CONFIDENTIAL

PEP005 (ingenol mebutate) Gel

2.7.6 Synopses of Individual Studies

Module 2

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Clinical Development

Final
05-MAY-2011

Module 2
Synopses of Individual Studies
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1 LISTING OF CLINICAL STUDIES

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

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-006	5.3.5.1 head 5.3.5.1 non-head	Safety, efficacy (dose ranging)	Randomized, vehicle-controlled	0.025% or 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	222 162 PEP005 Gel 60 vehicle	AK lesions scalp, trunk, and extremities	2 Days or 3 Days	Complete; Full
Safety	PEP005-015	5.3.5.1 head	Safety, efficacy (dose ranging)	Randomized, vehicle-controlled	0.005%, 0.01%, or 0.015% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	265 199 PEP005 Gel 66 vehicle	AK lesions face and scalp	2 Days or 3 Days	Complete; Full
Safety	PEP005-001	5.3.5.1 head 5.3.5.1 non-head	Safety, efficacy	Randomized, vehicle-controlled	0.0025%, 0.01%, or 0.05% PEP005 Gel, qd Vehicle Gel, qd Lesion-specific topical application on Day 1 and Day 2 or 8	63 51 PEP005 Gel 12 vehicle	AK lesions face, scalp, trunk and extremities	2 Days	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	PEP005-014	5.3.5.1 non-head	Efficacy, safety	Randomized, vehicle-controlled	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	255 126 PEP005 Gel 129 vehicle	AK lesions trunk and extremities	2 Days	Complete; Full
Efficacy	PEP005-028	5.3.5.1 non-head	Efficacy, safety	Randomized, vehicle-controlled	0.05% PEP005 Gel, qd Vehicle Gel, qd Topical field application (25 cm^2 treatment area)	203 100 PEP005 Gel 103 vehicle	AK lesions trunk and extremities	2 Days	Complete; Full
Safety	AGN-204332-004	5.3.5.1 non-head	Pilot safety	Randomized, vehicle-controlled	0.01% PEP005 Gel, qd Vehicle Gel, qd Lesion-specific topical application	16 11 PEP005 Gel 5 vehicle	AK lesions trunk and extremities	1 Day	Complete; Full
Safety	PEP005-004	5.3.5.2	Determine MTD, safety, efficacy	Open-label	0.01%, 0.025%, 0.05%, 0.075% PEP005 Gel, qd Topical field application (9 cm^2 treatment area)	22	AK lesions trunk and extremities	2 Days	Complete; Full

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

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

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-003	5.3.5.4	Safety, efficacy	Randomized, vehicle-controlled	0.0025%, 0.01%, 0.05% PEP005 Gel, qd Vehicle Gel, qd Topical application on Day 1 and Day 2 or 8	60 48 PEP005 Gel 12 vehicle	NMSC superficial BCC on the face, scalp, trunk and extremities	2 Days	Complete; Full
Safety	PEP005-005	5.3.5.4	Dermal sensitization	Randomized, vehicle-controlled	0.01% PEP005 Gel Vehicle Gel Topical application ($4\ cm^2$ treatment area)	238	Healthy subjects	10 doses of both PEP005 Gel and vehicle over 6–8 weeks	Complete; Full
Efficacy	PEP005-008	5.3.5.4	Efficacy, safety	Open-label	0.05% PEP005 Gel, qd Topical application	25	NMSC SCCIS on the face, trunk, and extremities	2 Days	Complete; Abbreviated

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Admin	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PEP005-009	5.3.5.4	Determine MTD, safety, efficacy	Open-label	0.025%, 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, 0.175%, 0.2%, 0.225% or 0.25% PEP005 Gel Topical application on Day 1 or Days 1 and 8	101	NMSC superficial BCC on the trunk	1 Day or 2 Days	Complete; Full
Safety	PEP005-023	5.3.5.4	Dermal photo-irritation	Randomized, within subject comparison to vehicle	0.01% PEP005 Gel Vehicle Gel Topical application (two 4 cm^2 treatment areas)	34	Healthy subjects	1 Day	Complete; Full
Safety	PEP005-024	5.3.5.4	Dermal photo-sensitization	Randomized, within subject comparison to vehicle	0.01% PEP005 Gel Vehicle Gel Topical application (two 4 cm^2 treatment areas)	60	Healthy subjects	7 doses of both PEP005 Gel and vehicle over 6–8 weeks	Complete; Full

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

2 SYNOPSES OF INDIVIDUAL STUDIES

PEP005-017	A randomized, double-blind, vehicle-controlled study to evaluate the pharmacokinetics of PEP005 (ingenol mebutate) Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis
PEP005-013	A Phase I, pharmacokinetic study to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel to a 100 cm2 (5 cm x 20 cm) contiguous actinic keratosis (AK) treatment area on the extensor (dorsal aspect) forearm
PEP005-016	A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% in patients with actinic keratoses ON the head (face or scalp) (REGION-IIa)
PEP005-025	A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% in patients with actinic keratoses ON the head (face or scalp) (REGION-IIb)
PEP005-006	A Multi-center, randomized, double-blind, double-dummy, vehicle-controlled sequential cohort study to determine the safety of PEP005 0.025% and 0.05% Topical Gel in patients with actinic keratoses
PEP005-015	A multicenter, randomized, double-blind, vehicle-controlled, dose-ranging study to evaluate the safety and efficacy of 0.005%, 0.01% and 0.015% PEP005 Topical Gel when used to treat actinic keratoses on the head (face or scalp)

PEP005-001	A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to actinic keratoses
PEP005-014	A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses on non-head locations (REGION-I)
PEP005-028	A multi-center, Randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses ON non-head locations (REGION-Ib)
AGN-204332-004	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
PEP005-004	An open-label, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel when applied on day 1 and day 2 to actinic keratoses on the shoulders, chest, back, or arms followed by a post-treatment follow-up period lasting at least four weeks
PEP005-018	A multicenter, open-label study to examine the safety and toleration of 0.05% PEP005 Topical Gel in patients with actinic keratoses on the dorsum of the hand
PEP005-020	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)

PEP005-007	An open-label, multi-centre, dose-escalation, cohort study to determine the optimal tolerated regime and safety of PEP005 Topical Gel when applied to a 25 cm2 contiguous actinic keratoses treatment area on the face or face and scalp
PEP005-022	A multicenter, open-label, dose-area escalation, cohort study to evaluate the safety and tolerability of 0.05% PEP005 Topical Gel applied for two consecutive days to treatment area(s) of up to a total of 100 cm2 in patients with actinic keratoses on the extensor (dorsal aspect) forearm(s)
PEP005-030	A 12-month, long-term follow-up study of patients with actinic keratosis on the head (face or scalp) who have completed Day 57 in studies PEP005-016 or PEP005-025 (REGION IIa and IIb)
PEP005-031	A 12-month, long-term follow-up study of patients with actinic keratosis on non-head areas (trunk and extremities) who have completed Day 57 in study PEP005-020
PEP005-032	A 12 month, long-term follow-up study of patients with actinic keratosis on non-head locations (trunk and extremities) who have completed Day 57 in study PEP005-028
PEP005-002	A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 Topical Gel, 0.0025%, 0.01%, and 0.05%, with two treatment schedules, day 1 and day 2 or day 1 and day 8 applications to nodular basal cell carcinoma
PEP005-003	A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, day 1 and day 2 or day 1 and day 8 applications to superficial basal cell carcinoma

PEP005-005	A randomized, controlled study to evaluate the sensitizing potential of PEP005 Topical Gel (0.01% concentration) in healthy volunteers using a repeat insult patch test design
PEP005-008	Multi-centre, open-label study to determine the safety and efficacy of PEP005 0.05% Topical Gel in patients with cutaneous Squamous Cell Carcinoma in situ (SCCIS, Bowen's Disease).
PEP005-009	An open-label, multicenter, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel given as either a single application (on day 1) or as two applications (on day 1 and day 8) to a superficial basal cell carcinoma (sBCC) on the trunk
PEP005-023	A 4-day, randomized, controlled, open application study to evaluate the photoirritation potential of PEP005 (ingenol mebutate) Gel, 0.01% in healthy volunteers, using a phototoxicity test design
PEP005-024	A randomized, controlled study to evaluate the photoallergic potential of PEP005 (ingenol mebutate) Gel, 0.01% in healthy volunteers using an open application photoallergic test design

2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to (For National Authority Use only) Part of the Dossier** Volume: Page:

Name of Finished Product:
PEP005 (ingenol mebutate) Gel

Name of Active Ingredient:
Ingenol Mebutate

Title:
A randomized, double-blind, vehicle-controlled study to evaluate the pharmacokinetics of PEP005 (ingenol mebutate) Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis

Investigators and Sites: Single site in the US (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: March 18, 2009
Last patient completed Day 57: May 27, 2009

Phase of Development: 2

Objectives:

The primary objective was to evaluate the potential for systemic exposure of ingenol mebutate when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis.

The secondary objectives were to evaluate the safety and efficacy of PEP005 Gel, 0.05%, when applied in a maximal use setting to the dorsal aspect of the forearm in patients with actinic keratosis.

Methodology:

This was a randomized, double-blind, vehicle-controlled study.

Following screening for eligibility, patients were randomized, through an Interactive Voice Response (IVR) system, to receive either PEP005 Gel, 0.05%, or vehicle gel in a 4:1 ratio, respectively, on study Day 1. Study medication was applied on Days 1 and 2 in the clinic, by site staff. Pharmacokinetic (PK) blood samples were collected for all patients prior to study medication application on Day 1, through to 24 hours following the Day 2 study medication application. Study visits for safety and efficacy assessments occurred on Days 2, 3, 8, 15, 29 and 57 (study exit).

Post-study follow-up visits were required for all patients with unresolved treatment-related adverse events (AEs), local skin responses (LSRs), pigmentation or scarring, greater than observed at baseline, at the Day 57 visit.

Number of Patients (Planned and Analyzed):
Approximately 15 patients were planned for enrollment. A total of 16 patients were randomized (analyzed) (13 patients randomized to PEP005 Gel and three to vehicle gel). All 16 patients completed the study to Day 57.

Diagnosis and Main Criteria for Inclusion:

Male or female patients at least 18 years of age with multiple actinic keratosis (AK) lesions within a contiguous 100 cm^2 treatment area on the dorsal aspect of one forearm.

Test Product and Reference Therapy, Dose, Mode of Administration, and Lot:
Study medication was supplied as PEP005 Gel, 0.05% (Lot: AKW-C) test product, or vehicle gel (Lot: ZMAB-C) reference therapy. Study medication was applied topically to the 100 cm^2 selected treatment area by the clinic site staff, once daily for two consecutive days (Days 1 and 2).

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Name of Finished Product:
PEP005 (ingenol mebutate) Gel

Name of Active Ingredient:
Ingenol Mebutate

Pharmacokinetic Evaluation:

Blood samples for PK analysis were collected prior to study medication application on Day 1, prior to study medication application on Day 2 (+24 hr Day 1), and at 30 minutes, 1, 2, 4, 8, 12 and 24 hours following study medication application on Day 2.

Whole blood samples were quantified (C_{max}, T_{max} and $AUC_{(0–24)}$) for ingenol mebutate and its primary metabolites, PEP015 and PEP025 (lower limit of quantification [LLOQ] = 0.1 ng/mL).

Randomization Scheme:
Patients were randomized through an IVR system to receive either PEP005 Gel, 0.05%, or vehicle gel in a 4:1 ratio, respectively. Approximately 12 patients were to be treated with PEP005 Gel and approximately three patients were to be treated with vehicle gel.

Criteria for Evaluation:
The primary criteria for evaluation were whole blood samples, quantified (C_{max}, T_{max} and $AUC_{(0–24)}$) for ingenol mebutate and PEP015 and PEP025.

The secondary criteria for evaluation were the:

- Incidence rate of AEs, serious adverse events (SAEs) and AEs leading to discontinuation through Day 57;
- Incidence rate and grade of LSRs, pigmentation and scarring, following study treatment through Day 57;
- Complete clearance rate, defined as no clinically visible AK lesions in a 25 cm^2 area within the selected treatment area; and
- Percentage (%) reduction in AK lesions at Day 57, compared to baseline, in a 25 cm^2 area within the selected treatment area.

Statistical Methods:
Results were summarized into tabulations, case listings, plots, and histograms for comparison. Descriptive summaries were created to include the mean, standard deviation, median, and range for continuous variables, and counts and percentages for categorical variables.

The PK analysis was performed using the PK population, defined as all randomized patients who had received at least one dose of study medication with at least one post-baseline PK blood sample.

The safety analysis was based on the safety population, defined as all randomized patients who had received at least one dose of study medication and who had at least one post-baseline safety evaluation. In the safety population, patients were counted in the group in which they were treated.

The efficacy analysis was based on the intent-to-treat (ITT) population, defined as any patient randomized to the study.

Summary of Results:

Pharmacokinetic Results:

No systemic absorption was detected. Levels of ingenol mebutate and its acyl isomers were below the LLOQ in samples from all patients following two consecutive once-daily applications of PEP005 Gel, 0.05%.

Efficacy Results:

AK lesion clearance was assessed at Day 57 in a 25 cm^2 contiguous area of skin located within the larger treatment

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Name of Finished Product:
PEP005 (ingenol mebutate) Gel

Name of Active Ingredient:
Ingenol Mebutate

area. Of the patients who received treatment with PEP005 Gel, 0.05%, 77% (10/13) had complete clearance of all AK lesions, and all patients had partial clearance. None of the three patients treated with vehicle gel had complete or partial clearance of their AK lesions.

The percentage change from baseline in the total AK lesion count in the selected 25 cm^2 area was also assessed at Day 57. The median percentage reduction in AK lesion count was 100% in patients treated with PEP005 Gel, 0.05%, and zero in those patients treated with vehicle gel.

Safety Results:

PEP005 Gel, 0.05%, appeared to be safe and well tolerated when applied in a maximal use setting to the dorsal forearm in patients with AK. All patients received the scheduled treatment of two consecutive once-daily doses of study medication. Three patients (23%; 3/13) treated with PEP005 Gel, 0.05%, experienced a total of five AEs and two patients (67%; 2/3) treated with vehicle gel experienced a total of two AEs. The only AE category (by system organ class) reported in more than one patient treated with PEP005 Gel was 'injury, poisoning and procedural complications' (15%; 2/13). No individual AE by preferred term was reported in more than one patient.

Of the seven reported AEs, one (mild diarrhea) was deemed "possibly" treatment-related; however, upon unblinding, this patient was found to be randomized to vehicle gel. One patient experienced an insect bite within the treatment area. No SAEs occurred in this study.

Among patients who received active treatment, the mean composite LSR score was 0.1 at baseline, reached a maximum of 6.6 on Day 3, and returned to pretreatment levels by Day 57. In patients who received vehicle gel, the mean composite LSR score was 0.3 at baseline, and zero throughout the remainder of the study.

All patients treated with PEP005 Gel, 0.05%, experienced erythema and flaking/scaling. Swelling and vesiculation/pustulation were reported in 69% (9/13) and 54% (7/13) of patients, respectively. One patient had Grade 1 erythema at Day 57, while all other LSRs resolved during the study. Grade 4 erythema and/or flaking/scaling occurred in five of 13 patients (38%) following treatment with active medication. All Grade 4 LSRs resolved by Day 57 on study. No LSRs occurred following treatment in the vehicle group.

Compared to baseline, there were no changes in hypopigmentation or hyperpigmentation at Day 57. Transient pigmentation changes occurred in two patients treated with PEP005 Gel, 0.05% (one case each of Grade 1 hypopigmentation and Grade 1 hyperpigmentation, both of which resolved by the end of the study). No patients had scarring or abnormal proliferation.

There were no clinically relevant changes in vital signs or physical examination findings. Patient [redacted] had a moderate gamma-glutamyl transpeptidase (GGT) increase on Day 8 that was considered unrelated to treatment with PEP005 Gel, 0.05%.

Conclusion:
The results of this study demonstrate that there is no evidence of systemic absorption when PEP005 Gel, 0.05%, is applied once daily for two consecutive days to a 100 cm^2 contiguous AK treatment area on the dorsal forearm. PEP005 Gel, 0.05%, appears safe and well tolerated in this maximal use setting.

Final Report Date: January 28, 2010

2 SYNOPSIS

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only)** **Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	
Title of Study: A Phase I, pharmacokinetic study to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel to a 100 cm^2 (5 cm x 20 cm) contiguous actinic keratosis (AK) treatment area on the extensor (dorsal aspect) forearm	
Investigator: s 22(1)	
Study Centers: Office of the Investigator: Siller Medical, 9th Floor, Silverton Place, 101 Wickham Terrace, Brisbane, QLD 4000, Australia (Screening and follow-up visits) Phase I Unit: Q-Pharm Pty Limited, Level D, Clive Berghofer Cancer Research Centre, 300 C Herston Road, Herston QLD 4029, Australia (Days 1, 2, and 3)	
Study Period: 17 October 2007 23 April 2008	**Clinical Phase:** Phase I
Publications: None	
Objectives: The primary objective of the study was to evaluate the extent of systemic absorption of PEP005, when applied as 0.05% PEP005 Topical Gel on two consecutive days (Day 1 and Day 2) to a 100 cm^2 (5 cm x 20 cm) contiguous AK treatment area on the extensor (dorsal aspect) forearm. The secondary objective of the study was to evaluate the safety and tolerability of two consecutive days' application of 0.05% PEP005 Topical Gel, when applied to a 100 cm^2 (5 cm x 20 cm) contiguous AK treatment area on the extensor (dorsal aspect) forearm.	

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only)** **Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Methodology: This Phase I open-label study was designed to confirm the lack of systemic absorption of PEP005 and its major metabolites PEP015 and PEP025 when 0.05% PEP005 Topical Gel was applied once daily to an unoccluded 100 cm^2 (0.05 $\mu g/mm^2$) contiguous AK treatment area on the extensor forearm for two consecutive days. The 100 cm^2 contiguous treatment area served as a maximal use treatment area, utilizing the maximum AK body field-therapy concentration of PEP005 Topical Gel (i.e., 0.05% for two consecutive days). Blood samples for pharmacokinetic analysis were taken prior to and during the 24 hours following the Day 2 application.
One patient was enrolled into the study during Week 1. A second patient was enrolled during Week 2 after no significant tolerability concerns were assessed in Week 1. Following assessment of the second patient at the end of Week 2, the remaining patients were enrolled into the study.

A dermatologic examination was performed by a qualified dermatologist, photographs of the selected treatment area were taken, and local skin responses (LSRs) were assessed at baseline (prior to study drug application) and at every study visit including all unscheduled visits and post-treatment follow-up visits except Day 3.

Concomitant medications were recorded. Clinical laboratory evaluations were performed at the screening visit and the Day 8 follow-up visit. Vital signs were assessed at every study visit (twice on Days 1, 2, and 3). A physical examination was performed at screening (Days -21 to -3) and Day 57. Adverse events were assessed at Day 1 to Day 57 (end of study) visits and at post-treatment follow-up visits, if necessary.

Number of Patients: Eight patients were planned so that six patients would be available for analysis. Eight patients were enrolled. Six of the eight patients completed the study and were included in the safety analysis. Three patients were treated on both study dosing days (Days 1 and 2) and therefore contributed blood specimens for the pharmacokinetic analysis.

Diagnosis and Main Criteria for Inclusion: Male patients who were at least 18 years of age with a contiguous 100 cm^2 treatment area containing at least five AK lesions on either the right or left extensor (dorsal aspect) forearm.

Dosage, Administration, and Duration of Treatment: PEP005 Topical Gel, 0.05%, was applied to the AK treatment area by micro-pipette on two consecutive days as 1 mL in four aliquots of 250 µL.

Criteria for Evaluation:

Safety:
The following safety parameters were assessed:

- Incidence of adverse events (AEs) throughout the study;
- Incidence rate and grade of LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, scarring) using the LSR Grading Scale (rated Grade 0 to 4). Assessments were performed at baseline (Day 1 pre-dose), Days 1 (post-dose), 2 (pre- and post-dose), 8, 29, 57, and all post-treatment follow-up and unscheduled visits;
- Fasting laboratory results (hematology, serum chemistry, and urinalysis) at screening and Day 8; and
- Vital sign measurements (at every visit [pre-dose on Days 1 and 2] and additionally at the end of the study visit on Days 1, 2, and 3) and physical examination findings at screening and Day 57 (end of study) or early termination.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only)** **Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Pharmacokinetics:

- The pharmacokinetic (PK) blood samples (Days 1, 2, and 3) were to be quantified for PEP005 and the two major metabolites, PEP015 and PEP025.
- Following administration of PEP005 Topical Gel, C_{max}, T_{max}, and $AUC_{(0–24)}$ were to be evaluated for PEP005, PEP015, and PEP025 to determine systemic exposure to PEP005 Topical Gel in patients receiving two consecutive days of treatment.

Statistical Methods:
Data were summarized and listed.

Summary:
Pharmacokinetic Results:
All six enrolled patients received at least one dose of 0.05% PEP005 Topical Gel. Only three of the six treated patients met the requirement of the PK population and had full PK assessments; the other three patients had only partial PK assessments and were not included in the PK population.

All blood samples from the six patients (three patients treated for two days; three patients treated for one day) were below the lower limit of quantification (0.100 ng/mL) for PEP005 and its metabolites PEP015 and PEP025. Therefore, no PK parameters could be calculated.

Safety Results:
This maximal use study intended to treat a larger 100 cm^2 contiguous treatment area on the extensor forearm of a single arm with 0.05% PEP005 Topical Gel, once daily for two consecutive days. Patients in this study had more intense LSRs than were observed in earlier studies treating smaller 25 cm^2 areas. Because of these more intense responses, only 50% of patients (three out of six) were able to tolerate two consecutive days of treatment. Although LSRs and AEs precluded three patients from being treated on the second day, reactions were similar to those observed in earlier AK field-therapy studies treating 25 cm^2 areas of skin (i.e., Protocol PEP005-006), with peak composite LSR scores on or around Day 8 and limited or no residual AEs and/or LSRs at the end of the study.

The mean composite LSR and peak score were able to describe the general course of LSR events in this study. Mean composite LSR scores generally peaked on or before Day 8, showed marked improvement by Day 29, and most returned to baseline levels by Day 57 (end of study). It should be noted that there were several unscheduled visits that occurred and that only six patients that were assessed. Three patients (Patients [redacted] and [redacted] were followed for LSRs after Day 57 (refer to pigmentary LSR below), but there were no LSRs greater than Grade 2 following the Day 57 assessment, with the exception of Patient [redacted] again, refer to pigmentary LSR below).

Erythema and flaking/scaling were the most frequently occurring LSRs. Both erythema and flaking/scaling had the highest rated post-dose LSR grade. Four patients (66.7%) had a Grade 4 LSR for both erythema and flaking/scaling.

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Vesiculation/pustulation was recorded for the first time at Day 2 pre-dose in four patients (66.7%), and by a fifth patient at Day 6 (unscheduled). The vesiculation/pustulation continued in three patients to Day 8 and resolved by Day 29 (note that there were no scheduled study visits between Day 8 and Day 29). The highest rated post-dose LSR for vesiculation/pustulation was recorded as a Grade 4 (three patients; 50%). The investigator assessed one of the three patients with vesiculation/pustulation as having moderate cellulitis and treated the patient successfully with oral antibiotics.

Scarring rated no higher than a Grade 1 LSR throughout the study and already existed in three patients (50%) at baseline (Day 1 pre-dose). The incidence of scarring decreased during the study and was no longer recorded in any patient from Day 2 onwards. Three patients (50%) actually improved their scarring LSR rating from baseline.

Pigmentary changes were observed in this study. Five patients (83.3%) had either hypopigmentation or hyperpigmentation noted at baseline. By Day 57 (end of the study), two patients (33.3%; [redacted] and [redacted] had improved, one patient (16.7% [redacted]) was unchanged, and three patients (50.0%; [redacted] and [redacted] had pigmentary changes greater than baseline at Day 57 that were followed until improvement to baseline levels or for a period of four months following the Day 57 visit. Of the three patients, only one [redacted] had pigmentary change recorded out to Day 154 that was one grade above baseline (Grade 2). The other two patients either returned to baseline [redacted] or improved [redacted] from their baseline value. Most of the pigmentation changes described above were in the direction of hypopigmentation. Hyperpigmentation was reported only in one patient [redacted] who had an overall pigmentation Grade 3 at baseline that improved to Grade 0 by Day 8.

There were two instances of patients with abnormal proliferation within the treatment area. One patient [redacted] with a history of keratoacanthoma and non-melanoma skin cancer, presented with keratoacanthoma on Day 15 post-treatment (lasted for approximately one month) and squamous cell carcinoma (Bowen's disease) on Day 57 post-treatment. No action was taken for the keratoacanthoma following a confirmatory biopsy, and the squamous cell carcinoma was excised on Day 92 post-treatment and remained clear at follow-up on Day 183. The investigator felt that the keratoacanthoma was definitely related to study treatment and the Bowen's disease was possibly related to study treatment. Another patient [redacted] with a prior history of melanoma and non-melanoma skin cancer, was diagnosed with lentigo following a [redacted]matory biopsy (which cleared the lesion) on Day 36 post-treatment. The investigator recorded the lentigo as possibly related to study treatment.

There was one SAE recorded in this study for the patient with Bowen's disease (described above). There were no patient deaths in this study, and no patients were discontinued from the study due to an AE, although three patients did not receive study drug on Day 2 due to either a treatment emergent adverse event (TEAE) or an LSR. All AEs and SAEs resolved and all LSRs resolved to baseline values or better, except for the one case of pigmentary change (described above) for Patient [redacted] and one patient [redacted] who had a baseline erythema Grade 0 that remained a Grade 1 at the end of study (actual grading was assessed on Day 44). The two patients who did discontinue from the study, did so during the screening period, one due to laboratory abnormalities and one withdrawal of consent.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only)** **Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Conclusions:

The PK data suggest that treatment of a 100 cm^2 area of skin with 0.05% of PEP005, once daily for one or two consecutive days does not demonstrate systemic absorption of PEP005 or its metabolites PEP015 or PEP025.

More intense LSRs were observed in this study treating 100 cm^2 areas than in earlier studies treating smaller, 25 cm^2 areas. Because of these more intense responses, only 50% of patients (three out of six) were administered two consecutive days of treatment. Although LSRs and AEs precluded these three patients from being treated on two consecutive days, all reactions observed in this study were similar to those observed over a 25 cm^2 treatment area-of skin (i.e., Protocol PEP005-006). This study, treating larger areas of skin demonstrated a greater mean composite LSR intensity at peak and a longer time to have LSRs completely resolve. It should be noted that all LSRs, except for pigmentary changes, decreased by Day 29 and resolved to baseline or better by Day 57 (end of study). The three patients with hypopigmentation above baseline levels at Day 57 were followed until resolution to baseline value. Reassuringly, all LSR pigmentation changes eventually resolved, with the exception of one patient [redacted] who had pigmentary change that was one grade above baseline (baseline, Grade 1; Day 154, Grade 2) at the last evaluation. Of note, 50% (three of six) of patients reported an ultimate improvement in their pigmentary change, compared to their baseline (Day 1 pre-dose) score. There was no treatment emergent scarring observed in this study, and 50% (three of six) of patients had actually improved scarring from baseline to end of study. All TEAEs and SAEs reported for patients in this study resolved. Overall, there were no long term sequelae to treating a 100 cm^2 area of skin in this population of six patients with sun damaged skin, wherein 83.3% (five out of six patients) had approximately 21 to 50 AK lesions on their extremities at the time of study enrollment.

In terms of the abnormal proliferation observed in this study, a feature of topical therapies for the treatment of AK is the uncovering of subclinical lesions (so-called treatment-emergent lesions). Patient [redacted] developed abnormal proliferation (keratoacanthoma and Bowen's disease) within the treatment area during this study. Although the abnormal proliferation was deemed to be related to the study treatment by the investigator, it is in the opinion of the Sponsor that there were multiple long-standing risk factors reported in the patient's medical history that make it problematic to assign a causal relationship between drug therapy and the emergence of these lesions.

The Sponsor feels that there were no long-term or unexpected sequelae that manifested during this study; however, further evaluation of 0.05% Topical Gel is needed to assess the maximal area of skin that can safely be treated with PEP005 Topical Gel due to the small number of patients treated once daily for two consecutive days over a 100 cm^2 contiguous area in this study. An open-label, dose-area escalation, cohort study will be conducted to further assess this question prior to conducting another maximal use PK study.

Date of Report: January 22, 2009

PEP005-016

SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	**Volume:**	
Name of Active Ingredient: Ingenol Mebutate	**Page:**	

Title:
A multi-center, Randomized, parallel group, double-blind, vehicle-controlled study to evaluate the Efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% In patients with actinic keratoses ON the head (face or scalp) (REGION-IIa)

Investigators and Sites: Multi-center in the United States and Australia (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 05 June 2009
Last patient completed Day 57: 10 September 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel when administered once daily for three consecutive days to a contiguous 25 cm^2 area of skin on the head (face or scalp).

Methodology:
This was a multi-center, randomized, parallel group, double-blind, vehicle-controlled study.

Patients were randomized to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Study medication was patient-applied at home on Days 1, 2 and 3. Subsequent followup visits for safety assessments were conducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (End of Study). Patient-reported treatment satisfaction was assessed on Day 57 and Quality of Life (QOL) assessments were conducted at baseline and on Days 8, 29 and 57. Patients completed the study on Day 57.

Poststudy follow-up visits were required every 7 to 28 days for all patients who had unresolved treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57. Patients were to be followed until either resolution or assessed as clinically stable. Patients with unresolved hypopigmentation or hyperpigmentation and/or scarring greater than baseline were required to undergo further poststudy followup every 28 days until resolution or for a period of six months postbaseline (an additional four visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: Approximately 250 patients (125 per treatment arm) were planned for enrollment.
Analyzed: A total of 269 patients were randomized (135 to PEP005 Gel 0.015% and 134 to vehicle gel); 259 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 246 patients were included in the per-protocol (PP) population. The safety population included 267 patients.

Diagnosis and Main Criteria for Inclusion:
Male or female patients at least 18 years of age with four to eight clinically typical, visible and discrete actinic keratotis (AK) lesions within a contiguous 25 cm^2 treatment area on the head (face or scalp).

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:
Test product: PEP005 Gel, 0.015% (Lot BBW-C).
Reference therapy: Vehicle gel (Lots BCA-C and BCA-1C).
Study medication was packaged individually for each patient in a study medication kit containing three unit-dose tubes. Each unit-dose tube contained PEP005 Gel 0.015% or vehicle gel.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	**Volume:**	
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Duration of Treatment:

Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1, 2 and 3.

Randomization Scheme:

Patients were randomized centrally to treatment in a 1:1 ratio through an interactive voice / web response (IVR/IWR) system. Randomization was stratified by investigational site and by the location of the treatment area (face or scalp). Enrollment was controlled so that approximately 20% of patients were treated on the scalp and approximately 80% of patients were treated on the face. The IVR/IWR system assigned a study medication kit number for each patient randomized into the study.

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

Complete clearance rate of AK lesions at the Day 57 visit. A patient with no clinically visible AK lesions in the selected treatment area was defined to have complete clearance.

Secondary Endpoint:

Partial clearance rate of AK lesions at the Day 57 visit. A patient with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline, in the selected treatment area was defined to have partial clearance.

Additional Endpoint:

The percent change from baseline to Day 57 in the total number of AK lesions.

Exploratory:

Patient-reported outcomes, including the Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

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 clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

Statistical Methods:

The primary efficacy analysis was based on the intent-to-treat (ITT) population. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

For the analyses of complete and partial clearance, all missing values were imputed using last observation carried forward (LOCF). Baseline data were carried forward if no postbaseline data existed for the patient. That is, those patients were considered to have not achieved complete or partial clearance.

The safety analysis was based on the safety population, which was defined as all randomized patients who received at least one dose of study medication and had at least one postbaseline safety evaluation. In the safety population, patients were analyzed according to the actual treatment received.

All treatment comparisons were tested with two-tailed tests and a 0.05 significance level.

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Efficacy:

The primary efficacy endpoint was complete clearance rate at Day 57 of all clinically visible AK lesions in the selected treatment area. The complete clearance rate was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. The secondary efficacy endpoint was the partial clearance rate of AK lesions at Day 57. The statistical analysis 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 percent change from baseline in the number of AK lesions was summarized for each treatment group. Summaries were also provided by each anatomical location.

Patient-Reported Outcomes:

The TSQM transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at baseline and Days 8, 29, and 57 were summarized by treatment group. The transformed scores were treated as a continuous variable and analyzed using analysis of variance (ANOVA) with treatment, anatomical location, and analysis site as factors to test for treatment effect.

Safety:

The safety endpoints included: incidence of patients who experienced AEs, SAEs and AEs leading to discontinuation of study medication; incidence and grade of LSRs and/or pigmentation/scarring; changes in clinical laboratory tests, vital signs, physical examinations, and ECG findings. The treatment effect was explored by inspection of observed means or rates for the treatment groups.

Summary of Results:

Efficacy:

The primary efficacy endpoint was complete AK lesion clearance overall (face and scalp combined) at Day 57. The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (37% compared to 2%, $p<0.001$, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population. For patients treated on the face ($n = 109$ for each treatment group), PEP005 Gel also demonstrated a statistically significant, higher complete clearance rate compared to vehicle gel (42% versus 3%, $p<0.001$, Fisher's Exact test). For scalp-treated patients ($n = 26$ for PEP005 Gel; $n = 25$ for vehicle gel), the difference between the treatment groups was not statistically significant but was numerically in favor of PEP005 Gel (15% versus 0%, $p=0.110$, Fisher's Exact test).

The secondary efficacy endpoint was partial (≥ 75% reduction) AK lesion clearance at Day 57. Consistent with the primary endpoint, the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (60% compared to 7%, $p<0.001$, CMH test stratified by analysis site) based on the ITT population. The results of the PP population were consistent with the results of the ITT population. Patients treated on the face with PEP005 Gel also demonstrated statistically significant, higher partial clearance rates than vehicle gel patients (69% versus 7%, $p<0.001$, Fisher's Exact test). For scalp-treated patients, the difference between the treatment groups was not statistically significant but was numerically in favor of PEP005 Gel (23% versus 4%, $p=0.099$, Fisher's Exact test).

The median percent reduction in the number of AK lesions compared to baseline overall (face and scalp combined) was substantially greater for the PEP005 Gel group (83%) versus 0% in the vehicle group. For patients treated on the face, the median reduction was 83% for the PEP005 Gel group versus 0% in the vehicle group. For patients treated on the scalp, the median reduction was 49% for the PEP005 Gel group versus 25% in the vehicle group.

In the subgroup analyses, the complete clearance rate for each treatment group was analyzed by geographic region (US or AUS), gender, age group (<65 or ≥65 years), baseline AK lesion count (4, 5, 6 or 7, 8), skin type (Fitzpatrick I/II or III/IV/V/VI), and analysis site. Findings showed a higher complete clearance rate for PEP005 Gel-treated patients compared to vehicle patients in each category; the only category that did not show statistical significance was the geographic region of Australia.

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Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey. Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group compared to the vehicle gel group ($p < 0.001$). For the Skindex-16 Dermatology Survey, a statistically significant difference was seen with PEP005-treated patients less bothered by each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 ($p < 0.001$, each domain) and continued at Day 57 ($p < 0.001$, each domain).

Safety:

PEP005 Gel, 0.015% was, in general, well tolerated when applied once daily for three consecutive days. Compliance to the treatment regimen was 96% for the PEP005 Gel group and 100% for the vehicle gel group (ITT population).

No deaths occurred during the study. Four patients (two in each treatment group) experienced seven SAEs. In the PEP005 Gel group, one patient had Campylobacter infection and a small bowel obstruction and another patient had a meniscus tear and hypoxia. In the vehicle gel group, one patient had a multiple trauma injury and a pulmonary embolism and one patient had a vascular pseudoaneurysm. None of these events were considered related to study medication. Three patients discontinued the study or study medication due to adverse events. One PEP005 Gel patient discontinued study medication due to application site pain; this event was severe, definitely related, and resolved without sequelae. Two patients discontinued the study after applying all three doses of study medication. One PEP005 Gel patient experienced application site burning, eye pain, eye burning, and periorbital edema; all events were severe, the application site pain was considered definitely related to study medication and the other events were considered to be probably related to study medication. One vehicle patient experienced multiple trauma (explained above as an SAE) which resulted in study discontinuation.

Application site reactions were the most common treatment-related AEs reported for the PEP005 Gel patients, with pain and pruritus reported as the most frequent application site events. Application site infection occurred in five PEP005 Gel patients, all cases were first documented at Day 4, were considered mild in severity, and typically resolved within a week or two. Bleeding and discharge at the application site occurred in only 1 patient each. Other treatment-related events included headache, eye pain, conjunctivitis, and eyelid/periorbital edema, adjacent to the treatment area. The majority of treatment-related adverse events were mild or moderate in severity. Only three PEP005 Gel-treated patients (2%) experienced treatment-related events that were considered severe. In all cases, the treatment-related events resolved without sequelae.

The most common LSRs were erythema (100% for PEP005, 63% for vehicle), flaking/scaling (99% for PEP005, 73% for vehicle) and crusting (86% for PEP005, 29% for vehicle). Grade 4 LSRs were observed in approximately 30% of the PEP005 Gel group. Mean composite LSR scores (maximum score of 24) peaked at Day 4 for the PEP005 Gel group (9.47) and at Day 8 for the vehicle gel group (1.42); by Day 29, scores were lower than baseline levels. All LSRs resolved without sequelae.

Hypopigmentation and hyperpigmentation assessments remained unchanged from baseline at Day 57 in the majority of patients. Four patients (three PEP005 patients and one vehicle patient) had hypopigmentation or hyperpigmentation at Day 57 which was not present at baseline. One PEP005 patient with hypopigmentation required followup and was deemed clinically stable by the investigator on Day 80. No treatment emergent scarring was observed. No patients had confirmed abnormal proliferation within the treatment area during the study.

No clinically meaningful differences were observed between the treatment groups when actual and change from baseline values were assessed for hematology and serum chemistry tests, vital signs, and interval-valued ECG parameters. Results of physical examinations showed no clinically relevant findings.

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Conclusion:

The following conclusions are based on the results of this study:

- The treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days was shown to be effective in completely clearing a contiguous 25cm^2 treatment area of AK lesions on the head (face and scalp).
- Other efficacy endpoints provided confirmation of the treatment effect. The partial clearance rate was significantly higher in patients treated with PEP005 Gel and the median percent reduction from baseline in the number of AK lesions was substantially greater.
- Patient compliance with the treatment regimen was high; 96% of PEP005 Gel patients completed the full course of therapy.
- PEP005 Gel, 0.015%, in general, appeared to be safe and well-tolerated when used to treat AK lesions on the face and scalp. No serious adverse events were considered treatment-related. All treatment-related application site adverse events and local skin responses resolved without sequelae.

Final Report Date: 8 September 2010

PEP005-025

SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
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Title:
A multi-center, Randomized, parallel group, double-blind, vehicle-controlled study to evaluate the Efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.015% In patients with actinic keratoses ON the head (face or scalp) (REGION-IIb)

Investigators and Sites: Multicenter in the United States and Australia (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 05 June 2009
Last patient completed Day 57: 02 September 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.015%, compared to vehicle gel when administered once daily for three consecutive days to a contiguous 25 cm^2 area of skin on the head (face or scalp).

Methodology:
This was a multi-center, randomized, parallel group, double-blind, vehicle-controlled study.

Patients were randomized to receive treatment with PEP005 Gel, 0.015%, or vehicle gel once daily for three consecutive days. Study medication was patient-applied at home on Days 1, 2 and 3. Subsequent followup visits for safety assessments were conducted on Days 4, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (End of Study). Patient-reported treatment satisfaction was assessed on Day 57 and Quality of Life (QOL) assessments were conducted at baseline and on Days 8, 29 and 57. Patients completed the study on Day 57.

Poststudy followup visits were required every 7 to 28 days for all patients who had unresolved treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57. Patients were to be followed until either resolution or assessed as clinically stable. Patients with unresolved hypopigmentation or hyperpigmentation and/or scarring greater than baseline were required to undergo further poststudy followup every 28 days until resolution or for a period of six months postbaseline (an additional four visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: Approximately 250 patients (125 per treatment arm) were planned for enrollment.

Analyzed: A total of 278 patients were randomized (142 to PEP005 Gel 0.015% and 136 to vehicle gel); 277 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 266 patients were included in the per-protocol (PP) population. The safety population included 278 patients.

Diagnosis and Main Criteria for Inclusion:
Male or female patients at least 18 years of age with four to eight clinically typical, visible and discrete actinic keratosis (AK) lesions within a contiguous 25 cm^2 treatment area on the head (face or scalp).

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:
Test product: PEP005 Gel, 0.015% (Lot BBX-C).

Reference therapy: Vehicle gel (Lots BCA-C and BCA-1C).

Study medication was packaged individually for each patient in a study medication kit containing three unit-dose tubes. Each unit-dose tube contained PEP005 Gel 0.015% or vehicle gel.

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Duration of Treatment:

Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1, 2 and 3.

Randomization Scheme:

Patients were randomized centrally to treatment in a 1:1 ratio through an interactive voice / web response (IVR/IWR) system. Randomization was stratified by investigational site and by the location of the treatment area (face or scalp). Enrollment was controlled so that approximately 20% of patients were treated on the scalp and approximately 80% of patients were treated on the face. The IVR/IWR system assigned a study medication kit number for each patient randomized into the study.

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

Complete clearance rate of AK lesions at the Day 57 visit. A patient with no clinically visible AK lesions in the selected treatment area was defined to have complete clearance.

Secondary Endpoint:

Partial clearance rate of AK lesions at the Day 57 visit. A patient with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline, in the selected treatment area was defined to have partial clearance.

Additional Endpoint:

The percent change from baseline to Day 57 in the total number of AK lesions.

Exploratory:

Patient-reported outcomes, including the Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

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 clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

Statistical Methods:

The primary efficacy analysis was based on the intent-to-treat (ITT) population. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

For the analyses of complete and partial clearance, all missing values were imputed using last observation carried forward (LOCF). Baseline data were carried forward if no postbaseline data existed for the patient. That is, those patients were considered to have not achieved complete or partial clearance.

The safety analysis was based on the safety population, which was defined as all randomized patients who received at least one dose of study medication and had at least one postbaseline safety evaluation. In the safety population, patients were analyzed according to the actual treatment received.

All treatment comparisons were tested with two-tailed tests and a 0.05 significance level.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume:	
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Efficacy:

The primary efficacy endpoint was complete clearance rate at Day 57 of all clinically visible AK lesions in the selected treatment area. The complete clearance rate was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. The secondary efficacy endpoint was the partial clearance rate of AK lesions at Day 57. The statistical analysis 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 percent change from baseline in the number of AK lesions was summarized for each treatment group. Summaries were also provided by each anatomical location.

Patient-Reported Outcomes:

The TSQM transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at baseline and Days 8, 29, and 57 were summarized by treatment group. The transformed scores were treated as a continuous variable and analyzed using analysis of variance (ANOVA) with treatment, anatomical location, and analysis site as factors to test for treatment effect.

Safety:

The safety endpoints included: incidence rate of patients who experienced AEs, SAEs and AEs leading to discontinuation of study medication; incidence and grade of LSRs and/or pigmentation/scarring; changes in clinical laboratory tests, vital signs, physical examinations, and ECG findings. The treatment effect was explored by inspection of observed means or rates for the treatment groups.

Summary of Results:

Efficacy:

The primary efficacy endpoint was complete AK lesion clearance overall (face and scalp combined) at Day 57. The PEP005 Gel group demonstrated a statistically significant, higher complete clearance rate versus vehicle gel (47% compared to 5%, $p < 0.001$, CMH test stratified by analysis site) based on the ITT population. The results for the PP population were consistent with the results for the ITT population. Patients treated on the face with PEP005 Gel demonstrated a statistically significant, higher complete clearance rate compared to vehicle gel-treated patients (52% versus 5%, $p < 0.001$, Fisher's Exact test). For scalp-treated patients, the difference between the treatment groups was also statistically significant (29% versus 4%, $p = 0.031$, Fisher's Exact test).

The secondary efficacy endpoint was partial (≥ 75% reduction) AK lesion clearance at Day 57. Consistent with the primary endpoint, the PEP005 Gel group demonstrated a statistically significant, higher partial clearance rate versus vehicle gel (68% compared to 8%, $p < 0.001$, CMH test stratified by analysis site) based on the ITT population. The results for the PP population were consistent with the results for the ITT population. Patients treated on the face with PEP005 Gel demonstrated statistically significant, higher partial clearance rates than vehicle gel patients (74% versus 9%, $p < 0.001$, Fisher's Exact test). For scalp-treated patients, the difference between the treatment groups was also statistically significant (45% versus 4%, $p < 0.001$, Fisher's Exact test).

The median percent reduction in the number of AK lesions compared to baseline overall (face and scalp combined) was substantially greater for the PEP005 Gel group (87%) versus 0% in the vehicle group. For patients treated on the face, the median reduction was 100% for the PEP005 Gel group versus 0% in the vehicle group. For patients treated on the scalp, the median reduction was 63% for the PEP005 Gel group versus 0% in the vehicle group.

In the subgroup analyses, the complete clearance rate for each treatment group was analyzed by geographic region (US or AUS), gender, age group (<65 or ≥65 years), baseline AK lesion count (4, 5, 6 or 7, 8), skin type (Fitzpatrick I/II or III/IV/V/VI), and analysis site. Findings showed a higher complete clearance rate for PEP005 Gel-treated patients compared to vehicle patients in each category; the only category that did not show statistical significance was the geographic region of Australia.

Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey. Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group compared to the vehicle gel group ($p < 0.001$). For the Skindex-16 Dermatology Survey, a statistically significant

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difference was seen with PEP005 Gel-treated patients less bothered by each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 ($p < 0.001$, each domain) and continued at Day 57 ($p < 0.001$, each domain).

Safety:

PEP005 Gel, 0.015% was, in general, well tolerated when applied once daily for three consecutive days. Compliance to the treatment regimen was 99% for the PEP005 Gel group and 100% for the vehicle gel group.

No deaths occurred during the study. One patient in the PEP005 Gel group experienced two serious adverse events (hip arthroplasty and myocardial infarction); both were considered by the investigator to be not related to study medication. Two patients who received PEP005 Gel discontinued study medication due to application site reactions. One patient experienced pain and stinging which started on Day 1, and was considered by the investigator to be severe and definitely related to study medication. The patient applied study medication for two days. The adverse event resolved without sequelae on Day 7. The other patient experienced burning and pruritus which started on Days 1 and 2, respectively. Both events were considered by the investigator to be moderate and definitely related to study medication. The patient only applied study medication for one day. The burning resolved without sequelae on Day 3 and the pruritus resolved without sequelae on Day 7.

Application site reactions were the most common treatment-related AEs reported for the PEP005 Gel patients, with pain and pruritus reported as the most frequent application site events. Application site infection occurred in two PEP005 Gel patients, each case was first documented at Day 4, considered mild in severity, and resolved within 4 days. Paresthesia at the application site occurred in two patients and discomfort, discharge, and swelling at the application site occurred in only one patient each. Other treatment-related events included eyelid oedema, eye oedema, and periorbital edema. The majority of treatment-related adverse events were mild or moderate in severity. Only one PEP005 Gel-treated patient (1%) experienced two treatment-related events that were considered severe (pain and stinging at the application site which led to discontinuation of study drug). All treatment-related events resolved without sequelae.

The most common LSRs were erythema (99% for PEP005, 72% for vehicle), flaking/scaling (97% for PEP005, 62% for vehicle) and crusting (82% for PEP005, 10% for vehicle). Grade 4 LSRs were observed in 25% of the PEP005 Gel group. Mean composite LSR scores (maximum score of 24) peaked at Day 4 with a score of 8.08 for the PEP005 Gel group and 1.17 for the vehicle gel group; by Day 29, scores were lower than baseline levels. All LSRs resolved without sequelae.

Hypopigmentation and hyperpigmentation assessments remained unchanged from baseline at Day 57 in the majority of patients. Five patients (one PEP005 patient and four vehicle patients) had hypopigmentation or hyperpigmentation at Day 57 which was not present at baseline. No treatment emergent scarring was observed. One patient in the vehicle group had abnormal proliferation in the treatment area which was noted on Day 57. The lesion was excised on Day 99 and confirmed to be basisquamous carcinoma which was recorded as an adverse event. No further followup was necessary.

No clinically meaningful differences were observed between the treatment groups when actual and change from baseline values were assessed for hematology and serum chemistry tests, vital signs, and interval-valued ECG parameters. Results of physical examinations showed no clinically relevant findings.

Conclusion:

The following conclusions are based on the results of this study:

- The treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days was shown to be effective in completely clearing a contiguous 25cm^2 treatment area of AK lesions on the head (face and scalp).
- Other efficacy endpoints provided confirmation of the treatment effect. The partial clearance rate was significantly higher in patients treated with PEP005 Gel and the median percent reduction from baseline in the number of AK lesions was substantially greater.

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- Patient compliance with the treatment regimen was high; 99% of PEP005 Gel patients completed the full course of therapy.
- PEP005 Gel, 0.015%, in general, appeared to be safe and well-tolerated when used to treat AK lesions on the face and scalp. No serious adverse events were considered treatment-related. All treatment-related application site adverse events and local skin responses resolved without sequelae.

Final Report Date: 8 September 2010

2 SYNOPSIS

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005)	
Title of Study: A Multi-center, Randomized, Double-blind, Double-dummy, Vehicle-controlled Sequential Cohort Study to Determine the Safety of PEP005 0.025% and 0.05% Topical Gel in Patients With Actinic Keratoses	
Investigators: Multi-center study (22 US investigators)	
Study Centers: Multi-center study (22 US centers)	
Study Period: 11 September 2006 to 19 June 2007	**Clinical Phase:** Phase IIb
Publications: None	

Objectives:

The primary objectives of this study were as follows:

- To evaluate the safety and tolerability of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel, administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous actinic keratoses (AK) treatment area.
- To evaluate the efficacy of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel when administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous AK treatment area.
  - To determine the *partial clearance rate* defined as the proportion of patients at the Day 57 post-treatment visit with a 75% or greater reduction in the number of AK lesions identified at baseline, in the selected AK treatment area.

The secondary objectives of the study were the following:

- To further evaluate the efficacy of 0.025% and 0.05% PEP005 Topical Gel compared to vehicle gel when administered according to 2 treatment schedules, Day 2 and Day 3 (0.05%) or Day 1, Day 2, and Day 3 (0.025% and 0.05%) to a 25-cm^2 contiguous AK treatment area.
  - To determine the *baseline clearance rate*, defined as the proportion of patients at Day 57 post-treatment visit with 100% reduction in the number of AK lesions identified at baseline in the selected AK treatment area.
  - To determine the c*omplete clearance rate*, defined as the proportion of patients at the Day 57 post-treatment visit with no clinically visible AK lesions in the selected AK treatment area.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel	

Name of active ingredient:
3-angeloyl ingenol (PEP005)

Methodology:
This was a multi-center, double-blind, double-dummy, vehicle-controlled, sequential cohort study to determine the safety and tolerability of 0.025% and 0.05% PEP005 Topical Gel in patients with AK lesions. The study included 2 treatment phase cohorts. During Treatment Phase 1, patients were randomly assigned to 1 of 3 treatment groups: vehicle gel applied on Days 1, 2, and 3; 0.025% PEP005 Topical Gel applied on Days 1, 2, and 3; or vehicle gel applied on Day 1 and 0.05% PEP005 Topical Gel applied on Days 2 and 3. After all patients enrolled in Treatment Phase 1 reached Day 29, an independent Data Monitoring Committee (DMC) reviewed safety data from these patients, including the frequency and severity of local skin response (LSR), global severity rating (GSR), and treatment-emergent adverse events (TEAEs). Based on these safety results, the DMC recommended continued enrollment of new patients into Treatment Phase 2. During Treatment Phase 2, the 0.025% PEP005 Topical Gel dose was eliminated and patients were randomly assigned to 1 of the 3 following treatment groups: vehicle gel applied on Days 1, 2, and 3; vehicle gel applied on Day 1 and 0.05% PEP005 Topical Gel applied on Days 2 and 3; or 0.05% PEP005 Topical Gel applied on Days 1, 2, and 3.

The duration of the study for each patient was approximately 71 days, including a screening period of up to 14 days, treatment period of 3 days (Day 1, Day 2, and Day 3), and an observation period comprising 4 post-treatment follow-up visits (Day 8, Day 15, Day 29, and Day 57). Additional follow-up visits beyond Day 57 were conducted every 7 to 28 days for patients who had unresolved TEAE, LSR (other than pigmentation or scarring), or GSR, that were not stable, until the TEAE, LSR or GSR resolved or was assessed as being clinically stable by the investigator. Additional follow-up visits were also conducted every 28 days for patients who had unresolved treatment-emergent pigmentation (hypo/hyper) or scarring until resolution of the event, or for a period of 6 months post-treatment (4 additional visits).

Number of Patients:
The total number of patients planned was approximately 200 with 100 patients enrolled into each treatment phase. A total of 222 patients were enrolled in the study.

Diagnosis and Main Criteria for Inclusion:
Male and postmenopausal female patients who were at least 18 years of age with 4 to 8 clinically typical, visible and discrete AK lesions within a contiguous 25-cm^2 treatment area on the arm, shoulder, chest, back, or scalp.

Dosage, Administration, and Duration of Treatment:
PEP005 Topical Gel (250 µL) at concentrations of 0.025% and 0.05% or vehicle gel was applied to the AK treatment area as shown below:

Treatment Phase 1: 3 dosing groups:

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

Treatment Phase 2: 3 dosing groups:

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

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005)	

Criteria for Evaluation:

Safety:

Safety variables evaluated at each post-treatment visit were as follows:

- Incidence of adverse events (AEs);
- Incidence rate and grade of local skin responses (LSR) (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, scarring) using the LSR Grading Scale and the overall severity rating (none, mild, moderate, or severe) of the response to treatment using the global severity rating (GSR) Scale;
- Changes in 8-hour fasting hematology, serum chemistry, and urinalysis test results; and
- Changes in vital sign measurements and physical examination findings during the study.

Efficacy:

Clinical response to treatment with PEP005 Topical Gel was determined at each post-treatment visit by assessing the clearance of AK lesions identified at baseline (presence/absence), assessing the number of subclinical lesions appearing/emerging that were not clinically identifiable at baseline within the selected treatment area, and assessing patient satisfaction of treatment outcome at Day 57.

Statistical Methods:

Summary statistics were performed on all baseline, demographic, and safety parameters. Demographic and baseline data were presented globally for the All-Patients-Treated population (APT). Drug exposure and compliance was summarized descriptively for the APT Population. All safety analyses were presented for the APT. The incidence and severity of LSR were analyzed using the chi-square test. The 95% confidence intervals (CIs) were determined using the binomial approximation to the normal distribution. Adverse events were summarized for number and percentage of patients with any TEAE, serious adverse event (SAE), discontinuation due to AE, drug-related and severe AEs were analyzed using the chi-square test. Changes from baseline in vital signs and laboratory parameters were analyzed using analysis of variance (ANOVA). The National Cancer Institute Common Toxicity Criteria grade was determined and a summary listing of significant out-of-reference range clinical laboratory results were determined for selected laboratory parameters.

Efficacy endpoints were analyzed for the modified Intent-to-Treat (mITT) Population with a Per Protocol (PP) Population as supplemental information for the primary and secondary efficacy endpoints. The chi-square test was used to analyze complete AK clearance, baseline AK lesion clearance, and partial clearance rate at end of study. The 95% CIs were determined using binomial approximation to the normal distribution. Median percentage reduction was analyzed across treatment groups using the Kruskal-Wallis test and between treatment groups using the Wilcoxon Rank Sum test. The time to initial complete AK lesion clearance was estimated by the Kaplan-Meier product-limit method.

This study was statistically powered (80% power, alpha of 0.05 significance level) to evaluate a comparison in severe GSR incidence rates between the PEP005 Topical Gel (active) doses and vehicle gel.

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Summary - Conclusions:

Safety Results:

Overall, the incidence of treatment-emergent AEs was higher in the PEP005 Topical Gel treatment groups (36.4% to 46.0% of patients) compared to the vehicle gel group (21.7%). The most common TEAEs in the PEP005 Topical Gel treatment groups were application site pruritus, pain, and irritation. No patients in the vehicle gel group had application site pain or irritation. An apparent dose response of treatment-related AEs was observed, with a higher incidence of treatment-related AEs with increasing dose. All of PEP005 Topical Gel treatment-related TEAEs resolved during the study. There were no deaths and no patients were discontinued from the study due to an AE. Twelve patients had a total of 16 SAEs; none of which were considered to be related to study treatment.

The composite mean LSR scores peaked between Day 3 and Day 8 and were largely resolved by Day 15. The most common LSR observed was erythema, followed by flaking/scaling and crusting, reported for 96.9%, 96.3%, and 82.1% of patients, respectively, in the combined PEP005 Topical Gel treatment groups on Day 8. By Day 29, the proportion of patients with LSRs that had returned to their baseline (Day 1 predose) level or below, with the exception of erythema which was still seen in 60.5% of patients, was comparable to a baseline level of 33.3%. By Day 57 the proportion of patients with erythema had also decreased to the baseline level.

The mean duration in days for Grade 2 or higher LSRs was similar across all treatment groups for LSRs. Erythema, flaking/scaling, and crusting had mean ranges of between 11.2 to 17.8 days. Vesiculation/pustulation ranged from a mean duration of 7.0 to 9.0 days, and erosion/ulceration ranged from 8.0 to 9.8 days. The mean duration of Grade 2 and above pigmentation was longer for patients in the 0.05% for 2 days group (18.0 days) compared with the 0.025% (8.0 days) and 0.05% for 3 days group (8 days). No patients in the vehicle gel group had Grade 2 and above swelling, vesiculation/pustulation, erosion/ulceration, and no patients in any treatment group had Grade 2 or higher scarring.

A decrease in pigmentation from predose to Day 57 was seen in each treatment group. About 5% of the patients on the 0.05% PEP005 concentration had worsened pigmentation on Day 57 than predose. Scarring was present in only 6 patients at predose. Three of these were in the vehicle gel group. All were Grade 1. By Day 57 the scarring had disappeared in 2 of the patients on PEP005 and 1 patient on vehicle gel.

In the majority (>80%) of patients, the highest GSR was mild to moderate. The most frequent GSR reported in the active treatment groups at Day 3 was mild – [88 patients (54.3%)]. At Day 8, moderate was the most frequently reported GSR, [78 patients (48.1%)]. Fourteen patients (8.6%) at the Day 8 visit had a severe GSR. At Day 15 there was a significant reduction in the number of patients having a moderate or severe GSR [27 (16.7%) and 1 (0.6%), respectively]. By Day 57, the GSRs had returned to baseline or lower.

The magnitude of LSRs and GSRs exhibited within the treatment groups showed a clear dose response relationship.

The application of all 3 daily doses of PEP005 Topical Gel was achieved for 74% of patients in the highest PEP005 Topical Gel dose group (0.05% for 3 days) and 88% of patients in the lowest PEP005 Topical Gel dose group (0.025%). Two consecutive daily doses of PEP005 Topical Gel were achieved in 96% of patients at the highest PEP005 Topical Gel dose level and lowest PEP005 Topical Gel dose level.

No trends of clinical concern regarding clinical laboratory results, vital signs, or physical examination findings were observed during the study.

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Efficacy Results:

A statistically significant difference in partial clearance rate (≥75%) was observed for patients treated with PEP005 Topical Gel compared with vehicle gel. The partial clearance rate for patients treated with PEP005 Topical Gel ranged from 56.0% to 75.4% compared with vehicle gel (21.7%) ($p = 0.0002$ to $p < 0.0001$). This ≥75% clearance of baseline AK lesions was statistically significant across all dose levels ($p < 0.0001$).

Baseline clearance rate was statistically significantly higher ($p \leq 0.0007$) in the PEP005 Topical Gel treatment groups (range: 42.0% to 57.9% of patients) compared with the vehicle gel group (13.3% of patients). Baseline clearance rate was statistically significant across all dose levels ($p < 0.0001$).

Complete clearance rate was also statistically higher ($p \leq 0.0006$) for patients in the PEP005 Topical Gel treatment groups (range: 40.0% to 54.4%) compared with vehicle gel (11.7%). Complete clearance rate was statistically significant across all dose levels ($p < 0.0001$).

The median percent reduction in the number of AK lesions was statistically significantly higher ($p < 0.0001$) in the PEP005 Topical Gel treatment groups (range: 75.0% to 100.0%) compared with vehicle gel (0.0%) and was statistically significant across all dose levels and the majority of patients had lesion clearance between Day 29 and Day 57. Overall, the proportion of patients with emergent subclinical AK lesions was low (≤8.3%) across treatment groups and study visits.

Patient impression of treatment, assessed using a 1 to 7 Likert Scale with 7 the most positive and 1 most negative, demonstrated a median overall patient level of satisfaction score of 7.0 for all 3 PEP005 Topical Gel treatment groups, while the overall median score of patient satisfaction was 4.0 for patients in the vehicle gel group.

Conclusions:

PEP005 Topical Gel was safe and well tolerated when applied for up to 3 days as a field treatment to an area of skin on the arm, shoulder, chest, back, or scalp containing AK lesions. Local skin responses occurred with PEP005 Topical Gel treatment and were transient. There was no treatment-emergent scarring. All PEP005 Topical Gel treatment groups showed significant benefit when compared with vehicle gel in the clearance of AK lesions, and there was a dose response relationship across the PEP005 Topical Gel treatment groups. In addition, a high overall patient level of satisfaction with all 3 PEP005 Topical Gel treatment groups was demonstrated.

Date of Report: 10 March 2008

2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd **Name of Finished Product**: PEP005 (ingenol mebutate) Gel	**Individual Study Table Referring to Part of the Dossier** **Volume:**	***(For National Authority Use only)***
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Title:
A multicenter, randomized, double-blind, vehicle-controlled, dose-ranging study to evaluate the safety and efficacy of 0.005%, 0.01% and 0.015% PEP005 Topical Gel when used to treat actinic keratoses on the head (face or scalp)

Investigators and Sites: Multicenter in the United States and Australia (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 24 June 2008
Last patient completed Day 57: 20 October 2008

Phase of Development: 2

Objectives:

The primary objectives of the study were to evaluate the safety, toleration, and efficacy of PEP005 Gel, 0.005%, 0.01%, and 0.015%, compared to vehicle gel, administered once daily as either a two or three consecutive day treatment regimen, to a 25 cm^2 contiguous actinic keratoses (AK) treatment area on the face or scalp as measured by the following:

Primary safety and tolerability variables:

- Incidence of adverse events (AEs) and serious adverse events (SAEs) recorded throughout the study;
- Incidence and severity (i.e., grade) of local skin responses (LSRs), and incidence of pigmentation and scarring following study medication application; and
- Dosing compliance/tolerability, defined as the proportion of patients completing assigned treatment regimen (two or three day treatment).

Primary efficacy variable:

- Complete clearance rate, defined as the proportion of patients at the Day 57 visit with no clinically visible AK lesions in the selected treatment area.

The secondary objective of the study was to evaluate the efficacy of PEP005 Gel, 0.005%, 0.01%, and 0.015%, compared to vehicle gel, administered once daily as either a two or three consecutive day treatment regimen, to a 25 cm^2 contiguous AK treatment area on the face or scalp as measured by the following:

Secondary efficacy variable:

- Partial clearance rate, 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.

Methodology:

This was a multicenter, randomized, double-blind, vehicle-controlled, dose-ranging study.

Patients were screened and randomized to one of three PEP005 Gel concentrations (0.005%, 0.01%, 0.015%) or vehicle gel and were treated once daily for either two or three consecutive days. Patients were evaluated on the basis of safety, tolerability, and efficacy for 57 days following study treatment. Patient satisfaction with treatment and quality of life were also evaluated at time points throughout the study.

Poststudy followup visits were required if patients had unresolved, treatment-related adverse events, LSRs, pigmentation and/or scarring at Day 57.

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Number of Patients (Planned and Analyzed):
Approximately 240 patients were planned for enrollment (30 patients per treatment group; eight treatment groups). A total of 265 patients were randomized and 260 patients completed the study. All randomized patients were included in the intent-to-treat (ITT) population; 250 patients were included in the per-protocol (PP) population. The safety population included 264 patients.

Diagnosis and Main Criteria for Inclusion:
Male or female patients at least 18 years of age with four to eight clinically typical, visible, and discrete AK lesions within a contiguous 25 cm^2 treatment area on the face or scalp.

Dosage, Administration and Duration of Treatment:
Study medication was supplied as: PEP005 Gel, 0.005%, 0.01%, 0.015%, and vehicle gel.

One lot of study medication was used for each concentration of PEP005 Gel and for vehicle gel. The following lots were used: ZMAB-C (vehicle); AEG-C (0.005%), AHB-C (0.015%); and ADB-C (0.01%).

Study medication was packaged individually for each patient in a study medication kit containing two or three unit-dose-tubes. Each tube contained PEP005 Gel or vehicle gel. Study medication was applied topically to the selected treatment area by the patient, at home, once daily on Days 1 and 2 or Days 1, 2, and 3, as directed by the Investigator.

Randomization Scheme:
Patients were assigned to a treatment group by an Interactive Voice Response/Interactive Web Response (IVR/IWR) system. Patients were randomized centrally, to treatment in a 1:1:1:1:1:1:1:1 fashion and were stratified across treatment groups (as per the table below) based on location of AK lesions on the head (i.e., face or scalp). Enrollment was controlled so that approximately 20% of the patients enrolled were treated on the scalp and approximately 80% of the patients enrolled were treated on the face.

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

Statistical Methods and Criteria for Evaluation:
The primary efficacy analyses were based on the PP population. The PP population included patients without major protocol violations; patients were analyzed according to the actual treatment received. Secondary analyses were based on the ITT population, defined as all patients randomized; patients were analyzed according to the treatment to which they were randomized.

The safety analyses were based on the safety population. The safety population included patients who received at least one dose of study medication; patients were analyzed according to the actual treatment received.

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For the analyses of the efficacy variables and LSRs, all missing values due to patient early termination from the study were imputed using the last observation carried forward (LOCF) method. For each patient, the baseline values were defined as those values recorded at Day 1 prior to dosing or screening, as appropriate.

All hypotheses were tested for statistical significance with two-tailed tests. Results of all tests were considered statistically significant if their p-value was less than or equal to 0.05, with the exception of Hochberg's multiple comparison procedure. Results of Hochberg's multiple comparisons were considered statistically significant if the p-value was less than or equal to 0.05, 0.025, or 0.0167, according to the procedure.

Efficacy: The primary efficacy endpoint was the *complete clearance rate* of AK lesions at Day 57. A Cochran-Mantel-Haenszel (CMH) test, adjusting for treatment area (face, scalp), was used to test for treatment effect. The secondary efficacy endpoint was the *partial clearance rate* of AK lesions at Day 57. The statistical analysis was the same as the one used for the primary efficacy endpoint.

Dose effect was explored by inspection of observed means or rates for the PEP005 Gel and vehicle gel groups within each treatment regimen.

Safety: The primary safety endpoints were the rates of patients who had (1) one or more AEs; (2) SAEs; and (3) AEs leading to discontinuation of study medication; the percentage of patients who had one or more LSRs and severity of responses and/or pigmentation and scarring; and patient compliance/tolerance to the regimen. Other safety endpoints of interest were laboratory results and vital sign measurements.

Patient Reported Outcomes: The results were summarized for the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Skindex-16 Dermatology Survey. The derived scores were analyzed using an analysis of variance (ANOVA) to test for treatment effect.

Summary of Results:

Efficacy Results

The primary efficacy endpoint was complete AK lesion clearance on the face and scalp at Day 57. Five of the six PEP005 Gel groups demonstrated statistically significant, higher complete clearance rates versus vehicle gel (CMH test corrected for multiple comparisons) based on both the PP and ITT populations.

Observed complete clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed complete clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 15% in the 0.005% two-day group to 50% in the 0.015% three-day group. The trends for complete clearance rates on the face and scalp, assessed separately, were similar to those observed for the face and scalp combined. Complete clearance rates for scalp-treated patients were lower compared to face-treated patients; however, the sample sizes were small (< 10 patients per group). Similarly, data trends toward concentration and treatment-regimen dependence were weaker than those for face-treated and combined face and scalp-treated patients.

The secondary efficacy endpoint was partial (≥ 75% reduction) AK lesion clearance at Day 57. Five of the six PEP005 Gel groups demonstrated statistically significant, higher partial clearance rates versus vehicle gel (CMH test corrected for multiple comparisons) based on both the PP and ITT populations. Partial clearance rates were concentration and treatment regimen-dependent with the highest observed complete clearance rates in the 0.015% two-day and three-day groups. The observed partial clearance rates for PEP005 Gel at Day 57 for the ITT population ranged from 33.3% in the 0.005% two-day group to 71.9% in the 0.015% three-day group. Similar to what was observed for complete clearance rates, when separated by anatomic treatment location (face and scalp), the partial clearance rates trended toward concentration and treatment-regimen dependence.

The percent changes in number of AK lesions for the face and scalp combined were also concentration and treatment regimen-dependent, with the greatest median percent reduction seen in the 0.015% three-day group

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(84.5%). Median percent reduction in number of AK lesions was also similar when face-treated and scalp-treated patients in the 0.015% three-day group were analyzed separately (87.5% and 80.0%, respectively).

While study results support a concentration and treatment regimen-dependent relationship across the eight treatment groups, complete and partial clearance rates and median percent reduction in number of AK lesions in the 0.01% three-day treatment group were lower compared to other PEP005 Gel three-day groups. Statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were shown for all PEP005 Gel groups, relative to vehicle gel; the mean satisfaction scores were highest in the 0.01% and 0.015% two-day groups, followed by the 0.01% and 0.015% three-day groups. No statistically significant differences from vehicle gel were noted for the three domains (symptoms, emotions, and functioning) of the Skindex-16 Dermatology Survey for the face and scalp at Day 57.

In the subgroup analyses, there were statistically significant differences in both the complete clearance and partial clearance rates for the following subgroups: females had higher rates than males (complete clearance, $p = 0.0054$; partial clearance, $p = 0.0142$) and patients with ≤ six baseline lesions had higher rates than patients with ≥ seven baseline lesions (complete clearance, $p = 0.0067$; partial clearance, $p = 0.0172$). Additionally, the face demonstrated a statistically significant, higher partial clearance than the scalp ($p = 0.0141$). There were no other statistically significant differences in complete or partial clearance rate for any of the other subgroups: age, Fitzpatrick skin type, or geographic location.

Safety Results

PEP005 Gel was well tolerated when applied once daily for two or three consecutive days. Overall, the compliance to the treatment regimen, for all treatment groups was 97.4% (258 of 265 patients).

Three patients had four SAEs (fever in one patient not randomized; gastroesophageal reflux and muscle strain in one patient; and death due to coronary artery atherosclerosis and hypertension in one patient). None of these events were considered related to study medication.

Application site reactions were the most common treatment-related AEs reported. Irritation and pruritus at the application site were most common, followed by application site discomfort, swelling, and pain. A lower percentage of patients in the two-day groups had application site reactions than in the three-day groups. In all cases, the treatment-related events resolved without any sequelae.

LSRs (grade 0-4) were assessed at baseline, Day 1 (pre-dose), and each subsequent study visit for the presence and grade (0 to 4) of the following LSRs: erythema, flaking/scaling, crusting, swelling vesiculation/pustulation, and erosion/ulceration. A composite LSR score (0 to 24), reflecting the sum of each individual LSR grade, was calculated for each patient at each visit. The most common LSRs for all patients were flaking/scaling, erythema, and crusting. Grade 4 LSRs were reported primarily in the 0.015% three-day group, and all Grade 4 LSRs resolved to baseline levels or lower by Day 57, except for one patient (Patient [redacted] who had Grade 3 erythema and flaking/scaling at Day 57.

Mean composite LSR scores were concentration and treatment-regimen dependent with a peak score occurring at Day 4 in all PEP005 Gel groups. The highest peak mean composite LSR score (9.8) was observed in the 0.015% three-day group. Mean composite LSR scores returned to baseline levels or lower by Day 57.

No apparent differences were observed in peak mean LSR scores between face-treated and scalp-treated patients; however, peak mean composite LSR scores were higher for the face than they were for the scalp. Regardless of peak scores, the mean LSR scores for both the face and scalp returned to baseline grade or better at Day 57.

Pigmentation (hyperpigmentation and hypopigmentation) assessments remained unchanged from baseline in 75% of patients. None of the cases of pigmentation were considered clinically important by the Investigator.

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Scarring assessments remained unchanged from baseline in 99% of patients. Scarring improved in all three patients (< 1%) with changes in scarring compared to baseline assessments.

No patients had abnormal proliferation within the treatment area during the study. Administration of PEP005 Gel had no apparent impact on laboratory tests or vital sign values.

Conclusion:

PEP005 Gel, at a concentration of 0.01% once daily for two consecutive days and at a concentration of 0.015% once daily for two or three consecutive days, demonstrated statistically significant and clinically meaningful improvements in complete clearance of AK lesions on the face and scalp compared to vehicle gel. The median number of AK lesions was reduced with all PEP005 Gel concentrations and regimens tested with the highest reduction in the 0.015% two-day and three-day groups.

Efficacy results for treatment on the face and scalp separately were consistent with what was seen for both the face and scalp combined, with generally lower clearance rates and smaller magnitudes of percent reduction in number of AK lesions for the scalp compared to the face.

Safety and efficacy appear to be concentration and treatment regimen-dependent.

At all treatment regimens evaluated (0.005%, 0.01%, and 0.015% applied once daily for two or three consecutive days), PEP005 Gel appears safe and well-tolerated when used to treat AK lesions on the face or scalp.

Final Report Date: 14 September 2009

2 SYNOPSIS

Name of company: Peplin Operations Pty Ltd	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol		
Title of Study: A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to actinic keratoses		
Investigators: Prof R. Barnetson[1]; Dr P. Cowen[2]; Dr P. Foley[3]; Dr C. Quirk[4]; Dr K. Gebauer[5]; Dr .G. Siller[6]; Dr. L. Spelman[7]		
Study Centers: [1]Sydney, New South Wales, Australia ; [2]Clayton, Victoria, Australia; [3]East Melbourne, Victoria, Australia; [4]Fremantle, Western Australia; [5]Fremantle, Western Australia; [6]Brisbane, Queensland, Australia; [7]Brisbane, Queensland, Australia		
Study Period: First patient entered: 17 March 2005 Last patient completed: 14 October 2005	**Clinical Phase:** Phase IIa	
Publications: None		
Objectives: The primary objective of the study was to determine the safety of PEP005 Topical Gel at 0.0025%, 0.01%, and 0.05% administered as two applications to patients with actinic keratosis (AKs) on the arms, shoulders, chest, face, and/or scalp under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. The secondary objectives of the study were the following: • to evaluate the efficacy of PEP005 0.0025%, 0.01% and 0.05% Topical Gel administered under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8 • to determine a recommended treatment regimen for AK • to evaluate patients for cosmetic outcome		
Methodology: This was a multi-center, double-blind, randomized, vehicle-controlled, parallel-group comparison of two treatment schedules, Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B) of three concentrations (0.0025%, 0.01%, and 0.05%) of PEP005 Topical Gel in patients with at least five AK lesions located on the arms, shoulders, chest, face, and/or scalp. All patients were required to have confirmed AK by punch biopsy of one representative lesion prior to study entry. Punch biopsy specimens were read by a central reviewer. Patients were screened for study entry, and after randomization to Treatment Arm A or B, were assessed for safety and efficacy at visits occurring on Days 2, 8, 15, 29, 57, and 85 following the last day of study drug application. Additional, post-Day 85 safety visits were allowed to confirm adequate healing of the punch biopsy areas or resolution of any ongoing local skin adverse events (AEs).		

Name of company: Peplin Operations Pty Ltd	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
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Name of active ingredient: 3-angeloyl ingenol		
Number of Patients: The number of patients planned was approximately 60. A total of 72 patients were screened, 63 were randomized and analyzed for efficacy, and 58 were analyzed for safety.		
Diagnosis and Main Criteria for Inclusion: Adults with at least five individual AK lesions on the arm, shoulders, chest, face, and/or scalp.		
Dosage, Administration, and Duration of Treatment: Test Product: Two single applications of PEP005 Topical Gel (at a concentration of 0.0025%, 0.01%, or 0.05%) were applied directly to each of the selected lesions on Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B) using a positive displacement micropipette. The volume of study gel applied to each lesion was based on the longest lesion diameter as measured on Day 1, 10 µL for lesions <10 mm and 20 µL for lesions ≥10 mm. Reference Therapy: Study vehicle gel was applied according to the guidelines used for active study gel. Duration of Treatment: Patients received 2 single applications of study gel applied to each of the selected lesions on Day 1 and Day 2 (Treatment Arm A) or Day 1 and Day 8 (Treatment Arm B).		
Criteria for Evaluation: **Efficacy:** All randomized patients were evaluated for efficacy, regardless of whether or not treatment was received or administered (Intent-to-Treat [ITT] population). The histological clearance of each individual lesion was determined by assessing the extent of AK lesion clearance based on the histology results from Day 85 for patients included in the ITT population. Clinical response to treatment of each selected lesion was evaluated at each scheduled visit until End of Study (Day 85) for patients included in the mITT population. Clinical response was evaluated as: complete clearance (100% improvement, no evidence of residual disease), marked clearance (50% to 90% improvement), slight clearance (10% to 50% improvement), unchanged (±10%), worsened (clinically observable growth), or unable to be assessed (e.g., heavy scabbing, bruise, trauma, inflammatory response). Photographs were taken of AK lesions before application of study treatment at pre-dose on Day 1 and again at End of Study (Day 85) and Investigators assessed the cosmetic outcome of study treatment at End of Study (Day 85) using the photographs taken at the Day 1 visit as a reference. Cosmetic outcomes of lesional and perilesional skin were assessed at Day 85, in terms of skin texture, skin markings, scarring, skin atrophy, hypopigmentation and hyperpigmentation for patients included in the mITT population.		

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Safety (mITT): All patients who met the screening eligibility criteria for the study and received at least one dose of study medication were evaluated for safety. Safety was evaluated by monitoring the incidence of AEs, including the incidence and severity of local skin reactions following study drug treatment; changes in hematology, serum chemistry, and urinalysis test results; vital signs; and physical examination results during the study. The presence or absence of local skin reactions or abnormal proliferation of skin was assessed at all visits and if clinically warranted, a biopsy and/or lesion excision was to be performed during the post-treatment period followed by histological evaluation of local skin AEs that required further evaluation. Additional follow-up visits were scheduled every 7 to 14 days until local skin AEs were resolved.

Statistical Methods: The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing.

Summary - Conclusions:
Efficacy Results: In the histological review of punch biopsies, there was no significant difference in the presence or absence of AK lesions at the end of the study between each of the PEP005 Topical Gel dose groups and vehicle gel in either Treatment Arm A or Treatment Arm B. Between Treatment Arms, there was no significant difference in the presence or absence of AK lesions within treatment groups.

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

Clinically significant improvement in skin texture and skin marking was seen in some patients in all dose groups and both treatment arms. The percentage of patients with significant improvement in skin texture ranged from 12.5% (Treatment Arm A; PEP005 0.01% group) to 55.6% (Treatment Arm A; PEP005 0.05% group) and the percentage of patients who had significant improvement in skin marking ranged from 11.1% (Treatment Arm B; PEP005 0.05% group) to 50.0% (Treatment Arm A; vehicle gel group). In addition, the majority (≥62.5%) of patients in all treatment groups had no scarring, skin atrophy, or skin pigmentation at Day 85.

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Safety Results: Overall, the occurrence of AEs reported during the study was low (47 events in Treatment Arm A and 49 events in Treatment Arm B) and no unexpected AEs, SAEs, or trends of clinical concern were observed during the study. Although not statistically significant, an apparent dose-related trend in the incidence of AEs and number of AEs was observed for patients in PEP005 Topical Gel groups.

Overall, the majority of local skin reactions were rated as mild or moderate in severity and primarily tumor specific or with perilesional involvement for both treatment arms. The most common local skin reactions experienced by patients in both treatment arms were flaking/scaling/dryness, erythema, and scabbing/crusting. Eight patients experienced a total of 13 severe local skin reactions during the study period; six patients randomized to treatment Arm A (11 reactions) and two patients in Arm B (2 reactions). Of these eight patients, four experienced severe scabbing/crusting, two experienced severe erythema, one experienced severe itch, and one patient experienced severe flaking/scaling/dryness. No patients experienced local skin reactions of weeping/exudates, vesicles, hyperpigmentation or scarring. Two severe events of erythema were recorded for treatment Arm B; one each in the 0.0025% PEP005 and 0.01% PEP005 Topical Gel groups and all but one severe local skin reaction resolved by End of Study (Day 85).
Across treatment arms, there did not appear to be any clinically significant changes from baseline in laboratory results, vital signs, or physical examination findings during treatment.

Conclusions: This study demonstrated that two topical applications (Treatment Arm A and B) of PEP005 Topical Gel, at doses of 0.0025%, 0.01%, and 0.05%, is safe and well tolerated in patients with AK lesions. Promising results were observed in the clinical assessment of lesion clearance, although further work is necessary to define the optimal dose level and treatment regimen. In addition, a clinically significant improvement in cosmetic outcome of the selected AK lesion was observed.

Date of Report: 12 March 2008

PEP005-014

SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
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Title:
A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratoses on non-head locations (REGION-I)

Investigators and Sites: Multicenter in the United States and Australia (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 05 September 2008
Last patient completed Day 57: 23 February 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel, when administered once daily for two consecutive days (Day 1 and Day 2) to a 25 cm^2 contiguous actinic keratosis (AK) treatment area on non-head locations.

Methodology:
This was a multicenter, randomized, double-blind, parallel group, vehicle-controlled study. Eligible patients were randomized to receive PEP005 Gel, 0.05% or vehicle gel once daily for two consecutive days (Days 1 and 2). Study medication was patient-applied at home.

Safety assessments were performed during study visits on Days 3, 8, 15, 29, and 57 following treatment. Efficacy assessments were performed at baseline (Day 1 predose) and Day 57 (end of study). Patient-reported treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM) was assessed on Day 57, and skin-related quality of life using the Skindex-16 Dermatological Survey was assessed on Days 1, 8, 29, and 57. Patients completed the study on Day 57.

Poststudy followup visits were required every 7 to 28 days for all patients with unresolved, treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57 (if LSR grade was greater than baseline grade). These patients were to be followed until the events resolved or were assessed as clinically stable. Additionally, patients with treatment related pigmentation changes (hypo/hyper) or scarring greater than that present at baseline were required to undergo further poststudy followup every 28 days until resolution of the event or for a period of 6 months postbaseline (an additional 4 visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: approximately 250 patients (125 per treatment group)
Analyzed:
Intent-to-treat (randomized): 255 patients (126 to PEP005 Gel, 0.05% and 129 to vehicle gel)
Safety: 254 patients (125 PEP005 Gel, 0.05%; 129 vehicle gel)

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 cm^2 treatment area on the trunk and extremities (i.e., non-head locations).

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Test Product and Reference Therapy, Dose, Mode of Administration and Batch Nos.:

Test product: PEP005 Gel, 0.05% (Batch No. AGK-C).

Reference therapy: Vehicle gel (Batch No. ZMAB-C).

Study medication (PEP005 Gel, 0.05% or vehicle gel) was packaged individually for each patient in a study medication kit containing two unit-dose tubes. Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1 and 2.

Duration of Treatment:

Two consecutive days (Days 1 and 2)

Randomization Scheme:

Patients were randomized in a 1:1 ratio to study medication (PEP005 Gel, 0.05% or vehicle gel) using a central Interactive Voice Response/Interactive Web Response (IVR/IWR) system. Randomization was stratified by study site and also by anatomical location of the selected treatment area. A dynamic randomization scheme was used to obtain an approximate 1:1 ratio between treatment groups. Hierarchy levels were overall balance, balance within each anatomical location, and balance within each study site. A biased-coin approach was used when imbalance at a given level exceeded the specified threshold. The specified threshold level (i.e., difference between the number of randomized patients in each treatment group) for triggering the biased-coin approach was 4 for overall balance, 2 for balance within each anatomical location, and 2 for balance within each study site.

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint:

Complete clearance rate of AK lesions at Day 57, defined as the proportion of patients with no clinically visible AK lesions in the selected treatment area at Day 57.

Secondary efficacy endpoint:

Partial clearance rate of AK lesions at Day 57, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area.

Additional efficacy endpoint:

Percent change from baseline to Day 57 in the total number of AK lesions.

Exploratory:

Patient-reported outcomes, including the TSQM at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

Safety:

- Incidence of AEs, serious adverse events (SAEs), and AEs leading to discontinuation of study medication.
- Incidence and grade of LSRs.
- Incidence and grade pigmentation and scarring.
- Clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

Statistical Methods:

All statistical tests were two-sided with a significance level of $\alpha = 0.05$, unless specified otherwise. Data were summarized using descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency and percentages for discrete variables. Missing values were imputed using the last observation carried forward (LOCF) method, unless specified otherwise.

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Efficacy:

Complete clearance rates were calculated using observed rates and using weighted estimates based on the Cochran-Mantel-Haenszel (CMH) test statistic stratifying on anatomical location. Treatment groups were compared using the CMH test. A logistic analysis of variance (ANOVA) with treatment, anatomical location, and country as factors was also used to test for treatment effect. Partial clearance rates were calculated and the treatment groups were compared using the same methods as those used for the primary efficacy endpoint. Percent reduction from baseline in AK lesions at Day 57 was summarized using descriptive statistics. For exploratory purposes, summaries of complete clearance, partial clearance, and percent reduction from baseline in AK lesions at Day 57 were presented by anatomical location. Efficacy analyses were based primarily on the intent-to-treat (ITT) population, which included all patients randomized into the study. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

Patient-Reported Outcomes:

Treatment Satisfaction Questionnaire for Medication transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at each scheduled visit were summarized by treatment group. The transformed scores were treated as a continuous variable and analyzed using ANOVA with treatment, anatomical location, and study site as factors to test for treatment effect.

Safety:

The safety analysis was based on the safety population, which included all randomized patients who received at least one dose of study medication and had at least one postbaseline safety evaluation. In the safety population, patients were analyzed according to the actual treatment received. Treatment effect for safety endpoints was explored by inspection of observed means or frequency rates between treatment groups. Treatment groups were compared in terms of the incidence of AEs using the CMH test. ANOVA was used to compare the treatment groups in terms of change in LSR grade.

Summary of Results:

Efficacy:

The observed complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (28%) than the vehicle group (5%) ($p < 0.0001$). Sensitivity analyses, including a multiple imputation method for handling missing data and analyses based on evaluable and PP populations, all demonstrated a statistically significantly higher complete clearance rate in the PEP005 Gel, 0.05% group than in the vehicle group ($p < 0.0001$ for all comparisons). Observed complete clearance rates by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 26% (22/84) vs. 5% (4/82); back of hand, 16% (4/25) vs. 0 (0/29); chest, 89% (8/9) vs. 13% (1/8); and other (shoulder, back, and leg), 13% (1/8) vs. 10% (1/10).

The results of the analysis of the secondary efficacy endpoint, partial clearance (≥75% reduction) in AK lesions at Day 57, support the results of the primary efficacy analysis. The observed partial clearance rate at Day 57 overall in the PEP005 Gel, 0.05% group was 44% (56/126) versus 7% (9/129) in the vehicle group ($p < 0.0001$). Observed partial clearance rates by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 48% (40/84) vs. 9% (7/82); back of hand, 24% (6/25) vs. 0 (0/29); chest, 89% (8/9) vs. 13% (1/8); and other (shoulder, back, and leg), 25% (2/8) vs. 10% (1/10).

Treatment with PEP005 Gel, 0.05% resulted in a greater reduction in AK lesion count than treatment with vehicle. Median percent reduction from baseline in lesion count at Day 57 overall in the PEP005 Gel, 0.05% group was 69% versus 0 (zero) in the vehicle group. Median percent reduction in AK lesion count by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, was as follows: arm, 75% vs. 0; back of hand, 50% vs. 0; chest, 100% vs. 0; and other (shoulder, back, and leg), 57% vs. 0.

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Patient-reported Global Satisfaction mean score at Day 57, as measured by the TSQM, was statistically significantly higher in the PEP005 Gel, 0.05% group (71.3) relative to the vehicle group (47.8) ($p < 0.0001$), indicating a significantly higher level of overall satisfaction with PEP005 Gel, 0.05% relative to vehicle. For the Skindex-16 Dermatology Survey, mean scores for all three domain scores (Symptoms, Emotions, and Functioning) at Day 57 were decreased from baseline both in the PEP005 Gel, 0.05% group and the vehicle group, indicating improvement in patient concern regarding their skin condition in both treatment groups. There were no statistically significant differences between treatment groups in any of the three domains at Day 57.

Safety:

PEP005 Gel, 0.05% applied topically once daily for two consecutive days was well tolerated in this study. In the PEP005 Gel, 0.05% group, 98% of patients applied study medication on both days of dosing. Two patients did not apply the second dose due to application site reactions (application site pain [AE] in one patient; erythema and erosion [LSRs] in one patient).

The most common treatment related AEs were general disorders and administration site conditions relating to the application site (5 patients in the PEP005 Gel, 0.05% group; 0 patients in the vehicle group). All application site AEs were mild or moderate in intensity. Three patients had treatment related AEs other than application site reactions. Patient [redacted] in the PEP005 Gel, 0.05% group (treatment area, left leg) had vesiculation (blister) and erythema on the right leg at the point of contact with the treatment area. Patient [redacted] in the PEP005 Gel, 0.05% group (treatment area, left arm) had dermatitis on the right cheek due to cross-contamination with the treatment area. Patient [redacted] in the vehicle group developed a staphylococcal skin infection in the treatment area (chest) confirmed by a pustule swab culture. Four patients had SAEs, 1 patient in the PEP005 Gel, 0.05% group and 3 patients in the vehicle group. All SAEs were assessed by the investigator as not related to study medication. One patient in the PEP005 Gel, 0.05% group discontinued study medication due to an AE, i.e., application site pain (treatment area, chest) after the Day 1 dose that precluded further application on Day 2. A second patient in the PEP005 Gel, 0.05% group discontinued study medication due to LSRs, i.e., erythema and erosion (treatment area, arm) after the Day 1 dose that precluded further application on Day 2. No AEs leading to discontinuation of the study (2 patients in the PEP005 Gel, 0.05% group and 1 patient in the vehicle group) were considered related to study medication. Abnormal proliferation in the treatment area was reported for one patient in the PEP005 Gel, 0.05% group. Biopsy of the treatment area (thigh) revealed chronic eczematous dermatitis associated with focal AK, which was assessed by the investigator as mild in intensity and probably related to study medication. The patient completed the post study followup on Day 146. Outcome of the event, which was ongoing at last contact, was listed as "little or no change."

The treatment area was assessed for LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) at baseline (Day 1 predose) and each subsequent study visit. The mean LSR composite score (maximum score of 24) for the PEP005 Gel, 0.05% was 1.0 at baseline, peaked at 5.4 at Day 8, and returned to below baseline (0.8) at Day 57. The mean LSR composite score in the vehicle group did not change substantially across study visits. In the PEP005 Gel, 0.05% group, the most frequently reported LSRs were erythema (92 of patients at Day 8) and flaking/scaling (90% of patients at Day 8). Erythema, flaking/scaling, crusting, erosion/ ulceration peaked at Day 8; swelling and vesiculation/pustulation peaked at Day 3. By Day 57, patient frequency of most LSRs (erythema, flaking/scaling, crusting, and vesiculation/pustulation) had returned to or was below baseline level; patient frequency of swelling and erosion/ulceration was reduced substantially from peak level and had returned to close to baseline level. In the vehicle group, patient frequencies of LSRs were generally unchanged over time. The difference between PEP005 Gel, 0.05% and vehicle treatment in patient frequency of LSRs was greatest at Day 8. Thirteen patients in the PEP005 Gel, 0.05% group had one or more Grade 4 LSRs during the study. For all except 2 patients, Grade 4 LSRs had returned to or near baseline grade by Day 57. Three patients, 1 patient in the PEP005 Gel, 0.05% group and 2 patients in the vehicle group, had one or more LSRs that required poststudy followup. All of these LSRs returned to or near baseline grade during the follow-up period.

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For the majority (>95%) of patients, pigmentation (hyper and hypo) and scarring remained unchanged during the study (baseline [Day 1] to Day 57). Four (3%) patients in the PEP005 Gel, 0.05% group experienced greater hypopigmentation and/or hyperpigmentation relative to baseline. No patients in the PEP005 Gel, 0.05% group experienced scarring greater than what was observed at baseline. One patient in the vehicle group experienced greater hyperpigmentation and scarring (atrophic) relative to baseline. Two patients with hyperpigmentation in the PEP005 Gel, 0.05% group required poststudy followup. At completion of the followup period, hyperpigmentation had resolved in one patient and remained at Grade 2 in the other patient.

Changes from baseline in clinical laboratory tests and vital signs were unremarkable and similar between the PEP005 Gel, 0.05% and vehicle treatment groups. There were no apparent differences between treatment groups in ECG findings and no mean QT/QTc prolongations were observed.

Conclusion:

- PEP005 Gel, 0.05% applied topically once daily for two consecutive days was shown to be safe and efficacious for the treatment of AK lesions on non-head locations (trunk and extremities).
- Nearly all patients (98% in the PEP005 Gel, 0.05% group) were compliant with the treatment regimen, i.e., applied study medication on both days of dosing.
- Complete clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group.
- Other efficacy variables support the results of the primary efficacy endpoint. The partial clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. Median percent reduction from baseline in lesion count at Day 57 was substantially reduced in the PEP005 Gel, 0.05% group relative to the vehicle groups.
- The most common treatment related AEs were application site reactions. There were no deaths and no treatment related SAEs. All treatment related application site AEs and LSRs resolved without sequelae.

Final Report Date: 16 September 2010

PEP005-028

SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume: Page:	
Name of Active Ingredient: Ingenol Mebutate		

Title:
A multi-center, Randomized, parallel group, double-blind, vehicle-controlled study to evaluate the Efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% In patients with actinic keratoses ON non-head locations (REGION-Ib)

Investigators and Sites: Multicenter in the United States (refer to Appendix 16.1.4.1)

Publications: None

Study Period:
First patient randomized: 22 July 2009
Last patient completed Day 57: 14 October 2009

Phase of Development: 3

Objectives:
To evaluate the efficacy and safety of PEP005 Gel, 0.05% compared to vehicle gel when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous actinic keratosis (AK) treatment area on non-head locations.

Methodology:
This was a multicenter, randomized, parallel group, double-blind, vehicle-controlled study. Eligible patients were randomized to receive treatment with PEP005 Gel, 0.05% or vehicle gel once daily for two consecutive days (Days 1 and 2). Study medication was patient-applied at home.

Safety assessments were performed at follow-up visits on Days 3, 8, 15, 29, and 57. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (end of study). Patient-reported treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM) was assessed on Day 57, and skin-related quality of life using the Skindex-16 Dermatological Survey was assessed at baseline and on Days 8, 29, and 57. Patients completed the study on Day 57.

Poststudy follow-up visits were required every 7 to 28 days for all patients who had unresolved treatment related adverse events (AEs) or local skin responses (LSRs) at Day 57 (if LSR grade was greater than baseline grade). These patients were to be followed until the events resolved or were assessed as clinically stable. Additionally, patients with treatment related pigmentation changes (hypo/hyper) and/or scarring greater than that observed at baseline were required to undergo further poststudy followup every 28 days until resolution of the event or for a period of 6 months postbaseline (an additional 4 visits) unless deemed clinically insignificant.

Number of Patients (Planned and Analyzed):
Planned: Approximately 200 patients (100 per treatment group).
Analyzed:
Intent-to-treat (randomized): 203 patients (100 PEP005 Gel, 0.05%; 103 vehicle gel)
Safety: 203 patients (100 PEP005 Gel, 0.05%; 103 vehicle gel)

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 cm^2 treatment area on non-head locations.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume:	
Name of Active Ingredient: Ingenol Mebutate	Page:	

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:

Test product: PEP005 Gel, 0.05% (Lot AKW-C).

Reference therapy: Vehicle gel (Lots BCA-C and BCA-1C).

Study medication (PEP005 Gel, 0.05% or vehicle gel) was packaged individually for each patient in a study medication kit containing two unit-dose tubes. Study medication was applied topically to the selected treatment area by the patient, at home, once daily on study Days 1 and 2.

Duration of Treatment:

Two consecutive days (Days 1 and 2).

Randomization Scheme:

Patients were randomized centrally to treatment in a 1:1 ratio using an interactive voice/web response (IVR/IWR) system. Randomization was stratified by study site and also by anatomical location of the selected treatment area. A randomization scheme was used to obtain an approximately 1:1 ratio between treatment groups.

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

Complete clearance rate of AK lesions at the Day 57 visit, defined as the proportion of patients with no clinically visible AK lesions in the selected treatment area at Day 57.

Secondary Endpoint:

Partial clearance rate of AK lesions at the Day 57 visit, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected treatment area.

Additional Endpoint:

Percent change from baseline to Day 57 in the total number of AK lesions.

Exploratory:

Patient-reported outcomes, including the TSQM at Day 57 and the Skindex-16 Dermatological Survey at baseline and Days 8, 29, and 57.

Safety:

- Incidence rate of AEs, serious adverse events (SAEs), and AEs leading to discontinuation of study medication.
- Incidence rate and grade of LSRs, pigmentation, and scarring following study treatment.
- Clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) findings.

Statistical Methods:

The primary efficacy analysis was based on the intent-to-treat (ITT) population. In the ITT population, patients were counted in the treatment group to which they were randomized, regardless of receiving any dose of study medication.

For the analyses of complete and partial clearance, all missing values were imputed using last observation carried forward (LOCF). Baseline data were carried forward if no postbaseline data existed for the patient. That is, those patients were considered to have not achieved complete or partial clearance.

The safety analysis was based on the safety population, defined as all randomized patients who received at least one dose of study medication and had at least one postbaseline safety evaluation. In the safety population, patients were analyzed according to the actual treatment received.

All treatment comparisons were tested with two-tailed tests and a 0.05 significance level.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume:	
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Efficacy:

Complete clearance rate at Day 57 was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis site. Partial clearance rate at Day 57 was compared using the same analysis as that used for the primary efficacy endpoint. The number of AK lesions and percent change from baseline were summarized for each treatment group. Summaries were also provided by each anatomical location.

Summaries of complete clearance rates for each treatment group were provided for subgroups defined by gender, age group (<65 or ≥65), 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 [leg, back, shoulder]). Within each subgroup, treatment groups were compared using Fisher's Exact test.

Patient-Reported Outcomes:

The TSQM transformed scores at Day 57 and the Skindex-16 Dermatological Survey transformed scores at each scheduled visit were summarized by treatment group. The transformed scores were treated as a continuous variable and analyzed using analysis of variance (ANOVA) with treatment, anatomical location, and analysis site as factors to test for treatment effect.

Safety:

The safety endpoints included: incidence rate of patients who experienced AEs, SAEs and AEs leading to discontinuation of study medication; incidence and grade of LSRs, pigmentation and scarring; changes in clinical laboratory tests, vital signs, physical examinations, and ECG findings. The treatment effect was explored by inspection of observed means or rates for the treatment groups.

Summary of Results:

Efficacy:

The complete clearance rate at Day 57 (ITT LOCF) overall was statistically significantly higher in the PEP005 Gel, 0.05% group (42%) than the vehicle group (5%) ($p < 0.001$). Complete clearance rates by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 46% (27/59) vs. 5% (3/67) ($p < 0.001$); back of hand, 21% (6/28) vs. 0 (0/27) ($p = 0.023$); chest, 60% (3/5) vs. 33% (1/3) ($p = 1.000$); and other (leg, back, and shoulder combined), 75% (6/8) vs. 17% (1/6) ($p = 0.103$). The difference between treatment groups was statistically significant for arm and back of hand.

Complete clearance rates were statistically significantly higher in the PEP005 Gel, 0.05% group than the vehicle group in all subgroups, i.e., patients <65 years of age and those ≥65 years of age, males and females, patients with Fitzpatrick skin type I or II and those with Fitzpatrick skin type III, IV, V, or VI, and patients with 4–6 baseline lesion counts and those with 7 or 8 baseline lesion counts.

The results of the analysis of the secondary efficacy endpoint, partial clearance (≥75% reduction) in AK lesions at Day 57, support the results of the analysis of complete clearance. The partial clearance rate at Day 57 overall was statistically significantly higher in the PEP005 Gel, 0.05% group (55%) than the vehicle group (7%) ($p < 0.001$). Partial clearance rates by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 61% (36/59) vs. 6% (4/67) ($p < 0.001$); back of hand, 32% (9/28) vs. 4% (1/27) ($p = 0.012$); chest, 80% (4/5) vs. 33% (1/3) ($p = 0.464$); and other, 75% (6/8) vs. 17% (1/6) ($p = 0.103$). The difference between treatment groups was statistically significant for arm and back of hand.

The results of the analysis of the additional efficacy endpoint, percent change from baseline to Day 57 in the total number of AK lesions, also support the results of the primary efficacy analysis. Overall, median percent reduction from baseline in lesion count in the PEP005 Gel, 0.05% group was 75% versus 0 (zero) in the vehicle group. Median percent reduction in lesion count by anatomical location in the PEP005 Gel, 0.05% group versus vehicle group, respectively, were as follows: arm, 80% vs. 0; back of hand, 59% vs. 0; chest, 100% vs. 0; and other, 100% vs. 0.

Patient-reported Global Satisfaction mean score at Day 57, as measured by the TSQM, was statistically significantly higher in the PEP005 Gel, 0.05% group (71.9) than in the vehicle group (34.3) ($p < 0.001$), indicating a significantly

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
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higher level of overall satisfaction with PEP005 Gel, 0.05% relative to vehicle. For the Skindex-16 Dermatology Survey, mean scores for all three Skindex-16 domains (Symptoms, Emotions, and Functioning) at Day 57 were decreased from baseline to a significantly greater degree in the PEP005 Gel, 0.05% group relative to the vehicle group ($p \leq 0.013$), indicating a greater improvement in patient concern regarding their skin condition in the PEP005 Gel, 0.05% group relative to the vehicle group.

Safety:

PEP005 Gel, 0.05% applied topically once daily for two consecutive days was well tolerated in this study. Only 1 of 100 PEP005 Gel, 0.05% treated patients failed to apply the study medication as instructed. This patient missed the second dose due to losing the study medication tube.

The most common treatment related AEs were in the general disorders and administration site conditions system organ class and occurred in a higher percentage of patients in the PEP005 Gel, 0.05% group (22%) than the vehicle group (1%). All treatment related AEs were mild or moderate in intensity and resolved by Day 57. There were 4 treatment related AEs that occurred outside the treatment area, all in the PEP005 Gel, 0.05% group, i.e., erythema on the neck due to contact with the treatment area (shoulder), application site pruritus around the perimeter of the treatment area (arm), pain (investigator's term, body aches), and rash on the abdomen (treatment area, back of hand). Four patients had SAEs, 2 patients in the PEP005 Gel, 0.05% group and 2 patients in the vehicle group. All 4 SAEs were assessed by the investigator as not related to study medication. One patient in the vehicle group discontinued the study due to an SAE. No patients discontinued study medication due to an AE. Evidence of abnormal proliferation in the treatment area was recorded for 3 patients, 1 patient in the PEP005 Gel, 0.05% group and 2 patients in the vehicle group. The case of abnormal proliferation in the PEP005 Gel, 0.05% group was reported as an AE of pale cell acanthoma.

The treatment area was assessed for LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) at baseline (Day 1 predose) and each subsequent study visit. The mean LSR composite score (maximum score of 24) in the PEP005 Gel, 0.05% group was 1.0 at baseline, peaked between Day 3 and Day 8 (6.3 and 6.1, respectively), and returned to below baseline (0.7) at Day 57. The mean LSR composite score in the vehicle group did not change substantially across study visits (1.0–1.4). In the PEP005 Gel, 0.05% group, the most frequently reported LSRs with an increased grade from baseline were erythema (94% of patients) and flaking/scaling (92% of patients). Erythema, swelling, and vesiculation/pustulation peaked at Day 3; flaking/scaling, crusting, and erosion/ulceration peaked at Day 8. By Day 57, mean grade of all LSRs had returned to or was below baseline grade. In the vehicle group, mean LSR grade and patient frequency of LSRs did not change substantially from baseline values during the study. Twenty-five patients treated with PEP005 Gel, 0.05% had one or more Grade 4 LSRs following dosing. Most Grade 4 LSRs occurred on Day 3 and/or Day 8. All Grade 4 LSRs had returned to or near baseline grade by Day 57. There were no Grade 4 LSRs in the vehicle group.

The majority of patients had either no change or improvement in hyperpigmentation and hypopigmentation at Day 57 relative to baseline. In the PEP005 Gel, 0.05% group, 8 patients, experienced hypopigmentation change from Grade 0 (not present or color unchanged from skin surrounding treatment area) to Grade 1 (less pigmented than skin surrounding treatment area); 1 patient experienced hyperpigmentation change from Grade 0 to Grade 1 (patchy/blotchy and dark skin surrounding the treatment area). Three patients in the PEP005 Gel, 0.05% group with hypopigmentation changes at Day 57 were followed poststudy, and in all 3 patients, hypopigmentation returned to Grade 0 at the poststudy visit. One patient in the PEP005 Gel, 0.05% group had Grade 1 scarring (scarring restricted to within treatment area – hypertrophic) at Day 57. For all other patients (PEP005 Gel, 0.05% or vehicle), pigmentation and scarring either remained unchanged or improved.

Changes from baseline in clinical laboratory tests and vital signs were unremarkable and similar between the PEP005 Gel, 0.05% and vehicle treatment groups. There were no apparent differences between treatment groups in ECG findings and no mean QT/QTc prolongations were observed.

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Conclusion:

- PEP005 Gel, 0.05% applied topically once daily for two consecutive days was shown to be safe and efficacious for the treatment of AK lesions on non-head locations (trunk and extremities).
- Nearly all patients (99% in the PEP005 Gel, 0.05% group) were compliant with the treatment regimen, i.e., applied study medication on both days of dosing.
- Complete clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group.
- Other efficacy variables support the results of the primary efficacy endpoint. Partial clearance rate at Day 57 was significantly higher in the PEP005 Gel, 0.05% group relative to the vehicle group. Median percent change from baseline in lesion count at Day 57 was substantially reduced in the PEP005 Gel, 0.05% group relative to the vehicle group.
- The most common treatment related AEs were administration site reactions. All treatment related application site AEs and LSRs resolved without sequelae. No serious AEs were considered treatment related.

Final Report Date: 8 September 2010

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 4)** **INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

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: [redacted]

Study Centres:
[1] Private Practice, San Antonio, Texas; [2] Gwinnett Clinical Research Center Inc, Snellville, Greater Atlanta; [3] Dermatology Associates of Tyler, Tyler, Texas; [4] Private Practice, West Palm Beach, Florida.

Publications based on study (reference): Not applicable

Study Period:	**Phase of Development**: I
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

NAME OF COMPANY:	INDIVIDUAL STUDY SYNOPSIS (Page 2 of 4)	
Peplin Limited **NAME OF FINISHED PRODUCT:** PEP005 0.01% Gel **NAME OF ACTIVE INGREDIENT:** 3-angeloyl ingenol	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

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.

NAME OF COMPANY:	INDIVIDUAL STUDY SYNOPSIS (Page 4 of 4)	
Peplin Limited **NAME OF FINISHED PRODUCT:** PEP005 0.01% Gel **NAME OF ACTIVE INGREDIENT:** 3-angeloyl ingenol	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

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. $\geq$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

2. Synopsis

Name of company: Peplin Limited	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: PEP005 Topical Gel	Volume: Page:	
Name of active ingredient: 3-angeloyl ingenol		

Clinical Study Report Synopsis: Study PEP005-004

Title: An Open-label, Dose-escalation, Cohort Study to Determine the Maximum Tolerated Dose and Safety of PEP005 Topical Gel When Applied on Day 1 and Day 2 to Actinic Keratoses on the Shoulders, Chest, Back, or Arms Followed by a Post-treatment Follow-up Period Lasting at Least Four Weeks

Investigator: [redacted]

Study Center: Dermatology Associates of Tyler; 1367 Dominion Plaza; Tyler, TX 75703 USA

Dates of Study: 07 September 2005 to 14 March 2006

Clinical Phase: Phase IIa

Publications: None

Objectives:

The primary objective of this study was to determine the maximum tolerated dose (MTD) for PEP005 Topical Gel, administered once daily for two consecutive days, by applying 90 µL of PEP005 Topical Gel over a 3 cm x 3 cm field surrounding a target actinic keratosis (AK) lesion comprising both diseased and perilesional skin.

The secondary objectives of this study were:

1. To evaluate the clinical efficacy of PEP005 Topical Gel by determining the complete clinical response rate.
2. To determine the systemic absorption of PEP005 Topical Gel following application once daily for two consecutive days.

Methodology: This was an open-label, non-randomized, uncontrolled, dose-escalation, cohort study designed to determine the MTD of PEP005 Topical Gel, administered once daily for two consecutive days to patients with AK lesions.

Number of Patients Planned and Analyzed: Enrollment of up to 34 patients was planned. A total of 23 patients were screened, 22 patients were enrolled and analyzed for efficacy and safety, and two patients provided data for the pharmacokinetic (PK) analysis.

Name of company: Peplin Limited	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: PEP005 Topical Gel	Volume: Page:	
Name of active ingredient: 3-angeloyl ingenol		
Diagnosis and Main Criteria for Inclusion: Male or female patients who were at least 18 years of age and had one AK lesion with a diameter between 3 mm and 15 mm on the shoulders, chest, back, or arms.		
Dosage, Administration, and Duration of Treatment: A single application (90 µL) of PEP005 Topical Gel (at a dose of 0.01%, 0.025%, 0.05%, 0.075%, or 0.1%) was applied to the target AK lesion on two consecutive days using a positive displacement micropipette.		
Criteria for Evaluation: **Safety:** Safety was evaluated by monitoring the incidence of AEs (including the incidence and severity of local skin reactions following study drug treatment); and changes in hematology, serum chemistry, and urinalysis test results; vital signs measurements; and physical examination results during the study. Determination of MTD was the primary endpoint of this study. **Efficacy:** Clinical response to treatment with PEP005 Topical Gel was determined by assessing the extent of AK lesion clearance at each post-Day 1 visit compared with the Baseline assessment. Clinical response was evaluated as: complete clearance (100% improvement, no evidence of residual disease), marked clearance (50-90% improvement), slight clearance (10-50% improvement), unchanged (±10%), worsened (clinically observable growth), or unable to be assessed (eg, heavy scabbing, bruising, trauma, inflammatory response). **Pharmacokinetics:** Samples for PK analysis were taken at baseline (before Day 1 treatment) and at 0.5, 1, 2, and 4 hours post-treatment on study Day 2 in selected patients treated at the MTD to determine the systemic absorption of PEP005 Topical Gel.		
Statistical Methods: No hypothesis/inferential testing was conducted for this study. Data was summarized using descriptive statistics for continuous variables and using frequency and percentage for discrete variables.		
Summary of Results: **Safety Results:** Overall, the incidence of AEs was low. Only one patient (0.05% PEP005 Topical Gel cohort) experienced an SAE (aortic valve disease). This SAE was severe in intensity and considered unrelated to treatment with PEP005 Topical Gel. The most common treatment emergent AEs in this study were related to application of PEP005 Topical Gel to the lesion site. Six (60.0%) patients in the 0.05% PEP005 Topical Gel, five (83.3%) patients in the 0.075% PEP005 Topical Gel, and one (33.3%) patient in the 0.01% PEP005 Topical Gel cohorts experienced application site reactions. These events included application site reaction (skin cracked on lesion site), bleeding, discharge, irritation, pain, and pruritus. Most AEs were mild or moderate in intensity. No patients discontinued treatment because of an AE.		

Name of company: Peplin Limited	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: PEP005 Topical Gel	Volume: Page:	
Name of active ingredient: 3-angeloyl ingenol		

Safety Results (continued):

Most of the patients had at least one mild skin reaction before the application of study drug (3 patients in the 0.01%, 3 patients in the 0.025%, 9 patients in the 0.05%, and 6 patients in the 0.075% PEP005 Topical Gel cohorts) and continued to have mild skin reactions over the course of the study. Patients may have had more than one local skin reaction at each time point.

Moderate local skin reactions occurred predominately in the 0.05% and 0.075% PEP005 Topical Gel cohorts. In the 0.05% PEP005 Topical Gel cohort, 1 patient on Day 1 (pre-dose), 1 patient on Day 1 (post-dose), 4 patients on Day 2, 8 patients on Day 8, 2 patients on Day 15, 0 patients on Day 29 (End of Study) had at least one moderate local skin reactions. In the 0.075% PEP005 Topical Gel cohort, 1 patient on Day 2, 5 patients on Day 8, and 2 patients on Day 15 had at least one moderate skin reaction.

Severe local skin reactions occurred only in the 0.05% and 0.075% PEP005 Topical Gel cohorts. One patient in the 0.05% PEP005 Topical Gel cohort had at least one severe skin reaction on Day 15. Two patients in the 0.075% PEP005 Topical Gel cohort had at least one severe skin reaction on Day 8.

Patients were evaluated at all study visits for the following local skin reactions: erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudates, vesicles, flaking/scaling/dryness, hypopigmentation and hyperpigmentation. Most patients had mild flaking/scaling/dryness and mild erythema before the application of PEP005 Topical Gel (at Baseline). The incidence of local skin reactions was maximal at Days 2 and 8. In addition to flaking/scaling/dryness and erythema, local skin reactions included edema, scabbing/crusting, vesicles and erosion/ulceration.

With the exception of mild flaking/scaling/dryness and mild erythema, most local skin reactions had resolved by the End of Study. Time to resolution of symptoms was longest for erythema, followed by flaking/scaling/dryness, scabbing/crusting, edema, erosion/ulceration, vesicles, and hyperpigmentation. Duration of local skin reactions ranged from 6 days to 43 days.

Most of the local skin reactions were tumor specific. Perilesional involvement was maximal on Day 2. Approximately 35% of all local skin reactions reported on Day 2 had perilesional involvement. Approximately 17% of all local skin reactions reported had perilesional involvement. About 90% of all skin reactions with perilesional involvement and about 96% with tumor specific involvement were of mild intensity.

Two patients in the 0.075% PEP005 Topical Gel cohort experienced dose-limiting toxicities (DLTs). One experienced severe scabbing/crusting and severe flaking/scaling/dryness and the other experienced severe scabbing/crusting. The MTD as determined by data collected in this study was 0.05% PEP005 Topical Gel.

There were no apparent clinically significant changes in vital signs, physical examination findings, or clinical laboratory results from Baseline to the End of Study assessment.

Name of company: Peplin Limited	Summary table referring to Part of the dossier,	(For National Authority use only)
Name of finished product: PEP005 Topical Gel	Volume: Page:	
Name of active ingredient: 3-angeloyl ingenol		

Efficacy Results: Clinical response to treatment with PEP005 Topical Gel was reported for the Intent-to-Treat (ITT) population. At the Day 8 assessment, complete clearance was not reported in any of the treatment groups; marked clearance was reported for two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort and for one (10.0%) patient in the 0.05% PEP005 Topical Gel cohort.

At the Day 15 assessment, complete clearance was reported for three (30.0%) patients in the 0.05% PEP005 Topical Gel cohort, and two (33.3%) patients in the PEP005 Topical Gel 0.075% cohort; marked clearance was reported for two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, four (40.0%) patients in the 0.05% PEP005 Topical Gel cohort, and one (16.7%) patient in the 0.075% PEP005 Topical Gel cohort.

At the Day 29 (End of Study) assessment, complete clearance was reported in two (66.7%) patients in the 0.01% PEP005 Topical Gel cohort, one (33.3%) patient in the 0.025% PEP005 Topical Gel cohort, six (60.0%) patients in the 0.05% PEP005 Topical Gel cohort, and three (50.0%) patients in the 0.075% PEP005 Topical Gel cohort. Marked clearance was reported in only the 0.05% PEP005 Topical Gel and 0.075% PEP005 Topical Gel cohorts; two (20.0%) patients and two (33.3%) patients, respectively.

Four patients (one in the 0.05% PEP005 Topical Gel cohort and three in the 0.075% PEP005 Topical Gel cohort) had an unscheduled follow-up visit 12 to 15 days after the End of Study assessment. All four patients had an improved clinical response at the unscheduled follow-up visit. Three of the four patients had complete clearance and one had marked clearance.

Pharmacokinetics Results: Blood samples were obtained from two patients in the 0.05% PEP005 Topical Gel cohort for PK analysis. Whole blood concentrations of PEP005, and its two main isomers, PEP015 and PEP025, for both patients were below the quantifiable limit (<0.01 ng/mL) of the assay indicating that there was no detectable systemic absorption of PEP005 Topical Gel.

Conclusions: This study demonstrated that the MTD of 0.05% PEP005 Topical Gel administered once daily for two consecutive days is a safe and effective treatment for clearance of AK lesions.

Date of Report: 31 August 2006 (Final)

2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Summary Table Referring to Part of the Dossier**	*(For National Authority use only)*
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume:	
Name of Active Ingredient: Ingenol Mebutate	Page:	

Title:
A multicenter, open-label study to examine the safety and toleration of 0.05% PEP005 Topical Gel in patients with actinic keratoses on the dorsum of the hand

Investigators and Sites: Multicenter in the US. Description of investigators and sites has been provided in Appendix 16.1.4

Publications: None

Study Period:
First patient enrolled: October 11, 2007
Last patient completed Day 57: December 18, 2007

Phase of Development: 2

Objectives:
Primary Objective:
To examine the safety and toleration of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm^2 contiguous actinic keratosis (AK) treatment area on the dorsum of a single hand as determined by:

- incidence of adverse events (AEs) and serious adverse events (SAEs); and
- local skin responses (LSRs).

Secondary Objective:
To examine the efficacy of PEP005 Gel, 0.05%, administered on two consecutive days, to a 25 cm^2 contiguous AK treatment area on the dorsum of a single hand as determined by the:

- complete clearance rate: the proportion of patients at the Day 57 post-treatment visit with no clinically visible AK lesions in the selected AK treatment area;
- partial clearance rate: the proportion of patients at the Day 57 post-treatment visit with a 75% or greater reduction in the number of AK lesions identified at baseline in the selected AK treatment area; and
- baseline clearance rate: the proportion of patients at the Day 57 post-treatment visit with a 100% reduction in the number of AK lesions identified at baseline in the selected AK treatment area.

Methodology:
This was a Phase 2, multicenter, open-label study to evaluate the safety and tolerability of PEP005 Gel, 0.05%, administered once daily on two consecutive days to patients with AK lesions on the dorsum of one hand.

Patients were screened for study eligibility from Day -14 through Day -3. All eligible patients had study medication applied on Days 1 and 2. Patients were assessed for safety, tolerability, and efficacy on Days 2, 8, 15, 29, and 57. Additional post-Day 57 follow-up visits were planned, if clinically indicated.

Number of Patients (Planned and Analyzed):
Approximately 12 patients were planned for enrollment. A total of 12 patients were enrolled, 11 of which were treated with study medication and analyzed.

Sponsor: Peplin Operations Pty Ltd	**Summary Table Referring to Part of the Dossier**	*(For National Authority use only)*
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume: Page:	
Name of Active Ingredient: Ingenol Mebutate		

Diagnosis and Main Criteria for Inclusion:
Male and/or postmenopausal female patients at least 18 years of age with 4–8 clinically typical, visible, and discrete AK lesions within a contiguous 25 cm^2 treatment area on the dorsum of one hand. One lot of study medication, Lot0325C, was used in this study.

Dosage, Administration, and Duration of Treatment:
All patients received PEP005 Gel, 0.05%, once daily for two consecutive days (study Days 1 and 2). The study medication was applied topically to the selected AK treatment area by a board-certified dermatologist.

Randomization Scheme:
Not applicable, this was an open-label study.

Statistical Methods and Criteria for Evaluation:
This was an open-label, nonrandomized study with no formal hypothesis testing. The analysis was primarily descriptive in nature. Due to the small number of patients at each site, data from all sites were pooled.

Safety and tolerability assessments included AEs, SAEs, and LSRs. AEs and SAEs were summarized by the number and percentage of patients for each event. LSRs were assessed using a 4-point grading scale for each LSR. A composite score representing the sum of the individual LSRs was calculated for each study visit and the results were summarized using descriptive statistics. Other safety assessments included clinical laboratory evaluations, vital signs data, and physical examination findings, all of which were summarized using descriptive statistics.

Primary efficacy variables included complete clearance, partial clearance, and baseline clearance rates. The number and percentage of patients with lesion clearance and 95% confidence intervals (determined using the binomial approximation to the normal distribution) were calculated for each study visit. Additional efficacy variables included the overall clearance rate by number of doses received, the median percentage reduction in AK lesions, and the number and percentage of patients with subclinical AK lesions, visible AK lesions, and remaining baseline AK lesions within the treatment area. Additional efficacy variables were summarized using descriptive statistics.

An interim analysis was conducted on all patients once they had completed their Day 29 scheduled visit (including patients who were withdrawn prematurely). The interim analysis was performed on selected safety, tolerability, and efficacy data. No p-value adjustment was required and the interim analysis was not expected to bias or influence the integrity of the final analysis.

Summary of Results:

Safety results
All patients received two consecutive once-daily doses of PEP005 Gel, 0.05%, as planned. No deaths or discontinuations occurred during the study. There was one SAE, which the investigator deemed unrelated to study medication; this was a squamous cell carcinoma in situ (SCCIS) on the chest in a patient with a prior history of SCC, and was considered to be resolved by Day 57.

The most common AE class was 'general disorders and administration-site conditions' (27.3%; 3/11 patients). All AEs were mild or moderate in intensity, except for one case of severe cystitis that was unrelated to treatment. All but three AEs resolved by Day 57; these three AEs occurred in the same patient and were considered to be unrelated to study treatment.

Three patients experienced a total of seven treatment-related AEs, all of which occurred in the treatment area. This total included four reports of application-site reactions, and one report each of hypersensitivity, irritation, and paresthesia in the treatment area. All treatment-related AEs were mild in intensity and all but one resolved within 1 day; the exception was application-site hypersensitivity, which resolved within 6 days.

The mean composite LSR score was 1.5 at baseline, peaked on Day 8 with a score of 4.5, and returned to near pretreatment levels (1.6) at Day 29. The maximum composite LSR score reported in the study was 8, from a maximum possible score of 32.

Sponsor: Peplin Operations Pty Ltd	**Summary Table Referring to Part of the Dossier**	*(For National Authority use only)*
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume: Page:	
Name of Active Ingredient: Ingenol Mebutate		

Throughout the study, the most common LSRs were flaking/scaling and erythema, followed by crusting. Flaking/scaling was reported in 63.6% (7/11) of patients at baseline, and occurred in all patients on Days 8 and 15; the incidence of flaking/scaling improved to below baseline levels by Day 57. Erythema was present in 36.4% (4/11) of patients prior to treatment, and in all patients following dosing on Day 2. At Day 57, erythema was present in five patients (45.5%; 5/11). Only one patient (9.1%; 1/11) had signs of crusting at baseline. The incidence of crusting peaked at 72.7% (8/11 patients) on Day 8, and equaled baseline levels at Day 57. Swelling was observed only on Day 2, in two patients. The combined incidence of hyperpigmentation and hypopigmentation remained unchanged throughout the study, and no erosion/ulceration, scarring, or vesiculation/pustulation was reported at any time.

There were no Grade 4 LSRs, and Grade 3 post-dose LSRs were limited to flaking/scaling and erythema in 18.2% (2/11) of patients each. Grade 2 flaking/scaling occurred post-dose in 54.5% (6/11) of patients. For the remaining LSRs, the highest recorded post-dose grade was either Grade 0 (absent) or Grade 1 in the majority of patients: 100% (11/11) for erosion/ulceration, scarring, and vesiculation/pustulation, 90.9% (10/11) for pigmentation abnormalities and swelling, 63.6% (7/11) for erythema, and 54.5% (6/11) for crusting.

By Day 57, most LSRs were unchanged from baseline or had improved. Two patients had a total of four Grade 1 LSRs at Day 57 that were not present at baseline. Overall, the highest LSR grade at Day 57 was pre-existing Grade 2 hyperpigmentation in one patient.

No abnormal proliferation was reported in the treatment area, and no patients had clinically significant laboratory abnormalities, changes in vital signs or physical examination findings.

Efficacy results

Efficacy was a secondary objective in this study.

At Day 57, the complete clearance rate was 27.3% (3/11 patients), and the partial clearance rate was 45.5% (5/11 patients). The complete clearance rate was highest on Day 15 (45.5%; 5/11 patients), while the partial clearance rate was highest on Day 29 (63.6%; 7/11 patients).

The median percentage reduction in AK lesion count from baseline to Day 57 ranged from an increase of 12.5% to a decrease of 100.0%, with an overall median reduction of 66.7%. The median lesion count in the treatment area decreased from 6.0 on Day 2 to 0.0 on Day 15, increasing to 2.0 by Day 57. However, AK lesions were unable to be determined/assessed in a percentage of patients on Days 8 (5/11; 45.5%) and 15 (4/11; 36.4%).

Treatment-emergent subclinical lesions were identified in three patients (27.3%) on Day 57, based on a comparison of the total number of lesions at Day 57 with the lesions identified at baseline.

Conclusion:

The results of this study demonstrate that PEP005 Gel, 0.05%, is safe and well tolerated when applied once daily on two consecutive days to a 25 cm^2 contiguous AK treatment area on the dorsum of a single hand. Although complete clearance was observed in this study, the sample size was small and further study in a larger patient population is needed to confirm the response rates in this treatment area.

Final Report Date: 12 August 2009

PEP005-020

SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume:	
Name of Active Ingredient: Ingenol Mebutate	Page:	

Title:
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)

Investigators and Sites: 11 sites in the United States and Australia

Publications: None

Study Period:
First patient enrolled: 08 June 2009
Last patient completed Day 57: 02 September 2009

Phase of Development: 3b

Objectives:
Primary: To evaluate the safety of PEP005 Gel, 0.05% when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous actinic keratosis (AK) treatment area on non-head locations.
Secondary: To evaluate the efficacy of PEP005 Gel, 0.05% when administered once daily for two consecutive days (Days 1 and 2) to a 25 cm^2 contiguous AK treatment area on non-head locations.

Methodology:
This was a multi-center, open-label, single-arm study. Eligible patients received treatment with PEP005 Gel, 0.05% once daily for two consecutive days (Days 1 and 2). Study medication was patient-applied at home. Subsequent follow-up visits for safety assessments were conducted on Days 3, 8, 15, 29 and 57. Efficacy assessments were conducted at baseline (Day 1 pre-dose) and on Day 57 (end of study). Patients completed the study on Day 57.
Poststudy follow-up visits were required every 7 to 28 days for all patients who had unresolved treatment-related adverse events (AEs) or local skin responses (LSRs) at Day 57 (if LSR grade was greater than baseline grade). These patients were to be followed until either the events resolved or were assessed as clinically stable. Patients with unresolved hypopigmentation, hyperpigmentation, and/or scarring greater than that observed at baseline were required to undergo further poststudy followup every 28 days until resolution of the event or for a period of 6 months postbaseline (an additional 4 visits) unless deemed clinically insignificant.

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 cm^2 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 AKW-C).
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.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel	Volume:	
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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.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
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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.

Sponsor: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
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- 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

2 SYNOPSIS

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	
Title of Study: An open-label, multi-centre, dose-escalation, cohort study to determine the optimal tolerated regime and safety of PEP005 Topical Gel when applied to a 25 cm^2 contiguous actinic keratoses treatment area on the face or face and scalp	
Investigators: Multicenter Study	
Study Centers: Six sites in Australia and three sites in New Zealand	
Study Period: January 18, 2007 November 13, 2007	**Clinical Phase:** Phase IIa
Publications: None	
Objectives: The primary objective was to determine the optimal tolerated regimen of PEP005 Topical Gel when administered to patients once daily as a two or three consecutive day application schedule to a 25 cm^2 contiguous actinic keratosis (AK) treatment area on the face or face and scalp. The secondary objectives were to evaluate the efficacy of a two or three consecutive day application of PEP005 Topical Gel, when applied once daily to a 25 cm^2 contiguous AK treatment area on the face or face and scalp. Efficacy assessments were based on the following: • Determination of the partial clearance rate, defined as the proportion of patients at the Day 57 post-treatment visit with a 75% or greater reduction in the number of AK lesions identified at baseline in the treatment area. • Determination of the complete clearance rate, defined as the proportion of patients at the Day 57 post-treatment visit with no clinically visible AK lesions in the treatment area. • Determination of the baseline clearance rate, defined as the proportion of patients at the Day 57 post-treatment visit with 100% reduction in the number of AK lesions identified at baseline in the treatment area.	

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Methodology:

This Phase IIa open-label study was originally designed to confirm the safety and tolerability of 0.025% and 0.05% PEP005 Topical Gel when applied once daily for two or three consecutive days (Days 1 and 2 or Days 1, 2, and 3). A dose escalation design was chosen with a cohort of three patients at each escalation level. Application of 0.025% PEP005 Topical Gel applied once daily for three days and for two days was established as the dose limiting toxicity (DLT) and the maximally tolerated dose (MTD), respectively, for treatment of the face or face and scalp. There was no intra-patient dose escalation in this study and no randomization to assign dose levels.

The two subsequent protocol amendments were introduced to evaluate the safety and tolerability of lower concentrations of PEP005 Topical Gel (0.0175%, 0.0125%, 0.0075%, 0.0050%, and 0.0025%) with similar treatment regimens (once daily for two or three consecutive days). The resultant analysis and treatment groups are shown in the following table.

Analysis Group	Treatment Group	Escalation Protocol or Amendment	Number of Patients	PEP005 Topical Gel Concentration	Planned Treatment Regimen
1	Group 1	1	30	0.025%	Day 1 and Day 2
	Group 2	1	3	0.0175%	Day 1 and Day 2
	Group 2	1	3	0.0125%	Day 1 and Day 2
2	Cohort 1	Escalation	6	0.025%	Day 1, Day 2, and Day 3
	Groups 2 and 3	1 and 2	10	0.0175%	Day 1, Day 2, and Day 3
	Groups 2 and 3	1 and 2	11	0.0125%	Day 1, Day 2, and Day 3
	Group 3	2	9	0.0075%	Day 1, Day 2, and Day 3
	Group 3	2	8	0.0050%	Day 1, Day 2, and Day 3
	Group 3	2	8	0.0025%	Day 1, Day 2, and Day 3

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	
At the screening visit, the treatment area containing four to eight AK lesions was identified by a qualified dermatologist and documented. On Day 1 and Day 2 or Day 1, Day 2 and Day 3, the study medication was applied by the patient to the selected area under the supervision of the Investigator. Response to treatment was based on AK lesions clearance (complete, partial, and baseline). The safety evaluation was based on recorded adverse events (AEs), serious adverse events (SAEs), relationship of AEs to the study medication, Local Skin Response (LSR) grading (scale 0–4), Global Severity Rating (GSR: none, mild moderate, severe). These assessments were made at each visit and at post-treatment follow-up and unscheduled visits, if necessary. Concomitant medications were recorded in the case report form (CRF). Two photographs of the treatment area were done at Screening and at each visit. Physical examinations were performed at screening (Days -3 to -14) and Day 57, vital signs were measured at each visit, and clinical laboratory tests were performed at screening and Day 8.	
Number of Patients: Following Protocol Amendments 1 and 2, it was expected that up to 93 patients would be enrolled in the study. A total of 94 patients were actually enrolled; 88 patients were treated with at least one dose of PEP005 Topical Gel; Analysis Group 1 included 30, 3, and 3 patients in the 0.025%, 0.0175%, and 0.0125% concentrations, respectively; Analysis Group 2 included 6, 10, 11, 9, 8, and 8 patients in the 0.025%, 0.0175%, 0.0125%, 0.0075%, 0.0050%, and 0.0025% concentration respectively; 86 patients completed the study; 87 patients were included in the Full Analysis Set Population; and 78 patients were included in the Per Protocol Population.	
Diagnosis and Main Criteria for Inclusion: Male patients at least 18 years of age or post-menopausal female patients, (i.e., no menses for at least 12 consecutive months, or post-hysterectomy) with four to eight clinically typical, visible, and discrete AK lesions within a contiguous 25 cm^2 treatment area on the face or face and scalp.	
Dosage, Administration, and Duration of Treatment: PEP005 Topical Gel 0.025%, 0.0175%, and 0.0125% applied once daily for two consecutive days (Analysis Group 1) or three consecutive days (Analysis Group 2); 0.0075%, 0.0050%, 0.0025% applied once a day for three consecutive days (Analysis Group 2); 250 µL of gel was applied for each application.	

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	

Name of active ingredient:
3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate

Criteria for Evaluation:

Efficacy:

The following efficacy parameters were assessed:

- Partial AK clearance rate;
- Complete AK clearance rate;
- Baseline AK clearance rate;
- Median percentage reduction in the number of AK lesions (only Analysis Group 2);
- Number and proportion of emergent sub-clinical AK lesions (only Analysis Group 2); and
- Patient impression of treatment (Analysis Group 2).

Safety:

The following safety parameters were assessed:

- Incidence of AEs and SAEs throughout the study;
- Incidence and rate of LSRs (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration, pigmentation [hyperpigmentation or hypopigmentation], and scarring) using the LSR Grading Scale (Version 3) and the overall severity (none, mild, moderate, or severe) of the response to treatment using the GSR at Day 1, pre- and post-application of study medication, and at each subsequent study visit until Day 57 and at all follow-up/unscheduled visits;
- Changes in hematology, serum chemistry, and urinalysis test results (screening and Day 8); and
- Changes at the end of study relative to baseline for vitals measurements and changes in physical examination findings from screening.

Statistical Methods:

Analysis was mostly descriptive in nature. No hypothesis/inferential testing was conducted. Data were summarized using descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and used frequency and percentage for discrete variables. Patient listings of all data from the CRFs, as well as any derived variables, were presented.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Summary:

Efficacy Results:

The study was not statistically powered to evaluate efficacy, and the resulting groups have a small number of patients.

For the MTD, 0.025% PEP005 Topical Gel, once daily for two consecutive days, the percentage of patients with partial clearance (PC) was 66.7%; complete clearance (CC) was 38.9%; and baseline clearance (BC) was 36.7%. The 0.0175% concentration achieved the highest complete (100% Analysis Group 1; 80% Analysis Group 2) and baseline (100% Analysis Group 1; 80% Analysis Group 2) AK lesion clearance. The 0.0125% concentration achieved the best partial clearance (100%) in Analysis Group 1 and shared the designation with 0.025% in Analysis Group 2 (100%).

Overall, PEP005 Topical Gel, at higher concentrations of 0.0125% and above, achieves complete AK lesion clearance more often than do lower concentrations; however, the highest concentration of PEP005 Topical Gel evaluated in this study (0.025%) does not achieve better results than the next two lower concentrations evaluated (0.0175% and 0.0125%). The 0.0175% concentration achieved the highest complete and baseline AK lesion clearance. The lowest concentration, 0.0025%, underperformed all others.

Although the study was not statistically powered for an assessment of efficacy, clearance of AK lesions was observed in at least one of the three efficacy measures (CC, PC, BC) in all concentration strengths evaluated.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Safety Results:

PEP005 Topical Gel was well tolerated when applied once daily for up to three consecutive days as a field treatment to a 25 cm^2 area on the face and scalp containing AK lesions. In Analysis Group 1, from 33.3% to 100.0% of patients received study medication once daily for two consecutive days (0.025% had 76.7% compliance; 0.0175% had 100%; 0.0125% had 33.3%). In Analysis Group 2, from 40.0% to 100.0% of patients received study medication once daily for three consecutive days (0.025% had 50% compliance; 0.0175% had 40%; 0.0125% had 45.5%; 0.0075% had 44.4%; 0.0050% had 50%; 0.0025% had 100%).

There were no deaths and no patients discontinued from the study due to a treatment-emergent AE in either Analysis Group. One patient in Analysis Group 1 and two patients in Analysis Group 2 had SAEs: back pain, COPD, cellulitis, and SCC; but none were treatment related.

Among all patients treated, a total of 54 patients (61.4%) had treatment-emergent AEs, and 40 patients (45.5%) had treatment-related AEs. The incidence of treatment-related AEs did not correlate with study medication concentration or number of days of dosing. Application site reactions, primarily application site irritation and pain, were the main reason for patient discontinuation of dosing. Only in Analysis Group 2 did treatment-related AEs lead to discontinuation from dosing, which occurred in 11 patients (21.2%). The majority of these occurred on Day 2 and, except for two severe instances in the 0.025% group, were either mild or moderate in severity. All 11 patients recovered. No discontinuation of dosing occurred at the lowest concentration (0.0025%).

The most common treatment-emergent AEs were application site conditions of which "application site reaction" featured most prominently. Application site irritation, pain, paresthesia and pruritus featured second most prominently and other events such as application site bleeding, dryness, edema, discomfort and dermatitis were also observed. Other AEs of note included headache, which was observed in 4 out of 36 (11%) patients in Analysis Group 1 and in 6 out of 52 (11.5%) patients in Analysis Group 2. Additionally, eye disorders – blepharitis, eye swelling, lacrimation increased, eyelid and orbital edema and dry eye – were observed; 3 out of 36 (8%) patients in Analysis Group 1 had these AEs and 4 out of 52 (7.7%) had them in Analysis Group 2.

Review of the treatment area LSR in both Analysis Groups showed an improvement at Day 57 in comparison to baseline for the two common manifestations; i.e., erythema and flaking/scaling. In both analysis groups, scarring, hypopigmentation, and hyperpigmentation were not prominent at baseline and did not worsen during the study, except for one patient in Analysis Group 2 whose pigmentation worsened above Grade 2 at the end of study. For Patient [redacted] who received 3 days of 0.025%, pigmentation worsened from baseline Grade 0 to Grade 3 hypopigmentation. At the end of the study, scarring was absent in all dose groups in Analysis Group 1 and was at the baseline level or better in Analysis Group 2. The LSR composite score was the highest value on Day 3 pre-dose and Day 8, improved markedly by Day 15, and was at the baseline level or better on Day 57.

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Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Neither time to onset nor duration of LSR Grade 2 and above seemed to be consistently correlated with concentration strength or number of applications.

The highest GSR for response to treatment was mostly mild or moderate. The GSRs generally reached the maximum rating on Day 2 or 3, decreased thereafter, and returned to baseline or lower by Day 57. Severe responses were observed only in patients receiving the three highest concentrations (0.025% Analysis Groups 1 and 2; 0.0175% Analysis Group 2; and 0.0125% Analysis Groups 1 and 2). The duration of severe GSRs was similar for the three concentrations and dosing regimens with a suggestion of a more rapid severity decline for the lowest of the three concentrations (0.0125%).

No clinically significant changes from baseline or trends, related to study medication, were observed in vital signs or laboratory parameters.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
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Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	

Conclusions:

The primary objective of this study was to determine both the optimal concentration and regimen of PEP005 Topical Gel, when applied to treat AK lesions on the face or face and scalp. The MTD was determined by the DESC as being 0.025% PEP005 Topical Gel, once daily for two consecutive days.

PEP005 Topical Gel was well tolerated across all concentration strengths. The MTD concentration was tolerated by 80.6% of patients (this percentage includes patients who were scheduled to receive three days of dosing, but tolerated only two). The majority of patients in Analysis Group 1 were able to tolerate two consecutive days of dosing, while Analysis Group 2 only achieved 100% dosing for three consecutive days at the lowest formulation strength (0.0025%). Only half (n = 28) of the patients receiving higher concentrations in Analysis Group 2 were able to receive their full course of treatment.

Specific treatment-related AEs included application site reactions, disorders of pruritus or discomfort at treatment site, localized “dependent” edema (periocular or adjacent to treatment area), and headache. In both Analysis Groups, the most common LSR was erythema, followed by flaking/scaling, and then crusting. LSR peaked between Day 3 and Day 8 and largely resolved by Day 29. Scarring, hypopigmentation, and hyperpigmentation were not prominent at baseline in either Analysis Group and did not worsen during the study with the exception of one case in Analysis Group 2 where pigmentation did worsen above Grade 2 at the end of study from baseline pigmentation Grade 0 to Grade 3 hypopigmentation. The GSRs were mild to moderate in the majority of patients, and all severe GSRs resolved to "none" by Day 57.

In terms of efficacy, PEP005 Topical Gel 0.0175% achieved the highest complete and baseline AK lesion clearance in both Analysis Groups. No further increase in efficacy was observed when the next higher concentration, PEP005 Topical Gel 0.025%, was administered. These two concentrations (0.0175% and 0.0125%) appear to be most effective, but were not as well tolerated as the next two lower concentrations (0.0075% and 0.0050%).

Although the study was not statistically powered for an assessment of efficacy, clearance of AK lesions was observed in at least one of the three efficacy measures in all concentration strengths evaluated.

There was also a high rate of overall patient satisfaction with study medication (only evaluated for Analysis Group 2), at all concentration strengths evaluated.

Name of company: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only) Part of the dossier** Volume: Page:
Name of finished product: PEP005 Topical Gel, presently referred to as PEP005 (ingenol mebutate) Gel	
Name of active ingredient: 3-angeloyl ingenol (PEP005), presently referred to as ingenol mebutate	
This study, although not powered for efficacy, allowed for an assessment of the safety and tolerability of various concentrations (low to high) and dosing regimens (two or three consecutive daily doses) of PEP005 Topical Gel, in an effort to determine a safe and efficacious concentration and dosing regimen for the field-treatment of AK lesions on the face or face and scalp. Based upon the local toleration profiles and complete clearance rates observed, concentrations of 0.005% to 0.0125% PEP005 Topical Gel, applied once daily for two or three consecutive days, appears to offer a suitable balance of patient safety and toleration for further Phase IIb evaluation.	
Date of Report: April 22, 2009	

2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only)** **Part of the Dossier** Volume: Page:
Name of Finished Product: PEP005 (ingenol mebutate) Gel	
Name of Active Ingredient: Ingenol Mebutate	
Title: A multicenter, open-label, dose-area escalation, cohort study to evaluate the safety and tolerability of 0.05% PEP005 Topical Gel applied for two consecutive days to treatment area(s) of up to a total of 100 cm^2 in patients with actinic keratoses on the extensor (dorsal aspect) forearm(s).	
Investigators and Sites: Multiple centers in the United States and Australia (see Appendix 16.1.4).	
Publications: See Appendix 16.1.11.	
Study Period: First patient screened: 03 April 2008 Last patient completed (Day 57): 4 September 2008	
Phase: 1	
Objectives: To evaluate the safety and tolerability of two, once-daily, consecutive applications of PEP005 Gel, 0.05%, when applied to 25, 50, 75, or 100 cm^2 actinic keratosis (AK) treatment area(s) on the dorsal forearm(s). The following criteria were assessed: • Incidence of adverse events (AEs), serious adverse events (SAEs) and AEs leading to discontinuation of study medication; • Incidence and grade of local skin responses (LSRs), pigmentation, and scarring following study treatment; and • Patient tolerability to treatment regimen.	
Methodology: This Phase 1, multicenter, open-label, cohort study was designed to study AK treatment areas on the dorsal forearm(s) following treatment of escalating size areas, from 25 to 100 cm^2, with PEP005 Gel, 0.05%, once daily for two consecutive days (Days 1 and 2). Patients were assigned to escalating treatment Cohorts starting with Cohort 1 and escalating through to Cohort 8. Patients in each Cohort were evaluated on the basis of safety and tolerability to study treatment. The decision to escalate to the next treatment Cohort(s) was made when the assessments of safety and tolerability (up to Day 15 for at least 80% of patients in a Cohort) were acceptable to an independent review team consisting of two dermatologists who were not involved with recruiting patients to this study. The review team evaluated individual patient LSRs, photographs, AEs, and any other relevant safety data for each Cohort. The review team had to assess the safety and tolerability data for the current dose-area treatment and had to agree to the next escalation before any additional Cohorts could be treated. The first patients were allocated into Cohorts 1, 2, or 3. Treatment of patients in Cohorts 4 or 5 did not begin until the safety and tolerability data were evaluated for Cohorts 1, 2, and 3. The decision to treat patients in Cohort 6 was made following a review of patients in Cohort 4 and the decision to treat patients in Cohorts 7 and 8 was not to be made until the safety and tolerability of patients in Cohort 5 were assessed. Post-study follow-up visits were required for any patients with unresolved, treatment-related AEs, LSRs, pigmentation, and/or scarring at Day 57 (end of study) that worsened from Day 1 predose (baseline). Post-study follow-up for AEs and LSRs was to occur every 7–28 days until resolution of the event or until the event was assessed as being clinically stable by the investigator. Post-study follow-up for pigmentation and scarring was to occur every 28 days until resolution of the event or for a period of 6 months post Day 1 (an additional four visits), unless deemed clinically insignificant by the investigator.	

Sponsor: Peplin Operations Pty Ltd	**Summary table referring to (For National Authority use only)** **Part of the Dossier** Volume: Page:
Name of Finished Product: PEP005 (ingenol mebutate) Gel	
Name of Active Ingredient: Ingenol Mebutate	

Number of Patients (Planned and Analyzed): It was planned that there would be eight patients per Cohort with a maximum of eight Cohorts and a total of 64 enrolled patients. A total of 74 patients were enrolled in the study, 65 of whom were assigned to treatment. Eight patients were assigned to Cohorts 1–5, 7, and 8, and 9 patients to Cohort 6. There were 64 patients who received at least one dose of study medication and were included in the safety analysis. Of these, 63 patients completed the treatment phase (screening to Day 57).

Diagnosis and Main Criteria for Inclusion: Male patients who were at least 18 years of age with a contiguous 100 cm^2 treatment area on both the right and left dorsal forearms, each containing a minimum of five AK lesions.

Test Product, Dose and Mode of Administration: The study medication, PEP005 Gel, 0.05% (Lot ZMAC-C), was packaged in individual patient study medication kits, each of which contained two boxes, labeled for use on Day 1 and Day 2. Each box contained one to four individual unit dose tubes, specific to the Cohort to which the patient was assigned. Each unit dose tube contained sufficient PEP005 Gel, 0.05%, for the treatment of one 25 cm^2 treatment area. Study medication was applied to the specified treatment area by the patient under the supervision of the investigator.

Up to eight different dosing Cohorts were to be evaluated during this study:

Cohort	Treatment Area
Cohort 1	1 × 25 cm^2 treatment area, one arm
Cohort 2	1 × 50 cm^2 contiguous treatment area, one arm
Cohort 3	2 × 25 cm^2 treatment areas, one on each arm
Cohort 4	1 × 25 cm^2 treatment area 1 × 50 cm^2 contiguous treatment area, one on each arm
Cohort 5	1 × 75 cm^2 contiguous treatment area, one arm
Cohort 6	2 × 50 cm^2 contiguous treatment areas, one on each arm
Cohort 7	1 × 25 cm^2 treatment area 1 × 75 cm^2 contiguous treatment area, one on each arm
Cohort 8	1 × 100 cm^2 contiguous treatment area, one arm

Duration of Treatment: Patients participated in the study from Day 1 to Day 57. There was a 42-day screening period. Following screening, treatment days occurred on Days 1 and 2, and follow-up visits for safety assessments were made on Days 2, 3, 8, 15, 29, and 57 (end of study). Post-study follow-up visits were required for any patients with unresolved treatment-related AEs, LSRs, pigmentation, and/or scarring at Day 57 (end of study).

Statistical Methods and Criteria for Evaluation: Patients who were assigned to receive study medication formed the intent-to-treat (ITT) population. Patients in the ITT population who received at least one dose of study medication formed the safety population. Safety reporting and analysis were performed on the safety population.

No statistical hypothesis testing was planned. For LSRs, the treatment effect was explored by inspection of observed means across treatment Cohorts, least squares (LS) mean difference, and two-sided 95% confidence intervals (CI) of the LS mean difference with control groups. All LSR, pigmentation and scarring data were also summarized descriptively and listed.

- Patient tolerability to the treatment regimen was assessed as the largest single forearm contiguous treatment area that could be administered study medication. LSR grade and LSR composite score changes from baseline

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(Day 1 predose) were first compared across ascending single contiguous treatment areas (25, 50, 75, 100 cm^2). Furthermore, the LS mean difference between ascending contiguous areas (50, 75, 100 cm^2) was compared pairwise with the 25 cm^2 treatment Cohort.

- Drug load evaluation was assessed by comparison of the same base size treatment areas to examine any effect associated with increasing drug load (pairwise comparisons are presented in the summary table below). LSR grade and LSR composite score changes from baseline (Day 1 predose) were first compared across all treatment areas with the same base size. Furthermore, the LSR least squares (LS) mean difference for the drug load of increasing treatment areas was evaluated using pairwise comparisons with the control treatment Cohort (single forearm contiguous area). For Cohorts containing two treatment areas of the same size (e.g., Cohorts 3 and 6), the comparison was performed for each designated treatment area versus the control group rather than pooled data.

Drug Load Evaluation Table

Base Size Treatment Area	Control Group	Comparison Group	Drug Load Evaluated
25 cm^2	Cohort 1	Cohort 3 (Tx Areas 1/2)	+ 25 cm^2
		Cohort 4 (25 cm^2)	+ 50 cm^2
		Cohort 7 (25 cm^2)	+ 75 cm^2
50 cm^2	Cohort 2	Cohort 4 (50 cm^2)	+ 50 cm^2
		Cohort 6 (Tx Areas 1/2)	+ 25 cm^2
75 cm^2	Cohort 5	Cohort 7 (75 cm^2) +	25 cm^2

- The potential effect of disease severity, country, and treated forearm side was investigated using the pooled 25, 50, 75, and 100 cm^2 treatment areas. Pooled treatment areas of the same size were analyzed by subset with regard to (1) baseline disease severity, (2) country (US or Australia) and (3) treated forearm side (left or right).
- The incidence rates of AEs, SAEs, and AEs leading to discontinuation of study medication were examined by single contiguous treatment area and total body exposure.
- Pigmentation and scarring were assessed descriptively for presence, distribution, and grade at baseline (Day 1 predose) and end of study (Day 57). Scarring was further assessed by palpability. Furthermore, change from baseline (determined as improved, unchanged, or worsened) was presented for pigmentation and scarring grade and distribution.

Summary of Results:

All patients in Cohorts 1, 2, and 8 received two consecutive daily doses of PEP005 Gel, 0.05%, as planned. Five of 64 (7.8%) patients in the safety population had the second dose withheld because of LSRs and/or AEs in the treatment area; treatment area sizes that experienced reactions included: one 25 cm^2 area (one patient), two 25 cm^2 areas (one patient), one 25 cm^2 area and one 50 cm^2 area (one patient), two 50 cm^2 areas (one patient), and one 75 cm^2 area (one patient). A sixth patient was withdrawn prior to the second dose due to a protocol violation. All patients with a treatment area of 100 cm^2 tolerated two doses.

There were no deaths during the study and no patient withdrew from the study due to AEs. Three SAEs were reported, including one squamous cell carcinoma (SCC) that the investigator classified as possibly treatment-related.

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Patient [redacted] who was treated in Cohort 4, developed a keratotic nodule on the right forearm in the 50 cm^2 treatment area during follow-up. A biopsy on Day 29 revealed a well-differentiated SCC, which was completely excised on Day 39. This patient had an extensive history of non-melanoma skin cancer. The remaining two SAEs (one case each of exacerbation of pre-existing hypertension and pancreatitis) were considered unrelated to treatment. All three SAEs resolved during the study.

Only one severe AE was reported during the study. This was a case of polymyalgia rheumatica that was considered unrelated to treatment. There were a total of 49 individual treatment-related AEs, of which 45 were of mild intensity and four were of moderate intensity. The overall incidence of treatment-related AEs was 42.2% (27/64 patients). A comparison among the single contiguous treatment area cohorts (Cohorts 1, 2, 5, and 8) showed that the incidence was highest for 75 cm^2 (62.5%; 5/8 patients), followed by 50 and 100 cm^2 (both 37.5%; 3/8), and least for 25 cm^2 (12.5%; 1/8).

The most common treatment-related AEs were general disorders and administration-site conditions, which occurred in 37.5% (24/64) of all patients, and in 56.3% (9/16) of the subset of patients with a total body exposure of 75 cm^2. Specifically, application-site pruritus (17/64 patients, 26.6%) and application-site irritation (9/64 patients, 14.1%) were the most common treatment-related AEs, both in this category and overall. Most local reactions were mild, but patients had application-site pruritus or application-site irritation of moderate intensity. Systemic AEs that were possibly treatment-related included two cases of dysgeusia, and one case each of dry mouth, frequent bowel movement, and rales.

In terms of the LSRs observed, erythema and flaking/scaling were prevalent at baseline and increased following the first application of study medication. All patients had some degree of erythema and flaking/scaling during the study. Prior to treatment, swelling, vesiculation/pustulation, and erosion/ulceration were not observed, and crusting was uncommon. The incidence of swelling and vesiculation/pustulation peaked on Day 3, whereas crusting and erosion/ulceration peaked on Day 8. Investigators deemed that cultures were not required for any of the patients with pustules.

Pigmentation changes and scarring were assessed at baseline and Day 57 (end of study). At baseline, hypopigmentation was noted in 53.1% (51/96) of treatment areas, hyperpigmentation in 45.8% (44/96), and scarring in 25.0% (24/96). New or worsened pigmentation changes or scarring occurred during the study in 17.2% (11/64) of patients. These changes were rated not clinically significant in eight patients and mild in two patients; one patient had worsened hypopigmentation that was graded as moderate at Day 57.

The mean composite LSR score in each Cohort ranged from 0.8 to 1.6 prior to treatment and from 0.1 to 1.6 by Day 57 (end of study). During the treatment phase, the mean composite LSR score peaked during Days 3 and 8. The peak score was generally similar between Cohorts with the same treatment area size, but was higher in Cohort 4 (25 cm^2, 50 cm^2) compared to other Cohorts with the same treatment area sizes. The mean change from baseline in the composite LSR score demonstrated an apparent dose-response across the four Cohorts with a single contiguous treatment area, reaching a maximum of 4.4 for 25 cm^2, 4.9 for 50 cm^2, 6.6 for 75 cm^2, and 8.1 for 100 cm^2. Overall, the results of the drug load evaluation showed an apparent absence of a drug load effect, despite several statistically significant pairwise comparisons, most of which were associated with Cohort 4. Based on these results, treatment areas of the same size were pooled.

Exploratory analyses based on the pooled treatment groups indicated that neither the country of enrollment nor the treatment site (left or right forearm) had any effect on the composite LSR score. However, there was an apparent association between the baseline severity of AK in the treatment area and the LSR intensity for the 25 cm^2 and 50 cm^2 treatment areas, whereby patients with severe disease had greater LS mean differences from baseline in the composite LSR score than patients with mild or moderate disease. However, the results for all treatment areas were

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inconclusive and involved small patient numbers.

Four patients had significantly out-of-range clinical laboratory results during the study. Two of these patients had abnormal results (one gamma-glutamyl transpeptidase [GGT], one calcium) at screening and on Day 8, while the other two patients returned abnormal results for calcium and serum glucose on Day 8 only. None of the out-of-range values were considered to be treatment-related by the investigators.

Conclusion:

PEP005 Gel, 0.05%, was safe and well tolerated when applied once daily for two consecutive days to a dorsal forearm treatment area of up to 100 cm^2 in patients with AK. Five of 64 (7.8%) patients did not receive the full treatment course of two days due to LSRs and/or AEs at the treatment site; of these five patients, one patient each had reactions in: a single 25 cm^2 treatment area, two 25 cm^2 areas, one 25 cm^2 and one 50 cm^2 area, two 50 cm^2 areas, and a single 75 cm^2 area. All eight patients with a single contiguous treatment area of 100 cm^2 were able to tolerate two consecutive daily applications. For Cohorts with a single contiguous treatment area, an apparent dose-response was observed for the mean composite LSR score, which peaked during Days 3 and 8. Increasing the drug load by including a second treatment area on the opposite arm did not influence the intensity of LSRs in the base treatment area.

PEP005-013, an initial Phase 1 single-center maximal use study, evaluated the potential for systemic absorption of PEP005 Gel, 0.05%, when applied once daily for two consecutive days by treating a 100 cm^2 contiguous area of skin on the dorsal forearm (n = 6). Although no systemic absorption of ingenol mebutate or its two major metabolites was detected in this study, patients experienced more intense individual LSR scores and mean composite LSRs than had been observed in other studies treating smaller (25 cm^2) contiguous treatment areas; only three of six treated patients (50%) were able to tolerate once-daily dosing for two consecutive days. In contrast, this PEP005-022 Phase 1 multicenter study demonstrated that treating a 100 cm^2 area was both safe and well tolerated (n = 8). The 100 cm^2 treatment area showed no increase in treatment-related AEs compared with the 25, 50 or 75 cm^2 treatment areas, although there was a small apparent increase in the overall intensity of mean composite LSR scores at this treatment area size.

The safety and tolerability results from studies PEP005-013 and PEP005-022 demonstrated that a contiguous treatment area of 100 cm^2 was the maximum treatment area that would be used to evaluate the pharmacokinetics of ingenol mebutate in a subsequent study, PEP005-017. Further, a contiguous treatment area of 100 cm^2 has practical relevance in a clinical setting in that it represents a standard anatomical unit for application of topical therapy (e.g., a contiguous 100 cm^2 area covers an entire dorsal forearm). Based on the interplay of safety, tolerability to treatment and practical clinical use of PEP005 Gel, further studies to increase the contiguous treatment area above 100 cm^2 are not warranted at this time.

Final Report Date: 07 July 2009

2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: PEP005 (ingenol mebutate) Gel		
Name of Active Ingredient: Ingenol Mebutate		

Title:
A 12-month, long-term follow-up study of patients with actinic keratosis on the head (face or scalp) who have completed Day 57 in studies PEP005-016 or PEP005-025 (REGION IIa and IIb)

Investigators and Sites: 38 centers in the United States and 4 centers in Australia

Publications: None

Study Period:
First patient enrolled: 29 July 2009
Last patient completed: 16 September 2010

Phase of Development: 3

Objectives:
To summarize treatment area recurrence of actinic keratosis (AK) lesions, in the selected treatment area, during a 12-month followup period for patients who achieved complete clearance of AKs at Day 57 in studies PEP005-016 and PEP005-025.

To summarize long-term safety data, in the selected treatment area over a 12-month followup period for patients who completed Day 57 in studies PEP005-016 and PEP005-025.

Methodology:
This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025. No study medication was administered during PEP005-030.

The original protocol dated July 1, 2009, allowed entry of patients who completed the Day 57 visit in studies PEP005-016 and PEP005-025. With implementation of Amendment #1, dated September 28, 2009, eligibility was restricted to only those patients who achieved complete clearance at Day 57. Consequently, enrolled patients who had not achieved complete clearance at Day 57 were terminated from the study at the next regularly scheduled PEP005-030 study visit, or sooner if feasible.

Following enrollment (at Day 57 or within 4 weeks after Day 57 of studies PEP005-016 and PEP005-025), patients were to return to the clinic for followup visits at 3, 6, 9, and 12 months after the Day 57 visit in the previous study. Information was collected for all patients on adverse events (AEs) in the selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. AK lesions in the selected treatment area were counted at each visit. Information regarding intercurrent disorders, therapeutics that could have resulted in immunosuppression, and treatment with agents known to alter AK were collected.

Number of Patients (Planned and Analyzed):
Planned: Approximately 160 patients
Analyzed: A total of 117 patients who had demonstrated complete clearance of AK lesions in either study PEP005-016 or PEP005-025 were enrolled in this long-term followup study. Of these 117 patients, 108 had received 0.015% PEP005 Gel and 9 had received vehicle in the previous study.

Sponsor: Peplin Operations Pty Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: PEP005 (ingenol mebutate) Gel		
Name of Active Ingredient: Ingenol Mebutate		

Diagnosis and Main Criteria for Inclusion:

Patients had to achieve complete clearance of AK lesions at Day 57 in either study PEP005-016 or PEP005-025.

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:

Test product: Not applicable; no study medication was administered during this study.

Reference therapy: Not applicable

Duration of Study:

It was estimated that it would take 15 months to complete this study from the first patient enrolled to the last patient followup visit.

Randomization Scheme:

Not applicable

Criteria for Evaluation:

Efficacy:

Number of AK lesions in the selected treatment area. Recurrence was defined as any identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study.

Concomitant therapies (medications and procedures) for treatment of AK lesions in the selected treatment area.

Safety:

AEs in the selected treatment area.

Statistical Methods:

The statistical evaluations were planned to be performed after the 6-month followup visit and again after the 12-month followup visit (i.e., completion of the study). This clinical study report is based on data obtained through the 12-month followup visit.

Three analysis populations were defined: (1) the 'All Patients Enrolled' population included all patients who provided informed consent for participation in the study; (2) the 'CC57' population included all patients enrolled who showed complete clearance of AK lesions in the selected treatment area at the Day 57 visit in study PEP005-016 or PEP005-025; and (3) the 'Non-CC57' population included all patients enrolled who did not show complete clearance of AK lesions in the selected treatment area at the Day 57 visit in the previous study. Patients were classified into treatment groups according to the treatment received in the previous study.

Efficacy: For the CC57 population, AK recurrence was summarized using Kaplan-Meier methods. All event times were imputed to their target study day prior to performing the calculations. The recurrence rate was estimated by the Kaplan-Meier "failure" estimate at the target study day expressed as a percentage. The estimates, along with 95% confidence intervals, were calculated at Days 91, 183, 274, and 365. The time to recurrence was also summarized. The recurrence rate at Day 365 (12 months) was summarized for the subgroups of treatment location, geographic region, Fitzpatrick skin type, gender, age group, and baseline lesion count. The number of AK lesions in the treatment area was summarized at each visit.

Safety: For the CC57 population, the incidence rate of AEs was summarized as the number and percentage of patients with one or more episodes of an AE classified using the MedDRA (Version 11.0) preferred term and system-organ class. An overall summary of AEs was presented and included the number and percentage of patients with any AE, any serious AE (SAE), any fatal AE, any severe AE, and any AE resulting in discontinuation of study. The incidence of all AEs by preferred term regardless of the relationship to previous study treatment was summarized for each treatment group. Patients with SAEs, fatal AEs, severe AEs, and AEs leading to study

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discontinuation were presented in data listings. AE data for the Non-CC57 population were presented in data listings.

Summary of Results:

Efficacy: At 12 months of followup, 53.9% of patients who had been treated with PEP005 Gel in the previous Phase 3 studies (N=108), had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 365 days. Based on the number of lesions observed within the treatment area during 12 months of followup relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 studies), the mean lesion-based recurrence rate was 12.8%.

At 12 months of followup, 72.2% of vehicle-treated patients (N=9) had a new or recurrent AK lesion, with a median time to recurrence of 183 days. For this group of patients, the mean lesion-based recurrence rate at 12 months was 16.3%.

Safety: Over the 12-month followup study, only 1 AE in the selected treatment area (mild sunburn, considered unrelated to study drug) was reported.

Conclusion:

During 12 months of followup, 53.9% of patients had at least one new or recurrent AK lesion within the area on the face or scalp that had been treated with PEP005 Gel, 0.015% in study PEP005-016 or PEP005-025; the median time to recurrence was 365 days. Relative to the total number of AK lesions observed prior to treatment in either study PEP005-016 or PEP005-025, the lesion recurrence rate at 12 months of long-term followup was 12.8%. With only one reported AE of mild, unrelated sunburn, there was no safety concern in the selected treatment area.

Final Report Date: 28 March 2011

2 SYNOPSIS

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Name of Active Ingredient: Ingenol Mebutate		

Title:
A 12-month, long-term follow-up study of patients with actinic keratosis on non-head areas (trunk and extremities) who have completed Day 57 in study PEP005-020

Investigators and Sites: 8 centers in the United States and 3 centers in Australia

Publications: None

Study Period:
First patient enrolled: 29 July 2009
Last patient completed: 14 September 2010

Phase of Development: 3

Objectives:
To summarize treatment area recurrence of actinic keratosis (AK) lesions, in the selected treatment area, during a 12-month followup period for patients with complete clearance who completed Day 57 in study PEP005-020.
To summarize long-term safety data, in selected treatment area over a 12-month followup period for patients who completed Day 57 in study PEP005-020.

Methodology:
This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in study PEP005-020. No study medication was administered during PEP005-031.
The original protocol dated July 1, 2009, allowed entry of patients who completed the Day 57 visit in study PEP005-020. With implementation of Amendment #1, dated September 30, 2009, eligibility was restricted to only those patients who achieved complete clearance at Day 57. Consequently, enrolled patients who had not achieved complete clearance at Day 57 were terminated from the study at the next regularly scheduled PEP005-031 study visit or sooner, if feasible.
Following enrollment (at Day 57 or within 4 weeks after Day 57 of study PEP005-020), patients then returned to the study clinic for followup visits at 3, 6, 9, and 12 months after the Day 57 visit in the previous study. Information was collected for all patients on adverse events (AEs) in the selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. AK lesions in the selected treatment area were counted at each visit. Information regarding intercurrent disorders, therapeutics that could have resulted in

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immunosuppression, and treatment with agents known to alter AK were collected.

Number of Patients (Planned and Analyzed):

Planned: Approximately 30 patients

Analyzed: A total of 38 patients who had demonstrated complete clearance of AK lesions in study PEP005-020 were enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Patients had to achieve complete clearance of AK lesions (lesion count = 0) at Day 57 in study PEP005-020.

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:

Test product: Not applicable; no study medication was administered during this study.

Reference therapy: Not applicable

Duration of Study:

It was estimated that it would take 13 months to complete this study from the first patient enrolled to the last patient followup visit.

Randomization Scheme:

Not applicable

Criteria for Evaluation:

Efficacy:

Number of AK lesions in the selected treatment area. Recurrence was defined as any identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study.

Concomitant therapies (medications and procedures) in the selected treatment area.

Safety:

AEs in the selected treatment area.

Statistical Methods:

The statistical evaluations described below were planned to be performed after the 6-month followup visit and again after the 12-month followup visit (i.e., completion of the study).

Three analysis populations were defined: (1) the 'All Patients Enrolled' population included all patients who provided informed consent for participation in the study; (2) the 'CC57' population included all patients enrolled who showed complete clearance of AK lesions in the selected treatment area at the Day 57 visit in study PEP005-020; and (3) the 'Non-CC57' population included all patients enrolled who did not show complete clearance of AK lesions in the selected treatment area at the Day 57 visit in the previous study.

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Efficacy: For the CC57 population, AK recurrence was summarized using Kaplan-Meier methods. All event times were imputed to their target study day prior to performing the calculations. The recurrence rate was estimated by the Kaplan-Meier "failure" estimate at the target study day expressed as a percentage. The estimates, along with 95% confidence intervals, were calculated at Days 91, 183, 274, and 365. The time to recurrence was also summarized. The recurrence rate at Day 365 (12 months) was summarized for the subgroups of treatment location, geographic region, Fitzpatrick skin type, gender, age group, and baseline lesion count. The number of AK lesions in the treatment area was summarized at each visit.

Safety: For the CC57 population, the incidence rate of AEs was summarized as the number and percentage of patients with one or more episodes of the AE classified using the MedDRA (Version 11.0) preferred term and system-organ class. An overall summary of AEs was presented and included the number and percentage of patients with any AE, any serious AE (SAE), any fatal AE, any severe AE, and any AE resulting in discontinuation of study. The incidence of all AEs by preferred term regardless of the relationship to previous study treatment was summarized. Patients with SAEs, fatal AEs, severe AEs, and AEs leading to study discontinuation were presented in data listings. AE data for the Non-CC57 population were presented in data listings.

Summary of Results:

Efficacy:

At 12 months of followup, 62.5% of patients in the CC57 population treated with PEP005 Gel, 0.05% in study PEP005-020 (N=38) had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 274 days. Based on the number of lesions observed within the treatment area during 12 months of followup relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 study), the mean lesion-based recurrence rate was 11.3%.

Safety:

Over the 12 months of followup in this observational study, only 1 AE in the selected treatment area was reported for the 38 patients in the CC57 population (haematoma of moderate severity, considered unrelated to study drug).

Among the 60 patients in the Non-CC57 population (who had not shown complete clearance of AK lesions at the Day 57 visit in study PEP005-020 and who were terminated from this followup study), 1 patient had an AE (basal cell carcinoma of moderate severity, considered by the investigator as not related to study medication).

Conclusion:

During 12 months of followup, 62.5% of patients who had complete clearance of AK lesions at the Day 57 visit following treatment with 0.05% PEP005 Gel on the trunk and extremities in study PEP005-020 had a new or recurrent AK lesion within the treatment area, with a median time to recurrence of 274 days. Relative to the total number of AK lesions observed prior to treatment in study PEP005-020, the lesion recurrence rate at 12 months of long-term followup was 11.3%. Among the patients in this study, there was no safety concern in the selected

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treatment area.		
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2 SYNOPSIS

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Name of Finished Product: PEP005 (ingenol mebutate) Gel		
Name of Active Ingredient: Ingenol Mebutate		

Title:
A 12 month, long-term follow-up study of patients with actinic keratosis on non-head locations (trunk and extremities) who have completed Day 57 in study PEP005-028

Investigators and Sites: 15 centers in the United States

Publications: None

Study Period:
First patient enrolled: 09 September 2009
Last patient completed: 11 October 2010

Phase of Development: 3

Objectives:
To summarize treatment area recurrences of actinic keratosis (AK) lesions, in the selected treatment area during a 12-month followup period for patients with complete clearance, who completed Day 57 in study PEP005-028.
To summarize long-term safety data, in selected treatment area over a 12-month followup period for patients with complete clearance, who have completed Day 57 in study PEP005-028.

Methodology:
This was a prospective, longitudinal, observational study in patients who achieved complete clearance at Day 57 in study PEP005-028. No study medication was administered during PEP005-032.
Patients were enrolled at Day 57 (or within 4 weeks after Day 57) of the previous study. Patients were to return to the clinic for followup visits at 3, 6, 9, and 12 months after the Day 57 visit in the previous study. Information was collected for all patients on adverse events (AEs) in the selected treatment area and concomitant therapies (medications and procedures) specific to the selected treatment area. 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 actinic keratosis was collected.

Number of Patients (Planned and Analyzed):
Planned: Approximately 40 patients
Analyzed: A total of 43 patients were enrolled (38 received PEP005 Gel 0.05% and 5 received vehicle gel in the previous study [PEP005-028]).

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Diagnosis and Main Criteria for Inclusion:

Patients had to achieve complete clearance of AK lesions at Day 57 in the previous study, PEP005-028.

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:

Test product: Not applicable; no study medication was administered during this study.

Reference therapy: Not applicable

Duration of Study:

It was estimated that it would take 15 months to complete this study from the first patient enrolled to the last patient followup visit.

Randomization Scheme:

Not applicable

Criteria for Evaluation:

Efficacy:

Number of AK lesions in the selected treatment area. Recurrence was defined as any identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study.

Concomitant therapies (medications and procedures) for treatment of AK lesions in the selected treatment area.

Safety:

AEs in the selected treatment area.

Statistical Methods:

The statistical evaluations described below were planned to be performed after the 6-month followup visit and again after the 12-month followup visit (i.e., completion of the study).

Two analysis populations were defined as follows: (1) the 'All Patients Enrolled' population included all patients who signed an informed consent for participation in the study within 4 weeks of the Day 57 visit in the previous study (PEP005-028) and (2) the 'CC57' population included all patients enrolled who showed complete clearance of AK lesions in the selected treatment area at Day 57 in the previous study. Patients were classified into treatment groups according to the treatment received in the previous study.

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

Sponsor: Peplin Operations Pty Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: PEP005 (ingenol mebutate) Gel		
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Safety: For the CC57 population, the incidence rate of AEs was summarized as the number and percentage of patients with one or more episodes of the AE classified using the MedDRA (Version 11.0) preferred term and system-organ class. An overall summary of AEs was presented and included the number and percentage of patients with any AE, any serious AE (SAE), any fatal AE, any severe AE, and any AE resulting in discontinuation of study. The incidence of all AEs by preferred term regardless of the relationship to previous study treatment was summarized for each treatment group. Patients with SAEs, fatal AEs, severe AEs, and AEs leading to study discontinuation were presented in data listings.

Summary of Results:

Efficacy: At 12 months of followup, 50% of patients treated with PEP005 Gel, 0.05% in study PEP005-028 (N=38) had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to recurrence was > 183 days. Based on the number of lesions observed within the treatment area during 12 months of followup relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 studies), the mean lesion-based recurrence rate was 14.9%.

At 12 months of followup, 80% of patients treated with vehicle gel in the previous study (N=5) had a new or recurrent AK lesion, with a median time to recurrence of 183 days, and the mean lesion-based recurrence rate at 12 months was 19.2%.

Safety: Over the 12 months of followup, only 1 AE in the selected treatment area (mild rash, considered unrelated to study drug) was reported among the 38 subjects treated with PEP005 Gel, 0.05% in study PEP005-028; no other AEs or safety concerns were reported.

Conclusion:

During 12 months of followup, 50% of patients had at least one new or recurrent AK lesion within the treatment area on the trunk or extremities that had been treated with PEP005 Gel, 0.05% in study PEP005-028; the median time to recurrence was > 183 days. Relative to the total number of AK lesions observed prior to treatment in study PEP005-028, the lesion-based recurrence rate at 12 months of long-term followup was 14.9%. With only one reported AE of mild, unrelated rash, there was no safety concern in the selected treatment area.

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2 SYNOPSIS

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		
Title of Study: A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 Topical Gel, 0.0025%, 0.01%, and 0.05%, with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to nodular basal cell carcinoma		
Investigators: [redacted]		
Investigational Sites: E. Peth, WA Australia[1]**;** Clayton, VIC Australia[2]; East Melbourne, VIC Australia[3]; Benowa, QLD Australia[4]; Fremantle, WA[5]; Kogarah NSW Australia[6]; Kogarah NSW Australia[6]; Brisbane, QLD Australia[8]; East Melbourne, VIC Australia[9]; Brisbane, QLD, Australia[10]		
Study Period: 06 April 2005 to 19 May 2006		
Clinical Phase: Phase IIa		
Publications: None		
Objectives: The primary objective of this study was to determine the safety of PEP005 Topical Gel at 0.0025%, 0.01%, and 0.05% administered as two applications to patients with nodular basal cell carcinoma (nBCC) under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. The secondary objectives of the study were the following: • to evaluate the efficacy of PEP005 Topical Gel, 0.0025%, 0.01% and 0.05%, administered under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8 • to determine a recommended treatment regimen for nBCC • to evaluate patients for cosmetic outcome.		
Methodology: This was a multi-center, double-blind, randomized, vehicle-controlled, parallel-group comparison of two treatment schedules, Day 1 and Day 2 (Arm A) or Day 1 and Day 8 (Arm B) applications of three concentrations (0.0025%, 0.01%, and 0.05%) of PEP005 Topical Gel or vehicle gel to a single nBCC lesion. The duration of this study was approximately 85 days (12 weeks). The study included a screening visit, a punch biopsy of the lesion for histological confirmation, followed by treatment (two single applications of study treatment on Day 1 and Day 2 or Day 1 and Day 8) with approximately 11-weeks or 12-weeks post-treatment follow-up (Arm B and Arm A, respectively), and terminating with a complete elliptical excision of the lesion on Day 85. Additional visits every 7 to 14 days were conducted as necessary until adequate healing of the punch biopsy or until resolution of any ongoing local skin reactions (LSRs).		

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		

Name of active ingredient:

3-angeloyl ingenol (PEP005)

Number of Patients: The total number of patients planned was approximately 60, with 30 patients enrolled in each treatment Arm. A total of 58 patients were enrolled and all 58 patients were included in the Intent-to-Treat and Safety analyses, with 29 patients randomized to each treatment Arm.

Diagnosis and Main Criteria for Inclusion: Male or female patients who were at least 18 years of age who had at least one nBCC lesion on the arm, shoulder, chest, face, neck, abdomen, back, leg, or scalp.

Dosage and Administration:

Test Product

Two single topical applications of PEP005 Topical Gel (at a concentration of 0.0025%, 0.01%, or 0.05%) were applied directly to each of the selected lesions on Day 1 and Day 2 (Arm A) or Day 1 and Day 8 (Arm B) using a positive displacement micropipette. The volume of study medication applied to each lesion was based on the longest lesion diameter as measured on Day 1, 70 µl for lesions 4 mm to <10 mm and 100 µl for lesions 10 mm to 15 mm.

Reference Therapy

Vehicle gel was applied according to the guidelines used for PEP005 Topical Gel.

Duration of Treatment: Patients received 2 single applications of study medication applied to the selected lesion on Day 1 and Day 2 (Arm A) or Day 1 and Day 8 (Arm B)

Criteria for Evaluation:

Safety: Safety was evaluated by monitoring the incidence of AEs (including the incidence and severity of local skin reactions following study medication treatment); changes in hematology, serum chemistry, and urinalysis test results; vital signs measurements; and physical examination results during the study.

Efficacy:

Histological response to treatment with PEP005 Topical Gel was determined by assessing the histological clearance of the lesion based on expert review of the post-treatment excision obtained on Day 85.

Clinical response was determined by Investigator assessment of the extent of nBCC lesion clearance at each post-Day 1 visit, compared with the Baseline assessment. Clinical response was defined as: complete lesion clearance (complete clearance), almost complete lesion clearance (complete clearance and marked clearance) and incomplete lesion clearance (slight clearance, unchanged, worsened and unable to determine).

Cosmetic outcome of treatment was assessed by the Investigator on Day 85 using the photographs taken prior to treatment at the Day 1 visit as a reference with particular attention to: skin texture, skin markings, scarring, skin atrophy, hypopigmentation, and hyperpigmentation.

Statistical Methods: The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing. Data were summarized using descriptive statistics for continuous variables and using frequency and percentage for discrete variables.

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Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		

Summary of Results:

Efficacy Results: Clinical efficacy was evaluated by histological and clinical assessment (global response to treatment, clearance rate of nBCC, and composite clearance rate of nBCC) of the extent of lesion clearance, and by post-treatment cosmetic outcome.

The histological response to treatment in Arm A demonstrated: 25.0% of patients in both the 0.01% and 0.05%, 14.3% of patients in the 0.0025% PEP005 Topical Gel group, and 0 of patients in the vehicle gel group, had no histological evidence of nBCC in the excised lesion at the End of Study assessment. The histological response to treatment in Arm B demonstrated: 25.0% of patients in the 0.05%, 37.5% of patients in the 0.01%, 14.3% of patients in the 0.0025% PEP005 Topical Gel group, and 40.0% of patients in the vehicle gel group, had no histological evidence of nBCC in excised lesion at the End of Study assessment. No statistically significant difference among treatment groups was observed for Arms A or B, and no statistically significant difference was revealed when individual concentrations of PEP005 Topical Gel in Arms A or B were compared to vehicle gel. No statistically significant difference in histological response was revealed between treatment Arms at any concentration level.

When clearance rate of nBCC was assessed clinically, the percentage of patients (Arm A vs Arm B) who had complete clearance at the End of Study was: 25.0% vs 25.0% for 0.05%, 25.0% vs 12.5% for 0.01% and 0% vs 16.7% for the vehicle gel group. No patients in either treatment Arm of the 0.0025% PEP005 Topical Gel group had complete lesion clearance at End of Study. No statistically significant difference was revealed for the clinically assessed clearance rate between treatment Arms, at any concentration level.

Assessing composite clearance rate of nBCC, the percentage of patients in treatment Arm A with composite clearance at the End of Study was 25.0% in the 0.05% PEP005 Topical Gel group and 12.5% in the 0.01% PEP005 Topical Gel group. No patients in either the 0.0025% PEP005 Topical Gel or vehicle gel groups had composite clearance at End of Study. The percentage of patients in treatment Arm B with composite clearance at the End of Study was 12.5% in the 0.05% PEP005 Topical Gel group and 16.7% in the vehicle gel group. No patients in either the 0.01% PEP005 Topical Gel or 0.0025% PEP005 Topical Gel groups had composite clearance at End of Study. No statistically significant difference among treatment groups was observed fro Arms A or B, and no statistically significant difference was revealed when individual concentrations of PEP005 Topical Gel in Arms A or B were compared to vehicle gel. No statistically significant difference in composite clearance was revealed between treatment Arms at any concentration level.

There was no clinically significant difference in clearance rates when the global response to treatment was evaluated by lesion location or by longest lesion diameter when treatment Arm A was compared to treatment Arm B

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Name of finished product: PEP005 Topical Gel		

Name of active ingredient:

3-angeloyl ingenol (PEP005)

When cosmetic outcome after treatment was evaluated, improvement in skin texture and skin marking was observed for at least one patient in all four treatment groups and treatment Arms, with the exception of the Arm B, 0.0025% PEP005 Topical Gel group, where no patients showed improvement in skin texture or skin marking. The percentage of patients with an improvement in skin texture for Arm A vs Arm B at Day 85 was 50.0% vs 37.5% in the 0.05% PEP005 Topical Gel group, 12.5% vs 25.0% in the 0.01% PEP005 Topical Gel group, 42.8% vs 0% in the 0.0025% PEP005 Topical Gel group, and 33.3% vs 16.7% in the vehicle gel group. The percentage of patients with an improvement in skin marking for Arm A vs Arm B at Day 85 was 37.5% vs 25.0% in the 0.05% PEP005 Topical Gel group, 12.5% vs 25% in the 0.01% PEP005 Topical Gel group, 28.6% vs 0% in the 0.0025% PEP005 Topical Gel group, and 33.3% vs 16.7% in the vehicle gel group. Conditions of skin atrophy, hypopigmentation, hyperpigmentation, and scarring were absent at Day 85 for the majority (range: 67% to 100%) of patients in all treatment groups and both treatment Arms. In Arm A, only five patients had skin atrophy, scarring, hypopigmentation or hyperpigmentation present at Day 85. It is possible that the screening biopsy of the lesion may have affected the cosmetic outcome. One patient each in the vehicle gel group had scarring, one patient in the 0.0025% PEP005 Topical Gel group had hyperpigmentation, and one patient in the 0.01% PEP005 Topical Gel group had hypopigmentation and all three cosmetic conditions were improved from the baseline assessment. Two patients in the 0.0025% PEP005 Topical Gel group had skin atrophy at Day 85, one patient had no change from the baseline assessment and one patient had mild worsening. In Arm B, 13 patients had skin atrophy, scarring, hypopigmentation, or hyperpigmentation at Day 85; six patients in the vehicle gel group, four patients in the 0.05% PEP005 Topical Gel group, and two patients in the 0.01% PEP005 Topical Gel group. Of these twelve conditions present at Day 85, ten had no change from baseline noted and three had mild worsening.

An apparent concentration response was observed in the occurrence of moderate and severe local skin reactions, with a higher frequency of severe events reported for the 0.01% and 0.05% PEP005 Topical Gel groups.

Safety Results: Overall, with the exception of the expected local skin reactions, the incidence of AEs was low and the most common treatment-emergent AEs were erythema extending outside of the treatment area (five patients) and basal cell carcinoma (BCC) (five patients). All five patients who experienced erythema extending outside of the treatment area were in the 0.05% PEP005 Topical Gel group. Five patients were diagnosed with BCC, three patients in one of the PEP005 Topical Gel groups and two patients in the vehicle gel group. Of these five events of BCC, only one was considered as possibly related to study medication. Patient [redacted] randomized to vehicle gel application to a lesion on his back, was diagnosed with BCC on his upper back considered by the Investigator to be possibly related to study medication. Two patients in treatment Arm A [redacted] and [redacted] and one patient [redacted] in treatment Arm B experienced an SAE, all were considered not related to study medication by the Investigator. One patient [redacted] in Arm A of the 0.01% PEP005 group was discontinued due to progression of neoplasm that, in the opinion of the Investigator, was possibly related to study medication.

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
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Name of active ingredient: 3-angeloyl ingenol (PEP005)		

Most treatment-emergent AEs were classified as mild or moderate in intensity. In Arm A, a total of five events classified as severe were reported. Application site irritation, erythema extending outside of the treatment area, skin ulcer, and animal bite to the hand that were assessed as severe were reported for three patients in the 0.05% PEP005 Topical Gel group and one patient in the vehicle gel group developed a new lesion on his back (approximately 15 cm away from a treated nBCC lesion), diagnosed with malignant melanoma Stage IV on his upper back, that was assessed as severe in intensity. The events of application site irritation, erythema extending outside of the treatment area, and skin ulcer were considered as probably related to study medication. In Arm B, a total of two events classified as severe were reported. Neoplasm progression assessed as severe in intensity was reported for one patient in the 0.0025% PEP005 Topical Gel group and severe malignant melanoma was reported for one patient in the 0.05% PEP005 Topical Gel group. Neither event was considered related to study medication.

Patients were evaluated for the following local skin reactions: itching, erythema, edema, erosion/ ulceration, scabbing/crusting, weeping/exudates, vesicles, flaking/scaling/dryness, hypopigmentation, hyperpigmentation, and scarring. The most common local skin reactions were erythema (Arm A: 15 patients; Arm B: 17 patients) and flaking/scaling/dryness (13 patients in each treatment Arm). A higher incidence of local skin reactions were reported by patients in the 0.01% and 0.05% PEP005 Topical Gel groups than in the 0.0025% PEP005 Topical Gel or vehicle gel groups. The incidence of mild or moderate local skin reactions were comparable for both treatment Arms.

For Arm A, the percentage of severe local skin reactions was 50.0% (95% CI: 8.20%, 91.80%) in the 0.05% PEP005 Topical Gel group and 12.5% (95% CI: -15.15%, 40.15%) for the 0.01% PEP005 Topical Gel group. No lesions were rated as severe in the 0.0025% PEP005 Topical Gel or vehicle gel groups. Fisher's Exact test revealed no statistically significant difference (p=0.0527) among treatment groups for treatment Arm A and no statistically significant differences when individual PEP005 Topical Gel concentrations or concentration levels were compared to vehicle gel. For Arm B, the percentage of severe local skin reactions was 25.00% (95% CI: -11.20%, 61.20%) for the 0.05% PEP005 Topical Gel group and 12.50%.

No patients discontinued from the study because of a local skin reaction; however, two patients in the 0.05% PEP005 Topical Gel group of Arm A received only one application of PEP005 Topical Gel due to a severe local skin reaction (severe vesiculation/severe erosion) and two patients had study treatment delayed to Day 8 due to a severe local skin reaction; one patient in the 0.05% PEP005 Topical Gel group of Arm A had severe skin lesion and one patient in the 0.01% PEP005Topical Gel group of Arm A had severe blistering.

Local skin reactions that were severe in nature included vesicles reported for two patients in the 0.01% PEP005 Topical Gel group and four patients in the 0.05% PEP005 Topical Gel group; erythema, experienced by three patients in the 0.05% PEP005 Topical Gel group; edema, reported for one patient in the 0.01% PEP005 Topical Gel group; and flaking/scaling/dryness, reported for one patient in the 0.05% PEP005 Topical Gel group.

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		
Conclusions: Overall, results obtained in this study demonstrate that the application of PEP005 Topical Gel at concentrations of 0.0025%, 0.01%, and 0.05% is safe and well tolerated. Due to the small numbers of patients per treatment group, no statistically significant differences were observed among treatment groups. However, the complete lesion clearance rate of nBCC (12.5% to 25.0%) or the composite clearance rate of nBCC (12.5% to 25.0%) was higher in the 0.01% and 0.05% PEP005 Topical Gel groups than either the 0.0025% PEP005 Topical Gel group or the vehicle group (0 % to 16.7%). A higher frequency of moderate or severe local skin reactions were reported for the 0.01% and 0.05% PEP005 Topical Gel groups of Arm A and Arm B.		
Date of Report: 18 August 2008 and 23 January 2007		

2 SYNOPSIS

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		
Title of Study: A multi-center, randomized, double-blind, parallel-group, vehicle-controlled study to determine the safety of PEP005 0.0025%, 0.01%, and 0.05% gel with two treatment schedules, Day 1 and Day 2 or Day 1 and Day 8 applications to superficial basal cell carcinoma		
Investigators: [redacted]		
Investigational Sites: [1]Clayton, VIC Australia; [2]East Melbourne, VIC Australia; [3]Benowa, QLD Australia; [4]Fremantle, WA; [5]Kogarah NSW Australia; [6]Brisbane, QLD, Australia; [7]East Melbourne, VIC Australia[8]		
Study Period: 07 April 2005 to 07 March 2006		
Clinical Phase: Phase IIa		
Publications: None		
Objectives: The primary objective of this study was to determine the safety of 0.0025%, 0.01%, and 0.05% PEP005 Topical Gel, administered as two applications to patients with superficial basal cell carcinoma (sBCC) under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8. The secondary objectives of the study were: • to evaluate the efficacy of 0.0025%, 0.01% and 0.05% PEP005 Topical Gel administered under the following two treatment schedules: Day 1 and Day 2 or Day 1 and Day 8; • to determine a recommended treatment regimen for sBCC; and • to evaluate cosmetic outcome.		
Methodology: This was a multi-center, double-blind, randomized, vehicle-controlled, parallel-group comparison of two treatment schedules: Day 1 and Day 2 (Arm A) or Day 1 and Day 8 (Arm B) applications of three concentrations (0.0025%, 0.01%, and 0.05%) of PEP005 Topical Gel to a single sBCC lesion. The duration of this study was approximately 85 days (12 weeks). The study included a screening visit, a punch biopsy of the lesion for histological confirmation, study medication treatment (two single applications of study treatment on Day 1 and Day 2 or Day 1 and Day 8), approximately 11-weeks or 12-weeks post-treatment follow-up (Arm B and Arm A, respectively) and terminating with an excision of the lesion on Day 85. Additional visits every 7 to 14 days were conducted, as necessary, until adequate healing of the punch biopsy or until resolution of any ongoing local skin reactions.		
Number of Patients: The total number of patients planned was approximately 60, with 30 patients enrolled in each treatment arm. A total of 92 patients were screened, 60 were analyzed for efficacy, and 60 were analyzed for safety.		

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		
Diagnosis and Main Criteria for Inclusion: Male or female patients, who were at least 18 years of age, who had at least one sBCC lesion on the arm, shoulder, chest, face, neck, abdomen, back, leg or scalp.		
Dosage and Administration: Test Product: Two individual topical applications of PEP005 Topical Gel (at a concentration of 0.0025%, 0.01%, or 0.05%) were applied directly to each of the selected lesions using a positive displacement micropipette. The volume of study medication applied to each lesion was based on the longest lesion diameter as measured on Day 1: 70 µl for lesions <10 mm; and 100 µl for lesions ≥ 10 mm. Reference Therapy: Vehicle gel was applied according to the same guidelines used for PEP005 Topical Gel.		
Duration of Treatment: Patients received 2 individual applications of study medication, applied to the selected lesion: on Day 1 and Day 2 (Arm A); or Day 1 and Day 8 (Arm B).		
Criteria for Evaluation: **Safety:** Safety was evaluated by monitoring the incidence of AEs (including the incidence and severity of local skin reactions to study medication); and changes in hematology, serum chemistry and urinalysis test results; vital signs measurements; and physical examination during the study. **Efficacy:** Histological response to treatment with PEP005 Topical Gel was determined by assessing the histological clearance of the lesion based on expert review of the post-treatment excision obtained on Day 85. Clinical response was determined by Investigator assessment of the extent of sBCC lesion clearance at each post-Day 1 visit, compared with the Baseline assessment. Clinical response was defined as: complete lesion clearance (complete clearance), almost complete lesion clearance (complete clearance and marked clearance) and incomplete lesion clearance (slight clearance, unchanged, worsened and unable to determine). Cosmetic outcome of treatment was assessed by the Investigator on Day 85 using the photographs taken prior to treatment at the Day 1 visit as reference. Particular attention was paid to: skin texture, skin markings, scarring, skin atrophy, hypopigmentation and hyperpigmentation.		
Statistical Methods: The analysis in this study was primarily descriptive in nature. The study was not statistically powered to conduct formal hypothesis/inferential testing. Data were summarized using: descriptive statistics for continuous variables and frequency and percentage for discrete variables.		

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		

Summary of Results:

Efficacy Results: Clinical efficacy was evaluated by histological and clinical assessment (global response to treatment, clearance rate of sBCC and composite clearance rate of sBCC) of the extent of lesion clearance, and by post-treatment cosmetic outcome. When the histological response to treatment Arm A was reviewed: 62.5% of patients in the 0.05%; 25.0% of patients in the 0.01%; 0% of patients in the 0.0025% PEP005 Topical Gel group; and 0% of patients in the vehicle gel group, had no histological evidence of sBCC in the excised lesion at the End of Study assessment. A statistically significant difference among treatment groups (p=0.0109) was revealed, and the pairwise analysis revealed a statistically significant difference (p=0.0310) when the 0.05% PEP005 Topical Gel group was compared with vehicle gel group.

When the histological response to treatment Arm B was reviewed: 37.5% of patients in the 0.05%; 0% of patients in the 0.01%; 12.5% of patients in the 0.0025% PEP005 Topical Gel group; and 16.7% of patients in the vehicle gel group, had no histological evidence of sBCC in the excised lesion at the End of Study assessment. No statistically significant difference among treatment groups was observed, and no statistically significant difference was revealed when individual concentrations of PEP005 Topical Gel were compared to vehicle gel. No statistically significant difference in histological response was revealed between treatment arms at any concentration level.

When clearance rate of sBCC was assessed clinically, the percentage of patients (Arm A vs Arm B) who had complete clearance at the End of Study was: 62.5% vs 12.5% for 0.05%, 37.5% vs 12.5% for 0.01%, 12.5% vs 12.5% for 0.0025% PEP005 Topical Gel groups; and 16.7% vs 0% for the vehicle gel group. No statistically significant differences between treatment arms at any concentration level were revealed.

When the composite clearance rate (combining histological and clinical assessments) of sBCC was evaluated, the percentage of patients in treatment Arm A with the composite clearance at the End of Study was: 50.0% in the 0.05%; 25.0% in the 0.01%;0% in the 0.0025% PEP005 Topical Gel group; and 0% in the vehicle group. A statistically significant difference (p=0.0444) among treatment groups for treatment Arm A was revealed; however, there were no statistically significant differences when individual concentrations of PEP005 Topical Gel were compared to vehicle gel. The percentage of patients in treatment Arm B with composite clearance at the End of Study was: 12.5% in the 0.05%; 0% in the 0.01%; 12.5% in the 0.0025% PEP005 Topical Gel groups; and 0% in the vehicle group. There were no statistically significant differences among treatment groups for treatment Arm B, and there were no statistically significant differences when individual concentrations of PEP005 Topical Gel were compared to vehicle gel.

When cosmetic outcome after treatment was evaluated, improvement in skin texture and skin marking was seen in some patients. The percentage of patients with an improvement in skin texture for Arm A vs Arm B at Day 85 was: 25.0% vs 37.5% in the 0.05%; 62.5% vs 62.5% in the 0.01%; 12.5% vs 37.5% in the 0.0025% PEP005 Topical Gel group; and 16.7% vs 16.7% in the vehicle gel group. Similar results were observed for skin marking. Although scarring, skin atrophy, hypopigmentation, and hyperpigmentation were absent in most patients, these cosmetic outcomes worsened in a small number of patients. It is possible that the screening biopsy of the lesion may have affected the cosmetic outcome.

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		

Due to the incorrect application of study medication at Site 04, yielding a higher local concentration of study medication, additional analyses, including and excluding Site 04 only, were performed. A total of 10 patients were enrolled at Site 04. Eight patients were assigned to treatment in Arm A and 2 patients were assigned to Arm B. Of the 8 patients in Arm A: 1 patient was in the vehicle gel group; 2 patients were in the 0.0025%; 2 patients were in the 0.01%; and 3 patients were in the 0.05% PEP005 Topical Gel group. Two patients were assigned to treatment Arm B: 1 in the vehicle gel group; and 1 in the 0.05% PEP005 Topical Gel group. Although not statistically significant, the higher exposure of study medication per treatment area for patients at Site 04 was evidenced by a higher rate of sBCC composite clearance in treatment Arm A at the 0.05% and 0.01% PEP005 Topical Gel concentrations. The composite clearance rate in the 0.05% PEP005 Topical Gel group of Arm A was 66.7% for Site 04 only vs 40.0% for all pooled sites excluding Site 04. Similarly, the composite clearance rate for the 0.01% PEP005 Topical Gel group of Arm A was 50.0% for Site 04 only vs 16.7% for all pooled sites excluding Site 04.

Much of the difference between the response rates of the treatment arms is accounted for by the patients treated by Site 04. Excluding Site 04, 27.3% of patients in the 0.01% PEP005 Topical Gel and 0.05% PEP005 Topical Gel treatment groups of Arm A had composite clearance and 0% in the same concentration groups of Arm B. Excluding Site 04, the percentage of patients (Arm A vs Arm B) with composite clearance was: 40.0% vs 0% for the 0.05% PEP005 Topical Gel group; 16.7% vs 0% for the 0.01% PEP005 Topical Gel group; 0% vs 12.5% for the 0.0025% PEP005 Topical Gel group; and 0% vs 0% for the vehicle group.

Safety Results: Overall, the incidence of AEs was low. No patients enrolled in this study had any serious adverse events (SAEs). Of the 60 patients enrolled in this study, four patients had a wound infection and three patients experienced a fall. Each of the following AEs were experienced by two patients: application site pain, erythema, back pain, increased blood glucose, headache, postoperative infection and viral infection.

Most treatment-emergent AEs were classified as mild or moderate in intensity. Only one patient (0.05% PEP005 Topical Gel, Arm A) had an AE (skin exfoliation) that was classified as severe. The skin exfoliation occurred outside the treatment area and was considered probably related to treatment with PEP005 Topical Gel.

Patients were evaluated for the following local skin reactions: itching, erythema, edema, erosion/ ulceration, scabbing/crusting, weeping/exudates, vesicles, flaking/scaling/dryness, hypopigmentation, hyperpigmentation and scarring. Most of these local skin reactions were mild in nature for both treatment arms. The most common mild local skin reactions were erythema (Arm A: 17 patients; Arm B: 15 patients) and flaking/scaling/dryness (15 patients in each treatment arm). A higher incidence of mild itching was reported by patients in Arm B (15 patients) than Arm A (3 patients) and the incidence of mild hypopigmentation was higher in Arm A (11 patients) than Arm B (3 patients). The incidence of moderate local skin reactions were comparable for both treatment arms and the most frequently reported reactions were erythema (Arm A: 6 patients; Arm B: 11 patients) and scabbing/crusting (Arm A: 8 patients; Arm B: 7 patients). The majority of local skin reactions occurred within two days of the application of study

Name of company: Peplin Limited	Summary table referring to Part of the dossier, Volume: Page:	(For National Authority use only)
Name of finished product: PEP005 Topical Gel		
Name of active ingredient: 3-angeloyl ingenol (PEP005)		

medication and resolved within one month in both treatment arms.

A total of 6 patients had at least one severe local skin reaction, 4 patients in the 0.05% PEP005 Topical Gel group and 2 patients in the 0.01% PEP005 Topical Gel group of Arm A. The following severe local skin reactions were reported: vesicles (4 patients), flaking/scaling/dryness (2 patients), erythema (1 patient), edema (1 patient), erosion/ulceration (1 patient), and scabbing/crusting (1 patient). All severe reactions occurred in treatment Arm A in either the 0.01% or 0.05% PEP005 Topical Gel groups and were resolved by the End of Study.

Of the 6 patients who experienced severe local skin reactions, 4 patients were enrolled at Site 04, where study medication was applied to a smaller area resulting in a higher effective local concentration.

No patients discontinued from the study because of an AE; however, two patients in treatment Arm A received only one application of study medication because of severe local skin reactions after the first application of PEP005 Topical Gel. Both of these patients were enrolled at Site 04.

There were no clinically significant changes in vital signs measurements, physical examination findings or clinical laboratory results from Baseline to the End of Study assessment.

Conclusions: Data obtained from all pooled sites in this study demonstrates that 0.05% PEP005 Topical Gel, administered once daily, for two consecutive days (Day 1 and Day 2) or one week apart (Day 1 and Day 8), is a safe and effective treatment for sBCC. Efficacy was demonstrated, but the highest responses were observed in patients from Site 04 where study medication was applied to a smaller area resulting in a higher local concentration. In subsequent clinical trials, higher concentrations of appropriately applied PEP005 Topical Gel should be assessed.

Date of Report: 01 July 2008 Version 2 and 31 August 2006 Version 1

SYNOPSIS

Name of Sponsor: Peplin Operations, Level 2, Brisbane Portal, 1 Breakfast Creek Road, Newstead, Queensland 4006, Australia

Name of Finished Product: PEP005-005 (0.01% concentration)

Name of Active Ingredient: PEP005

Title of Study: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of PEP005 Topical Gel (0.01% concentration) in Healthy Volunteers Using a Repeat Insult Patch Test Design

Investigator: [redacted]

Study Center: TKL Research, Inc., 4 Forest Avenue, Paramus, New Jersey, USA 07652

Publication(s): None

Pilot study period: First subject enrolled: 03-Jul-2006 Last subject completed: 12-Aug- 2006

Main study period: First subject enrolled: 14-Aug-2006 Last subject completed: 07-Oct-2006

Development Phase: Phase 1

Objectives: The primary objective of this study was to determine the sensitization potential of PEP005 Topical Gel (0.01% concentration) on normal skin. The secondary objective was to evaluate skin irritation. Additionally, safety was assessed by evaluation of adverse events reported during the study. The study completed as planned.

Methodology: This was a single-center, double-blind, randomized,, controlled, within-subject comparison study of the investigational product and its vehicle under open application conditions in healthy volunteers.

Number of Subjects: Two hundred evaluable subjects planned, 10 in a pilot group and 190 in the main group. A total of 238 were enrolled. Two hundred twenty were evaluable for sensitization analysis and 226 were evaluable for irritation analysis.

Indication and Main Criteria for Inclusion: Healthy male and female subjects 18 to 65 years of age with Fitzpatrick skin types of I, II, III, and IV.

Investigational Drug: PEP005 Topical Gel (0.01% concentration) was applied topically in the amount sufficient to cover a 4 cm^2 area of skin (10 µL) 3 times weekly for 3 weeks (9 applications total) during the induction phase, and 1 time during the challenge phase. Lot no. 0224A.

Reference Therapy: PEP005 Topical Gel Vehicle was applied topically in the amount sufficient to cover a 4-cm^2 area of skin (10 µL) 3 times weekly for 3 weeks (9 applications total) during the induction phase, and 1 time during the challenge phase. Lot no. 0177B.

Duration of Treatment: Six weeks including a 2-week rest period when there was no product application.

Name of Sponsor: Peplin Operations, Level 2, Brisbane Portal, 1 Breakfast Creek Road, Newstead, Queensland 4006, Australia

Name of Finished Product: PEP005-005 (0.01% concentration)

Name of Active Ingredient: PEP005

Criteria for evaluation:

Efficacy: Not applicable.

Safety: The determination of dermal sensitization potential was based on specific scoring criteria derived from observations in the challenge phase of the study, and confirmed in the rechallenge phase, if necessary.

Observed responses (eg, erythema, edema, and vesiculation) were graded according to a protocol-specified grading scale.

Statistical Methods: Individual subjects' cutaneous responses after challenge were classified as indicative of sensitization or not indicative of sensitization based on specific criteria defined in terms of an ordinal rating scale. The occurrence in this study of even a single reaction indicative of sensitization was sufficient to suggest that the test product may have the potential to cause hypersensitivity. Cumulative irritancy during induction was quantified by means of the mean and total cumulative irritancy scores received during the induction phase (9 readings). The mean and total irritation scores during induction were tested pairwise for product differences using Fisher's protected least significant differences in the context of the 2-way analysis of variance (ANOVA), including main effects of subject and product, without interaction. Pairwise differences were tested only if the null hypothesis of a common mean score for all products was rejected at the 5% level. There were no interim analyses performed.

Summary - Conclusions:

Efficacy Results: Not applicable.

Safety Results: A pilot study was conducted prior to the initiation of the main study. Seven (7) subjects were enrolled, and 6 subjects completed the study. One subject (No. 3) discontinued the study due to a protocol violation. There was mild irritation (minimal erythema) seen during induction for 2 subjects (Nos. 1 and 4), which resolved by the 5th and 6th induction evaluations respectively. There were no reactions at challenge observed. At the request of the sponsor the study continued onto a full panel. The total study duration was approximately 13-14 weeks. Target enrollment was 200 completed subjects evaluable for analysis. Actual enrollment was 238 subjects; 226 subjects completed induction, and 220 subjects completed all aspects of the study.

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. The mean cumulative irritation score (standard deviation) for PEP005 Topical Gel (0.01% concentration) was 0.04 (0.15), and for the vehicle control it was 0.00 (0.00). The total cumulative irritation score for PEP005 Topical Gel (0.01% concentration) was 0.34 (1.31), and for the vehicle control it was 0.00 (0.00). There was a statistically significant difference (P<.001) between the investigational product and the vehicle control in both the mean cumulative irritation score and the total cumulative irritation score.

There were no reactions at challenge indicative of a possible sensitization response, nor any that required rechallenge. 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, ie, oozing, crusting and/or superficial erosions, at all 4 challenge

Name of Sponsor: Peplin Operations, Level 2, Brisbane Portal, 1 Breakfast Creek Road, Newstead, Queensland 4006 Australia

Name of Finished Product: PEP005-005 (0.01% concentration)

Name of Active Ingredient: PEP005

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.

A total of 3 treatment-emergent adverse events were reported by 3 (1.3%) subjects. Subject No. 37 became pregnant while enrolled in the study. The subject returned to TKL for the final pregnancy test which had a positive result. The subject was discontinued from the study prior to the challenge application. In a follow-up phone call 9 days later, the subject informed the site the baby's expected due date was in May, 2007. The subject did not respond to 2 later follow-up telephone messages. This AE was considered unrelated to the study product. The Sponsor and the IRB were informed about the pregnancy. Subject No. 101 experienced a mild headache that was treated with Tylenol, and Subject No. 106 had an abscess of gums which was treated with 500 mg of amoxicillin 3 times daily for 8 days. Both AEs were considered unlikely to be related to the study product, and the subjects completed the study.

Conclusion: Under the conditions used in this study, there was no evidence of a sensitization potential or significant irritation following repeated applications of PEP005 Topical Gel (0.01% concentration).

Date of the final report: 04-Dec-2007

2 SYNOPSIS

Name of Sponsor Peplin Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	***(For National Authority Use Only)***
Name of Finished Product PEP005 0.05% Topical Gel		
Name of Active Ingredient Ingenol-3-Angelate		

Title of Study:
Multi-centre, open-label study to determine the safety and efficacy of PEP005 0.05% Topical Gel in patients with cutaneous Squamous Cell Carcinoma in situ (SCCIS, Bowen's Disease).

Investigators and Study Centres:
[redacted]

Publication (reference): None

Date of First Screening: 17 May 2006 **Date of Last Screening:** 15 Sept 2006 **Date of Last Visit Completed:** 30 Nov 2006	**Phase of Development:** IIa

Primary Objective:

- To evaluate the efficacy of PEP005 0.05% Topical Gel administered on Day 1 and Day 2 to subjects with SCCIS. Efficacy was assessed as the proportion of subjects at each End of Study Visit (Day 57 or 85) with histologically confirmed clearance of the SCCIS lesion following excision of the treatment site (Histological Clearance Rate).

Secondary Objective(s):

- To further evaluate the efficacy of PEP005 0.05% Topical Gel by assessing:
  - the proportion of subjects at each End of Study Visit (Day 57 or 85) with a complete clinical response to treatment (Clinical Clearance Rate).
- To evaluate the safety and tolerability of PEP005 0.05% Topical Gel applied once daily for two days.

Methodology:

This multi-centre, open-label study was conducted to determine the safety and efficacy of PEP005 0.05% Topical Gel applied once daily for two days, for the treatment of subjects with SCCIS. The study comprised a Screening Visit (Day -14 to -3), Treatment Visits (Day 1, Day 2), Follow-up Visits (Day 8, Day 29), an End of Study Visit (Day 57 or 85) and Post-Study Wound Evaluations (Day 62 to 71 or 90 to 99 and every 7 to 14 days thereafter until resolution of any adverse events [AEs]). The location of the histologically confirmed SCCIS lesions was documented at the Screening Visit and was verified at the Treatment Visits. The entire treatment area was excised at the End of Study Visit. The amount of PEP005 0.05% Topical Gel applied to the selected SSCIS lesion and treatment area was dependent on the longest diameter of the lesion measured at Day 1. Photographs were taken for visual documentation of the selected SCCIS lesion at all study visits.

Number of Subjects (Planned and Analysed):

The planned number of enrolments was 24 subjects from three centres.

A total of 34 subjects were screened and 25 were enrolled in the study. All 25 subjects received at least one dose of PEP005 0.05% Topical Gel and also had at least one post-baseline assessment of lesion clearance (Intent-To-Treat [ITT] population). All 25 subjects were included in the analyses of efficacy and safety.

Diagnosis and Main Criteria for Inclusion:

Male subjects or post-menopausal female subjects (no menses for at least 12 consecutive months or without a uterus) of at least 18 years of age were to have a histological diagnosis of a primary, clinically diagnosed SCCIS lesion within 90 days of the screening visit. The longest diameter of the SCCIS lesion was to be between 5 mm and 20 mm.

Name of Sponsor Peplin Limited	Individual Study Table Referring to Part of the Dossier Volume: Page:	***(For National Authority Use Only)***
Name of Finished Product PEP005 0.05% Topical Gel		
Name of Active Ingredient Ingenol-3-Angelate		

Test Product, Dose and Mode of Administration, Batch Number:

Subjects received a once daily topical dose of PEP005 0.05% Topical Gel on Day 1 and Day 2 at a concentration of 0.1 µL per mm^2 of lesion.

Duration of Treatment: Two days.

Reference Therapy, Dose and Mode of Administration, Batch Number:
A reference therapy was not used in this study.

Criteria for Evaluation:

Efficacy:
Efficacy was evaluated by assessing the histological and clinical clearance of the SSCIS lesion at the End of Study Visit (Day 57 or 85).

Safety:
Safety was evaluated by (1) the incidence and severity of drug-related Local Skin Responses (LSRs), (2) the incidence of treatment-related AEs and (3) the incidence of changes in vital signs from baseline (Day 1) through to the End of Study Visit (Day 57 or 85).

Statistical Methods:

Efficacy analyses were conducted with the last observation carried forward. Primary and secondary efficacy endpoints were summarised using frequency tables. The proportion of subjects (and 95% confidence intervals) with lesions showing histologically confirmed clearance or complete clinical clearance were determined for each follow-up visit. Comparison of SCCIS clearance rates between the Day 57 and Day 85 groups were evaluated using Fisher's Exact Test. The study was not statistically powered to evaluate efficacy.

Safety parameters were assessed using summary statistics. Local Skin Responses were summarised using descriptive statistics and the incidence of AEs was summarised by frequency tables. Vital signs were presented for each study visit.

Summary of Results: The mean age of the 25 subjects included in the analyses was 71 years (min-max: 54 to 85 years). Most subjects were men (19 / 25; 76%) and had skin that burns easily and tans rarely or minimally (24 / 25; 96%). Subjects' lesions were mostly on the arm or leg (19 / 25; 76%) and were more than 10 mm in diameter (19 / 25; 76%). Twelve subjects (48%) were assigned to the Day 57 End of Study Visit group and 13 (52%) subjects the Day 85 End of Study Visit group.

Efficacy results: Histologically confirmed clearance of lesions was achieved in 36% (9 / 25) of all subjects who were treated with PEP005 0.05% Topical Gel; complete clinical clearance was achieved in 64% (16 / 25) of subjects. The proportion of subjects with histologically confirmed clearance of lesions was 39% (5 / 13) in the Day 57 group and 33% (4 / 12) in the Day 85 group. The proportion of subjects with complete clinical clearance of lesions was 69% (9 / 13) at Day 57 and 58% (7 / 12) at Day 85.

Safety results: All 25 subjects experienced at least one expected LSR greater than baseline within the first week after receiving PEP005 0.05% Topical Gel. Of these, the most frequently reported responses were erythema (25 / 25; 100%), skin desquamation (20 / 25; 80%) and swelling (14 / 25; 56%). Scarring was not reported. Most LSRs were mild in severity and resolved by the end of the study. Of the 25 subjects who received treatment, 12 (48%) reported 17 AEs; all events were mild to moderate in severity and only one, diarrhoea, was considered to be possibly related to the study treatment. One serious adverse event (SAE) was reported in the study but this event (worsening of chronic heart failure) was a result of the subject's medical condition before enrolment and was considered to be unrelated to the study medication. There were no reported deaths. There were no clinically relevant changes in vital signs throughout the study

Conclusions: PEP005 0.05% Topical Gel applied to SCCIS lesions once daily for two days was well-tolerated with a favourable safety profile. This study was not statistically powered to evaluate efficacy

Date of Report: 8 Jun 2007

2 SYNOPSIS

Sponsor: Peplin Operations Pty Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: PEP005 (ingenol mebutate) Gel		
Name of Active Ingredient: Ingenol Mebutate		

Title: An open-label, multicenter, dose-escalation, cohort study to determine the maximum tolerated dose and safety of PEP005 Topical Gel given as either a single application (on Day 1) or as two applications (on Day 1 and Day 8) to a superficial basal cell carcinoma (sBCC) on the trunk

Investigators and Sites: Multicenter in the United States (refer to Appendix 16.1.5.1)

Publications: There is one publication based on this study at the time of completion of this report.

Study Period:
First patient screened: February 9, 2007
Last patient completed wound healing visit: March 17, 2010

Phase of Development: 2

Objectives:
The primary objective was to determine the maximum tolerated dose (MTD) of PEP005 (ingenol mebutate) Gel when administered either as a single application or as two applications to a selected superficial basal cell carcinoma (sBCC) lesion (dose-escalation phase).

The secondary objective was to evaluate the efficacy of PEP005 Gel when administered at the MTD either as a single application or as two applications to a selected sBCC lesion (expansion phase).

Methodology:
This was a multicenter, open-label study consisting of two phases, a dose-escalation phase to determine the MTD of PEP005 Gel for the treatment of sBCC, and an expansion phase to evaluate the efficacy of PEP005 Gel in the treatment of sBCC at the MTD. Study medication was investigator-applied to a single histologically confirmed 4 to 15 mm sBCC lesion on the trunk (i.e., the back, chest, abdomen or shoulder). Two treatment arms, Arms 1 and 2, were evaluated in this study. Arm 1 patients were treated on Day 1 and had follow-up evaluations on Days 2, 8, 15, 29, 57 and 85 and subsequently for wound healing following Day 85. Arm 2 patients were treated on Days 1 and 8 and had follow-up evaluations on Days 2, 9, 15, 29, 57 and 85, and subsequently for wound healing following Day 85. On Day 85, all patients in both treatment arms had a complete elliptical excision of the lesion, which was histologically assessed for the presence or absence of sBCC by an independent central dermatopathologist.

The dose-escalation phase assessed the safety of patients in each treatment arm within each escalation cohort. An escalation cohort consisted of a group of three patients, treated at a given concentration within either the Arm 1 or Arm 2 dosing regimen. Ten concentrations were evaluated in the dose-escalation phase: 0.025%, 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, 0.175%, 0.2%, 0.225%, and 0.25%. Dose escalation was contingent on the results of the safety evaluation for each cohort of three patients treated at a given concentration in each treatment arm. Safety was evaluated by a dose-escalation steering committee (DESC) consisting of all participating study investigators together with an independent dermatologist who chaired each meeting. Patient photos, local skin responses (LSRs), global severity ratings (GSRs) and adverse event (AE) data from screening to Day 15 were evaluated for each cohort of three patients. Following review of the data, the DESC had to reach a voting majority regarding escalation to the next concentration.

The expansion phase began in each arm once the MTD for that arm was reached. The expansion phase enrolled

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additional patients at the MTD concentration in both treatment arms. No DESC meetings were planned for the expansion phase.

Number of Patients (Planned and Analyzed):

Dose escalation planned: Enrollment of three to six patients was planned for each cohort. A total of between 28 and 58 patients were expected per treatment arm, depending on the concentration level reached during the dose-escalation phase.

Dose escalation analyzed: Three patients were enrolled and treated in each of the following PEP005 Gel dose-escalation cohorts for Arm 1 and Arm 2: 0.025%, 0.05%, 0.075%, 0.1%, 0.125%, 0.15%, 0.175%, 0.2%, 0.225%, and 0.25%. A total of 30 patients were treated in each arm during the dose-escalation phase. PEP005 Gel, 0.25%, was the maximum concentration used in the dose-escalation phase; despite the fact that no dose-limiting toxicities (DLTs) were reported at this concentration, for the purposes of the analyses this concentration was defined as the MTD in the tables and listings of the study. Additional patients were then enrolled at this concentration in the expansion phase.

Expansion planned: A total of 25 patients (three from the dose-escalation phase and 22 from the expansion phase) were expected per arm.

Expansion analyzed: Twenty-five patients in Arm 1 and 22 patients in Arm 2 were treated at the MTD (PEP005 Gel, 0.25%). These totals included three patients in each arm from the dose-escalation phase. The total number of patients treated in the study was 101 (52 in Arm 1 and 49 in Arm 2).

Diagnosis and Main Criteria for Inclusion: Eligible patients were men and women of non-childbearing potential (i.e., postmenopausal or without a uterus) who were aged at least 18 years and had a clinically diagnosed and histologically confirmed 4 to 15 mm sBCC lesion located on the trunk that was suitable for excision. The initial biopsy for histological confirmation should have removed no more than 20% of the total tumor mass.

Test Product and Reference Therapy, Dose, Mode of Administration and Lots:

Test product: PEP005 Gel at concentrations of 0.025% (Lot 0337 B), 0.05% (Lots 0338 B and 0134 C), 0.075% (Lot 0135 C), 0.1% (Lot 0294 C), 0.125% (Lot 0295 C), 0.15% (Lot 0086 D), 0.175% (Lot 0280 D), 0.2% (Lot 9334 D), 0.225% (Lot 0385 D), and 0.25% (Lot 0386 D).

Reference therapy: None

Duration of Treatment:

Arm 1: Study medication was administered once daily for one day (Day 1).

Arm 2: Study medication was administered once daily for two non-consecutive days (Days 1 and 8).

Randomization Scheme: This was an open-label study.

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Criteria for Evaluation:

Primary Efficacy: Complete (histological) clearance: the percentage of patients at Day 85 with histologically confirmed clearance of the sBCC lesion in each expansion-phase cohort (Arm 1 and Arm 2).

Secondary Efficacy:

Composite clearance: the percentage of patients at Day 85 with both histologically confirmed clearance and clinically assessed clearance of the sBCC lesion in each expansion-phase cohort.

Additional Efficacy:

Clinical clearance: categorized as 'complete clearance', 'incomplete clearance' and 'unable to assess', as determined by the investigator. The clinical clearance assessment was performed on Days 8, 9 (Arm 2 only), 15, 29, 57, and 85. A global response to treatment was used to compare the investigator-assessed response between arms for patients treated in the expansion phase.

Safety**:**

The following safety variables were assessed:

- Extent of study medication exposure, based on the total number of doses administered and the total volume (a calculation of volume [mL] of gel applied based on lesion size);
- Incidence of AEs and serious AEs (SAEs);
- Grade and change from baseline for LSRs;
- Grade and change from baseline for GSR;
- Incidence of abnormal proliferation within the treatment area;
- Incidence of abnormalities in laboratory tests (urinalysis, hematology, and chemistry);
- Incidence of change in vital signs and physical examination.

Statistical Methods:

Efficacy: The full analysis set was used for all efficacy endpoints. The per-protocol population was also presented as supplemental information for all efficacy endpoints, except for the descriptive summary of the global response to treatment as assessed by the investigator. No imputation was performed for missing data.

The number and percentage of patients with Day 85 histological clearance (primary endpoint), composite clearance and clinical clearance of the sBCC lesion were reported with their 95% confidence intervals (CIs). The 95% CIs were calculated using the normal approximation to the binomial distribution and were also determined for the difference in histological clearance, composite clearance, and clinical clearance between both arms in the expansion phase. A Chi-squared test was used to compare the percentage of patients in each arm with histological clearance, composite clearance, and clinical clearance. Exact methods were used where appropriate.

Composite clearance was summarized by the number and percentage of patients in the following four categories:

- histologically cleared/clinically cleared,
- histologically cleared/clinically not cleared,
- histologically not cleared/clinically cleared, and
- histologically not cleared/clinically not cleared.

Counts and percentages for the investigator-assessed global response to treatment were summarized for both expansion-phase cohorts on Days 8, 15, 29, 57, and 85. A Chi-squared test was used to compare the global response to treatment between both arms in the expanded cohorts. All cases in which the investigator rated a patient's clinical clearance on Day 85 as 'unable to assess' were summarized in a listing, together with the reason given for the

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inability to perform the assessment.

Safety: The safety analysis was performed using the all patients treated (APT) population. Due to the large number of cohorts in each treatment arm, safety assessments for AEs, LSRs, and GSRs were summarized by grouping the cohorts into three categories based on the concentration of PEP005 Gel used: low (0.025% to 0.1%), medium (0.125% to 0.175%), and high (0.2% to 0.25%).

The number of doses of study medication administered and the total volume of gel administered (based on the lesion size) was summarized by descriptive statistics and presented by cohort and treatment arm. The number and percentage of patients who completed the scheduled number of doses was summarized by counts and percentages.

AEs were summarized by concentration category (low, medium, and high) and separately for each expansion-phase cohort. If a patient reported multiple AEs within the same system organ class (SOC), the patient was only counted once per SOC and once per preferred term.

LSRs were recorded as graded responses ranging from 0 to 4 for each individual LSR parameter within each treatment area: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration, pigmentation and scarring. The change from baseline was categorized as a score ranging from –4 to +4, where a positive score represented a worsening from baseline. Pigmentation was further categorized into hyperpigmentation and hypopigmentation. A composite LSR score, ranging from 0 to 24, was calculated by summing the individual LSR scores (excluding pigmentation and scarring) for each treatment area at all scheduled time points. The change from baseline in the composite LSR score was presented for each post-treatment visit as a continuous variable by cohort and treatment arm.

The treatment area was also assessed at each time point for the intensity of the overall GSR (none, mild, moderate, or severe). The change from baseline (ranging from –3 to +3) was presented as a continuous variable.

The highest post-baseline LSR grade, GSR, and composite score, together with the presence of pigmentation by type (hypo- or hyperpigmentation) was summarized and presented as counts and percentages of patients within each PEP005 Gel concentration category (low, medium, or high). The change from baseline in the LSR grade, composite score and GSR was also presented by concentration category for each scheduled post-baseline time point using descriptive statistics. The least squares (LS) mean difference and 95% CIs between concentration categories (low versus medium, and low versus high) were presented. Pigmentation type was not included in this summary.

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Summary of Results:

Efficacy:

One hundred and one patients were treated at 10 concentration levels. Patients had a mean age of 58.9 years (range, 37 to 84), and 75% were men. All patients were Caucasian and most had a Fitzpatrick skin type of 2 (61%; 62/101), or 3 (29%; 29/101). The treated lesion was located on the back in 66% of patients.

Efficacy was evaluated in 46 patients treated with the highest concentration evaluated, which was PEP005 Gel, 0.25%. The histological clearance rate was higher in Arm 1 compared with Arm 2: 68% [95% CI, 49.7–86.3%] (17/25) versus 38% [95% CI, 17.3–58.9%] (8/21); p = 0.0425. The composite clearance rate was 24% (6/25) in Arm 1 and 5% (1/21) in Arm 2 (p = 0.0846 in the full analysis set and p = 0.0577 in the per-protocol population). The clinical clearance rate was also higher in Arm 1, but the difference was not statistically significant: 40% (10/25) versus 19% (4/21) (p = 0.1479). The two treatment arms were comparable at baseline with respect to demographics, other characteristics, and the mean diameter of the treated sBCC lesion. No post-hoc subgroup analyses were performed.

Histological clearance rates were higher than complete clinical clearance rates in both treatment arms, while the lowest rates were observed for composite clearance. The lower rates of clinical and composite clearance were attributable to the high proportion of patients rated as ‘not assessable’ for clinical clearance at Day 85. Patients were most commonly not assessable for clinical clearance (i.e., determined by visual inspection) due to the presence of residual LSRs at Day 85, or because the investigator felt unable to assess lesion clearance in the absence of histology reports. A comparison of the histological and clinical clearance rates suggested that Arm 1 had higher efficacy than Arm 2 based on the composite clearance rate (24% versus 5%) and the proportion of patients with neither histological nor clinical clearance (16% versus 48%).

Safety:

PEP005 Gel was safe and well tolerated when applied once daily as either a single application or as two applications administered one week apart to sBCC lesions on the trunk. The highest concentration used in both arms of the study, PEP005 Gel, 0.25%, was based on exhaustion of the available concentrations of study medication. No DLT occurred during the study (one patient had a severe GSR during the dose-escalation phase, but on review this was not considered to meet the criteria for DLT).

All but one patient received treatment as planned. One patient in Arm 2 received PEP005 Gel, 0.25%, on Day 1, but the Day 8 application was withheld because of severe treatment-related, chemically induced lymphangitis. There were three SAEs, none treatment-related. One of these SAEs (mesenteric vein thrombosis during follow-up and deemed unrelated by the investigator) led to study discontinuation. No deaths occurred during the study.

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

The most common LSR was erythema, which was present in all patients at some time during the study. Flaking or scaling, swelling, crusting and vesiculation/pustulation each occurred in 66% to 97% of patients. A dose-response was apparent, and several LSRs showed a trend towards a higher incidence and/or severity in Arm 2 compared with Arm 1. The majority of LSRs were rated Grade 1–2, but 17% of patients experienced one or more Grade 4 LSRs,

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which typically occurred in the high PEP005 Gel concentration groups and were more common in Arm 2.

The mean composite LSR score peaked on Days 2 and 8 (pre-dose) in Arm 1, reaching a maximum of 6.0 (from a possible score of 24) in patients treated with the highest concentration. In Arm 2, the mean composite LSR score increased following the first and second applications of PEP005 Gel (i.e., Day 2 and Day 9), with a maximum score of 8.1 on Day 9 for patients treated with PEP005 Gel, 0.25%. Mean scores returned to baseline levels or lower by Day 29 in both treatment arms.

Most GSRs were mild or moderate, with moderate GSRs observed predominantly on Days 2 to 15. The GSR tended to be more intense in Arm 2; in the high concentration groups, the proportion of patients with a moderate GSR was 61% (19/31) in Arm 1 and 86% (24/28) in Arm 2. Only two patients had severe GSRs. Fourteen patients (14%) had GSRs that worsened from baseline to the end-of-study assessment.

At Day 85, 31% of patients overall (31/101) had scarring and/or pigmentation changes that were new or worsened compared with baseline: 37% (19/52) in Arm 1 and 24% (12/49) in Arm 2. Among patients with new or worsened pigmentation changes, hypopigmentation was more common than hyperpigmentation (22 and two patients, respectively), and most changes were Grade 1. New scarring was recorded in 17 patients (16 Grade 1 and one Grade 2), but it should be noted that all lesions were biopsied prior to the screening visit.

No abnormal proliferation was observed in the treatment area, and there were no skin infections related to study medication. One patient had an abnormal laboratory result that was considered an AE and four AEs were noted at the end-of-study physical examination; however, none of these AEs was considered related to study treatment.

Conclusion:

PEP005 Gel at concentrations of up to 0.25% was safe and well tolerated when applied directly to an sBCC lesion on the trunk as either a single application (Arm 1) or two non-consecutive daily applications (Arm 2). The highest concentration used in both treatment arms was PEP005 Gel, 0.25%, based on exhaustion of the available drug concentrations; no DLT occurred during the study and 100 of 101 patients completed the planned treatment. Efficacy was higher in Arm 1, with histological clearance rates of 68% in Arm 1 versus 38% in Arm 2 for patients treated at the highest concentration level.

Final Report Date: Final , September 28, 2010

2 SYNOPSIS

Name of Sponsor/Company: Peplin Operations Pty Ltd **Name of Finished Product:** PEP005 (ingenol mebutate) Gel, 0.01% **Name of Active Ingredient:** Ingenol Mebutate	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	***(For National Authority Use Only)***

Title of Study: A 4-Day, Randomized, Controlled, Open Application Study to Evaluate the Photoirritation Potential of PEP005 (ingenol mebutate) Gel, 0.01% in Healthy Volunteers, Using a Phototoxicity Test Design

Investigator: [redacted]

Study Center: TKL Research, Inc, 4 Forest Avenue, Paramus, NJ 07652

Publication (reference): None

Studied period (years):
30 March 2009 - first subject enrolled
03 April 2009 - last subject completed

Phase of Development: I

Objectives:
The primary objective of this study was to determine the photoirritation potential of PEP005 Gel, 0.01% and its vehicle when topical application to skin was followed by light exposure.

In addition, the safety of PEP005 Gel, 0.01% was assessed by evaluation of any adverse events (AEs) reported during the study.

Methodology:
This was a single-center, randomized, within-subject comparison study of PEP005 Gel, 0.01% and vehicle. Each subject received applications of the study medications at 4 separate treatment areas, of which 2 were irradiated and 2 remained non-irradiated. A fifth untreated area was also irradiated.

Prior to determining the photoirritation potential of the active and vehicle gel, each subject's minimal erythemal dose (MED) was determined. A defined area (approximately 50 cm^2 divided into 6 equal treatment areas) on the subscapular region of each subject's back was irradiated to determine the MED of ultraviolet (UV) light.

Following MED determination, for each subject, a total of 4 treatment areas (2 irradiated and 2 non-irradiated) in the subscapular region of the back were designated for study medication application and/or irradiation. The study medication was applied to the assigned treatment areas under open conditions. After 24 hours, the designated treatment areas were exposed to irradiation. The treatment areas were examined 24 and 48 hours after irradiation for the purpose of determining the phototoxicity irritation potential. Dermal reactions at the treatment areas were evaluated using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

Number of Patients (Planned and Analyzed):
Approximately 30 subjects were planned for enrollment; 34 subjects were enrolled; 33 subjects completed the study and were evaluable.

Diagnosis and Main Criteria for Inclusion:
Healthy males or females between the ages of 18 and 65 with Fitzpatrick Skin Type I, II or III who were free of any visible skin disease at the treatment area.

Test Product, Dose and Mode of Administration, Batch Number:
PEP005 Gel, 0.01% was applied once topically in an amount (10 µL) sufficient to cover a 4 cm^2 area of skin.
Lot No. BAN-1

Duration of Treatment:
24 hours

Reference Therapy, Dose and Mode of Administration, Batch Number:
Vehicle was applied once topically in an amount (10 µL) sufficient to cover a 4 cm^2 area of skin. Lot No. BAP-1

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Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this study.

Safety:

Local Tolerability: Assessment of the treatment areas was performed once daily, on Days 2 through 4. Assessment of the untreated, irradiated control area was performed once daily, on Days 3 and 4.

Adverse Events: All local and systemic AEs observed including intensity, duration, and casual relationship to study medication.

Statistical Methods:

Efficacy:
Not applicable

Safety:
Local Tolerability: Selected pairwise comparisons were performed on the mean of the ordinal response scores assigned on Day 3 and Day 4 in the context of the analyses of variance (ANOVA). Pairs compared were: Study medications irradiated versus non-irradiated and study medications irradiated versus untreated irradiated control.
Adverse Events: All adverse events were listed by subject.

SUMMARY - CONCLUSIONS

Efficacy Results:
Not applicable

Safety Results:
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 statistically 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 statistically 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.

Conclusion:

Under the conditions employed in this study, the study medication was safe. Neither PEP005 Gel, 0.01% nor vehicle showed any potential for phototoxicity. Based on the pre-specified working criteria, neither the study medication nor vehicle are photoirritant.

Date of Report: August 25, 2009

2 SYNOPSIS

Name of Sponsor/Company: Peplin Operations Pty Ltd	**Individual Study Table Referring to Part of the Dossier:**	***(For National Authority Use Only)***
Name of Finished Product: PEP005 (ingenol mebutate) Gel, 0.01%	**Volume:**	
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Title of Study: A Randomized, Controlled Study to Evaluate the Photoallergic Potential of PEP005 (ingenol mebutate) Gel, 0.01% in Healthy Volunteers Using an Open Application Photoallergic Test Design		
Investigators: [redacted]		
Study Center: TKL Research, Inc, 4 Forest Avenue, Paramus, NJ 07652		
Publication (reference): None		
Studied period (years): 02 March 2009 – first subject enrolled 24 April 2009 – last subject completed		
Phase of development: 1		
Objectives: The primary objective of this study was to determine the photoallergic (sensitizing) potential of PEP005 Gel, 0.01% on normal skin. In addition, the safety of PEP005 Gel, 0.01% was assessed by evaluation of any adverse events (AEs) reported during the study.		
Methodology: This was a photoallergic (sensitization) test study. The trial design was a single-center, randomized within-subject comparison study. MED Determination: A series of 6 doses of UVR (full spectrum UVA and UVB) which differed by a factor of 1.25 (i.e., each irradiated site received 25% more exposure than the site to its left) was administered to each subject's subscapular area of the back to determine MED. Induction Phase: Following MED determination, patients entered the Induction Phase of the study where 4 treatment sites (2 for active gel and 2 for vehicle gel) were selected on the subscapular area on the back. The application, of PEP005 Gel, 0.01% and vehicle gel, was designated through a predetermined randomization scheme. The active gel and vehicle gel were applied to the selected treatment sites 2 times a week for 3 weeks. The treatment sites were irradiated approximately 24 hours after each application two times a week for 3 weeks. All application sites were evaluated prior to irradiation and 48 and 72 hours post irradiation. Rest Period/Challenge Phase: After a Rest Period of approximately 10 to 17 days, patients entered the Challenge Phase of the study. Four naïve treatment sites on the subscapular area of the back (2 for active and 2 for vehicle) were identified using a predetermine randomization scheme for application of PEP005 Gel, 0.01% and vehicle as well as a fifth untreated area. One active and one vehicle treatment site and the fifth untreated area were irradiated with 6 J/cm^2 of UVA (320–400 nm) using a filtered light source and ½ MED of UVA/UVB (290-400 nm) 24 hours after application. All treatment areas were assessed visually for local sensitization and photosensitization using an ordinal scoring system prior to irradiation and 24, 48 and 72 hours post irradiation. If a cutaneous response, indicating possible photosensitization, was observed, a re-challenge was to occur.		
Number of patients (planned and analyzed): Approximately 50 subjects were planned for enrollment; 60 subjects were enrolled; 55 subjects completed the study and were evaluable.		

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Diagnosis and main criteria for inclusion:

Healthy males or females between the ages of 18 and 65 with Fitzpatrick Skin Type I, II or III who were free of any visible skin disease at the treatment area.

Test product, dose and mode of administration, batch number:

PEP005 Gel, 0.01% was applied topically twice weekly for 3 weeks in an amount sufficient to cover a 4 cm^2 (10 µL) area of skin during the induction phase, and 1 time at challenge phase. Lot No. BAN-1

Duration of treatment:

6 weeks, 7 applications and subsequent irradiation procedures.

Reference therapy, dose and mode of administration, batch number:

Vehicle gel was applied topically twice weekly for 3 weeks in an amount sufficient to cover a 4 cm^2 (10 µL) area of skin during the induction phase, and 1 time at challenge phase. Lot No. BAP-1

CRITERIA FOR EVALUATION

Efficacy:

Efficacy was not assessed or evaluated in this study.

Safety:

Local Tolerability: Assessment of the treatment areas was performed 4 times weekly during the 3-week induction period except for Monday of Week 1 and 4 times following 24-hour challenge study medication application.

Adverse Events: All local and systemic AEs observed including intensity, duration, and causal relationship to study medication.

STATISTICAL METHODS:

Efficacy: Not applicable

Safety:

Photosensization: All assigned scores during induction and challenge were summarized by frequency counts by time point and treatment. The incidence of photosensitization reactions were summarized by frequency counts for each treatment.

Local Tolerability: The mean numerical equivalent score by subject and treatment, including all scores assigned during induction, was analyzed in the analysis of variance with factors subject and treatment. All pairwise treatment comparisons were performed.

Adverse Events: All adverse events were listed by subject.

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SUMMARY – CONCLUSIONS:

Efficacy Results: Not applicable.

Safety Results:

All subjects except 1 had met all the inclusion and exclusion criteria prior to enrollment. Thirteen subjects experienced at least 1 adverse event. There were no deaths or serious adverse events reported during the study. One subject was discontinued due to bronchitis. During the entire course of the study, 3 subjects reported use of exclusionary medications, 1 of which violated the inclusion and exclusion criteria prior to enrollment All female subjects of childbearing potential had a negative result from the urine pregnancy test. Subjects were free of any systemic or dermatologic disorders and significant illness which could have impacted the outcome of the study.

Local Tolerability:

Mean scores showed moderate erythema at the treatment areas irradiated after the application of PEP005 Gel, 0.01% and the vehicle. Non-irradiated treatment areas showed mild irritation for PEP005 Gel, 0.01% and no irritation to vehicle.

There was a statistically significant difference between:

- the irradiated PEP005 Gel 0.01% treatment area and the irradiated vehicle treatment area (P=0.035). There was a statistically significant increase in irritation to PEP005 Gel, 0.01% than the vehicle when irradiated
- the non-irradiated treatment areas of PEP005 Gel, 0.01% and the vehicle (P=0.003). There was a statistically significant increase in irritation to PEP0005 Gel, 0.01% than vehicle when not irradiated
- the irradiated and non-irradiated treatment areas of PEP005 Gel (P<0.001). There was a statistically significant increase in irritation to PEP0005 Gel, 0.01% when irradiated
- and the irradiated and non-irradiated treatment areas of the vehicle (P<0.001). There was a statistically significant increase in irritation to the vehicle when irradiated

Photosensitization:

PEP005 Gel, 0.01% and vehicle were found to have no evidence of photosensitization. PEP005 Gel, 0.01%, 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 the 72-hour reading. There were no safety findings of clinical significance in this study.

CONCLUSION:

Under the conditions employed in this study, the study medication was safe and well tolerated. Neither PEP005 Gel, 0.01% nor vehicle showed any potential for photosensitization. Mean scores showed moderate erythema at the treatment areas irradiated after the application of PEP005 Gel, 0.01% and the vehicle. Non-irradiated treatment areas showed mild irritation for PEP005 Gel, 0.01% and no irritation to vehicle.

Date of Report: 11 December 2009