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Stephens & Associates, Inc. Study Number C06-D262

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A 12 Week, Single Center Clinical Trial Evaluating the Effectiveness and Tolerability of the Eternox Wrinkle Reduction System

STUDY NUMBER:	C06-D262
SPONSOR STUDY NUMBER:	N/A
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SPONSOR'S REPRESENTATIVE:	Jim Beckman, M.D. Phone: (800) 433-7549 Email: jbeckman@therapon.com
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INVESTIGATOR:	Thomas J. Stephens, Ph.D.
SUB-INVESTIGATOR/STUDY PHYSICIAN:	James H. Herndon, Jr., M.D.
PROPOSED STARTING DATE:	December , 2006
PROPOSED COMPLETION DATE:	March , 2006
FINAL PROTOCOL DATE:	November 28, 2006

APPROVALS: Investigator _____
DATE

Sub-Investigator/Study Physician: _____
DATE

Sponsor: _____
DATE

A 12 Week, Single Center Clinical Trial Evaluating the Effectiveness and Tolerability of the Eternox Wrinkle Reduction System

PURPOSE

This clinical study is being conducted in order to assess the efficacy and safety of Eternox Wrinkle Reduction System when used by females on the face and neck.

HYPOTHESIS

Eternox Wrinkle Reduction System applied as indicated in this study protocol will provide the following benefits:

Primary:
Demonstrate statistical significance ($p \leq 0.05$) in the average improvement of:

1. Fine lines (0=None; 9=numerous deep lines) and/or wrinkles (0=None; 10=numerous deep wrinkles) from baseline to post treatment; as determined by clinical grading.
2. Firmness/Elasticity of the face and neck (0= firm, tight appearing skin with good stretch properties, 9=loose appearing skin with poor stretch properties) from baseline to post treatment; as determined by clinical grading.

Secondary:
Demonstrate statistical significance ($p \leq 0.05$) in the average improvement of:

1. Globellar lines (0=none; 9=numerous deep lines) from baseline to post treatment; as determined by clinical grading.
2. Evenness of skin tone (0=very blotchy, uneven color; 9=no blotchiness, smooth even color) from baseline to post treatment; as determined by clinical grading.
3. Clarity of the skin (0=dull, matte finish; 9=bright radiant finish) from baseline to post treatment; as determined by clinical grading.
4. Lift effect or defined contours of the skin (0=well defined tight skin that contours the anatomical structures of the face and jaw or neck; 9=sagging skin that poorly contour the underlying anatomical structures of the face and jaw or neck) from baseline to post treatment; as determined by clinical grading.
5. Overall Facial Appearance (0=unhealthy, dull aged appearance; 9=bright, healthy, youthful appearance) from baseline to post treatment; as determined by clinical grading.
6. Hydration of skin barrier by comparing instrumental measurements from baseline to post treatment visits (by the NOVA Meter).
7. Skin firmness and/or elasticity by comparing instrumental measurements from baseline to post treatment visits (by the Cutometer).
8. Skin recoil times by comparing measurements from baseline to post treatment visits (by the pinch recoil test).
9. Collagen, hyaluronic acid, epidermal thickness, stratum corneum compaction, granular layer thickness and glycosaminoglycans (by skin biopsy)
10. Skin density and thickness (by ultrasound).
11. Skin texture by comparing replicas from baseline to post treatment visits (by Profilometry).

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

TEST MATERIAL INFORMATION

Identification Numbers
Stephens & Associates assigns each test material a unique test material identification number (TMIN) in order to provide proper identification in records and reports.

Characterization and Stability
The Sponsor assumes responsibility for chemical characterization and stability of the test materials.

Test Material Description(s)

Sponsor Code	Description
N/A	Eternox Wrinkle Reduction System

Retention of Test Materials
At the completion of the study, all remaining test materials will be disposed of according to Stephens & Associates standard procedures. Test materials will not be weighed prior to distribution or at completion of the study.

SUBJECT ENROLLMENT

Number of Subjects
Fifteen subjects meeting the eligibility requirements will be enrolled in this study.

INSTITUTIONAL REVIEW BOARD

This study (protocol, informed consent agreement and all addenda) will be reviewed and approved by an Institutional Review Board. The study will not be activated, subjects will not be consented or receive test materials until such time as the Board has approved the protocol and the informed consent agreement. In addition, the Board will review the study before any significant change in the protocol is initiated. After each review, the Board's approval will be documented in a letter to the Investigator. A copy of the Board's approval letter will be forwarded to the Sponsor.

Informed Consent
Two copies of a statement of informed consent, consistent with the requirements in 21 CFR 50.25, will be given to each subject before the start of this study. The subject will be given the opportunity to have his/her questions answered to his/her satisfaction. However, if further questions exist, the subject will be given sufficient time on the first visit to clarify open questions and concerns regarding the study and/or the Informed Consent with the Investigator or the Study Coordinator prior to signing. An original signed copy for each subject participating in the study will be retained in the study file. Each subject will receive a signed copy. The subject will be ineligible to participate in this study without a signed Informed Consent.

Subject Identification
Subjects will be assigned a three-digit number which, when used in conjunction with the clinical study number, will uniquely identify every subject on the study. This number will remain with the subject throughout the study and should be used in all references to the individual in this study. No number will be reassigned once the study begins.

Eligibility Criteria

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

Inclusion Criteria

Subjects must meet the following conditions for study participation:

1. Complete and sign an informed consent agreement and Photographic Release Form.

2. Skin Types: Fitzpatrick types I, II, and III.

3. Women 30 to 60 years of age.

4. Glogau score of II-III where lines and wrinkles (in the range of 3-6 on a 10 point scale) are present in the crow's foot area.

5. Scores for laxed skin around the jaw and/or neck areas in the range of 3-6 on a 10 point scale.

6. NOVA meter readings of 160 or less at the baseline reading. Exceptions may be approved by the Investigator.

7. Good general health and 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.

8. 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.

9. 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.

10. 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.

11. Willingness not to begin the use of any new brands of skin or hair care products for the duration of the study.

12. Willingness to use sunscreens and protective head cover to avoid sunburn on the face.

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

14. 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).

Exclusion Criteria
The following conditions will exclude subjects from study participation:

1. Known sensitivities to ingredients in the test products..

2. Concurrent participation in any other controlled usage study.

3. Pregnant or nursing mothers.

4. Use of topical steriods or other topical medications on the face within 4 weeks before enrollment.

5. Women who have used Retin-A®, Retin-A Micro®, Renova®, Avita®, Tazorac®, Soriatane®, or Differin® within 4 months of the study start or have taken Accutane® within one year of the study start.

6. Presence of skin condition such as eczema, psoriasis, other scaly inflammatory disease, severe acne, sunburn, vitiligo, atopic skin, etc.

7. Use of depigmentation products (e.g., hydroquinone, tretinoin, prescription strength AHA, BHA and polyhydroxy acids, 4-hydroxyanisole alone or in combination with tretinoin etc.) within 4 months before enrollment.

8. Individuals are receiving anticancer or immunosuppressive treatments/medications.

9. Uncontrolled disease such as diabetes, hyperthyroidism, hypothyroidism active hepatitis, immune deficiency, autoimmune disease or respiratory disease as determined by the health questionnaire.

10. Having undergone a mid-depth or superficial facial chemical peel or laser resurfacing within 6 months of the study start.

11. Having undergone Thermage treatment or equivalent type of treatment on the face within the last 12 months.

12. Start of hormone use (including for birth control) or changed hormones less than three months prior to the start of the study. Qualified subjects must not be taking hormones or must have been taking them for at least three months prior to the study start.

Subjects will be admitted to the study at the discretion of the Investigator based on medical history and findings of the pre study interview and examination. Each person is expected to complete the full course of the study. Individuals will be admitted to study at the discretion of the Investigator or designate based on medical history and findings of the pre-study interview and examination.

CONDUCT OF STUDY

Study Design
This single-center, controlled usage study will evaluate efficacy and safety of the Eternox Wrinkle Reduction System. The study will last for 12 weeks and will involve the following visits: Day 1 (baseline), 15 minutes post regimen application, Week 6, and Week 12. Trial assessments will include visual grading, pinch recoil

measurements, Cutometer measurements, Ultrasound measurements, NOVA meter measurements, skin biopsy and Self-Assessment Questionnaires. Subjects will have VISIA photographs taken at the baseline and final visits. Five subjects will have a 2mm biopsy taken on the face at the baseline and final visits.

Schedule of Procedures

Procedures	**Baseline**	**15 minutes Post regimen application**	**Week 6**	**Week 12**
Safety and Efficacy Grading: Face and 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	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 will be performed at each study visit:

Safety Evaluations
Subjects will be graded globally at each of the grading locations (face and neck) for objective irritation (erythema, edema, and 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 will be 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)
Globellar 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)
Lift or Defined Contours (0=well defined tight skin that contours the underlying anatomical structures of the face and 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 will be preformed in triplicate and will be timed to the hundredths of a second to assess elasticity and resiliency. Pinch Recoil is assessed by pinching the skin at the edge of the left eye area (Crow's Foot Area) between the thumb and forefinger. The skin is held in place approximately 3 seconds and a stopwatch is started upon release. The time that is taken for the skin to return to its original conformation is measured in hundredths of a second. Based on skin structure or tightness, a pinch recoil measurement may not be obtainable for a given individual.

CUTOMETER SEM 575

Cutometer SEM 575 (Courage and Khazaka) measurements will 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 will be applied and released through an 8-mm probe. The movement of the skin into and out of the probe will recorded during the application and release of suction, and values in millimeters (mm) will reported for resiliency and recoil. As the skin becomes more elastic, scores for resiliency and recoil will increase.

ULTRASOUND

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

NOVA METER DPM 9003

Female subjects have 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, and increases as the skin becomes more hydrated. The readings are directly related to the skin's electrical capacitance (picoFarads). Subjects will equilibrate in the clinic for at least 15 minutes, and then a measurement will be 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 will take 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 will be determined by the Investigator's staff at the Baseline visit. Results will be analyzed using image analyses.

VISIA IMAGING

A VISIA imaging system uses multi-spectral imaging and 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), and UV spots (characteristic of photodamaged skin, typically from overexposure to the sun). Subjects will have VISIA imaging at each designated study visits of the left and right sides of the face. The Sponsor will be provided with VISIA reports and images on each subject from each visit.

SKIN BIOPSIES

A subset of five (5) subjects will have skin biopies taken at baseline and at the final visit. A board certified dermatologist, will perform a full thickness 2 mm punch biopsy of facial skin. An injection of lidocaine or other anesthetic will be given prior to biopsies being taken, and the sites will be sutured at the doctor's discretion. At baseline, a 2 mm biopsy will be 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 will be taken on a naïve location on the cheek as close to the original site as possible. Tissue will be fixed in 10% buffered formalin and sent to ProPath Laboratories (Dallas, TX) for processing and grading of collagen, hyaluronic acid, epidermal thickness, corneal and granular layer compaction, and glycosaminoglycans.

CONDUCT OF THE STUDY

SELF ASSESSMENT QUESTIONNAIRES
At baseline, subjects will complete a questionnaire evaluating the overall condition of their skin. At Week 6 and Week 12 visits, subjects will complete a questionnaire regarding their degree of agreement or disagreement to statements involving improvement in facial photodamage as a result of treatment with the Eternox Wrinkle Reduction System. They will also be asked to record any positive open ended comments that 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 will arrive having completed 2 to 5 days of washout on their face, where they will have discontinued the use of all moisturizing products. They will read and sign an Informed Consent Agreement and Photographic Release Form prior to any clinical procedures. After the Informed Consent has been signed and witnessed, and the subject's questions answered to her satisfaction, a clinical grader will examine the subject's face.

All prospective subjects will be 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). The subject may be disqualified if a condition of the skin exists that would be inappropriate for study participation (severe acne, redness, eczema, moderate rosacea, etc., on the face and neck).

Those who qualify will be graded for the efficacy and safety parameters as well as having pinch recoil measurements completed. Once the clinical grading is complete, the subject will complete a Health and Eligibility Questionnaire and sign a Confidentiality Agreement. Subjects will be assigned unique subject numbers.

Each subject will have VISIA photographic imaging following the procedure described above. Following imaging, subjects will have NOVA meter measurements, Cutometer measurements, Ultrasound measurements and silicone replicas performed as detailed above.

Upon completion of all baseline assessments, the subject will apply the Eternox Wrinkle Reduction System in the clinic under the supervision of a clinical staff. The subject will sit quietly in the clinic for at least 15 minutes, and then will have NOVA Meter measurements performed at the same location as the baseline measurement. Upon completion of all baseline clinical assessments, the subject will receive the test materials, a daily diary to record usage, a calendar of future visits, and verbal and written usage instructions.

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

Visit 2: Week 6
Approximately six weeks after Visit 1, subjects will return to the clinic having cleansed their face at least 30 minutes prior to arrival. Subjects will return their diary and receive a new one, and will complete a self-assessment questionnaire. Clinical grading, pinch recoil, NOVA meter measurements, Cutometer measurements and Ultrasound measurements will be performed. Subjects will be dispensed additional test products as needed to complete the study.

Visit 3: Week 12
Approximately 12 weeks after Visit 1, subjects will return to the clinic, having cleansed their face at lest 30 minutes prior to arrival. Subjects will return their daily diary and test materials, and will complete a self-assessment questionnaire. Clinical grading, pinch recoil, NOVA meter measurements, Cutometer measurements, Ultrasound measurements and silicone replicas will be performed. Subjects will be

photographed using the VISAI imaging system. The subset of five (5) subjects selected by the Investigator will return within 24-72 hours from the baseline visit for skin biopsies.

Adverse Events
The test material may produce mild facial irritation such as erythema, scaling/dryness, burning and/or stinging. Symptoms that are persistent and moderate to severe in nature, or that involve elevation (e.g. edema, papules, vesicles, spreading) will be considered adverse events (AEs). AEs will be documented and followed to completion. The sponsor will be notified in a timely manner of their occurrence. The subject may be referred to the study physician for examination and possible treatment and medical expenses will be billed separately to the Sponsor.

Attrition
Clinical studies are subject to attrition. If a subject fails to return for a scheduled examination, a representative of Stephens and Associates will attempt to contact the subject and determine whether the subject has continued to follow study instructions and intends to continue participation in the study. Subjects who cannot make up the visit +/- 5days will be dropped from the study or at the discretion of the Investigator and the Sponsor. Changes to the study schedule under these circumstances will be documented in a file memo. Subjects lost from the study will be documented using the attrition form.

Adverse Weather Provision
Study visits may be delayed if adverse weather conditions present a risk to the safety of persons traveling to the test facility. Visits will be resumed immediately with the earliest acceptable improvement of travel conditions and staff availability. The Sponsor will be notified of changes in scheduled visit dates. Changes will be documented in a file memo.

Protocol Amendments/Deviations
If the study design or subject eligibility for an approved protocol require revision, a protocol amendment or deviation (whichever is applicable) will be written describing the change. The amendment or deviation will be signed by the Study Investigator and sent to the Sponsor for an approval signature. Amendments/deviations will not be written for changes to approved protocols that do not affect subject eligibility, study conduct/design, or final results (for example: typos, administrative changes, proposed start/end dates).

Monitoring of the Study
The sponsor may visit the site to monitor study visits during the course of the study and may inspect all case report forms and other documentation directly associated with the study.

RESULTS

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

Final Study Report
A draft report will be submitted to the sponsor for review and changes may be made to the draft report at the sponsor's request. Upon approval, the report will be finalized and forwarded to the sponsor. The final report will include (but is not limited to) the following information:

-Descriptions of test materials
-Dates of study initiation and completion
-Protocol deviation(s) and/or amendment(s), if applicable
-Statistics
-General Summary
-Description of objectives

-Interpretation with discussion of results
-Number of subject completing the study
-Conclusions
-Copy of Attrition Form, if applicable
-Copy of Observation Records
-Copy of Questionnaires
-Copy of Adverse Event Form(s), if applicable

Maintenance of Records

Original records (including the study protocol, observation records, medical histories, informed consents, attrition form, and any other records or forms used in the study) and a copy of the final report will be retained on file in the Stephens and Associates archives for two years. When the archive time has expired, the study files will be either destroyed or sent to the sponsor at the sponsor's expense.

RESULTS

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