

Poster 2915

Multicenter, Open-label, Dose-Area Escalation, Cohort Study

**to Evaluate the Safety and Tolerability of PEP005
(ingenol mebutate) Gel, 0.05% Applied for 2 Consecutive
Days to Treatment Area(s) of Up to a Total of 100 cm²
in Patients With Actinic Keratoses (AK)
on the Extensor (Dorsal Aspect) Forearm(s)**

George J. Schmieder, DO

*Park Avenue Dermatology, PA
Orange Park, Florida, USA*

Acknowledgments

- Participating investigators included Judy Cole, MD; Frank E. Dunlap, MD; Peter A. Foley, MBBS, BMedSc, MD, FACD; Kenneth G. Gross, MD; Karen S. Harkaway, MD; Terry M. Jones, MD; Mark R. Ling, MD, PhD; Virginia A. Schekorra, DO; George J. Schmieder, DO; Stephen P. Shumack, MD; James A. Solomon, MD, PhD; Lynda Spelman, MBBS, FACD; Ernest Tan, MBBS, FACD
- This study was sponsored by Peplin Inc., a wholly owned subsidiary of LEO Pharma
- Editorial support was provided by ProHealth

Abstract

We conducted a study to determine the safety and tolerability of PEP005 (ingenol mebutate) Gel, 0.05% applied for 2 consecutive days to 25, 50, 75, or 100 cm² AK treatment areas on the extensor forearm(s). Safety was assessed by the rate of adverse events (AEs) and the rate and grade of local skin responses (LSRs), pigmentation, and scarring on days 3, 8, 15, 29, and 57. Tolerability was assessed by the patient's ability to complete the 2-day treatment course. A total of 64 patients were randomly assigned to 1 of 8 treatment cohorts based on treatment area size (Table).

Table. Treatment Cohorts

Cohort (n = 8 in each)							
1	2	3	4	5	6	7	8
One 25-cm ² area on 1 arm	One 50-cm ² area ^a on 1 arm	Two 25-cm ² areas ^a ; 1 on each arm	One 25- and one 50-cm ² area ^a ; 1 on each arm	One 75-cm ² area ^a on 1 arm	Two 50-cm ² areas ^a ; 1 on each arm	One 25- and one 75-cm ² area ^a ; 1 on each arm	One 100-cm ² area ^a on 1 arm

^aContiguous treatment area.

Escalation from a total treatment area of 25 cm² or 50 cm² to 75 cm² and then to 100 cm² required the approval of a review team.

A total of 36 patients (56.3%) reported a total of 74 treatment-emergent AEs, the most common of which was application-site pruritus, followed by application-site irritation, hyperesthesia, or reaction. A higher percentage of patients (68.8%) in the 75-cm² total-body-exposure cohorts experienced treatment-related AEs when compared with patients in the 100-cm² (37.5%), 50-cm² (31.1%), and 25-cm² (12.5%) total-body-exposure cohorts. Other treatment-related AEs at the application site included burning, pain, paresthesia, or warmth. The most frequently reported LSRs were erythema and flaking/scaling. A dose-area response was observed in composite LSR score change from baseline for a single contiguous area. However, the same trend was not observed when the same drug load was applied on separate arms. All patients in cohorts 1, 2, and 8 received both days of dosing, whereas 5 patients (2 in cohort 3 and 1 each in cohorts 4, 5, and 6) were unable to tolerate both days of dosing. One patient in cohort 7 was withdrawn prior to treatment on the second treatment day; the other 7 tolerated both days of dosing.

The results showed that 0.05% ingenol mebutate gel is well tolerated when applied to treatment areas up to 100 cm² for 2 days in the majority of patients. No increases in the composite LSR score change from baseline were noted when additional areas were treated on the opposite arm.

Introduction (1)

- It is common for actinic keratoses (AK) to present as multiple, poorly defined lesions over large areas of skin, with the potential for subclinical lesions that are not discernible on the skin surface^{1,2}
- Accurate and fast diagnosis and treatment of AK are critical because these lesions can progress to squamous cell carcinoma³
- Ingenol mebutate gel, an ingenol derivative extracted from *Euphorbia peplus* (a common annual herb), is being developed for topical treatment of AK and non-melanoma skin cancers

1. Roewert-Huber J et al. *Br J Dermatol*. 2007;157(suppl 2):18-20.

2. Spencer JM et al. *J Drugs Dermatol*. 2005;4:296-301.

3. Criscione VD et al. *Cancer*. 2009;115:2523-2530.

Introduction (2)

- Ingenol mebutate gel, 0.05% has been shown to be well tolerated with a favorable safety profile when used to treat AK lesions on 25-cm² contiguous areas of skin¹
- A pharmacokinetics study demonstrated that ingenol mebutate gel, 0.05% did not cause any systemic exposure when applied to contiguous 100-cm² areas of skin on the dorsal forearm²
- This study was conducted to determine whether ingenol mebutate gel, 0.05% is safe and tolerable when applied to AK lesions on skin areas greater than 25 cm²

1. Anderson L et al. *J Am Acad Dermatol*. 2009;60:934-943.

2. Jarratt M. Poster presented at: 7th Annual Orlando Dermatology Aesthetic & Clinical (ODAC) Meeting; January 15-18, 2010; Orlando, FL.

Objectives

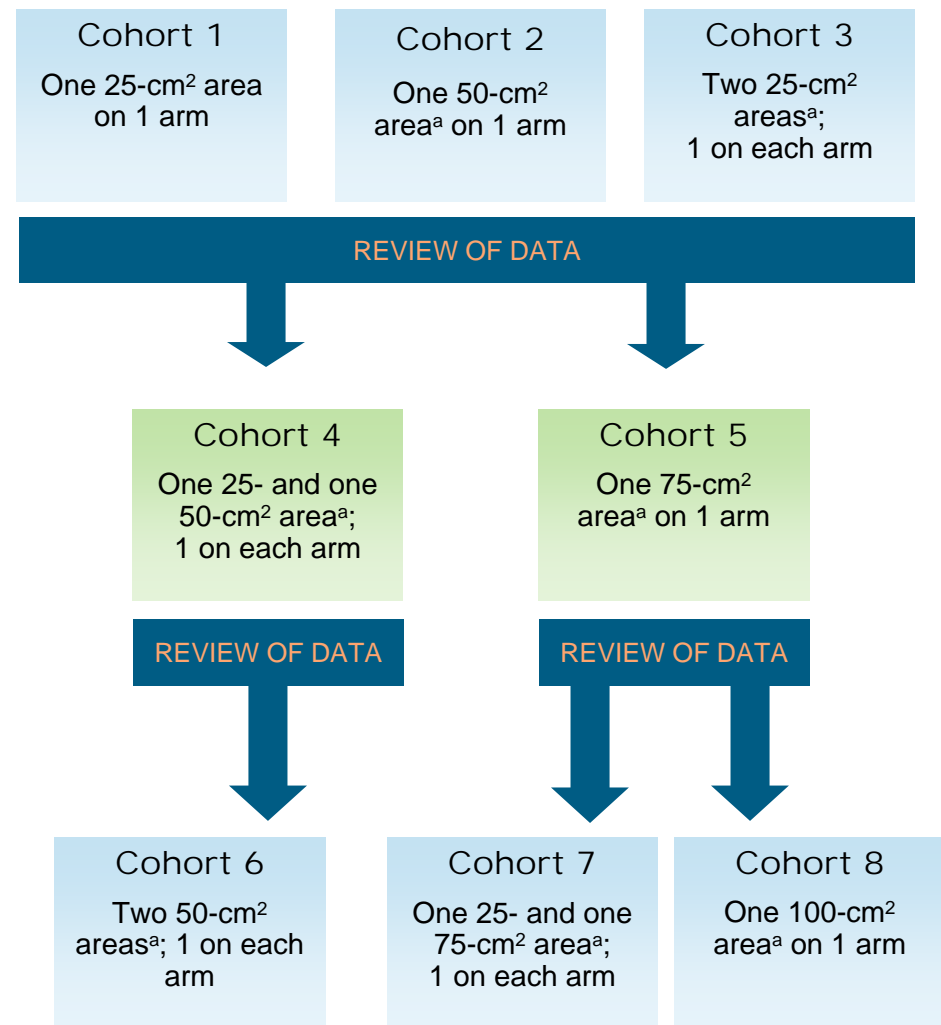
- Assess the safety and tolerability of 2 consecutive days of application of ingenol mebutate gel, 0.05% when applied to 25-, 50-, 75-, or 100-cm² AK body area(s) on the extensor (dorsal aspect) forearm(s)
- The inclusion of either 1 or 2 body areas in each cohort was intended to detect any effect of total-body exposure to ingenol mebutate gel, 0.05% on the intensity of LSRs in a standard treatment area
- No assessment of efficacy was planned or performed for this study

Methods: Study Design (1)

- This was a phase I, multicenter, open-label, dose-area escalation, cohort study
- Patients with at least 5 AK lesions on 100-cm² areas of each dorsal forearm were randomly assigned to 8 dose-escalation cohorts for treatment with ingenol mebutate gel, 0.05% once daily for 2 consecutive days (days 1 and 2)
- Patients were evaluated for safety and tolerability before application of the second dose on day 2 and at follow-up visits on days 3, 8, 15, 29, and 57

Methods: Study Design (2)

- 64 patients, in total, were randomized to 1 of the 8 cohorts based on treatment area size (n = 8 for each cohort)
- Initial allocation was into cohorts 1, 2, or 3
- Assignment of new patients into later cohorts did not begin until 2 dermatologists assessed safety and tolerability through day 15 for at least 80% of patients in the preceding cohorts



^aContiguous treatment area.

Methods: Safety and Tolerability

- Safety was assessed by the following criteria:
 - Incidence rate of AEs, SAEs, and AEs leading to discontinuation of study medication
 - Incidence and rate of LSRs, pigmentation, and scarring
- Tolerability was assessed by patients' ability to complete the 2-day treatment course as required by their assigned cohort
 - Tolerability was also measured in terms of the largest single contiguous treatment area on the forearm that could be administered study medication

Methods: LSRs, Pigmentation, and Scarring

- Patients were assessed for the following LSRs graded on a scale of 0 (not present) to 4 (maximum possible response) at each study visit
 - Erythema
 - Flaking/scaling
 - Crusting
 - Swelling
 - Vesiculation/pustulation
 - Erosion/ulceration
- Patients were assessed for pigmentation and scarring at baseline and on day 57
- All other application-site reactions were considered AEs

Results: AEs

	Surface Area Exposure				Total (N = 64) n (%)
	25 cm ² (Cohort 1) (n = 8) n (%)	50 cm ² (Cohorts 2, 3) (n = 16) n (%)	75 cm ² (Cohorts 4, 5) (n = 16) n (%)	100 cm ² (Cohorts 6, 7, 8) (n = 24) n (%)	
Patients with 1 or more treatment-emergent AEs inside treatment area	1 (12.5)	5 (31.3)	11 (68.8)	9 (37.5)	26 (40.6)
Patients with 1 or more treatment-related AEs ^a	1 (12.5)	6 (37.5)	10 (62.5)	10 (41.7)	27 (42.2)
Treatment-related administration-site conditions	1 (12.5)	5 (31.3)	9 (56.3)	9 (37.5)	24 (37.5)
Pruritus	0	5 (31.3)	5 (31.3)	7 (29.2)	17 (26.6)
Irritation	0	0	4 (25.0)	5 (20.8)	9 (14.1)
Hyperesthesia	0	1 (6.3)	2 (12.5)	0	3 (4.7)
Reaction	1 (12.5)	0	2 (12.5)	0	3 (4.7)

A total of 36 patients (56.3%) reported a total of 74 treatment-emergent AEs, the most common being application-site reactions

The incidence of treatment-related AEs was highest in patients with a surface area exposure of 75 cm² (cohorts 4 and 5)

^aTreatment-related AEs included any event assessed as either possibly, probably, or definitely related to study medication.

Results: Treatment-Related AEs

- Other treatment-related AEs included application-site
 - Burning (3.1%)
 - Pain (3.1%)
 - Paresthesia (3.1%)
 - Warmth (1.6%)
- Other AEs that occurred inside the treatment area and were considered possibly treatment related were folliculitis and hyperkeratosis/SCC in 1 patient each
- Systemic AEs that were considered possibly treatment related included 2 cases of dysgeusia and 1 case each of dry mouth, frequent bowel movements, and rales

Results: Serious AEs

- 3 patients (4.7%) had a total of 3 SAEs during the study
 - Hypertension
 - Pancreatitis
 - Squamous cell carcinoma
- Only 1 SAE — squamous cell carcinoma within 1 of the treatment areas — was considered possibly related to treatment
- All 3 SAEs resolved by day 57 and none of the 3 patients withdrew from the study

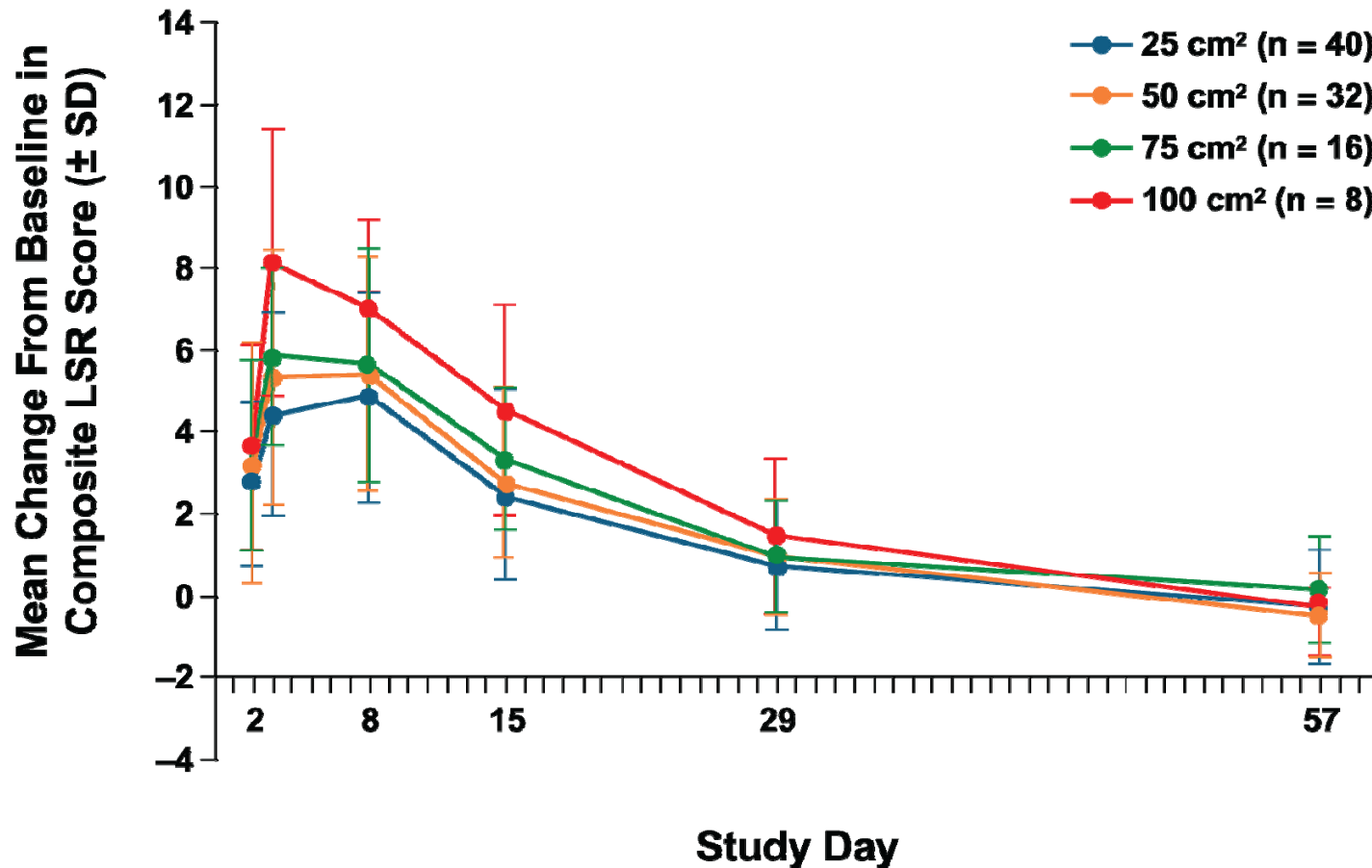
Results: LSRs, Pigmentation, and Scarring

- The most frequent LSRs were erythema and flaking/scaling, both of which were prevalent at baseline
- The majority of LSRs were rated grade 1 or 2, although grade 3 LSRs were relatively common on days 3 and 8
- In most patients, pigmentation and scarring either remained unchanged or improved during the study
- A minority of patients (17.2%) experienced new or worsened pigmentation^a changes or scarring
- All cases of new or worsened pigmentation or scarring were evaluated as clinically insignificant or mild, except 1 episode of hypopigmentation, which was evaluated as moderate

^aSome patients experienced both hyperpigmentation and hypopigmentation.

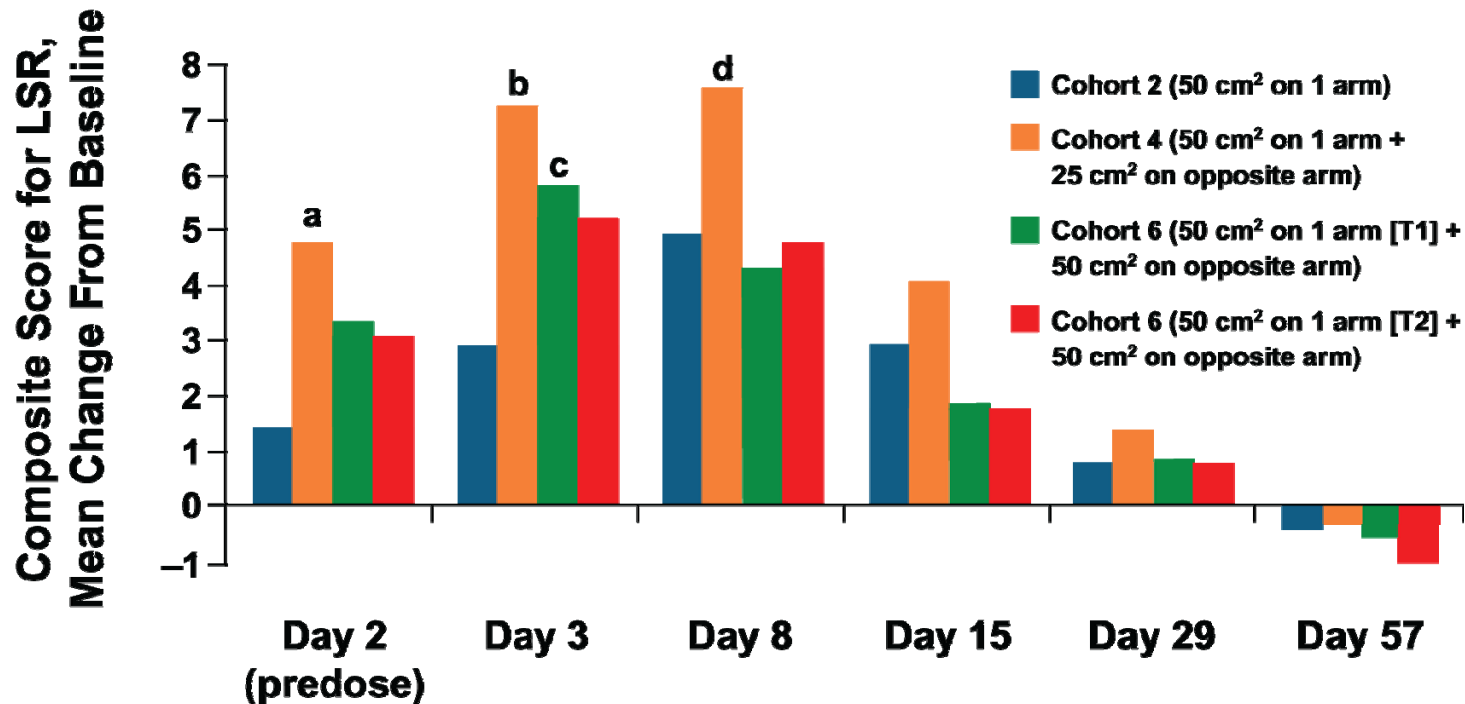
Results: Mean Change From Baseline in Composite LSR (Pooled Treatment Area)

Mean composite LSR scores for pooled treatment areas of the same size peaked between days 3 and 8, returning to near pretreatment levels or better by day 57



Results: Effect of Drug Load on Composite LSR Scores

Overall, an additional 25-cm² or 50-cm² drug load in patients treated with a base area of 50 cm² had no significant effect on mean change from baseline in composite LSR score. Also, increases in composite LSR score were consistently smaller with an additional drug load of 50 cm² compared with one of 25 cm²

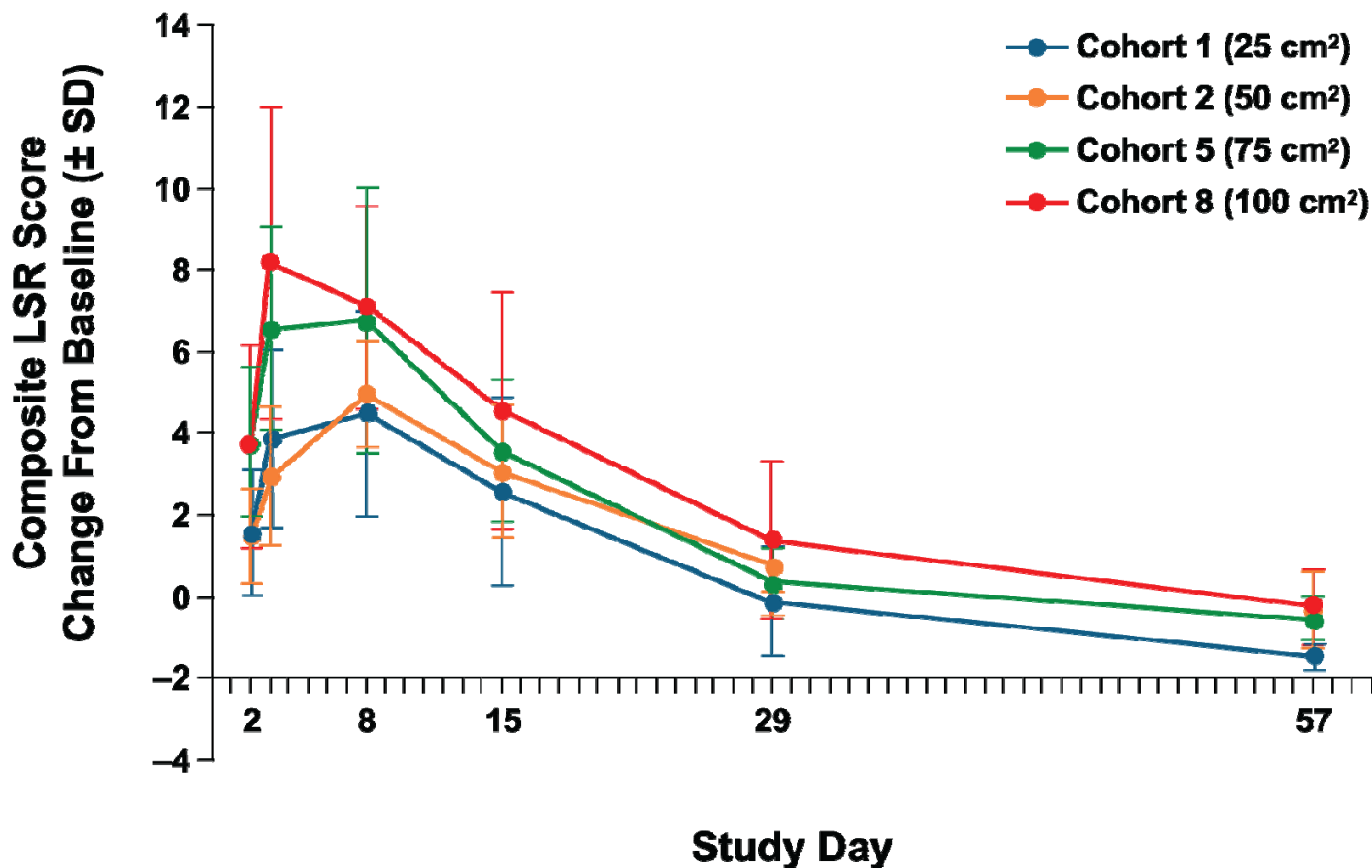


T1, treatment area 1; T2, treatment area 2.

^a $P = 0.0229$, ^b $P = 0.0041$, ^c $P = 0.0494$, ^d $P = 0.0468$; all pairwise comparisons vs cohort 2 for mean change from baseline.

Results: LSR Time Course for Single Contiguous Area

A dose-area response was observed for composite LSR score change from baseline for a single contiguous area, but this was not the case when the same drug load was applied on separate arms



Results: Tolerability

- All patients in cohorts 1, 2, and 8 received both days of dosing
- Five patients (2 in cohort 3 and 1 each in cohorts 4, 5, and 6) were not able to tolerate both days of dosing
 - Due to brisk reactions, LSRs, blisters, and other AEs such as itching and burning
- In addition, 1 patient in cohort 7 was withdrawn from the study prior to treatment on day 2 due to a protocol violation (use of prohibited medication) and therefore did not receive 2 days of dosing
 - The other 7 patients in the cohort tolerated both days of dosing

Discussion

- The forearm is a very common area for sun damage and AK, which can appear as multiple lesions over a large area
- A contiguous treatment area of 100 cm² is clinically relevant, as it represents a standard anatomical unit for application of topical therapy covering the entire dorsal forearm
- Being able to apply a field-directed therapy that can be tolerated over a large area would present an attractive treatment option for physicians and patients

Conclusions

- Ingenol mebutate gel, 0.05%, applied as topical field-directed therapy once daily for 2 consecutive days to the dorsal forearm(s), was safe and well tolerated on areas of up to 100 cm²
- Treatment with ingenol mebutate gel, 0.05% on 1 arm does not seem to affect tolerability or safety on the other arm
- No systemic absorption of ingenol mebutate gel, 0.05% was detected in a maximal-use pharmacokinetic study¹ with a treatment area of up to 100 cm²

1. Jarratt M. Poster presented at: 7th Annual Orlando Dermatology Aesthetic & Clinical (ODAC) Meeting; January 15-18, 2010; Orlando, FL.

References

- Anderson L, Schmieder GJ, Werschler WP, et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. *J Am Acad Dermatol*. 2009;60:934-943.
- Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF; Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial Group. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer*. 2009;115:2523-2530.
- Jarratt M. A randomized, double-blind, vehicle-controlled study to evaluate the pharmacokinetics of PEP005 (ingenol mebutate) gel, 0.05%, when applied to dorsal forearms with multiple actinic keratoses (AK) in a maximal-use setting, defined as a contiguous 100-cm² area of skin. Poster presented at: 7th Annual Orlando Dermatology Aesthetic & Clinical (ODAC) Meeting; January 15-18, 2010; Orlando, FL.
- Roewert-Huber J, Stockfleth E, Kerl H. Pathology and pathobiology of actinic (solar) keratosis – an update. *Br J Dermatol*. 2007;157(suppl 2):18-20.
- Spencer JM, Hazan C, Hsiung SH, Robins P. Therapeutic decision making in the therapy of actinic keratoses. *J Drugs Dermatol*. 2005;4:296-301.