A New Ecamsule-Containing SPF 40 Sunscreen Cream for the Prevention of Polymorphous Light Eruption: A Double-blind, Randomized, Controlled Study in Maximized Outdoor Conditions

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Polymorphous light eruption (PMLE) is an idiopathic photodermatosis elicited by UV radiation (UVR). The objective of this double-blind, randomized, controlled, intraindividual, bilateral comparison was to determine the efficacy of the UVA filters (ecamsule, avobenzone) present in the new sun protection factor (SPF) 40 sunscreen cream in preventing PMLE in maximized outdoor conditions (ie, exaggerated sun exposure). Safety also was assessed. Each participant was treated with SPF 40 sunscreen cream containing ecamsule 3%, octocrylene 10%, avobenzone 2%, and titanium dioxide 5% (tetrad) on one side of the body and either an ecamsule-deprived (triad-E) or avobenzone-deprived (triad-A) cream on the other side. Participants were subsequently exposed to incremental doses of sunlight for up to 6 days. The primary efficacy assessment was a composite relative success rate with 3 components. Success was defined as either a delayed time to onset of PMLE or a lower global severity of PMLE comparing one side of the body to the other side in the same participant. Safety evaluations included systemic adverse events (AEs). Of the 144 participants enrolled and randomized, 22 did not experience PMLE during the study duration under these maximized sun exposure conditions. A significantly greater number of successes were detected on the tetrad-treated side compared with either triad: 41 of 73 participants (56%) versus 8 of 73 participants (11%; P<.001*) in the triad-E treatment group and 26 of 71 participants (36%) versus 11 of 71 participants (16%;* P=.02*) in the triad-A treatment group. Polymorphous light eruption appeared later with the tetrad than with either triad. The global severity of the PMLE flares was significantly lower with the tetrad than with both triads at end point (*P<.001 *and* P=.02 *for tetrad vs triad-E and tetrad vs triad-A, respectively). In this study, the SPF 40 sunscreen cream containing ecamsule 3%, octocrylene 10%, avobenzone 2%, and titanium dioxide 5% prevented PMLE flares significantly better than similar formulations with only one of the UVA filters (triad-E treatment group,* P<.001*; triad-A treatment group,* P=.02*). The inclusion of both ecamsule and avobenzone provides clinical benefit to patients with PMLE compared with formulations containing only one UVA filter.*

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Polymorphous light eruption (PMLE) is a recurring idiopathic photodermatosis elicited by UV radiation (UVR).[1-4] As the name suggests, PMLE manifests as varied morphology of recurrent erythema, papules, vesicles, or plaques appearing on sunlight-exposed areas of the skin and often is accompanied by pruritus. These nonscarring cutaneous lesions emerge principally on the chest, arms, abdomen, and legs; in the most severe cases, lesions can extend further, affecting the face.[3,5] Lesions may subside after a few days in the absence of additional sun exposure.

Polymorphous light eruption is considered to be an immunologic response elicited primarily by UVR exposure; however, its pathophysiology remains unknown.[6-10] More recent literature suggests the pathogenesis includes the existence of a cutaneous antigen generated in the skin by the action of UVR, leading to a delayed cellular hypersensitivity reaction.[11-13] The therapeutic regimen for severe cases of PMLE can include the use of immunosuppressive agents that have serious side effects. Generally, prevention of PMLE is the primary therapeutic goal rather than treatment.[1]

No products currently are approved in the United States for the prevention, attenuation, or treatment of PMLE. UV radiation protection with sunscreens is one of the more effective means to reduce sun exposure and thus PMLE flares.[14-16] Sun avoidance and use of protective clothing as preventative measures are effective but are not always practical or feasible. The specific wavelengths triggering a PMLE flare vary among patients and have been reported to occur within the range of 290 to 400 nm (UVB, UVA). Sunscreens are widely used and recommended by physicians for the prevention and attenuation of PMLE flares; however, there is little clinical evidence that they reduce PMLE flares. It has been reported that topical sunscreens with only UVB filters or with only modest UVA protection usually are ineffective in preventing PMLE.[17-20]

A new ecamsule-containing sun protection factor (SPF) 40 sunscreen cream (tetrad) has been formulated with 4 sunscreen ingredients. Three of these sunscreen agents are widely recognized in North America: octocrylene, which provides UVB protection with peak absorbance between 300 and 310 nm; avobenzone, a long-wavelength UVA filter that exhibits peak absorbance at 360 nm; and titanium dioxide, a physical filter that further augments UVR protection across the UV spectrum. In addition, ecamsule, which was approved by the US Food and Drug Administration in 2006, was added as the fourth filter, specifically to enhance protection in the short-wavelength UVA range (optimal absorbency, 345 nm). This new short-wavelength UVA organic sunscreen agent fills the gap in absorbance between avobenzone and most UVB filters (Figure 1).[21] Adding ecamsule as a fourth filter should deliver continuous balanced photoprotection across the entire UVR spectrum, with more extensive UVA radiation protection than could be obtained with a single UVA filter.

The objective of this study was to determine the efficacy of the UVA filters (ecamsule, avobenzone) present in the new SPF 40 sunscreen cream and

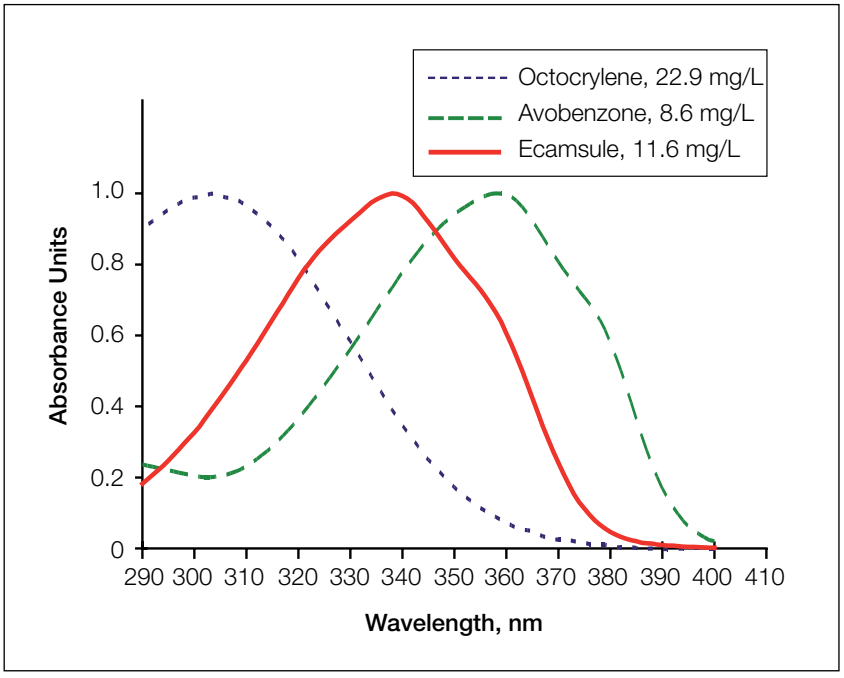

Figure 1. Spectrophotometric protection curves for octocrylene, avobenzone, and ecamsule in methanol solutions based on in vitro methodology.[21]

their contribution in preventing PMLE in maximized outdoor conditions. This study represents one of the largest controlled trials in outdoor conditions in the PMLE population.

Methods

Study Design—This study was a double-blind, randomized, controlled, intraindividual, bilateral comparison in maximized outdoor conditions (ie, exaggerated sun exposure) in participants with PMLE. The study was conducted at one site (Puerto Rico), but participants were recruited from across the United States. Men and women 18 years and older who were previously diagnosed with PMLE, had negative serum antinuclear and serum anti-Ro antibodies test results, and had no concomitant photosensitive-causing medications were included. Exclusion criteria included participants with a history of skin cancer and/or uncontrolled systemic disease; known sensitivity to any ingredients of the study preparations; exposure to significant UVR within 3 months before the start of the study sun exposure; history of photodermatoses or other photosensitive diseases/conditions, other than PMLE; and use of study medications that would interfere with interpretation of study results.

At least 15 minutes prior to sun exposure, each participant was treated on all exposed body areas other than the face and hands by a specifically trained study nurse who applied an SPF 40 sunscreen cream containing ecamsule 3%, octocrylene 10%, avobenzone 2%, and titanium dioxide 5% (tetrad) to one side of the body; the other side received either an ecamsule-deprived (triad-E) or avobenzone-deprived (triad-A) cream.

At baseline, participants were randomized to either treatment group, and treatment was randomized to either side of the body. To elicit PMLE flares (in spite of the already high protection expected with the triads), participants were exposed to incremental doses of sunlight for up to 6 days (once on the first day and twice daily thereafter)(Table 1); assessments were done twice on the first day and 3 times daily thereafter: before the morning exposure, and before and after the afternoon exposure at approximately 1 to 3 hours after the end of the previous sun exposure. UV radiation doses were measured and participants were exposed to the sunlight to receive an equal amount of sunlight on both sides. Participants were withdrawn from the study when a clear-cut diagnosis of PMLE flare on both sides of the body was made. If only one side reacted, irradiation continued on the other side and the involved side was covered with protective towels.

Outcome Assessments—Polymorphous light eruption was declared when a score of 2 or more was reached on the global severity scale (Table 2). The primary efficacy assessment was a composite success rate with 3 components. Success of the tetrad relative to either of the triads was defined as follows for each participant:

- PMLE flare occurred on the triad-treated side at any time and not on the tetrad-treated side.
- PMLE flare occurred later on the tetrad-treated side than on the triad-treated side.
- PMLE flare occurred on both sides at the same time with a global severity score on the triad-treated side that was at least 2 grades higher than the tetrad-treated side.

The success of the triad relative to the tetrad was defined in a similar way. Secondary criteria included the time and cumulative UVA doses to the onset of PMLE flares; global severity of the PMLE flare; as well as symptoms of erythema, pruritus, and burning/stinging, and lesion counts (papules, vesicles, plaques, total lesions) at the visit when PMLE flare was first observed (end point). Global severity was assessed as outlined in Table 2. Efficacy end point assessments, including primary and secondary assessments, were performed at the time of a PMLE flare. The last evaluation visit was used for end point if PMLE flares did not develop on either side of the body.

Safety was assessed through reporting of adverse events (AEs). Safety measurements were conducted once daily in the evening (at the same time as the secondary criteria evaluation), approximately 1 to 3 hours after the end of the afternoon exposure.

Statistical Analyses—Using a 2-sided sign test, a sample size of 66 evaluable participants per group

Table 1.

UVA Dosing[a]

Day	UVA Dose, J/cm²
1	20
2	40
3	45
4	50
5	55
6	60

[a]Participants were exposed to incremental doses of UVA (sunlight). The duration of exposure was determined according to the daily sunlight energy level of UVA.

Table 2.

Global Severity Scale[a]

Severity	Grade	Description
None	0	No detectable signs of PMLE.
Mild Slight itching sensation with minimal to few clinical signs (≈10 papules or plaques); not really bothersome. Grade 1 does not constitute a clear-cut diagnosis of PMLE.	1	Only traces or scarce lesions and no relevant symptoms. The clinical signs and symptoms are not significant enough for the diagnosis of PMLE. At least 1 PMLE-prone area is involved.
	2	Slight itching sensation with minimal clinical signs (≈10 papules or plaques, which are confluent papules, and slight erythema) that are not really bothersome; clear-cut diagnosis of PMLE is possible. At least 1 PMLE-prone area is involved.
	3	Mild itching sensation, erythema, and some lesions (10–20, mostly papules and plaques). At least 1 PMLE-prone area is involved.
Moderate Moderate itching sensation or other clinical symptoms that are somewhat bothersome; associated with erythema and several (20–50) papules, plaques, or vesicles that are still countable.	4	Mainly papules or plaques (≈20–30 lesions) that are bothersome and accompanied with other symptoms, like but not limited to mainly moderate itching. At least 1 PMLE-prone area is involved.
	5	Itching sensation or other clinical symptoms that are more bothersome, associated with erythema and ≈30–40 papules, plaques, or vesicles. At least 1 PMLE-prone area is involved.
	6	Itching sensation and erythema that are more bothersome; some excoriations are seen; lesions are still countable (≈40–50 lesions, mainly papules and coalescent papules). At least 1 PMLE-prone area is involved.
Severe Itching and possibly a burning sensation with uncountable papules and/or vesicles that cause definite discomfort.	7	>50 papules and vesicles with excoriations. Symptoms, especially itching, interact with everyday activities. Several PMLE-prone areas are involved.
	8	Uncountable lesions (papules and/or vesicles and plaques). Definite discomfort with severe itching and/or even burning sensation or other symptoms such as heavy dizziness. Several PMLE-prone areas are involved.
	9	Very severe form of PMLE. Uncountable lesions with papules, vesicles, and plaque formation. Very severe itching and erythema. Disturbances of every day activities during the day and night. Definite excoriations. Several PMLE-prone areas are involved.

Abbreviation: PMLE, polymorphous light eruption.

[a]Definitions of each point on the global severity scale as defined for a half-body assessment.

was deemed appropriate to detect, with 90% power, a significant difference in success rates between the tetrad and each triad at $\alpha=.05$, assuming the relative success rates were 40% for the tetrad relative to the triad and 10% for the triad relative to the tetrad (and 50% no-difference). To account for unevaluable participants, 75 participants per group were planned to be randomized (total of 150 participants). Statistical hypotheses were to test if there were differences in relative success rates between the tetrad and each triad within each parallel group using the sign (binomial) test in the intention-to-treat (ITT) population. Global severity of PMLE; lesion counts; and PMLE symptoms of erythema, pruritus, and burning/stinging at end point were compared using the Wilcoxon signed rank test. All tests were 2-sided, performed at the .05 nominal probability level (α level). Adverse events were summarized in frequency tables by body system, coded term, relationship to study drug, severity, and treatment group/treatment.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and its amendments, the International Conference on Harmonisation's Good Clinical Practice guidelines, and in compliance with local regulatory requirements. The study was reviewed and approved by institutional review boards. All participants provided their written informed consent prior to entering the study.

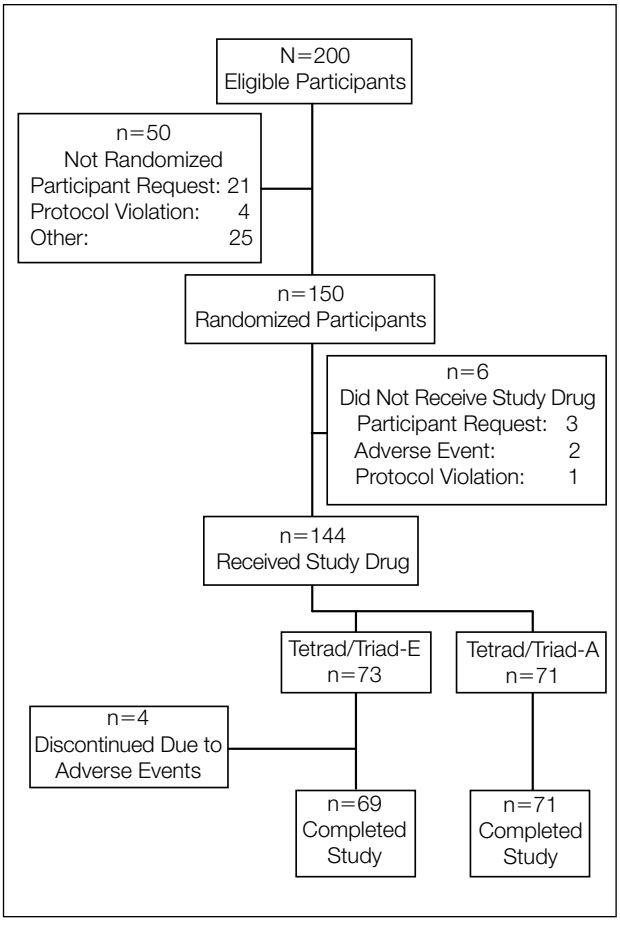

Figure 2. Summary of participant disposition.

Results

Participant Disposition and Baseline Characteristics—A total of 150 participants were randomized, of which 144 received study drug (tetrad/triad-E treatment group, 73; tetrad/triad-A treatment group, 71) (Figure 2). Participant disposition was similar between the treatment groups. Among the 144 participants who received the study drug, 140 completed the study (tetrad/triad-E treatment group, 69; tetrad/triad-A treatment group, 71). Four participants discontinued due to AEs, of which none were considered to be related to study drugs.

The baseline characteristics of the ITT population are summarized in Table 3. The treatment groups were comparable regarding the demographic characteristics. Most participants were female (81.9%) and white (97.9%). Mean age was 40.3 years. Baseline characteristics of sex, race, and age were similar in both treatment groups and reflect the typical PMLE population. Fitzpatrick skin types I to III were predominant, with approximately half of the participant population with Fitzpatrick skin type II.

Efficacy Evaluation—Results of the primary efficacy assessment are shown in Figure 3. For success rates, the tetrad was superior in the triad-E treatment group (56% vs 11%; $P<.001$) and in the triad-A treatment group (36% vs 16%; $P=.02$) at end point (ITT population). A summary of success rates by response category (individual components) for the tetrad versus each triad is presented in Table 4. Similar results by components confirmed the tetrad was superior to both triads; overall results were consistent across the 3 success-rate components.

Secondary efficacy parameters confirmed these results. Most participants (tetrad/triad-E treatment group, 75.4%; tetrad/triad-A treatment group, 83.1%) developed PMLE on both treated sides of the body. Twelve participants (16.4%) in the tetrad/triad-E treatment group and 10 participants (14.1%) in the tetrad/triad-A treatment group did not develop PMLE on either side during the study. Polymorphous light eruption generally appeared later and with a higher cumulative UVA dose with the tetrad than with either triad. The global severity results of the PMLE flares are shown in Figure 4. The differences between the tetrad and both triads at end point were statistically significant (tetrad vs triad-E, $P<.001$; tetrad vs triad-A, $P=.02$).

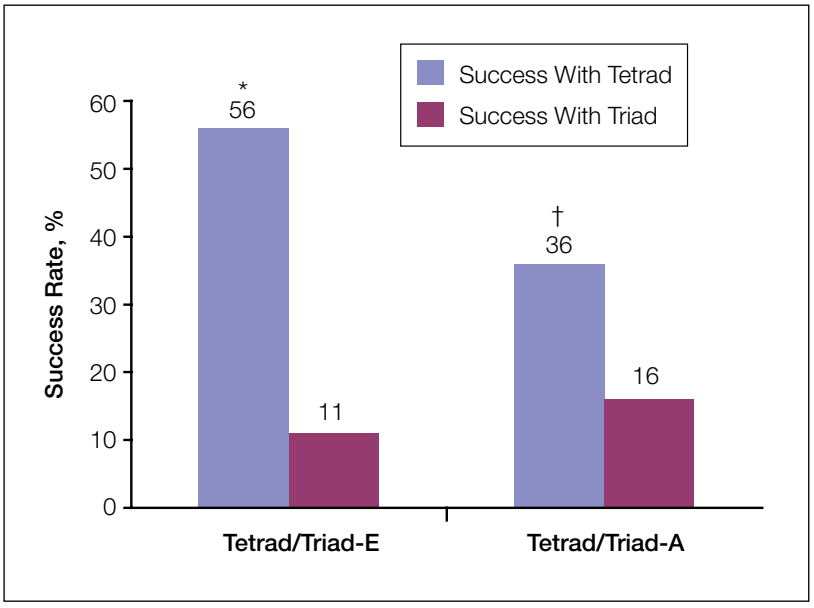

Figure 3. Results of the primary efficacy assessment (success rate). Asterisk indicates $P<.001$; dagger, $P=.02$.

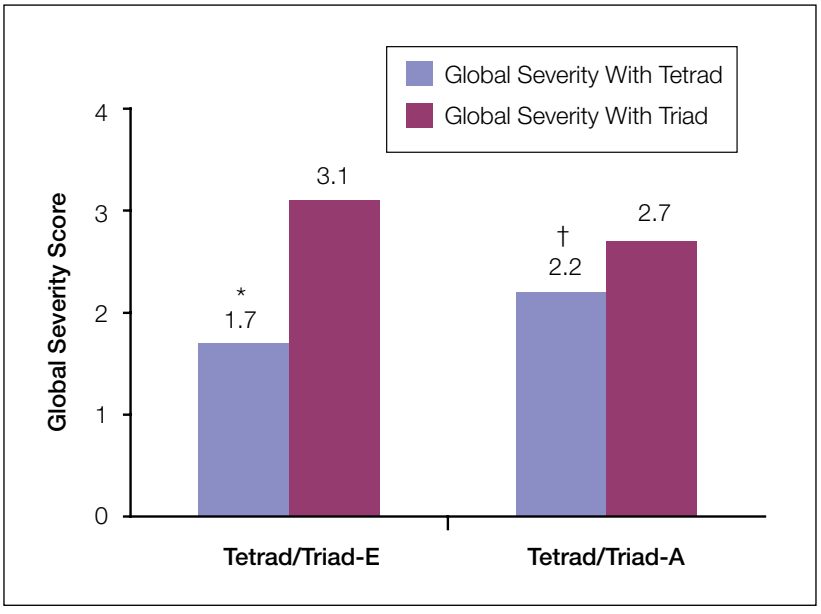

Figure 4. Global severity (see Table 2 for a detailed description of the global severity scale) results of polymorphous light eruption flares. Asterisk indicates $P<.001$; dagger, $P=.02$.

For lesion counts, differences at end point were significant for both treatment groups, favoring the tetrad (triad-E treatment group, $P<.001$; triad-A treatment group, $P=.018$). The global severity scores for each PMLE symptom (erythema, pruritus, burning/stinging) at end point were lower with the tetrad in both parallel treatment groups. The differences in PMLE symptom severity between treatments were significant in the tetrad/triad-E treatment group ($P<.001$), favoring the tetrad.

Safety Evaluation—Adverse events were experienced by 96 of 144 (66.7%) total treated participants (54 of 73 participants [74.0%] in the tetrad/triad-E treatment group; 42 of 71 participants [59.2%] in the tetrad/triad-A treatment group). The most frequently occurring AEs were dermatologic and were reported by 50 participants (68.5%) in the tetrad/triad-E treatment group and 40 participants (56.3%) in the tetrad/triad-A treatment group. Four (1.9%) of the 210 total AEs were considered possibly related to study drug; no AEs were considered probably or definitely related. All related AEs were disorders of the skin, occurred on both body sides treated, were considered nonserious, were moderate in severity, and had possible relationship to study drug. Three of the 4 possibly related AEs were sunburn and the other was contact dermatitis. There were no serious AEs. Four participants (5.5%), all in the tetrad/triad-E treatment group, were discontinued

Table 3.

Participant Demographics and Baseline Characteristics (Intention-to-Treat Population)

	Tetrad/Triad-E (n=73)	Tetrad/Triad-A (n=71)	Total (N=144)
Sex, n (%)			
Male	12 (16.4)	14 (19.7)	26 (18.1)
Female	61 (83.6)	57 (80.3)	118 (81.9)
Race, n (%)			
White	73 (100.0)	68 (95.8)	141 (97.9)
Black	—	1 (1.4)	1 (0.7)
Hispanic	—	2 (2.8)	2 (1.4)
Age, y			
Mean (SD)	38.8 (13.18)	41.8 (11.48)	40.3 (12.42)
Minimum	18	19	18
Median	39.0	42.0	40.0
Maximum	72	73	73
Fitzpatrick skin type, n (%)			
I	21 (28.8)	11 (15.5)	32 (22.2)
II	37 (50.7)	35 (49.3)	72 (50.0)
III	12 (16.4)	23 (32.4)	35 (24.3)
IV	3 (4.1)	2 (2.8)	5 (3.5)

due to AEs. No participants were discontinued due to AEs that were related to study drugs.

Comment

Overall, this study showed the efficacy of a new ecamsule-containing SPF 40 sunscreen cream (tetrad) in preventing flares in participants with a PMLE history under maximized outdoor conditions (ie, exaggerated sun exposure) compared with similar sunscreen formulations devoid of 1 UVA filter (the triads). The tetrad containing 1 UVB, 1 physical UVR, and 2 UVA filters does prevent PMLE flares significantly better than similar formulations with only one of the UVA filters (triad-E treatment group, $P<.001$; triad-A treatment group, $P=.02$). Therefore, under the conditions of the study, the contribution of each UVA filter—the recently US Food and Drug Administration–approved ecamsule and avobenzone—to an already high protection containing 3 UVR filters was justified in the outcome of the study: prevention of PMLE flares. The protection factors (PFs) for the test sunscreens varied among the tetrad (SPF 42.5; UVA-PF, 23.2), triad-E (SPF 28.5; UVA-PF, 15.3), and triad-A (SPF 38.7; UVA-PF, 13.2). Persistent pigment darkening was the method of assessment.

The design of the study is unique, as it used maximized outdoor natural sun conditions to elicit PMLE flares. Incremental doses previously have been shown to elicit PMLE flares in indoor conditions.[15,20] A single site was chosen to minimize the heterogeneity in participant behavior, to control the sun's UVR, and to mimic a scenario of sudden and high sun exposure, which typically may elicit PMLE flares. However, the patients were recruited from various locations across the United States. The products were applied by a nurse in a controlled manner with the median line left out of the

Table 4.

Success Rates by Response Category (Intention-to-Treat Population)

	Tetrad/Triad-E, n (%) (n=73)	Tetrad/Triad-A, n (%) (n=71)
Success of Tetrad Relative to Triad	41 (56.2)	26 (36.6)
PMLE not on tetrad-treated side (only on triad-treated side)	5 (6.8)	2 (2.8)
PMLE occurred later on tetrad-treated side	26 (35.6)	13 (18.3)
PMLE occurred on both sides at the same time and global severity score was lower on tetrad-treated side (by ≥2 grades)	10 (13.7)	11 (15.5)
Success of Triad Relative to Tetrad	8 (11.0)	11 (15.5)
PMLE not on triad-treated side (only on tetrad-treated side)	1 (1.4)	0 (0)
PMLE occurred later on triad-treated side	4 (5.5)	7 (9.9)
PMLE occurred on both sides at the same time and global severity score was lower on triad-treated side (by ≥2 grades)	3 (4.1)	4 (5.6)
Other	24 (32.9)	34 (47.9)
No PMLE on either side	12 (16.4)	10 (14.1)
PMLE occurred on both sides at the same time with similar severity	12 (16.4)	24 (33.8)

Abbreviation: PMLE, polymorphous light eruption.

evaluation; additionally, participants were exposed to the sun for up to twice daily until a PMLE flare was observed. Right-left bias was avoided and sun exposure was equal on both sides of the body. No sun exposure was allowed during the rest of the study period once PMLE flare occurred.

The primary end point of the study was designed to account for the 2 essential components of PMLE prevention. The efficacy of potential products in the treatment of PMLE should be assessed regarding the prevention of PMLE flares or delay in their onset as well as the reduction in the severity of PMLE flares (attenuation). The integration of both prevention and attenuation into a single success rate variable allows the efficacy of the product to be more accurately assessed regarding actual clinical benefit to the patient.

Ecamsule fills the gap in absorbance between avobenzone and most UVB filters, delivering continuous balanced photoprotection across the entire UVR spectrum. The ecamsule-containing SPF 40 sunscreen cream evaluated in this study may help to fill a need for new therapies to prevent PMLE. The results of this study demonstrate a substantial contribution of ecamsule and avobenzone in the prevention or attenuation of PMLE flares. The global severity of the PMLE flares at end point also was significantly and clinically reduced when using tetrad in comparison with the same formulations without either ecamsule or avobenzone (tetrad vs triad-E, $P<.001$; tetrad vs triad-A, $P=.02$), which supports the contribution of each of these UVA filters to reduce the severity of PMLE flares. These results are consistent with data from in vitro and pharmacologic studies that consistently show an incremental contribution of ecamsule and avobenzone to the entire UVR protective effects of tetrad.[21]

Currently, there are no products in the United States approved for the prevention or attenuation of PMLE. Nontherapeutic measures such as sun avoidance and use of protective clothing as preventative measures are only partially successful because they are not always practical or feasible. UV radiation

protection with sunscreens is one of the more effective means to reduce sun exposure. However, the specific wavelengths that trigger a PMLE flare vary among patients and have been reported to occur within the range of UVB and UVA. Regular application of a sunscreen with a high-factor broadband cover, such as a combination of UVB and UVA filters, is needed for the prevention of PMLE.[18,20,22-24] The results of this large outdoor study give further evidence that both UVA filters enhance the protection against PMLE flares. The availability of a new therapy with broad UVR protection (UVB, UVA) will provide patients and physicians more options for preventing PMLE flares.

Conclusion

The tetrad containing 1 UVB, 1 physical UVR, and 2 UVA filters prevents PMLE flares significantly better than similar formulations with only one of the UVA filters. Therefore, the inclusion of both UVA filters safely provides additional protection and clinical benefit to patients with PMLE compared with formulations containing only one UVA filter.

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