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Extension Phase of a Multi-Center, Randomized, Blinded Clinical Study Evaluating the Efficacy and Safety of a Novel Topical Product for Facial Dyschromia

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ABSTRACT

Background: Dyschromia can be associated with increased production and/or reduced clearance of pigmentation in the skin. Multiple pathways are involved in causality. A novel topical product was recently developed, which contains actives that have been validated through in-vitro and clinical studies to counteract pigmentation related to photodamage, PIH, and melasma. This study further evaluates the safety and efficacy of this product for facial dyschromia during an additional 3-month extension period following the completion of the previous 12-week multi-center trial.

Study Design: Subjects from the previous multi-center trial with mild to severe facial dyschromia at baseline were eligible to participate in this 3-month extension study upon completion of that trial. This extension study evaluated the continued use of the novel topical product with PATH-3 Technology (Alastin Skincare, Carlsbad, CA) over a 3-month period. Subjects who were previously randomized to the novel topical product continued using it and for those previously randomized to hydroquinone 4% discontinued its use. Both cohorts continued daily sunscreen use. Blinded investigators assessed subjects at follow-up visits at 16, 20, and 24 weeks.

Results: Twenty-six (26) subjects completed the extension phase of the pivotal trial, with 13 subjects in each of the AL and HQ-BREAK cohorts. Significant improvements were seen within the AL cohort from weeks 12 to 24 for facial dyschromia (P=0.0158) and skin tone/clarity/evenness (P=0.0067), while there were no significant improvements seen in the HQ-BREAK cohort. The HQ-BREAK cohort had more subjects who worsened with facial dyschromia and skin tone/clarity/evenness. For the mMASI, the HQ-BREAK cohort demonstrated regression at week 24 compared to week 12, while the AL cohort instead experienced continued improvement. This difference was found to be significant (P=0.02). No study related adverse events were reported for either cohort.

Conclusion: A novel topical product designed to counteract various steps in pigmentation pathways using PATH-3 Technology has been demonstrated to be safe and effective in treating facial dyschromia on a long-term basis. In contrast to the significant rebound experienced by subjects with HQ, the AL cohort continued to demonstrate ongoing improvement.

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INTRODUCTION

Dyschromia continues to be a challenging cutaneous condition to treat, which has been complicated by the complex pathways involved and the nuances of individual cases. The sheer number and variety of potential triggers are vast, which mimic the nature of the signaling pathways and cellular interactions involved, especially those between melanocytes, keratinocytes, and endothelial cells. Recent gene expression and cellular studies using melanocytes, keratinocytes, and endothelial cells, as well as melanocyte production models, have identified novel topical agents that are active in the pigmentary pathways, including those pertaining to photodamage, post-inflammatory hyperpigmentation (PIH), and melasma.[1] Many of these ingredients were more recently formulated into a novel topical product aimed at improving dyschromia without any limitations in long-term use.

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A previous multi-center pivotal trial was completed evaluating the clinical outcomes of this novel topical product (AL) (A-LUMINATE Brightening Serum, Alastin® Skincare, Inc., Carlsbad, CA) compared to hydroquinone 4% (HQ4%).[2] Subjects applied either AL or HQ4% twice daily, and every subject was dispensed a cleanser (Gentle Cleanser, Alastin® Skincare, Inc., Carlsbad, CA), sunscreen (SilkSHIELD SPF 30, Alastin® Skincare, Inc., Carlsbad, CA or Cetaphil® SPF 30+, Galderma Laboratories, L.P, USA), and moisturizer (Cetaphil® Daily Lotion, Galderma Laboratories, L.P, USA) to use throughout the study. A total of 43 subjects were enrolled and randomized to either the AL (n=22) or HQ4% (n=21) cohort. At 12 weeks, the AL cohort had significant improvements in mMASI scores for the right cheek (P=0.0097), left cheek (P=0.0123), combined cheeks (P=0.0019), and total facial area (P=0.0046), while the HQ4% cohort had none of these significant improvements. Although both cohorts demonstrated improvements in dyschromia and skin tone using investigator grading, the AL cohort also had significant improvements in skin radiance (P=0.0015) and skin texture (P=0.0058), which the HQ4% cohort did not demonstrate. The HQ4% cohort experienced 5 adverse events in contrast to none in the AL cohort. Subjects in the HQ4% cohort also more frequently experienced burning, stinging, tingling, itching, erythema, and dryness.

While the pivotal trial originally evaluated subjects for up to 12 weeks with topical use, an extension phase was more recently completed to continue evaluation from week 12 to week 24. During this extension period, the AL cohort continued their topical regimen with the novel topical product, while the HQ4% cohort discontinued their use of hydroquinone to mimic real-world conditions of a drug holiday (HQ-BREAK).

MATERIALS AND METHODS

This multi-center extension study was approved by the US Investigational Review Board (Miami, FL). Subjects who previously enrolled into and completed the initial 3-month pivotal trial were eligible to participate in this 3-month extension study. For the original trial, eligible subjects were men and women, who were 18-71 years old presenting with mild to severe facial dyschromia at baseline, as graded by the investigator using the modified Griffiths 10-point scale. Subjects agreed not to use any new topical products or have any procedures on the facial area during the duration of the study and to avoid extended periods of sun exposure and the use of tanning beds. Subjects were excluded if they had known allergies or reactions to any of the ingredients within the study products, a dermatologic disease or uncontrolled systemic disease, had used prescription strength retinol or lightening products within 1 month, used any skin lightening or anti-wrinkle products known to affect dyschromia or aging skin within 2 weeks, or used isotretinoin within 12 months. Additionally, subjects were excluded if they underwent laser/light treatments, microneedling, or chemical peels within 2 months, initiated hormone replacement therapies (HRT) or hormones for birth control within 3 months, or planned on modifying doses of HRT or hormones for birth control. Additionally, individuals nursing, pregnant, or planning to become pregnant were excluded.

The extension study evaluated the continued use of the novel topical product with PATH-3 Technology (Alastin® Skincare, Carlsbad, CA) over a 3-month period. All subjects previously randomized to HQ4% discontinued its use and only used the study provided cleanser (Gentle Cleanser, Alastin® Skincare, Inc., Carlsbad, CA), sunscreen (SilkSHIELD SPF 30, Alastin® Skincare, Inc., Carlsbad, CA or Cetaphil® SPF 30+, Galderma Laboratories, L.P, USA) and moisturizer (Cetaphil® Daily Lotion, Galderma Laboratories, L.P, USA) to use throughout the study. Both cohorts were followed for an additional 3 months, with visits occurring at 16, 20, and 24 weeks to evaluate safety and efficacy. Evaluation included modified MASI (mMASI), modified Griffiths 10-point scale for the overall appearance of dyschromia, skin tone/clarity/evenness, skin radiance, and skin texture, and tolerability assessments using a 5-point scale (0: none, 1: minimal, 2: mild, 3: moderate, and 4: severe).

An independent statistician completed the analyses using the following methods. Mean, standard deviation, and two-sample t-tests were used to summarize and compare changes in the blinded investigator assessments and mMASI scores from week 12 to week 24 between the AL and HQ4-BREAK cohorts. In addition, paired t-tests were used to test for significant changes from week 12 to week 24 within each cohort. Chi-square tests were used to compare the percentages of favorable ratings between AL and HQ-BREAK cohorts for subject questionnaires.

RESULTS

Overall, 26 subjects completed the extension phase of the pivotal trial. Mean age was 48.9 years (R: 26-70 years), and 88.5% (n=23) were women. For Fitzpatrick skin type, 3.8% (n=1) were Type I, 19.2% (n=5) were Type II, 34.6% (n=9) were Type III, 34.6% (n=9) were Type IV, and 7.7% (n=2) were Type V. There were 13 subjects each in the AL and HQ-BREAK cohorts. There were no significant differences in the collected demographic data between them.

Investigator assessments demonstrated significant improvements within the AL cohort from week 12 to week 24 for facial dyschromia (P=0.0158) and skin tone/clarity/evenness (P=0.0067), while there were no significant improvements seen in the HQ-BREAK cohort (Figure 1). The HQ-BREAK cohort had more subjects who worsened with facial dyschromia (4 vs 1) and skin tone/clarity/evenness (5 vs 1) compared to the AL cohort. Interestingly in the first 12-week segment of the original trial, patients on HQ4% had poor radiance and texture scores, which were generally related to the skin reactions to the topical. However, upon stopping the HQ4%, skin recovery is represented by an improvement in these scores as sun protection and moisturization took effect. In contrast, subjects using AL had

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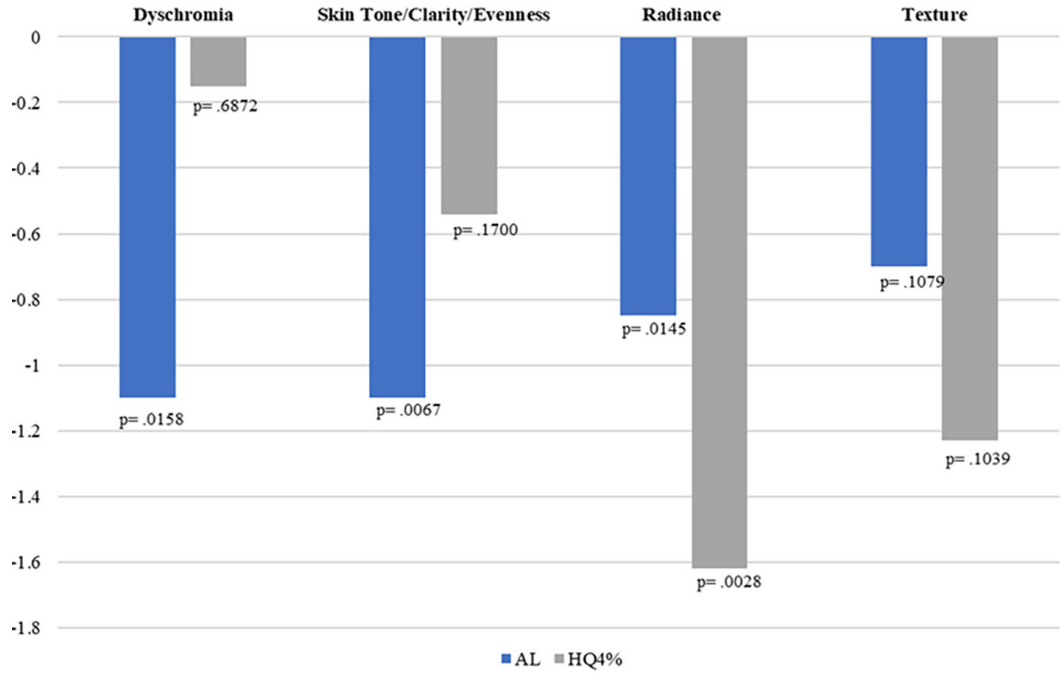
FIGURE 1. Blinded Investigator Assessments - Mean Change from Week 12 to week 24



improved scores across the board at 12 weeks (ie, dyschromia, skin tone/clarity/evenness, radiance, and texture), which even continued to improve at 24 weeks.

Analyses were again conducted using AI-enabled skin imaging software that can precisely score skin based on an image, which was developed to conform to existing validated scales (Skintelligent, Atlanta, GA). For the automated skin measurements of mMASI, the HQ- BREAK cohort demonstrated regression at week 24 compared to week 12 (0.39 +/- 0.53), while the AL cohort instead experienced continued improvement (-0.12 +/- 0.50; Figure 2). This difference was found to be statistically significant (*P*=0.02). These changes were reflected in clinical photography with long-term improvements noted in the AL cohort (Figure 3) and dramatic rebound pigmentation noted in the HQ-BREAK cohort (Figure 4).

FIGURE 2. Mean changes in mMASI from baseline in HQ-BREAK cohort (left) and AL cohort (right).

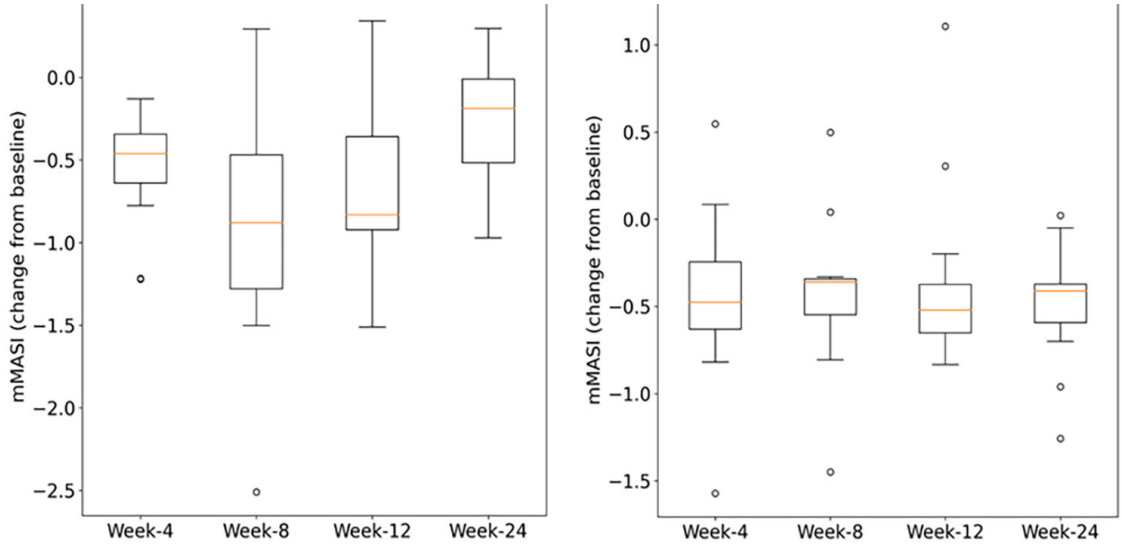


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FIGURE 3. AL subject showing mMASI improvement between weeks 12 (left) and 24 (right).

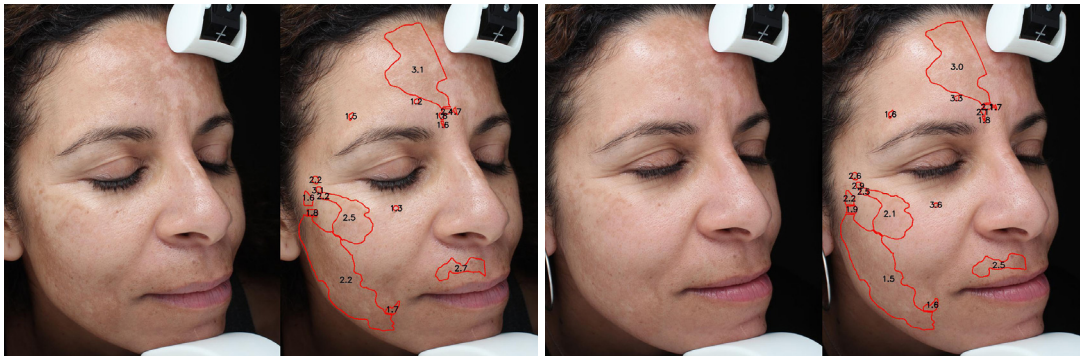
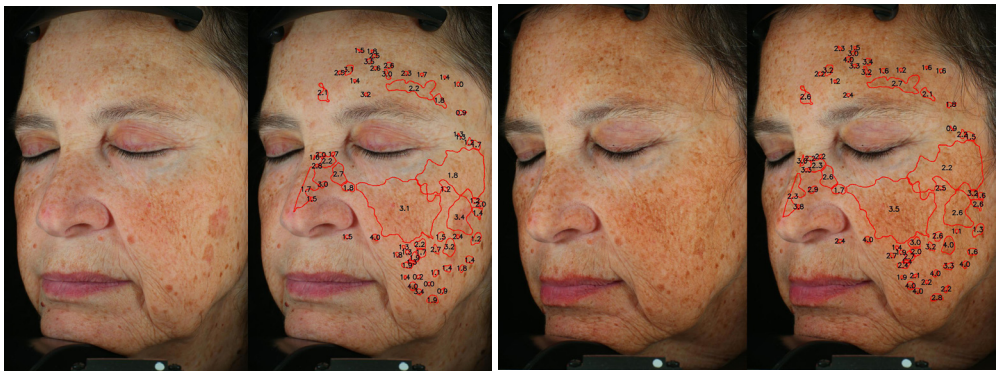


FIGURE 4. HQ-BREAK subject showing rebound between weeks 12 (left) and 24 (right). The larger distinct lesion on the lateral cheek largely disappears at week 24, but the overall pigmentation is much darker, which is reflected in the mMASI scores.



The tolerability assessments performed by both subjects and investigators demonstrated no significant differences between the AL and HQ-BREAK cohorts. This included no additional tolerability issues from long-term use of the AL product in terms of burning, stinging, tingling, itching, erythema, dryness, and peeling, compared to using no product at all. At the 24-week follow-up visit, 92.3% of subjects in the AL cohort believed the AL product faded their brown spots, 84.6% believed it improved evenness in their skin tone, and 92.3% believed it made their skin appear brighter and more radiant.

DISCUSSION

Over the years, hydroquinone has become the gold standard for topical lightening agents. Although it can be effective in improving various forms of dyschromia, it also has several limitations. Firstly, it has been associated with low tolerability and various side effects, which can limit its use in many patients. These include irritation, stinging, burning, tightness, peeling, scaling, and contact dermatitis. Secondly, its use is typically limited to 1-3 months in practice, due to the increased risk of patients developing exogenous ochronosis. Patients are usually instructed to take drug holidays at this point to prevent the development of this irreversible pigmentary condition. During this time, their dyschromia may flare, which is especially common in melasma. Thirdly, more recent concerns have increased about its cytotoxic and carcinogenic potential. These undesirable effects have caused the product to be banned in Europe for use in cosmetic products and to be pulled off the shelves more recently in the United States.

There is a great need for a topical product that can successfully and safely lighten various forms of dyschromia over the long term. The novel topical product used in this trial incorporates PATH-3 Technology, which targets prominent pigmentary pathways, including those associated with photodamage, PIH, and melasma. The novel ingredients within this formulation have all been validated in cellular models to simultaneously impact multiple levels of these pathways, which can influence melanocyte activation, melanin synthesis, melanin transfer, and melanin breakdown and clearance. Its effects not only work on melanocytes but also on both keratinocytes and endothelial cells, which play significant roles in influencing melanocytic pathways. The novel topical product can decrease inflammation and increase autophagy of melanosomes and exfoliation of keratinocytes containing melanosomes.

Using gene expression studies and cellular models, the various ingredients involved with PATH-3 Technology have been validated to counteract these pigmentary pathways. While hexapeptide-12 can significantly downregulate several

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melanogenic genes, hexapeptide-11 can downregulate the delivery of melanin to keratinocytes and impact autophagy. Lactoferrin not only decreases melanin production and the transfer of melanosomes to keratinocytes, but it also prevents reactive oxygen species (ROS) formation and local inflammation. Phosphatidylserine can additionally prevent inflammation and vascular dilation through downregulating various factors associated with endothelial cells. Tranexamic acid can also downregulate melanin synthesis and positively impact autophagy. In combination, these ingredients have been clinically shown to offer improvements in facial dyschromia over an extended period of time.

Although the original pivotal trial demonstrated AL to be superior to HQ4% up to 12 weeks, this extension phase demonstrated its long-term effects and tolerability profile. Investigator assessments demonstrated continued improvements in dyschromia, skin tone, clarity, and evenness associated with the AL product, while computerized measurements revealed continued improvements in mMASI. In contrast, the HQ-BREAK group demonstrated regression in their mMASI, which mimics frequently experienced real-world cases, where patients tend to flare soon after beginning their drug holiday. With the AL product, no drug holiday is required due to its hydroquinone-free formula. Its high degree of tolerability was shown to continue up to 24 weeks, which is due to a lack of irritating chemicals and ingredients, such as retinol or salicylic acid. This novel product offers patients a long-term solution for their dyschromia.

CONCLUSION

In the extension phase of this multi-center, randomized, blinded clinical trial, a novel topical product with PATH-3 Technology, designed to counteract various steps in pigmentation pathways, has been demonstrated to be effective and tolerable long-term in treating facial dyschromia.

DISCLOSURES

JVW, SGF, and DMR are consultants for Alastin Skincare, Inc., a Galderma company; ADW is the Chief Scientific Officer of Galderma. MB and TR are Clinical Research Director & Manager, Alastin Skincare, Inc., a Galderma company.

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