CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202833Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review

NDA: 202-833
Submission Date: 03/31/11; 11/03/11
Product: Ingenol Mebutate Gel, 0.015%, 0.05% (Picato)
Type of Submission: Original NDA
Applicant: Leo Pharma A/S.
Reviewer: Tapash K. Ghosh, Ph.D.

Submission: Leo Pharma A/S submitted this 505(b)(1) New Drug Application (NDA) for the prescription use of Picato (inenol mebutate). Two strengths are proposed: 0.015% for the treatment of actinic keratosis on the face and scalp and 0.05% for actinic keratosis on the trunk and extremities.

This review is focused on the evaluation of the proposed *in vitro* release method and acceptance of the bridging results from the study conducted to link the formulations manufactured at different stages and different sites.

Recommendation:

The in-vitro drug release rate comparisons support the approval of both manufacturing sites for the drug product at DPT Laboratories Ltd., US (DPT) and LEO Laboratories Ltd. (LEO) in Ireland. From the Biopharmaceutics viewpoint, NDA 202-833 for Ingenol Mebutate Gel, 0.015%, 0.05% (Picato) is recommended for approval.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer

Signed by Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

The proposed drug products, Picato (ingenol mebutate) gel, 0.015% and 0.05% are clear, colorless gel packaged in (b) (4) laminated aluminum tubes with high-density-polyethylene screw caps. The capacity of the tubes is 1 mL, the fill weight is 0.47 g, and the deliverable is approximately 0.25 g. Each tube should be discarded after one use. The composition of the formulation for the drug product is shown below:

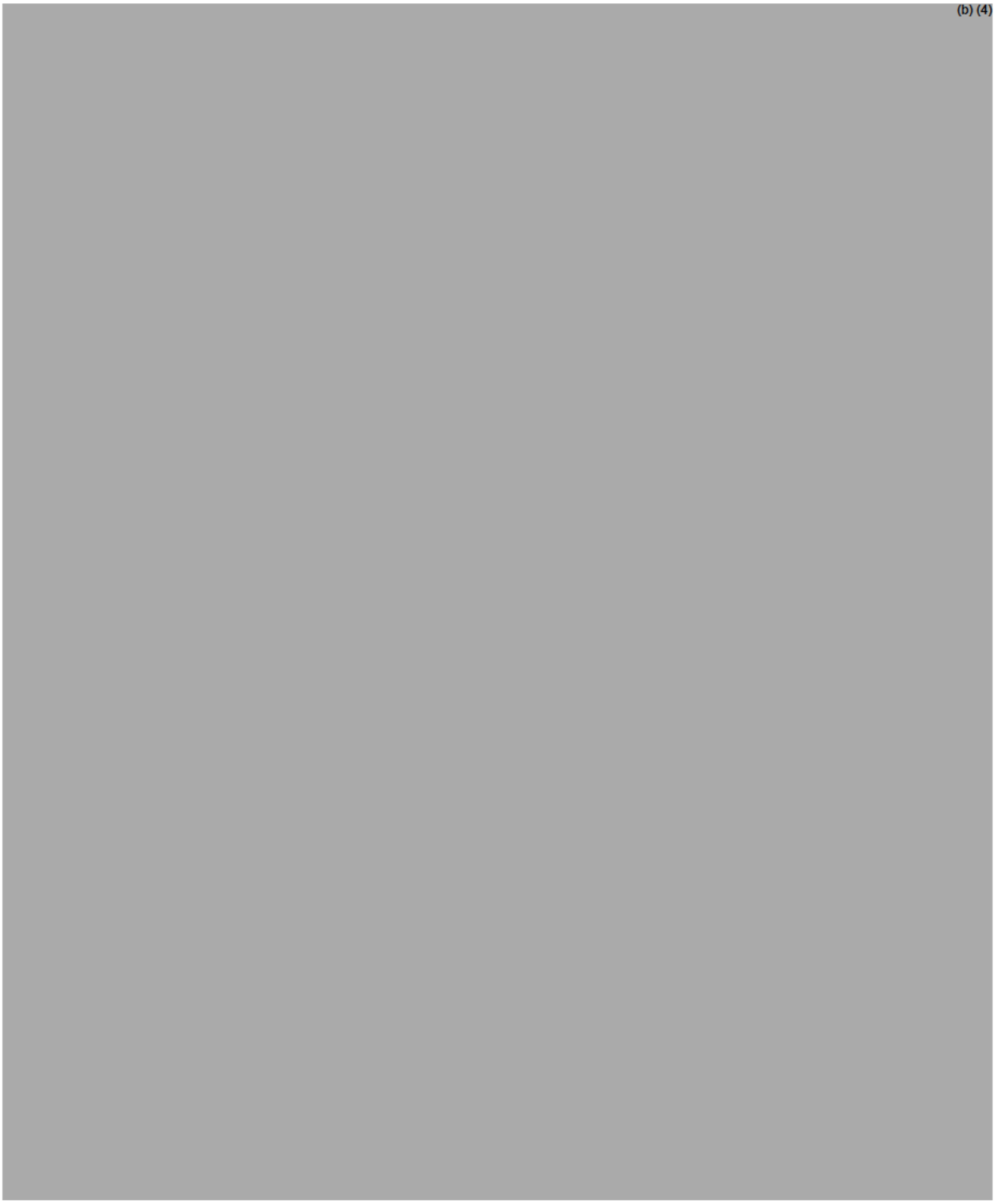
Name of Components	% w/w	Function	Reference to Quality Standard(s)
Drug Substance			
Ingenol mebutate	0.015	Drug substance	In-house
Excipients	(b) (4)		
Isopropyl alcohol			USP
Hydroxyethyl cellulose			USP-NF
Benzyl alcohol			USP-NF
Citric acid monohydrate			USP
Sodium citrate (b) (4)			USP
Purified water			USP

Technology Transfer: During development the manufacturing process was optimized to ensure a simple and robust commercial manufacturing process. A summary of the process description/changes for the sites respectively is given in the table below:

(b) (4)

The proposed commercial manufacturing scale is (b) (4) Two commercial drug product sites, DPT Laboratories in Texas and Leo Laboratories in Ireland, are proposed. DPT was the manufacturing site for Phase 3 supplies and registration stability batches. Leo has not manufactured any clinical batches. Leo's batches are bridged to DPT Phase 3 batches through an in-vitro drug release study. The Biopharmaceutics Reviewer was requested to evaluate the *in-vitro* release studies used to bridge the formulations.

(b) (4)



10 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Overall Conclusions:

- *The in vitro analytical and release methods passed the acceptance criteria for* (b) (4) *Medium Solubility, Selection of time points, Method Precision and Method Sensitivity. The sponsor's method development and validation are acceptable.*

- *The in-vitro drug release rate comparison data support the approval of the proposed manufacturing sites for the drug product at DPT Laboratories Ltd., US (DPT) and LEO Laboratories Ltd. (LEO) in Ireland.*

- *From the Biopharmaceutics viewpoint, NDA 202-833 for Ingenol Mebutate Gel, 0.015%, 0.05% (Picato) is recommended for approval.*

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

/s/

TAPASH K GHOSH
11/10/2011

ANGELICA DORANTES
11/11/2011

Office of Clinical Pharmacology (OCP)

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202833**	**Brand Name**	**Picato**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Ingenol Mebutate Gel, 0.015 % and 0.05%**
Medical Division	**Division of Dermatology and Dental Products**	**Drug Class**	**(b) (4) cell death inducer (b) (4)**
OCP Reviewer	**Abimbola Adebowale**	**Indication(s)**	**For the topical treatment of actinic keratosis (AK) on the face and scalp and on the trunk and extremities**
OCP Team Leader	**Doanh Tran**	**Dosage Form**	**Topical gel**
Pharmacometrics Reviewer	**Not Applicable**	**Dosing Regimen**	**Two indications and dosing regimens are being requested for marketing approval:** **For the treatment of AK on the face and scalp the 0.015% Gel should be applied to the affected area once daily for 3 consecutive days** **For the treatment of AK on the trunk and extremities the 0.05% Gel should be applied to the affected area once daily for 2 consecutive days**
Date of FDA Receipt of Submission	**March 25th, 2011**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**November 14th, 2011**	**Sponsor**	**Leopharma A/S**
Medical Division Due Date	**November 14th, 2011**	**Priority Classification**	**Standard**
PDUFA Due Date	**January 25th, 2012**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clinical Pharmacology and Biopharmaceutics Information

Ingenol mebutate Gel is an aqueous gel containing the drug substance ingenol mebutate dissolved in a gel vehicle. The gel is manufactured in two strengths: 0.015% and 0.05%. The code name for the proposed Gel is PEP005 gel. The Gel is proposed to be applied to a defined treatment area defined as one contiguous area of approximately 25 cm^2 (e.g. 5 cm x 5 cm)

The clinical pharmacology development plan consisted of four studies. Pharmacokinetic samples were collected from a total of 32 patients (25 on PEP005 Gel and 7 on vehicle) enrolled in four independent PEP005 Gel clinical studies for the treatment of non-head (trunk and extremities) AK lesions [AGN 204332-004, PEP005-004, PEP005-013, PEP005-017].

Table 1 Clinical Pharmacology studies (Age range (42-87 years old)

Study ID Locations (No. Study Centers)	**Study Design and Control Type (Phase)**	**Study Objectives**	**Diagnosis Inclusion Criteria**	**PEP005 and Vehicle Dose, Regimen**	**No. Patients providing blood samples**
AGN204332-004	Double-blind, parallel group, vehicle-controlled (Phase 1)	Safety	≥5 AK lesions on shoulder, chest back, and/or arm	0.01% x 1d Vehicle x 1d	8 4
PEP005-004	Open-label, nonrandomized, uncontrolled, dose escalation (Phase 2a)	Safety (MTD), efficacy, PK	Target AK lesion diameter 3 mm to 15 mm on the shoulder, chest, back, or arm.	0.01% x 2d 0.025% x 2d 0.05% x 2d 0.075% x 2d	0 0 2 0
PEP005-013	Open-label, nonrandomized, uncontrolled, maximal use (Phase 1)	PK, safety	Male, ≥5 AK lesions in a 100 cm2 contiguous area on dorsal aspect of forearm	0.05% x 2d	3
PEP005-017	Double-blind, parallel group, vehicle-controlled, maximal use (Phase 2)	PK, safety, efficacy	Multiple AK lesions in a 100 cm2 contiguous area on dorsal aspect of one forearm	0.05% x 2d Vehicle x 2d	13 3

No systemic levels of ingenol mebutate or its two isomers, [redacted](b) (4), were quantifiable in any of the blood samples collected for PK analysis (i.e., concentrations were below the LLOQ of 0.1 ng/mL using LC-MS/MS)).
No clinical metabolism studies have been performed to date because ingenol mebutate shows no systemic absorption when administered topically. However, in vitro studies indicated that ingenol mebutate undergoes significant metabolism in human hepatocytes, with the principal routes of metabolism identified as hydrolysis and hydroxylation. The major metabolic product was identified as a hydroxylated metabolite of PEP0XX (an unnamed metabolite of ingenol mebutate). Metabolic profiles of ingenol mebutate in blood and skin homogenates were similar across species, and chemical rearrangement of ingenol mebutate to yield [redacted](b) (4) was reported as evident.

No clinical drug interaction studies have been conducted. The applicant stated that such studies would be impractical, as no systemic levels of ingenol mebutate or its two isomers, [redacted](b) (4), have been quantifiable in any clinical studies evaluating PK to date (i.e., concentrations were below the LLOQ). In vitro studies indicated that ingenol mebutate did not inhibit or induce major human cytochrome P450 (CYP) isoforms and did not significantly inhibit or stimulate receptors or enzymes. Therefore, the applicant concluded that Ingenol mebutate has no potential to cause clinically significant drug interactions.

No clinical studies on human pharmacodynamics have been conducted to date. Consequently, human PD data are not available and no PK/PD correlation studies have been performed nor has any PK/PD relationship been established.

The applicant did not conduct a QT study based on the lack of quantifiable levels in the PK study. However, they did conduct a nonclinical HERG study and also they collected ECG's in their Phase 3 studies. The clinical reviewerwill address the adequacy of the QT information.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments, If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			**Study 2174/16, 2174/066, 2174/005 and 2174/034**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	**2**			**Study 2174/028 and 774824**
Blood/plasma ratio:				
Plasma protein binding:	**1**			**Study 182813**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**4**			**Study # AGN 204332-004 (0.01 % formulation only), PEP005-004, PEP005-013 and PEP005-017 (All 0.05 % formulation only)**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	**3**			**Study #'s 779162, 779157 and 13753**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD –				
Phase 2:				
Phase 3/4:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Applicant submitted a request for a waiver of pediatric studies in all subsets of the pediatric population.**
Literature References				
Other				
Total Number of Studies	**10**			

A rationale for not assessing PK following application to the head and scalp under maximal use conditions was not provided. However, At the End of Phase 2 meeting (held on June 3rd, 2009) the Agency did convey to the applicant that "their maximal use study (PEP005-017), together with their previous PK data from PEP005-004 and PEP005-013 appeared sufficient to allow for us to evaluate the systemic potential of their drug product. Adequacy would ultimately be a review issue." It is noted that the treatment area and # of lesions for the face and scalp and the trunk and extremities are similar therefore one would not expect the extent of application for both anatomical locations to be different. Also the strength proposed for the face and scalp is 3 fold lower than that of the trunk and extremities. We will ask the applicant to provide their rationale in the 74 day letter to better inform our review.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	The formulations of the to-be-marketed (TBM) drug products (0.015 % and 0.05 %), and those used in the pivotal clinical trials are the same. The 0.05% formulation used in the maximal use PK studies are the same as the TBM formulations. Basically, the formulations for the 0.015% and 0.05 % strength are the same (b) (4) according to the strength of the product. Therefore bioequivalence data is not needed
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			The maximal use study was only conducted with the 0.05 % strength applied to the extremities. No PK studies were conducted with the 0.015 % strength following application to the face and scalp. The absence of this information is a review issue.
4	Did the sponsor submit data to allow the evaluation of the validity of the	x			

	analytical assay?				
5	Has a rationale for dose selection been submitted?	x			No clinical PK studies were conducted to support dose selection because PEP005 gel applied topically was not systemically detected. Dose selection was based on clinical dose-ranging studies (PEP005-007, PEP005-015 and PEP005-006).
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			See response to Question # 5
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might		x		This is a fixed dose topical drug product. Dose adjustments for intrinsic/extrinsic factors would need to be based on full clinical trials. In addition, there were no systemic levels observed therefore PK could

	affect the pharmacokinetic or pharmacodynamics?				not be determined.
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Applicant submitted a request for a waiver of pediatric studies in all subsets of the pediatric population.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			Adequate information on the pharmacokinetics only. There is no exposure-response information in the clinical pharmacology section of the label.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	There were no clinical pharmacology or biopharmaceutics study reports or study information in another language provided in this submission.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Clinical Pharmacology Comments to be conveyed to the Applicant in the 74-day letter:

Provide a rationale for not assessing the PK of your drug product under maximal use conditions following application to the head and scalp.

Abimbola Adebowale, PhD 05/11/2011

Reviewing Clinical Pharmacologist Date

Doanh Tran, PhD 05/11/2011

Team Leader Date

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

/s/

ABIMBOLA O ADEBOWALE
05/17/2011

DOANH C TRAN
05/17/2011

Clinical Pharmacology Review

NDA #	202833
Letter Date (s)	March 15th, 2011
Brand Name	PICATO Gel
Generic Name	Ingenol Mebutate Gel, 0.015 % and 0.05 %
Reviewer	Abimbola Adebowale, Ph.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology (DCP)-3
OND division	Division of Dermatology and Dental Products (DDDP)
Applicant	Leo Pharma A/S
Submission Type	Original New Drug Application (NDA)
Indication	Topical treatment of actinic keratosis (AK) on the face and scalp and on the trunk and extremities

Table of Contents

1 Executive Summary

This NDA application is for Ingenol Mebutate Gel (0.015% and 0.05 %) for the topical treatment of actinic keratosis (AK) on the face and scalp and on the trunk and extremities, respectively, with two different dosing regimens in adults 18 years and older. The proposed dosing regimens are as follows:

- For the treatment of AK lesions on the head (face and scalp) locations, PEP005 Gel, 0.015% is to be applied topically to a 25 cm^2 treatment area once daily for three consecutive days.

- For the treatment of AK lesions on the non-head (trunk and extremities) locations, PEP005 Gel, 0.05%, is to be applied topically to a 25 cm^2 treatment area once daily for two consecutive days

The applicant requested for a waiver of pediatric studies in all subsets of the pediatric population because AK is a condition not generally seen within the pediatric population.

1.1 Recommendations

From a clinical pharmacology perspective, this NDA is acceptable pending agreements on the recommended labeling changes (see section 3).

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings and Biopharmaceutics Findings

The clinical pharmacology development plan consisted of four studies. Pharmacokinetic samples were collected from a total of 32 patients (25 on PEP005 Gel and 7 on vehicle) enrolled in four independent PEP005 Gel clinical studies for the treatment of non-head (trunk and extremities) AK lesions [AGN 204332-004, PEP005-004, PEP005-013, PEP005-017]. The maximal use PK studies PEP005-013 and PEP005-017 had 16 patients in total on ingenol mebutate gel, 0.05 %. Study PEP005-004 had 2 patients in total on ingenol mebutate gel, 0.05 %; however this was not considered a maximal use study because the treatment area (9 cm^2) was less than the proposed 25 cm^2 treatment area. Ingenol Mebutate with strengths (i.e. 0.01 %) other than the proposed 0.015 % or 0.05 % and a single day application was used in study AGN204334-004, therefore this study was not reviewed in detail.

Bioavailability under Maximal Use Conditions

The results of studies PEP005-017 and PEP005-013 indicated that treatment of a 100 cm^2 area of skin with ingenol mebutate gel, 0.05 %, once daily for two consecutive days, demonstrated minimal systemic exposure of PEP005 or its acyl isomers (b) (4) The blood levels of ingenol mebutate, and its acyl isomers (b) (4) were below the LOQ (0.1 ng/mL) in all the samples collected.

PEP005-017 was a Phase 2, single center, randomized, double-blind, vehicle-controlled study. The primary objective of this study was to evaluate the potential for systemic exposure of Ingenol mebutate gel, 0.05 % when applied in a maximal use setting in patients with multiple AK lesions within a 100 cm^2 (5 cm x 20 cm) contiguous treatment area on the dorsal aspect of one forearm. Study medication was applied on two consecutive days. The total volume of study gel applied to treatment area was approximately 1 mL (4 individual unit dose tubes). Blood samples were collected at pre-dose on Day 1, pre-dose on Day 2, and at 30 minutes and 1, 2, 4, 8,

12 and 24 hours following the Day 2 dose application. Sixteen (16) patients (13 on ingenol mebutate gel, 0.05 % and 3 on the vehicle) completed treatment. Blood levels of ingenol mebutate, and its acyl isomers (b) (4) were below the LOQ (0.1 ng/mL) in all samples collected.

PEP005-013 was a Phase 1, open label, PK, maximal use study. The primary objective of this study was to evaluate the extent of systemic absorption of ingenol mebutate when applied as Ingenol mebutate gel, 0.05% on two consecutive days to a 100 cm^2 (5 cm x 20 cm) contiguous treatment area on the dorsal aspect of one forearm with at least 5 AK lesions on either the right or left extensor (dorsal aspect) forearm. The total volume of study gel applied to the treatment area was approximately 1 mL. Blood samples were collected pre-dose on Day 1, pre-dose on Day 2, and at 30 minutes and 1, 2, 4, 8, 12 and 24 hours following the Day 2 application. Six (6) patients completed the study. However, only three (3) patients completed 2 days of study treatment and provided a complete set of blood samples for pharmacokinetic analysis. Blood levels of ingenol mebutate, and its acyl isomers (b) (4) were below the LOQ (0.1 ng/mL) in all samples collected.

Therefore, the estimated expected systemic exposure for ingenol mebutate would be less than 0.1 ng/mL (~0.23 nM) which is minimal compared to the No Observed Adverse Effect Level (NOAEL) reported in the pharmtox studies. The Pharm Tox reviewer informed this reviewer that the Cmax at which the NOAEL was observed in the non clinical studies was about 2.9 ng/mL in the minipig and 2.3 ng/mL in the rats. No systemic levels (LOQ=0.1 ng/mL) were observed in most of the topical non clinical studies conducted in animals (see Pharm Tox review for further details).

Metabolism

The metabolism of [^{3}H]-ingenol mebutate was evaluated in Nonclinical Study 774824. In this study the in vitro metabolism of [^{3}H]-ingenol mebutate was evaluated by incubating [^{3}H]-ingenol mebutate (1 or 10 μM) with whole blood, skin (skin homogenates), or liver (cryopreserved hepatocytes) from humans for up to 180 minutes. [^{3}H]-ingenol mebutate was relatively metabolically stable in both blood and skin homogenates from humans. Significant isomerization of [3H]-ingenol mebutate to yield (b) (4) (isomers of ingenol mebutate) was also observed in both skin and blood. In contrast to skin and blood, [3H]-ingenol mebutate was found to undergo extensive metabolism in cryopreserved hepatocytes in humans (see Pharm/Tox review for details).

Distribution:

The in vitro plasma protein binding of ingenol mebutate was evaluated in Nonclinical Study 182813. Ingenol mebutate was found to have high plasma protein binding in humans (>99%) (see Pharm/Tox review for details).

Drug-Drug Interactions: The applicant stated that no formal drug-drug interaction (in vivo) studies were performed. This is because the blood levels of ingenol mebutate were below the LOQ (0.1 ng/mL) following topical application. However, the potential for drug-drug

interactions of ingenol mebutate were evaluated in two nonclinical in vitro studies (779162 and 779157). Study 779162 was an *in vitro* investigation to assess the potential inhibition of human cytochrome P450 enzymes by PEP005. Study 779157 was an evaluation of PEP005 as an inducer of CYP1A2, CYP2C9 and CYP3A4 in fresh human hepatocytes (see Pharm/Tox review for details). The following conclusions are based on the results of these two studies:

- No notable inhibition was observed in vitro for the co-incubations or pre-incubations of ingenol mebutate at up to 20 μM concentrations with the CYP isoforms CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

- No notable increase in metabolism (i.e. induction) was observed in vitro following exposure of fresh human hepatocytes to ingenol mebutate at up to 2 μM concentrations for 72 hours with the probes for the CYP isoforms CYP1A2, 2C9, and 3A4 compared to the corresponding positive control inducers.

The estimated expected systemic exposure (< 0.1 ng/mL or 0.00023 μM) following topical application of PICATO Gel, 0.05 % to AK subjects in the maximal use PK studies is negligible compared to the concentrations of ingenol mebutate evaluated in the in vitro drug interaction studies.

QT Prolongation: The applicant did not conduct a "Thorough QT/Qtc Study (TQT)" based on the lack of quantifiable levels in the PK study. In lieu, they performed ECG analysis throughout Phase 3, and submitted a "Combined Cardiac ECG Safety Report". In addition the applicant also conducted a nonclinical HERG study.

The QT Interdisciplinary Review Team (IRT) were consulted by the Division of Dermatology and Dental Products (DDDP) and in their review (dated August 7th, 2011 in DARRTS) IRT-QT agreed that a TQT study is not needed because the systemic exposure of ingenol mebutate is within the subnanomolar range (estimated to be ~0.23nM or less) and ingenol exhibits neither nonclinical effects consistent with QTc prolongation nor clinically relevant QTc prolonging effects in the clinical program. The IRT-QT team also recommended that the applicant should perform routine safety ECG monitoring as clinically indicated in ongoing and future clinical trials. The clinical reviewer will address the adequacy of the ECG safety report and the TQT waiver information.

Pediatrics: The applicant requested for a waiver of pediatric studies in all subsets of the pediatric population because AK is a condition not generally seen within the pediatric population.

Clinical Trial versus To-be-marketed Formulation: The to-be-marketed formulation was used in all the Phase 3 clinical studies and pivotal clinical pharmacology studies PEP005-013 and PEP005-017.

Signatories:

_____ Date: _____
Abimbola Adebowale, Ph.D.
Senior Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

_____ Date: _____
Doanh Tran, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

_____ Date: _____
CAPT E. Dennis Bashaw, Pharm.D.
Division Director
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

2 Question-Based Review

2.1 General Attributes of the drug

Q What is ingenol mebutate?

Ingenol mebutate has the molecular formula of $C_{25}H_{34}O_6$ and a molecular weight of 430.5 g/mol. The structural formula of ingenol mebutate is provided in Figure 1 below:

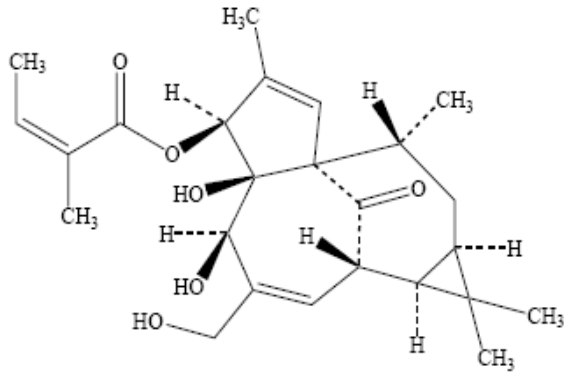


Figure 1: Structure of Ingenol mebutate

Q What is the proposed indication and dosing regimen for Ingenol mebutate?

The proposed indication of ingenol mebutate is for the treatment of AK lesions on the head (face and scalp) and on the non-head (trunk and extremities). The proposed dosing regimens are as follows:

- For the treatment of AK lesions on the head (face and scalp) locations ingenol mebutate gel, 0.015% is to be applied topically to a 25 cm^2 treatment area once daily for three consecutive days.

- For treatment of AK lesions on the non-head (trunk and extremities) locations, ingenol mebutate gel, 0.05% is to be applied topically to a 25 cm^2 treatment area once daily for two consecutive days.

Q What is actinic keratosis (AK)?

Actinic keratosis (AK) is a skin condition that is visible as thickened, cornified, scaly lesions and characterized histologically by atypical epithelial proliferation. Actinic keratoses usually develop on areas that are frequently exposed to the sun (e.g., face, lips, ears, scalp, neck, forearms, and back of the hands). Current treatment options for AK lesions consist of cryotherapy, photodynamic therapy, and topical products. Topical products include 5-fluorouracil (5-FU), diclofenac, and imiquimod.

Q What is the pharmacological rationale for ingenol mebutate in the treatment of AK?

The mechanism of action of ingenol mebutate in AK is unknown.

2.2 General Clinical Pharmacology

Q What are the design features of the clinical pharmacology and clinical studies?

In total, there were 25 studies in the clinical development program for PEP005 Gel. Figure 2 displays all 25 studies. Of these, 18 studies were conducted in patients with actinic keratosis. The remaining seven studies contribute data to the safety profile of PEP005 Gel. Three were topical safety studies performed in healthy volunteers and four were studies conducted in patients with non-melanoma skin cancer (NMSC).

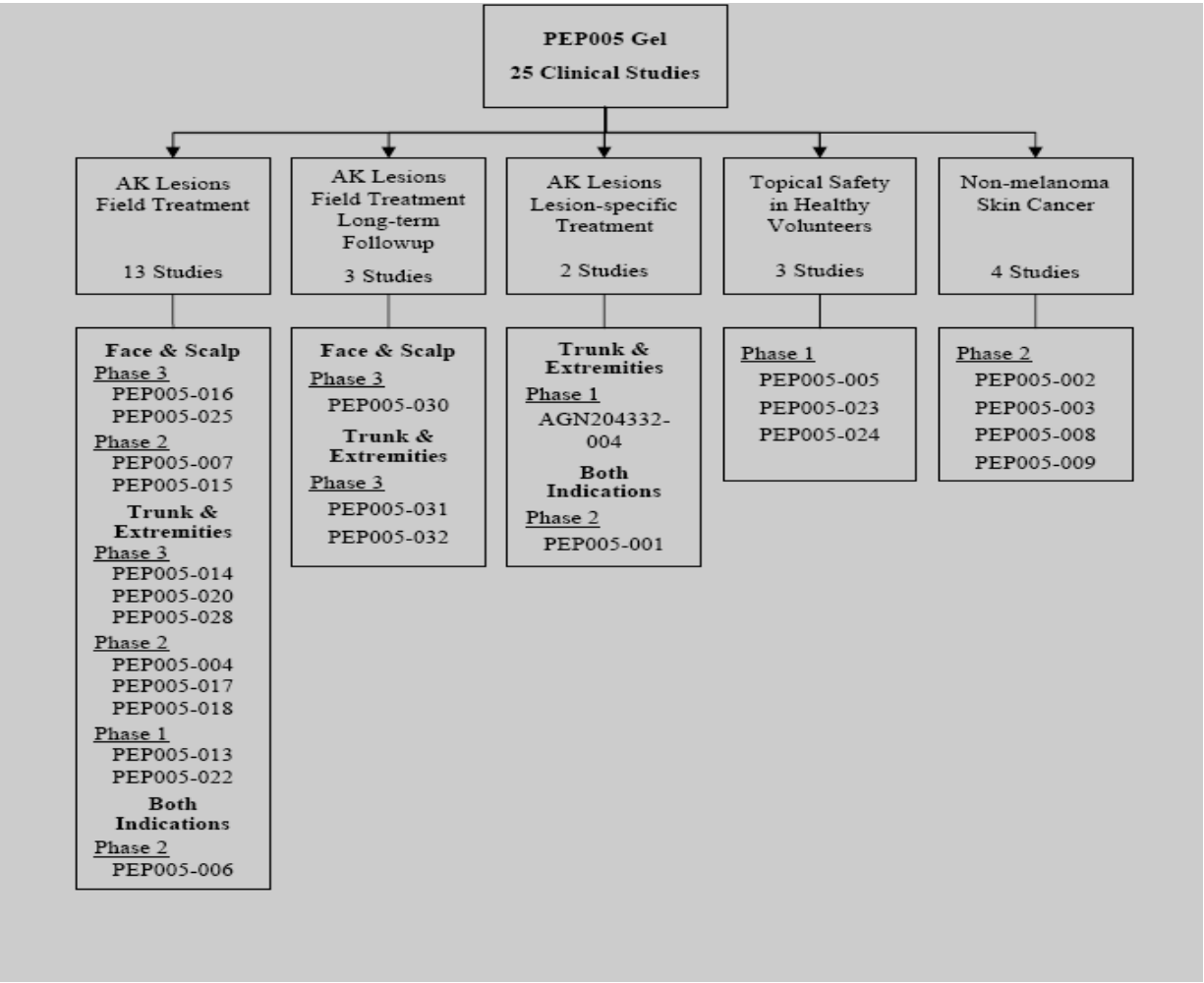


Figure 2: Overview of PEP005 Gel Clinical Development Program

Listed below (table 1) are the clinical studies that had information relevant to the clinical pharmacology of ingenol mebutate

Table 1 Tabular Listing of Clinical Studies with Information Relevant to the Clinical Pharmacology of Ingenol Mebutate

Study ID Locations (No. Study Centers)	Study Status Study Dates Enrollment[b]	Study Design and Control Type (Phase)	Study Objectives	Diagnosis Inclusion Criteria	PEP005 and Vehicle Dose, Regimen	No. Patients[d,e]	Gender, M/F[e] Age Range (years)
AGN204332-004 US	Completed 12-Aug-04 15-Oct-04 16 / 16	Double-blind, parallel group, vehicle-controlled (Phase 1)	Safety	≥5 AK lesions on shoulder, chest back, and/or arm	0.01% x 1d Vehicle x 1d	11/11 5/4	10/1 4/1 42 – 82
PEP005-004 US	Completed 7-Sep-05 14-Mar-06 22 / up to 34	Open-label, nonrandomized, uncontrolled, dose escalation (Phase 2a)	Safety (MTD), efficacy, PK	Target AK lesion diameter 3 mm to 15 mm on the shoulder, chest, back, or arm.	0.01% x 2d 0.025% x 2d 0.05% x 2d 0.075% x 2d	3/3 3/3 10/10 6/6	2/1 2/1 7/3 5/1 64 – 87
PEP005-013 AUS	Completed 17 Oct 2007 23 Apr 2008 8 / 8	Open-label, nonrandomized, uncontrolled, maximal use (Phase 1)	PK, safety	Male, ≥5 AK lesions in a 100 cm2 contiguous area on dorsal aspect of forearm	0.05% x 2d	8/6	8/0 56 – 81
PEP005-017 US	Completed 18-Mar 09 27May09 16 / 15	Double-blind, parallel group, vehicle-controlled, maximal use (Phase 2)	PK, safety, efficacy	Multiple AK lesions in a 100 cm2 contiguous area on dorsal aspect of one forearm	0.05% x 2d Vehicle x 2d	13/13 3/3	6/7 0/3 48 – 79

AK = actinic keratosis; AUS = Australia; d = day; F = female; hr = hour; M = male; min = minute; MTD = maximum tolerated dose; PK =pharmacokinetics; US = United States

a First patient randomized/treated to last patient/last follow-up

b Total enrolled / enrollment goal.

c All study and control drugs were applied topically.

d Number of patients entered / number of patients completed

e By dose group

f Patients who completed two consecutive days of treatment and provided a complete set of blood samples for PK analysis.

Q What is the systemic exposure of ingenol mebutate under maximal use conditions for the non-head (trunk and extremities) indication**?**

The results of the maximal use PK studies PEP005-017 and PEP005-013 indicated that treatment of a 100 cm^2 area of skin with ingenol mebutate gel, 0.05 %, once daily for two consecutive days demonstrated minimal systemic exposure of PEP005 or its acyl isomers [redacted] (b) (4) The blood levels of ingenol mebutate, and its acyl isomers [redacted] (b) (4) were below the LOQ (0.1 ng/mL) in all the samples collected.

PEP005-017 was a Phase 2, single center, randomized, double-blind, vehicle-controlled study. The primary objective of this study was to evaluate the potential for systemic exposure of Ingenol mebutate gel, 0.05 % when applied in a maximal use setting in patients with AK. Eligible patients were male or female, ≥ 18 years of age, with multiple AK lesions within a 100 cm^2 (5 cm x 20 cm) contiguous treatment area on the dorsal aspect of one forearm. Study medication was applied on two consecutive days in the clinic by site staff. The total volume of study gel applied to treatment area was approximately 1 mL (4 individual unit dose tubes). Blood samples were collected at pre-dose on Day 1, pre-dose on Day 2, and at 30 minutes and 1, 2, 4, 8, 12 and 24 hours following the Day 2 dose application. Whole blood samples were quantified for ingenol mebutate and its acyl isomers, [redacted] (b) (4) using a validated Liquid chromatography with tandem mass spectrometric detection (Limit of quantitation (LOQ) =0.1 ng/mL). Sixteen (16) patients (13 on ingenol mebutate gel, 0.05 % and 3 on the vehicle) completed treatment. Blood levels of ingenol mebutate, and its acyl isomers [redacted] (b) (4) [redacted] (b) (4) were below the LOQ (0.1 ng/mL) in all samples collected.

PEP005-013 was a Phase 1, open label, PK, maximal use study. The primary objective of this study was to evaluate the extent of systemic absorption of ingenol mebutate when applied as 0.05% PEP005 Topical Gel on two consecutive days to a 100 cm^2 (5 cm x 20 cm) contiguous treatment area on the dorsal aspect of one forearm. Eligible patients were male, ≥ 18 years of age, with at least 5 AK lesions on either the right or left extensor (dorsal aspect) forearm. Five out of six patients (83%) had approximately 21 to 50 AK lesions on their extremities at the time of study enrollment. Study medication was applied in the clinic by site staff using a micropipette, as 1 mL in four aliquots of 250µL. Blood samples were collected pre-dose on Day 1, pre-dose on Day 2, and at 30 minutes and 1, 2, 4, 8, 12 and 24 hours following the Day 2 application. Six (6) patients completed the study. However, only three (3) patients completed 2 days of study treatment and provided a complete set of blood samples for pharmacokinetic analysis. Whole blood samples were quantified for ingenol mebutate and its acyl isomers, [redacted] (b) (4) using a validated Liquid chromatography with tandem mass spectrometric detection (Limit of quantitation (LOQ) =0.1 ng/mL). Blood levels of ingenol mebutate, and its acyl isomers [redacted] (b) (4) were below the LOQ (0.1 ng/mL) in all samples collected.

Based on the results above, the estimated expected systemic exposure for ingenol mebutate would be less than 0.1 ng/mL which is minimal compared to the No Observed Adverse Effect Level (NOAEL) reported in the pharm/tox studies. The Pharm/Tox reviewer informed this reviewer that the Cmax at which the NOAEL was observed in the non clinical studies was about 2.9 ng/mL in the minipig and 2.3 ng/mL in the rats. No systemic levels (LOQ=0.1 ng/mL) were observed in most of the topical non clinical studies conducted in animals (see Pharm/Tox review for further details).

Q What is the systemic exposure of ingenol mebutate under maximal use conditions for the head (face and scalp) indication**?**

The applicant did not conduct a maximal use PK study following application of ingenol mebutate gel, 0.015 % to the head and scalp of AK patients. The applicant stated that the results from the maximal use study – treatment of a 100 cm² area of skin with 0.05% of PEP005, once daily for two consecutive days (Clinical Study PEP005-017) demonstrated no systemic absorption of PEP005 or its acyl isomers, (b) (4) using a validated and highly sensitive assay for these compounds (LOQ = 0.1 ng/mL) (Applicant's response dated June 21st, 2011 to FDA 74-day letter request). Based on the results of this study, the rationale provided by the applicant for not conducting a maximal use PK study in a face and scalp setting was stated as follows: "A maximal use study on the face and scalp would use PEP005 gel 0.015% applied to a comparably sized area of skin. Given the lower concentration, the systemic exposure would not exceed the exposure conditions used in the PEP005-017 study and the predicted concentrations would be far below the LOQ". The applicant used the allometric scaling approach (based on PK data obtained in rats and mini-pigs) as an alternative method of estimating drug plasma levels because it was not possible to quantitate blood levels after dermal application to humans. The pharm/tox reviewer informed this reviewer that the allometric scaling report was not reviewed in detail because data obtained from the clinical pharmacokinetic study under maximal use conditions was to be relied on to evaluate potential systemic exposure following topical application of PEP005 Gel (see Pharm/Tox review for details).

This reviewer agrees with the applicant that a maximal use PK study of the ingenol mebutate, 0.015 % following application to the face and scalp of AK patients is not needed. The applicant's rationale based on the minimal systemic exposure observed in the maximal use PK study PEP005-017 conducted with a higher strength (0.05 %) and a dose that is 4 fold higher than that proposed for clinical use, is acceptable. This reviewer agrees with the Pharm/Tox reviewer that the predicted concentrations for the head and non-head indications obtained using the allometric scaling approach is not relevant since we have clinical PK data available for the non-head indication.

Q. What are the metabolism, distribution and excretion characteristics?

Metabolism

The metabolism of [^{3}H]-ingenol mebutate was evaluated in Nonclinical Study 774824 entitled "Tissue, strain and species variation in the in vitro metabolism of 20-[^{3}H]-ingenol mebutate". This study has been reviewed in detail by the Pharm/Tox reviewer (see Pharm/Tox review for details). A brief overview as it pertains to clinical pharmacology is presented below:

The in vitro metabolism of [^{3}H]-ingenol mebutate was evaluated by incubating [^{3}H]-ingenol mebutate (1 or 10 μM) with whole blood, skin (skin homogenates), or liver (cryopreserved hepatocytes) from humans and animals for up to 180 minutes. The metabolite profiles were assessed via HPLC with on-line radiodetection and HPLC-MS (MS). [^{3}H]-ingenol mebutate was relatively metabolically stable in both blood and skin homogenates from humans. In both skin and blood there was some hydrolysis to yield ingenol, but this generally accounted for less than

1% of the radioactivity. Significant isomerization of [3H]-ingenol mebutate to yield (b) (4) (b) (4) (isomers of ingenol mebutate) was also evident in both human skin and blood. In contrast to skin and blood, [3H]-ingenol mebutate was found to undergo extensive metabolism in cryopreserved hepatocytes from humans.

The Pharm/Tox reviewer concluded that because the systemic exposure of ingenol mebutate was minimal following topical administration, little metabolism of ingenol mebutate will occur after topical treatment of AK patients with PICATO Gel. Therefore, no further characterization of the metabolites of ingenol mebutate is needed within this NDA.

Distribution:

The applicant did not evaluate the tissue distribution of ingenol mebutate in humans. However, the in vitro plasma protein binding of ingenol mebutate was evaluated in Nonclinical Study 182813 entitled "In vitro binding of [3H]-Ingenol mebutate to the plasma proteins of male and female rat, dog, mini-pig and human". Plasma protein binding was evaluated by equilibrium dialysis at target concentrations of 0.5, 2, 5, and 20 ng/mL, following incubation at 37 ºC for 2 hrs. In this study, ingenol mebutate was shown to have high plasma protein binding in humans (>99%). These studies have been reviewed in detail by the Pharm/Tox reviewer (see Pharm/Tox review for details).

Excretion: The applicant did not evaluate the excretion of ingenol mebutate in humans.

Q. Does the drug product prolong QT intervals?

The applicant did not conduct a "Thorough QT/Qtc Study (TQT)" based on the lack of quantifiable levels in the PK study. In lieu, they performed ECG analysis throughout Phase 3, and submitted a "Combined Cardiac ECG Safety Report". In addition they also conducted a nonclinical HERG study.

The QT Interdisciplinary Review Team (IRT) were consulted by the Division of Dermatology and Dental Products (DDDP) and in their review (dated August 7th, 2011 in DARRTS) IRT-QT agreed that a TQT study is not needed because the systemic exposure of ingenol mebutate is within the subnanomolar range (estimated to be ~0.23nM or less) and ingenol exhibits neither nonclinical effects consistent with QTc prolongation nor clinically relevant QTc prolonging effects in the clinical program. The IRT-QT team also recommended that the applicant should perform routine safety ECG monitoring as clinically indicated in ongoing and future clinical trials. The clinical reviewer will address the adequacy of the ECG safety report and the TQT waiver information

Q What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Dose-Response studies were conducted to support dose selection. No concentration-response studies were conducted to support dose selection.

Exposure-Response for Efficacy:

Head (face and scalp) Indication: The proposed dosage regimen for the head indication is PEP005 Gel, 0.015% applied topically once daily for three consecutive days to a defined treatment area (contiguous 25 cm^2) on the face or scalp. The applicant stated that the key clinical studies that support the dosing recommendations of PEP005 Gel for the head indication are PEP005-007 and PEP005-015. The main difference between the two studies was that PEP005-007 studied concentrations ranging from 0.0025% to 0.025% applied once daily for two or three consecutive days whereas PEP005-015 evaluated three different concentrations (0.005 %, 0.01 % and 0.015 % applied once daily for two or three consecutive days) based on the findings of PEP005-007.

PEP005-015 was designed as a randomized, double-blind, vehicle-controlled, dose-ranging trial to assess potential regimen for treating AK lesions on the head (face and scalp). The applicant stated that the concentrations and treatment regimens selected for investigation (0.005%, 0.01%, and 0.015% applied once daily for two or three consecutive days) were based on the findings of PEP005-007, the dose-escalation study. Study medication was applied to a 25 cm^2 contiguous treatment area with four to eight clinically typical, visible, and discrete AK lesions on the face or scalp. A summary of the clearance rate by treatment group for PEP005-015 is summarized in table 2 below:

Table 2: Complete Clearance Rate by Treatment Group: PEP005-015 (Intent-to-treat Population)

	Two Day Dosing				**Three Day Dosing**			
Complete Clearance	**PEP005, 0.005%**	**PEP005, 0.01%**	**PEP005, 0.015%**	**Vehicle**	**PEP005, 0.005%**	**PEP005, 0.01%**	**PEP005, 0.015%**	**Vehicle**
	(N=33)	**(N=34)**	**(N=33)**	**(N=33)**	**(N=33)**	**(N=34)**	**(N=32)**	**(N=33)**
n (%)	5 (15.2)	10 (29.4)	12 (36.4)	0	11 (33.3)	6 (17.6)	16 (50.0)	3 (9.1)
95% CI	5.1, 31.9	15.1, 47.5	20.4, 54.9	0, 10.6	18.0, 51.8	6.8, 34.5	31.9, 68.1	1.9, 24.3
P value	0.053	<0.001	<0.001		0.033	0.476	<0.001	

CI = confidence interval
The 95% CI uses the exact binomial method.
P-value is for comparing Active vs. Vehicle, using Fisher's Exact test.

As shown in table 2 above, the PEP005-015 results indicated that the 0.015% three-day treatment group resulted in a complete clearance rate of 50%. Patients in the other PEP005 Gel groups achieved complete clearance rates which ranged from 15% in the 0.005% two-day group to 36% in the 0.015% two-day group. The 0.01 % and 0.015% two day dosing group and the 0.015 % three day dosing group were all statistically significant when compared to vehicle ($p < 0.001$). However, the results for the 0.01% three-day treatment group were not statistically significant when compared to vehicle. Therefore, the PEP005-015 results indicated that the highest concentration and regimen, 0.015% for three consecutive days, resulted in the highest complete clearance rate of 50%. The complete clearance results for the 0.01% three-day treatment group were not consistent with the two-day treatment group.

Non-Head (trunk and extremities) Indication: The proposed dosage regimen for the non-head indication is PEP005 Gel, 0.05% applied topically once daily for two consecutive days to a defined treatment area (contiguous 25 cm^2) on the trunk or extremities. The applicant stated that the key clinical studies that support the dosing recommendations for PEP005 Gel for the non-head indication are PEP005-004 and PEP005-006 (non-scalp patients). The main difference between the two studies was that PEP005-004 had a shorter efficacy endpoint (Day 29) and evaluated a smaller treatment area (9 cm^2) with a single target lesion whereas PEP005-006 investigated field treatment in a 25 cm^2 area with four to eight lesions with a longer efficacy endpoint (Day 57). In addition, PEP005-004 evaluated four different concentrations (0.01 %, 0.025 %, 0.05 % and 0.075 % applied daily for 2 consecutive days whereas PEP005-006 evaluated two different concentrations (0.025 % and 0.05 % applied once daily for two or three consecutive days) based on the findings of PEP005-004.

PEP005-006 was designed as a randomized, double-blind, double-dummy, vehicle-controlled, sequential cohort study Phase 2b, dose-ranging study. The applicant stated that PEP005-006 provided the primary basis for dosage selection for the non-head pivotal Phase 3 studies. The PEP005 Gel concentrations and treatment regimens selected for investigation (0.025%, 0.05%, and 0.05% applied once daily for two or three consecutive days) were based on the findings of PEP005-004. Patients had four to eight clinically typical, visible, and discrete AK lesions within the selected 25 cm^2 treatment area on the arm, shoulder, chest, back or scalp. Study medication was patient-applied at home.

Table 3: Efficacy Results Study PEP005-006 (Intent-to-treat Population)

	PEP005-006			
Efficacy Parameter	**PEP005, 0.025% x 3d (N=37)**	**PEP005, 0.05% x 2d[a] (N=42)**	**PEP005, 0.05% x 3d (N=39)**	**Vehicle x 3d (N=43)**
Complete Clearance				
n (%)	12 (32.4)	19 (45.2)	18 (46.2)	6 (14.0)
95% CI	18.0, 49.8	29.8, 61.3	30.1, 62.8	5.3, 27.9
P value	0.062	0.002	0.002	
Partial Clearance				
n (%)	20 (54.1)	27 (64.3)	29 (74.4)	9 (20.9)
95% CI	36.9, 70.5	48.0, 78.4	57.9, 87.0	10.0, 36.0
P value	0.003	<0.001	<0.001	
Percent Reduction in AK Lesions				
N	37	41	39	42
Median	75	83	86	0
Range	0, 100	-57, 100	0, 100	-20, 100

CI = confidence interval; d = day
All study medication was administered once-daily for two consecutive days on Day 1 and Day 2, except as indicated in PEP005-006 (double-blind, double-dummy). For PEP005-006, only patients with AK lesions on non-scalp locations are included in the analysis.
a PEP005 Gel, 0.05% administered on Day 2 and Day 3 (vehicle gel on Day 1)
Percent reduction = 100 · (baseline AK lesion count – Day 57 AK lesion count)/ (baseline AK lesion count)
p-values comparing active treatment vs. vehicle using Fisher's Exact test in PEP005-006.
The 95% CI using the exact binomial method.

As shown in Table 3 above, treatment effects were dose dependent over all 3 measures of efficacy tested. From lowest to highest PEP005 Gel concentration, complete clearance rates were 32%, 45%, and 46%, respectively, compared with 14% for vehicle gel ($p = 0.002$ for the two PEP005 Gel, 0.05% groups vs. vehicle gel); partial clearance rates were 54%, 64%, and 74%, respectively, compared with 21% for vehicle gel ($p < 0.001$ for the two PEP005 Gel, 0.05% groups vs. vehicle gel); and the median reductions in the number of AK lesions were 75%, 83%, and 86%, respectively, compared with 0% for vehicle gel. The PEP005-006 results indicated that the highest concentration, 0.05%, resulted in the highest complete clearance rates with little difference between the two-day and three-day regimens, i.e., 45% and 46% complete response rates and 64% and 74% partial clearance rates for the two-day and three-day regimens, respectively.

Exposure-Response for Safety:

Head (face and scalp) Indication: In the dose-ranging study PEP005-015, safety measures also showed dose related treatment effects. The applicant stated that common AEs included application site irritation and application site pruritus. As shown in table 4 below, the incidence of AEs and treatment-related AEs was higher in the three day PEP005 Gel treatment groups compared with the vehicle gel, with the highest incidence in patients receiving PEP005 Gel 0.015% for three days.

Table 4: Incidence of Adverse Events by PEP005 Gel Dosage Regimen: PEP005-015 (Safety Population)

Regimen Concentration	N	Adverse Events	Treatment-related Adverse Events
		n (%)	n (%)
Two Day Dosing			
PEP005 Gel 0.005%	32	12 (37.5)	6 (18.8)
PEP005 Gel 0.01%	34	12 (35.3)	8 (23.5)
PEP005 Gel 0.015%	33	8 (24.2)	6 (18.2)
Vehicle gel	33	11 (33.3)	2 (6.1)
Three Day Dosing			
PEP005 Gel 0.005%	33	11 (33.3)	6 (18.2)
PEP005 Gel 0.01%	34	14 (41.2)	10 (29.4)
PEP005 Gel 0.015%	32	22 (68.8)	17 (53.1)
Vehicle gel	33	6 (18.2)	4 (12.1)

The applicant stated that the treatment regimen, PEP005 Gel, 0.015%, applied once daily for three consecutive days despite its higher incidence of AE's was found to provide the optimum balance between AK lesion clearance, local skin irritation, and treatment compliance in the PEP005-015 study. This dosage regimen was therefore selected to treat AK lesion on the head in

the Phase 3 trials. The clinical reviewer informed this reviewer that this dosage selection was acceptable from a clinical perspective.

Non-Head (trunk and extremities) Indication:

In the dose-ranging study PEP005-006, safety measures also showed dose related treatment effects with higher incidence of with increasing dose in the three day regimen. The applicant stated that common AEs included application site irritation and application site pruritus. As shown in Table 5 below, the incidence of treatment-related AEs was higher in the PEP005 Gel treatment groups compared with the vehicle gel, with the highest incidence in patients receiving PEP005 Gel, 0.05% for three days.

Table 5: Incidence of Adverse Events by PEP005 Gel Dosage Regimen: PEP005-006 Non-Scalp Patients (Intent-to-treat Population)

Study Medication	N	Treatment-related Adverse Events
		n (%)
Vehicle gel	43	2 (4.7)
PEP005 Gel 0.025% x 3 days	37	8 (21.6)
PEP005 Gel, 0.05% x 2 days	42	6 (14.3)
PEP005 Gel, 0.05% x 3 days	39	10 (25.6)

The applicant stated that the treatment regimen, PEP005 Gel, 0.05% applied topically once daily for two consecutive days, was found to provide the optimum balance between AK lesion clearance, local skin irritation, and treatment compliance in the PEP005-006 study. This dosage regimen was therefore selected to treat AK lesion on non-head locations in the Phase 3 trials.

2.3 Intrinsic Factors

Q. What is the systemic exposure in the pediatric population?

The applicant requested for a waiver of pediatric studies in all subsets of the pediatric population because AK is a condition not generally seen within the pediatric population.

2.4 Extrinsic Factors

Q What extrinsic factors (e.g. drug-drug interactions) influence exposure and/or response?

Drug-Drug interactions:

The applicant stated that no formal drug-drug interaction (in vivo) studies were performed. This is because the blood levels of ingenol mebutate were below the LOQ (0.1 ng/mL) following topical application. However, the potential for drug-drug interactions of ingenol mebutate were evaluated in two nonclinical in vitro studies (779162 and 779157). Study 779162 was an *in vitro*

investigation to assess the potential inhibition of human cytochrome P450 enzymes by PEP005. Study 779157 was an evaluation of PEP005 as an inducer of CYP1A2, CYP2C9 and CYP3A4 in fresh human hepatocytes (see Pharm/Tox review for details). The following conclusions are based on the results of these two studies:

- No notable inhibition was observed in vitro for the co-incubations or pre-incubations of ingenol mebutate at up to 20 μM concentrations with the CYP isoforms CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

- No notable increase in metabolism (i.e. induction) was observed in vitro following exposure of fresh human hepatocytes to ingenol mebutate at up to 2 μM concentrations for 72 hours with the probes for the CYP isoforms CYP1A2, 2C9, and 3A4 compared to the corresponding positive control inducers.

Inserted below are the summaries of the Pharm/Tox review for studies 779162 and 779157:

An *In vitro* Investigation to Assess the Potential Inhibition of Human Cytochrome P450 Enzymes by PEP005 (779162): The potential of PEP005 to inhibit human hepatic cytochrome P450 (CYP) isoforms CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 was evaluated in vitro with pooled human hepatic microsomes using selective probe substrates. Human hepatic microsomal protein was incubated with selective CYP substrates in the presence of PEP005 at concentrations of 0.0002, 0.002, 0.02, 0.1, 0.2, and 2 μM for CYP 2B6, 2C9, 2C19, 2E1, and 3A4. Due to a calculation error, PEP005 was incubated at 0.002, 0.02, 0.2, 1, 2, and 20 μM concentrations for CYP 1A2, 2A6, 2C8 and 2D6. In addition, PEP005 (2 μM for CYP 2B6, 2C9, 2C19, 2E1, and 3A4; 20 μM for CYP1A2, 2A6, 2C8, and 2D6) was also pre-incubated with microsomal protein in the presence and absence of cofactor to investigate the potential for mechanism-based inhibition of the CYP isoforms. No notable inhibition was observed for the co-incubations or pre-incubations of PEP005 at the concentrations tested with the CYP isoforms CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. IC_{50} values were not calculated since less than 50% inhibition was observed for each of the CYP isoforms tested.

Evaluation of PEP005 as an Inducer of CYP1A2, CYP2C9 and CYP3A4 in Fresh Human Hepatocytes (779157): Following exposure of fresh human hepatocytes to PEP005 at concentrations of 0.0002, 0.02, or 2 μM for 72 hours, there was no increase in the metabolism of the probe substrates, phenacetin at 20 μM for CYP1A, [^{14}C]-tolbutamide at 100 μM for CYP2C9, and [^{14}C]-testosterone at 150 μM for CYP3A4, compared to the corresponding control article. However, there was actually a decrease in metabolism with increasing PEP005 concentration, when compared to the appropriate controls. The sponsor stated that the positive control inducers, omeprazole at 30 μM for CYP1A2 and rifampicin at 3 μM for CYP2C9 and CYP3A4, produced acceptable induction in the tested hepatocytes. No cytotoxicity was observed following treatment of PEP005 at up to 2 μM, the highest concentration tested.

Therefore, the estimated expected systemic exposure (< 0.1 ng/mL) following topical application of PICATO Gel, 0.05 % to AK subjects in the maximal use PK studies is negligible compared to the concentrations of ingenol mebutate evaluated in the in vitro drug interaction studies.

2.5 General Biopharmaceutics

Q. What is the final product composition of the drug product?

The final product composition is shown in Table 2 and 3 below.

Table 2: Qualitative and Quantitative Composition of Ingenol mebutate gel, 0.015 %

Name of Components	% w/w	Function	Reference to Quality Standard(s)
Drug Substance			
Ingenol mebutate	0.015	Drug substance	In-house
Excipients	[redacted] (b) (4)		
Isopropyl alcohol			USP
Hydroxyethyl cellulose			USP-NF
Benzyl alcohol			USP-NF
Citric acid monohydrate			USP
Sodium citrate [redacted] (b) (4)			USP
Purified water			USP

Table 3: Qualitative and Quantitative Composition of Ingenol mebutate gel, 0.05 %

Name of Components	% w/w	Function	Reference to Quality Standard(s)
Drug Substance			
Ingenol mebutate	0.05	Drug substance	In-house
Excipients	[redacted] (b) (4)		
Isopropyl alcohol			USP
Hydroxyethyl cellulose			USP-NF
Benzyl alcohol			USP-NF
Citric acid monohydrate			USP
Sodium citrate [redacted] (b) (4)			USP
Purified water			USP

Q. Was the to-be-marketed formulation (TBMF) used in the clinical studies?

Yes, the to-be-marketed formulation was used in all the Phase 3 clinical studies and pivotal clinical pharmacology studies PEP005-013 and PEP005-017.

2.6 Analytical Section

Q What Bioanalytical methods were used to assess the concentrations of ingenol and its acyl isomers in biological fluids?

Liquid Chromatography (LC) with tandem mass spectrometric detection-(MS/MS) was used for the simultaneous determination of ingenol mebutate and its potential acyl migration isomers,

(b) (4) in human whole blood containing EDTA as an anti-coagulant. Liquid/liquid extraction with methyl tert-butyl ether (MTBE) was used for sample preparation. The analytical test facility was reported as (b) (4)

Q Were the bioanalytical methods used adequately validated?

Yes, the bioanalytical methods were adequately validated (see tables below).

Table 4: Analytical method validation for Ingenol Mebutate

Method	LC-Tandem Mass Spectrometric Detection
Compound	Ingenol mebutate
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 98.9 % to 105.3 % 99% to 111%
Precision (% CV) ***Inter-Day*** ***Intra-Day***	 6.1 % to 14.1 % 3.4 % to 11.1%
Standard curve range	0.1 ng/mL to 20 ng/mL
Sensitivity (LOQ)	0.1 ng/mL
Mean Recovery	87.5 % , 86.3 % and 83.9 % respectively, for 3 separate QC samples (0.3ng/mL, 1.5 ng/mL and 15 ng/mL)
Specificity	No significant interfering peaks were observed in the retention window of ingenol mebutate and its internal standard.
Stability	Ingenol mebutate was stable in human whole blood for up to ten weeks when stored at nominal -20°C and for up to four months when stored at nominal –70°C.

Table 5: Analytical method validation for (b) (4)

Method	LC-Tandem Mass Spectrometric Detection
Compound	(b) (4)
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 93.7 % to 98.5 % 94.7 % to 99.7 %

Precision (% CV) ***Inter-Day*** ***Intra-Day***	 6.2 % to 10.1 % 2.3 % to 8.8 %
Standard curve range	0.1 ng/mL to 20 ng/mL
Sensitivity (LOQ)	0.1 ng/mL
Mean Recovery	83.6%, 85.4% and 87.9 % respectively, for 3 separate QC samples (0.3ng/mL, 1.5 ng/mL and 15 ng/mL)
Specificity	No significant interfering peaks were observed in the retention window of (b) (4) and its internal standard.
Stability	(b) (4) was stable in human whole blood for up to ten weeks when stored at nominal -20°C and for up to four months when stored at nominal –70°C

Table 6: Analytical method validation for (b) (4)

Method	LC-Tandem Mass Spectrometric Detection
Compound	(b) (4)
Accuracy (% Bias) ***Inter-Day*** ***Intra-Day***	 100.7 % to 104 % 102.7 % to 111.0 %
Precision (% CV) ***Inter-Day*** ***Intra-Day***	 5.3 % -11.1% 2.6 % to 5.1 %
Standard curve range	0.1 ng/mL to 20 ng/mL
Sensitivity (LOQ)	0.1 ng/mL
Mean Recovery	85.7 % , 87.8% and to 88.3 % respectively, for 3 separate QC samples (0.3ng/mL, 1.5 ng/mL and 15 ng/mL)
Specificity	No significant interfering peaks were observed in the retention window of PEP025 and its internal standard.
Stability	(b) (4) was stable in human whole blood for up to ten weeks when stored at nominal -20°C and for up to four months when stored at nominal –70°C.

3 Detailed Labeling Recommendations

Please note that the PK results of Study PEP005-004 were not included in the label as referenced by the applicant. This is because although this study had 2 patients in total on ingenol mebutate

gel, 0.05 % who provided PK samples, it was not considered a maximal use study because the treatment area ($9cm^2$) was less than the proposed 25 cm^2 treatment area. In addition only one target AK lesion was treated in this study as opposed to multiple AK lesions in the treatment areas for the proposed indication.

Labeling recommendations are inserted below (deletions are "strikethroughs" and additions are "underlined")

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of PICATO Gel for the treatment of actinic keratosis is unknown.

Note: The pharm tox reviewer has recommended deleting the applicants' proposed labeling language below and replacing with the text above. See pharm tox review for details and proposed labeling language for this section

(b) (4)

12.2 Pharmacodynamics

The pharmacodynamics of PICATO gel is unknown.

Note: The pharm tox reviewer has recommended deleting the applicants' proposed labeling language below and replacing with the text above. See pharm tox review for details and proposed labeling language for this section

(b) (4)

[redacted] (b) (4)

[redacted]

[redacted]

12.3 Pharmacokinetics

Absorption

[redacted] (b) (4)

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

[redacted] (b) (4)

Drug Interactions

[redacted] (b) (4)

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

5 WARNINGS AND PRECAUTIONS

(b) (4)

10 OVERDOSAGE

(b) (4)

17 PATIENT COUNSELING INFORMATION

(b) (4)

4 Appendices

4.1 Individual Study Reviews:

Synopsis for Study PEP005-017

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

Investigator(s) and Site(s): Dr. Jarrat of DermResearch, Inc. 8140 North Mopac, Building 3, Suite 120, Austin, TX 78759 USA

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. Within this 100 cm^2 area, a 25 cm^2 area of skin will contain 4 to 8 clinically typical, visible and discrete AK lesions. This maximal use study intended to treat a larger 100 cm^2 (compared with the proposed 25 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.

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). One unit dose was to be used for one 25 cm^2 treatment area.

Reviewer's Comments: PEP005 Gel, 0.05 % (Batch #: AKW-C) was also used in the Phase 3 trunk and extremities studies PEP005-020 and PEP005-028. The batch size of this batch # was (b) (4)

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 for ingenol mebutate and its acyl isomers (b) (4) (lower limit of quantification [LLOQ] = 0.1 ng/mL using 100 µL of blood) by Liquid Chromatography with tandem mass spectrometric detection by (b) (4). The applicant stated that a total of 142 samples were analyzed in two reported batches. All samples were analyzed within the known stability period of four months when stored at nominal -70°C.

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.

Results:

Demographic and Baseline Characteristics:

All patients were Caucasians of non-Hispanic/Latino ethnicity and 63% (10/16) were female. The mean age of the study population was 63.3 years.

Table 7: Demographics and Baseline Characteristics

	PEP005 Gel, 0.05% N = 13	Vehicle Gel N = 3	Total N = 16
Age (years)			
Mean (SD)	63.0 (9.7)	64.7 (12.0)	63.3 (9.7)
Range	48.0–79.0	53.0–77.0	48.0–79.0
Gender			
Male	6 (46%)	0	6 (38%)
Female	7 (54%)	3 (100%)	10 (63%)
Race			
Caucasian	13 (100%)	3 (100%)	16 (100%)

N = number of patients; SD = standard deviation.

The AK lesion counts in a 25 cm^2 treatment area were as follows:

Table 8: AK lesion Counts

	PEP005 Gel, 0.05% N = 13	Vehicle Gel N = 3
Baseline Lesion Count	(N=13)	(N=3)
Mean	4.9	4.3
Q1 Median	4.0 5.0	4.04.0
Q3 STD	5.0 1.0	5.00.6
Range (Min, Max)	4 to 7	4 to 5

Reviewer's Comments: This is consistent with the Phase 3 trials that enrolled subjects with 4 to 8 clinically typical, visible, discrete AK lesions within a 25 cm^2 contiguous treatment area. Based on the applicant's inclusion criteria, a 100 cm^2 area in the maximal use PK study will be expected to contain 4x the # of AK lesions in a 25 cm^2 area of skin (i.e. ranging between 16-28 lesions). It is noted that the applicant did not provide the final lesion count in the 100 cm^2 treatment area in this submission.

Pharmacokinetics:

All but two patients (Patient 1002, Day 1, 24 hours and Patient 1107, Day 2, 12 hours) provided full PK samples for the analysis. All samples analyzed had blood concentrations that were below the limit of quantification (0.1 ng/mL) for PEP005, (b) (4) following two consecutive once-daily applications of PEP005 Gel, 0.05%. Pharmacokinetic parameters could not be determined due to the lack of quantifiable blood concentrations. The applicant stated that all samples were analyzed (between March 18th, 2009 and April 14th, 2009) within the known stability period of four months when stored at nominal -70°C.
The blood concentration listings for PEP005 and its acyl isomers, (b) (4) were all

below the LOQ (i.e.< 0.1 ng/mL) in all the samples and will not be included in this review.

Applicant's Conclusions
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.

Reviewer's Comments: The data indicates that the concentrations of PEP005, (b) (4) (b) (4) were below the lower limit of quantification (0.1 ng/mL) following the application of PEP005 Gel, 0.05 % once daily for two consecutive days to multiple AK lesions in a 100 cm^2 contiguous AK treatment area on the dorsal forearm. Therefore, no PK parameters could be calculated.

Synopsis of Study PEP005-013

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: Dr. Gregory Siller

Study Center (s): 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 to 23 April 2008

Clinical Phase: Phase I

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.

Methodology: This Phase I open-label study was designed to confirm the lack of systemic absorption of PEP005 and its acyl isomers (b) (4) when 0.05% PEP005 Topical Gel was applied once daily to an unoccluded 100 cm^2 (5 cm x 20 cm; 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. 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.

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.

Number of Patients: Eight male 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. Five out of six patients (83%) had approximately 21 to 50 AK lesions on their extremities at the time of study enrollment.

Dosage, Administration, and Duration of Treatment: PEP005 Topical Gel, 0.05% (Batch No. 0325C), was applied by the investigator to the AK treatment area by micro-pipette on two consecutive days as 1 mL in four aliquots of 250 µL (total for two days was 2 mL). The PEP005 Topical Gel was applied by the investigator with a micro-pipette and rubbed in with his gloved finger, over a 5 x 20 cm area of the patients' skin on the extensor forearm (Each aliquot was applied to a 5 x 5 cm marked segment of the treatment area). The investigator applied the study drug from a vial assigned to each individual patient. The study drug was to be applied at approximately the same time of the day on each of the two treatment days.

Reviewer's Comment: Based on the information in Study PEP005-017, 4 individual dose units is equal to approximately 1 mL. Batch No. 0325 was also used in the Phase 2 clinical study PEP005-018 (safety and efficacy study (N=12)) and it had a batch size of (b) (4)

Pharmacokinetic Sampling: Blood samples were taken prior to and 24 hours following Day 1 applications of PEP005 Topical Gel, and at 30 minutes, 1, 2, 4, 8, 12, and 24 hours following the Day 2 application.

Bioanalytical Methods: Levels of PEP005 and its two major metabolites (PEP015 and PEP025) in blood were determined in human whole blood containing EDTA as anticoagulant using liquid/liquid extraction and a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). The method previously validated at (b) (4) (b) (4)) has a lower limit of quantification (LLOQ) of 0.1 ng/mL for PEP005, PEP015 and PEP025 using 100 µL of whole blood.

Statistical Analyses: No statistical hypothesis was to be evaluated. Analysis was to be descriptive in nature.

Results:

Demographics and Baseline Characteristics:

Table 9: Demographic and Baseline Characteristics:

Demographic Characteristics	**0.05% PEP005 Topical Gel (N = 6) n (%)**
Age (years)	
N	6
Mean ± SD	67.3 ± 8.82
Median	66.5
Min–Max	56–81
Sex	
Male	6 (100.0)
Race	
Caucasian	6 (100.0)
Height (cm)	
N	6
Mean ± SD	179.3 ± 6.86
Median	180.0
Min–Max	170–188
Weight (kg)	
N	6
Mean ± SD	87.83 ± 10.265
Median	84.50
Min–Max	78.0–105.0
BMI (kg/m2)[a]	
N	6
Mean ± SD	27.40 ± 3.680
Median	28.03
Min–Max	22.8–32.4

Demographic Characteristics	**0.05% PEP005 Topical Gel (N = 6) n (%)**
Treatment Area	
Left arm	1 (16.7)
Right arm	5 (83.3)
Duration of AK (Months)[b,c]	

N	6
Mean ± SD	303.5 ± 234.74
Median	273.0
Min–Max	12–645
Fitzpatrick Skin Typed	
Burns easily, rarely tans (I)	5 (83.3)
Burns easily, tans minimally (II)	1 (16.7)
Number of AK lesions (minimum of 5 visible lesions)	
Yes	6 (100.0)
No	0

Note: Percentages were based on the number of non-missing values in the treatment group.
[a] BMI was calculated as weight (kg)/[height (m)]2.
[b] Duration of AK was calculated as Integer of [(Date of informed consent - Date of first diagnosis) / 365.25]*12.
[c] If the year of diagnosis was known, unknown days were imputed to the first of the month, and unknown months were imputed to January.
[d] Fitzpatrick Skin Type: 1 = Burns easily, rarely tans; 2 = Burns easily, tans minimally; 3 = Burns moderately, tans gradually; 4 = Burns minimally, tans wells; 5 = Rarely burns, tans profusely; 6 = Never burns, deeply pigmented.

Patient AK History**:** The applicant stated that the majority of the patients (83.3%) had 1 to 20 lesions on the face, neck, and V of the chest. The majority of patients (83.3%) also had 1 to 20 lesions on the trunk (back, chest, abdomen, shoulders) and 21 to 50 lesions on the extremities.

Table 10: Location and Extent of AK

Location and Extent of AK	**0.05% PEP005 Topical Gel (N = 6) n (%)**
Face / Neck / V of chest	
1-20	5 (83.3)
21-50	1 (16.7)
Trunk (back, chest, abdomen, shoulders)	
1-20	5 (83.3)
21-50	1 (16.7)
Extremities (arms, legs)	
1-20	1 (16.7)
21-50	5 (83.3)

Note: The patient is counted only once within a category. The same patient may appear in different categories

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; three patients had only partial PK assessments and were not included in the PK

population. The three patients that met requirements received both scheduled applications of PEP005 Topical Gel on Days 1 and 2, as per the protocol. The other three patients received only one application of PEP005 Topical Gel on Day 1 due to skin responses (Treatment Emergent Adverse Events (TEAEs) and Local Skin Responses (LSRs)) that the investigator felt did not warrant further topical application on Day 2. The applicant state that Patient 0908 did not receive study dosing on Day 2 due to a Grade 4 LSR of erythema and vesiculation/pustulation.
One patient (16.7%; 0903) discontinued from dosing on Day 2 after receiving only one dose of study drug on Day 1 due to a TEAE of application site irritation (lasted less than one day) and application site warmth (lasted six days). The patient recovered and completed the study.

Pharmacokinetics
All blood samples from the six patients (three patients treated for two days and three patients treated for one day) were below the LOQ (0.100 ng/mL) for PEP005 and its metabolites PEP015 and PEP025. Therefore, no PK parameters could be calculated and the blood concentration listings for PEP005 and its acyl isomers, (b) (4) and will not be included in this review.

Applicant's 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 (b) (4)

Synopsis of 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: Lawrence Anderson, MD, FACP

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

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.

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 (90µL) 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. Twenty-two patients were enrolled in the study, 3 patients received 0.01% PEP005 Topical Gel, 3 patients received 0.025% PEP005 Topical Gel, 10 patients received 0.05% PEP005 Topical Gel, and 6 patients received 0.075% PEP005 Topical Gel. The MTD was determined to be 0.05%. Two patients from the 0.05% expansion group consented to provide blood samples for PK analysis.

Pharmacokinetic Evaluation: Samples for PEP005 pharmacokinetic analysis (5 mL) were taken at baseline (before Day 1 treatment) and at 0.5, 1, 2, and 4 hours post-dose on Day 2 for the additional patients being treated at the MTD dose. Pharmacokinetic assessments were performed to determine the level of systemic exposure (maximum concentration [Cmax]) following application of PEP005 Topical Gel.

Bioanalytical Methods: Levels of PEP005 and its two main isomers, (b) (4) in whole blood were determined using a validated Liquid Chromatography with Tandem Mass Spectrophotometric Detection (LC-MS/MS) method (2174/066). The method previously validated at (b) (4) has a lower limit of quantification (LLOQ) of 0.1 ng/mL for PEP005, (b) (4) using 100 µL of whole blood

Results

Table 11: Demographic Characteristics

Demographic Characteristic	PEP005 Topical Gel 0.01% N=3	0.025% N=3	0.05% N=10	0.075% N=6	Total N=22
Age (year)					
N	3	3	10	6	22
Mean	77.3	75.7	71.9	72.7	73.4
SD	5.51	9.81	5.07	5.50	5.87
Range	72 - 83	70 - 87	64 - 79	66 - 80	64 - 87
Race					
Caucasian	3 (100.0%)	3 (100.0%)	10 (100.0%)	6 (100.0%)	22 (100.0%)
Gender					

Male	2 (66.7%)	2 (66.7%)	7 (70.0%)	5 (83.3%)	16 (72.7%)
Female	1 (33.3%)	1 (33.3%)	3 (30.0%)	1 (16.7%)	6 (27.3%)

Note: Percentages were based on the number of non-missing values in each treatment group and based on the number of patients in the Safety population.

Table 12: Baseline Characteristics

	PEP005 Topical Gel				
Baseline Characteristic	**0.01% N=3**	**0.025% N=3**	**0.05% N=10**	**0.075% N=6**	**Total N=22**
Height (cm)					
N	3	3	10	6	22
Mean	177.80	171.45	173.99	175.47	174.57
SD	9.158	12.115	9.390	7.638	8.770
Range	170 - 188	159 - 183	156 - 183	169 - 191	156 - 191
Weight (kg)					
N	3	3	10	6	22
Mean	83.98	85.65	85.85	84.85	85.30
SD	27.532	24.455	10.379	10.958	14.296
Range	66 - 116	62 - 111	73 - 98	67 - 99	62 - 116
Range BMI (kg/m^2)[a]					
N	3	3	10	6	22
Mean	26.16	28.65	28.50	27.59	27.95
SD	5.866	4.280	3.890	3.538	3.898
Range	22 - 33	25 - 33	22 - 34	22 - 32	22 - 34
Duration of actinic keratoses (months)					
N	3	3	10	6	22
Mean	160.5	52.3	56.6	81.0	76.9
SD	76.86	24.80	53.16	23.48	56.99
Range	105 - 248	33 - 80	0 - 193	39 - 106	0 - 248
Fitzpatrick-Pathak skin type[b]					
1	1 (33.3%)	0	1 (10.0%)	2 (33.3%)	4 (18.2%)
2	1 (33.3%)	0	5 (50.0%)	0	6 (27.3%)
3	0	3 (100.0%)	4 (40.0%)	3 (50.0%)	10 (45.5%)
4	1 (33.3%)	0	0	1 (16.7%)	2 (9.1%)

Note: Percentages were based on the number of non-missing values in each treatment group and based on the number of patients in the Safety population.

[a] BMI was calculated as weight (kg) / (height [m])^2.

[b] Fitzpatrick-Pathak Skin Type: 1 = burns easily, rarely tans; 2 = burns easily, tans minimally; 3 = burns moderately, tans gradually; 4 = burns minimally, tans well; 5 - rarely burns, tans profusely; 6 = never burns, deeply pigmented.

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, [redacted] (b) (4) 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.

The blood concentration listings for PEP005 only are inserted below (PK listing for the acyl isomers, (b) (4) were similar (i.e. all < 0.1 ng/mL) and will not be included in this review).

Conclusions: The applicant concluded that 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.

Reviewer's Comments: The PK data suggest that treatment of a 9 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 acyl isomers (b) (4) ***The utility of this information is very limited and will not be included in labeling because***

- ***The treatment area of 9 cm^2 does not represent maximal use conditions since it is much less than the proposed treatment area of 25 cm2 for the proposed indications and the treatment was only applied to one target AK lesion as opposed to multiple AK lesions for the proposed indication***
- ***The number of patients (N=2) is too small to draw any conclusions from the study***

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

/s/

ABIMBOLA O ADEBOWALE
11/18/2011

DOANH C TRAN
11/18/2011

EDWARD D BASHAW
11/18/2011