Clinical Evidence of Cell-Targeted Topical Therapy for Treating Skin Dyspigmentation

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ABSTRACT

Background: New development of cell-targeted therapies to enable site-specific skin tissue drug delivery may reduce off-target effects, decrease unwanted toxicities, and enhance drug efficacy. These efforts have led to several targeting strategies that modulate active product delivery to include small molecule-, nucleic acid-, peptide-, antibody-, and cell-based strategies. Tissue specific cell-targeting strategies such as these may be useful in cosmetic dermatologic applications.

Objective: The aim of this 16-week clinical trial of a skin brightening composition containing melanocyte cell-targeted biodelivery was to assess its effectiveness in restoring the skin complexion evenness by modulating melanocyte activity in a cohort of 50 Fitzpatrick type I–VI subjects with moderate to severe dyspigmentation.

Results: Data from expert grading, skin surface colorimetry, and subject self-assessments reflected significant improvement in facial skin tone as early as 2 weeks after treatment initiation, with continual improvement through week 16. The most dramatic pigmentation improvement, based on investigator assessments, was a statistically significant improvement in skin brightness at week 2 that progressed to week 8 with significant improvement in skin evenness and brightness. By weeks 12 and 16, progressive levels of significant improvement in skin evenness and brightening became apparent. Colorimetry demonstrated progressive improvement in skin dyspigmentation starting at 2 weeks and continuing to week 16. Subject self-assessment data supported similar improvements in skin dyspigmentation.

Conclusion: These results demonstrate the ability of a cell-targeted topical therapy to achieve improvements in skin pigmentation through site-specific suppression of melanocyte activity.

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INTRODUCTION

The evolution of site-specific cell-targeted drug delivery systems chemically programmed to bind with a single cellular receptor have recently emerged as enablers toward delivering topical skin therapy. New technologies now afford the opportunity to promote enhanced skin repair by employing cell-targeted biodelivery systems capable of delivering therapeutic bioactive constituents to specific cellular receptors that minimize off-target delivery to maximize treatment efficacy of skin dyspigmentation conditions.

An array of technologies has been employed over the last century to interfere at various stages of the melanogenesis process to mitigate melanin production. The prevailing limitation with these existing technologies resides in their non-specific and off-targeting characteristics that limits efficacy. Therefore, it could be envisioned that technologies that can directly target the melanocyte to suppress melanocyte hyperactivity could provide for a more effective treatment method toward addressing skin dyspigmentation issues. The recent scientific advancement of a cell-targeted encapsulation technology that binds solely to the melanocortin 1 (MC1) receptors of melanocyte cells due to the presence of site-specific surface ligands affords such an opportunity to overcome off-target delivery. The technology exclusively binds with the MC1 receptors to deliver melanogenesis suppressing bioactive constituents directly into melanocyte cells through endocytosis, where the encapsulate is then metabolized within the melanocytes to release a bioactive peptide that suppresses tyrosinase expression.[1]

Structural changes occur to the melanocytes in photoaged skin, including nuclear heterogeneity, abundant cytoplasmic organelles, and elongation of dendrites.[2] This research demonstrates the effectiveness of a cell-targeted encapsulated technology that targets the MC1 receptor to down-regulate melanogenesis in human skin, disregarding any changes that may occur to the melanocytes due to intrinsic or extrinsic aging.

MATERIALS AND METHODS

An Institutional Review Board (IRB)-approved (Allendale Institutional Review Board, Old Lyme CT), open-label, historical control clinical study enrolled 50 subjects. All subjects possessed moderate to severe facial dyspigmentation. Upon study initiation, subjects were instructed to apply a topical formulation (ZO Skin Health Brightalive®) composed of a melanocyte site-specific, cell-targeted technology twice daily over a 16-week period. The dermatologist investigator evaluated skin tone evening, brightening, and pigmentation reduction. Instrumental measures of skin pigmentation changes using colorimetry were also employed. Additionally, subjective self-assessments were compiled through a questionnaire.

After the initial screening visit, participants who consented to the study protocol replaced their usual cleanser and sunscreen with investigator-supplied study support products: a gentle, proprietary cleanser (ZO Skin Health Gentle Cleanser) and a sunscreen (ZO Skin Health Broad Spectrum Sunscreen SPF 50). Participants were further instructed to use the following daily skin treatment regimen during the 16-week treatment period:

- Gentle cleanser am and pm
- Cell-targeted Skin Brightening Treatment am and pm
- Broad Spectrum SPF 50 Sunscreen AM, reapplied every 2 hours throughout the day
- Colorimetry was used to objectively assess changes in skin: A chroma meter (Konica Minolta Sensing Americas, Inc.: Ramsey, NJ)

Additionally, all subjects answered a detailed questionnaire about their treatment perceptions at all follow-up visits.

A Mann-Whitney two-tailed paired test was used to analyze the nonparametric ordinal expert grading data and subjective questionnaires. Statistical significance was set at $P<0.05$.

RESULTS

Investigator

A total of 50 empaneled female subjects between 30 and 70 years completed the study. Investigator-graded dyspigmentation improvement parameters began to show statistically significant improvement starting at week 2, with continual improvement over baseline at all follow-up visits (Table 1):

TABLE 1.

Weeks 2–16 Investigator Evaluations (% Change vs Baseline)				
Attribute/ Statistical	Complexion Evenness	*P* =	Pigmentation Brightening	*P* =
Week 2	0%	1.00	-5%	0.008
Week 8	-5%	0.008	-19%	<0.001
Week 12	-12%	<0.001	-29%	<0.001
Week 16	-20%	<0.001	-34%	<0.001

Instrumental

A Minolta Chroma Meter was used to measure differences in color lightness, chroma, and hue by utilizing the CIELAB mainstream color space coordinate system. Analysis of ΔE trends to measure cumulative changes in skin pigmentation affords the opportunity to validate the visually perceptible expert grading and self-assessment differences in skin pigmentation throughout the course of a clinical treatment program.

TABLE 2.

Weeks 2 - 16 Chroma Meter ΔE Table	
Assessment Interval	ΔE
Week 2	2.40
Week 8	2.63
Week 12	2.31
Week 16	3.43

Experimentally verified statistics have determined that both experienced and unexperienced observers can see difference in color when ΔE exceeds 2.0.[3] The ΔE values of >2.0 reported herein illustrate that noticeable and progressive cumulative changes in skin pigmentation were detectable that would be recognizable to both the experienced (expert grader) and inexperienced subjects, which is congruent with the expert visual grading and self-assessment data.

Subjective

Participants' perceptions of the study product and its effects were highly favorable and statistically relevant. Consistent with the expert grading and colorimetry data, the panelist

TABLE 3.

Weeks 2 - 16 Panelist Self-Assessment Table (% who saw noticeable improvement)						
Attribute/Statistical	Skin Appears Lighter	*P*=	Skin Appears Less Pigmented	*P*=	Skin Tone Appears More Even/ Uniform	*P*=
Week 2	46.8%	0.77	31.9%	0.019	31.9%	0.019
Week 8	75.5%	<0.001	65.3%	0.044	55.1%	0.568
Week 12	67.3%	0.021	67.3%	0.021	59.2%	0.253
Week 16	76.0%	<0.001	72.0%	0.003	72%	0.003

ratings depict escalating improvement from week 2 to 16 in skin dyspigmentation, including skin lightening, pigmentation, and evenness. The ratings at week 2 showed statistically significant improvements in skin pigmentation and tone. By weeks 8 through 16, panelists experienced significant improvement in skin pigmentation. By week 16, panelists also reported significant improvements in skin evenness. When viewed in conjunction with the expert grading and colorimetry data, subjects reported a positive perception of product performance.

DISCUSSION

The cell-targeted skin brightening test product's multi-modal technologies included the following:

- Cell-targeted "Drone" Encapsulate: the encapsulate technology is chemically engineered with multiple Palmitoyl sh-Tripeptide-5 Norisoleucyl sh-Nonapeptide-1 surface ligand peptides that solely target the melanocyte MC1 receptors to suppress melanogenesis. Once bound to the MC1 receptors, the encapsulate enters the cell by endocytosis and is metabolized in the cytoplasm where the encapsulate then releases a secondary peptide, Palmitoyl sh-Octapeptide-24 Amide, that antagonistically inhibits tyrosinase gene expression inside the melanocyte cell to restrict the biochemical pathway of melanogenesis.[4]
- Tranexamic acid: UV radiation induces the synthesis of plasminogen activator within keratinocytes. Plasminogen activator increases plasmin activity in keratinocytes, which in turn releases Arachidonic acid. Free Arachidonic acid stimulates pigment-producing cells, resulting in increased pigment synthesis. Tranexamic acid acts as a plasmin inhibitor, depleting the keratinocyte pool of Arachidonic acid to prevent excess pigment production.[5]
- Niacinamide: downregulates melanin transfer from the melanocyte dendrites to the skin surface keratinocytes cells to mitigate visible pigmentary accumulation at the upper skin surface.[6] Niacinamide also functions as an anti-inflammatory to prevent the onset of inflammatory induced new pigment formation.
- Diglucosyl Gallic Acid: inhibits the Microphthalmia-associated transcription factor (MITF) transcription factor involved in the melanin synthesis pathway.[7]

The investigator noted significant improvement in skin brightening and reduction of existing pigmentation by week 2. By week 8, significant improvement in brightening of pigmentation and skin evenness were noted. By weeks 12 and 16, increasing levels of significant improvement in both brightening and evenness were noted among the study subjects. The instrumental colorimetry data indicated a trend of improvement in reducing visible pigmentation. Combined with the gradually improving subject self-assessments reporting reduced pigmentation, less unevenness of skin complexion, and lightening of skin pigmentation, this research demonstrates the possible value of a cell-targeted dyspigmentation treatment modality.

CONCLUSION

Based on expert grading and subject self-assessment, the study technology resulted in highly significant skin dyspigmentation improvement. When correlated with the perceptible colorimetry ΔE differences, the study product demonstrated the ability to provide a safe and effective modality for facial skin dyspigmentation improvement.

DISCLOSURES

Zoe Diana Draelos, MD, received funding from ZO Skin Health to conduct the research detailed in this manuscript. Frederick Woodin is an employee of ZO Skin Health.

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