

Non-Melanoma Skin Cancer

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Safety and efficacy of 0.005%, 0.01%, and 0.015% PEP005 (ingenol mebutate) gel for actinic keratosis

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Introduction: PEP005 (ingenol mebutate) Gel is a novel, short-course (2-3 day) topical treatment being developed for treatment of actinic keratosis (AK). This study examined efficacy and safety of 8 regimens for treating AK lesions on the face and scalp.

Methods: This was a randomized, double-blind, vehicle-controlled study. Eligible patients with 4-8 lesions in a contiguous 25-cm² area on the face or scalp were randomized to once-daily treatment with ingenol mebutate gel, 0.005%, 0.01%, or 0.015%, or vehicle for 2 or 3 consecutive days. Patients returned to the clinic for follow-up visits on days 4, 8, 15, 29, and 57 following study drug application. Efficacy was assessed at day 57 by the proportion of patients with no clinically visible AKs in the selected treatment area (complete clearance rate). Safety was assessed by rate and grade of local skin response (LSR) following treatment and incidence of treatment-related adverse events.

Results: 265 patients were randomized into the study (ITT); 77% face, 23% scalp. 264 and 250 patients were included into the Safety and Per Protocol (PP) populations, respectively. At day 57 statistically significant differences in the PP population, compared with vehicle, were observed in the 2-day treatment regimens for 0.01% (P=0.001) and 0.015% (P<0.001) concentrations and the 3-day treatment groups for 0.005% (P=0.028) and 0.015% (P=0.005). Statistically significant differences were also observed in the ITT population for the 0.01% and 0.015% 2-day treatment groups (P<0.001) and the 0.015% 3-day treatment group (P<0.001). The complete clearance rate for 3 days' treatment with ingenol mebutate gel, 0.015% was 42.3% (P=0.005 vs vehicle; PP). At least a 50% median reduction in AK lesions was observed in all active treatment groups compared with baseline, with a 75%-85% median reduction in AK lesions in the 0.015% 2- and 3-day treatment groups. Responses for all end points were dose dependent. Treatment was well tolerated, with a favorable safety profile. The most common LSRs were erythema, flaking/scaling, or crusting in the treatment area.

Conclusion: Ingenol mebutate gel appears to be safe and well tolerated when used to treat AK lesions on the face or scalp in all treatment regimens. Statistically significant clearance rates in the 0.01% and 0.015% 2-day treatment groups and in the 0.015% 3-day treatment group were observed. Safety and efficacy parameters seem to be concentration- and treatment regimen-dependent.

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Study to determine the safety and tolerability of PEP005 (ingenol mebutate) gel for actinic keratosis of the dorsum of the hand

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Introduction: PEP005 (ingenol mebutate) Gel is being evaluated as a novel, short-course topical treatment of actinic keratosis (AK). Previous studies suggested that 0.05% may be a suitable concentration for treatment of AK lesions on the dorsum of the hand. We report a study to determine the safety and tolerability of this concentration of ingenol mebutate gel to dorsal hand AKs.

Methods: This open-label study evaluated ingenol mebutate gel, 0.05% administered on 2 consecutive days to male, non-Hispanic whites with Fitzpatrick skin type II or III, with 4 to 8 AK lesions in a contiguous 25-cm² area on the dorsum of the hand. Efficacy was assessed at day 57 by calculating the proportion of patients with no visible AKs (complete clearance rate), > or =75% reduction of baseline AKs (partial clearance rate), and 100% reduction of baseline AKs (baseline clearance rate). Safety was assessed by local skin responses (LSRs) after treatment and by treatment-related adverse events (AEs).

Results: Eleven of 12 patients screened were randomized and treated. By day 57, ingenol mebutate gel, 0.05% produced complete clearance in 27.3% of patients and partial clearance in 45.5% of patients. Mean AK lesion counts were reduced from 5.6 at baseline to 2.3. Treatment was well tolerated, with 100% of patients completing therapy for 2 days. The most common LSRs were erythema, flaking/scaling, and crusting, which peaked by day 8 and resolved by day 57 across all patients. No patients experienced erosion/ulceration, vesiculation/pustulation, or increased scarring through day 57. Three patients reported a total of 7 treatment-related AEs, mainly local skin reactions at the site of drug application. All events resolved by day 57 without sequelae. There were no early withdrawals due to AEs or deaths during the study.

Conclusion: Field treatment with ingenol mebutate gel, 0.05% once daily for 2 days appears to be safe, well tolerated, and potentially effective for treating multiple AK on the dorsum of the hands.

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Safety and efficacy of PEP005 (ingenol mebutate) gel for topical treatment of superficial basal cell carcinoma

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Topical agents are effective for superficial basal cell carcinoma (sBCC) but often fail to achieve the 90% histologic clearance rate and the 5-year cure rate of the acceptable standard, surgical excision. Histologic clearance rates of 79%-100% are reported with imiquimod 5% cream, applied 5 to 7 times weekly for 6 weeks, and 90% with 5-fluorouracil 5% cream, applied twice daily for up to 12 weeks. A topical agent with similar efficacy that requires a much shorter course of treatment would be valuable.

PEP005 (ingenol mebutate) Gel is being developed as a topical therapy for sBCC. It is the first in a new class of compounds purified from the sap of *Euphorbia peplus*, known as petty spurge or radium weed. *E. peplus* sap has a history of traditional use for a variety of conditions, including the topical self-treatment of nonmelanoma skin cancer. Ingenol mebutate gel has a novel, 2-stage mechanism of action involving the rapid induction of necrosis, followed by neutrophil-mediated, antibody-dependent cellular cytotoxicity of residual tumor cells. This mechanism of action distinguishes ingenol mebutate gel from current therapeutic options for sBCC and provides a rationale for its short-term use. A phase 2, double-blind, randomized, vehicle-controlled study of ingenol mebutate gel (PEP005-003) demonstrated that a relatively low concentration (0.05%) applied topically for 2 consecutive days completely cleared 71% of sBCC ($P = 0.02$ vs vehicle). Here we describe the design of a phase 2, open-label, multicenter, dose-escalation study (PEP005-009) of ingenol mebutate gel intended to determine a maximum tolerated dose (MTD) and to evaluate its safety and efficacy profile in the treatment of sBCC on the trunk.

Approximately half of enrolled subjects were randomized to a single application of ingenol mebutate gel on day 1 (arm 1), and the remainder to a single application of ingenol mebutate gel on days 1 and 8 (arm 2). Subjects in either treatment arm received escalating concentrations of ingenol mebutate gel, starting at 0.025% and increasing in increments of 0.025% until dose-limiting toxicity was observed. Safety was assessed at each follow-up visit by adverse events and local skin responses. Efficacy was evaluated by histologic clearance and composite clearance (histologic clearance plus clinical clearance) 3 months after initial treatment, when the sBCC was excised.

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Safety and tolerability of 0.05% PEP005 (ingenol mebutate) gel applied for 2 consecutive days to areas up to 100 cm² for actinic keratosis on the extensor forearm

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Introduction: PEP005 (ingenol mebutate) Gel is being developed for treatment of actinic keratosis (AK). Studies suggest that 0.05% applied for 2 days is the appropriate regimen for areas up to 25 cm² on the trunk and extremities. We conducted a study to evaluate safety and tolerability of 0.05% ingenol mebutate gel applied for 2 days on an area up to 100 cm².

Methods: This was an open-label, dose-area escalation, cohort study to evaluate the safety and tolerability of ingenol mebutate gel. Eligible patients had a minimum of 5 AK lesions within a 100-cm² area on each extensor forearm. All eligible patients were randomly assigned to 1 of 8 treatment cohorts: one 25-cm² area on one forearm (cohort 1); one 50-cm² area on one forearm (cohort 2); one 25-cm² area on each forearm (cohort 3); one 25-cm² area on one forearm and one 50-cm² area on the other forearm (cohort 4); one 75-cm² area on one forearm (cohort 5); one 50-cm² area on each forearm (cohort 6); one 25-cm² area on one forearm and one 75-cm² area on the other forearm (cohort 7); and one 100-cm² area on one forearm (cohort 8). Patients were treated on 2 consecutive days (days 1 and 2), with follow-up visits on days 3, 8, 15, 29, and 57. Safety and tolerability were assessed by the incidence of adverse events (AEs), rate and grade of local skin responses (LSRs), and ability to complete the 2-day treatment course.

Results: Sixty-five patients were randomly assigned to the 8 cohorts; 64 received at least one application of study medication, and 63 (96.9%) completed the study. Five patients (2 in cohort 3 and 1 each in cohorts 4, 5, and 6) were unable to tolerate both days of dosing due to AEs and/or LSRs. Three patients (4.7%) had a total of 3 SAEs during the study. Only one SAE, a squamous cell carcinoma within one of the treatment areas, was considered possibly related to treatment. The most common treatment-related AEs were application site pruritus, irritation, and hyperesthesia. Erythema and flaking/scaling were the most frequently reported LSRs. A dose-area response was observed when the increase in composite LSR score from baseline for a single contiguous area was analyzed. The mean composite LSR score peaked between days 3 and 8.

Conclusions: Ingenol mebutate gel appears safe and well tolerated when applied to areas up to 100 cm². Treatment on one arm does not seem to affect tolerability or safety on the other arm. Increasing the treatment-area size increases the robustness of LSRs.

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Three case reports of metastatic basal cell carcinoma

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We present three cases of metastatic basal cell carcinoma (MBCC), all of which have been confirmed by final pathology reports.

Case No. 1: A 52-year-old female presented with a basal cell carcinoma (BCC) of the right lateral cheek with perineural invasion of the marginal mandibular branch of the facial nerve. The tumor was removed, utilizing Mohs micrographic surgery fresh tissue technique, requiring two stages. During the second stage, tumor invasion of the marginal mandibular nerve was noted. The patient then underwent a deeper resection of the gross disease with facial nerve preservation. She later presented with multiple nodules on the back. PET-CT revealed innumerable foci of skeletal and soft tissue metastases of BCC with no pulmonary or major organ involvement.

Case No. 2: A 72-year-old male presented with a BCC of the left antecubital fossa. The patient had a ten year history of multiple incidences of several BCC's excised from the left chest and a recurrent infiltrative BCC of the right nasal wall. None of his BCC's were over 2 cm wide. During an evaluation of congestive heart failure, a solitary nodule was discovered in the left posterior lung. A new pulmonary nodule in the left upper lobe was discovered the following year. Computed tomography-guided lung biopsy of the tumor showed similar histological features to both the first pulmonary nodule and the infiltrative BCC excised from the right nasal wall ten years prior.

Case No. 3: A 44-year-old male presented with BCC of the forehead. The lesion had partially eroded through the outer table of the frontal bone. During a follow-up evaluation, a CT scan of the neck and parotids revealed three nodules in the right parotid gland and one in the left gland, all of which were confirmed as MBCC by fine needle aspiration cytology. Although, the overall incidence of MBCC is rare, in cases with perineural invasion or involvement of bone, a metastatic work up is warranted.

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