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PHASE 4 TRIAL FINDINGS ON THE SAFETY AND TOLERABILITY OF COMBINATION SOLUTION OF MEQUINOL 2%/TRETINOIN 0.01% IN DARK SKIN TYPES

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Introduction

- Solar lentigines are a common dermatologic condition characterized by localized, hyperpigmented, macular lesions usually found on sun-exposed areas of the skin. This benign condition is caused by an increased number of active melanocytes and increased melanin production in response to chronic, accumulated ultraviolet radiation exposure.[1-2]
- This condition currently causes significant cosmetic concerns for more than 20 million Americans and is becoming increasingly prevalent due to the aging US population.[1,4]
- The majority of therapeutic research has focused on Caucasian populations or those with skin types I or II (Table 1), given the epidemiological data on the disease.
- Solar lentigines affect all skin types, and research is required supporting its treatment in ethnic groups and those with darker skin.[3,7] Although multiple recent studies have shown mequinol 2%/tretinoin 0.01% combination therapy provides clinically significant improvement in up to 80% of patients, little work has been done to evaluate its efficacy in ethnic populations or in those with darker skin tones.[2,3]
- Ethnic populations are often underrepresented in dermatology study groups, although they account for nearly 80% of the world's population. This population is often at increased risk for adverse events (AEs), such as postinflammatory hyperpigmentation, following many dermatological treatments.
- Given the limited exploration in these patient populations, the present study was designed to assess the efficacy and safety of mequinol 2%/tretinoin 0.01% therapy in ethnic groups.

Table 1: Demographics Information

Subjects	N = 259
Mean age, y (SD)	55.8 (10.93)
Sex, n (%)	
Male	45 (17.4)
Female	214 (82.6)
Skin type, n (%)	
I – Always burns, never tans	0 (0.0)
II – Usually burns, tans less than average	17 (6.6)
III – Sometimes burns (mildly), tans about average	81 (31.3)
IV – Rarely burns, tans more than average	127 (49)
V – Rarely burns, tans profusely	34 (13.1)
VI – Never burns, deeply pigmented	0 (0.0)

Objective

- To evaluate the efficacy and safety of mequinol 2%/tretinoin 0.01% topical solution in the depigmentation of solar lentigines in an ethnic study population (skin types II to V).

Methods

- This multicenter, single-arm, uncontrolled, open-label study evaluated the efficacy of mequinol 2%/tretinoin 0.01% topical solution in the depigmentation of circumscribed macular solar lentigines for up to 24 weeks. Efficacy was assessed by clinical evaluations of the treatment areas.
- Safety was assessed via reported AEs, and laboratory tests for safety monitoring were performed at baseline and after 12 and 24 weeks of treatment.
- Inclusion criteria included men or women of Asian, Latin/Hispanic, and African American descent, age 30 and older, with skin types II to V. The subjects were diagnosed with solar lentigines on the dorsal forearms/hands (arm area) (≥10) and the face (≥3). Female subjects were demonstrably nongravid, postmenopausal, and/or using an approved method of birth control.
- Exclusion criteria included sensitivity to any of the ingredients in the test medication; pregnant or nursing mothers; recent use of topical or systemic steroids, systemic retinoids, or other topical medications on the forearms or face; history of eczema, skin cancer, or vitiligo; and recent use or exposure to depigmenting products, products containing hydroquinone (or its derivatives), or other solutions (photo sensitizers) that might augment photoxicity.

Patients

- After giving written, informed consent, 45 males and 214 females were enrolled into 17 study centers in the United States and 3 in Canada. The mean age of the subjects was 55.8, with a range of 31-82. Sixty-three (24.3%) of the subjects were Asian, 35 (13.5%) were African American, and 161 (62.2%) were Hispanic.
- At baseline, the Overall Lesion Pigmentation Index score was ≥6 on a 9-point scale ranging from 0 (lightest) to 8 (darkest), where 4 (equal) indicated equal pigment with surrounding skin (Table 2). The lentigines were circumscribed macular lesions with even-brown pigmentation, regular margins, and located on a sun-exposed area.
- One lesion in each area was designated as a target lesion. All lesions on the face and arm areas were treated.

Study Design

- Study medication (topical mequinol 2%/tretinoin 0.01%) was dispensed. The investigator supervised the first application. Subjects then applied the study medication twice daily and returned for clinical evaluations after 4, 8, 12, 16, 20, and 24 weeks, and 4 weeks later for follow-up.
- At each visit, a Target and Overall Lesion Pigmentation Index score was recorded for each area. Subjects were to discontinue use of the study medication if adequate depigmentation (to normal skin color) for all lesions in an area occurred prior to Week 24, based on clinical evaluation.
- Efficacy was determined by clinical assessment using Target Lesion and Overall Lesion Pigmentation Index scores for the face and arm areas and was quantified by dividing responders into 3 categories: (1) Complete responders (subjects who reached an Overall Lesion Pigmentation Index of 4); (2) Partial responders (subjects who had significant improvement in their pigmentation, defined as an improvement of at least 1 grade, compared to baseline); and (3) Treatment failures (subjects who did not fulfill the above criteria, or subjects achieving an Overall Lesion Pigmentation Index score of less than 4).
- The time to reach a response in partial and complete responders was defined as the time from first treatment application to the first measurable response.
- Selected sites took color photographs of overall and target lesions at baseline and at the end of study treatment (completion or discontinuation). Based on investigator interest, experience, and training, photographs for illustrative purposes were only taken at 3 selected study sites at baseline, at Week 24, or upon successful depigmentation to grade 4 (Figures 1 and 2, a and b).

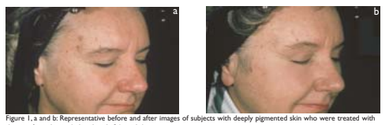

Figure 1, a and b: Representative before and after images of subjects with deeply pigmented skin who were treated with the test formulation (a, baseline; b, 24 weeks).

Safety and Tolerability Assessments

- Safety was assessed by evaluating the nature, frequency, and severity of reported AEs, including pigmentary changes in the treated areas.
- Routine laboratory tests (blood chemistry, hematology, and urinalysis) for safety monitoring were performed at baseline and after 12 and 24 weeks of treatment (or at last visit).
- Failure of pharmacological action included those subjects who completed 24 weeks of treatment with an unchanged or worsened Overall Lesion Pigmentation Index score in both areas during the treatment phase.

Table 2: Lesion Pigmentation Index

Lesion Score	Pigmentation
0	Extremely lighter than pigment of surrounding skin (depigmented)
1	Markedly lighter than pigment of surrounding skin
2	Moderately lighter than pigment of surrounding skin
3	Slightly lighter than pigment of surrounding skin
4	Equal with pigment of surrounding skin
5	Slightly darker than pigment of surrounding skin
6	Moderately darker than pigment of surrounding skin
7	Markedly darker than pigment of surrounding skin
8	Extremely darker than pigment of surrounding skin

Results

Efficacy

- Over 80% (range 81.5% to 88.8%) of subjects showed a clinically significant treatment effect (Lesion Pigmentation Index change of 1 grade or more) that was consistent with improvement.
- Up to 19% of subjects showed a complete response during the 24-week treatment period. In most subjects, therapeutic effect was sustained after a 4-week follow-up period during which time no study medication was applied.

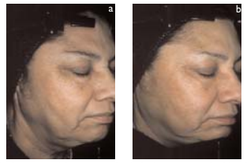

Figure 2, a and b: Facial pigmentation lightening occurred in the facial treatment sites after 24 weeks of therapy with the test formulation in an African American subject.

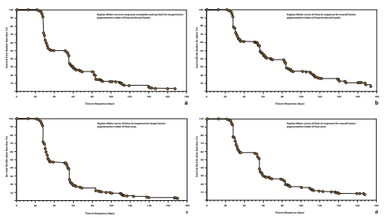

Figure 3, a-d: Kaplan-Meier curves of time to response (complete and partial). Complete response: reaching a pigmentation index of 4 (equal with pigment of surrounding skin). Partial response: an improvement in pigmentation by at least 1 grade compared to baseline (not going below grade 4).

Safety

- Mequinol 2%/tretinoin 0.01% treatment showed an overall favorable safety profile consistent with previous clinical studies.
- As shown in Table 3, of 259 subjects, 160 (61.8%) reported ≥1 AE; 125 (48.3%) subjects reported ≥1 dermatological AE.
- The most commonly reported AEs were erythema, skin discomfort, and halo-hypopigmentation, occurring in 24.7%, 20.1%, and 7.7% of subjects, respectively. Thirty-two (12.4%) reported hypopigmentation or halo-hypopigmentation (12 [4.6%] and 20 [7.7%], respectively).
- The majority of these events (84%) resolved during the study.
- Drug-related AEs were reported by 121 (46.7%) subjects, all of whom had dermatological AEs.
- Thirteen (5%) subjects discontinued treatment due to an AE, 9 (3.5%) were dermatological in nature.
- Fifteen (5.8%) subjects stopped treatment due to dermatological AEs in 1 area (either the face or arm) but continued undergoing treatment in the non-affected area.
- Serious AEs were reported by 6 (2.3%) subjects; all were non-dermatological.
- Laboratory AEs were infrequent; hematuria occurred in 9 (3.5%) subjects (7 were female). No laboratory AEs resulted in treatment discontinuation, and none were considered to be related to treatment by the investigators.
- No unexpected, drug-related AEs were reported.
- In a population with increased risk for treatment-related AEs, these safety data support the use of mequinol 2%/tretinoin 0.01% in ethnic or dark skin type subjects.

Table 3: Summary of Adverse Events

Total subjects	N = 259
	n (%)
Total subjects reporting AEs	160 (61.8)
Skin and appendages	125 (48.3)
Erythema	64 (24.7)
Skin discomfort	52 (20.1)
Halo-hypopigmentation	20 (7.7)
Irritant dermatitis*	17 (6.6)
Desquamation	16 (6.2)
Pruritus	13 (5.0)
Hypopigmentation	12 (4.6)
Dry skin	8 (3.1)
Body as a whole	35 (13.5)
Flu syndrome	17 (6.6)
Headache	9 (3.5)
Accidental injury	8 (3.1)
Respiratory system	22 (8.5)
Pharyngitis	13 (5.0)
Urogenital system	21 (8.1)
Hematuria	9 (3.5)

A subject was counted only once per AE regardless of the number of occurrences.
*Defined as erythema plus at least 2 additional, prespecified signs/symptoms (scaling, dryness, stinging/burning) starting at the same time

Conclusions

- Overall, mequinol 2%/tretinoin 0.01% combination therapy demonstrated a favorable benefit-to-risk ratio in the treatment of solar lentigines in Asian, Latin/Hispanic, and African American subjects with skin types II to V.
- This study has demonstrated that over 80% of treated subjects achieved a significant response to therapy for both arm and facial lesions, the majority of which maintained clinical benefit 4 weeks posttreatment.
- These results mirror efficacy findings previously reported for light-skinned individuals[2] and provide new evidence supporting the use of mequinol 2%/tretinoin 0.01%, specifically in ethnic and dark-skinned populations.
- The median response time for the Overall Lesion Pigmentation Index was 56 days (range 21 to 173) for both the arm and face; median response times were 51 and 35 days for the Target Lesion Pigmentation Index for the same respective regions. Noting the realistic amount of time necessary to achieve a noticeable difference when treating solar lentigines may help in the management of patient expectations for therapy and, ultimately, support compliance.
- Although AEs were reported by a significant number of patients, the treatment overall was tolerable, especially when considering the overwhelming treatment-response rate.
- The most commonly reported AEs were erythema, skin discomfort, and halo-hypopigmentation, occurring in 24.7%, 20.1%, and 7.7% of subjects, respectively. These results are significantly more favorable than AE results previously reported in light-skinned populations.[2]
- Many current treatment strategies for solar lentigines are associated with either inadequate depigmentation responses or unfavorable side effects, resulting in severe patient discomfort.[3]
- It has been widely reported that formulations containing hydroquinone and/or glucocorticoids are associated with an increased risk of ochronosis, a paradoxical hyperpigmentation response.[8]
- Such adverse reactions can be alarming to patients who initially sought treatment in order to resolve hyperpigmentation abnormalities. Through avoidance of undesirable side effects, such as ochronosis, mequinol 2%/tretinoin 0.01% topical solution offers patients an attractive alternative to other therapies being used to treat solar lentigo.
- The present study supports the use of mequinol 2%/tretinoin 0.01% combination therapy as an effective, tolerable treatment option for ethnic and dark-skinned subjects.

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