2. SYNOPSIS

| NAME OF COMPANY: | Peplin Limited |
| NAME OF FINISHED PRODUCT: | PEP005 0.01% Gel |
| NAME OF ACTIVE INGREDIENT: | 3-angeloyl ingenol |

**INDIVIDUAL STUDY SYNOPSIS (Page 1 of 3)**

**INDIVIDUAL STUDY TABLE REFERING TO PART OF THE DOSSIER**

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**Title of Study:** A multicentre, double-blind, parallel, randomised, vehicle-controlled study of the safety of a single application of up to 0.2 ml of 0.01% PEP005 gel to actinic keratoses on the shoulders, chest, back and/or arms followed by a post-treatment follow-up period lasting at least 2 weeks.

**Protocol Number:** 204332-004-00

**Investigators:** Dr. [Name 1], Dr. [Name 2], Dr. [Name 3], Dr. [Name 4].

**Study Centres:**

**Publications based on study (reference):** Not applicable

**Study Period:**
- First patient randomised: 12-Aug-04
- Last patient randomised: 23-Sep-04
- Cut-off date: 15-Oct-04

**Objective:** To determine the safety of 0.01% PEP005 gel after a single application in patients with AKs on the shoulders, chest, back and/or arms.

**Methodology:** This study was a two-arm, multicentre, double-blind, parallel, randomised, vehicle-controlled phase I trial, conducted in the USA, evaluating the safety of PEP005 0.01% gel in patients with AK. Patients received a single application of 0.01% PEP005 gel or PEP005 vehicle gel to five AK lesions.

**Number of Patients (planned and analysed):**
- A sample size of approximately 16 patients, 12 receiving active gel and 4 receiving vehicle gel was planned for enrolment into this study.
- A total of 16 patients were entered and treated, however 11 received treatment with active gel and 5 received treatment with vehicle.

**Diagnosis and Criteria for Inclusion:** Male or female patients, at least 18 years of age, with at least 5 individual AK lesions on the shoulders, chest, back and/or arms.
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**Duration of Treatment:** Patients received treatment on Day 0 and were considered to be on treatment until they had completed the Day 14 visit. Further follow-up visits every 7-14 days were required in the event of an AE being present at Day 14 (until resolution of the event).

**Reference Therapy, Dose, Mode of Administration, Batch Number(s):** Not applicable.

**Criteria for Evaluation**

**Safety:** All patients receiving study medication were evaluated for AEs by the investigator (dermatological symptoms in particular) and laboratory abnormalities throughout the study.

**Efficacy:** The global response to treatment was to be evaluated by the investigator at each post-baseline visit to determine response to treatment for each of the 5 selected lesions. The global response to treatment score was to be based on the investigator’s visual assessment of each lesion compared to the lesion at the baseline visit (using the photographs taken at baseline as a reference) using an 8-point scale. Response was analysed in the intent-to-treat population (all randomised patients). Efficacy was analysed at all visits and also using the last available data (i.e. Day 14 or Day 21).

**Pharmacokinetics:** Blood samples for PK analysis were to be collected from consenting patients on Day 0 of treatment prior to treatment application and approximately 3 to 9 hours after.

**Statistical Methods:**
The sample size reflects the typical number of study participants for investigation of new drug entities for the first time in humans.

**SUMMARY OF RESULTS**
A total of 16 patients were treated in 4 centres in the USA. No patients had major protocol violations. Of the 16 treated patients, 11 were treated with active PEP005 0.01% gel and 5 received PEP005 vehicle gel. Fifteen of the 16 treated patients completed study treatment. One patient treated in the vehicle group discontinued early for personal reasons.

**Patient Characteristics:**
Patient characteristics at baseline were well balanced between the two arms. Median age: 72 years (range: 42-82); 88% of patients were male; 57% of patients had a skin type that burns easily and tans rarely or minimally.

Lesion characteristics at baseline were well balanced between the two arms; 90% of selected AK lesions were located on the arm; median longest lesion diameter was 6 mm; 85% of lesions selected for treatment had a diameter between 3 mm and 10 mm. Only 16% of the treated lesions were more than 10 mm. Seventy-five percent of patients had a history of basal cell carcinoma, 81% had a history of squamous cell carcinoma and 13% had a history of melanoma.

All patients had undergone prior treatment for AK with liquid nitrogen; 56% of patients had been treated with topical 5-FU; 25% of patients had been treated with aminolevulinic acid.
Safety Results:
All 16 patients enrolled in the study received the planned application of study treatment to five selected lesions on Day 0. An estimated median of 86 mg (range 50-110 mg) of 0.01% PEP005 gel was applied in the active treatment arm and 73 mg (range 30-110 mg) in the vehicle treatment arm.
Toxicity was more prevalent in patients treated with 0.01% active gel. Local AEs were reported in 9 of the 11 patients (82%) treated in the active arm including 7 patients (64%) who had at least 2 AEs each. In addition, two of the five patients (40%) treated with vehicle reported one local AE each.
All reported events were mild. Erythema, scaly rash and scabbing were the most common events occurring in 73%, 27% and 27% of patients treated with active gel respectively. Tenderness and oedema were each reported in one patient. Two of the five patients (40%) treated with vehicle also experienced erythema. Median day of onset of erythema and scaling was the day after treatment application and median durations of these events were 7 and 13 days respectively.
Haematotoxicity and biochemistry abnormalities were rare and similar in the two arms. Most patients who experienced grade 1-2 abnormalities during the study had abnormal values at screening.
No scarring or abnormal proliferation was reported.
SAEs: No deaths or other SAEs were reported in this study.

Efficacy Results: All 16 patients were evaluable for efficacy. Efficacy could not be evaluated for one visit each for two patients (planned visit not performed). Four patients treated with 0.01% PEP005 gel had an additional follow-up visit on Day 21.
A total of 80 lesions were treated (55 with 0.01% PEP005; 25 with PEP005 vehicle). Complete clearance in all five lesions at last available follow-up was reported for one patient treated with 0.01% PEP005. Another 0.01% PEP005 patient had complete clearance in 4/5 treated lesions.
Extent of lesion clearance according to individual lesions showed that at Day 14, 8/55 lesions (15%) treated with active gel had complete clearance and by the last available follow-up, this had increased to 16/55 lesions (29%) treated with active gel. In addition, 6/55 lesions were classified as almost cleared (i.e. ≥90% clearance) at last available follow-up. The combined rate of almost and complete clearance at last follow-up in lesions treated with 0.01% active gel is 40% (26/55).
In the vehicle group, of the 25 treated lesions, 2 had complete clearance at last follow-up and 1 was classified almost cleared, giving a combined rate of almost and complete clearance of 15% (no data for one patient with 5 lesions).
Of the 12 lesions with an inflammatory response at Day 7, seven (58%) had complete clearance at the last available follow-up.
Lesion clearance at the last available follow-up according to longest lesion diameter did not show any obvious trends.

Pharmacokinetics Results: 11 patients provided PK samples for analysis. Data for all samples were below the limit of quantification for the assay.

Conclusion: This study has demonstrated that a single topical application of up to 0.2 mL of 0.01% PEP005 gel in patients with AK is safe, the predominant toxicity being mild, manageable erythema. Evidence of activity was seen, notably in patients with prolonged follow-up. There is also evidence that an inflammatory reaction may be needed for activity. Further studies using higher concentrations and different administration schedules with a more prolonged follow-up will be performed.

Date of Report: 09-May-05