A New Cosmeceutical for Estrogen Deficient Skin

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Disclosures

- Allergan
- Galderma
- Ortho Derm
- Almirall
- Ferndale
- J & J
- L’Oreal
- Aclaris
- P & G
- Dermira
- Sienna
- Revance
- Sonoma
Estrogen receptors and the skin

Estrogen receptors (ERs) in skin cells

- ERα and ERβ (keratinocytes, fibroblasts, and cells of epidermal appendages)
- ERβ more widespread
- ER expression highest on face, scalp and vagina
- Estrogen increases ER expression

Two pathways:
1. Genomic (DNA related)
2. Non-genomic

ER signaling results in visible effects on skin

Estrogen has been shown to¹-⁴:

↑ skin rigidity, elasticity, wound healing
↑ hydration, epidermal thickness, blood flow
↑ extracellular matrix components
  (collagen, elastin, fibrillin)

↑ moisture retention
  (hyaluronic acid, mucopolysaccharides, sebum production)
↑ thickness of cutaneous layers
  (epidermis: keratinocyte proliferation, dermis: fibroblast proliferation)
↓ wrinkling

Evidence of estrogen’s effect on skin comes primarily from studies of the application of exogenous estrogen to post-menopausal women

Estrogen is an essential component to skin functioning, health and wellness

The picture of Estrogen Deficient Skin (EDS)\textsuperscript{1-3}

**Histological Changes**

- Significant decrease in Collagen I & III and type 1 procollagen
- Decrease in glycoaminoglycan content
- Decrease in TGF-\(\beta\)1 expression
- Reduced expression of IGF-1 receptors and production of IGF-1
- Reduced ROS defense activity

**What the Patient experiences**

- Dryness
- Pruritis
- Increased wrinkles
- Thinning
- Atrophy
- Impaired wound healing

**References:**
2. Thornton MJ. *Dermo-Endocrinology.* 2013;5:2, 264-270
Significant collagen loss after onset of menopause

-30% LOSS
OF DERMAL COLLAGEN WITHIN
THE FIRST 5 YEARS OF MENOPAUSE

-2% LOSS
OF DERMAL COLLAGEN
IN EACH SUBSEQUENT YEAR

COLLAGEN LOSS IS MORE
CLOSELY RELATED TO
DURATION OF ESTROGEN
DEFICIENCY THAN TO
CHRONOLOGICAL AGE

EDS a serious condition for dermatology

Not a sudden event

• Between ages 45–55 (average: 51)\(^1\)
• Symptoms arise gradually during perimenopause\(^2\)

Patient Education needed

• Women generally don’t relate skin changes to menopause
  • Some associated “Dryness”
• Virtually none are aware of collagen loss associated with EDS\(^2\)
  • When informed of 30% loss statistic, menopausal women increased skin concerns to level of “hot flashes”
• Dermatologists rarely discuss with patients

Importance is growing

- Mean life expectancy, now 76.8, has increased 30 years since 1900\(^1\)
- Onset of menopause has been delayed by only 5 years in the same time so women spend more of life in menopause\(^3\)
- \(~6,000\) women enter menopause daily\(^2\)
- \(~46\) million women over 55 by 2020\(^2\)

Addressing EDS with HRT\textsuperscript{1-2}

- Indicated to treat postmenopausal symptoms, e.g., hot flashes, etc.
- Multiple documented ancillary benefits for the skin
  - Studies show improvement in moisture, thickness and signs of aging
  - One double-blind placebo controlled study showed no statistical difference in dryness, itching, bruising or thinning
  - An open-label study showed no significant difference in histology, including collagen content or skin thickness
- Declining use due to fears of coronary artery disease, stroke, hyperplasia or cancer of the endometrium, breast & ovaries
- Women turning to bioidentical HRT
  - No controlled studies

Addressing EDS with topical estrogen\(^1\-^2\)

- Topical estradiol & estradiol valerate
  - Indicated for VVA; use for EDS is off-label
  - 23+ studies evaluating effect on EDS
  - Concentrations of 0.01% - 0.062%
  - Documented benefits for the skin including skin thickness, dryness, wrinkles, etc
  - Risks of telangiectasias, irritation and tenderness
  - Some evidence of systemic absorption and, therefore, the associated risks (coronary artery disease, stroke, cancer, etc)

Addressing EDS with SERMs

- Selective estrogen receptor modulators (SERMs)
  - Phytoestrogens (soy, isoflavones, genistein)
  - Lack evidence of ER activation
  - Most positive effects were increased hydration & improvement in wrinkles
  - Most data regarding increased collagen and improved epidermal thickness as not significant
  - Effects most likely due to vehicle or antioxidant activity

Need for an EDS solution


Ideal solution:
A product that has estrogen’s beneficial cutaneous effects without the potential for effects elsewhere in the body.
Methyl Estradiolpropanoate (MEP):

\[
\text{Methyl } 3-((8R,9S,13S,14S,16R,17S)3,17\text{-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-16-yl)propanoate}
\]

**Synthetic estrogenic sterol ester**
- 1% ERβ binding affinity of estradiol
- No “off target” activity: rapidly converted by hydrolytic enzymes to inactivated hydrolysis carboxylic enzymes

**A new class of cosmeceutical agent**

**Non-hormonal Estrogen Receptor Agonist (NERA)**
ESTROGEN VS. MEP

CUTANEOUS EFFECTS
- Increased moisture retention
- Increased elasticity
- Increased collagen
- Improved wound healing

ESTROGEN → SYSTEMIC EFFECTS
Cutaneous and systemic effects
- Reactivation of the menstrual cycle
- Proliferation of uterine endometrium

MEP → NO SYSTEMIC EFFECTS
Cutaneous effects only
- Increased risk of heart disease
- Increased risk of cancer

Estrogen readily travels through the bloodstream
MEP is quickly degraded in the bloodstream to a single inactive metabolite
MEP Technology

Non-hormonal estrogen receptor agonist (NERA)

- Unlike estradiol, MEP is not a hormone
  - None of the potential risks

- Unlike SERMs, MEP is an agonist, not a modulator
  - Mode of action is known and demonstrably effective
Promising preclinical data for MEP precursor

“Compound C” is a molecule of similar structure to MEP and used for clinical proof of concept studies.

Preclinical findings:
- Produced the same healthy thickening response of the epithelium and vaginal wall subtypes as estradiol.

NOTE: MEP has not been and will not be tested on animals.
Promising preclinical data for MEP precursor, cont.

“Compound C” is a molecule of similar structure to MEP and used for clinical proof of concept studies

Preclinical findings:
- No undesired effect on the uterus at supra-therapeutic doses
- Subcutaneous dosing indicated potential for large safety margin compared to estradiol

NOTE: MEP has not been and will not be tested on animals.
Clinical Study

A Double-Blind Randomized Pilot Study Evaluating the Safety and Efficacy of Topical MEP in the Facial Appearance Improvement of Estrogen Deficient Females

Zoe Diana Draelos, MD

PUBLISHED NOVEMBER 2018
Safety study design

- Randomized, placebo-controlled
- N=60 (40 active; 20 placebo)
- Ages 53-80; all amenorrheic for 3+ years
- Applied twice daily to face for 12 weeks
- Blood samples at baseline and week 12
  - Evaluated* for presence of MEP and inactive metabolite (alkyl carboxylate E161,0,8)
- Investigator and subjects evaluated tolerability

* MicroConstants, Inc. San Diego, CA.
Safety study results

After 12 weeks of MEP use:

- BQL* for all at baseline & 6 weeks
- Week 12: detectable levels** for inactive metabolite; BQL for all but 1 for MEP
- No adverse events
- Investigator- and subject-rated tolerability of “Excellent”
  - No burning or itching
- MEP was rapidly converted to an inactive serum metabolite in the bloodstream

* Below Quantifiable Limit (20pg/mL)
** 27 – 1480 pg/mL for nearly all non-placebo subjects
Efficacy study design

• Randomized, placebo-controlled
• N=80 (60 active; 20 placebo)
• Ages 53-80 years, all amenorrheic for 3-10 years
• Rao-Goldman Wrinkle 3+; Glogau Aging II-IV
• Applied twice daily for 14 weeks
• Vehicle possessed minimal moisturizing qualities
  (water, glycerin, benzyl alcohol, magnesium aluminum silicate,
  saccharide isomerate, xanthan gum, phenoxyethanol, and ethylhexylglycerin)
• Subject compliance determined by diary entries and product weights
Efficacy study results

Blinded Investigator-assessed % improvement at 14 weeks

<table>
<thead>
<tr>
<th>VISUAL CRITERIA ASSESSMENT</th>
<th>MEP + VEHICLE (% IMPROVEMENT)</th>
<th>PLACEBO (% IMPROVEMENT)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRYNESS</td>
<td>54%</td>
<td>16%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>DULLNESS</td>
<td>39%</td>
<td>8%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>THICKNESS</td>
<td>20%</td>
<td>2%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>LAXITY</td>
<td>19%</td>
<td>6%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>ERYTHEMA</td>
<td>11%</td>
<td>NO CHANGE</td>
<td>P=0.001</td>
</tr>
<tr>
<td>ATROPHY</td>
<td>9%</td>
<td>NO CHANGE</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>FINE LINES</td>
<td>8%</td>
<td>2%</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

79/80 subjects completed study (1 subject missed 14-week visit for reasons unrelated to study product)

Statistical relevance was not achieved for deep wrinkles or telangiectasias
The effect of MEP on skin dryness

The study was designed to eliminate any moisturizer effect from the vehicle... The vehicle in many formulations is responsible for the observed benefits, not the hero ingredient... This was not the case in this research. Only the MEP could have produced the observations seen.
Upregulation of Fibroblast ER expression

Fibroblast ER positivity: estrogen receptor expression before and after MEP Treatment

BASELINE: no ER (+) fibroblasts
14 WEEKS’ MEP: 11 ER (+) fibroblasts

“Absent any other known mode of action of MEP, it is presumably the estrogen receptor binding activity that accounted for these findings. This novel ingredient uniquely addresses appearance issues common in estrogen deficient females.” — Zoe Diana Draelos, MD
Study conclusions

- Topical MEP is safe
  - Lack of active MEP in serum
  - Presence of carboxylic acid MEP inactive metabolite

- Topical MEP produced statistically improved investigator observations in:
  - Dryness
  - Dullness
  - Thickness
  - Laxity
  - Erythema
  - Atrophy
  - Fine lines
A Single Center Open-Label Study Evaluating the Efficacy of a Skin Care Regimen Containing Methyl Estradiolpropanoate (MEP) on Treating Estrogen Deficient Skin (EDS)

Joel L. Cohen, MD, FAAD
AboutSkin Research, LLC - Greenwood Village, CO

Objective:
to evaluate the efficacy and safety of Emepelle, a skin care regimen containing Methyl Estradiolpropanoate for the treatment of Estrogen Deficient Skin. The secondary objective is to assess patient tolerability and satisfaction.

Materials & Methods:
Period: 20 weeks
Application: Serum AM; Cream PM
Subjects: 15 Females
Age Range: 53-80 years of age; amenorrheic for 3 – 10 years
Skin Types: Fitzpatrick skin types I-IV; Glogau aging II-IV

Photography Endpoint:
The primary photography endpoint is the investigator obtained before and after photographs at baseline and weeks 8, 14 and 20.

Primary Efficacy Endpoint:
Improvement in visible signs of estrogen deficient skin as assessed by the investigator:
• Fitzpatrick-Goldman Classification of Wrinkling & Elastosis
• Alexiades-Armenakas Comprehensive Grading Scale
• Facial Hydration Scale
• Clinician Global Aesthetic Improvement Score (GAIS)

Secondary Efficacy Endpoint:
Improvement in visible signs of estrogen deficient skin as assessed by the subjects:
• Subject Global Aesthetic Improvement Score (GAIS)
• Quality of Life (QoL) Assessment

Tolerability Endpoint:
Investigator-assessed absence of skin irritation following application of investigational products.
<table>
<thead>
<tr>
<th>Serum - AM</th>
<th>Cream - PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% MEP</td>
<td>2% MEP</td>
</tr>
<tr>
<td>4% Niacinamide</td>
<td>8% Niacinamide</td>
</tr>
<tr>
<td>Vitamin C (ethyl ascorbic acid)</td>
<td>0.1% Retinol &amp; 0.05% Hydroxypinacolone Retinoate</td>
</tr>
<tr>
<td>Vitamin E (tocopheryl acetate)</td>
<td>Tetrapeptide-26</td>
</tr>
<tr>
<td>Ferulic Acid</td>
<td>Palmitoyl Oligopeptide &amp; Palmitoyl Tetrapeptide-7</td>
</tr>
<tr>
<td>Pentapeptide-28</td>
<td>Shea Butter, Grape Seed Oil, Apricot Kernel Oil</td>
</tr>
<tr>
<td>Dipeptide-4</td>
<td></td>
</tr>
<tr>
<td>Tetrapeptide-26</td>
<td></td>
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<tr>
<td>Hyaluronic Acid</td>
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</tbody>
</table>

Tolerability was good
Several had mild, transitory “burning/stinging” commonly associated with mild retinoid dermatitis
Only one showed mild erythema; none showed tenderness
Results at 8 weeks

• 50% or more of subjects report improvement in wrinkles, thickness and integrity, dullness, texture, hydration and color

• On a 0 to 5 Facial Hydration Scale, 100% of study participants showed at least one step improvement and 64% saw two steps or more

• Subjects showed 34% improvement in texture on the Alexiades-Armenakas Grading Scale

• QoL: 91% said Skin “more comfortable”; skin “looked better”; menopausal skin issues “somewhat alleviated”

• Investigator: “Eight weeks into this 20 weeks study, we are already seeing some very encouraging results – especially ... skin texture and hydration... I anticipate significant improvement at weeks 14 and 20.”
Subject reported improved skin thickness & texture; Investigator noted improved hydration & dyschromia

Age: 53

Unretouched photographs of patients at baseline and after morning use of Emepelle Serum and evening use of Emepelle Night Cream for 8 weeks
Investigator noted improvement in all categories except keratosis and telangiectasia; significant improvement in texture

Age: 60

Unretouched photographs of patients at baseline and after morning use of Emepelle Serum and evening use of Emepelle Night Cream for 8 weeks
Both Subject and Investigator noted improvement in all categories except keratosis and telangiectasia; significant improvement in hydration

Age: 60

Baseline

8 Weeks

Photos courtesy Joel L. Cohen, MD, Colorado, USA