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 ORIGINAL ARTICLE

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 caused by abnormalities in the increased production and/or reduced clearance of pigmentation in the skin. Causes of hyperpigmentation include excessive sun exposure, medications, hormones, post-inflammatory hyperpigmentation (PIH), and medical disorders, such as melasma. A novel topical product was recently developed, which contains actives that have been validated through in vitro studies to counteract various steps in the pigmentation pathways, including photodamage, PIH, and melasma. This study evaluates the safety and efficacy of this product for facial dyschromia.

Study Design: Subjects with mild to severe facial dyschromia were enrolled to receive either the novel topical product with PATH-3 Technology (Alastin Skincare, Carlsbad, CA) or hydroquinone 4% topical to apply twice daily. Both cohorts received cleanser, sunscreen, and moisturizer. Follow-up occurred at weeks 4, 8, and 12. Blinded investigators used the modified Melasma Area Severity Index (mMASI) and modified Griffiths scales at baseline and final follow-up. Tolerability assessments and subject questionnaires were completed.

Results: Forty-three subjects were enrolled and randomized to either the novel topical product (n=22) or hydroquinone 4% (n=21) cohort. At week 12 follow-up, subjects using the novel topical product 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). In contrast, subjects using hydroquinone 4% had no significant improvements in any of these areas. Although both cohorts demonstrated improvements in dyschromia and skin tone, the novel topical product also offered significant improvements in skin radiance (P=0.0015) and skin texture (P=0.0058), which the hydroquinone 4% cohort did not demonstrate. The hydroquinone 4% cohort experienced 5 adverse events, while there were no adverse events associated with the novel topical product. Subjects in the hydroquinone 4% cohort also more frequently experienced burning/stinging, tingling, itching, erythema, and dryness.

Conclusion: A novel topical product with PATH-3 Technology, designed to counteract various steps in pigmentation pathways, has been demonstrated to be safe and effective in treating facial dyschromia.

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INTRODUCTION

When considering treatment strategies and formulations that can target hyperpigmentation, two major challenges exist. Firstly, the causes, triggers, and pathways involved are multifaceted and plentiful. Not all pigmentary conditions are the same, nor do they always respond similarly between conditions and patients. There are many associated factors. This has likely contributed to the ongoing need for newer clinical research over the years as our field continues to search for effective treatment strategies. Secondly, multiple cell lines are involved in the process. A large portion of research and relevant treatment targets have traditionally been focused on melanocytes, as well as the pathways and products surrounding them. However, there is more to the story than simply melanocyte activation, melanin transfer and uptake, and melanin breakdown.

Some common triggers of dyschromia involve photodamage, aging, acne, inflammation, and hormones. These can influence various signaling pathways and cellular interactions, including those between melanocytes, keratinocytes, and endothelial cells. Although the melanocyte has been the focus of pigment targeting for many years (predominantly via tyrosinase enzyme), it has become more recently apparent that the keratinocyte is intricately associated with the melanocyte, particularly relating to inflammatory mediators (eg, plasmin, arachidonic acid,

prostaglandin E2, etc).[1-3] In addition, the endothelial cell can provide further stimuli to melanocytes, as clinically evidenced by the associated increased vascularity observed in patients with melasma.[1-5]

Due to our improved knowledge of these complex pigmentary pathways, including those pertaining to photodamage, post-inflammatory hyperpigmentation (PIH), and melasma, a novel topical formulation was recently developed. Certain active ingredients were included based on the results of gene expression studies in 3 different cell lines (melanocyte, keratinocyte, and endothelial cell) and melanocyte production models. These studies identified novel agents that are active in multiple pathways involving keratinocytes, endothelial cells, and melanocytes in the process of melanogenesis.[1] The science has been comprehensively detailed,[1] and this current randomized, blinded clinical trial was designed to assess the safety and efficacy of this new formulation in treating facial dyschromia, especially in comparison with a well-recognized and commonly used topical to treat hyperpigmentation in hydroquinone 4%.

MATERIALS AND METHODS

This multi-center study was approved by the US Investigational Review Board (Miami, FL). Eligible subjects were men and women, who were 18 to 71 years old presenting with mild to severe facial dyschromia, 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, had a known dermatologic disease or uncontrolled systemic disease, had used prescription strength retinol or lightening products within 1 month, had used any skin lightening or anti-wrinkle products known to affect dyschromia or aging skin within 2 weeks, or had used isotretinoin within 12 months. Additionally, subjects were excluded if they had undergone 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.

Enrolled subjects completed up to 5 visits, including screening, baseline, and follow-up visits at weeks 4, 8, and 12. At the baseline visit, subjects were randomized to receive either the novel topical product (A-Luminate, Brightening Serum; Alastin® Skincare, Inc., Carlsbad, CA) (AL) or hydroquinone 4% (HQ 4%). Stratified randomization was used based on dyschromia severity. Subjects applied either AL or HQ 4% 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), and moisturizer (Cetaphil® Daily Lotion, Galderma Laboratories, L.P) to use throughout the study.

At baseline and week 12, the blinded investigator graded the subject's skin using the modified Griffiths 10-point scale for the overall appearance of dyschromia, skin tone, clarity, evenness, skin radiance, and skin texture. Additionally, the modified MASI (mMASI) was used to score the area of involvement and darkness of each designated region of the face. At every follow-up visit, the blinded investigator assessed the tolerability of the randomized product using a 5-point scale for erythema, dryness, and peeling (0: none, 1: minimal, 2: mild, 3: moderate, and 4: severe).

At every follow-up visit, subjects assessed the tolerability of the randomized product using a 5-point scale for burning/stinging, tingling, and itching (0: none, 1: minimal, 2: mild, 3: moderate, and 4: severe). Additionally, subjects completed a questionnaire regarding the appearance of their skin by selecting 1 of 5 responses (agree, somewhat agree, neither agree nor disagree, somewhat disagree, and disagree), to the following statements: (1) lessened the appearance of the dark spots and discoloration on my skin, (2) improved the evenness of my skin tone, (3) made my skin look more youthful, (4) made my skin look brighter and more radiant, (5) made my skin look healthier, (6) improved the overall appearance of my skin, (7) made me feel more confident in the way my skin looks, (8) I would continue using this product, and (9) I would recommend this product to others.

Standardized facial imaging was taken at every visit of clean skin using the VISIA® camera system (Canfield Scientific, Inc.). Three different views were taken, including frontal view and 45-degree angles on both the left and right sides of the face.

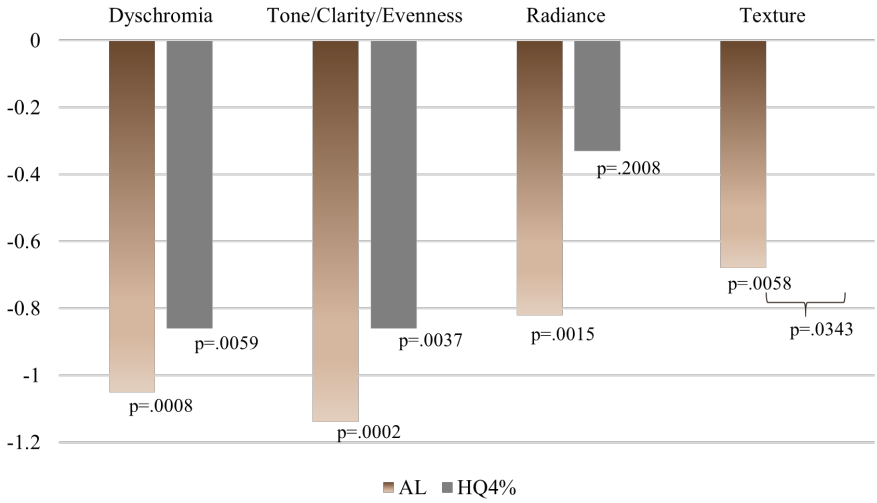
An independent statistician completed the analyses using the following methods. Mean, standard deviation, and 2-sample t-tests were used to summarize and compare changes in the blinded investigator assessments and mMASI scores from baseline to week 12 between AL and HQ 4% cohorts. In addition, paired t-tests were used to test for significant changes from baseline to week 12 within each cohort. Chi-square tests were used to compare the percentages of favorable ratings between AL and HQ 4% cohorts for the subject questionnaires.

RESULTS

Demographics

Overall, 43 of 46 subjects completed the study (1 subject withdrew consent in the AL cohort, 1 subject withdrew consent in the HQ 4% cohort, and 1 subject was lost to follow-up in the HQ 4% cohort). In the AL cohort, there were 22 subjects, which

FIGURE 1. Blinded investigator grading of overall appearance of dyschromia, skin tone/clarity/evenness, skin radiance, and skin texture using the modified Griffiths 10-point scale.



included 20 women and 2 men with a mean age of 48 years and Fitzpatrick skin types I (n=1), II (n=7), III (n=7), IV (n=6), and V (n=1). In the HQ 4% cohort, there were 21 subjects, which included 20 women and 1 man with a mean age of 50 years and Fitzpatrick skin types I (n=2), II (n=6), III (n=6), IV (n=6), and V (n=1).

Blinded Investigator Assessments

Significant improvements were seen within the AL cohort from baseline to week 12 in facial dyschromia (*P*=0.0008), skin tone/clarity/evenness (*P*=0.0002), radiance (*P*=0.0015), and texture (*P*=0.0058) (Figure 1). Within the HQ 4% cohort, only dyschromia (*P*=0.0059) and skin tone/clarity/evenness (*P*=0.0037) had significant improvements. The HQ 4% cohort had no significant improvements in either radiance or skin texture. The AL cohort demonstrated greater improvements than the HQ 4% cohort in all assessments. The AL cohort saw significantly improved skin texture compared to the HQ 4% cohort, with a mean change of -0.7 points (within-cohort *P*=0.0058; between-cohorts *P*=0.0343).

Automated Skin Measurements

Additional analyses were conducted using AI-enabled skin imaging software that can precisely and immediately score skin based on an image, which was developed to conform to existing validated scales (Skintelligent, Atlanta, GA). Analyses on the facial cheek photos for fine lines confirmed the blinded investigator assessments of improved texture within the AL cohort, with a mean change of -0.22 points compared to -0.05 points within the HQ 4% cohort.

FIGURE 2. Mean change from baseline in total mMASI scores.

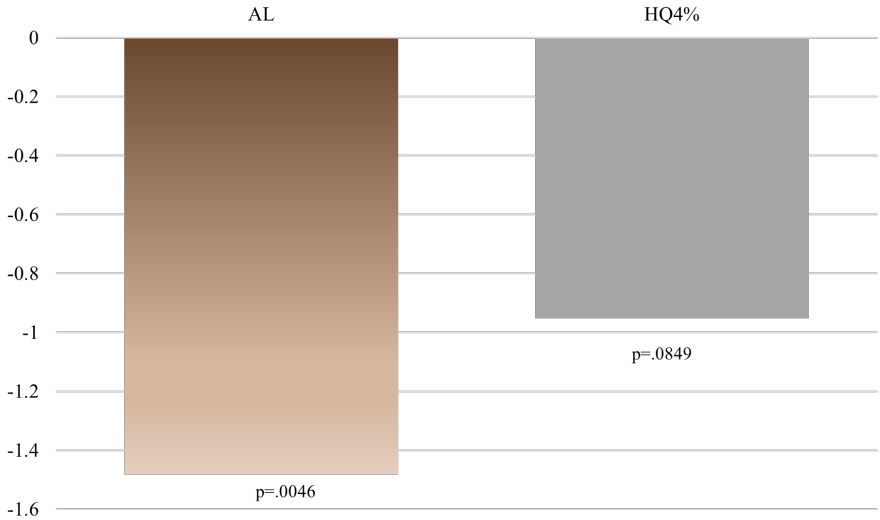


FIGURE 3. Female subject in the A-Luminate cohort at baseline (left) and at week 12 (right).

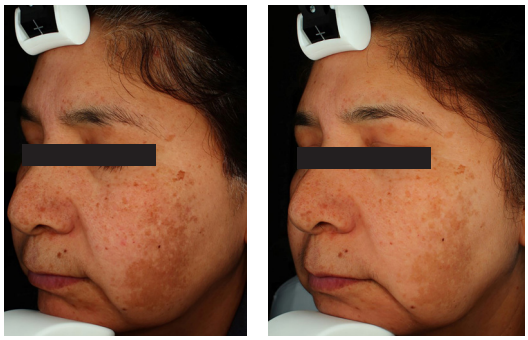
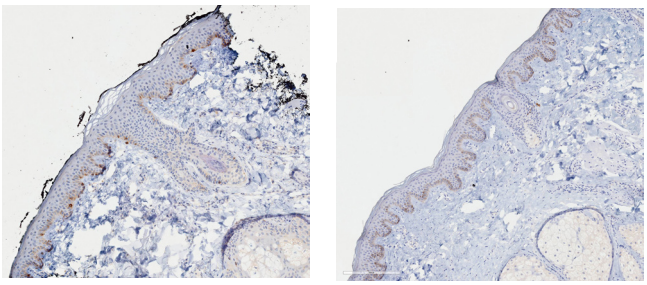


FIGURE 4. Biopsies at baseline (left) and at week 12 (right); (200X, MART-1).



For mMASI, there were significant improvements from baseline to week 12 in total (-1.5 points in AL cohort with *P*=0.0046 vs -1.0 point in HQ 4% cohort with *P*=0.0849), right malar (-1.9 points in AL cohort with *P*=0.0097 vs -1.1 points in HQ 4% cohort with *P*=0.1134), left malar (-1.6 points in AL cohort with *P*=0.0123 vs -1.1 points in HQ 4% cohort with *P*=0.1134), and combined (-1.8 points in AL cohort with *P*=0.0019 vs -1.1 points in HQ 4% cohort with *P*=0.0815) scores within the AL cohort, which was not seen in the HQ 4% cohort. For subjects who had severe dyschromia, there was regression of the initial improvement observed between week 8 and week 12 in the HQ 4% cohort (*P*=0.03). This was not seen within the AL cohort, which demonstrated continued improvement between week 8 and week 12.

Adverse Events and Tolerability

There were 5 adverse events related to the product within the HQ 4% cohort. There were 3 reports of contact dermatitis, including 2 moderate cases and 1 mild case, which required a dose regimen change of temporary discontinuation and then application of once daily with an increase to twice daily as tolerated. There was 1 report of eyelid erythema and 1 report of an acne breakout, which did not require regimen modifications. In contrast, there were no reported adverse events related to the product within the AL cohort.

In the AL cohort, the investigator tolerability assessment of erythema, dryness, and peeling was consistently lower than in the HQ 4% cohort at all time points. In the AL cohort, 2 subjects had erythema (1 minimal at week 4; 1 minimal at week 12). By contrast, 8 subjects in the HQ 4% cohort experienced erythema (3 minimal, 1 mild, and 1 moderate at week 4; 2 minimal and 1 mild at week 8; 4 minimal at week 12). Dryness and peeling were also less frequent in the AL cohort. A greater number of subjects reported minimal or mild itching, tingling, and burning/stinging within the HQ 4% cohort. At week 4, 36% of subjects reported minimal or mild itching in the HQ 4% cohort, while only 1 subject (4.3%) reported minimal itching within the AL cohort. Table 1 displays all tolerability assessment data.

Subject Questionnaire

At all follow-up visits occurring at weeks 4, 8, and 12, a greater percentage of subjects in the AL cohort agreed that the study product made their skin look more youthful, brighter, healthier, and more radiant. At week 12, 82% of subjects in the AL cohort felt more confident in the way their skin looked, compared to only 62% in the HQ 4% cohort.

DISCUSSION

Traditionally, hydroquinone has become the gold standard topical for lightening hyperpigmentation of the skin. It has been commonly used to treat various cutaneous conditions, including melasma, lentigines, and PIH. However, it is often associated with various side effects, including irritation, burning, and stinging. There is also a plateau that is commonly seen after initial improvement, and treatment duration must be limited to avoid exogenous ochronosis, which is a skin condition associated with darkening that is notoriously difficult to treat. Hydroquinone was previously banned in Europe for use in cosmetic products, and more recently, it has been pulled off the shelves in the United States. There remains concerns that hydroquinone is cytotoxic and carcinogenic. This obviates the need for a topical lightening product that can be effective and safe for regular use.

In this randomized, blinded clinical trial, the AL cohort demonstrated significant lightening of dyschromia throughout the 12 weeks (Figure 3), which was supported histologically on biopsies demonstrating decreased focal pigmentation in the basal layer with more even distribution (Figure 4). For several clinical measures, the AL cohort even experienced greater improvements than the HQ 4% cohort. For severe cases of pigmentation, there was also regression of the initial improvement seen within the HQ 4% cohort, which mimics real-world cases when there is a treatment plateau that is commonly experienced. This was not seen in the AL cohort. In many cases, when patients experience this plateau, they then use the hydroquinone more often and/or for a longer duration than recommended in hopes of experiencing the

TABLE 1.

Tolerability Assessments (Number of Subjects and Severity, Total Percentage of Subjects)						
Investigator Tolerability Assessment	**Week 4**		**Week 8**		**Week 12**	
	AL	**HQ4%**	**AL**	**HQ4%**	**AL**	**HQ4%**
Erythema	1 minimal; **4.3%**	3 minimal, 1 mild, 1 moderate; **22.7%**	0	2 minimal, 1 mild; **14%**	1 minimal; **4.5%**	4 minimal; **19%**
Dryness	1 minimal, 1 moderate; **8.6%**	1 minimal, 2 mild; **13.6%**	1 minimal, 1 moderate; **9%**	2 minimal, 1 mild; **14%**	2 minimal; **9%**	0
Peeling	1 minimal; **4.3%**	2 minimal, 1 mild; **13.6%**	1 minimal; **4.5%**	1 mild; **4.7%**	0	0
Subject Tolerability Assessment	**Week 4**		**Week 8**		**Week 12**	
	AL	**HQ4%**	**AL**	**HQ4%**	**AL**	**HQ4%**
Itching	1 minimal; **4.3%**	7 minimal, 1 mild; **36%**	1 minimal; **4.5%**	1 minimal; **4.7%**	0	1 minimal, 1 mild; **9.5%**
Burning/Stinging	4 minimal; **17%**	6 minimal; **27%**	1 moderate; **4.5%**	1 minimal, 1 mild; **9.5%**	1 minimal, 1 mild; **9%**	2 minimal; **9.5%**
Tingling	3 minimal; **13%**	3 minimal, 1 mild; **18%**	0	1 mild; **4.7%**	1 minimal; **4.5%**	1 minimal; **4.7%**

AL, A-Luminate; HQ4%, hydroquinone 4%

initial clinical improvement again, which then can inadvertently cause exogenous ochronosis. This is not a concern with the new novel topical product used by the AL cohort. In addition to demonstrating lightening of dyschromia, the AL cohort more often experienced improvements in skin texture, radiance, tone, clarity, and evenness, which is due to the compounded effects from the PATH-3 Technology and several additional ingredients that are known to support the skin barrier and function as well as offer antioxidant and anti-inflammatory benefits.

In terms of side effects and tolerability, the experiences of subjects in the AL cohort were in stark contrast to the HQ 4% cohort. The HQ 4% cohort more frequently experienced erythema, dryness, itching, tingling, burning, and stinging, which mimics real-world clinical experiences. There were also adverse events related to the product in the HQ 4% cohort, including contact dermatitis and acne breakout. The AL cohort demonstrated an overall improved tolerability profile with the topical, so it is highly likely that patients in the real world would be more apt to continue to use the product regularly. When treating pigmentary conditions, treatment adherence is crucial to achieving and maintaining clinical improvements.

Pigmentary conditions are often difficult to treat due to the many factors that can trigger worsening or flares and the complex nature of melanocyte interplay. The melanin pathway involves melanocyte activation, melanin synthesis, melanin transfer, and melanin breakdown and clearance. To effectively target pigmentation, these steps must be blocked at multiple levels simultaneously. The ideal topical product should decrease inflammation and melanocyte stimulation, downregulate melanin synthesis and transfer to surrounding cells, and increase autophagy of melanosomes and exfoliation of keratinocytes containing melanosomes. Although melanocytes are the main pigment-producing cells in the skin, both keratinocytes and endothelial cells play major roles in influencing the actions of melanocytes. These cell types must also be considered when trying to effectively downregulate pigmentary pathways, particularly in relation to PIH and melasma.

PATH-3 Technology has been formulated and validated through gene expression and cellular models to counteract the pigmentary pathways.[1] Hexapeptide-12 has potent downregulatory effects on melanogenic genes, while hexapeptide-11 positively impacts autophagy and downregulates the delivery of melanin from the melanocyte to the keratinocyte. Lactoferrin is a plasmin inhibitor that can decrease melanin production and melanosome transfer to keratinocytes, as well as prevent reactive oxygen species (ROS) formation and decrease local inflammation. Phosphatidylserine can downregulate various factors and messengers associated with endothelial cells to prevent inflammation and vascular dilation. Tranexamic acid is a plasmin inhibitor that can

impact autophagy and downregulate melanin synthesis. In combination, these ingredients have been clinically shown in this trial to offer improvements in facial dyschromia within the AL cohort.

CONCLUSION

In this multicenter, 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 safe and effective in treating facial dyschromia. This product was also well-tolerated and well-liked by subjects.

DISCLOSURES

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

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REFERENCES

1. Widgerow A, Wang J, Ziegler M, et al. Advances in pigmentation management: a multipronged approach. *J Drugs Dermatol.* 2022;21(11):1206-1220.
2. Yamaguchi Y, Hearing VJ. Physiological factors that regulate skin pigmentation. *Biofactors.* 2009;35(2):193-199.
3. Pillaiyar T, Manickam M, Jung SH. Recent development of signaling pathways inhibitors of melanogenesis. *Cell Signal.* 2017;40:99-115.
4. Pomerantz H, Christman MP, Bloom BS, et al. Dynamic optical coherence tomography of cutaneous blood vessels in melasma and vessel response to oral tranexamic acid. *Lasers Surg Med.* 2021;53(6):861-864.
5. Masub N, Nguyen JK, Austin E, et al. The vascular component of melasma: a systematic review of laboratory, diagnostic, and therapeutic evidence. *Dermatol Surg.* 2020;46(12):1642-1650.

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