

Study to Determine the Optimal Tolerated Regimen of Ingenol Mebutate (PEP005) Gel for Actinic Keratosis of the Face or Face and Scalp

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Abstract

Introduction: Ingenol mebutate (PEP005) gel is being evaluated for treatment of actinic keratosis (AK). Some studies suggest that 0.05% may be a suitable concentration for non-head AK lesions. Head lesions may respond to a lower dose. We report a study to determine a suitable regimen for facial or facial and scalp AK.

Methods: This open-label 57-day study evaluated 6 concentrations and 2 regimens of ingenol mebutate gel. Eligible patients had 4-8 AK lesions in a contiguous 25-cm² area on the face or face and scalp and were treated with 0.0125%, 0.0175%, or 0.025% once daily (QD) for a maximum of 2 days or with 0.0025%, 0.005%, 0.0075%, 0.0125%, 0.0175%, or 0.025% QD for a maximum of 3 days. Efficacy was assessed at day 57 (End of Study day) by calculating the proportion of patients with ≥75% reduction of baseline AKs (partial clearance rate), no visible AKs (complete clearance rate), and 100% reduction of baseline AKs (baseline clearance rate). Patient satisfaction was also evaluated at day 57. Safety was assessed by local skin responses (LSRs) after treatment and by adverse events (AEs) including treatment-related treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).

Results: 88 patients were randomized and treated; 78.4% of lesions were on the face and 21.6% were on the face and scalp. Based on local tolerability, the maximum tolerated dose was 0.025% QD for 2 days. All concentrations produced partial clearance of AK lesions in at least some patients, ranging from 25% with 0.0025% for 3 days to 100% with 0.0125% and 0.0175% for 2 days and 0.0125% and 0.025% for 3 days. All concentrations except 0.0125% for 2 days and 0.0025% for 3 days produced complete clearance in some patients, ranging from 36.7% with 0.025% for 2 days to 100% with 0.0175% for 2 days. Overall patient satisfaction was “very positive” at all concentrations. Tolerability was good, with 83% of patients able to apply any concentration of ingenol mebutate gel for 2 days; about half the patients were able to apply study medication for 3 days. The most common LSRs were erythema, flaking/scaling, or crusting, which generally resolved within 2-4 weeks. TEAEs included application site disorders and local edema, with no clear dose response.

Conclusion: A range of doses between 0.005% and 0.025% ingenol mebutate gel QD for 2 or 3 days was identified for further clinical development for treatment of AK on the face or face and scalp.

Introduction

- Ingenol mebutate (PEP005) gel is an investigational agent for short-course, field-directed therapy of AK
- Preclinical studies suggest that topical ingenol mebutate gel has a dual mechanism of action
 - Rapid induction of primary necrosis¹
 - Induction of neutrophil-mediated, antibody-dependent cellular cytotoxicity of residual dysplastic keratinocytes²
- In initial small clinical studies, ingenol mebutate gel produced substantial lesion clearance and good tolerability with only a 2- to 3-day dosing regimen^{3,4}
- The prolonged courses of therapy required by currently approved topical agents for AK can result in poor adherence, which may lead to lower clearance rates compared with a full course of therapy
- Ingenol mebutate gel requires only short-term application and therefore has the potential to enhance adherence

Methods

Study Design

- Patients were evaluated at a screening visit, enrolled in the study if they met the entry criteria of 4 to 8 AK lesions in a contiguous 25-cm² area on the face or face and scalp, and randomized at the day 1 (baseline) visit to one of the doses and dosing regimens
- Randomized patients applied the study medication to the treatment area as directed for a maximum of 2 or 3 days
- Follow-up visits were performed on days 8, 15, 29, and 57 (end of study). A dermatologic examination, including assessment of LSRs, and monitoring for AEs was performed at each visit by a qualified dermatologist. Clinical laboratory tests were performed during the screening visit and on day 8

Determination of MTD

- The study was originally designed to evaluate QD treatment for 3 consecutive days with ingenol mebutate gel, 0.025%, 2 consecutive days with ingenol mebutate gel, 0.05%, or 3 consecutive days with ingenol mebutate gel, 0.05%
- Following review of safety data for the first 6 patients treated with ingenol mebutate gel, 0.025%, for 3 consecutive days, it was determined that dose-limiting toxicity had been met with that dose and dosing regimen
- As a result, the protocol was amended. The cohort to be treated with ingenol mebutate gel, 0.025%, for 2 days was expanded, and assessment of the following lower formulation strengths was added to further define tolerability and examine efficacy
 - 0.0175% and 0.0125% QD for 2 consecutive days
 - 0.0075%, 0.0050%, 0.0025%, 0.0175%, and 0.0125% QD for 3 consecutive days
- Data were then analyzed in 2 separate groups based on the dosing regimen
 - Analysis Group 1 includes data from all concentrations of ingenol mebutate gel for patients scheduled to receive a maximum of 2 applications
 - Analysis Group 2 includes data from all concentrations of ingenol mebutate gel for patients scheduled to receive a maximum of 3 applications

Efficacy

- Primary End Point**
- Partial clearance rate, defined as the proportion of patients at day 57 with ≥75% reduction in the number of AK lesions identified at baseline in the selected AK treatment area
- Secondary End Points**
- Complete clearance rate, defined as the proportion of patients at day 57 with no clinically visible AK lesions in the selected AK treatment area (lesions present at baseline or emergent during the study period in the treatment area)
 - Baseline clearance rate, defined as the proportion of patients at day 57 with 100% reduction in the number of AK lesions identified at baseline in the selected AK treatment area
 - Percentage reduction of the number of AK lesions, defined as the number of lesions present at baseline minus the number of lesions present at the end of study, divided by the number of lesions present at baseline
 - Efficacy was evaluated using the modified ITT population (defined as all patients treated with at least 1 dose of study medication who had at least 1 post-baseline assessment of lesion clearance) was used for all efficacy analyses

Safety and Tolerability

- Number of applications of study drug
- Incidence rate and grade of LSRs following treatment
- GSR of the selected AK treatment area before and after treatment
- Incidence of treatment-related AEs recorded throughout the study
- Mean change in laboratory tests from the screening visit through day 8
- Safety analyses were performed on the all-patients-treated population (defined as all patients treated with at least 1 dose of study medication)

LSR and GSR

- LSR assessments were made using a grading scale from 0 (not present or slight) to 4 (maximum possible response) for the following:
 - Erythema
 - Flaking/scaling
 - Crusting
 - Swelling
 - Vasculature/pustulation
 - Erosion/ulceration
 - Pigmentation
 - Scarring
- GSR assessments were made according to the following:
 - None: no visible signs or symptoms present
 - Mild: signs visibly or palpably present and/or patient awareness of symptoms
 - Moderate: substantial signs or symptoms
 - Severe: extensive signs or symptoms

Results

Table 1
Number of Days Dosed

	Number of Days of Dosing		
	1 Day n (%)	2 Days n (%)	3 Days n (%)
Analysis Group 1			
0.0125% (n = 3)	30 (100)	1 (33.3)	—
0.0175% (n = 3)	3 (100)	3 (100)	—
0.025% (n = 30) ^a	30 (100)	23 (76.6)	—
Analysis Group 2			
0.0025% (n = 8)	8 (100)	8 (100)	8 (100)
0.005% (n = 8)	8 (100)	8 (100)	4 (50.0)
0.0075% (n = 9)	9 (100)	7 (77.8)	4 (44.4)
0.0125% (n = 11)	11 (100)	9 (81.8)	5 (45.5)
0.0175% (n = 10)	10 (100)	8 (80.0)	4 (40.0)
0.025% (n = 6) ^a	6 (100)	6 (100)	3 (50.0)

^a29 of the 36 patients (80.6%) treated with ingenol mebutate gel 0.025% tolerated therapy for 2 days.

Table 2
Efficacy

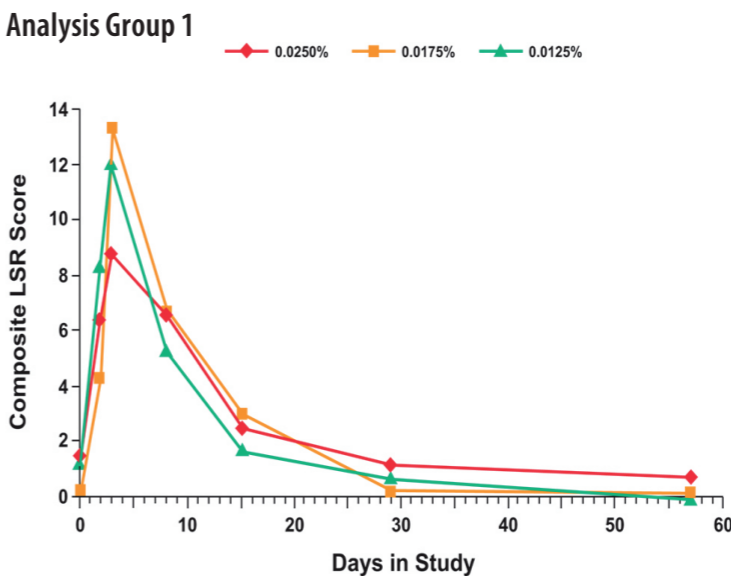
	Partial Clearance Rate, % (n)	Complete Clearance Rate, % (n)	Baseline Clearance Rate, % (n)
Analysis Group 1			
0.0125% (n = 3)	100 (3)	0 (0)	0 (0)
0.0175% (n = 3)	100 (3)	100 (3)	100 (3)
0.025% (n = 30) ^a	66.7 (20)	36.7 (11)	36.7 (11)
Analysis Group 2			
0.0025% (n = 8)	25.0 (2)	0 (0)	0 (0)
0.005% (n = 8)	62.5 (5)	37.5 (3)	37.5 (3)
0.0075% (n = 9)	75.0 (6)	37.5 (3)	37.5 (3)
0.0125% (n = 11)	100 (11)	54.5 (6)	54.5 (6)
0.0175% (n = 10)	80.0 (8)	80.0 (8)	80.0 (8)
0.025% (n = 6) ^a	100 (6)	50.0 (3)	50.0 (3)

^a26 of the 36 patients (72.2%) treated with ingenol mebutate gel 0.025% met the criteria for partial clearance; 14 of these 36 patients (38.9%) met the criteria for complete clearance and baseline clearance.

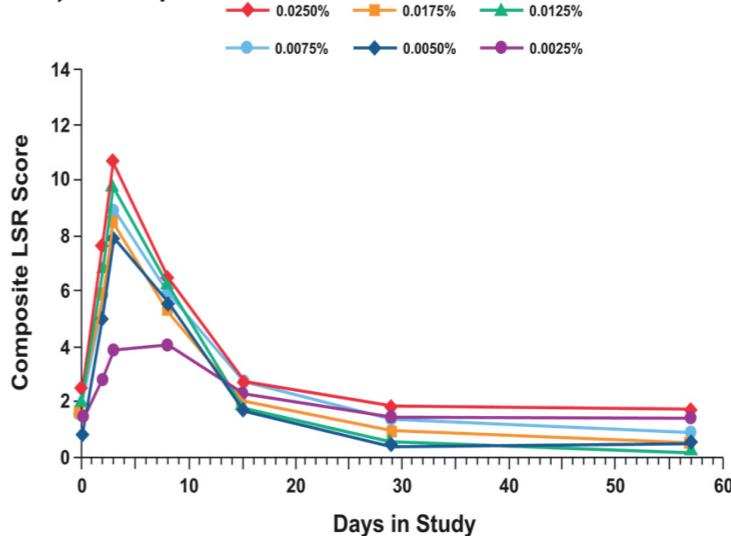
Discussion and conclusions

- Ingenol mebutate gel was well tolerated across all formulation strengths up to 0.025%
 - 80.6% of patients tolerated 2 days of treatment with ingenol mebutate gel 0.025%, the MTD
- Clearance of AK lesions was demonstrated by at least 1 of the 3 efficacy measures with all of the formulation strengths
- At the MTD, 0.025% for 2 days, the complete clearance rate was 38.9%
- The safety profile was favorable
 - Erythema was the most common LSR, followed by flaking/scaling and then crusting
 - LSRs peaked between days 3 and 8 and were largely resolved by day 29

Figure 1
Mean Composite LSR Scores



Analysis Group 2



^aPatients in the ingenol mebutate gel, 0.025%, group did not have a scheduled day 2 visit.

Table 3
Most Common TEAEs for All Patients

	Application Site Conditions % (n)	Headache % (n)	Eye Disorders % (n)
Analysis Group 1			
0.0125% (n = 3)	33.3 (1)	0 (0)	0 (0)
0.0175% (n = 3)	0 (0)	66.7 (2)	0 (0)
0.025% (n = 30)	20.0 (6)	3.3 (1)	6.7 (2)
Analysis Group 2			
0.0025% (n = 8)	12.5 (1)	0 (0)	0 (0)
0.005% (n = 8)	62.5 (5)	12.5 (1)	0 (0)
0.0075% (n = 9)	66.7 (6)	0 (0)	22.2 (2)
0.0125% (n = 11)	54.5 (6)	27.3 (3)	9.1 (1)
0.0175% (n = 10)	20.0 (2)	0 (0)	10.0 (1)
0.025% (n = 6)	50.0 (3)	33.3 (2)	0 (0)

Serious Adverse Events

- 3 patients experienced a total of 4 SAEs
 - 1 patient in the 0.005% dosing group experienced back pain on day 31
 - 1 patient in the 0.005% dosing group was hospitalized for preexisting chronic obstructive pulmonary disease and cellulitis of the left leg on day 47
 - 1 patient in the 0.025% dosing group was diagnosed with a squamous cell carcinoma on the left side of the neck on day 2
- No SAE was considered treatment-related, and all were treated and resolved by day 57

References Anderson L, Welburn P. Maximum tolerated dose of PEP005 Topical Gel for the treatment of actinic keratosis [ADA Poster P1503]. Paper presented at: American Academy of Dermatology 2007 Summer Meeting, August 1-5, 2007; New York, NY.
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