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An Open-Label Study Evaluating the Periorbital Skin Rejuvenation Efficacy of a Cosmeceutical Containing Methyl Estradiolpropanoate (MEP) in Women With Estrogen Deficient Skin (EDS)

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ABSTRACT

Background: A cosmeceutical topical formulation containing a non-hormonal estrogen receptor activator, Methyl Estradiolpropanoate (MEP), has been developed to address periorbital skin aging in post-menopausal women with estrogen-deficient skin (EDS).

Objective: The primary objective of the study was to evaluate the efficacy of Emepelle Eye Cream® (Biopelle, Ferndale Pharma Group, Ferndale, MI, USA) for the rejuvenation of the periorbital skin areas in women EDS. The secondary objectives were to assess the tolerability and satisfaction with Emepelle Eye Cream as assessed by the clinical investigator and the participants.

Methods: Clinical improvement (ie, change from baseline visit) to the end of study topical application in the periorbital areas were assessed by the clinical investigator using the clinician-rated quality of periorbital skin area visual scoring scale and by the participant using the participant's self-evaluation of the quality of periorbital skin area questionnaire. Secondary objectives and endpoints were assessed using a subject Quality of Life (QoL) evaluation, a clinician- and a participant-evaluation of tolerability and side effects, and the C-GAIS and P-GAIS questionnaires. Baseline scores were compared to scores at the follow-up visits.

Results: Clinician evaluations included a Global Aesthetic Improvement Scale (GAIS) rating of periorbital skin areas using a 6-point rating scale as well as tolerability and side effects. The averaged clinical GAIS improvement for all subjects who completed the study improved by 21%. The mean clinician GAIS score at study completion was 2.7, and 26 of the 31 subjects who completed the study showed improvement. A clinician GAIS score of 1 (very much improved) was observed in 3 study subjects. The averaged subject improvement results included improvements in each category at the primary endpoint. The subjects reported that their satisfaction with their periorbital appearance improved by 47% as compared to before treatment. The product was well tolerated by all subjects and no significant side effects were reported.

Conclusion: In an open label study of 31 female subjects who had been amenorrheic for at least one year, topical application of Emepelle Eye Cream for periorbital skin rejuvenation was effective and well-tolerated.

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INTRODUCTION

Estrogen levels change with aging, and these levels have a direct influence on skin estrogen biosynthesis and estrogen receptor expression. As women enter menopause, their intrinsic estrogen production sharply decreases, and this estrogen deficit worsens the effects of normal skin aging. This alteration in skin components, referred to as estrogen-deficient skin (EDS), can result in skin dryness, pruritus or itching, an increase in wrinkles, skin thinning and/or atrophy, and slowness in wound healing.[1-6]

One approach to treating the symptoms of EDS in women is through hormone-replacement therapy. Treatment with hormone-replacement therapy agents given either orally or through the skin has many potential benefits, however, hormone-replacement therapy was not specifically developed for skin-related benefits and may not improve skin wrinkles in most facial areas.[7] In addition, hormone-replacement therapy can precipitate serious side effects such as coronary artery disease, stroke, and breast and uterine cancer.[8]

More recently, newer topical cosmeceutical agents containing non-hormonal, skin-specific activators of estrogen receptors have been developed. These agents offer the advantage of delivering targeted treatment for EDS. Some studies have suggested that these agents improve skin dryness, thickness, and facial wrinkles.[9,10]

Among these recent advances in skin-care development is Methyl Estradiolpropanoate (MEP), a synthetic estrogenic sterol ester with approximately 1% of the estrogen receptor binding affinity of estradiol. The Emepelle line of cosmeceutical skin-care products contain not only proprietary MEP but also other ingredients that provide a multifactorial approach to treating skin aging and photoaging. In a recent study,[4] the application of Emepelle Night Cream and Emepelle Day Serum were found to improve skin hydration, skin wrinkles, skin texture, and skin color. This current periorbital specific study further evaluates the Emepelle line of skin-care products in women with EDS—specifically women with signs of periorbital skin aging treated with Emepelle Eye Cream® (Biopelle Inc., Ferndale, MI). The study was conducted for Biopelle Inc. (Ferndale Pharma Group, Ferndale, MI) and approved by an independent institutional review board.

MATERIALS AND METHODS

This study was designed as an open-label, 2-center, 12-week clinical trial designed to evaluate a skin cream (Emepelle Eye Cream, Biopelle Inc., Ferndale, MI) formulated for skin rejuvenation in women with signs of EDS and intrinsic aging around the periorbital areas.

The primary objective endpoints were the clinical improvement (ie, change from baseline visit) to the end of study intervention in the periorbital areas as assessed by the clinical investigator (using the clinician-rated quality of periorbital skin area visual scoring scale) and by the participant (using the participant's self-evaluation of the quality of periorbital skin area questionnaire). The improvements in EDS were also evaluated through photographic imaging obtained at baseline and at each follow-up visit. The secondary objectives of this study were to assess the tolerability and satisfaction with Emepelle Eye Cream as assessed by the clinical investigator and the participant. Secondary objectives and endpoints were assessed using a subject QoL evaluation, a clinician- and a participant-evaluation of tolerability and side effects, and C-GAIS and P-GAIS questionnaires. These instruments were to be completed at the baseline and compared to scores at the follow-up visits.

Study Population

The study enrolled females of non-childbearing potential who had a history of being amenorrheic for at least one (1) year and no more than 10 years, and at the same time had demonstrable fine or moderate wrinkles around both eyes and at least slightly visible dark areas, slightly coarse and grainy lower eyelids. Participants each agreed to refrain from using any other topical products on the periorbital skin or from undergoing any facial treatments during the 12-week study period. Participants agreed to avoid extended periods of sun exposure, including tanning beds, for the study period. When excessive sun exposure was unavoidable, participants agreed to wear appropriate protective clothing and to use the provided sunscreen.

Potential participants were excluded if they used any other semi-solid/prescription products on the periorbital areas, eye pads, or facial masks other than sunscreen products within one (1) month prior to the study participation; undergone any microdermabrasion, light or medium skin peel(s) within three (3) months prior to study participation; used any non-ablative laser, light or radiofrequency treatments within six (6) months prior to study participation; underwent any dermabrasion, deep skin peels, ablative laser treatments, botulinum toxin or filler injections on periorbital skin within 12 months prior to study participation; ever underwent blepharoplasty or cosmetic surgery affecting the periorbital skin, as well as those who were currently on hormone replacement therapy or who had been treated in the past year with hormone replacement therapy.

Upon the screening visit (day 14 to baseline), participants provided written informed consent and signed a Health Insurance Portability and Accountability Act (HIPAA) form. Medical history was reviewed including a review of current medications. Patients were advised of the potential adverse events associated with the study intervention including skin irritation, skin redness (erythema), edema (swelling due to the buildup of fluids), dryness or scaling skin, itchiness/pruritis, burning/stinging, and skin tenderness. Participants signed the consent document, their medical and surgical history was reviewed. Each participant was assessed by the study physician for fine lines/wrinkles around their eye area, the presence of dark areas around the eyes and the skin texture around the eyes and eyelids.

Study Intervention

Enrolled participants were instructed on how to treat their skin during the study intervention period, specifically to only use the skin care products provided by the study investigator. They were instructed to wash their face twice daily with a gentle cleanser (eg, Cerave) prior to applying the study intervention.

Participants were supplied with a 15 gm bottle with pump containing Emepelle Eye Cream at the baseline visit and given a daily diary to record the date and the time of their twice daily (ie, morning and evening) application. Participants were instructed to gently apply a pea-sized amount of the eye cream to both periorbital eye areas each morning of the study period immediately after washing/cleansing and drying the face. Participants were also instructed to apply the provided facial sunscreen (EltaMD UV Clear, SPF 30 or higher) approximately 15 minutes after applying the eye cream. Participants who were in direct sunlight or had significant window exposure (eg, driving car, work by window, or under skylights) were instructed to diligently reapply the facial sunscreen every 2 hours throughout the day.

Primary Efficacy Assessments

The quality of the periorbital skin areas assessed by the clinician

and by the participant were the primary efficacy assessments. The quality of the periorbital skin areas was assessed at baseline and at each follow-up visit (ie, week 4, week 8, and week 12). The primary endpoint of the clinician-scored and participant-rated periorbital skin quality assessments were the changes from baseline (day 1) to after the study intervention period. These assessments of skin quality were also established through review of the photographic/3D images obtained at baseline and at each follow-up visit.

At baseline and at each follow-up visit, the quality of the periorbital skin areas was evaluated by the clinical investigator using a 4- to 5-point visual scoring system that assesses skin color, texture, sagging, and wrinkles.

The averages of the clinician quality score of the periorbital skin areas at baseline and at each follow-up visit for participants who completed the study was calculated. The average improvement, which was the difference between the average score before and the average score after treatment expressed in percentages of the averaged baseline score, was calculated.

At baseline and at each follow-up visit, the quality of the periorbital skin areas was rated by the participants through their completion of an 11-item questionnaire.

The averages of the self-evaluation ratings at baseline and at follow-up visits for all participants who completed the study (74% completed) was then calculated. The averaged improvement, which was the difference between the averaged self-evaluation rating score at baseline and the averaged score at each follow-up visit expressed in percentages of the averaged baseline score, was calculated.

Secondary Efficacy and Tolerability Assessments

The secondary assessment parameters included clinician- and participant-rated evaluations such as a QoL evaluation (participants only), evaluations of tolerability and side effects, and completion of the Global Aesthetic Improvement Scale questionnaires. These instruments were completed at the baseline visit and at each follow-up visit.

At the baseline visit, the participant rated their level of "worry" and how "unhappy" they were about the quality of their periorbital skin areas since entering menopause. At the follow-up visits (ie, week 4, week 8, and week 12), participants rated questions related to periorbital skin changes and satisfaction with the study intervention (ie, Emepelle Eye Cream).

The baseline ratings and progress questions were answered using the following choices: Extremely, Very, Somewhat, or Not at All.

At each follow-up visit, the clinician and the participant completed the GAIS questionnaires. In these, they are asked to rate on a 1 to 6 scale their impression of their periorbital skin areas. Score ratings and description were as follows: 1 = very much improved; 2 = much improved; 3 = improved; 4 = no change; 5 = worse; and 6 = much worse.

At each follow-up visit, the clinician and the participant rated characteristics of local tolerability of the study intervention on the periorbital skin areas using a four (4)-point scale. Any adverse event(s) experienced by the participant during the study intervention period, whether related to the treatment or not, were recorded in the "Case Report Form".

RESULTS

Thirty-one female subjects, amenorrheic for at least one year, averaged 57 years of age (between 50 to 65 years) completed the study. Of the 42 subjects enrolled, one elected to withdraw from the study (no reason given), 5 were lost to follow up, 2 missed one follow up appointment, and 3 had incomplete evaluation data. Subjects ranged from II to VI on the Fitzpatrick Scale: Fitzpatrick II, 26%; Fitzpatrick III, 55%; Fitzpatrick IV, 12%; Fitzpatrick V, 5%; and Fitzpatrick VI, 2%.

FIGURE 1. Averaged improvement from baseline score of signs of periorbital skin aging as assessed by the *clinical investigator*. The improvement is shown as difference between the averaged clinical score before (baseline) and the averaged clinical score after (week 12) treatment expressed in percentages of the averaged baseline score and includes all 31 subjects completing the study.

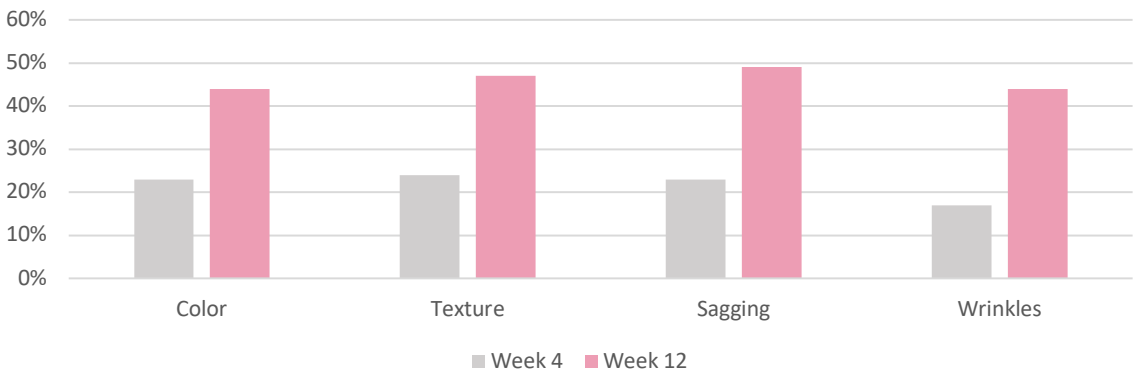
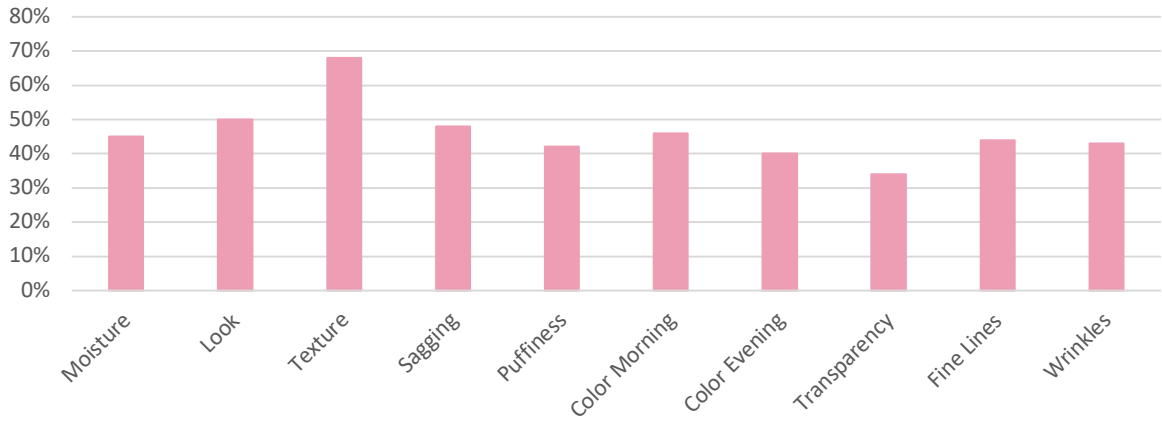


FIGURE 2. Averaged improvement of signs of periorbital skin aging as assessed by the *subjects*. The improvement is shown as difference between the average score before (baseline) and the average score after (week 12) treatment expressed in percentages of the averaged baseline score and includes all 31 subjects completing the study.



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Clinical Evaluation

Quality of periorbital skin area was assessed in each subject by a clinical investigator using a 4- to 5-point visual scoring system (Table 1). The averages of the clinical score before (baseline) and at each follow-up visit (week 4, week 8, and week 12) for all the subjects who completed the study were calculated. The averaged clinical improvement, which was the difference between the averaged clinical score before and the averaged clinical score at the primary endpoint (week 12) expressed in percentages of the averaged baseline score, was then calculated.

The averaged clinical-improvement results included improvements in each category. When expressing clinical results as averaged improvement for all subjects who completed the study, firmness or sagging improved by 49%, texture by 47%, dark circles by 44%, and periorbital wrinkles by 44%. Additionally, clinical improvement was seen at the first follow up appointment (week 4) in which texture improved by 24%, dark circles by 23%, firmness or sagging by 23%, and periorbital wrinkles by 17%, as shown in Figure 1.

Additional clinician evaluations included a Global Aesthetic Improvement Scale (GAIS) rating of periorbital skin areas using a 6-point scale (Table 2) as well as tolerability and side effects. The averaged clinical GAIS improvement for all subjects who completed the study improved by 21%. The mean clinician GAIS score at study completion was 2.7, and 26 of the 31 subjects who completed the study showed improvement. A clinician GAIS score of 1 (very much improved) was observed in 3 study subjects. The product was well tolerated by all subjects and no significant side effects were reported.

TABLE 1.

Clinician Evaluation of the Quality of Participants' Periorbital Skin Areas

Parameter	Score	Description
Skin Color	0	Skin color comparable to other facial skin areas
	1	Slightly visible dark area(s)
	2	Moderately dark areas or dark circle barely visible
	3	Dark circle clearly visible
Skin Texture	0	Smooth and even
	1	Slightly coarse and grainy
	2	Coarse and grainy
	3	Bumpy and uneven
Skin Sagging	0	Firm and elastic
	1	Slightly saggy
	2	Moderately saggy
	3	Saggy with lid or bag
Skin Wrinkles	0	Absent
	1	Shallow, but visible
	2	Moderately deep
	3	Deep with well-defined edges
	4	Very deep with redundant folds

TABLE 2.

Clinician and Participant Global Aesthetic Improvement Scale (GAIS) Rating of Periorbital Skin Areas

	GAIS Rating
1	Very much improved
2	Much improved
3	Improved
4	No change
5	Worse
6	Much worse

TABLE 3.

Participant Questionnaire for Quality of Periorbital Skin Areas	
Question	**Answer and Score Assignment**
1. Do you feel your skin under the eyes is:	0 = very moist; 1 = moist; 2 = dry; or 3 = very dry
2. Do you feel your skin under the eyes looks:	0 = normal; 1 = slightly fatigued; 2 = moderately fatigued; 3 = fatigued; or 4 = very fatigued
3. Do you feel your skin texture under the eyes is:	0 = smooth and soft; 1 = slightly coarse and grainy; 2 = coarse and grainy; or 3 = bumpy and uneven
4. Do you feel your skin under the eyes is:	0 = firm and elastic; 1 = slightly saggy; 2 = moderately saggy; or 3 = saggy with lid or bag
5. After getting up in the morning, do you feel your skin under the eyes is:	0 = not puffy; 1 = slightly puffy; 2 = moderately puffy; or 3 = puffy and swollen
6. After getting up in the morning, do you feel your skin color under the eyes is:	0 = normal; 1 = slightly dark but barely visible; 2 = moderately dark, but no clear circle visible; or 3 = dark circle clearly visible
7. In the evening, do you feel your skin color under the eyes is:	0 = normal; 1 = slightly dark, but barely visible; 2 = moderately dark, but no clear circle visible; or 3 = dark circle clearly visible
8. Do you feel your skin under the eyes is:	0 = thick; 1 = normal; 2 = thin and slightly transparent; or 3 = very thin and transparent
9. Do you feel your fine lines around the eyes are:	0 = not visible; 1 = shallow, but visible; 2 = moderately deep; 3 = deep; or 4 = very deep
10. Do you feel your wrinkles around the eyes are:	0 = not visible; 1 = shallow, but visible; 2 = moderately deep; 3 = deep; or 4 = very deep
11. Are you pleased with the appearance of your skin around the eyes:	0 = very pleased; 1 = mostly pleased; 2 = displeased; or 3 = very displeased

Subject Evaluation

Quality of the periorbital skin areas was rated by subjects through the completion of an 11-item questionnaire (Table 3). The averages of the self-evaluation ratings at baseline and at each follow-up visit for all participants who completed the study were calculated. The averaged improvement, which is the difference between the averaged self-evaluation rating score at baseline and the average score at each follow-up visit (week 4, week 8, week 12) expressed in percentages of the averaged baseline score, were calculated.

The averaged subject improvement results included improvements in each category at the primary endpoint. When expressing clinical results as averaged improvement for all subjects who completed the study, texture improved by 68%, under-eye fatigue by 50%, firmness or sagging by 48%, dark circles in the morning by 46%, moisture by 45%, fine lines by 44%, wrinkles by 43%, puffiness in the morning by 42%, dark circles in the evening by 40%, and transparency (visible appearance in skin thickness) by 34% (Figure 2). The subjects also reported that their satisfaction with their periorbital appearance improved by 47% as compared to before treatment. Additional subject evaluations included Global Aesthetic Improvement Scale (GAIS) using a 6-point scale (Table 2), subject-rated Quality of Life (QoL) questions, tolerability, and side effects. The averaged subject GAIS improvement for all subjects who completed the study improved by 22%. The mean subject GAIS score at study completion was 2.7, and 26 of the 31 subjects who completed the study showed improvement. A subject GAIS score of 1 (very much improved) was reported by four subjects.

All subjects who completed the trial liked the way the eye cream felt, and 85% said they would continue to use the eye cream on a regular basis. Furthermore, 73% of the subjects felt the eye cream alleviated some or all the periorbital skin issues they developed since entering menopause and would recommend the eye cream to other women undergoing menopause.

CONCLUSION

A 12-week clinical trial was completed by 31 postmenopausal women with estrogen-deficient skin in the periorbital area was conducted at 2 sites in the United States to examine the efficacy and tolerability of Emepelle Eye Cream, a topical formulation containing MEP, a synthetic estrogenic sterol ester. Clinician GAIS results showed improvement of the periorbital skin area in 84% of subjects who completed the study. The averaged clinical improvement by the clinician evaluation of the quality of periorbital skin showed improvement in all areas evaluated (color, texture, sagging, wrinkles) as early as week 4 and continued to improve through completion of the study. The averaged subject results included improvements in each category (moisture, look, texture, sagging, puffiness, color in the morning, color in the evening, skin thickness, fine lines, and wrinkles) at the primary

endpoint. The subjects also reported that their satisfaction with their periorbital appearance improved by 47% as compared to before treatment.

DISCLOSURES

Dr. Cohen has served as a consultant and clinical trial participant for Biopelle. Dr. Downie is a consultant for Emepelle and a researcher.

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