Clinical Trial Synopsis

The content and information given in this clinical trial synopsis does not replace medical advice provided by a patient's physician or other qualified healthcare providers. Patients should always consult their physician before making conclusions regarding their treatment. Healthcare professionals are advised to refer to the approved labelling and prescribing information. Results from a single study may not reflect the overall results of a drug and need to be interpreted in the context of all relevant scientific data.

Name of Sponsor/ Company: Dr. August Wolff GmbH & Co. KG Arzneimittel	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Linoladiol® N		
Name of Active Ingredient: Estradiol-hemihydrate		
Title of study: Clinical study to investigate the efficacy and safety of an estradiol containing cream (0.01 % estradiol) in patients with dermatoporosis		
Identifiers: Sponsor study code: ESA-13/2010 EudraCT number: 2011-002464-24 NCT number: -		
Study centre(s): The study was conducted at 1 investigational site in Germany.		
Publication (reference): -		
Study period: Date of first enrolment: September 12th, 2011 Date of last completed: December 14th, 2011	**Phase of development:** Phase IIa	

Objectives:

The aim of the study was to determine the efficacy and safety of a low dose estradiol containing cream in postmenopausal patients with dermatoporosis (chronic cutaneous insufficiency/fragility syndrome) in comparison to placebo.

Methodology:

Monocentric, randomized, placebo-controlled, double-blind, phase IIa clinical study, intra-individual comparison

Number of patients (planned and analysed)

Planned: 44

Analysed: 44 (SP), 41 (ITT), 40 (PP)

Diagnosis and main criteria for inclusion:

- Diagnosis: dermatoporosis stage I or II, i.e. at least the presence of the following three symptoms: skin atrophy, senile purpura, and pseudo scar, otherwise healthy skin
- Skin thickness < 1mm as measured by ultrasound
- Clinical assessment of skin atrophy of ≥ 2
- Postmenopausal women with last menstruation more than 24 months prior start of the study
- Serum estradiol < 30 pg/ml
- Fitzpatrick skin preferably type II to IV, I may be also included
- ≥ 60 years old
- Willingness to actively participate in the study and to come to the scheduled visits
- Signed written informed consent to participate in the study
- Willingness to discontinue the use of own cleansing and cosmetic products (e.g. soaps, creams, moisturizers) in the treatment areas throughout the course of the study

Test product, dose and mode of administration, batch number:

Product: Linoladiol® N, an estradiol-hemihydrate containing cream (Name, active substance, administration form)

Dose: 0.01033 % estradiol-hemihydrate (concentration, active substance)

Mode of administration: topical application, once daily (route, frequency)

Batch number: 10890

Duration of treatment:

8 weeks per subject

Reference therapy, dose and mode of administration, batch number:

Matching placebo to Linoladiol® N containing excipients only was administered as described for the test product. Batch number was 10890.

Criteria for evaluation: (Efficacy and Safety)

Primary objective

Comparison of test product and placebo on changes of epidermis thickness to baseline after 8 weeks of treatment as measured with a VivaScope.

Secondary objectives:

- Thickness of epidermis as measured with a VivaScope at baseline, after 4 weeks of treatment and at the follow-up visit
- Skin elasticity measured with a Cutometer at baseline, after 4 and 8 weeks of treatment and at the follow-up visit
- Phase shift rapid in vivo measurements of skin at baseline, after 4 and 8 weeks of treatment and at the follow-up visit
- Thickness of skin as measured by 22 MHz-ultrasound at baseline, after 4 and 8 weeks of treatment and at the follow-up visit
- Clinical assessment of skin atrophy (investigator)
- Changes in senile purpura, pseudo scars and if applicable skin laceration
- Self-assessment of skin fragility by patients once weekly
- Skin histology (PE, 4 mm punch biopsy at baseline and after 8 weeks of treatment): Immunohistochemistry: HE (tissues), collagen I + III, EVG
- Explorative: count of papillae on images taken with a VivaScope, if possible, at baseline, after 4 and 8 weeks of treatment and at the follow-up visit
- Physical examination focused on the skin
- Laboratory parameters: FSH, LH and estradiol at baseline, after 12, 14 and 16 days of treatment as well as after 8 weeks of treatment
- Tolerability assessed after 2, 4, 6 and 8 weeks of treatment by study personnel and patient

- Monitoring of blood pressure and heart rate
- Documentation and analysis of adverse events

Statistical methods:

- Paired t-test (skin thickness by ultrasound and VivaScope, PRIMOS roughness parameters Rz and Ra, Cutometer parameter R7)
- Wilcoxon signed rank test for matched pairs (clinical examination of skin atrophy)
- Dixon and Mood Sign-test (changes in symptoms: senile purpura, pseudo scars and, if present, skin laceration)
- Two-sided 95 % confidence intervals (skin thickness, skin roughness, skin elasticity)

Summary – Conclusions

Baseline data:

44 female patients with an average age of 72.2 years (ranging from 61 to 82 years of age), with a mean height of 164.5 cm and a mean weight of 68.3 kg were enrolled.

Skin Type Classification (Fitzpatrick)

Skin type	Number of subjects	Percentage of subjects
I	5	11.4 %
II	17	38.6 %
III	18	40.9 %
IV	4	9.1 %
V	-	-
VI	-	-

Efficacy Results:

Primary objective

A slight increase in epidermis thickness after 8 weeks of treatment was seen after application of Linoladiol®. However, when comparing Linoladiol® with its placebo the different treatment effects were statistically not significant.

Secondary objectives

Only little changes (slight decrease) in epidermal thickness were measured using VivaScope after 4 weeks of treatment. At the follow-up visit epidermal thickness was slightly thinner compared to baseline after treatment with Linoladiol®. When comparing placebo with Linoladiol®, treatment effects were statistically not significant.

Treatment with Linoladiol® and its placebo led to a slight increase in skin thickness measured by 22 MHz ultrasound 4 and 8 weeks after treatment which was still seen at the follow-up visit. The increase in skin thickness was slightly more pronounced after treatment with Linoladiol® compared to placebo, however, differences between both treatments were statistically not significant.

Two parameters were measured by Cutometer to assess skin elasticity: R0 (Uf) which represents the total extensibility of the skin and R7 (Ur/Uf) which is linked to the elastic fibers. Neither treatment with Linoladiol® nor with placebo had any effect on parameter R7 which is linked to the elastic fibers. After 4 weeks of treatment a decrease in the total extensibility of the skin (Uf) was seen after both treatments, which was more pronounced after treatment with placebo (statistically different to treatment with Linoladiol®). At all other assessment time points only slight effects on skin elasticity were determined.

Skin topography (Ra skin surface roughness and Rz roughness minor furrows and anatomically performed lines) was determined using PRIMOS. Only little changes in skin surface roughness were seen after both treatments. No statistically significant difference was seen between both treatments regarding the parameter Ra. Rz decreased slightly after treatment with placebo, while after treatment with Linoladiol® hardly any effect was seen.

Since aging is accompanied by a reduction of the density of papillae, papillae counts based on VivaScope picture was performed. This parameter was analyzed exploratively. A clear statement regarding an influence of the test product on the expression of dermal papillae cannot be made due to the presence of a high number of age spots at the test areas which are linked to a high number of papillae in the skin.

No statistically significant differences were seen between both treatments regarding skin histology.

Only little beneficial effects on skin atrophy (clinical assessment) were seen after treatment with Linoladiol® or placebo. No statistically significant difference was seen between both treatments.

Assessment of senile pupura 8 weeks after treatment showed an improvement of this parameter in 2 out of 7 patients. All other dermatoporosis parameter did not change or were not visible/not present based on clinical photography.

The result of the patients' judgment of skin fragility once weekly was another secondary objective. The majority of patients described the fragility of their skin as normal at beginning and after 8 weeks of treatment. No scores below "5" of a scale ranging from 1 (skin bruises very easily) to 10 (skin bruises normally) were given. Treatment effects were not seen.

The global tolerability of Linoladiol® and Placebo was assessed after 2, 4, 6, and 8 weeks of treatment by the study personnel and by patients. The study personnel and the patients judged the skin tolerability as very good and good (both products).

Safety Results:

36 non-serious and one serious adverse event (whiplash after car accident) were documented in 25 patients. 26 of these AEs were graded as mild, while 11 AEs were graded as moderate. In 35 AEs the patients recovered without sequelae, in one AE the patient's condition was improving and in one AE the outcome was unknown. 4 AEs of special interest (AESI) occurred in this study. These 4 AESIs were remotely related to the study medication (elevated estradiol levels). One additional AE was probably related to the study procedure (hematoma after biopsy). All other non-serious AEs and the serious AE were not related to the study.

Serum estradiol, FSH and LH levels were determined at days 13, 15, 17 and 56. In 4 patients serum estradiol slightly exceeded 30 pg/ml. Although the treatment was not changed, serum estradiol levels were decreased at the following laboratory evaluation and were all lower than 30 pg/ml. FSH and LH level were not elevated during study conduct. In one case elevated FSH levels were measured before treatment with the study medication started. This respective patient dropped-out of the study.

There were no relevant changes in heart rate and blood pressure between screening and final visit.

Conclusion:

The primary objective of the study was not proven. After 4 weeks of treatment and at the follow-up visit only slight changes in epidermal thickness were seen after both treatments. No beneficial effects could be seen for secondary efficacy parameters. Skin tolerability was judged as mainly very good to good by the study personnel and the patients.

Date of report: 13th of March 2012