

ASX AND MEDIA RELEASE

Peplin announces positive phase IIa trial results

- **PEP005 Topical well tolerated with favourable safety profile**
- **Statistically significant complete clearance of AK skin lesions**

BRISBANE, Australia, 28 November 2005: Peplin Limited (ASX:PEP) today announced positive results from its phase IIa clinical trial of its proprietary drug PEP005 Topical in actinic keratosis (AK) or solar keratosis, a skin condition which can develop into skin cancer.

The phase IIa clinical trial achieved its objectives. PEP005 Topical gel was well tolerated with a favourable safety profile. The majority of local skin reactions were mild or moderate. Application of PEP005 Topical (0.05%) gel for just two days completely cleared 71% of lesions. This result was statistically significant ($p < 0.0001$).

Managing Director & CEO Michael Aldridge said these positive results were a significant milestone for the company because they show that PEP005 Topical has the potential to be a safe, effective and convenient medication for the treatment of this very common pre-cancerous skin condition.

“The results of this early stage Australian trial exceeded our expectations. While the primary purpose of the trial was to evaluate the safety of the drug, we have clearly shown that a short course of treatment with PEP005 Topical can clear AK lesions safely and effectively,” he said.

“Our next steps will be to undertake larger trials in Australia and the US starting in 2006 in order to obtain regulatory approval to market the product as quickly as possible.”

Dermatologist and principal investigator Dr. Greg Siller said the study had shown the drug to be well tolerated with a favourable safety profile.

“The drug appears to be active following just two treatment applications, which is quite unique,” Dr Siller said.

“If these results are validated in larger trials this product would be a great advance for our patients in the treatment of solar keratoses.”

The phase IIa clinical trial was a double-blind, vehicle controlled, randomised, parallel group study at six centres across Australia. PEP005 Topical in one of three concentrations or vehicle gel was applied to AK lesions on two days and subjects were followed for 12 weeks.

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Further information:

Michael Aldridge
Managing Director & CEO
Tel: 07-3250 1200
michael.aldridge@peplin.com

Media:

Andrew Collett
Hill & Knowlton
Tel: 02-9286 1224
acollett@hillandknowlton.com.au

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Description of trial

The clinical trial was a phase IIa multi-centre, double-blind, randomised, vehicle controlled, parallel group comparison study to evaluate the safety of PEP005 Topical gel at 0.0025%, 0.01% and 0.05% administered according to two schedules: day 1 and day 2 (treatment arm A) or day 1 and day 8 (treatment arm B) with a 12 week follow-up period. Secondary objectives were to determine a recommended treatment regimen, evaluate the efficacy of PEP005 Topical and evaluate subjects for cosmetic outcome.

The study was initiated in March 2005 and ran for 8 months.

Description of trial subjects

There were 63 subjects enrolled and randomised to one of two treatment arms and one of four treatment groups (0.0025%, 0.01% or 0.05% active ingredient or vehicle gel). Five subjects withdrew from the study prior to receiving treatment; 58 subjects were treated. Of these 30 were randomised to treatment arm A (day 1 / day 2) and 28 to treatment arm B (day 1 / day 8). There were no drop-outs due to drug related adverse events.

Study subjects were of either gender and at least 18 years old (excluding women of child bearing potential) with at least five AK lesions located on the arms, shoulders, chest, face or scalp. Median lesion diameter was 8 millimetres, with range 4-15 millimetres. One of the five selected AK lesions was confirmed by small punch biopsy. All subjects were Caucasian and the majority of subjects in the study had Fitzpatrick-Pathak skin types that burn easily and tan rarely or minimally.

Treatment method

Study drug in the amount of 10 or 20 micro litres (depending on lesion size) was applied to each of five selected AK lesions once daily on the two treatment days and subjects were then followed for 12 weeks.

The preliminary results relating to the objectives of the study are presented below.

Safety: The primary objective of the trial was to evaluate safety. There were no drug related serious adverse events reported. All treated subjects completed their two day course of therapy.

Local skin reactions over and above a pre-treatment base line were assessed by the investigator and graded as mild, moderate or severe. The most frequently reported local skin reactions were erythema, scabbing/crusting and flaking/scaling/dryness and the majority were mild or moderate. All local skin reactions were expected and had been predicted based on the drug's mechanism. There was a dose response with higher concentrations resulting in more prevalent and increased local skin reactions.

Local skin reactions typically resolved within four weeks. The prevalence and severity of local skin reactions over base line in the first four weeks following treatment are set out below. The patient population comprises only study subjects that were treated (Safety population).

Local skin reactions (over base line) arm A + arm B in first 4 weeks (Percentage of subjects)									
Mild/Moderate									
Concentration of active	Vehicle		0.0025% PEP005		0.01% PEP005		0.05% PEP005		
	N=12		N=15		N=16		N=15		
Erythema	4	33%	8	53%	13	81%	12	80%	
Scabbing/crusting	1	8%	6	40%	8	50%	8	53%	
Flaking/scaling/dryness	4	33%	11	73%	11	69%	9	60%	
Erosion/ulceration	1	8%	1	7%	3	19%	3	20%	
Oedema	0	0%	0	0%	4	25%	5	33%	
Itch	0	0%	1	7%	3	19%	0	0%	
Hypopigmentation	1	8%	0	0%	1	6%	0	0%	
Weeping/exudates	0	0%	0	0%	2	13%	0	0%	
Vesicles	0	0%	0	0%	1	6%	2	13%	
Severe									
Concentration of active	Vehicle		0.0025% PEP005		0.01% PEP005		0.05% PEP005		
	N=12		N=15		N=16		N=15		
Erythema	0	0%	1	7%	1	6%	0	0%	
Scabbing/crusting	0	0%	0	0%	2	13%	1	7%	
Flaking/scaling/dryness	0	0%	0	0%	1	6%	1	7%	
Erosion/ulceration	0	0%	0	0%	0	0%	0	0%	
Oedema	0	0%	0	0%	0	0%	0	0%	
Itch	0	0%	0	0%	0	0%	1	7%	
Hypopigmentation	0	0%	0	0%	0	0%	0	0%	
Weeping/exudates	0	0%	0	0%	0	0%	0	0%	
Vesicles	0	0%	0	0%	0	0%	0	0%	

Secondary objectives of the trial were:

1. **The determination of a recommended treatment regimen.** There was no apparent difference in terms of safety or efficacy between treatment arm A and treatment arm B.
2. **Evaluation of the efficacy of PEP005 Topical.** There was a dose related response to drug. The most effective concentration of PEP005 Topical at all post treatment time points and on all measures of efficacy was the highest concentration, 0.05% PEP005 Topical. The efficacy of the 0.05% PEP005 Topical treatment group compared to vehicle, at week 12, combining treatment arms A and B is discussed below.

Two measures of efficacy are presented. The first (a per lesion evaluation) is the proportion of all treated lesions which were completely cleared compared to vehicle gel. The second (a per subject evaluation) is the proportion of treated subjects who completely cleared 100% (all five) of their lesions versus vehicle gel and the proportion of treated subjects who completely cleared 80% or more (four or more) of their treated lesions versus vehicle gel. This second measure is presented in two ways: on the basis of all study subjects including those that did not receive medication (Intent to treat population) and on the basis of only study subjects that received medication (Safety population).

- On a per lesion basis: 71% of lesions in the 0.05% PEP005 Topical group (n=75) were completely cleared versus 32% of lesions in the vehicle group (n=60). This difference was statistically significant with $p < 0.0001$.
- On a per subject basis (Intent to treat population):
 - i. 33% of subjects in the 0.05% PEP005 Topical group (n=18) completely cleared all five selected lesions versus 8% in the vehicle group (n=12) (not statistically significant);
 - ii. 56% of subjects in the 0.05% PEP005 Topical group cleared 80% or more of their lesions versus 17% in the vehicle group. This difference was statistically significant with $p = 0.0334$.
- On a per subject basis (Safety population):
 - i. 40% of subjects in the 0.05% PEP005 Topical group (n=15) completely cleared all five selected lesions versus 8% in the vehicle group (n=12) (not statistically significant);
 - ii. 67% of subjects in the 0.05% PEP005 Topical group cleared 80% or more of their lesions versus 17% in the vehicle group. This difference was statistically significant with $p = 0.0114$.

Comparison of PEP005 Topical to vehicle gel

Concentration of active	Vehicle	0.0025% PEP005		0.01% PEP005		0.05% PEP005	
		%	<i>p value</i>	%	<i>p value</i>	%	<i>p value</i>
Per lesion basis	<i>N</i> =60	<i>N</i> =75		<i>N</i> =75		<i>N</i> =75	
Lesions completely cleared	32%	53%	NS	25%	NS	71%	<0.0001
Per subject basis (Intent to treat population)	<i>N</i> =12	<i>N</i> =17		<i>N</i> =16		<i>N</i> =18	
100% of lesions completely cleared	8%	18%	NS	6%	NS	33%	NS
80% of lesions completely cleared	17%	30%	NS	13%	NS	56%	0.0334
Per subject basis (Safety population)	<i>N</i> =12	<i>N</i> =15		<i>N</i> =16		<i>N</i> =15	
100% of lesions completely cleared	8%	20%	NS	6%	NS	40%	NS
80% of lesions completely cleared	17%	33%	NS	13%	NS	67%	0.0114

NS=not statistically significant

3. **Evaluation of subjects for cosmetic outcome:** There was a positive impact on cosmetic outcome in the highest concentration group the difference was not statistically significant.

Implications

The results of this trial exceed Peplin's expectations for PEP005 Topical's safety and efficacy based on an assessment of the results of its pre-clinical studies and its phase I clinical trial in AK announced on 10 January 2005 and the efficacy of leading treatment alternatives for AK.

Importantly, the phase IIa trial results highlight the potential for a new convenient, safe and well tolerated topical medication which clears AK lesions following only two days of treatment. Peplin believes a short treatment period will be an important differentiating factor in the large and growing markets for the topical treatment of AK and non melanoma skin cancer.

Three other observed factors may also be important:

1. There was no apparent difference in safety or efficacy between day 1, day 2 treatment and day 1, day 8 treatment. As a result, Peplin should have the

flexibility to develop a treatment regimen which aligns with the preferences of both clinicians and their patients.

2. In this study, the highest concentration (0.05%) of PEP005 Topical was the most effective. In its presently ongoing US open label dose escalation clinical trial a cohort of subjects has been treated at a concentration higher than 0.05%.

This US dose escalation study is designed to establish the maximum tolerated dose (MTD) of PEP005 Topical when applied on day 1, day 2 to an area of sun damaged skin containing an AK. While the MTD has not as yet been established in this trial a MTD equal to or higher than 0.05% will facilitate more advanced clinical trials of PEP005 Topical on an area of sun damaged skin with multiple or contiguous AK lesions at this concentration .

3. The observed favourable safety profile of two days treatment gives Peplin confidence that it could explore the activity of PEP005 Topical in a three day course of treatment in the next phase of clinical trials.

Peplin plans to conduct more advanced clinical trials of PEP005 Topical in AK in the US and Australia in 2006 in larger patient populations to progress the product to market as quickly as possible. Peplin intends to conduct these trials under its presently open IND application with FDA.

ABOUT PEPLIN

Peplin is focused on the development and commercialisation of prescription human therapeutic products for the treatment of cancer. Its lead compound is PEP005, the first in a new class of investigational agents. Peplin's lead product is PEP005 Topical, which is being studied in clinical trials for the treatment of actinic keratosis (AK) (a pre-cancerous lesion) and non-melanoma skin cancer (NMSC). PEP005 Topical works by a powerful mode of action, directly killing most cancer cells and then recruiting and activating the local immune system to clean-up these dead cancer cells and kill any remaining cancer cells. PEP005 Topical is potentially a rapidly acting and cosmetically attractive non-surgical topical treatment for AK and NMSC. Peplin's product development activities are supported by the Australian Federal Government under its Pharmaceuticals Partnerships Program.

Peplin's earlier stage pipeline is targeted at leukemia (a blood borne cancer) using its lead compound PEP005 in an intravenous formulation (PEP005 IV) and bladder cancer using an intra-cavitary or intravesical formulation (PEP005 IC). PEP005 has demonstrated selective and potent anti-leukemia activity in pre-clinical disease models. PEP005 induces apoptosis in leukemia cells via the activation of PKC delta. Peplin holds global proprietary rights for PEP005 Topical and other oncology applications of PEP005. Its research portfolio of EPUFA compounds opens additional potential opportunities in cancer and pain.

ABOUT ACTINIC KERATOSIS

AK is a common skin condition characterised by rough, red, scaly patches, crusts or sores on the top layer of skin. If left untreated AKs can progress to squamous cell carcinoma, an invasive skin cancer that can be fatal. AKs usually develop on the face, lips, ears, scalp, neck, forearms and back of hands- areas that are most commonly exposed to the sun.

AKs are the most common pre-cancerous skin lesions worldwide affecting 50% of Caucasians over the age of 40 years with the average patient having 6-8 lesions. The treatment of AKs is the most common dermatologic procedure performed in the out-patient setting. Based on a 2001 study, in the US each year there are 3.7 million office visits and about 5.2 million procedures for AK. According to the American Academy of Dermatology AK affects more than 10 million Americans. The worldwide prevalence of AK is highest in Australia.

Current treatment alternatives comprise surgical techniques (primarily cryotherapy) and topical medications (e.g. 5-fluorouracil, imiquimod and diclofenac). Current treatment approaches whilst mostly effective can cause scarring and hypopigmentation at the treatment site, can be inconvenient or may require long treatment duration for effect.