



A multi-centre, Randomised, parallel group, double-blind, vehicle-controlled study to evaluate the Efficacy of 0.05% PEP005 Topical Gel In patients with actinic keratoses ON non-head locations

PEP005-014 – study design (non-head)

OBJECTIVE	Determine the efficacy and safety of PEP005 (ingenol mebutate) Gel compared to vehicle gel
DESIGN	Multi-center, randomized, double-blind, vehicle-controlled study
PATIENTS	4 to 8 clinically typical, visible and discrete AK lesions within a contiguous 25 cm ² treatment area on non-head locations (arms, back of hands, legs, shoulders, chest and back)
NUMBER	Approximately 250 (125 per treatment group)
DOSE	0.05% Topical Gel Vehicle
REGIMEN	Two consecutive daily applications
OUTCOME	Evaluate efficacy and safety <ul style="list-style-type: none">– Complete clearance rate of AK lesions– Partial clearance rate (≥75% reduction) of AK lesions– Incidence rate of AEs & SAEs– Incidence and grade of LSRs, pigmentation and scarring
ASSESSMENTS	Screening, Day 1, 3, 8, 15, 29, 57 (extra follow up if/as required)

PEP005-014 Patient characteristics

- 255 patients randomized
- 159 male, 96 female
- Mean age 67.1 (36 – 88) years
- 6 anatomical locations:
 - 166 arm, 54 back of hand, 17 chest, 11 legs, 5 back, 2 shoulder
- ITT efficacy population – 235 patients
 - Site 59 excluded (major protocol violations)

PEP005-014 Complete Clearance Rate

	Active	Vehicle	p value	Test
Overall	27% (32/117)	5% (6/118)	p<0.0001	CMH
Arm	25% (19/75)	6% (4/72)	p=0.0002	Fisher's Exact
Back *	0% (0/2)	0% (0/3)	Insufficient patients	
Back of hand	16% (4/25)	0% (0/29)	p=0.0400	Fisher's Exact
Chest	89% (8/9)	13% (1/8)	p=0.0034	Fisher's Exact
Leg	17% (1/6)	25% (1/4)	Insufficient patients	
Shoulder **		0% (0/2)		



* No patients had complete clearance on active or vehicle
 ** No patients were treated with active drug



PEP005-014 Partial Clearance Rate

	Active	Vehicle	p value	Test
Overall	44% (52/117)	8% (9/118)	p<0.0001	CMH
Arm	48% (36/75)	10% (7/72)	P<0.0001	Fisher's Exact
Back	50% (1/2)	0% (0/3)	Insufficient patients	
Back of hand	24% (6/25)	0% (0/29)	p=0.0069	Fisher's Exact
Chest	89% (8/9)	13% (1/8)	p=0.0034	Fisher's Exact
Leg	17% (1/6)	25% (1/4)	Insufficient patients	
Shoulder **		0% (0/2)		



** No patients were treated with active drug



PEP005-014 Percent reduction in lesions (median)

	Active	Vehicle	p value	Test
Overall	67% (113)	0% (117)	P<0.0001	Wilcoxon Two-sample
Arm	73% (72)	0% (72)	P<0.0001	Wilcoxon Two-sample
Back	46% (2)	0% (3)	Insufficient patients	
Back of hand	50% (25)	0% (29)	p=0.0005	Wilcoxon Two-sample
Chest	100% (9)	0% (8)	p=0.0040	Wilcoxon Two-sample
Leg	57% (5)	56% (4)	Insufficient patients	
Shoulder **			Insufficient patients	

PEP005-014 vs PEP005-006

- Complete clearance rate for lesions only on arms/shoulders/chest/back
 - 014 0.05% for 2 days 31% (27/86) vs Vehicle 6% (5/85)
 - 006 0.05% for 2 days 45% (19/42) vs Vehicle 14% (6/43)
- Partial clearance rate for lesions only on arms/shoulders/chest/back
 - 014 0.05% for 2 days 52% (27/86) vs Vehicle 9% (5/85)
 - 006 0.05% for 2 days 67% (28/42) vs Vehicle 21% (9/43)
- Of interest is the much higher vehicle responses seen in the 006 study vs the 014 study - Difference between active & vehicle is almost identical for both studies
 - Complete clearance rate: 014 - 25%, 006 – 31%
 - Partial clearance rate: 014 – 43%, 006 – 46%

PEP005-014 Key messages (1)

- Study met both the primary and secondary efficacy endpoints with the data demonstrating a highly statistically significant benefit of PEP005 0.05% gel over vehicle
 - CCR Active 27% vs Vehicle 5%
 - PCR Active 44% vs Vehicle 8%
 - Median % reduction in lesion count Active 67% vs Vehicle 0%
- Highly statistically significant benefit was also demonstrated in traditionally difficult to treat anatomical locations - arms, back of hand and chest
 - CCR's ranged from 16% (BOH) to 89% (chest)
 - PCR's ranged from 17% (leg) to 89% (chest)
 - Median % reduction in lesions ranged from 46% (back) to 100% (chest)
- First product to demonstrate statistically significant benefit over vehicle on difficult to treat non-head anatomical locations (trunk and extremities) using current FDA accepted endpoints

PEP005-014 Key messages (2)

- PEP005 0.05% gel was well tolerated, with excellent compliance (98%). No drug related SAE's were recorded and no deaths
 - Only 11 treatment related AE's reported from 8 patients (7 active, 1 vehicle)
- Composite LSR score peaked at Day 8 and had returned to baseline by Day 29
 - Erythema and flaking/scaling were the most frequently reported LSR's
 - No cases of worsening of scarring were reported and only 3 patients in the active group reported a worsening of pigmentation
- No ECG changes or cardiac signals were reported as being drug related

AK is a Growing Health Problem



- Actinic Keratoses (solar keratosis or sun spots) are caused by accumulated sun damage
- AKs often occur in clusters on exposed skin, requiring treatment of large areas of skin
- AKs can cause pain and disfigurement for patients
- AKs can unpredictably progress to squamous cell carcinoma (SCC), a type of skin cancer that can be life-threatening
- AKs are one of the most frequent skin problem diagnosed by dermatologists in the US

Major Shortcomings with Existing Treatments

1. Liquid nitrogen (cryotherapy)

- Effectively burns off lesions
- Painful and prone to scarring

2. Photodynamic therapy (PDT)

- Requires dedicated equipment
- Significant side effects
- Minimal use in current market
- Poor reimbursement



3. Topical therapies (Creams, Gels)

- Currently 4 products on the market (Aldara, Efudex, Carac & Solaraze)
- All have long treatment times (1 – 4 months)
- Patients prone to significant discomfort, weeping during treatment and/or potential scarring post treatment
- Patients often fail to complete course of treatment

PEP005 Gel's Compelling Advantages

- Unique, dual mechanism of action
 - Directly kills cancer cells
 - Activates immune system to improve treatment and potentially prevent recurrence
- Significantly shorter treatment time (2–3 days vs. months)
- Potentially fewer and less severe side effects
- Much shorter duration of side effects
- Improved patient compliance – treatment completion

Large and Growing Market for Topical Treatments for AK

- Over 5.6m office visits for AK each year in the US⁽¹⁾
- 90% of visits result in treatment (ie: approx 5M treatments)
- 25% treatments involve topical medication (1.25M)⁽²⁾
- Full course of existing topical treatments cost up to US \$500-750⁽³⁾
- US available market for topicals (2005) 1.25m x US\$500-US\$750 = US\$625 million - \$937.5 million
- Market growing rapidly:
 - Ageing population
 - Increasing awareness and prevention
 - Increasing trend from liquid nitrogen treatment to topical treatments

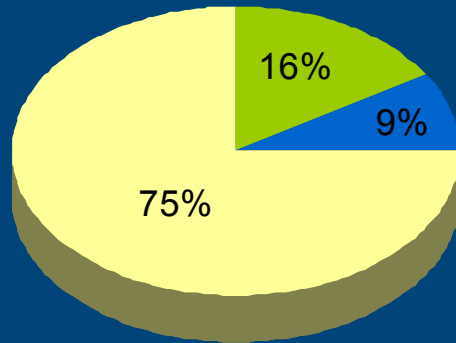
1) *US office visits for AK, NAMCS database (Aug. for 2001-2005)*

2) *Journal of Dermatological Treatment, 2006; 17: 162-166*

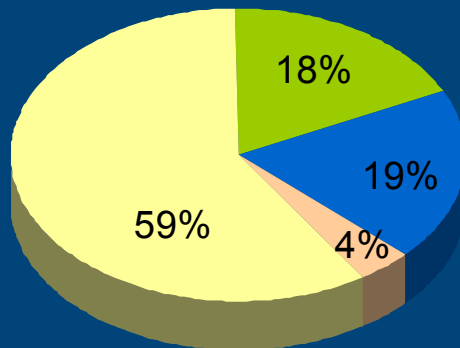
3) *Redbook 2008*

Clear Trend Towards AK Topical Treatment

2005⁽¹⁾



2007⁽²⁾



■ Cryotherapy ■ Topical
■ Combination ■ Other

- Cryotherapy trend decreasing:
 - Reimbursement rates rapidly deteriorating
 - Emerging clinical data question patient outcomes
- Topical trends increasing:
 - Increased use of “field treatment” of clinical and sub-clinical lesions
 - Higher awareness of patients and physicians means virtually all AK’s are treated aggressively
- Dissatisfied patients also led to quick product uptake with more recent topical launches
 - Year 1 ~10%, Year 2 ~22%



1) *Journal of Dermatological Treatment*, 2006; 17: 162-166
2) Peplin marketing research 2007



Market Dynamics Demonstrate PEP005 Exciting Potential

1. Growing patient population
2. Cryosurgery decline (reimbursement, efficacy)
3. Emerging role of combination therapy
4. Less than ideal current topical therapies (duration, compliance)
6. Lack of new competitors

Available AK
Topical
Therapy market
is US\$750m
and growing
rapidly

Clear Route to Market

- Highly targeted sales approach
 - Small specialty sales force can cover key customers
 - 10,500 practicing dermatologists in the US
 - 6,000 treat 90% of all the AK cases
 - Effectively covered with sales force of 50-60 reps
- Reimbursement is established
 - Existing reimbursement scheme for AK treatments
 - Payers receptive, anxious to “get their money’s worth”
- Operating PEP005 manufacturing plant
 - GMP manufacturing plant established in Queensland

