A Clinical Study to Assess the Facial Anti-Aging Efficacy of Topical Estriol and Estradiol

June 30, 2024

STUDY NUMBER	DCS-102-23
INVESTIGATOR	Zoe Diana Draelos, MD
STUDY SITE	Dermatology Consulting Services, PLLC
INSTITUTIONAL REVIEW BOARD	Allendale Institutional Review Board (AIRB) 30 Neck Road Old Lyme, CT 06371
SPONSOR	Alloy Women's Health
INVESTIGATIONAL PRODUCT	0.3% Estriol, 0.01% Estradiol
SPONSOR PRIMARY CONTACT	Monica Molenaar
STUDY DESIGN	Randomized Double Blind Placebo/Vehicle-Controlled
VERSION NUMBER	2

PROTOCOL NUMBER: DCS-102-23

STUDY TITLE: A Clinical Study to Assess the Facial Anti-Aging Efficacy of Topical Estriol and Estradiol

PROTOCOL SYNOPSIS AND BUDGET DATE: September 24, 2023
PROTOCOL DATE: October 19, 2023
REPORT DATE: June 30, 2024

The signatures below indicate this is the final and accepted report.

_____ _____
Representative Date
Alloy Women's Health

_____ _____
Zoe Diana Draelos, M.D. Date
Primary Investigator
Dermatology Consulting Services, PLLC

1. PROTOCOL SYNOPSIS

Title of Study:	A Clinical Study to Assess the Facial Anti-Aging Efficacy of Topical Estriol and Estradiol
Study Period:	12 weeks
Test Products:	3 study arms: 1. Placebo/vehicle control/Vehicle Control (Alloy M4 cream base, no actives), 30 subjects 2. Current M4 Formula (Alloy M4 cream base, Active: 0.3% Estriol), 30 subjects 3. Estradiol Cream (Alloy M4 cream base, Active: 0.01% Estradiol), 30 subjects Apply 3 pumps (approximately 1 ml of product) to face (forehead, cheeks, under/around eyes) and neck at bedtime to entire face after cleansing.
Objective:	The objective of this study was to investigate the efficacy of a 0.3% estriol topical facial cream and a 0.01% estradiol topical facial cream as compared to placebo/vehicle controlledon the signs of skin health after 12 weeks of bedtime use.
Design:	Female subjects were enrolled in this single site, double blind, placebo/vehicle controlled 3-arm study on facial appearance and signs of photoaging. Subjects who signed consent and met all inclusion criteria and none of the exclusion criteria were enrolled at the baseline visit. Subjects presented to the research center with a clean washed face. Subjects who did not present with a clean washed face were asked to clean with a Simple wipe. Subjects were randomized to receive one of three study arm products: a 0.3% estriol facial moisturizer, a 0.01% estradiol facial moisturizer, or a placebo/vehicle control facial moisturizer. The assigned product was to be applied at bedtime following facial washing. 30 subjects were randomly assigned to each arm, however the arms were balanced for age, skin color, and severity of photoaging to the best degree possible. Subjects used their own self-selected other skin care products and cosmetics, as long as they contained no anti-aging ingredients, that they had used without problem for the past 30 days. Subjects received a compliance diary to record the bedtime applications. Blood was taken at baseline to determine serum levels of estriol and estradiol for safety considerations. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline.

	Subjects returned to the research center with a clean washed face at week 4, week 8, and week 12. A reminder text was sent out before the visits to encourage compliance. Diaries and study product were checked for compliance. Additional product was dispensed as needed. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline. Subjects returned to the research center at week 12. Study product and diaries were checked for compliance and collected. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline. Blood was drawn for a study completion estradiol and estriol levels. Subjects completed their study participation. *(There was an allowance for an unscheduled visit at any time, if necessary.)*
Study Population:	Healthy female subjects 50-60 years of age of Fitzpatrick skin types I-VI with mild to moderate photoaging
Number of Subjects:	90 subjects (30 subjects in each of the 3 study arms)
Inclusion Criteria:	The following represented the inclusion criteria: 1. Subjects with mild to moderate facial photoaging. 2. Subjects who were in menopause (no period for at least 12 months). 3. Female subjects age 50-60 years. 4. Subjects with Fitzpatrick skin types I-VI, with at least 10-15% of subjects being African American. Each study arm contained 5 African Americans. 5. Subjects who had never taken systemic hormone replacement therapy (HRT). 6. Subject agreed not to introduce any new colored cosmetics (lipsticks, eye shadows, facial foundations, blush, powder) or skin care products, such as cleansers or sunscreens, during the study. 7. Subject had signed an Informed Consent Form in compliance with 21CFR Part 50: "Protection of Human Subjects." 8. Subject was dependable and able to follow directions and was willing to comply with the schedule of visits. 9. Subject was in generally good physical and mental health.

Exclusion Criteria:	The following represented the exclusion criteria: 1. A subject who was that was receiving Hormone Replacement Therapy (HRT). 2. A subject who had regular menstrual cycles. 3. A subject with any **UNCONTROLLED** systemic disease. A potential subject in whom therapy for a systemic disease was not yet stabilized was not considered for entry into the study. 4. A subject with a significant history or current evidence of a medical, psychological or other disorder that, in the investigator's opinion, would preclude enrollment into the study. 5. A subject with a known hypersensitivity to any of the components of the study medications. 6. A subject using any topical product containing a *retinoid, retinol, or other vitamin A derivative within 3 months* prior to or during the study period, other than the study medication. 7. A subject using any systemic steroid therapy within 6 months prior to or during the study period. 8. A patient that had been treated with Botox/Dysport or filler/biostimulatory molecule injections to his/her face, facial dermabrasion (deep skin peel), laser treatments, microdermabrasion or chemical peels within the past six months; patients also refrain from these treatments throughout the entire course of the study. 9. A subject using any topical medicated creams, lotions, powders, etc. on the treatment areas during the study period, other than the study treatment regimen. 10. A subject using any topical sunless tanning products containing dihydroxyacetone (DHA) on the treatment areas for at least 7 days prior to the start of the study as well as throughout the entire course of the study. 11. A subject that had previously been treated with systemic retinoids within the past year (*e.g., isotretinoin*). 12. A subject that underwent facial waxing, bleaching, or depilatory cream use within 30 days prior to entering the study as well as throughout the entire course of the study. 13. A subject had used any topical products containing alpha-hydroxy acids, salicylic acid, or vitamin C on the face for at least 7 days prior to the start of the study, as well as throughout the entire course of the study. 14. A subject with recently excessive facial exposure to sunlight or artificial UV light (e.g.: use of tanning beds/booths and/or sunbathing). During the study, when excessive sun exposure was unavoidable, subjects wore appropriate protective clothing (e.g. hat) and wore sunscreen..

	15. A subject with a recent history or active presence of any facial skin condition/disease that might interfere with the diagnosis or evaluation of study parameters (i.e. moderate to severe acne vulgaris, atopic dermatitis, psoriasis, rosacea, seborrheic dermatitis, excessive facial hair or coloration). 16. Cannot have a hormonal IUD (e.g. Mirena)
Endpoints:	Tolerability Endpoint: The tolerability endpoint was the investigator-assessed absence of skin irritation from the study products at any time during the 12-week study. Primary Safety Endpoint: The primary safety endpoint was the overall incidence of all adverse events reported during the study. Secondary Safety Endpoint: The secondary safety endpoint was the absence of elevated serum estradiol and estriol levels in all subjects. Efficacy Endpoint: The primary efficacy endpoint was the statistically significant improvement in the dermatologist investigator's assessment of overall facial appearance in subjects using the study products for 12 weeks comparing the 0.3% estriol, 0.01% estradiol, and placebo/vehicle control groups to each other, as well as to baseline.
Measures:	Dermatologist Investigator assessed efficacy parameters: Fine lines, wrinkles, lack of even skin tone/dark spots, lack of radiance/brightness, skin roughness (tactile), skin roughness (visual), lack of firmness, pores, hydration, elasticity, and overall appearance issues. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. Dermatologist Investigator assessed tolerability parameters: dryness, peeling, erythema, edema. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. Subject assessed efficacy parameters: Fine lines, wrinkles, lack of even skin tone/dark spots, lack of radiance/brightness, skin roughness (tactile), skin roughness (visual), lack of firmness, pores, hydration, elasticity, and overall appearance issues. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. Subject assessed tolerability parameters: dryness, peeling, stinging, and itching. All assessments were made on a 5-point ordinal scale (0=none,

	1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. Noninvasive Biomeasurements: Corneometry, TEWL, DSP for melanin at a target site, and elasticity measurements on the face was conducted at baseline, week 4, week 8, and week 12. Photography: Color photographs were taken at each time point with standard 1 lighting of the central, right, and left face with a Visia CR4.3. Photographs were performed at the following time points: baseline, week 4, week 8, and week 12.
Statistical Methods:	Along with descriptive statistics (means, standard deviations and percentages), investigator ordinal nonparametric data were analyzed using Wilcoxon signed rank test and sign test for paired comparison at different time points. The noninvasive parametric data were analyzed using paired t-test. Change was considered significant at the alpha level of 0.05.

1. STUDY VISIT SCHEDULE

Procedures	Visit 1	Visit 2	Visit 3	Visit 4
	BL	Week 4	Week 8	Week 12
Informed Consent Procedure	X			
Inclusion/Exclusion Criteria	X			
Brief Medical History and Concomitant Medications Review	X	X	X	X
Phlebotomy for Serum Estradiol and Estriol Levels	X			X
Investigator Clinical Grading for Tolerability	X	X	X	X
Investigator Clinical Facial Grading for Efficacy	X	X	X	X
Subject Clinical Grading for Tolerability	X	X	X	X
Subject Clinical Facial Grading for Efficacy	X	X	X	X
Product Dispensing	X			
Photography (Visia Standard 1 (C/L/R))	X	X	X	X
Corneometry, TEWL, Elasticity	X	X	X	X
Adverse Events	X	X	X	X
Subject Diary Assessment and Compliance Check		X	X	X
Subject Product Accountability and Study Completion			X	X

2. INTRODUCTION

Moisturization of the face is an important method of inducing appearance improvement. Many active ingredients are available for incorporation into anti-aging facial formulations. This vehicle-controlled study examined the value of 0.3% estriol and 0.01% estradiol for their value for improving facial skin appearance.

3. STUDY OBJECTIVE

The objective of this study was to investigate the efficacy of a 0.3% estriol topical facial cream as compared to a 0.01% estradiol topical facial cream as compared to a placebo/vehicle control on the signs of skin health after 12 weeks of bedtime use.

4. STUDY DESIGN OVERVIEW

Female subjects were enrolled in this single site double blind placebo/vehicle controlled 3-arm study on facial appearance and signs of photoaging. Subjects who signed consent and met all inclusion criteria and none of the exclusion criteria were enrolled at the baseline visit. Subjects presented to the research center with a clean washed face. Subjects who did not present with a clean washed face were asked to clean with a Simple wipe.

Subjects were randomized to receive one of three study arm products: a 0.3% estriol facial moisturizer, a 0.01% estradiol facial moisturizer, or a placebo/vehicle control facial moisturizer. The assigned product was to be applied at bedtime following facial washing. 30 subjects were randomly assigned to each arm, however the arms were balanced for age, skin color, and severity of photoaging to the best degree possible. Subjects used their own self-selected other skin care products and cosmetics, as long as they contained no anti-aging ingredients, that they had used without problem for the past 30 days. Subjects received a compliance diary to record the bedtime applications.

Blood was taken at baseline to determine serum levels of estriol and estradiol for safety considerations. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline.

Subjects returned to the research center with a clean washed face at week 4, week 8, and week 12. A reminder text was sent out before the visits to encourage compliance. Diaries and study product were checked for compliance. Additional product was dispensed as needed. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the

research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline.

Subjects returned to the research center at week 12. Study product and diaries were checked for compliance and collected. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline. Blood was drawn for a study completion estriol and estradiol levels. Subjects completed their study participation.

5. STUDY POPULATION

5.1 POPULATION DESCRIPTION

Healthy female subjects 50-60 years of age of Fitzpatrick skin types I-VI with mild to moderate photoaging

5.2 POPULATION SIZE

90 subjects (30 subjects in 3 study arms) were enrolled and 86 subjects successfully completed the study.

5.3 INCLUSION CRITERIA

The following items represented the inclusion criteria:

1. Subjects with mild to moderate facial photoaging.
2. Subjects who were in menopause (no period for at least 12 months).
3. Female subjects age 50-60 years.
4. Subjects with Fitzpatrick skin types I-VI, with at least 10-15% of subjects being African American. Each study arm contained 5 African Americans.
5. Subjects who had never taken systemic hormone replacement therapy (HRT).
6. Subject agreed not to introduce any new colored cosmetics (lipsticks, eye shadows, facial foundations, blush, powder) or skin care products, such as cleansers or sunscreens, during the study.
7.
8. Subject had signed an Informed Consent Form in compliance with 21CFR Part 50: "Protection of Human Subjects."
9. Subject was dependable and able to follow directions and was willing to comply with the schedule of visits.
10. Subject was in generally good physical and mental health.

5.4 EXCLUSION CRITERIA

The following items represented the exclusion criteria:

1. A subject who was that was receiving Hormone Replacement Therapy (HRT).
2. A subject who had regular menstrual cycles.
3. A subject with any **UNCONTROLLED** systemic disease. A potential subject in whom therapy for a systemic disease was not yet stabilized was not considered for entry into the study.
4. A subject with a significant history or current evidence of a medical, psychological or other disorder that, in the investigator's opinion, would preclude enrollment into the study.
5. A subject with a known hypersensitivity to any of the components of the study medications.
6. A subject using any topical product containing a *retinoid, retinol, or other vitamin A derivative within 3 months* prior to or during the study period, other than the study medication.
7. A subject using any systemic steroid therapy within 6 months prior to or during the study period.
8. A patient that had been treated with Botox/Dysport or filler/biostimulatory molecule injections to his/her face, facial dermabrasion (deep skin peel), laser treatments, microdermabrasion or chemical peels within the past six months; patients also refrain from these treatments throughout the entire course of the study.
9. A subject using any topical medicated creams, lotions, powders, etc. on the treatment areas during the study period, other than the study treatment regimen.
10. A subject using any topical sunless tanning products containing dihydroxyacetone (DHA) on the treatment areas for at least 7 days prior to the start of the study as well as throughout the entire course of the study.
11. A subject that had previously been treated with systemic retinoids within the past year (*e.g., isotretinoin*).
12. A subject that underwent facial waxing, bleaching, or depilatory cream use within 30 days prior to entering the study as well as throughout the entire course of the study.
13. A subject had used any topical products containing alpha-hydroxy acids, salicylic acid, or vitamin C on the face for at least 7 days prior to the start of the study, as well as throughout the entire course of the study.
14. A subject with recently excessive facial exposure to sunlight or artificial UV light (e.g.: use of tanning beds/booths and/or sunbathing). During the study, when excessive sun exposure was unavoidable, subjects wore appropriate protective clothing (e.g. hat) and comply with the study dosing regimen of daily application of the dispersed sunblock.
15. A subject with a recent history or active presence of any facial skin condition/disease that might interfere with the diagnosis or evaluation of study parameters (i.e. moderate to severe acne vulgaris, atopic dermatitis, psoriasis, rosacea, seborrheic dermatitis, excessive facial hair or coloration).
16. Cannot have a hormonal IUD (e.g. Mirena)

5.5 CONCOMITANT MEDICATIONS

All oral and topical prescription medications remained unchanged during the study, but there were no prohibited medications. No topical medications were allowed on the face. No facial moisturizers other than the study moisturizer were allowed during the study.

6. CONDUCT OF STUDY: METHODS AND PROCEDURES

6.1 ENROLLMENT

6.1.1 INFORMED CONSENT

A signed informed consent form was obtained from each subject prior to performing any study procedures. No study related procedures or activities were performed until each subject was fully informed and the consent form was signed and dated.

6.1.2 DERMATOLOGICAL EXAMINATION

A skin examination was performed to ensure all subject meet inclusion/exclusion criteria.

6.1.3 STUDY PROCEDURES

The subjects were screened for the inclusion and exclusion criteria prior to study enrollment. Only subjects who met the requirements, had signed an informed consent, and had given a medical history were entered into the study. All other subjects were considered screening failures.

6.1.4 STUDY MATERIAL ADMINISTRATION

The subjects were randomized to use 3 pumps (1ml) of the 0.3% estriol topical facial cream, the 0.01% estradiol topical facial cream, or the the placebo/vehicle controlmoisturizer, once daily to the face.

6.1.5 SCREENING PROCEDURES

Potential volunteers were enrolled based on their ability to meet the inclusion/exclusion criteria required for study enrollment.

6.2 STUDY CONDUCT PROCEDURES

6.2.1 BASELINE

Female subjects were enrolled in this single site, double blind, placebo/vehicle control 3-arm study on facial appearance and signs of photoaging. Subjects who signed consent and met all inclusion criteria and none of the exclusion criteria were enrolled at the baseline visit. Subjects presented to the research center with

a clean washed face. Subjects who did not present with a clean washed face were asked to clean with a Simple wipe.

Subjects were randomized to receive one of three study arm products: a 0.3% estriol facial moisturizer, a 0.01% estradiol facial moisturizer, or a placebo/vehicle control facial moisturizer. The assigned product was to be applied at bedtime following facial washing. 30 subjects were randomly assigned to each arm, however the arms were balanced for age, skin color, and severity of photoaging to the best degree possible. Subjects used their own self-selected other skin care products and cosmetics, as long as they contained no anti-aging ingredients, that they had used without problem for the past 30 days. Subjects received a compliance diary to record the bedtime applications.

Blood was taken at baseline to determine serum levels of estriol and estradiol for safety considerations. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline.

6.2.2 WEEK 4

Subjects returned to the research center with a clean washed face at week 4. A reminder text was sent out before the visits to encourage compliance. Diaries and study product were checked for compliance.. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline. Subjects returned to the research center at week 8.

6.2.3 WEEK 8

Subjects returned to the research center with a clean washed face at week 8. A reminder text was sent out before the visits to encourage compliance. Diaries and study product were checked for compliance. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline. Subjects returned to the research center at week 12.

6.2.4 WEEK 12

Subjects returned to the research center at week 12. Study product and diaries were checked for compliance and collected. The dermatologist investigator and subjects assessed efficacy and tolerability on a 5-point ordinal scale. Photographs were taken of all subjects with the Visia CR 4.3 using standard lighting 1 of the central, right, and left face. The subjects underwent noninvasive assessments of the face after acclimating to the research center for at least 30 minutes. The noninvasive assessments consisted of facial corneometry, elasticity, DSP for melanin at a target site, and TEWL at baseline. Blood was drawn for a study completion estriol and estradiol level. Subjects completed their study participation.

7. EFFICACY MEASURES

7.1 STUDY MEASURES

Dermatologist Investigator assessed efficacy parameters: Fine lines, wrinkles, lack of even skin tone/dark spots, lack of radiance/brightness, skin roughness (tactile), skin roughness (visual), lack of firmness, pores, hydration, elasticity, and overall appearance issues. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12.

Dermatologist Investigator assessed tolerability parameters: dryness, peeling, erythema, edema. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12.

Subject assessed efficacy parameters: Fine lines, wrinkles, lack of even skin tone/dark spots, lack of radiance/brightness, skin roughness (tactile), skin roughness (visual), lack of firmness, pores, hydration, elasticity, and overall appearance issues. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12.

Subject assessed tolerability parameters: dryness, peeling, stinging, and itching. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12.

Noninvasive Biomeasurements: Corneometry, TEWL, DSP for melanin at a target site, and elasticity measurements on the face was conducted at baseline, week 4, week 8, and week 12.

Photography: Color photographs were taken at each time point with standard 1 lighting of the central, right, and left face with a Visia CR4.3. Photographs were performed at the following time points: baseline, week 4, week 8, and week 12.

7.2 SUBJECT COMPLIANCE

The diary sheets were used to determine compliance. Subjects recorded product application and any comments on the provided weekly diary. Diary sheets remained at the study center as part of the source documentation records.

7.3 NONCOMPLIANT SUBJECTS

No subjects were found to be noncompliant. All collected data was used in the final analysis.

8. FINAL SUBJECT STATUS

86/90 subjects successfully completed the study. The subjects who discontinued were unable to return to the research facility to complete the study. The study enrolled all Fitzpatrick skin types. The study enrolled 3 Asians, 24 African Americans, and 60 Caucasians. The summary enrollment table is presented below.

Demographic Log

Subject #	FITZ I-VI	Age	Gender	Race
1	V	54	F	AA
2	III	56	F	C
3	I	57	F	C
4	IV	59	F	AA
5	VI	60	F	AA
6	I	55	F	C
7	III	57	F	C
8	II	60	F	C
9	III	60	F	C
10	V	51	F	AA
11	V	59	F	AA
12	II	53	F	C
13	IV	51	F	AA
14	V	56	F	AA
15	II	58	F	C
16	I	51	F	C
17	I	54	F	C
18	V	58	F	AA
19	II	53	F	H
20	II	53	F	C
21	II	57	F	C
22	I	60	F	C
23	II	54	F	C
24	II	53	F	C
25	V	52	F	AA
26	II	56	F	C
27	II	58	F	C
28	II	56	F	C
29	II	59	F	C
30	III	58	F	C
31	II	56	F	C
32	II	56	F	C
33	I	56	F	C
34	I	52	F	C
35	II	54	F	AS
36	II	52	F	C
37	I	56	F	C
38	I	58	F	C
39	I	52	F	C
40	II	58	F	C
41	II	51	F	C
42	II	54	F	C
43	II	51	F	C
44	V	51	F	AA
45	V	59	F	AA
46	V	57	F	AA
47	III	52	F	C
48	VI	58	F	AA
49	III	51	F	H
50	IV	53	F	AA
51	II	57	F	AS
52	I	56	F	C
53	II	54	F	C
54	II	54	F	C
55	II	57	F	C
56	II	57	F	C
57	I	60	F	C
58	I	54	F	C
59	II	57	F	C
60	I	59	F	C
61	I	59	F	C
62	II	58	F	C
63	II	60	F	C
64	V	54	F	AA
65	II	53	F	C
66	II	55	F	C
67	V	52	F	AA
68	V	56	F	AA
69	V	49	F	AA
70	II	55	F	C
71	VI	60	F	AA
72	V	54	F	AA
73	II	60	F	C
74	III	52	F	AS
75	II	60	F	C
76	I	58	F	C
77	II	51	F	C
78	II	56	F	C
79	II	56	F	C
80	II	61	F	C
81	III	61	F	H
82	VI	55	F	AA
83	V	51	F	AA
84	I	57	F	C
85	V	55	F	AA
86	II	62	F	C
87	V	58	F	AA
88	II	58	F	C
89	I	56	F	C
90	I	60	F	C

9. STUDY PRODUCTS & ADMINISTRATION

9.1 FORMULATIONS

The study formulation was attached as a separate document.

9.2 PRECAUTIONS

Study products were used in their intended fashion and not orally consumed or placed in the eyes.

9.3 STUDY PRODUCT ADMINISTRATION

The subjects applied the study product at bedtime to the entire face after washing.

9.4 PACKAGING, LABELING, DISTRIBUTION

Study products were dispensed in the packaging provided by the sponsor. Each dispenser contained 45ml of product and dispensed 0.3ml per pump.

9.5 STORAGE AND ACCOUNTABILITY OF STUDY PRODUCT

The study products were stored at room temperature in a locked, limited access area at the study site. Only the investigator and staff members designated to dispense study medication was allowed access to the study products. Study product logs were used to record the dispensation and return of all study products. The subject number/initials, and the initials and date of the person dispensing and receiving the returned study products were documented on this form.

9.6 CODE DISCLOSURE

A randomization code was maintained indicating the 30 subjects who were using the placebo/vehicle, the 30 subjects who were using the 0.3% estriol cream and the 30 subjects who were using the 0.01% estradiol cream. An independent dispenser maintained the blind and performed dispensing such that both the investigator and the subjects were blinded providing for a double-blind study design. The randomization code is presented below.

Randomization Key:
P=Placebo/vehicle control
ET=Estradiol
ES=Estriol

Subject Number	Product Randomization

1	P
2	ET
3	ES
4	ET
5	P
6	P
7	P
8	ES
9	ET
10	ES
11	P
12	P
13	ES
14	ET
15	ET
16	ES
17	P
18	P
19	ET
20	ES
21	P
22	ES
23	P
24	ET
25	P
26	ET
27	P
28	ET
29	ES
30	ES
31	P
32	ET
33	ES
34	ES
35	ET
36	ET
37	ET
38	P
39	P
40	P
41	P
42	ES
43	ET
44	ET

45	ES
46	ES
47	P
48	ET
49	ET
50	ES
51	ES
52	P
53	ES
54	ET
55	P
56	ES
57	ES
58	ET
59	P
60	ES
61	ET
62	ET
63	ES
64	ES
65	ES
66	ET
67	ET
68	P
69	ET
70	ES
71	ES
72	P
73	ET
74	ES
75	P
76	ET
77	ES
78	ES
79	ET
80	P
81	P
82	ET
83	ET
84	P
85	P
86	P
87	ES
88	ET

89	ES
90	P

10. ADVERSE EVENTS

10.1 ADVERSE REACTIONS PREVIOUSLY REPORTED

The study products had been reported to rarely produce skin irritation.

11. STATISTICAL METHODS

Along with descriptive statistics (means, standard deviations and percentages), investigator ordinal nonparametric data were analyzed using Wilcoxon signed rank test and sign test for paired comparison at different time points. The noninvasive parametric data were analyzed using paired t-test. Change was considered significant at the alpha level of 0.05.

11.1 SAMPLE SIZE RATIONALE

A sample size of 90 study subjects was chosen by the study sponsor.

11.2 SIGNIFICANCE LEVEL

Significance was defined at the $p<0.05$ level based on a two-sided test.

12. RESULTS

The results are presented in the attached Excel spreadsheets
Table 1: Corneometry
Table 2: Elasticity
Table 3: Investigator Efficacy
Table 4: Investigator Tolerability
Table 5: Laboratory Results
Table 6: Melanin Readings
Table 7: Subject Efficacy
Table 8: Subject Tolerability
Table 9: Transepidermal Water Loss (TEWL)

13. DISCUSSION

The results are discussed separately for each of the data sets.
Table 1: Corneometry
Corneometry measurements were taken from the cheek to evaluate the amount of water in the skin. A higher number is indicative of increased skin water content.

Estradiol Corneometry Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	125.30 ± 43.96			
	Week 4	28	141.50 ± 48.34	16.20 ± 47.68	13%	0.074
	Week 8	28	145.50 ± 46.08	20.20 ± 48.60	16%	**0.032**
	Week 12	28	150.93 ± 54.58	25.63 ± 47.35	20%	**0.007**

Estriol Corneometry Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	128.10 ± 46.80			
	Week 4	30	131.50 ± 55.63	3.40 ± 47.89	3%	0.700
	Week 8	30	139.23 ± 50.81	11.13 ± 53.77	9%	0.266
	Week 12	30	160.90 ± 56.56	32.80 ± 49.23	26%	**0.001**

Placebo Corneometry Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	119.10 ± 42.98			
	Week 4	29	133.66 ± 51.09	14.56 ± 39.28	12%	0.074
	Week 8	28	127.18 ± 45.83	8.08 ± 41.43	7%	0.598
	Week 12	28	128.00 ± 39.12	8.90 ± 45.96	7%	0.570

Both the estriol and the estradiol produced statistically significant increases in skin water content after 12 weeks of product use. There was a statistically significant 26% increase in skin hydration (p=0.001) after 12 weeks of use with the estriol, statistically significant 20% increase in skin hydration (p=0.007) after 12 weeks of use with the estradiol and no statistically significant improvement in skin hydration from the placebo/vehicle control.

Table 2: Elasticity
Skin elasticity measurements were taken from the cheek. The summary table is presented below

Estradiol Elasticity Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
E	Baseline	30	1.91 ± 0.38			
	Week 4	28	1.91 ± 0.39	0.00 ± 0.36	0%	0.714
	Week 8	28	1.88 ± 0.34	-0.03 ± 0.35	-2%	0.372
	Week 12	28	1.94 ± 0.40	0.02 ± 0.39	1%	0.961
VE	Baseline	30	4.03 ± 1.25			
	Week 4	28	3.75 ± 1.15	-0.27 ± 1.31	-7%	0.155
	Week 8	28	3.80 ± 1.01	-0.23 ± 1.21	-6%	0.181
	Week 12	28	3.93 ± 1.03	-0.09 ± 1.41	-2%	0.499
R	Baseline	30	126.97 ± 19.18			
	Week 4	28	135.93 ± 20.27	8.96 ± 19.86	7%	**0.007**
	Week 8	28	123.39 ± 35.32	-3.57 ± 32.32	-3%	0.790
	Week 12	28	130.89 ± 17.28	3.93 ± 19.46	3%	0.123

Estriol Elasticity Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
E	Baseline	30	1.95 ± 0.34			
	Week 4	30	1.91 ± 0.43	-0.04 ± 0.47	-2%	0.620
	Week 8	30	1.86 ± 0.42	-0.09 ± 0.39	-5%	0.206
	Week 12	30	1.87 ± 0.42	-0.08 ± 0.37	-4%	0.246
VE	Baseline	30	4.18 ± 1.16			
	Week 4	30	3.77 ± 0.97	-0.41 ± 1.22	-10%	0.077
	Week 8	30	3.83 ± 1.59	-0.35 ± 1.62	-8%	0.247
	Week 12	30	3.94 ± 1.46	-0.24 ± 1.44	-6%	0.374
R	Baseline	30	126.60 ± 24.91			
	Week 4	30	135.17 ± 30.24	8.57 ± 24.78	7%	0.068
	Week 8	30	129.60 ± 22.42	3.00 ± 25.91	2%	0.531
	Week 12	30	129.60 ± 20.03	3.00 ± 22.32	2%	0.467

Placebo Elasticity Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
E	Baseline	30	1.88 ± 0.35			
	Week 4	29	1.90 ± 0.46	0.02 ± 0.32	1%	0.562
	Week 8	28	1.95 ± 0.50	0.07 ± 0.40	4%	0.332
	Week 12	28	1.98 ± 0.40	0.10 ± 0.29	5%	0.051
VE	Baseline	30	3.96 ± 1.02			
	Week 4	29	3.97 ± 1.23	0.02 ± 0.99	0%	0.809
	Week 8	28	3.82 ± 1.01	-0.13 ± 0.94	-3%	0.500
	Week 12	28	4.13 ± 1.12	0.18 ± 1.04	4%	0.353
R	Baseline	30	127.43 ± 16.76			
	Week 4	29	128.52 ± 17.94	1.08 ± 15.55	1%	0.759
	Week 8	28	128.18 ± 17.06	0.75 ± 19.57	1%	0.796
	Week 12	28	126.57 ± 22.36	-0.86 ± 25.05	-1%	0.893

There were no consistent changes in skin elasticity induced by the estradiol, estriol, or placebo/vehicle control facial products.

Table 3: Investigator Efficacy

The investigator assessed fine lines, wrinkles, lack of even skin tone/dark spots, lack of radiance/brightness, skin roughness (tactile), skin roughness (visual), lack of firmness, pores, hydration, elasticity, and overall appearance issues. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline,

week 4, week 8, and week 12. The summary table is presented below. This table is an intragroup analysis comparing each product to itself at baseline. In the estriol arm, there was a statistically significant ($p<0.001$) 29% improvement in radiance, 31% improvement in tactile roughness, 31% improvement in visual roughness, 15% improvement in firmness, 2% improvement in hydration, 12% improvement in elasticity, and a 19% improvement in overall skin health. Similar improvements were seen in the estradiol group at week 12. There were statistically significant ($p<0.001$) increases in the estradiol group in terms of radiance with a 19% increase at week 8 and a 29% increase at week 12. Additional statistically significant ($p<0.001$) improvement was seen at week 12 in terms of visual roughness (31% improvement), tactile roughness (33% improvement), firmness (15% improvement), hydration (26% improvement), and overall skin health (18% improvement).

Estradiol Inv Efficacy Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table 0	1	2	3	4
Fine Lines	Baseline	30	2.77 ± 0.43				0.0%	0.0%	23.3%	76.7%	0.0%
	Week 4	28	2.79 ± 0.42	0.02 ± 0.00	1%	1.000	0.0%	0.0%	21.4%	78.6%	0.0%
	Week 8	28	2.79 ± 0.42	0.02 ± 0.00	1%	1.000	0.0%	0.0%	21.4%	78.6%	0.0%
	Week 12	28	2.79 ± 0.42	0.02 ± 0.00	1%	1.000	0.0%	0.0%	21.4%	78.6%	0.0%
Wrinkles	Baseline	30	2.70 ± 0.47				0.0%	0.0%	30.0%	70.0%	0.0%
	Week 4	28	2.75 ± 0.44	0.05 ± 0.00	2%	1.000	0.0%	0.0%	25.0%	75.0%	0.0%
	Week 8	28	2.75 ± 0.44	0.05 ± 0.00	2%	1.000	0.0%	0.0%	25.0%	75.0%	0.0%
	Week 12	28	2.75 ± 0.44	0.05 ± 0.00	2%	1.000	0.0%	0.0%	25.0%	75.0%	0.0%
Tone	Baseline	30	2.77 ± 0.43				0.0%	0.0%	23.3%	76.7%	0.0%
	Week 4	28	2.79 ± 0.42	0.02 ± 0.19	1%	1.000	0.0%	0.0%	21.4%	78.6%	0.0%
	Week 8	28	2.79 ± 0.42	0.02 ± 0.19	1%	1.000	0.0%	0.0%	21.4%	78.6%	0.0%
	Week 12	28	2.79 ± 0.42	0.02 ± 0.19	1%	1.000	0.0%	0.0%	21.4%	78.6%	0.0%
Radiance	Baseline	30	2.87 ± 0.35				0.0%	0.0%	13.3%	86.7%	0.0%
	Week 4	28	2.61 ± 0.57	-0.26 ± 0.46	-9%	**0.008**	0.0%	3.6%	32.1%	64.3%	0.0%
	Week 8	28	2.32 ± 0.61	-0.55 ± 0.50	-19%	**<.001**	0.0%	7.1%	53.6%	39.3%	0.0%
	Week 12	28	2.04 ± 0.58	-0.83 ± 0.52	-29%	**<.001**	0.0%	14.3%	67.9%	17.9%	0.0%
Tactile Roughness	Baseline	30	2.73 ± 0.45				0.0%	0.0%	26.7%	73.3%	0.0%
	Week 4	28	2.43 ± 0.69	-0.30 ± 0.48	-11%	**0.004**	0.0%	10.7%	35.7%	53.6%	0.0%
	Week 8	28	2.00 ± 0.61	-0.73 ± 0.44	-27%	**<.001**	0.0%	17.9%	64.3%	17.9%	0.0%
	Week 12	28	1.82 ± 0.67	-0.91 ± 0.54	-33%	**<.001**	0.0%	32.1%	53.6%	14.3%	0.0%
Visual Roughness	Baseline	30	2.73 ± 0.45				0.0%	0.0%	26.7%	73.3%	0.0%
	Week 4	28	2.46 ± 0.64	-0.27 ± 0.46	-10%	**0.008**	0.0%	7.1%	39.3%	53.6%	0.0%
	Week 8	28	2.18 ± 0.61	-0.55 ± 0.50	20%	**<.001**	0.0%	10.7%	60.7%	28.6%	0.0%
	Week 12	28	1.89 ± 0.63	-0.84 ± 0.45	-31%	**<.001**	0.0%	25.0%	60.7%	14.3%	0.0%
Firmness	Baseline	30	2.73 ± 0.45				0.0%	0.0%	26.7%	73.3%	0.0%
	Week 4	28	2.71 ± 0.46	-0.02 ± 0.19	-1%	1.000	0.0%	0.0%	28.6%	71.4%	0.0%
	Week 8	28	2.57 ± 0.63	-0.16 ± 0.39	-6%	0.063	0.0%	7.1%	28.6%	64.3%	0.0%
	Week 12	28	2.32 ± 0.67	-0.41 ± 0.50	-15%	**0.002**	0.0%	10.7%	46.4%	42.9%	0.0%
Pores	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	28	2.61 ± 0.50	0.04 ± 0.00	2%	1.000	0.0%	0.0%	39.3%	60.7%	0.0%
	Week 8	28	2.61 ± 0.50	0.04 ± 0.00	2%	1.000	0.0%	0.0%	39.3%	60.7%	0.0%
	Week 12	28	2.61 ± 0.50	0.04 ± 0.00	2%	1.000	0.0%	0.0%	39.3%	60.7%	0.0%
Hydration	Baseline	30	2.80 ± 0.41				0.0%	0.0%	20.0%	80.0%	0.0%
	Week 4	28	2.75 ± 0.44	-0.05 ± 0.26	-2%	1.000	0.0%	0.0%	25.0%	75.0%	0.0%
	Week 8	28	2.46 ± 0.64	-0.34 ± 0.56	-12%	**0.004**	0.0%	7.1%	39.3%	53.6%	0.0%
	Week 12	28	2.07 ± 0.60	-0.73 ± 0.59	-26%	**<.001**	0.0%	14.3%	64.3%	21.4%	0.0%
Elasticity	Baseline	30	2.73 ± 0.45				0.0%	0.0%	26.7%	73.3%	0.0%
	Week 4	28	2.75 ± 0.44	0.02 ± 0.00	1%	1.000	0.0%	0.0%	25.0%	75.0%	0.0%
	Week 8	28	2.71 ± 0.46	0.02 ± 0.19	1%	1.000	0.0%	0.0%	28.6%	71.4%	0.0%
	Week 12	28	2.61 ± 0.50	-0.13 ± 0.36	-5%	0.125	0.0%	0.0%	39.3%	60.7%	0.0%
Overall	Baseline	30	2.80 ± 0.41				0.0%	0.0%	20.0%	80.0%	0.0%
	Week 4	28	2.82 ± 0.39	0.02 ± 0.00	1%	1.000	0.0%	0.0%	17.9%	82.1%	0.0%
	Week 8	28	2.68 ± 0.55	-0.12 ± 0.36	-4%	0.125	0.0%	3.6%	25.0%	71.4%	0.0%
	Week 12	28	2.29 ± 0.53	-0.51 ± 0.51	-18%	**<.001**	0.0%	3.0%	64.3%	32.1%	0.0%

Estriol Inv Efficacy Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table 0	1	2	3	4
Fine Lines	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	30	2.57 ± 0.50	0.00 ± 0.00	0%	1.000	0.0%	0.0%	43.3%	56.7%	0.0%
	Week 8	30	2.57 ± 0.50	0.00 ± 0.00	0%	1.000	0.0%	0.0%	43.3%	56.7%	0.0%
	Week 12	30	2.50 ± 0.57	-0.07 ± 0.25	-3%	1.000	0.0%	3.3%	43.3%	53.3%	0.0%
Wrinkles	Baseline	30	2.53 ± 0.51				0.0%	0.0%	46.7%	53.3%	0.0%
	Week 4	30	2.53 ± 0.51	0.00 ± 0.00	0%	1.000	0.0%	0.0%	46.7%	53.3%	0.0%
	Week 8	30	2.53 ± 0.51	0.00 ± 0.00	0%	1.000	0.0%	0.0%	46.7%	53.3%	0.0%
	Week 12	30	2.50 ± 0.57	-0.03 ± 0.18	-1%	1.000	0.0%	3.3%	43.3%	53.3%	0.0%
Tone	Baseline	30	2.73 ± 0.45				0.0%	0.0%	26.7%	73.3%	0.0%
	Week 4	30	2.73 ± 0.45	0.00 ± 0.00	0%	1.000	0.0%	0.0%	26.7%	73.3%	0.0%
	Week 8	30	2.73 ± 0.45	0.00 ± 0.00	0%	1.000	0.0%	0.0%	26.7%	73.3%	0.0%
	Week 12	30	2.73 ± 0.45	0.00 ± 0.00	0%	1.000	0.0%	0.0%	26.7%	73.3%	0.0%
Radiance	Baseline	30	2.87 ± 0.35				0.0%	0.0%	13.3%	86.7%	0.0%
	Week 4	30	2.67 ± 0.48	-0.20 ± 0.41	-7%	**0.031**	0.0%	0.0%	33.3%	66.7%	0.0%
	Week 8	30	2.30 ± 0.70	-0.57 ± 0.57	-20%	**<.001**	0.0%	13.3%	43.3%	43.3%	0.0%
	Week 12	29	2.03 ± 0.78	-0.83 ± 0.71	-29%	**<.001**	0.0%	27.6%	41.4%	31.0%	0.0%
Tactile Roughness	Baseline	30	2.70 ± 0.47				0.0%	0.0%	30.0%	70.0%	0.0%
	Week 4	30	2.37 ± 0.72	-0.33 ± 0.48	-12%	**0.004**	0.0%	13.3%	36.7%	50.0%	0.0%
	Week 8	30	2.03 ± 0.81	-0.67 ± 0.61	-25%	**<.001**	0.0%	30.0%	36.7%	33.3%	0.0%
	Week 12	29	1.86 ± 0.79	-0.84 ± 0.60	-31%	**<.001**	0.0%	37.9%	37.9%	24.1%	0.0%
Visual Roughness	Baseline	30	2.70 ± 0.47				0.0%	0.0%	30.0%	70.0%	0.0%
	Week 4	30	2.37 ± 0.67	-0.33 ± 0.48	-12%	**0.004**	0.0%	10.0%	43.3%	46.7%	0.0%
	Week 8	30	2.07 ± 0.78	-0.63 ± 0.56	-23%	**<.001**	0.0%	26.7%	40.0%	33.3%	0.0%
	Week 12	29	1.86 ± 0.79	-0.84 ± 0.60	-31%	**<.001**	0.0%	37.9%	37.9%	24.1%	0.0%
Firmness	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	30	2.57 ± 0.50	0.00 ± 0.00	0%	1.000	0.0%	0.0%	43.3%	56.7%	0.0%
	Week 8	30	2.33 ± 0.66	-0.23 ± 0.43	-9%	**0.016**	0.0%	10.0%	46.7%	43.3%	0.0%
	Week 12	29	2.17 ± 0.71	-0.39 ± 0.56	-15%	**0.005**	0.0%	17.2%	48.3%	34.5%	0.0%
Pores	Baseline	30	2.50 ± 0.51				0.0%	0.0%	50.0%	50.0%	0.0%
	Week 4	30	2.50 ± 0.51	0.00 ± 0.00	0%	1.000	0.0%	0.0%	50.0%	50.0%	0.0%
	Week 8	30	2.50 ± 0.51	0.00 ± 0.00	0%	1.000	0.0%	0.0%	50.0%	50.0%	0.0%
	Week 12	29	2.48 ± 0.51	-0.02 ± 0.00	-1%	1.000	0.0%	0.0%	51.7%	48.3%	0.0%
Hydration	Baseline	30	2.70 ± 0.47				0.0%	0.0%	30.0%	70.0%	0.0%
	Week 4	30	2.57 ± 0.57	-0.13 ± 0.35	-5%	0.125	0.0%	3.3%	36.7%	60.0%	0.0%
	Week 8	30	2.23 ± 0.77	-0.47 ± 0.51	-17%	**0.001**	0.0%	20.0%	36.7%	43.3%	0.0%
	Week 12	29	2.10 ± 0.82	-0.60 ± 0.50	-22%	**<.001**	0.0%	27.6%	34.5%	37.9%	0.0%
Elasticity	Baseline	30	2.67 ± 0.48				0.0%	0.0%	33.3%	66.7%	0.0%
	Week 4	30	2.57 ± 0.50	-0.10 ± 0.31	-4%	0.250	0.0%	0.0%	43.3%	56.7%	0.0%
	Week 8	30	2.50 ± 0.57	-0.17 ± 0.38	-6%	0.063	0.0%	3.3%	43.3%	53.3%	0.0%
	Week 12	29	2.34 ± 0.67	-0.32 ± 0.54	-12%	**0.008**	0.0%	10.3%	44.8%	44.8%	0.0%
Overall	Baseline	30	2.87 ± 0.35				0.0%	0.0%	13.3%	86.7%	0.0%
	Week 4	30	2.73 ± 0.45	-0.13 ± 0.35	-5%	0.125	0.0%	0.0%	26.7%	73.3%	0.0%
	Week 8	30	2.40 ± 0.56	-0.47 ± 0.51	-16%	**0.001**	0.0%	3.3%	53.3%	43.3%	0.0%
	Week 12	29	2.31 ± 0.60	0.56 ± 0.51	19%	**<.001**	0.0%	6.9%	55.2%	37.9%	0.0%

Placebo Inv Efficacy Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table 0	1	2	3	4
Fine Lines	Baseline	30	2.70 ± 0.47				0.0%	0.0%	30.0%	70.0%	0.0%
	Week 4	29	2.69 ± 0.47	-0.01 ± 0.00	0%	1.000	0.0%	0.0%	31.0%	69.0%	0.0%
	Week 8	28	2.68 ± 0.48	-0.02 ± 0.00	-1%	1.000	0.0%	0.0%	32.1%	67.9%	0.0%
	Week 12	28	2.68 ± 0.48	-0.02 ± 0.00	-1%	1.000	0.0%	0.0%	32.1%	67.9%	0.0%
Wrinkles	Baseline	30	2.60 ± 0.50				0.0%	0.0%	40.0%	60.0%	0.0%
	Week 4	29	2.59 ± 0.50	-0.01 ± 0.00	-1%	1.000	0.0%	0.0%	41.4%	58.6%	0.0%
	Week 8	28	2.57 ± 0.50	-0.03 ± 0.00	-1%	1.000	0.0%	0.0%	42.9%	57.1%	0.0%
	Week 12	28	2.57 ± 0.50	0.03 ± 0.00	1%	1.000	0.0%	0.0%	42.9%	57.1%	0.0%
Tone	Baseline	30	2.63 ± 0.49				0.0%	0.0%	36.7%	63.3%	0.0%
	Week 4	29	2.62 ± 0.49	-0.01 ± 0.00	0%	1.000	0.0%	0.0%	37.9%	62.1%	0.0%
	Week 8	28	2.61 ± 0.50	-0.03 ± 0.00	-1%	1.000	0.0%	0.0%	39.3%	60.7%	0.0%
	Week 12	28	2.61 ± 0.50	-0.03 ± 0.00	-1%	1.000	0.0%	0.0%	39.3%	60.7%	0.0%
Radiance	Baseline	30	2.83 ± 0.38				0.0%	0.0%	16.7%	83.3%	0.0%
	Week 4	29	2.55 ± 0.69	-0.28 ± 0.45	-10%	**0.008**	0.0%	10.3%	24.1%	65.5%	0.0%
	Week 8	28	2.29 ± 0.76	-0.55 ± 0.58	-19%	**0.001**	0.0%	17.9%	35.7%	46.4%	0.0%
	Week 12	28	2.39 ± 0.74	-0.44 ± 0.57	-16%	**0.003**	0.0%	14.3%	32.1%	53.6%	0.0%
Tactile Roughness	Baseline	30	2.80 ± 0.41				0.0%	0.0%	20.0%	80.0%	0.0%
	Week 4	29	2.48 ± 0.69	-0.32 ± 0.47	-11%	**0.004**	0.0%	10.3%	31.0%	58.6%	0.0%
	Week 8	28	2.29 ± 0.76	-0.51 ± 0.64	-18%	**0.002**	0.0%	17.9%	35.7%	46.4%	0.0%
	Week 12	28	2.43 ± 0.74	-0.37 ± 0.62	-13%	**0.008**	0.0%	14.3%	28.6%	57.1%	0.0%
Visual Roughness	Baseline	30	2.80 ± 0.41				0.0%	0.0%	20.0%	80.0%	0.0%
	Week 4	29	2.52 ± 0.69	-0.28 ± 0.45	-10%	**0.008**	0.0%	10.3%	27.6%	62.1%	0.0%
	Week 8	28	2.36 ± 0.73	-0.44 ± 0.57	-16%	**0.003**	0.0%	14.3%	35.7%	50.0%	0.0%
	Week 12	28	2.43 ± 0.74	-0.37 ± 0.62	-13%	**0.008**	0.0%	14.3%	28.6%	57.1%	0.0%
Firmness	Baseline	30	2.60 ± 0.50				0.0%	0.0%	40.0%	60.0%	0.0%
	Week 4	29	2.59 ± 0.50	0.01 ± 0.00	1%	1.000	0.0%	0.0%	41.4%	58.6%	0.0%
	Week 8	28	2.50 ± 0.58	-0.10 ± 0.26	-4%	1.000	0.0%	3.6%	42.9%	53.6%	0.0%
	Week 12	28	2.43 ± 0.69	-0.17 ± 0.36	-7%	0.125	0.0%	10.7%	35.7%	53.6%	0.0%
Pores	Baseline	30	2.33 ± 0.48				0.0%	0.0%	66.7%	33.3%	0.0%
	Week 4	29	2.31 ± 0.47	-0.02 ± 0.00	-1%	1.000	0.0%	0.0%	69.0%	31.0%	0.0%
	Week 8	28	2.29 ± 0.46	-0.05 ± 0.00	-2%	1.000	0.0%	0.0%	71.4%	28.6%	0.0%
	Week 12	28	2.32 ± 0.48	-0.01 ± 0.19	-1%	1.000	0.0%	0.0%	67.9%	32.1%	0.0%
Hydration	Baseline	30	2.80 ± 0.41				0.0%	0.0%	20.0%	80.0%	0.0%
	Week 4	29	2.79 ± 0.41	-0.01 ± 0.00	0%	1.000	0.0%	0.0%	20.7%	79.3%	0.0%
	Week 8	28	2.57 ± 0.63	-0.23 ± 0.42	-8%	**0.031**	0.0%	7.1%	28.6%	64.3%	0.0%
	Week 12	28	2.61 ± 0.63	-0.19 ± 0.39	-7%	0.063	0.0%	7.1%	25.0%	67.9%	0.0%
Elasticity	Baseline	30	2.73 ± 0.45				0.0%	0.0%	26.7%	73.3%	0.0%
	Week 4	29	2.72 ± 0.45	-0.01 ± 0.00	0%	1.000	0.0%	0.0%	27.6%	72.4%	0.0%
	Week 8	28	2.68 ± 0.48	-0.05 ± 0.19	-2%	1.000	0.0%	0.0%	32.1%	67.9%	0.0%
	Week 12	28	2.68 ± 0.55	-0.05 ± 0.19	-2%	1.000	0.0%	3.6%	25.0%	71.4%	0.0%
Overall	Baseline	30	2.87 ± 0.35				0.0%	0.0%	13.3%	86.7%	0.0%
	Week 4	29	2.83 ± 0.38	0.04 ± 0.19	1%	1.000	0.0%	0.0%	17.2%	82.8%	0.0%
	Week 8	28	2.71 ± 0.46	-0.15 ± 0.36	-5%	0.125	0.0%	0.0%	28.6%	71.4%	0.0%
	Week 12	28	2.68 ± 0.61	-0.19 ± 0.39	-7%	0.063	0.0%	7.1%	17.9%	75.0%	0.0%

The estriol and estradiol results were also compared to each other and to the placebo/vehicle control. The intergroup summary table is presented below.

Inv Efficacy											
	Week 12										
Mann-Whitney two tailed unpaired	**Fine Lines**	**Wrinkles**	**Tone**	**Radiance**	**Tactile Roughness**	**Visual Roughness**	**Firmness**	**Pores**	**Hydration**	**Elasticity**	**Overall**
Mean Estradiol	0.00	0.00	-0.04	-0.86	-0.93	-0.86	-0.43	0.00	-0.75	-0.14	-0.54
Mean Estriol	-0.07	-0.03	0.00	-0.83	-0.83	-0.83	-0.38	0.00	-0.59	-0.31	-0.55
Sample Estradiol SD	0.00	0.00	0.19	0.52	0.54	0.45	0.50	0.00	0.59	0.36	0.51
Sample Estriol SD	0.25	0.18	0.00	0.71	0.60	0.60	0.56	0.00	0.50	0.54	0.51
% Change	NA	NA	-100%	-3%	-11%	-3%	-11%	NA	-22%	117%	3%
Difference	-0.07	-0.03	0.04	0.03	0.10	0.03	0.05	0.00	0.16	-0.17	-0.02
Difference SD	1.98	1.00	1.00	1.21	2.04	0.55	0.78	0.00	2.04	4.93	1.18
Estradiol v. Estriol p =	0.228	0.450	0.418	0.758	0.487	0.760	0.601	1.000	0.314	0.214	0.905
Median Estradiol	0.00	0.00	0.00	-1.00	-1.00	-1.00	0.00	0.00	-1.00	0.00	-1.00
Median Estriol	0.00	0.00	0.00	-1.00	-1.00	-1.00	0.00	0.00	-1.00	0.00	-1.00
Mean Estradiol	0.00	0.00	-0.04	-0.86	-0.93	-0.86	-0.43	0.00	-0.75	-0.14	-0.54
Mean Placebo	0.00	0.00	0.00	-0.43	-0.36	-0.36	-0.14	0.04	-0.18	-0.04	-0.18
Sample Estradiol SD	0.00	0.00	0.19	0.52	0.54	0.45	0.50	0.00	0.59	0.36	0.51
Sample Placebo SD	0.00	0.00	0.00	0.57	0.62	0.62	0.36	0.19	0.39	0.19	0.39
% Change	NA	NA	-100%	-50%	-62%	-58%	-67%	NA	-76%	-75%	-67%
Difference	0.00	0.00	0.04	0.43	0.57	0.50	0.29	0.04	0.57	0.11	0.36
Difference SD	1.98	1.00	1.00	1.21	2.04	0.55	0.78	0.00	2.04	4.93	1.18
Estradiol v. Placebo p =	1.000	1.000	0.434	**0.004**	**<.001**	**<.001**	**0.020**	0.434	**<.001**	0.186	**0.006**
Median Estradiol	0.00	0.00	0.00	-1.00	-1.00	-1.00	0.00	0.00	-1.00	0.00	-1.00
Median Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mean Estriol	-0.07	-0.03	0.00	-0.83	-0.83	-0.83	-0.38	0.00	-0.59	-0.31	-0.55
Mean Placebo	0.00	0.00	0.00	-0.43	-0.36	-0.36	-0.14	0.04	-0.18	-0.04	-0.18
Sample Estriol SD	0.25	0.18	0.00	0.71	0.60	0.60	0.56	0.00	0.50	0.54	0.51
Sample Placebo SD	0.00	0.00	0.00	0.57	0.62	0.62	0.36	0.19	0.39	0.19	0.39
% Change	-100%	-100%	NA	-48%	-57%	-57%	-62%	NA	-70%	-88%	-68%
Difference	0.07	0.03	0.00	0.40	0.47	0.47	0.24	0.04	0.41	0.27	0.37
Difference SD	1.98	1.00	0.00	11.80	12.78	12.78	5.93	1.00	11.79	7.87	11.79
Estriol v. Placebo p =	0.228	0.450	1.000	**0.029**	**0.003**	**0.003**	0.077	0.426	**0.002**	**0.016**	**0.004**
Median Estriol	0.00	0.00	0.00	-1.00	-1.00	-1.00	0.00	0.00	-1.00	0.00	-1.00
Median Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

There were no statistically significant differences between the study products at week 4 or week 8. The most dramatic improvement and differentiation from placebo/vehicle control occurred at week 12. There was no difference between the estriol and estradiol in the eyes of the investigator, however both products were demonstrated to be superior to placebo/vehicle control in several qualities. The estriol demonstrated a statistically significant 48% improvement in radiance, 57% improvement in tactile roughness, 57% improvement in visual roughness, 70% improvement in hydration, 88% improvement in skin elasticity, and 68% improvement in overall skin health as compared to placebo/vehicle control. The estradiol demonstrated a statistically significant 50% improvement in radiance, 62% improvement in tactile roughness, 58% improvement in visual roughness, 67% improvement in firmness, 76% improvement in hydration, and 67% improvement in overall skin health as compared to placebo/vehicle control.

Table 4: Investigator Tolerability

The dermatologist evaluated tolerability in terms of dryness, peeling, erythema, edema. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. The summary table is presented below.

Estradiol Inv Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table				
							0	1	2	3	4
Dryness	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Peeling	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Erythema	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Edema	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%

Estriol Inv Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table				
							0	1	2	3	4
Dryness	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Peeling	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Erythema	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Edema	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	30	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%

Placebo Inv Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table				
							0	1	2	3	4
Dryness	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	29	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Peeling	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	29	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Erythema	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	29	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
Edema	Baseline	30	0.00 ± 0.00				100.0%	0.0%	0.0%	0.0%	0.0%
	Week 4	29	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 8	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%
	Week 12	28	0.00 ± 0.00	0.00 ± 0.00	NA	1.000	100.0%	0.0%	0.0%	0.0%	0.0%

No tolerability issues were identified by the investigator in any of the study arms.

Table 5: Laboratory Results
Estriol and estradiol levels were drawn on all subjects to evaluate possible systemic absorption of the study creams. The summary table is presented below.

	Baseline		Week 12	
T-test two tailed paired	**Estradiol**	**Estriol**	**Estradiol**	**Estriol**
Mean Estradiol	12.92	0.10	16.60	0.10
Baseline Estradiol			12.92	0.10
Sample Estradiol SD	7.19	NA	8.99	NA
% Change			28%	0%
Change From Baseline			3.68	0.00
Baseline Change SD			6.40	NA
Estradiol v. Baseline p =			**0.037**	NA
Median Estradiol	9.80	0.10	14.40	0.10
Mean Estriol	23.07	NA	20.95	0.10
Baseline Estriol			23.07	NA
Sample Estriol SD	28.51	NA	18.38	0.00
% Change			-9%	
Change From Baseline			-2.11	
Baseline Change SD			20.29	NA
Estriol v. Baseline p =			0.313	NA
Median Estriol	11.60	NA	12.70	0.10
Mean Placebo	14.48	0.10	14.93	0.10
Baseline Placebo			14.48	0.10
Sample Placebo SD	11.71	NA	10.18	0.00
% Change			3%	0%
Change From Baseline			0.45	0.00
Baseline Change SD			5.41	NA
Placebo v. Baseline p =			0.861	NA
Median Placebo	11.00	0.10	10.70	0.10

There was no statistically significant change in estriol levels in the blood from baseline to week 12. There was a slight increase in estradiol levels from baseline to week 12, but this change is within laboratory error going from 12.92 to 16.60.

Table 6: Melanin Readings
Melanin readings were taken with a dermaspectrophotometer from the cheek. The summary table is presented below.

Estradiol Melanin Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	41.51 ± 9.80			
	Week 4	28	40.70 ± 10.14	-0.81 ± 1.62	-2%	**0.041**
	Week 8	28	40.58 ± 9.98	-0.93 ± 2.13	-2%	0.063
	Week 12	28	40.82 ± 10.70	-0.69 ± 2.30	-2%	0.227

Estriol Melanin Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	41.77 ± 11.91			
	Week 4	30	41.04 ± 11.76	-0.73 ± 1.36	-2%	**0.007**
	Week 8	30	40.87 ± 11.91	-0.91 ± 1.47	-2%	**0.002**
	Week 12	30	41.19 ± 11.24	-0.59 ± 2.32	-1%	0.177

Placebo Melanin Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	40.95 ± 11.67			
	Week 4	29	41.24 ± 12.05	0.29 ± 1.69	1%	0.829
	Week 8	28	41.51 ± 12.51	0.56 ± 2.84	1%	0.863
	Week 12	28	41.49 ± 12.07	0.54 ± 2.44	1%	0.887

Estrogens have been thought to possibly induce skin pigmentation as an unwanted side effect. No increase in pigmentation was noted with the estriol or estradiol products. As a matter of fact, there was a slight 1-2% decrease in facial pigmentation in both the estriol and estradiol arms.

Table 7: Subject Efficacy

The subjects assessed efficacy in terms of fine lines, wrinkles, lack of even skin tone/dark spots, lack of radiance/brightness, skin roughness (tactile), skin roughness (visual), lack of firmness, pores, hydration, elasticity, and overall appearance issues. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. The subjects were unable to distinguish between the estriol, estradiol, and placebo/vehicle control, as they only had exposure to one product. Excellent ratings were given to all products. The summary table is presented below.

Estradiol Subj Efficacy Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table 0	1	2	3	4
Fine Lines	Baseline	30	2.53 ± 0.51				0.0%	0.0%	46.7%	53.3%	0.0%
	Week 4	28	2.29 ± 0.71	-0.25 ± 0.80	-10%	**0.031**	0.0%	14.3%	42.9%	42.9%	0.0%
	Week 8	28	2.04 ± 0.69	-0.50 ± 0.99	-20%	**0.002**	0.0%	21.4%	53.6%	25.0%	0.0%
	Week 12	28	1.71 ± 0.90	-0.82 ± 0.85	-32%	**<.001**	10.7%	25.0%	46.4%	17.9%	0.0%
Wrinkles	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	28	2.36 ± 0.62	-0.21 ± 0.50	-8%	0.063	0.0%	7.1%	50.0%	42.9%	0.0%
	Week 8	28	2.18 ± 0.72	-0.39 ± 0.83	-15%	**0.004**	0.0%	17.9%	46.4%	35.7%	0.0%
	Week 12	28	1.79 ± 0.88	-0.78 ± 0.88	-30%	**0.001**	7.1%	28.6%	42.9%	21.4%	0.0%
Tone	Baseline	30	2.63 ± 0.49				0.0%	0.0%	36.7%	63.3%	0.0%
	Week 4	28	2.25 ± 0.59	-0.36 ± 0.57	-15%	**0.005**	0.0%	7.1%	60.7%	32.1%	0.0%
	Week 8	28	2.18 ± 0.77	-0.45 ± 0.88	-17%	**0.015**	0.0%	21.4%	39.3%	39.3%	0.0%
	Week 12	28	1.86 ± 1.08	-0.78 ± 1.17	-29%	**0.003**	14.3%	21.4%	28.6%	35.7%	0.0%
Radiance	Baseline	30	2.43 ± 0.50				0.0%	0.0%	56.7%	43.3%	0.0%
	Week 4	28	2.18 ± 0.61	-0.25 ± 0.83	-10%	0.129	0.0%	7.1%	71.4%	17.9%	3.6%
	Week 8	28	2.00 ± 0.72	-0.43 ± 0.79	-18%	**0.022**	3.6%	14.3%	60.7%	21.4%	0.0%
	Week 12	28	1.64 ± 0.95	-0.79 ± 0.93	-32%	**0.001**	14.3%	25.0%	42.9%	17.9%	0.0%
Tactile Roughness	Baseline	30	2.23 ± 0.43				0.0%	0.0%	76.7%	23.3%	0.0%
	Week 4	28	1.86 ± 0.52	-0.38 ± 0.50	-17%	**0.003**	0.0%	21.4%	71.4%	7.1%	0.0%
	Week 8	28	1.64 ± 0.83	-0.59 ± 0.79	-26%	**0.002**	3.6%	46.4%	32.1%	17.9%	0.0%
	Week 12	28	1.43 ± 0.79	-0.80 ± 0.77	-36%	**<.001**	10.7%	42.9%	39.3%	7.1%	0.0%
Visual Roughness	Baseline	30	2.30 ± 0.47				0.0%	0.0%	70.0%	30.0%	0.0%
	Week 4	28	1.82 ± 0.67	-0.48 ± 0.89	-21%	**0.002**	3.6%	21.4%	64.3%	10.7%	0.0%
	Week 8	28	1.61 ± 0.88	-0.69 ± 0.90	-30%	**0.001**	7.1%	42.9%	32.1%	17.9%	0.0%
	Week 12	28	1.36 ± 0.83	-0.94 ± 0.79	-41%	**<.001**	14.3%	42.9%	35.7%	7.1%	0.0%
Firmness	Baseline	30	2.60 ± 0.50				0.0%	0.0%	40.0%	60.0%	0.0%
	Week 4	28	2.29 ± 0.71	-0.31 ± 0.81	-12%	**0.021**	0.0%	14.3%	42.9%	42.9%	0.0%
	Week 8	28	2.11 ± 0.69	-0.49 ± 0.99	-19%	**0.003**	0.0%	17.9%	53.6%	28.6%	0.0%
	Week 12	28	1.86 ± 0.89	-0.74 ± 0.80	-29%	**0.001**	7.1%	25.0%	42.9%	25.0%	0.0%
Pores	Baseline	30	2.50 ± 0.51				0.0%	0.0%	50.0%	50.0%	0.0%
	Week 4	28	2.36 ± 0.68	-0.14 ± 0.91	-6%	0.195	0.0%	10.7%	42.9%	46.4%	0.0%
	Week 8	28	2.07 ± 0.72	-0.43 ± 0.89	-17%	**0.006**	0.0%	21.4%	50.0%	28.6%	0.0%
	Week 12	28	1.93 ± 0.94	-0.57 ± 0.83	-23%	**0.003**	7.1%	25.0%	35.7%	32.1%	0.0%
Hydration	Baseline	30	2.47 ± 0.51				0.0%	0.0%	53.3%	46.7%	0.0%
	Week 4	28	2.04 ± 0.84	-0.43 ± 0.79	-17%	**0.012**	0.0%	28.6%	42.9%	25.0%	3.6%
	Week 8	28	1.86 ± 0.85	-0.61 ± 0.87	-25%	**0.003**	0.0%	39.3%	39.3%	17.9%	3.6%
	Week 12	28	1.50 ± 0.88	-0.97 ± 1.02	-39%	**<.001**	10.7%	42.9%	32.1%	14.3%	0.0%
Elasticity	Baseline	30	2.63 ± 0.49				0.0%	0.0%	36.7%	63.3%	0.0%
	Week 4	28	2.36 ± 0.62	-0.28 ± 0.46	-10%	**0.008**	0.0%	7.1%	50.0%	42.9%	0.0%
	Week 8	28	2.14 ± 0.65	-0.49 ± 0.64	-19%	**0.002**	0.0%	14.3%	57.1%	28.6%	0.0%
	Week 12	28	1.79 ± 0.88	-0.85 ± 0.93	-32%	**<.001**	10.7%	17.9%	53.6%	17.9%	0.0%
Overall	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	28	2.32 ± 0.67	-0.25 ± 0.53	-10%	**0.016**	0.0%	10.7%	46.4%	42.9%	0.0%
	Week 8	28	2.18 ± 0.72	-0.39 ± 0.74	-15%	**0.008**	0.0%	17.9%	46.4%	35.7%	0.0%
	Week 12	28	1.75 ± 0.93	-0.82 ± 0.93	-32%	**<.001**	10.7%	25.0%	42.9%	21.4%	0.0%

Estriol Subj Efficacy Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table 0	1	2	3	4
Fine Lines	Baseline	30	2.40 ± 0.50				0.0%	0.0%	60.0%	40.0%	0.0%
	Week 4	30	2.23 ± 0.57	-0.17 ± 0.38	-7%	0.063	0.0%	6.7%	63.3%	30.0%	0.0%
	Week 8	30	2.07 ± 0.64	-0.33 ± 0.61	-14%	**0.013**	0.0%	13.3%	70.0%	13.3%	3.3%
	Week 12	30	1.70 ± 0.65	-0.70 ± 0.70	-29%	**<.001**	3.3%	30.0%	60.0%	6.7%	0.0%
Wrinkles	Baseline	30	2.37 ± 0.49				0.0%	0.0%	63.3%	36.7%	0.0%
	Week 4	30	2.27 ± 0.58	-0.10 ± 0.31	-4%	0.250	0.0%	6.7%	60.0%	33.3%	0.0%
	Week 8	30	2.13 ± 0.63	-0.23 ± 0.50	-10%	**0.039**	0.0%	13.3%	60.0%	26.7%	0.0%
	Week 12	30	1.80 ± 0.89	-0.57 ± 0.82	-24%	**0.003**	6.7%	30.0%	40.0%	23.3%	0.0%
Tone	Baseline	30	2.43 ± 0.50				0.0%	0.0%	56.7%	43.3%	0.0%
	Week 4	30	2.43 ± 0.57	0.00 ± 0.53	0%	1.000	0.0%	0.0%	60.0%	36.7%	3.3%
	Week 8	30	2.37 ± 0.72	-0.07 ± 0.69	-3%	0.634	0.0%	6.7%	56.7%	30.0%	6.7%
	Week 12	30	1.93 ± 0.74	-0.50 ± 0.82	-21%	**0.008**	3.3%	16.7%	66.7%	10.0%	3.3%
Radiance	Baseline	30	2.43 ± 0.50				0.0%	0.0%	56.7%	43.3%	0.0%
	Week 4	30	2.27 ± 0.52	-0.17 ± 0.59	-7%	0.195	0.0%	3.3%	66.7%	30.0%	0.0%
	Week 8	30	2.13 ± 0.63	-0.30 ± 0.65	-12%	**0.032**	0.0%	13.3%	60.0%	26.7%	0.0%
	Week 12	30	1.67 ± 0.76	-0.77 ± 0.94	-32%	**0.001**	10.0%	20.0%	63.3%	6.7%	0.0%
Tactile Roughness	Baseline	30	2.23 ± 0.43				0.0%	0.0%	76.7%	23.3%	0.0%
	Week 4	30	1.97 ± 0.49	-0.27 ± 0.58	-12%	**0.038**	0.0%	13.3%	76.7%	10.0%	0.0%
	Week 8	30	1.83 ± 0.53	-0.40 ± 0.67	-18%	**0.009**	0.0%	23.3%	70.0%	6.7%	0.0%
	Week 12	30	1.40 ± 0.72	-0.83 ± 0.91	-37%	**<.001**	10.0%	43.3%	43.3%	3.3%	0.0%
Visual Roughness	Baseline	30	2.13 ± 0.35				0.0%	0.0%	86.7%	13.3%	0.0%
	Week 4	30	1.93 ± 0.52	-0.20 ± 0.55	-9%	0.089	0.0%	16.7%	73.3%	10.0%	0.0%
	Week 8	30	1.77 ± 0.63	-0.37 ± 0.81	-17%	**0.027**	3.3%	23.3%	66.7%	6.7%	0.0%
	Week 12	30	1.53 ± 0.63	-0.60 ± 0.77	-28%	**0.001**	6.7%	33.3%	60.0%	0.0%	0.0%
Firmness	Baseline	30	2.70 ± 0.47				0.0%	0.0%	30.0%	70.0%	0.0%
	Week 4	30	2.40 ± 0.67	-0.30 ± 0.80	-11%	**0.016**	0.0%	10.0%	40.0%	50.0%	0.0%
	Week 8	30	2.17 ± 0.70	-0.53 ± 0.88	-20%	**0.001**	0.0%	16.7%	50.0%	33.3%	0.0%
	Week 12	30	1.77 ± 0.86	-0.93 ± 0.83	-35%	**<.001**	6.7%	30.0%	43.3%	20.0%	0.0%
Pores	Baseline	30	2.40 ± 0.50				0.0%	0.0%	60.0%	40.0%	0.0%
	Week 4	30	2.30 ± 0.60	-0.10 ± 0.40	-4%	0.313	0.0%	6.7%	56.7%	36.7%	0.0%
	Week 8	30	2.03 ± 0.67	-0.37 ± 0.56	-15%	**0.006**	0.0%	16.7%	60.7%	13.3%	3.3%
	Week 12	30	1.73 ± 0.69	-0.67 ± 0.71	-28%	**<.001**	3.3%	30.0%	56.7%	10.0%	0.0%
Hydration	Baseline	30	2.53 ± 0.51				0.0%	0.0%	46.7%	53.3%	0.0%
	Week 4	30	2.30 ± 0.65	-0.23 ± 0.50	-9%	**0.039**	0.0%	6.7%	60.0%	30.0%	3.3%
	Week 8	30	2.07 ± 0.58	-0.47 ± 0.57	-18%	**0.001**	0.0%	13.3%	66.7%	20.0%	0.0%
	Week 12	30	1.73 ± 0.78	-0.80 ± 0.92	-32%	**0.001**	6.7%	26.7%	53.3%	13.3%	0.0%
Elasticity	Baseline	30	2.37 ± 0.49				0.0%	0.0%	63.3%	36.7%	0.0%
	Week 4	30	2.20 ± 0.61	-0.17 ± 0.53	-7%	0.150	0.0%	6.7%	70.0%	20.0%	3.3%
	Week 8	30	2.07 ± 0.58	-0.30 ± 0.90	-13%	**0.021**	0.0%	10.0%	76.7%	10.0%	3.3%
	Week 12	30	1.70 ± 0.75	0.67 ± 0.84	28%	**0.001**	6.7%	26.7%	56.7%	10.0%	0.0%
Overall	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	30	2.30 ± 0.60	-0.27 ± 0.52	-10%	**0.023**	0.0%	3.3%	66.7%	26.7%	3.3%
	Week 8	30	2.07 ± 0.64	-0.50 ± 0.86	-19%	**0.002**	0.0%	13.3%	70.0%	13.3%	3.3%
	Week 12	30	1.80 ± 0.81	-0.77 ± 0.73	-30%	**<.001**	6.7%	23.3%	53.3%	16.7%	0.0%

Placebo Subj Efficacy Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table 0	1	2	3	4
Fine Lines	Baseline	30	2.67 ± 0.48				0.0%	0.0%	33.3%	66.7%	0.0%
	Week 4	29	2.38 ± 0.62	0.29 ± 0.53	11%	**0.016**	0.0%	6.9%	48.3%	44.8%	0.0%
	Week 8	28	2.14 ± 0.71	-0.52 ± 0.58	-20%	**0.001**	0.0%	17.9%	50.0%	32.1%	0.0%
	Week 12	28	1.86 ± 0.89	-0.81 ± 0.74	-30%	**<.001**	7.1%	25.0%	42.9%	25.0%	0.0%
Wrinkles	Baseline	30	2.60 ± 0.50				0.0%	0.0%	40.0%	60.0%	0.0%
	Week 4	29	2.55 ± 0.57	-0.05 ± 0.33	-2%	0.750	0.0%	0.0%	48.3%	48.3%	3.4%
	Week 8	28	2.36 ± 0.62	-0.24 ± 0.50	-9%	0.055	0.0%	7.1%	50.0%	42.9%	0.0%
	Week 12	28	2.00 ± 0.94	-0.60 ± 0.79	-23%	**0.003**	10.7%	10.7%	46.4%	32.1%	0.0%
Tone	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	29	2.28 ± 0.65	-0.29 ± 0.90	-11%	**0.021**	0.0%	10.3%	51.7%	37.9%	0.0%
	Week 8	28	2.18 ± 0.67	-0.39 ± 0.99	-15%	**0.008**	0.0%	14.3%	53.6%	32.1%	0.0%
	Week 12	28	2.07 ± 0.81	-0.50 ± 0.92	-19%	**0.010**	3.6%	17.9%	46.4%	32.1%	0.0%
Radiance	Baseline	30	2.73 ± 0.52				0.0%	0.0%	30.0%	66.7%	3.3%
	Week 4	29	2.31 ± 0.66	-0.42 ± 0.83	-15%	**0.006**	0.0%	10.3%	48.3%	41.4%	0.0%
	Week 8	28	2.11 ± 0.63	-0.63 ± 0.99	-23%	**0.001**	0.0%	14.3%	60.7%	25.0%	0.0%
	Week 12	28	1.96 ± 0.79	-0.77 ± 0.97	-28%	**0.001**	3.6%	21.4%	50.0%	25.0%	0.0%
Tactile Roughness	Baseline	30	2.33 ± 0.48				0.0%	0.0%	66.7%	33.3%	0.0%
	Week 4	29	2.14 ± 0.64	-0.20 ± 0.71	-8%	0.250	0.0%	10.3%	69.0%	17.2%	3.4%
	Week 8	28	1.89 ± 0.63	-0.44 ± 0.83	-19%	**0.029**	0.0%	25.0%	60.7%	14.3%	0.0%
	Week 12	28	1.75 ± 0.80	-0.58 ± 0.96	-25%	**0.012**	7.1%	25.0%	53.6%	14.3%	0.0%
Visual Roughness	Baseline	30	2.40 ± 0.50				0.0%	0.0%	60.0%	40.0%	0.0%
	Week 4	29	2.07 ± 0.65	-0.33 ± 0.72	-14%	**0.027**	0.0%	17.2%	58.6%	24.1%	0.0%
	Week 8	28	1.82 ± 0.72	-0.58 ± 0.89	-24%	**0.001**	0.0%	35.7%	46.4%	17.9%	0.0%
	Week 12	28	1.68 ± 0.90	-0.72 ± 0.89	-30%	**0.001**	10.7%	28.6%	42.9%	17.9%	0.0%
Firmness	Baseline	30	2.57 ± 0.50				0.0%	0.0%	43.3%	56.7%	0.0%
	Week 4	29	2.41 ± 0.63	-0.15 ± 0.52	-6%	0.188	0.0%	6.9%	44.8%	48.3%	0.0%
	Week 8	28	2.18 ± 0.61	-0.39 ± 0.73	-15%	**0.027**	0.0%	10.7%	60.7%	28.6%	0.0%
	Week 12	28	2.00 ± 0.77	0.57 ± 0.88	22%	**0.007**	3.6%	17.9%	53.6%	25.0%	0.0%
Pores	Baseline	30	2.37 ± 0.49				0.0%	0.0%	63.3%	36.7%	0.0%
	Week 4	29	2.31 ± 0.60	-0.06 ± 0.59	-2%	0.578	0.0%	6.9%	55.2%	37.9%	0.0%
	Week 8	28	1.93 ± 0.66	-0.44 ± 0.53	-19%	**0.005**	0.0%	25.0%	57.1%	17.9%	0.0%
	Week 12	28	1.82 ± 0.82	-0.55 ± 0.79	-23%	**0.003**	7.1%	21.4%	53.6%	17.9%	0.0%
Hydration	Baseline	30	2.63 ± 0.61				0.0%	0.0%	43.3%	50.0%	6.7%
	Week 4	29	2.24 ± 0.69	-0.39 ± 0.58	-15%	**0.012**	0.0%	10.3%	58.6%	27.6%	3.4%
	Week 8	28	2.04 ± 0.69	-0.60 ± 0.92	-23%	**0.007**	0.0%	21.4%	53.6%	25.0%	0.0%
	Week 12	28	1.82 ± 0.72	-0.81 ± 0.96	-31%	**0.001**	3.6%	25.0%	57.1%	14.3%	0.0%
Elasticity	Baseline	30	2.67 ± 0.55				0.0%	0.0%	36.7%	60.0%	3.3%
	Week 4	29	2.45 ± 0.69	-0.22 ± 0.56	-8%	0.078	0.0%	6.9%	44.8%	44.8%	3.4%
	Week 8	28	2.21 ± 0.63	-0.45 ± 0.69	-17%	**0.008**	0.0%	10.7%	57.1%	32.1%	0.0%
	Week 12	28	2.11 ± 0.74	-0.56 ± 0.84	-21%	**0.005**	3.6%	10.7%	57.1%	28.6%	0.0%
Overall	Baseline	30	2.67 ± 0.48				0.0%	0.0%	33.3%	66.7%	0.0%
	Week 4	29	2.45 ± 0.69	-0.22 ± 0.54	-8%	0.073	0.0%	6.9%	44.8%	44.8%	3.4%
	Week 8	28	2.14 ± 0.65	-0.52 ± 0.99	-20%	**0.002**	0.0%	14.3%	57.1%	28.6%	0.0%
	Week 12	28	2.11 ± 0.83	-0.56 ± 0.92	-21%	**0.006**	3.6%	17.9%	42.9%	35.7%	0.0%

Table 8: Subject Tolerability
The subjects assessed tolerability in terms of dryness, peeling, stinging, and itching. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, week 4, week 8, and week 12. The summary tables are presented below. The subjects did not identify any tolerability issues.

Estradiol Subj Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table				
							0	1	2	3	4
Dryness	Baseline	30	1.03 ± 1.00				36.7%	33.3%	20.0%	10.0%	0.0%
	Week 4	28	0.89 ± 0.92	-0.14 ± 1.09	-14%	0.570	35.7%	46.4%	14.3%	0.0%	3.6%
	Week 8	28	0.79 ± 1.03	-0.25 ± 1.39	-24%	0.542	50.0%	32.1%	10.7%	3.6%	3.6%
	Week 12	28	0.32 ± 0.61	-0.71 ± 1.06	-69%	**0.006**	75.0%	17.9%	7.1%	0.0%	0.0%
Peeling	Baseline	30	0.17 ± 0.46				86.7%	10.0%	3.3%	0.0%	0.0%
	Week 4	28	0.21 ± 0.50	0.05 ± 0.33	29%	0.750	82.1%	14.3%	3.6%	0.0%	0.0%
	Week 8	28	0.32 ± 0.86	0.15 ± 0.85	93%	0.438	82.1%	10.7%	3.6%	0.0%	3.6%
	Week 12	28	0.21 ± 0.57	0.05 ± 0.69	29%	0.813	85.7%	7.1%	7.1%	0.0%	0.0%
Stinging	Baseline	30	0.07 ± 0.37				96.7%	0.0%	3.3%	0.0%	0.0%
	Week 4	28	0.18 ± 0.55	0.11 ± 0.42	168%	1.000	89.3%	3.6%	7.1%	0.0%	0.0%
	Week 8	28	0.14 ± 0.45	0.08 ± 0.47	114%	0.500	89.3%	7.1%	3.6%	0.0%	0.0%
	Week 12	28	0.11 ± 0.42	0.04 ± 0.58	61%	0.750	92.9%	3.6%	3.6%	0.0%	0.0%
Itching	Baseline	30	0.20 ± 0.48				83.3%	13.3%	3.3%	0.0%	0.0%
	Week 4	28	0.18 ± 0.48	-0.02 ± 0.43	-11%	0.813	85.7%	10.7%	3.6%	0.0%	0.0%
	Week 8	28	0.21 ± 0.69	0.01 ± 0.82	7%	0.938	89.3%	3.6%	3.6%	3.6%	0.0%
	Week 12	28	0.18 ± 0.55	-0.02 ± 0.69	-11%	0.938	89.3%	3.6%	7.1%	0.0%	0.0%

Estriol Subj Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table				
							0	1	2	3	4
Dryness	Baseline	30	1.13 ± 1.11				40.0%	20.0%	26.7%	13.3%	0.0%
	Week 4	30	1.20 ± 1.00	0.07 ± 0.58	6%	0.582	30.0%	30.0%	30.0%	10.0%	0.0%
	Week 8	30	0.93 ± 0.87	-0.20 ± 1.13	-18%	0.370	36.7%	36.7%	23.3%	3.3%	0.0%
	Week 12	30	0.73 ± 0.91	-0.40 ± 1.25	-35%	0.104	50.0%	33.3%	10.0%	6.7%	0.0%
Peeling	Baseline	30	0.30 ± 0.70				83.3%	3.3%	13.3%	0.0%	0.0%
	Week 4	30	0.37 ± 0.72	0.07 ± 0.58	22%	0.625	76.7%	10.0%	13.3%	0.0%	0.0%
	Week 8	30	0.33 ± 0.71	0.03 ± 0.81	11%	0.938	80.0%	6.7%	13.3%	0.0%	0.0%
	Week 12	30	0.23 ± 0.57	-0.07 ± 0.74	-22%	0.688	83.3%	10.0%	6.7%	0.0%	0.0%
Stinging	Baseline	30	0.40 ± 0.81				76.7%	10.0%	10.0%	3.3%	0.0%
	Week 4	30	0.27 ± 0.58	-0.13 ± 0.51	-33%	1.000	80.0%	13.3%	6.7%	0.0%	0.0%
	Week 8	30	0.30 ± 0.70	-0.10 ± 0.80	-25%	0.625	83.3%	3.3%	13.3%	0.0%	0.0%
	Week 12	30	0.20 ± 0.55	-0.20 ± 0.71	-50%	0.188	86.7%	6.7%	6.7%	0.0%	0.0%
Itching	Baseline	30	0.60 ± 1.13				73.3%	6.7%	10.0%	6.7%	3.3%
	Week 4	30	0.33 ± 0.66	-0.27 ± 0.83	-44%	0.125	76.7%	13.3%	10.0%	0.0%	0.0%
	Week 8	30	0.33 ± 0.71	-0.27 ± 1.14	-44%	0.313	80.0%	6.7%	13.3%	0.0%	0.0%
	Week 12	30	0.20 ± 0.48	-0.40 ± 1.13	-67%	0.078	83.3%	13.3%	3.3%	0.0%	0.0%

Placebo Subj Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value	Frequency Table				
							0	1	2	3	4
Dryness	Baseline	30	1.67 ± 1.18				23.3%	20.0%	23.3%	33.3%	0.0%
	Week 4	29	1.34 ± 1.08	-0.32 ± 0.84	-19%	0.115	31.0%	17.2%	37.9%	13.8%	0.0%
	Week 8	28	1.11 ± 0.92	-0.56 ± 1.00	-34%	**0.012**	32.1%	28.6%	35.7%	3.6%	0.0%
	Week 12	28	0.96 ± 0.92	-0.70 ± 0.99	-42%	**0.006**	39.3%	28.6%	28.6%	3.6%	0.0%
Peeling	Baseline	30	0.43 ± 0.73				70.0%	16.7%	13.3%	0.0%	0.0%
	Week 4	29	0.48 ± 0.74	0.05 ± 0.68	11%	0.813	65.5%	20.7%	13.8%	0.0%	0.0%
	Week 8	28	0.29 ± 0.53	-0.15 ± 0.55	-34%	0.164	75.0%	21.4%	3.6%	0.0%	0.0%
	Week 12	28	0.18 ± 0.48	-0.25 ± 0.66	-59%	**0.039**	85.7%	10.7%	3.6%	0.0%	0.0%
Stinging	Baseline	30	0.20 ± 0.48				83.3%	13.3%	3.3%	0.0%	0.0%
	Week 4	29	0.24 ± 0.58	0.04 ± 0.50	21%	0.875	82.8%	10.3%	6.9%	0.0%	0.0%
	Week 8	28	0.14 ± 0.45	-0.06 ± 0.38	-29%	0.375	89.3%	7.1%	3.6%	0.0%	0.0%
	Week 12	28	0.21 ± 0.57	0.01 ± 0.47	7%	1.000	85.7%	7.1%	7.1%	0.0%	0.0%
Itching	Baseline	30	0.37 ± 0.61				70.0%	23.3%	6.7%	0.0%	0.0%
	Week 4	29	0.24 ± 0.69	-0.13 ± 0.90	-34%	0.496	86.2%	6.9%	3.4%	3.4%	0.0%
	Week 8	28	0.21 ± 0.63	-0.15 ± 0.85	-42%	0.301	85.7%	10.7%	0.0%	3.6%	0.0%
	Week 12	28	0.14 ± 0.45	-0.22 ± 0.57	-61%	0.078	89.3%	7.1%	3.6%	0.0%	0.0%

Table 9: Transepidermal Water Loss (TEWL)
TEWL measurements were taken from the cheek. TEWL is a measure of the water leaving the skin and a lower number indicates superior skin barrier function. The summary table is presented below.

Estradiol TEWL Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	8.31 ± 2.16			
	Week 4	28	8.23 ± 2.03	-0.08 ± 2.18	-1%	0.900
	Week 8	28	8.35 ± 1.96	0.04 ± 1.87	0%	0.851
	Week 12	28	8.59 ± 1.61	0.28 ± 1.78	3%	0.369

Estriol TEWL Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	8.30 ± 2.33			
	Week 4	30	8.86 ± 2.39	0.56 ± 2.41	7%	0.209
	Week 8	30	9.51 ± 2.65	1.21 ± 2.71	15%	**0.021**
	Week 12	30	9.38 ± 2.31	1.08 ± 2.55	13%	**0.027**

Placebo TEWL Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	p-value
Reading	Baseline	30	8.53 ± 2.17			
	Week 4	29	8.34 ± 1.69	-0.19 ± 1.89	-2%	0.659
	Week 8	28	9.36 ± 2.44	0.83 ± 2.32	10%	0.069
	Week 12	28	8.86 ± 2.24	0.33 ± 2.42	4%	0.472

The estriol produced a statistically significant increase in water leaving the skin of 13% at week 12 (p=0.027). The estradiol and placebo/vehicle control demonstrated barrier neutrality. None of the products were shown to induce irritation as evidenced by the subject tolerability ratings.

14. SUMMARY

14.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint was the statistically significant improvement in the dermatologist investigator's assessment of overall facial appearance in subjects using the study products for 12 weeks, comparing the 0.3% estriol, 0.01% estradiol, and placebo/vehicle control groups to each other, as well as to baseline. The estriol and estradiol formulations produced a statistically significant improvement in facial appearance as compared to placebo/vehicle control. The primary efficacy endpoint was met.

14.2 TOLERABILITY ENDPOINT

The tolerability endpoint was the investigator-assessed absence of skin irritation from the study products at any time during the 12-week study. No skin irritation occurred. The tolerability endpoint was met.

14.3 PRIMARY SAFETY ENDPOINT

The safety endpoint was the overall incidence of all adverse events reported during the study. No adverse events occurred during the conduct of the study. The primary safety endpoint was met.

14.4 SECONDARY SAFETY ENDPOINT

The secondary safety endpoint was the absence of elevated serum estriol and estradiol levels in all subjects. The secondary safety endpoint was met.