A multi-center, open-label study to evaluate the safety and efficacy of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses on non-head locations (trunk and extremities) at 11 sites in the United States and Australia.

**Number of Patients (Planned and Analyzed):**
Planned: Approximately 100 patients

Analyzed: 102 patients were enrolled, received treatment and completed the study. All 102 patients were included in the intent-to-treat (ITT) and safety analysis populations; 95 patients were included in the per-protocol (PP) population.

**Diagnosis and Main Criteria for Inclusion:**
Male or female patients at least 18 years of age with 4 to 8 clinically typical, visible and discrete AK lesions within a contiguous 25 cm² treatment area on non-head locations (trunk and extremities).

**Test Product and Reference Therapy, Dose, Mode of Administration and Lots:**
Test product: PEP005 Gel, 0.05% (Lot )

Reference therapy: No reference therapy was administered in this study.

Study medication was packaged individually for each patient in a study medication kit containing two unit-dose tubes. Each unit-dose tube contained PEP005 Gel, 0.05%. Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1 and 2.
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**Individual Study Table Referring to Part of the Dossier**

**Name of Finished Product:**
PEP005 (ingenol mebutate) Gel

**Name of Active Ingredient:**
Ingenol Mebutate

**Duration of Treatment:**
Two consecutive days (Days 1 and 2).

**Randomization Scheme:**
This was an open-label study; no randomization scheme was employed.

**Criteria for Evaluation:**

**Efficacy:**
- Complete clearance rate of AK lesions at the Day 57 visit, defined as no clinically visible AK lesions in the selected treatment area.
- Partial clearance rate of AK lesions at the Day 57 visit, defined as a 75% or greater reduction in the number of AK lesions in the selected treatment area.
- The percent change from baseline to Day 57 in the total number of AK lesions.

**Safety:**
- Incidence rate of AEs, serious adverse events (SAEs) and AEs leading to discontinuation of study medication as recorded throughout the study.
- Incidence rate and grade of LSRs, pigmentation and scarring following study treatment.
- Results of vital signs and physical examination findings.

**Statistical Methods:**
The primary population of interest for the efficacy analyses was the ITT population. The ITT population included all patients who were dispensed study medication. Summaries were also provided for the PP population, which included patients in the ITT population who completed the study without any major protocol deviations. Major deviations included: failure to meet all inclusion/exclusion criteria; usage of restricted medications/treatments; failure to present an evaluable endpoint (AK lesion count) within a prespecified visit window of Day 57 (i.e., 50 ≤ study day ≤ 85); or noncompliance with the study treatment regimen (i.e., <2 applications of study medication). The safety analysis was based on the safety population, which was defined as all patients dispensed study medication who received at least one dose of study medication and had at least one postbaseline safety evaluation.

No hypotheses were tested and no inferential analyses were performed in this study.

**Efficacy:**
The primary efficacy endpoint was the complete clearance rate at Day 57 of all clinically visible AK lesions in the selected treatment area. The complete clearance rate was summarized by frequency count and 95% confidence interval (Clopper-Pearson exact). The secondary efficacy endpoint was the partial clearance rate of AK lesions at Day 57. The statistical summary was the same as that used for the primary efficacy endpoint.

An additional efficacy endpoint was the percent change from baseline to Day 57 in the total number of AK lesions. The number of AK lesions at baseline and Day 57 and percent change from baseline was summarized using descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum).

For complete and partial clearance rates and AK lesion counts, summaries were done overall (arm, back of hand, chest, and other treatment locations combined) and by each anatomic location.

Subgroup analyses were performed on complete clearance rates. Summaries were provided by gender, geographic region (US or Australia), age group (<65 or ≥65 years), baseline lesion count (4, 5, 6 or 7, 8), skin type (Fitzpatrick I/II or III/IV/V/VI), and by location of treatment area (arm, back of hand, chest, and other). For each subgroup, frequency counts and 95% confidence intervals were provided.

**Safety:**
The safety endpoints included: incidence of AEs, SAEs and AEs leading to discontinuation of study medication; incidence and grade of LSRs and/or pigmentation/scarring; changes in vital signs and physical examination findings.
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**Individual Study Table Referring to Part of the Dossier**

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**Summary of Results:**

**Efficacy:**
Overall, 40/102 (39.2%) patients had a complete clearance of AK lesions at Day 57. By treatment location, complete clearance was observed in 26/51 (51%) patients treated on the arm, 5/41 (12.2%) patients treated on the back of the hand, 6/7 (85.7%) patients treated on the chest, and 3/3 (100%) patients treated in other locations (i.e., back, shoulder, or leg). There were no meaningful differences across the subgroups of gender, age, Fitzpatrick skin type, and baseline lesion count with respect to overall clearance rate; there was an apparent difference by geographic region, but this was confounded by treatment location.

Partial clearance (≥75% reduction) of AK lesions at Day 57, support the results observed for complete clearance. The overall partial clearance rate was 54.9%, and by treatment location, the rates were 70.6% for the arm, 26.8% for the back of the hand, 85.7% for the chest, and 100% for the combined locations of the back, shoulder, and leg.

The median percent reduction in AK lesion count over the course of the study was 75%; the median percent reduction by anatomic location was 50% for the back of the hand and 100% for all other locations.

**Safety:**
PEP005 Gel, 0.05% was well tolerated in patients treated for two consecutive days on the trunk and extremities. The most common treatment-related AEs were general disorders and administration site conditions (25.5% of patients). All treatment-related AEs were mild or moderate in intensity. Two treatment-related AEs occurred outside the treatment area: mild myalgia and mild skin exfoliation on the side of the forehead (the latter attributed to contact with study medication on the treatment area [back of hand]). Three patients each had one SAE; all 3 SAEs were assessed by the investigator as not related to study medication. One patient discontinued study medication (but remained in the study through completion) due to an AE of moderate treatment-related application site vesicles. There were no trends of clinical concern regarding vital signs.

Two patients had an abnormal proliferation in the treatment area; for one patient, biopsy results showed hypertrophic solar (actinic) keratosis, considered normal by the investigator; for the other patient, biopsy results indicated SCC that was reported as a treatment-related AE; the SCC was excised and considered resolved.

Erythema was the most commonly observed LSR, showing a worsening from baseline after application of PEP005 Gel, 0.05% in 87.3% of patients; this was followed by flaking/scaling (77.5% of patients). The mean composite LSR reached peak intensity on Day 3, with a mean composite score of 6.05 out of a maximum possible score of 24. LSRs resolved by Days 29; of the 6 categories of LSRs monitored in this study, erythema appeared to take the longest time to resolve. Across treatment locations (arm, back of hand, chest, and combined locations of back, shoulder, and leg), the timing and intensity of LSR appearance as well as the time course to resolution were generally similar.

At the end of the study, all patients either showed no change in pigmentation (hyperpigmentation and hypopigmentation) or improved results. Scarring was unchanged from baseline for all patients.

**Conclusion:**
- PEP005 Gel, 0.05%, when applied topically once daily for two consecutive days on the trunk and extremities was safe and well tolerated, with 99% of patients complying with the treatment regimen.
- Treatment-related AEs most frequently involved mild or moderate application site reactions (e.g., pruritus). There were no treatment-related SAEs or deaths.
- Erythema and flaking/scaling were the most commonly reported LSRs. Mean composite LSR scores in this study were comparable to those seen in other studies evaluating treatment with PEP005 Gel, 0.05% on the trunk and extremities.
- All treatment-related application site AEs and LSRs resolved without sequelae.
- Pigmentation (hyperpigmentation and hypopigmentation) was either unchanged or improved from baseline observations for all patients. Scarring remained unchanged from baseline.
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| **Name of Finished Product:** | PEP005 (ingenol mebutate) Gel |
| **Name of Active Ingredient:** | Ingenol Mebutate |

- An overall complete clearance rate of 39.2% and a partial clearance rate of 54.9% were observed. These results are comparable to those obtained from other Phase 3 studies (REGION-I and REGION-Ib) that evaluated PEP005 Gel, 0.05% treatment for the trunk and extremities. There was an overall median percent reduction in AK lesions of 75% across treatment locations.

**Final Report Date:** 24 May 2010