theraderm®
CLINICAL SKIN CARE

A 12 Week, Single Center Clinical Trial

Evaluating the Effectiveness of Eternox Peptide Crème & NuPeel Natural Enzyme Peel

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Purpose

This clinical study was conducted to assess the efficacy & safety of Eternox Peptide Crème & NuPeel Natural Enzyme Peel when used by females on the face & neck.

A combination of clinical grading, pinch recoil, Cutometer measurements, Corneometer measurements, Ultrasound measurements, Profilometric analysis (using silicone replica), full thickness 2 mm skin biopsy & self assessment analysis will be used to establish an improvement from baseline to final visit.

Subject Enrollment

15 subjects meeting the eligibility requirements were enrolled in this study

Subjects meet the following conditions for study participation:

1. **Skin Types:** Fitzpatrick types I, II, and III.
2. **Women** 39 - 60 years of age
3. Glogau score of II-III where lines & wrinkles **(in the range of 3-6 on a 10 point scale)** are present in the crow's foot area.
4. Skin laxity scores around the jaw and/or neck areas in the range of **3-6 on a 10 point scale.**
5. **NOVA meter** readings of 160 or less at the baseline reading. Exceptions may be approved by the Investigator.
6. Good general health & **FREE** of any disease state or physical condition **(e.g., hair, scars, tattoos, etc.)** which might impair evaluations of the test sites or increase the health risk to the subject by study participation.

7. Willingness to **have clinical examinations,** non-invasive bio-instrumentation, skin biopsies and photographs taken of the face. Willingness to cooperate and participate with all study requirements and to report any adverse symptoms immediately.

8. Willingness to **discontinue** the use of all facial products other than the assigned test materials and their regular brands of glamour products. The glamour products must be the subject's regular brand and have been used for a minimum of one month prior to the start of the study.

9. Willingness to **remove makeup** approximately 30 minutes or longer prior to each scheduled clinic visit. No other topical products should be applied to the face until the study visit has been completed.

10. Willingness NOT to **begin the use** of any new brands of skin or hair care products for the duration of the study.

11. Willingness to **use sunscreens & protective head cover** to avoid sunburn on the face.

12. Willingness to **refrain from using sunless tanners** on the face or artificially tan the face.

13. Willingness to **undergo a 3-5 day washout** from regular facial moisturizers or facial topical products (regular brands of non-moisturizing cleanser and glamour products are acceptable).

The Fitzpatrick skin classification is based on the skin's unprotected response to the first 30-45 minutes of sun exposure after a winter season without sun exposure. The categories of the skin types are as follows:

Fitzpatrick Skin Classification

I. Always burns easily; never tans.
II. Always burns easily; tans minimally
III. Burns moderately; tans gradually
IV. Burns minimally; always tans well
V. Rarely burns; tans profusely
VI. Never burns; deeply pigmented

Modified Glogau Classification

I. **Mild:** no keratoses or scarring; little wrinkling
II. **Moderate:** early actinic keratoses – slight yellow skin; discoloration; early wrinkling – parallel smile line
III. **Advanced:** actinic keratoses – obvious yellow skin; discoloration with telangiectasia; wrinkling – present at rest
IV. **Severe:** actinic keratoses; skin cancers have occurred; wrinkling – much cutis laxa of actinic, gravitational, and dynamic origin

Conduct of Study

STUDY DESIGN

This single-center, controlled usage study evaluated the efficacy and safety of using Eternox Peptide Crème & NuPeel Natural Enzyme Peel together. The study lasted for 12 weeks & involved the following visits: Day 1 (baseline), 15 minutes post regimen application, Week 6 and Week 12. Trial assessments included visual grading, pinch recoil measurements, Cutometer measurements, Ultrasound measurements, NOVA meter measurements, skin biopsy & Self-Assessment Questionnaires. Subjects had VISIA photographs taken at the baseline and final visits. Five subjects had a 2mm biopsy taken on the face at the baseline & final visits.

SCHEDULE OF PROCEDURES

PROCEDURES	BASELINE	15 MINS POST REGIMEN APPLICATION	WEEK 6	WEEK 12
Safety & Efficacy Grading: Face & Neck	X		X	X
Pinch Recoil: Left Eye Area	X		X	X
Cutometer: Left Cheek	X		X	X
Ultrasound: Right Side of the Face	X		X	X
NOVA meter of Right Cheek		X	X	X
Silicone Replicas (Right or left periocular eye area selected by Investigator)	X			X
VISIA Photographs will be taken of the front, right and left sides of the face	X			X
Subject will complete a Self-Assessment Questionnaire	X		X	X
A board certified dermatologist will take a 2 mm full thickness skin biopsy and samples will be analyzed by ProPath Laboratories.	X			X

Conduct of the Study

PROCEDURES

CLINICAL GRADING: The following clinical grading was performed at each study visit:

The Fitzpatrick skin classification is based on the skin's unprotected response to the first 30-45 minutes of sun exposure after a winter season without sun exposure. The categories of the skin types are as follows:

SAFETY EVALUATIONS

Subjects were graded globally at each of the grading locations **(face & neck)** for objective irritation **(erythema, edema, & scaling)** as well as subjective irritation **(burning, stinging, itching, tightness, tingling)** using a four **(4) point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).**

EFFICACY EVALUATIONS

The following efficacy parameters were assessed using 10 point scales where:
0=none, 1<3=mild, 4<6=moderate and 7<9=severe (half-points may be used).

Face:

» Fine Lines **(0 = none, 9 = numerous, deep fine lines)**

» Coarse Wrinkles **(0 = none, 9 = numerous, deep wrinkles)**

» Glabellar Lines **(0 = none, 9 = numerous, deep fine lines)**

» Tactile Roughness - Left cheek only **(0 = smooth and 9 = rough/coarse to the touch)**

» Firmness/Elasticity **(0= firm, tight appearing skin with good stretch properties, 9=loose appearing skin with poor stretch properties)**

» Defined Contours **(0=well defined tight skin that contours the underlying anatomical structures of the face & jaw, 9=sagging skin that poorly contour the underlying anatomical structures of the face and jaw)**

» Evenness of Skin Tone **(0= very blotchy, uneven color and 9=no blotchiness, smooth even color)**

» Skin Clarity **(0=dull, matte finish; 9=bright radiant finish)**

» Overall Facial Appearance **(0=unhealthy, dull aged appearance; 9=bright, healthy, youthful appearance)**

Neck:

» Tactile Roughness **(0 = smooth and 9 = rough/coarse to the touch)**

» Firmness/Elasticity **(0= firm, tight appearing skin with good stretch properties, 9=loose appearing skin with poor stretch properties)**

» Left or Defined Contours **(0=well defined tight skin that contours the underlying anatomical structures of the neck, 9=sagging skin that poorly contour the underlying anatomical structures of the neck)**

Conduct of the Study

CLINICAL GRADING (Continued): Pinch Recoil measurements were preformed in triplicate & were timed to hundredths of a second to assess elasticity & resiliency. Pinch Recoil was assessed by pinching the skin at the edge of the left eye area (Crow's Foot Area) between the thumb & forefinger. The skin was held in place approximately 3 seconds & a stopwatch was started upon release. The time that was taken for the skin to return to its original conformation was measured in hundredths of a second. Based on skin structure or tightness, a pinch recoil measurement may not have been obtainable for a given individual.

CUTOMETER SEM 575

Cutometer SEM 575 **(Courage & Khazaka)** measurements were be taken on the left cheek, in line with the center of the eye on the ocular bone. Three-hundred **(300)** mbar of negative pressure was applied & released through an 8-mm probe. The movement of the skin into & out of the probe was recorded during the application & release of suction & values in millimeters **(mm)** were reported for resiliency & recoil. As the skin became more elastic, scores for resiliency & recoil increased.

ULTRASOUND

Ultrasound measurements were performed to assess the density and thickness of the facial skin in the right crow's foot area. Measurements were performed using a 50 MHz ultrasonic transducer interfaced to a DUB 6100 OEM System **(Taberna, Pro Medicum, AG).**

NOVA METER DPM 9003

Female subjects had **Nova DPM 9003** measures taken on the right cheek. This device measures the moisture content in the stratum corneum **(SC)** by an electrical capacitance method. The measurement has no units, but is proportional to the dielectric constant of the surface layers of the skin & increases as the skin becomes more hydrated. The readings are directly related to the skin's electrical capacitance **(picoFarads).** Subjects equilibrated in the clinic for at least 15 minutes, & then a measurement was performed in triplicate on a right cheek **(at the intersection of lines extending down from the corner of the eye and horizontally across the bottom of the nose).**

SILICONE REPLICAS

The Investigator's staff took a silicone replica **(negative cast)** of skin in the right or left crow's foot area according to Stephens & Associates' standard operating procedure. Selection of the site was determined by the Investigator's staff at the Baseline visit. Results were analyzed using image analyses.

VISIA IMAGING

A VISIA imaging system uses multi-spectral imaging & analysis to capture key visual information for six areas affecting facial appearance: wrinkles, spots, pores, evenness **(color variation in the skin tone)**, porphyrins **(evidence of bacteria in pores)**, & UV spots **(characteristic of photodamaged skin, typically from overexposure to the sun).** Subjects had VISIA imaging at each designated study visits of the left & right sides of the face. The Sponsor was provided with VISIA reports & images on each subject from each visit.

SKIN BIOPSIES

A subset of five **(5)** subjects had skin biopies taken at baseline and at the final visit. A board certified dermatologist performed a full thickness 2 mm punch biopsy of facial skin. An injection of lidocaine or other anesthetic were given prior to biopsies being taken & the sites were sutured at the doctor's discretion. At baseline, a 2 mm biopsy was taken on the right or left cheek **(per a pre-determined randomization)** approximately 4-5 cm from the middle of the ear. At Week 12, the biopsy was taken on a naïve location on the cheek as close to the original site as possible. Tissue was fixed in 10% buffered formalin & sent to ProPath Laboratories **(Dallas, TX)** for processing & grading of collagen, hyaluronic acid, epidermal thickness, corneal & granular layer compaction & glycosaminoglycans.

Conduct of the Study

SELF ASSESSMENT QUESTIONNAIRES

At baseline, subjects completed a questionnaire evaluating the overall condition of their skin. At Week 6 & Week 12 visits, subjects completed a questionnaire regarding their degree of agreement or disagreement to statements involving improvement in facial photodamage as a result of treatment with Eternox Peptide Crème & NuPeel Natural Enzyme Peel. They were also asked to record any positive open-ended comments they may have had as a result of treatment as well as any suggestions that they have for improvement of the treatment procedure.

VISIT 1: BASELINE

Candidate subjects arrived having completed 2 to 5 days of washout on their face, where they would have discontinued the use of all moisturizing products.

All subjects were screened to ensure the presence of mild to moderate lines and wrinkles in the periocular area (scores of 3-6 on a 10 point scale) on the face and mild to moderate laxed skin on the jaw and /or neck areas (scores of 3-6 on a 10 point scale).

Those who qualified were graded for the efficacy & safety parameters as well as having pinch recoil measurements completed. Once the clinical grading was complete, the subject completed a Health & Eligibility Questionnaire. Each subject also had VISIA photographic imaging following the procedure described above. Following imaging, subjects had NOVA meter measurements, Cutometer measurements, Ultrasound measurements & silicone replicas performed as detailed above.

Upon completion of all baseline assessments, the subject applied the two products in the clinic under the supervision of a clinical staff member. The subject waited at least 15 minutes & then had NOVA Meter measurements performed at the same location as the baseline measurement. Upon completion of all baseline clinical assessments, the subject received the test materials, a daily diary to record usage, a calendar of future visits & verbal & written usage instructions.

A subset of five **(5)** subjects were selected by the Investigator to return within 24-72 hours from the baseline visit for skin biopsies. During the 24-72 hour period, subjects were asked to refrain from using their test materials.

VISIT 2: WEEK 6

Approximately six weeks after Visit 1, subjects returned to the clinic having cleansed their face at least 30 minutes prior to arrival. Subjects returned their diary, received a new one & completed a self-assessment questionnaire. Clinical grading, pinch recoil, NOVA meter measurements, Cutometer measurements & Ultrasound measurements were performed. Subjects were dispensed additional test products as needed to complete the study.

VISIT 3: WEEK 12

Approximately 12 weeks after Visit 1, subjects returned to the clinic, having cleansed their face at least 30 minutes prior to arrival. Subjects returned their daily diary & test materials and completed a self-assessment questionnaire. Clinical grading, pinch recoil, NOVA meter measurements, Cutometer measurements, Ultrasound measurements & silicone replicas were performed. Subjects were also photographed using the VISAI imaging system. The subset of five **(5)** subjects selected by the Investigator would return within 24-72 hours from the baseline visit for skin biopsies.

Results

BIOSTATISTICS & DATA MANAGEMENT

Clinical grading parameters and instrumentation measurements from each visit were compared to baseline for significant differences using a paired t-test. Mean percent change from baseline & incidence of improvement were reported for all attributes. Differences were considered significant at the $p < 0.05$ level. Top box analysis of self-assessment questionnaires were performed.

UPON COMPLETION OF THE CLINICAL STUDY, PARTICIPANTS SHOWED SIGNIFICANT IMPROVEMENT IN THE FOLLOWING AREAS:

- Appearance of photo-damaged skin
- Skin dryness and roughness
- Amount of wrinkles in the eye and mouth areas
- Visibility of wrinkles in the eye and mouth areas
- Evenness of skin tone
- Skin firmness, elasticity and resiliency
- Overall appearance of skin
- Skin softness and texture
- Pore size

	6 WEEKS	12 WEEKS
SKIN LAXITY: JAW/NECK AREA	▼ 29%	▼ 40%
LINES/WRINKLES: EYES	▼ 37%	▼ 41%
LINES/WRINKLES: MOUTH	▼ 43%	▼ 43%
SKIN SOFTNESS	▼ 44%	▼ 67%
SKIN SMOOTHNESS	▲ 63%	▲ 68%
SKIN FIRMNESS	▲ 54%	▲ 68%
SKIN TONE	▲ 41%	▲ 53%
YOUTHFUL LOOK OF SKIN	▲ 25%	▲ 40%
IRRITATION/SENSITIVITY	NONE PRESENT	NONE PRESENT

*Results were measured using biopsies, VISIA digital imaging, clinical grading, pinch recoil, NOVA meter measurement, cutometer, silicone replicas & ultrasound measurement.

*This independent study was conducted by Thomas J. Stephens & Associates, an international leader in independent skin care efficacy studies, at their Dallas research center. This study was conducted in a single-center, controlled clinical environment.