE	0.025% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN IN TREATMENT AREA	NO	Scalp	DOSE DISCONTINUED
006	006-106-02007	63	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE ERYTHEMA	ERYTHEMA AT THE APPLICATION SITE	NO	Arm	DOSE DISCONTINUED
006	006-106-02007	63	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	SORENESS AT THE APPLICATION SITE	NO	Arm	DOSE DISCONTINUED
006	006-106-02007	63	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE VESICLES	LARGE VESICLE AT THE APPLICATION SITE	NO	Arm	DOSE DISCONTINUED
006	006-119-02158	64	MALE	0.05% PEP005 Gel, Days 1, 2, 3	3	INFECTIONS AND INFESTATIONS	APPLICATION SITE PUSTULES	PUSTULAR LOCAL SITE REACTION (APPLICATION SITE)	NO	Arm	DOSE DISCONTINUED
006	006-122-02028	70	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING AT APPLICATION SITE	NO	Scalp	DOSE DISCONTINUED
006	006-103-02074	64	MALE	0.05% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING SENSATION TREATED AREA	NO	Scalp	DOSE DISCONTINUED
006	006-103-02145	65	MALE	0.05% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING SENSATION TREATED AREA	NO	Scalp	DOSE DISCONTINUED
006	006-103-02077	49	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING SENSATION TREATMENT AREA	NO	Scalp	DOSE DISCONTINUED
006	006-103-02074	64	MALE	0.05% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN UPON TOUCHING TREATED AREA	NO	Scalp	DOSE DISCONTINUED
006	006-103-02077	49	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAINFUL TO TOUCH TREATED AREA	NO	Scalp	DOSE DISCONTINUED

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
006	006-103-02145	65	MALE	0.05% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	THROBBING SENSATION TREATED AREA	NO	Scalp	DOSE DISCONTINUED
006	006-103-02074	64	MALE	0.05% PEP005 Gel, Days 1, 2, 3	3	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE SCAB	SCALP CRUSTING (APPLICATION AREA)	NO	Scalp	DOSE DISCONTINUED
006	006-103-02077	49	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	NERVOUS SYSTEM DISORDERS	HEADACHE	HEADACHE	NO	Scalp	DOSE DISCONTINUED
006	006-103-02077	49	MALE	0.05% PEP005 Gel, Days 1, 2, 3	3	NERVOUS SYSTEM DISORDERS	HEADACHE	HEADACHE	NO	Scalp	DOSE DISCONTINUED
006	006-135-02046	74	MALE	0.05% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING AT APPLICATION SITE	NO	Shoulder	DOSE DISCONTINUED
006	006-135-02046	74	MALE	0.05% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE VESICLES	VESICULATION AT APPLICATION SITE	NO	Shoulder	DOSE DISCONTINUED
007	007-007-00718	64	MALE	0.0050% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING SENSATION TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-008-00806	70	FEMALE	0.0050% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	TENDERNESS OVER TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-009-00914	46	MALE	0.0075% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	MODERATE BURNING TO TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-008-00805	55	FEMALE	0.0075% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	TENDERNESS OVER TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-007-00716	61	FEMALE	0.0075% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	TREATMENT AREA PAIN.	NO	Face	DOSE DISCONTINUED
007	007-007-00716	61	FEMALE	0.0075% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PRURITUS	TREATMENT AREA ITCH	NO	Face	DOSE DISCONTINUED
007	007-007-00716	61	FEMALE	0.0075% PEP005 Gel, Days 1, 2, 3	49	INFECTIONS AND INFESTATIONS	URINARY TRACT INFECTION	URINARY TRACT INFECTION	NO	Face	DOSE DISCONTINUED
007	007-009-00915	61	MALE	0.0125% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE DISCOMFORT	SKIN TIGHTNESS IN TREATMENT AREA	NO	Face	DOSE DISCONTINUED

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
007	007-050-05013	56	FEMALE	0.0125% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING IN TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-009-00915	61	MALE	0.0125% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	SLIGHT BURNING SENSATION IN TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-050-05013	56	FEMALE	0.0125% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PARAESTHESIA	STINGING IN TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-050-05012	69	FEMALE	0.0175% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE DISCOMFORT	DISCOMFORT IN TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-011-01110	58	MALE	0.0175% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN IN THE TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-050-05012	69	FEMALE	0.0175% PEP005 Gel, Days 1, 2, 3	2	PSYCHIATRIC DISORDERS	INSOMNIA	UNABLE TO SLEEP DUE TO DISCOMFORT	NO	Face	DOSE DISCONTINUED
007	007-007-00702	45	FEMALE	0.025% PEP005 Gel, Days 1, 2, 3	3	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE OEDEMA	VESICULO - EDEMATUS REACTION TREATMENT AREA	NO	Face	DOSE DISCONTINUED
007	007-009-00901	69	MALE	0.025% PEP005 Gel, Days 1, 2, 3	3	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	MILD TENDERNESS AT APPLICATION SITE - TENDERNESS	NO	Face and Scalp	DOSE DISCONTINUED
008	008-007-00102	79	FEMALE	0.05% PEP005 Gel, Days 1, 2	3	GASTROINTESTINAL DISORDERS	DIARRHOEA	DIARRHOEA	NO	Leg	DISCONTINUED
009	009-121-12107	62	MALE	0.25% PEP005 Gel, Days 1, 8	1	INFECTIONS AND INFESTATIONS	LYMPHANGITIS	CHEMICAL LYMPHANGITIS LT NECK	NO	Chest	DOSE DISCONTINUED
013	013-009-00903	81	MALE	0.05% PEP005 Gel, Days 1, 2	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING-IN TREATMENT AREA	NO	Arm	DOSE DISCONTINUED
013	013-009-00903	81	MALE	0.05% PEP005 Gel, Days 1, 2	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE WARMTH	WARMTH IN TREATMENT AREA	NO	Arm	DOSE DISCONTINUED
014	014-050-50024	88	MALE	0.05% PEP005 Gel, Days 1, 2	59	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	CERVICAL VERTEBRAL FRACTURE	FRACTURED C4 & C5 SECONDARY TO FALL	YES	Arm	NONE
014	014-064-	69	MALE	0.05%	63	MUSCULOSKELETAL AND	SPINAL	EXACERBATION	NO	Arm	NONE

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
	64005			PEP005 Gel, Days 1, 2		CONNECTIVE TISSUE DISORDERS	OSTEOARTHRITIS	OF SPONDYLOSTENOSIS			
014	014-066-66011	84	FEMALE	0.05% PEP005 Gel, Days 1, 2	3	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN IN TREATMENT AREA	NO	Chest	DOSE DISCONTINUED
014	014-068-68024	72	MALE	Vehicle Gel, Days 1, 2		INJURY, POISONING AND PROCEDURAL COMPLICATIONS	INJURY	INJURY DUE TO FALL ON ICE	NO	Shoulder	NONE
015	015-020-00010	55	MALE	0.005% PEP005 Gel, Days 1, 2	59	INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	COMMON COLD	NO	Face	DOSE DISCONTINUED
015	015-027-00002	58	MALE	0.005% PEP005 Gel, Days 1, 2, 3	36	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	DEATH	SUDDEN DEATH - CORONARY ARTERY ATHEROSCLEROSIS, HYPERTENSION	YES	Face	NONE
015	015-007-00004	71	MALE	0.010% PEP005 Gel, Days 1, 2, 3	1	EYE DISORDERS	EYELID OEDEMA	DRUG REACTION - EDEMA IN BILATERAL EYELIDS	NO	Face	DOSE DISCONTINUED
015	015-007-00002	79	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	EYE DISORDERS	EYE OEDEMA	DRUG REACTION - EDEMA BILATERAL EYES	NO	Face	DOSE DISCONTINUED
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	EYE DISORDERS	EYE SWELLING	RIGHT EYE SWOLLEN	NO	Face	DOSE DISCONTINUED
015	015-027-00022	55	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	EYE DISORDERS	EYELID OEDEMA	SWELLING UPPER EYE LID	NO	Face	DOSE DISCONTINUED
015	015-027-00022	55	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	EYE DISORDERS	EYELID PTOSIS	PTOSIS	NO	Face	DOSE DISCONTINUED
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE DISCHARGE	TRANSUDATE FLUID	NO	Face	DOSE DISCONTINUED
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE EROSION	EROSION	NO	Face	DOSE DISCONTINUED
015	015-017-00007	65	FEMALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING AT APPLICATION SITE	NO	Face	DOSE DISCONTINUED

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING SENSATION	NO	Face	DOSE DISCONTINUED
015	015-011-00010	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	FACIAL BURNING	NO	Face	DOSE DISCONTINUED
015	015-011-00010	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	WORSENING FACIAL BURNING	NO	Face	DOSE DISCONTINUED
015	015-027-00022	55	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE SWELLING	SWELLING FOREHEAD	NO	Face	DOSE DISCONTINUED
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE SWELLING	SWELLING RIGHT CHEEK	NO	Face	DOSE DISCONTINUED
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE VESICLES	VESICLES	NO	Face	DOSE DISCONTINUED
015	015-011-00010	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FACIAL PAIN	FACIAL PAIN	NO	Face	DOSE DISCONTINUED
015	015-027-00001	65	MALE	0.015% PEP005 Gel, Days 1, 2, 3	2	INFECTIONS AND INFESTATIONS	APPLICATION SITE INFECTION	POSSIBLE INFECTION IN WOUND	NO	Face	DOSE DISCONTINUED
015	015-011-00010	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	NERVOUS SYSTEM DISORDERS	HEADACHE	HEADACHE	NO	Face	DOSE DISCONTINUED
015	015-027-00022	55	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	NASAL CONGESTION	NASAL CONGESTION	NO	Face	DOSE DISCONTINUED
015	015-011-00010	56	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	NASAL CONGESTION	NASAL STUFFINESS	NO	Face	DOSE DISCONTINUED
016	016-014-00017	61	MALE	0.015% PEP005 Gel, Days 1, 2, 3	4	EYE DISORDERS	EYE PAIN	EYE BURNING	NO	Face	NONE
016	016-014-00017	61	MALE	0.015% PEP005 Gel, Days 1, 2, 3	4	EYE DISORDERS	EYE PAIN	EYE PAIN	NO	Face	NONE
016	016-014-	61	MALE	0.015%	1	GENERAL DISORDERS	APPLICATION	BURNING	NO	Face	NONE

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
	00017			PEP005 Gel, Days 1, 2, 3		AND ADMINISTRATION SITE CONDITIONS	SITE PAIN				
016	016-014-00003	59	FEMALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN	NO	Face	DOSE DISCONTINUED
016	016-014-00017	61	MALE	0.015% PEP005 Gel, Days 1, 2, 3	4	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	PERIORBITAL OEDEMA	PERIORBITAL EDEMA	NO	Face	NONE
016	016-006-00010	79	MALE	Vehicle Gel, Days 1, 2, 3	26	INJURY, POISONING AND PROCEDURAL COMPLICATIONS	INJURY	MULTIPLE TRAUMA	YES	Face	NONE
016	016-006-00010	79	MALE	Vehicle Gel, Days 1, 2, 3	26	NERVOUS SYSTEM DISORDERS	LOSS OF CONSCIOUSNESS	LOSS OF CONSCIOUSNESS	NO	Face	NONE
016	016-006-00010	79	MALE	Vehicle Gel, Days 1, 2, 3	44	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY EMBOLISM	PULMONARY EMBOLISM	YES	Face	NONE
020	020-070-00203	38	MALE	0.05% PEP005 Gel, Days 1, 2	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE VESICLES	BLISTERING	NO	Arm	DOSE DISCONTINUED
022	022-119-11905	66	MALE	0.05% PEP005 Gel, Days 1, 2 (50 cm^2, 50 cm^2)	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING TO APPLICATION SITE	NO	Arm	DOSE DISCONTINUED
022	022-119-11904	44	MALE	0.05% PEP005 Gel, Days 1, 2 (75 cm^2)	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PRURITUS	ITCHING TO APPLICATION SITE	NO	Arm	DOSE DISCONTINUED
024	024-001-00014	61	FEMALE	0.01% PEP005 Gel, Vehicle Gel, Several Days	37	INFECTIONS AND INFESTATIONS	BRONCHITIS	BRONCHITIS	NO		NONE
025	025-011-00012	54	FEMALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE IRRITATION	BURNING	NO	Face	DOSE DISCONTINUED
025	025-007-00009	58	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	PAIN	NO	Face	DOSE DISCONTINUED
025	025-007-00009	58	MALE	0.015% PEP005 Gel, Days 1, 2, 3	1	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PAIN	STINGING	NO	Face	DOSE DISCONTINUED

Study	SUBJID	AGE	SEX	Treatment	Study Day of AE Onset	Adverse event (AE) System Organ Class	AE (Preferred Term)	AE (Reported Term)	SAE	Treatment Location	Action
025	025-011-00012	54	FEMALE	0.015% PEP005 Gel, Days 1, 2, 3	2	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	APPLICATION SITE PRURITUS	ITCHING	NO	Face	DOSE DISCONTINUED
028	028-079-00023	84	MALE	Vehicle Gel, Days 1, 2		CARDIAC DISORDERS	MYOCARDIAL INFARCTION	HEART ATTACK	YES	Back of Hand	NONE

* Empty cells – missing values

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOANNA W KU
11/30/2011

JILL A LINDSTROM
12/06/2011

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 7, 2011

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Paul Phillips
RPM, Division of Dermatology and Dental Products

Subject: QT-IRT Consult to NDA 202833

This memo responds to your consult to us dated May 13 2011, regarding ECG safety report and TQT waiver request. The QT-IRT received and reviewed the following materials:

- Your consult
- Integrated Summary of Safety (3 December 2010)
- Combined Cardiac Safety Report (eCTD 5.3.5.3)
- Pharmacology Written Summary (module 2.6.2)
- Clinical Pharmacology Table.

QT-IRT Responses to Questions Posed by the Division

1. Do you agree that a TQT Study is not needed?

Yes, we agree. The systemic exposure of ingenol mebutate is within subnanomolar range. Ingenol exhibits neither nonclinical effects consistent with QTc prolongation nor clinically relevant QTc prolonging effects in the clinical program.

2. Do you have further recommendations regarding cardiac safety monitoring, including long term post-marketing cardiac surveillance with regards to proarrhythmic potential for QT interval prolongation?

The sponsor should perform routine safety ECG monitoring, as clinically indicated, in ongoing and future clinical trials.

BACKGROUND

The Sponsor has not conducted a "Thorough QT/Qtc Study". In lieu, they performed an ECG analysis throughout Phase 2-3, and submitted a "Combined Cardiac ECG Safety Report". At the end-of-Phase 2 meeting, the Division did not specifically request a TQT Study.

Non-Clinical Experience (from eCTD, module 2.6.2)

The sponsor's description of the non-clinical cardiovascular safety pharmacology studies is provided below.

"The potential effects of ingenol mebutate on the activating potassium selective Ikr tail current associated with QT interval prolongation in vivo was evaluated using a whole-cell patch-clamp technique in human embryonic kidney cells (HEK293 cells) stably transfected with a human ether-a-go-go-related gene (hERG) construct.

"Based on data obtained in previous studies in which significant cytotoxicity (>50% cell death) was observed at ingenol mebutate concentrations >5.0 μg/mL in dimethyl sulfoxide (DMSO), a maximum concentration of 5.0 μg/mL was utilised. This concentration represented an estimated 50,000-fold therapeutic safety margin based on a limit of detection (LOD) of 0.1 ng/mL for ingenol mebutate in whole blood.

"HEK293 cells (seven cells/concentration) were sequentially exposed to ingenol mebutate at concentrations of 0.5, 1.0, 2.5 and 5.0 μg/mL, and currents were recorded at the completion of a 5-minute exposure equilibration period. Two series of current recordings were averaged for each concentration, and the Ikr tail current amplitude and density were calculated relative to baseline measurements. E-4031 (a potent and selective Ikr inhibitor), a positive control, was tested concurrently (three cells) to verify system sensitivity.

"There was no statistically significant ($p<0.05$) inhibition of hERG tail current density for IKr at any ingenol mebutate concentration. Assay sensitivity was demonstrated by a significant (71.6%, $p<0.05$ compared to control, student's t test) decrease in average Ikr-selective tail current following exposure to 500 nM E-4031 compared with baseline values.

"These study results indicate that ingenol mebutate does not interact with the protein encoded by the hERG gene. A 50% inhibition (IC50) value could not be calculated.

"In the initial study, four anesthetized beagle dogs (two/sex/dose group) were given ingenol mebutate by IV infusion (0.27 mL/min) at doses of 0 [vehicle; 20% polyethylene glycol (PEG) 400/0.9% saline, four administrations] to Group 1 or 0.3, 1, 3, and 10 μg/kg to Group 2 in an escalating dose design (Table 2.6.3.4, Study Report 2174-010; GLP). Doses were administered with a minimum of 30 minutes between infusions. Haemodynamic and respiratory parameters were continuously measured for 25 minutes after the end of each dose of vehicle or ingenol

mebutate. Whole blood samples were obtained prior to the first dose, at the end of infusion, and 2, 10, and 30 minutes postinfusion at each dose level for determination of pharmacokinetics. There were no physiologically significant vehicle-related effects on any cardiovascular or respiratory parameter. No unexpected alterations in electrocardiographic (ECG) waveforms or intervals, or effect on QTc (Fredericia's correction) were observed at any dose. There were no physiologically significant effects on respiratory parameters following IV administration of ingenol mebutate at ≤10 µg/kg.

"There were no changes in blood pressure or heart rate following dosing at ≤3 µg/kg; however, at 10 µg/kg, increases in mean arterial blood pressure (18%) and heart rate (40%) were observed. A dose-related negative inotropic effect was noted from 1 to 3 µg/kg, but no further decrease was observed at 10 µg/kg. Transient decreases in femoral blood flow of 37% and 44% were observed at 3 and 10 µg/kg, respectively.

"Whole blood ingenol mebutate Cmax increased with increasing dose in both genders (0.097, 0.341, 1.10, and 3.32 ng/mL in males, respectively, and 0.106, 0.434. 1.48, and 4.29 ng/mL in females, respectively).

"In a subsequent study conducted in conscious, telemeterised beagle dogs, ingenol mebutate was administered IV to eight animals (four/sex) using a balanced Latin-Square crossover study design, replicated twice (Table 2.6.3.4, Study Report N106161; GLP). Animals received vehicle 0 (vehicle; 20%PEG 400/0.9% saline), 1.5, 7.5, or 15 µg/kg ingenol mebutate (0.25 mL/kg) as a slow IV infusion (~3 minutes) on 4 separate days with a minimum 48-hour washout between doses. Cardiovascular (ECG morphology and haemodynamic) parameters were continuously measured via implanted radiotelemetry devices. Rectal body temperature was measured on Days 4, 8, and 11 prior to dosing and 15 minutes and 1 hour postdose.

"Respiratory endpoints (respiratory rate, tidal volume, and minute volume ventilation) were recorded via a head-only plethysmograph beginning a minimum of 1 hour before dosing through approximately 5 hours postdose. Minor body temperature decreases, salivation, panting, and soft mucoid faeces were noted following IV ingenol mebutate administration at ≥7.5 µg/kg. Emesis was observed at all doses and was more prevalent at ≥7.5 µg/kg.

"IV administration of vehicle or ≤15 µg/kg ingenol mebutate was not associated with any alterations in ECG rhythm or morphology or changes in ECG intervals [PR, RR, QRS, QT, or QTc (Fredericia's correction)]. Non-dose-dependent decreases in diastolic (7% to 35%) and mean (9% to 29%) blood pressures, compared to the vehicle control group, were noted up to approximately 1.5 hours postdosing in males and females in all dose groups. Dose-related increases in heart rate (20% to 64%) were observed in both genders given ≥7.5 µg/kg with the duration of effect increasing with increasing dose and persisting for up to approximately 1 hour. Transient increases in respiratory rate (68% to 140%) were observed following IV ingenol mebutate administration at ≥7.5 µg/kg (males, statistically significant at p=0.05/3=0.0167 level, ANOVA and t test compared to vehicle) and at 15 µg/kg (females, statistically significant at p=0.05/3=0.0167 level, ANOVA and t test compared to vehicle). Tidal volumes were similar to vehicle for males in all dose groups but were increased in females at the 10-minute interval in the 15 µg/kg dose group (statistically significant at p=0.05/3=0.0167 level, ANOVA and t test

compared to vehicle). Due to the increase in rate, minute volume ventilation values were also transiently increased in the same dose groups that showed the rate increase in comparison with baseline values. Changes in respiratory parameters persisted for up to 1.5 hours postdosing.

"The results of these studies in dogs demonstrated that IV administration of ≤15 µg/kg ingenol mebutate did not produce any adverse effects on ECG waveform morphology, intervals, or QT/QTc endpoints. Ingenol mebutate at IV doses of ≥7.5 µg/kg produced generally mild and transient haemodynamic effects (blood pressure alterations and increased heart rate) and transient increases in some respiratory parameters (respiratory rate and minute volume ventilation). The observed respiratory alterations may be partially associated with the observed emesis/salivation and blood pressure changes following IV dosing in dogs."

Reviewer's comments:
Ingenol tested negative for hERG inhibition in whole cell voltage clamp studies performed in HEK 293 cells at concentrations up to 5 µg/ml (11 µM). The concurrent positive control, E-4031, when tested at a supratherapeutic concentration (500 nM) inhibited hERG current by approximately 70%. Given the high concentration of the positive control, assay sensitivity was not adequately evaluated. Nevertheless, this reviewer concludes that ingenol tested negative for hERG inhibition.

Intravenous administration of ingenol tested negative for QTc prolongation in anesthetized dogs. Dose levels were 0, 0.3, 1, 3 and 10 mg/kg. $Cmax_{(total)}$ at the highest dose administered reached 3.32 µg/ml (7.7 µM) and 4.29 ng/ml (10 µM) in males and females, respectively, which greatly exceed total plasma levels in patients (see Clinical Pharmacology section, below). Lack of QTc effect was confirmed in a second intravenous administration study in conscious dogs given 1.5, 7.5 and 15 µg/ml – plasma drug levels were not determined in this study. It should be noted that assay sensitivity was not evaluated nor commented upon in the in vivo studies. Nevertheless, there was no signal for QTc prolongation in these studies.

In summary, ingenol did not exhibit nonclinical effects consistent with QTc prolongation.

Clinical Pharmacology:

The features of ingenol mebutate gel's clinical pharmacology are summarized in the Appendix.

Per the PI, the molecular weight of ingenol mebutate is 430.5. Ingenol gel 0.015% and 0.05% contains per gram 150 mcg and 500 mcg of ingenol mebutate, respectively. The systemic pharmacokinetic profile of ingenol mebutate and its metabolites has not been characterized in humans due to an absence of quantifiable whole blood levels following topical administration. No systemic absorption was detected at or above the lower limit of detection (0.1 ng/mL) when ingenola gel 0.05% from 4 unit dose tubes was applied to an area of 100 cm^2 of the dorsal forearm in AK patients once daily for two consecutive days.

Reviewer's comment: The systemic exposure of ingenol mebutate is within subnanomolar range. Ingenol mebutate can be detected in human blood using an assay with the limit of detection of

0.1 ng/mL. Therefore, the estimated total exposure for ingenol mebutate should be less than 0.23nM.

Combined Cardiac ECG Safety Report

"Central Tendency Analysis
At Screening, one ECG was collected to provide a point estimate of the ECG interval's value and that ECG was used as the baseline for the post-treatment time point, which was for each trial the day following the last administration of either vehicle or study agent [Day 3 for trials 014 and 028 (non-head using 0.05% concentration of PEP005) and Day 4 for trials 016 and 025 (head area using 0.015%)]. The data were analyzed combining studies 014 and 028 and then 016 and 025 and showing the results separately for the two dose groups (0.015% vs. 0.05%) as defined separately by studies 016 and 025 vs. studies 014 and 028.
Descriptive statistics (e.g., frequency, percent, mean, standard deviation (SD), median, maximum and minimum) were used to summarize the ECG variables and the corresponding changes from the baseline to the post-treatment ECG. This provided a time point analysis which is detailed in the tables but also demonstrated graphically with the x-axis showing the time (time point) and the y-axis showing the change from baseline for each of the ECG interval parameters separately (i.e., heart rate, PR, QRS, QT, QTcF and QTcB). Each graph displays the 2 vehicle-corrected dose groups superimposed (0.05% vs. 0.015%).

"Outliers Analyses
An outlier analysis supplements the central tendency analysis by determining if there were patients who had an exaggerated effect on any ECG interval that would not be revealed in a mean change from baseline central tendency analysis. Each patient would be considered having an outlier value based on comparing the baseline to the post-treatment time point.

"Therefore, the data are presented as the frequency and percent of patients with each type of outlier. The following criteria ("study endpoints") are defined for this analysis ("new" means not present at baseline and becomes present on at least one post-treatment ECG time point):

- PR change from baseline: more than 25% increase when PR > 200 ms;
- QRS change from baseline: more than 25% increase when QRS > 100 ms;
- HR changes reflecting a more than 25% decrease from baseline to a HR < 50 bpm (bradycardic event) or a more than 25% increase from baseline reflecting a HR > 100 bpm (individually) (tachycardic event).
- For QT parameter: from mean baseline value to determine patients who attain new QT values > 500 ms;
- For all QTc data (QTcF and QTcB): from mean baseline value to the determine patients who:
    - attain new QTc values > 500 ms,
    - attain new QTc values > 480 ms,
    - attain new QTc values > 450 ms,
    - QTc, categorizations of changes from baseline of >30 to 60 ms,
    - QTc categorization of change from baseline of > 60 ms;

"The data are presented by dose groups: vehicle vs. 0.015% (studies 016 and 025 combined) and vehicle vs. 0.05% (studies 014 and 028 combined).

"A categorical or outlier analysis is considered exploratory since the study was not powered to pick up unusual individual responses to the potential effects of drugs. Outlier analyses produced data as percentage of patients in each treatment group that met the criteria as defined for this analysis. All outliers are summarized for each dose group on the basis of incidence rates. The outlier summary tables include counts of patients. Therefore, if a patient experienced more than 1 episode of a particular outlier event, the patient was counted only once for that event.

"Morphological Analysis
Morphological analyses were performed with regard to the ECG waveform interpretation as defined by the central ECG laboratory's cardiologist. Changes from baseline to the post-treatment ECG were done. The data are presented by dose groups: vehicle vs. 0.015% (studies 016 and 025 combined) and vehicle vs. 0.05% (studies 014 and 028 combined).
All findings are presented in the ECG listings. New onset (presented as percentage of patients meeting the new criteria) for the following variables are detailed in the tables:

- Atrial fibrillation or flutter
- Second degree heart block,
- Third degree heart block,
- Complete right bundle branch block,
- Complete left bundle branch block,
- ST segment depression,
- T wave abnormalities,
- Myocardial infarction pattern, and
- Any new abnormal U waves.

"Table 1 (shown below) details the results as a mean change from baseline and new outliers from baseline for the 2 PEP005 dose groups and for the 2 vehicle groups.

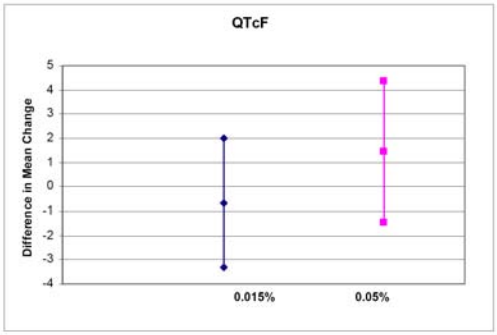
Table 1: Mean Change from Baseline and New Outliers by Dose Group for ECGs

Dose of PEP005	0.015%	Vehicle	0.05%	Vehicle
Studies	**016+025**	**016+025**	**014+028**	**014+028**
Sample Size [some parameters with less sample size by 1-2 subjects]	274	271	225	232
Heart Rate in bpm (mean change)	1.9	3.4	2.8	1.2
Heart Rate Bradycardic Outliers N (%)	0	0	0	0
Heart Rate Tachycardic Outliers N (%)	0	1 (0.4%)	0	0
PR in ms (mean change)	-1.3	-1.6	-2.0	-0.6
PR Outliers N (%)	0	2 (0.8%)	0	1 (0.5%)
QRS in ms (mean change)	-0.2	-0.1	-0.6	-0.1
QRS Outliers N (%)	0	0	0	1 (0.5%)
QT in ms (mean change)	-6.9	-8.8	-9.6	-7.2
QT new >500 ms N (%)	0	0	0	0
QTcF in ms (mean change)	-2.8	-2.1	-3.1	-4.5
QTcF new >500 ms N (%)	0	0	0	0
QTcF new >480 ms N (%)	0	0	0	0
QTcF 30-60 ms N (%)	5 (1.9%)	5 (1.9%)	2 (1.0%)	1 (0.5%)
QTcF >60 ms N (%)	0	1 (0.4%)	0	0
QTcB in ms (mean change)	-0.6	1.5	0.2	-3.2
QTcB new >500 ms N (%)	0	0	0	0
QTcB new >480 ms N (%)	2 (0.7%)	1 (0.4%)	0	0
QTcB 30-60 ms N (%)	14 (5.2%)	15 (5.6%)	9 (4.4%)	7 (3.2%)
QTcB >60 ms N (%)	0	1 (0.4%)	0	0
New abnormal U wave N (%)	0	0	0	0
New ST segment depression N (%)	9 (3.4%)	9 (3.4%)	8 (3.9%)	4 (1.8%)
New T wave abnormality N (%)	12 (4.5%)	8 (3.0%)	8 (4.0%)	7 (3.2%)
New Second or Third Degree Heart Block N (%)	0	0	0	0
New RBBB N (%)	0	0	0	1 (0.5%)
New LBBB N (%)	0	0	0	3 (1.4%)
New AF N (%)	0	2 (0.8%)	0	0
New MI N (%)	0	0	4 (2.0%)	3 (1.4%)

bpm=beats per minute; ms=milliseconds; QTcF= Fridericia correction; QTcB: Bazett correction; LBBB= left bundle branch block; RBBB=right bundle branch block; AF= atrial fibrillation/flutter; MI=myocardial infarction pattern; "new" means not present at baseline, i.e. at any evaluation pre dose, and only seen post baseline.

Source: Combined Cardiac Safety Report, Table 4-1.

Figure 1: Mean Change from Baseline Vehicle-Corrected QTcF



Plotted values are difference (+/- 95% CI) between PEP005 Gel and Vehicle for mean change from baseline at Day 3/4

Source: Combined Cardiac Safety Report, Figure 4-6

"The time point data showed that the central tendency mean change vehicle-corrected for QTcF duration was -0.7 ms and +1.4 ms for all patients in the 0.015% and 0.05% dose groups respectively. These changes are no clinical relevance and do not suggest any change on cardiac repolarization.
"T wave changes were observed in 4.5% of the PEP005 0.015% group vs. 3% on vehicle and there were slightly more of such changes in the PEP005 0.05% group (4.0%) vs. vehicle group (3.2%). Overall no new signal of a morphological change was identified.

Reviewer's comments:

- *In studies PEP005-014, PEP005-028, PEP005-016, and PEP005-025, 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). All were multi-center, randomized, double-blind, parallel group and vehicle-controlled studies.*
- *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.*
- *There were no significant mean change from baseline in vehicle corrected QTcF, no subject had a QTcF >480 ms, one subject treated with vehicle had a >60-ms increase in QTcF over baseline and none in the PEP005 groups.*
- *There were no significant mean change from baseline in vehicle corrected PR and QRS.*

Integrated Summary of Safety

eCTD **5.2.5.4 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 25). 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 5.3.3.1). Electrocardiogram abnormalities that were reported as AEs are discussed in Section 9.2. 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 9.3 and Appendix).

Table 2: 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

Source: ISS, Table 25, Page 60

9. 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 3).

Table 3: 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

Source: ISS, Table 37, page 98

"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 3 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. 50/019 and 68/023], and 3 treated with vehicle [Nos. 52/003, 59/009, and 68/018], 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 11/005 (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 18/006 (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 11/018 (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 13/009 (vehicle) in 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".

Reviewer's Comments:

- *No clinically relevant ECG changes have been reported.*
- *Twenty nine ECG abnormalities were reported as AEs , three were QT prolongation that were ruled by the investigator as possibly related to study drug (two while on PEP005 Gel 0.015% and one on vehicle). Both subjects under PEP005 had normal ECGs at baseline and a mild increase in QTcF (<480 ms) on treatment day 4 (24 hours post-dose). One subject on vehicle had 80-ms increase in QTcF, this case was confounded by co-morbidities (old MI, 1st degree AV block).*
- *There were no differences in the incidence in cardiac disorders and ECG abnormalities reported between placebo and PEP005-treated arms.*

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Appendix:

HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	PEP005 Gel, 0.015% for 3 days for patients with AK lesions on the face or scalp PEP005 Gel 0.05% for 2 days for patients with AK lesions on the trunk or extremities	
Maximum tolerated dose	In clinical trials, the maximum tolerated dose was determined to be: PEP005 Gel, 0.025% once daily for two consecutive days (Study PEP005-007) PEP005 Gel, 0.05% for 3 days (Study PEP005-004)	
Principal adverse events	Most common adverse events are erythema, flaking/scaling followed by crusting and vesiculation/pustulation The dose limiting toxicities were application site reactions: severe scabbing/crusting and severe flaking/scaling/dryness for trunk and extremities The dose limiting toxicities were application site reactions: oedema, vesiculation, pain and irritation	
Maximum dose tested	**Single Dose**	Not Applicable – PEP005 Gel is applied for either 2 or 3 days
	Multiple Dose	In clinical trials, the maximum dose tested was PEP005 Gel, 0.025% for two days for patients with AK lesions on the face and scalp In clinical trials, the maximum dose tested was PEP005 Gel, 0.075% for two days for patients with AK lesions on the trunk and extremities
Exposures Achieved at Maximum Tested Dose	**Single Dose**	Not available
	Multiple Dose	Not available
Range of linear PK	PEP005 Gel is not absorbed systemically – data not available	
Accumulation at steady state	PEP005 Gel is not absorbed systemically – data not available	

Metabolites	No clinical metabolism studies have been performed to date because ingenol mebutate shows no systemic absorption when administered topically. However, in vitro studies have demonstrated that ingenol mebutate undergoes significant metabolism in human hepatocytes, with the principal routes of metabolism identified as hydrolysis and hydroxylation. In vitro, the major metabolite in human hepatocytes was a hydroxylated product, likely hydroxy-PEP005 (i.e., hydroxylated ingenol mebutate). Ingenol was also formed in significant amounts and there was also chemical rearrangement of PEP005 to both PEP015 and PEP025 The activity of all the metabolites is not known but several pharmacology studies indicate that ingenol mebutate is more potent than PEP015 and PEP025	
Absorption	**Absolute/Relative Bioavailability**	PEP005 Gel is not absorbed systemically – data not available
	Tmax	PEP005 Gel is not absorbed systemically – data not available
Distribution	**Vd/F or Vd**	PEP005 Gel is not absorbed systemically – data not available
	% bound	PEP005 Gel is not absorbed systemically – data not available
Elimination	**Route**	PEP005 Gel is not absorbed systemically – data not available
	Terminal t½	PEP005 Gel is not absorbed systemically – data not available
	CL/F or CL	PEP005 Gel is not absorbed systemically – data not available
Intrinsic Factors	**Age**	PEP005 Gel is not absorbed systemically – data not available
	Sex	PEP005 Gel is not absorbed systemically – data not available
	Race	PEP005 Gel is not absorbed systemically – data not available

	Hepatic & Renal Impairment	PEP005 Gel is not absorbed systemically – data not available
Extrinsic Factors	**Drug interactions**	PEP005 Gel is not absorbed systemically – data not available
	Food Effects	PEP005 Gel is not absorbed systemically – data not available
Expected High Clinical Exposure Scenario	In maximum use conditions (0.05% applied for 2 consecutive days to a contiguous area of skin of 100 cm2), PEP005 Gel was not detected systemically (LLOQ = 0.1 ng/mL)	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA L FISZMAN
08/08/2011

JOHN E KOERNER
08/08/2011

HAO ZHU
08/08/2011

NORMAN L STOCKBRIDGE
08/08/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 202833 **Applicant: Leo Pharmaceutical Products Ltd. A/S** **Stamp Date: March 31, 2011**

Drug Name: Ingenol Mebutate Gel **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.,* Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	x			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			Under review. The Sponsor did not conduct a "thorough QT/QTc" study but submitted a "Combined Cardiac ECG Safety Report" in lieu.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	provided documentation for a waiver and/or deferral?				
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?		x		Datasets for non-melanoma skin cancer studies (4 studies), topical safety studies (3 studies), and AK lesion-specific studies (2 studies) were not submitted. Will request.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes.

The following IR items should be sent to the Sponsor in the 74 day letter.

1. Datasets for non-melanoma skin cancer studies (4 studies), topical safety studies (3 studies), and AK lesion-specific studies (2 studies) have not been submitted. Only legacy reports were submitted for these studies. Please submit individual subject data listing (including data tabulation, analysis datasets, and annotated CRFs) for all clinical studies used to support the application.

2. Clarify your procedures for coding and counting serious adverse events (SAEs), i.e., why certain AEs (e.g., melanoma, hip fracture) that are typically coded as serious (SAEs)

were not coded as such in the AE datasets. For example, Subject PEP-005-06-016 experienced hip fracture, loss of consciousness, pneumothorax, etc. but these AEs were not coded as SAEs.

Joanna Ku, MD/DDDP	May 23, 2011
Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOANNA W KU
05/23/2011

JILL A LINDSTROM
05/31/2011