Crema RETORNA® (Catalysis S.L.Madrid) aplicada como preparado antienvejecimiento en mujeres de 35 a 60 años con la piel envejecida y dañada con arrugas de clase I a I I I

Reporte final

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Para: CATALYSIS, S. L. Madrid
Svidník, junio de 2009

Objetivo del ensayo

Verificar la eficacia y tolerabilidad de la aplicación de la crema **RETORNA®**, como preparación profiláctica en mujeres participantes del ensayo con piel envejecida o dañada por NOx en la cara, cuello y escote, con arrugas de clase I a III. y para verificar los efectos positivos sobre la hidratación, elasticidad y reducción o estabilización del contenido de grasa cutánea.

Para validar los resultados fue necesario comparar el producto con placebo en un centro seleccionado al azar.

Fue necesario verificar los resultados en 3 centros midiendo la elasticidad, hidratación y producción de sebo de la piel utilizando el Multi Skin Test Center®.

Tipo de prueba

Tipo IV con seguimiento posterior al registro.

Ensayo abierto aleatorio simple ciego con inclusión continua de pacientes según criterios establecidos.

En un grupo de pacientes, el ensayo fue simple ciego y tuvo como objetivo evaluar la aplicación de la crema **RETORNA®** en comparación con placebo.

Número de pacientes: 4 centros con 15 mujeres cada uno, 60 mujeres participantes del ensayo en total.

Aplicación

2 veces al día durante al menos 3 meses.

Desarrollo de la prueba

Se aplico crema **RETORNA®** en 60 mujeres con una edad media de 47 años, la paciente menor tenía 36 años y la mayor 60. El tiempo medio de aplicación fue de 78.33 días. La mayoría de las mujeres del grupo eran foto tipo de piel II (46 mujeres). Había 10 mujeres con foto tipo de piel 1 y 4 mujeres con foto tipo de piel III. No se incluyeron mujeres de otras etnias con foto tipo de piel IV. Con mayor frecuencia presentaron arrugas de clase I y II en la frente, alrededor de los ojos, boca y cuello. Las arrugas clase III generalmente aparecen alrededor de los ojos y la boca. Se instruyo a todas las mujeres sobre el sistema de aplicación y el uso prohibido de productos similares y antioxidantes sistémicos, así como la necesidad de usar protectores solares (la preparación no contiene filtros UV)

Todas las mujeres recibieron información por escrito y se les ofreció asesoramiento personal. Se informo a las mujeres la posibilidad de usar la crema **RETORNA®** como base de maquillaje lo que fue realizado por un 45%.

Las 60 mujeres se aplicaron la crema **RETORNA®** durante al menos 4 semanas (el perido de aplicación corto fue de 10 días y el periodo de aplicación mas largo fue de 86 días) sin interrupción, 1 paciente que se aplico placebo, desarrollo una reacción adversa y fue excluida del ensayo después de 10 días.

En el centro 4 también hubo una reacción adversa y la paciente suspendió su participación después de 3 días.

58 mujeres terminaron el ensayo de acuerdo con el cronograma y 2 lo interrumpieron.

Resultados

Tras la aplicación de la crema **RETORNA®**, la piel estaba más suave y ligeramente estirada. En el transcurso de las primeras 4 semanas observamos una reducción de las arrugas finas y en algunas mujeres también una mejoría de las manifestaciones inflamatorias, por ejemplo, en aquellas pacientes que sufren de acné menstrual. La textura (así como el empaque) de la crema **RETORNA®**, fue apreciada por todas las mujeres. Aquellas mujeres con piel seca se aplicarían la crema tres veces al día, que es el régimen de aplicación que algunas de ellas siguieron realmente después de la finalización del ensayo.

En algunos pacientes se observó una mejora general moderada de los parámetros estéticos hasta 5 semanas después de la finalización del ensayo.

RETORNA® fue evaluado (clínicamente y por mediciones) como el producto más eficaz.

Los efectos más significativos se observaron en mujeres que no habían usado ningún producto especial antes de la inclusión en el ensayo y cuya piel había estado previamente expuesta al sol, el clima y las influencias agresivas.

Muchas mujeres se alegraron de saber que la aplicación de la crema **RETORNA®** tuvo una influencia positiva en los ojos hinchados y la hiperpigmentación periocular (11 mujeres). La piel del contorno de ojos se aclara visiblemente durante la aplicación de la crema Retorna® y sus parámetros estéticos mejoran. Las 11 mujeres con hiperpigmentación periocular apreciaron este hecho más que los efectos generales de la crema **RETORNA®**.

Durante el ensayo no se aplicaron modalidades de rejuvenecimiento ni tratamientos físicos, como microdermoabrasión, escáner láser, láser de bioestimulación, etc.

El ensayo se llevó a cabo en invierno y primavera, sin embargo, este hecho no pareció influir en el efecto final.

Los resultados de comparar el efecto terapéutico de la crema **RETORNA®**, y el placebo en un grupo de 60 pacientes recomiendan el uso de la crema Retorna®.

Los efectos adversos durante la aplicación, como sensación de ardor, eritema o prurito, se observaron solo en 1 paciente al que se aplicó placebo y 1 paciente al que se aplicó crema **RETORNA®**.

Excelente tolerancia, prácticamente sin efectos adversos y la posibilidad de aplicar la crema en mujeres de 30 a 35 años y un alto porcentaje de eficacia en mujeres mayores para prevenir y reducir las arrugas de clase II y III son atributos que abogan por un uso más amplio de la crema **RETORNA®**.

El efecto estético final influye de hecho en la bienestar mental de los pacientes.

Según los resultados obtenidos, la aplicación de la crema **RETORNA®**, representa una eficaz modalidad dermatocosmética preventiva. Para potenciar el efecto es necesario aplicar la crema **RETORNA®** dos veces al día durante al menos 3 meses, proteger la piel de los rayos UV o potenciar el efecto mediante el uso de antioxidantes sistémicos.

No se recomienda la aplicación en pacientes con alergias cutáneas conocidas. En tales casos, se deben realizar pruebas epicutáneas antes de la aplicación.

La crema RETORNA® representa una moderna preparación anti-envejecimiento con influencia positiva sobre las arrugas. Ayuda a rejuvenecer la piel con buenos parámetros cosméticos y estéticos.

Retorna® cream (Catalysis S. L. Madrid) applied as an anti- ageing preparation in women aged 35 to 60 years with ageing and damaged skin and class I - III wrinkles

Final Report

Main Trial Coordinator: **Dr. Hana Zelenková, Ph.D.**

Submitted by: **Dr. Hana Zelenková, Ph.D.**

Submitted to: **CATALYSIS, P. L. Madrid**

Svidník, June 2009

Contents

Introduction

From June 1st, 2006 to January 31st 2007 a pilot trial to verify the effects of applying Retorna® cream CATALYSIS, P. L. Madrid in 30 patients with ageing and damaged skin on the face, neck, and décolleté and class I to III wrinkles was carried out at the private department of Dermatovenereology DOST in Svidník, Slovakia. Since the obtained results verified the effects of applying the said topical anti-ageing preparation, it was decided by CATALYSIS, P. L. Madrid, to verify the effects in an international multicentre trial.

A group of women with ageing and damaged skin on the face, neck, and décolleté and class I to III wrinkles was selected to participate in the trial.

It was decided that the trial shall include the application of a placebo preparation in a control group in a randomly selected centre.

Fr the purposes of the trial, the centres were provided with Retorna® cream CATALYSIS, P. L. Madrid. The product had previously undergone molecular activation.
One centre was also supplied with a placebo preparation.

1 Anti-aging medicine

Ageing is a natural process starting at birth of every individual. Ageing is fair and affects every living organism on the planet, including humans.

However, humans have always tried to stop or at least slow down the process and ameliorate its manifestations of ageing. In ancient times, alchemists and shamans would use drugs and produce immortality drinks, drugs, and potions, and prepare topical and systemic preparations. Therapeutic procedures were developed which in the end, actually seemed to have an effect on ageing. There are legends about places where the time stopped and people stay young forever, like the Šangri-La n Chinese mythology, or stories in literature about deals with the devil or the picture of Dorian Gray.

Fact is that people live longer, which brings advantages and disadvantages. Ageing has recently been perceived as a serious medical problem, although, there of course are . geographic and social differences. Our task is to tackle the problem in a complex way.

It is therefore o wonder that a new medicinal branch emerged - anti-aging medicine. This novel branch is developing with great dynamics into a certified medical specialisation. The objectives have been clearly determined and are pursued within a network of national organisations.

The objectives of anti-ageing medicine are as follows:

1. To achieve the best possible health condition of a human being and slow down the process of ageing
2. To achieve the best possible quality of life and safeguard longevity
3. Carry out research in methods which could slow down or prevent ageing
4. Develop the prophylaxis and prevention of age-related diseases
5. Gather scientific information on possible ways of prolonging human life

6. Organise and support further education of medical practitioners, scientists and anti-ageing association members
7. Educate general public with the aim of safeguarding their best possible health condition

Of course, anti-ageing medicine is aimed at all age categories, and is based on healthcare and healthy lifestyle of every human being. It is thus not to be mistaken with geriatric medicine or dermatology, since it represents individual and complex approach towards ageing , the main aim of which is to keep a human being in a condition of a 30 year old organism.

The oldest woman with documented age was Jeanne Calment (France), who died at the age of 122 years. The oldest documented case was Shirali Muslimov from Azerbaijan, who allegedly died at 168 years.

Japan is known for the longevity, with Okinawa province counting most inhabitants aged over 100 years. Around the world there is one individual of 10 older than 60 at present, however, in 2050 every fifth citizen will be of that age, and in 2150 that will be every third citizen.

Anti-ageing medicine combines the advantages of classic western medicine with the medicine of the Middle East. It rejuvenates the human organism also from the inside and tackles minor problems that are usually omitted by classic medicine.

Anti-aging examination is based on carefully selected procedures based on which an individual programme is elaborated for every client, including consultancy on nutrition and nutrition supplements and antioxidants, hormonal therapy (of plant, animal or synthetic origin) and many other measures.

1.1 Human skin

The skin is the first to reflect ageing of an organism. Its quality and beauty are determined by genes or targeted care. Skincare includes elimination and reduction of unwanted manifestations. Cell apoptosis and ageing are irreversible, but humans have always tried to eliminate the manifestations of ageing on the skin caused by internal or external influences. Unfortunately, the beauty of young skin is temporary.

In ancient Greece the skin was especially important. For example harmony was perceived in connection with the quality of skin, where a skin disease or changes in its aesthetic parameters could result in isolation. The same is true also today, for example in connection with leprosy or even psoriasis or naevi.

The skin can reveal the age of a human being and is the first to show whether a person takes cakes care of their health or suffer from a serious disease. Aesthetics is imprinted in children at early age, including the idea about the beauty of the skin. Congenital diseases affecting the appearance or various (for example ritual) adjustments may affect communication and prevent normal contact. In this context we may not omit the special way in which we perceive the function of hair, nails, and sweat glands.

The skin is an extremely important sensory organ with multiple physiological functions and millions of nerve terminations - extrareceptors and intrareceptors. The skin protects the human body from mechanic and thermic damage and the effects of sun exposure (producing the skin pigment melanin). The skin participates in thermoregulation, respiration, transpiration, sebum production, and perspiration – perspiratio insensibilis of approximately 600-800ml water a day.

Skin layers (epidermis, dermis, subcutis) and the physiological changes thereof have been studied and described in detail. Youthful look and beauty are given by the quality of dermis. Ageing thus is a process within which dermis loses elasticity, which results in wrinkling and skin laxity. The changes are similar to dry skin; however, dry skin only reflects the relative humidity of stratum corneum.

Skin ageing is intrinsic or extrinsic. Intrinsic ageing is a biological, genetically predetermined process reflecting a certain life period. Skin ageing caused by external factors is mainly influenced by UV exposure – photo-ageing, chemical pollution, geographic and climatic influences, stress, smoking (also passive), consumption of certain foods, toxins, etc. Reactive oxygen species and free radicals play an important role in skin ageing as well.

Not only the skin on the face ages. Ageing affects the skin of the body, too. Literature offers numerous examples where the ageing of certain body parts has been described in various social groups (for example the neck of farmers and fishermen (Morbus Favre Racauchaut) versus the skin on the neck in people working in offices). There are huge differences in the quality of skin on various parts of the body (neck, trunk, thighs, hands), due to sun exposure.

In order to objectivise ageing processes various methods have been elaborated, such as imprint methods, computer models and special examination methods such as Skin aging score – SAS. Changes in pigmentation, teleangiectasia, wrinkles, hydration, sebum production, elasticity, suppleness, skin tone and other parameters are monitored as well.

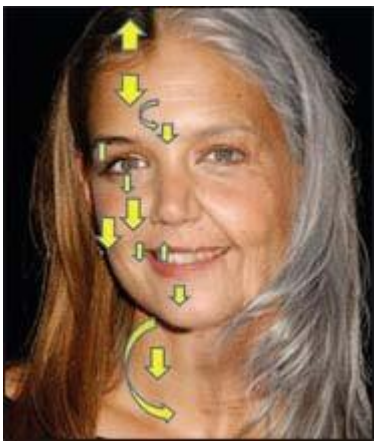


Figure. 1 Computer model with skin ageing vectors in a young celebrity

Figure 2 A "before and after" image produced by simulating the vectors and changes associated with head and neck aging.

Changes appearing on the skin in the process of ageing are well known – the “peach skin” of teenage years disappears and degenerative changes in skin elasticity occur, making the skin look lax and tired. The quality of skin affects the appearance of the whole face which loses contours radial wrinkles appear around the eyes and mouth, the skin is marked with periocular hyperpigmentations and the skin gets thinner (young skin 35-50μm, aged skin 25-40 μm)

Combined effects of sun exposure and lower estrogen and androgen production cause white scars on the forearms to appear. Vessels are more visible, negative influences on uncovered skin cause pigmentation changes, such as lentigo solaris, lentigo maligna. Changes in fibroblasts and collagen fibres cause characteristic changes of the skin on the neck - erythrosis intefolicularis coli. Wrinkles occur, which we perceive as the most serious problem.

Wrinkles may be superficial – fine, or deep (class I to V) and reflect degenerative changes in skin elasticity. With age, the number of wrinkles increases, radial wrinkles around eyes and mouth, on the forehead and neck become more prominent.

The physiological process of ageing is not accepted by some men and women.

As has been previously mentioned, the skin is exposed to a number of negative factors. Skin discomfort and malfunctions leas to various diseases. Lacks in appearance cause stress situation and may result in mental deprivation in some individuals.

Dermatologists and other therapists dealing with anti-aging medicine have been trying to foster targeted skin protection and care for many year. Beautiful healthy skin is the dream of many young people. The basics of care include consultations with specialist, awareness of ones skin type, and skin phototype, knowledge of cosmetic products, antioxidants and nutrition supplements as well as prophylactic measures and systematic care.

People should also have basic knowledge of cosmetic products available on the market, daily usage of high quality cosmetic products, regular skin cleansing at specialised clinics and protection from UV rays. In cases where the usage of cosmetics is no longer sufficient, therapists must employ devices.

2 Aesthetic dermatology

In the last 15 years **aesthetic medicine** is becoming the centre of attention at many renowned clinics apart from anti-aging medicine. This branch of dermatology develops novel techniques and methods. Specialisations have occurred also in this branch, focusing on superficial and deep fillers, lipofilling, various types of peels, dermatosurgery, liposuction, microliposuction, lipolysis, resurfacing, application of gold and polypropylene threads, skin repositioning - lifting, laser and IPL treatments - rejuvenation, Dermabrasion, mesotherapy, camouflage systems, dermal rollers etc..

The usage of high quality **dermatocosmetics** plays an extremely important role, whereby dermatocosmetics represents the combination of a therapeutic agent and cosmetic product. high quality products have been accepted and produced by renowned pharmaceutical companies. The interest in such products has increased. The results of clinical trials testing dermatocosmetics are presented at world congresses, being the results of the cooperation between experts in the field and the companies producing novel preparations. High quality dermatocosmetics reduces the unwanted changes of appearance.

The availability and accessibility of dermatocosmetics to all target groups and the scientifically proven effects thereof make it a lucrative object of interest of many producers.

3 Novel anti-aging preparation

Retorna® cream is produced by Catalysis Madrid represent newly developed products with declared anti-ageing skin nutritive cosmetic properties. Active principles contained in Retorna® cream include Mimosa Extract 0.25%, Aloe Vera 5.0% and Glycyrrhizinic Acid 0.1%. The employment of Aloe Vera and Glycyrrhizinic Acid in cosmetics is well known and the company uses the said substances in other preparations as well.

Aloe vera

Glycyrrhiza glabra

Vedecká klasifikácia Mimosa hostilis

Type: Liophyta

Divízie: Magnoliophyta

Trieda: Magnoliopsida

Poradie: Fabales

Čeľaď: Fabaceae

Podčeľadí: Mimosoideae

Genus: Mimosa

Druh: Mimosa hostilis

Many trials have proven that Mimosa hostilis also contains psychoactive substances - DMT, 5-Meo-DMT, a beta-carbolines. Retorna® cream contains glycolic extract of Mimosa tenuiflora, The extract of Mimosa tenuiflora is a glycolic extract obtained from the crushed bark of the Tepescohuite tree called “wooden skin” by ancient Maya civilisation.

The extracts show extraordinary regenerative properties and are therefore used in the process of producing specialised dermatological and cosmetic preparations. Intensive research started in the laboratories of Mexiko City after 1985 in connection with the treatment of severe burns. At present it is used in cosmetic industry, whereby the research still continues with great intensity.

The bark is obtained from 5 year old trees and heated to 160^{o}C on top of terracotta plates. This way, powder of chocolate colour is produced, that is not soluble in water or other organic products. The active extract is obtained from the powder by purification, and is then soluble in water, but non soluble in ethyl alcohol. It smells typically of wood and has bitter astringent taste. The extract is stabilised by 30% propylene glycol. The content of various substances is as follows: tannins (130 mg per 10g) and oligoelements (Zinc, Magnesium, Cupper, and Manganese). All those constituents show anti-aging effect, as has been proven by numerous studies. They also demonstrate bacteriostatic action especially against Staphyloccocus aureus, Staphyloccocus epidermidis, and Propionibacterium Acnes, as well as physiological effects. The glycolic extract of Mimosa tenuiflora may only be used topically. It does not irritate the skin. Ocular irritations are very mild and occur sporadically. Mimosa

tenuiflora partially inhibits the activity of hyaluronase and protects the integrity of Hyaluronic Acid. It is therefore used in the production of various cosmetic products such as lotions, creams, gels (especially to treat acne). The preparations show regenerative properties and accelerate healing. Their effects are comparable to those of bioflavonoids (increase in capillary resistance, improvement of peripheral microcirculation and activity against free radicals).

Retorna® cream by Catalysis S. L. Madrid:

Retorna® cream, Catalysis S. L. Madrid is a product designed to treat ageing and damaged skin with Class I to III wrinkles. It contains active ingredients such as Mimosa Extract 0.25 %, Aloe Vera 5, 0%, Glycyrrhizinic Acid 0.1%. The said active agents and **molecular activation** are responsible for the activity of the product in adequate indications under daily application regimen. According to producer, molecular activation increases the activity of molecules 20 to 100 times. Other ingredients include Creatine, Panthenol, Sodium Hydroxide, Allantoin etc.

4 Trial objective

To verify the efficacy and tolerability of applying Retorna® cream, a product of CATALYSIS S.L.Madrid, Spain as a prophylactic preparation in female trial participants with ageing or NOx- damaged skin of the face, neck and décolletage, with wrinkles of class I to III, and to verify the positive effects on skin hydration, elasticity, and reduction or stabilisation of skin fat content.

To validate the results it was necessary to compare the product with placebo in a randomly selected centre.

It was necessary to verify the results in 3 centres by measuring skin elasticity, hydration and sebum production using the Multi Skin Test Center®.

5 Trial type:

Type IV with post registration monitoring.

Single blind randomised open trial with continuous inclusion of patients according to set criteria.

In one group of patients the trial was simple blind and aimed at assessing the application of Retorna ® cream by CATALYSIS S. L. Madrid compared to placebo.

6 Trial Design and Time Schedule:

Trial Centres and participating countries:

1. Slovakia Svidník I and II, Žilina

2. Czech Republic Brno

Slovakia		**Centre No.**
Svidník I	**(Dr. Hana Zelenková, Ph.D.)**	**01**
Svidník II	**(Dr. Júlia Stracenská)**	**02**
Žilina I	**(Dr. Alena Nejdková)**	**03**
Czech Republic		
Brno	**(Dr. Zuzana Vykutilová)**	**04**

Group of patients: 4 Centres with 15 women each, 60 female trial participants in total

Diagnosis: ageing and damaged skin with class I – III wrinkles (see notes**)

Trial participants: females aged 35 – 60 years

Local finding assessment: performed 4 times, at inclusion, and after 4, 8, and 12, weeks

Note *: *trial participants shall be then followed for the subsequent 3 months after therapy discontinuation*

Tested preparation: Retorna® cream, Catalysis P .L. Madrid

Placebo – Centre 02

Time schedule:

November 2008	continuous inclusion and exclusion of the patients
December 2008 – March 2009	performance of the trial
April - May 2 009	assessment and processing of obtained results
June 2009	handing over the completely processed results
July-December 2009	presenting and publishing of the results

7 Material and methods

The investigators undertook to elaborate the documentation, take pictures, and inform the trial coordinator and producer on adverse effects or possible complications.

The trial was carried out according to the set plan and protocols, using the **basis set of documents**:

- Basic Working Protocol plus tables (Annex 1)
- Inclusion and Exclusion Criteria (Annex 2)
- Table including the List of Patients (Annex 3)
- Patient Consent Form (Annex 4)
- Adverse Effects Documentation Form (Annex 5)

Centres and numbers of trial participants:

Slovakia	**Centre No.**	**No. of patients**
Svidník I (Dr. Hana Zelenková, Ph.D.)	**01**	**15**
Svidník II (Dr. Júlia Stracenská)	**02**	**15**
Žilina I (Dr. Alena Nejdková)	**03**	**15**
Czech Republic		
Brno (Dr. Zuzana Vykutilová)	**04**	**15**

Trial duration 8 months, from October 1, 2008 to May 31, 2009

Group of patients: 60 female trial participants

Average age: 47 years. (youngest patient 35, oldest patient of 60 years)

Diagnosis: ageing and damaged skin with class I – III wrinkles (see notes.**)

Note: At inclusion, it is inevitable to adhere to the following Wrinkle classification system**

Class I Very superficial wrinkles. No specific treatment or intervention (using filling material injection) is required.

Class II Superficial wrinkles and lines. It is advisable to treat such wrinkles once in a time using semi-permanent filling materials.

Class III Moderately deep wrinkles – It is advisable to treat such wrinkles once in a time using absorbable, semi-permanent and/or permanent filling materials.

Class IV Deep wrinkles. Recommended semi-permanent and permanent filler injections, with reduced frequency of interventions.

Class V Very deeps wrinkles fixed in connective tissue. Filler injections are not recommended

Class IV and V wrinkles are not subject of the trial and inclusion criteria!!!

Note: In Centre 02 two comparable localities were selected:

- **Retorna® cream** was applied on the **right** side of the face, neck or décolleté
- **Placebo** was applied on the **left** side of the face, neck or décolleté

Application regimen: Retorna® cream and placebo (Centre 02) were applied on the face, neck and décolleté **twice a day** for 12 weeks (3 months)

Concomitant application or administration of other preparations:
In emergency cases exclusively and based solely on recommendation of other medical experts

Drinking regimen:
All women have been instructed in the necessity to adhere to a drinking regimen

Laboratory screening:
Performed 2 times - before therapy commencement and upon therapy termination

Documentation : Work Protocol (see Annex 13, 79 - 90)

Centres 01, 02, 03

Monitored certain parameters using the Multi Skin Test Center® by Courage + Khazaka

at every single visit, including the level of**:**

- elasticity
- hydration
- sebum production
- objective assessment of wrinkling and skin quality (skin tone)

Centre 04 used photodocumentation and clinical and objective assessment criteria.

Photodocumentation:	pictures taken during every check-up to assess the condition of single patients, 4 times in total
Application duration:	at least 90 days (3 months)
Basic laboratory screening:	performed in every patient
Special examinations:	possible in every patient, however, the results are not subject of this trial
Recommended daily hygiene:	non irritating preparations having no influence on the process of healing
Final assessment:	at exclusion from the group
Tested preparation:	Retorna® cream, Catalysis S.L.Madrid placebo
Composition:	provided by the producer, see below unknown in case of placebo preparation

The qualitative and quantitative composition of RETORNA CREAM is as follows:

ACTIVE PRINCIPLE:		
Mimosa Extract	0.25	%
Aloe Vera	5.0	%
Glycyrrhizinic Acid	0.1	%
EXCIPIENTS:		
C12-C15 Alkyl Benzoate	6.4	%
Caprylic/Capric Triglyceride	3.0	%
Salicyloyl Phytophingosine; PPg-3Myristyl Ether	3.0	%
Glycerin	3.0	%
Glyceryl Stearate	2.0	%
Stearyl Alcohol	2.0	%
Polyglyceryl-3-Methylglucose Distearate	1.5	%
Decyl Oleate	1.5	%
Stearic Acid	1.0	%
Euxyl K300	1.0	%
Ceteareth -25	0.5	%
Tecopheryl Acetate	0.5	%
Creatine	0.5	%
Panthenol	0.2	%
Sodium Hydroxide	0.2	%
Allantoin	0.1	%
Carbomer 134	0.1	%
Parfum	0.1	%
Aqua	62.3	%

Inclusion criteria

- Aging or damaged skin on the face, neck and décolleté
- **wrinkles of class I to III (see wrinkle classification system**)**
- Outpatient status
- Age: 35 to 60 years of age
- Voluntary participation in the trial
- Written patient consent form confirmation
- One-time participation in the trial

Exclusion criteria

Specific exclusion criteria

- Known allergies to the tested preparation
- Disease focus infection manifestations (superinfection requiring therapy)
- Immunosuppressive therapy
- Cancer
- Malignancies
- Employment of other drug/p and /or preparation/p in therapy

General exclusion criteria:

- Alcohol and drug abuse
- Painkiller abuse
- Participation in another clinical trial within the past 30 days
- Simultaneous participation in any other clinical trial
- Other reasons excluding the patient from the trial
- Restricted ability of the patient to follow therapy instructions
- Other physical or mental disorders disturbing the trial plan
- Possible consent withdrawal, presumed patient unreliability

Therapy effect assessment made by the therapist: scale 1 – 5

1 significant reduction in wrinkling with great aesthetic and cosmetic effect

2 slight reduction in wrinkling with satisfactory aesthetic and cosmetic effect

3 insignificant improvement

4 dissatisfactory effect, without visible changes or with undesired effects

5 exclusion

Therapy effect assessment made by trial participants: scale 1 – 4

1 excellent aesthetic and cosmetic effect with no undesired effects

2 satisfactory cosmetic effect

3 insignificant improvement, lack of satisfaction on the side of the patient

4 dissatisfactory effect with progressive wrinkling and other ageing symptoms

Therapy tolerability assessment made by the therapist and the patients: scale 1 – 4

(1- excellent, 2 – very good, 3 – good, 4 – intolerance)

Assessment of possible undesired effects of applying Retorna® cream or placebo:

1 burning sensation

2 skin dryness

3 erythema

4 pruritus

8 Results:

Elaboration and processing:

Obtained results were forwarded from the centres to the main trial coordinator for elaboration and processing, and eventual publishing. The Work protocols and photodocumentation are with the main trial coordinator, open to inspection.

The results are included here as follows, for easier orientation:

1. **Assessment in Centres 01, 02, 03, and 04**
2. **Assessment of the effects of placebo preparation in Centre 02**
3. **Summary assessment of Centres 01 - 04**
4. **Comparison of the effects and percentage assessment of Retorna® cream versus placebo in the whole series of patients**

Results: **Centre 01 Svidník** **Dr. Hana Zelenková, Ph.D.**

Basic data: **15 women** number of patients, age (lowest and highest age)
average application time (in days),
possible complications, application discontinuation, hospitalisation
see Table 1, Graph 1 to 2, Annex II, p. 97 -98

Specific data: skin phototype
see Table 2 Graph 3, Annex II, p. 99

Specific data: condition of facial skin and wrinkle severity assessment – visit 1 to 4,
condition at the end of trial, improvement
see Table 3, Graphs 4 to 8, Annex II, p. 100-103

Specific data: quality of skin on the face - smoothness, suppleness, elasticity,
visit 1 to 4, condition at the end of trial, improvement
see Table 4 Graph 9 to 12, Annex II, p. 104 - 106

Specific data: skin fat content – forehead, chin, visit 1 to 4,
condition at the end of trial, improvement
see Table 5, Graph 13-14, Annex II, p. 107-108

Specific data: skin hydration measured on the left cheek,
visit 1 to 4, condition at the end of trial, improvement
see Table 6 Graph 15-16, Annex II, p. 109 -110

Specific data: skin elasticity, visit 1 to 4,
condition at the end of trial, improvement
see Table 7 Graph 17-18, Annex II, p. 111- 112

Specific data: condition of the skin on the face and on the neck, condition of wrinkles, visit 1 to 4, condition at the end of trial, improvement
see Table 8 Graph 19-20, Annex II, p. 113 - 114

Specific data: quality of skin on the neck and décolleté- smoothness, suppleness, elasticity, visit 1 to 4, condition at the end of trial, improvement

see Table 9 Graph 21-28, Annex II, p. 115 - 119

Specific data: skin fat content – on the neck and décolleté, visit 1 to 4, condition at the end of trial, improvement

see Table 10 Graph 29 – 32, Annex II, p. 120 -122

Specific data: skin hydration, on the neck and décolleté, visit 1 to 4, condition at the end of trial, improvement

see Table 11 Graph 33-36, Annex II, p. 123 - 125

Specific data: skin elasticity on the neck and décolleté, visit 1 to 4, condition at the end of trial, improvement

see Table 12 Graph 37-40, Annex II, p. 126 - 128

Specific data: complete assessment of efficacy and tolerability, undesirable effects on the face

see Table 13, Graph 41-45, Annex II, p. 129 -132

Specific data: complete assessment of efficacy and tolerability, undesirable effects on the neck and décolleté

see Table 14, Graph 46-50, Annex II, p. 133 - 136,

Specific data: undesirable effects on the face

see Table 13, Annex II, p. 129,

Specific data: undesirable effects on the neck and décolleté

see Table 14, Annex II, p. 133,

Specific data: Multi Skin Test Center® measurements at trial inclusion and trial conclusion, sebumetry and hydration level

see Table 15 a 16,Graph 51-56, Annex II, p. 137 – 141a

Diagnosis: in the group of 15 women Class I and II wrinkles were found on the face and on the neck and décolleté,

Class III wrinkles were found around the eyes and mouth in 5 women.

Concomitant application or administration of other preparations:
In emergency cases exclusively and based solely on recommendation of other medical experts.

Administration of systemic antioxidants was strictly prohibited during the trial

Recommended regimen: Retorna ® cream was applied 2 times a day
In the morning and evening by rubbing or patting

Other physical therapy: ***0***

Condition improvement: observed in 30% of women after 4 weeks,
continued while Retorna® cream was applied

Note: The women appreciated the application form ad texture of Retorna ® cream, and continued applying the cream spontaneously also after the trial

Therapy efficacy at trial conclusion– condition of the skin on the face:

see Table 13 a 14, Graph 41, 43-45, Annex II, p. 126 - 132

Assessment made by the investigator:

2 women (13,33%)	significant wrinkle reduction excellent cosmetic and aesthetic effect
4 women (26,67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
6 women (40,00%)	insignificant improvement
3 women (20,00%)	dissatisfactory condition without visible improvement

Subjective assessment made by the patients:

3 women (20,00%)	significant wrinkle reduction excellent cosmetic and aesthetic effect
3 women (20,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
7 women (46,67%)	insignificant improvement
2 women (13,33%)	dissatisfactory condition without visible improvement

Therapy tolerance at trial conclusion on the face:

***(*see Table 13, Graph 42-45, Annex II, p. 129 - 132*)*:**

Assessment made by the investigator:

9 women (60,00%)	excellent tolerability
6 women (40,00%)	very good tolerability

Subjective assessment made by the patients:

9 women (60,00%)	excellent tolerability
6 women (40,00%)	very good tolerability

***Undesirable effects (*see Table 13*)*:** *0*

Therapy efficacy at trial conclusion– condition of the skin on the neck and décolleté:

see Table 14 , Graph 46, 48-50, Annex II, p. 132-135

Assessment made by the investigator:

1 woman (6,67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
7 women (46,67%)	moderate wrinkle reduction,

	satisfactory cosmetic and aesthetic effect
4 women (26,67%)	insignificant improvement
3 women (20,00%)	dissatisfactory condition without visible improvement

Subjective assessment made by the patients:

3 women (20,00%)	significant wrinkle reduction,
	excellent cosmetic and aesthetic effect
3 women (20,00%)	moderate wrinkle reduction,
	satisfactory cosmetic and aesthetic effect
7 women (46,67%)	insignificant improvement
2 women	dissatisfactory condition without visible improvement

Therapy tolerance at trial conclusion – on the neck and décolleté:

***(*see Table 14, Graph 47-50, Annex II, p. 133 - 136*)**:*

Assessment made by the investigator:

8 women (53,33%)	excellent tolerability
6 women (40,00%)	very good tolerability
1 woman (6,67%)	good tolerability

Subjective assessment made by the patients:

8 women (53,33%)	excellent tolerability
6 women (40,00%)	very good tolerability
1 woman (6,67%)	good tolerability

***Undesirable effects (*see Table 14*)**:* *0*

Comment: **Centre 01 Svidník** **Dr. Hana Zelenková, Ph.D.**

Retorna® cream by Catalysis S.L.Madrid was applied in the total of 15 women aged 45.67 years on the average, whereby the youngest woman was 35 and the oldest woman was 60 years of age. The average application duration comprised 84 days. In this group of women the dominant skin phototype was type II present in 10 women, there were 4 women with skin phototype I and 1 woman with skin phototype III. The application regimen consisted of the following steps:

1. The area of the face, neck, and décolleté was washed with micellar water and preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. Retorna® cream was gently rubbed or patted on the treated area
3. The condition was assessed at every visit, based on which further application was either continued or discontinued.

Before the commencement of therapy, all women were instructed in the technique of applying Retorna® cream and were informed about the strictly prohibited usage of other creams and systemic antioxidants (such as Evelle, Innéov, Pycnogenol and others.). During the duration of the trial rejuvenation treatments, special massages or cosmetic treatments were prohibited as well.

Undesirable effects :

No undesirable effects such as burning sensation, skin dryness, reddening or itching, which could cause application discontinuation, were observed.

Most significant effects were observed in women with class I and II wrinkles on the face. In this area the monitoring possibilities of the effects are ideal. In 6 cases (40%) the structure of the skin and its aesthetic parameters improved objectively (moderate wrinkle reduction). Smoothness, suppleness (most significantly in 6 patients) and elasticity (in 3 women – 20%) of the skin improved. In7 women (46%) the fat content changed, in 5 cases the skin changed from greasy to normal. Greatest improvement was achieved in hydration – this parameter improved in all women, with excellent results achieved in 7 patients (47%).

Similar results, although not so significant, were observed in the area of the neck and décolleté. However, the assessments by the patients and by the investigators differed dramatically. While the investigators determined significant and good improvement in 8 women (53.34%), only 6 women (40%) reported improvement of their condition. The fat content in the skin on the neck changed objectively, increasing to 67% on the neck and to 60% on the décolleté. This was very much influenced by the fact that these were mostly women who were treated by mesotherapy in the past, with significant but short term effect.

In general, the group consisted of older women who adhered strictly to the application and drinking regimen and avoided sun exposure and solariums.

Results: **Centre 02 Svidník** **Dr. Júlia Stracenská**

Basic data: **15 women** number of patients, age (lowest and highest age)
average application time (in days),
possible complications, application discontinuation, hospitalisation
see Table 1, Graph 1-3, Annex II, p. 142-144

Specific data: skin phototype
see Table 2, Graph 3, Annex II, p. 99

Specific data: condition of facial skin and wrinkle severity assessment – visit 1 to 4,
condition at the end of trial, improvement
see Table 3 Graph 4-8, Annex II, p 145 -148

Specific data: quality of skin on the face - smoothness, suppleness, elasticity
visit 1 to 4, condition at the end of trial, improvement
see Table 4, Graph 9-12, Annex II, p 149 - 151

Specific data: skin fat content, Retorna® applied on the right forehead and chin,
visit 1 to 4, condition at the end of trial, improvement
see Table 5 Graph 13, 15, 16 Annex II, p 152 - 155

Specific data: skin fat content – Placebo applied on the left forehead and chin,
visit 1 to 4, condition at the end of trial, improvement
see Table 5 Graph 14, 15, 17, Annex II, p 152 - 155

Specific data: skin hydration, Retorna® applied on the right,
visit 1 to 4, condition at the end of trial, improvement
see Table 6, Graph 18,20, Annex II, p 156 -158

Specific data: skin hydration, Placebo applied on the left
visit 1 to 4, condition at the end of trial, improvement
see Table 6, Graph 19,21, Annex II, p 156 - 158

Specific data: skin elasticity on the right side, visit 1 to 4,
condition at the end of trial, improvement

see Table 7, Graph 22 -23 Annex II, p 159 -160

Specific data: condition of the skin on the face and on the neck, condition of wrinkles on the right side

visit 1 to 4, condition at the end of trial, improvement

see Table 8, Graph 24-26, Annex II, p 161 - 163

Specific data: skin quality on the neck on the right side - smoothness, suppleness, elasticity,

visit 1 to 4, condition at the end of trial, improvement

see Table 9, Graph 27, 28, 31, 33, Annex II, p 164 -168

Specific data: skin quality on the décolleté, on the right side - smoothness, suppleness, elasticity, visit 1 to 4, condition at the end of trial, improvement

see Table 9, Graph 29, 30, 32,34, Annex II, p 164 - 168

Specific data: – skin fat content on the neck and décolleté, Retorna® cream on the right side

visit 1 to 4, condition at the end of trial, improvement

see Table 10, Graph 35, 36, 39, 40, Annex II, p 169, 170, 172

Specific data: skin fat content on the neck and décolleté after placebo applied

on the left side, visit 1 to 4, condition at the end of trial, improvement

see Table 10, Graph 37, 38, 41, 42, Annex II, p 169, 171, 173

Specific data: skin hydration on the neck and décolleté after Retorna® cream applied

on the right side, visit 1 to 4, condition at the end of trial, improvement

see Table 11, Graph 43, 45, 47, 48, Annex II, p 174 -177

Specific data: skin hydration of the neck and décolleté after placebo applied

on the left side visit 1 to 4, condition at the end of trial, improvement

see Table 11, Graph 44, 46, 49, 50, Annex II, p 174- 178

Specific data: – skin elasticity on the neck and décolleté, on the right side

visit 1 to 4,condition at the end of trial, improvement

see Table 12, Graph 51-54, Annex II, p 179 - 181

Specific data: complete assessment of efficacy and tolerability,

undesirable effects on the face after Retorna® cream on the right side

see Table 13 Graph 55-59, Annex II, p. 182, 184 -186

Specific data: complete assessment of efficacy and tolerability,

undesirable effects – on the face after placebo on the left side

see Table 13 Graph 60 – 65, Annex II, p. 183. 187 - 189

Specific data: complete assessment of efficacy and tolerability,

undesirable effects on the neck and décolleté,

Retorna® cream on the right side

see Table 14, Graph 66 -70, Annex II, p. 190, 192 - 194,

Specific data: complete assessment of efficacy and tolerability,

undesirable effects on the neck and décolleté,

placebo preparation used on the left side

See Table 14, Graph 71 - 75, Annex II, p. 191, 195 - 197,

Specific data: Undesirable effects on the right side of the face

see Table 13, Annex II, p. 182, 183

Specific data: undesirable effects on the right side of the neck and décolleté,

see Table 14, Annex II, p. 190, 191

Specific data: Multi Skin Test Center® measurements at trial inclusion and trial conclusion,

sebumetry and hydration level - Retorna® cream

see Table 15 graphs on Retorna® cream 76-78, 198-200

placebo Graph 79-81, Annex II, p. 198, 201 - 202

Specific data: Multi Skin Test Center® measurements at trial inclusion and trial conclusion,

sebumetry and hydration level - placebo

see Table 16 Graphs Retorna® cream 82-84, p. 203 -205

placebo Graph 85-87, Annex II, p. 203, 206 - 207

Diagnosis: in the group of 15 women Class I and II wrinkles were found

on the face and on the neck and décolleté,

Class III wrinkles were found around the eyes and mouth (Table 3).

Concomitant application or administration of other preparations:
In emergency cases exclusively and based solely on recommendation of other medical experts.

Administration of systemic antioxidants was strictly prohibited during the trial

Recommended regimen: Retorna ® cream was applied 2 times a day on the right side
in the morning and evening by rubbing or patting,
placebo was applied 2 times a day on the left side,
in the morning and evening by rubbing or patting

Other physical therapy: ***0***

Condition improvement: observed in 35% women after the application of Retorna ® cream after 4 weeks and continued until Retorna® cream application was terminated. In placebo, the effect was slower, and there was a case of irritative dermatitis after 10 days, accompanied by burning sensation and skin dryness, resulting in exclusion from the trial

Note: The women appreciated the application form ad texture of Retorna ® cream, and continued applying the cream spontaneously also after the trial

Retorna ® cream efficacy at trial conclusion on the face

see Table č. 13 Graph 55, 57-59, Annex II, p. 182, 184 - 186

Assessment made by the investigator:

2 women (13,33%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
8 women (53,55%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
4 women (26,67%)	insignificant improvement
1 woman	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

3 women (20%)	significant wrinkle reduction excellent cosmetic and aesthetic effect
5 women (33.33%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect

6 women (40,00%)	insignificant improvement
1 woman	undesirable effects, exclusion from the trial

Therapy tolerance at trial conclusion:

***(*see Table 13, Graph 56-59, Annex II, p. 182, 184 - 186*)**:*

Assessment made by the investigator:

11 women (73,33%)	excellent tolerability
2 women (13,33%)	very good tolerability
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

1 women (73,33%)	excellent tolerability
2 women (13,33%)	very good tolerability
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

PLACEBO efficacy at trial conclusion on the face

see Table 13 Graph 60, 62-65, Annex II, p. 183, 187 - 189

Assessment made by the investigator:

1 woman (6,67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
5 women (33,33%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
8 women (53,33%)	insignificant improvement
1 woman	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

1 woman (6,67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
6 women (40,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect

7 women (46,67%) insignificant improvement

1 woman (6,67%) undesirable effects, exclusion from the trial

Therapy tolerance PLACEBO at trial conclusion:

***(*see Table 13, Graph 61-65, Annex II, 183, 187 - 189*)*:**

Assessment made by the investigator:

11 women (73,33%) excellent tolerability

2 women (13,33%) very good tolerability

1 woman (6,67%) insignificant improvement

1 woman (6,67%) undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

11 women (73,33%) excellent tolerability

2 women (13,33%) very good tolerability

1 woman (6,67%) insignificant improvement

1 woman (6,67%) undesirable effects, exclusion from the trial

***Undesirable effects (*see Table 13, Graph 65, 182, 183, 189*)*:** *1 woman* developed burning sensation and severe erythema after 10 days (the manifestations started on the left side where she applied the placebo preparation and gradually spread all over the area of the face). The patient discontinued due to irritative dermatitis.

Retorna ® cream efficacy at trial conclusion on the neck and décolleté:

see Table 14 Graph 66, 68-70 , Annex II, p. 190, 192-194

Assessment made by the investigator:

5 women (33,33%) significant wrinkle reduction,
excellent cosmetic and aesthetic effect

3 women (20,00%) moderate wrinkle reduction,
satisfactory cosmetic and aesthetic effect

6 women (40,00%) insignificant improvement

1 woman (6,67%) undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

5 women (33,33%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
4 women (26,67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
5 women (33,33%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Retorna ® cream tolerability at trial conclusion on the neck and décolleté:

***(*see Table 14 Graph 67-70, Annex II, p. 190, 192 - 194*)**:

Assessment made by the investigator:

9 women (60,00%)	excellent tolerability
4 women (26,67%)	very good tolerability
1 woman (6,67%)	good tolerability
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

9 women (60,00%)	excellent tolerability
4 women (26,67%)	very good tolerability
1 woman (6,67%)	good tolerability
1 woman (6,67%)	undesirable effects, exclusion from the trial

Placebo efficacy at trial conclusion on the neck and décolleté:

see Table 14 Graph 71, 73-75 , Annex II, p. 191, 195 -197

Assessment made by the investigator:

1 woman (6,67%)	significant wrinkle reduction excellent cosmetic and aesthetic effect
6 women (40,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
6 women (40,00%)	insignificant improvement
1 woman (6,67%)	dissatisfactory condition without visible improvement

1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

2 women (13.33%)	significant wrinkle reduction excellent cosmetic and aesthetic effect
7 women (46.67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
4 women (26.67%)	insignificant improvement
1 woman (6.67%)	dissatisfactory condition without visible improvement
1 woman (6.67%)	undesirable effects, exclusion from the trial

Placebo tolerability at trial conclusion on the neck and décolleté:

***(*see Table 14 PLACEBO Graph 72-75, Annex II, p. 191, 195 - 197*)*:**

Assessment made by the investigator:

9 women (60.00%)	excellent tolerability
4 women (26.67%)	very good tolerability
1 woman (6.67%)	good tolerability
1 woman (6.67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

9 women (60.00%)	excellent tolerability
4 women (26.67%)	very good tolerability
1 woman (6.67%)	good tolerability
1 woman (6.67%)	undesirable effects, exclusion from the trial

***Undesirable effects (*see Table 14, s.191*)*:**

1 woman developed burning sensation and severe erythema - the manifestations started on the left side where she applied the placebo preparation and gradually spread all over the area of the neck and décolleté

Comment **Centre 02 Svidník** **Dr. Júlia Stracenská**

Retorna® cream by Catalysis S.L.Madrid was applied in the total of 15 women on the right side of the face, neck and décolleté, and placebo was applied on the left side of the face, neck and décolleté. The average age of trial participants was 45,67 years, whereby the youngest woman was 35 and the oldest woman was 59 years. Average application duration comprised 78,53 days. In this group of women the dominant skin phototype was type II , present in 13 women, and there was 1 woman with skin phototype I and 1 woman with skin phototype III.

The application regimen consisted of the following steps:

1. The area of the face, neck, and décolleté was washed with micellar water and preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. Retorna® cream or placebo was gently rubbed or patted on the treated area
3. The condition was assessed at every visit, based on which further application was either continued or discontinued

Before the commencement of therapy, all women were instructed in the technique of applying Retorna® cream and were informed about the strictly prohibited usage of other creams and systemic antioxidants (such as Evelle, Innéov, Pycnogenol and others.). During the duration of the trial rejuvenation treatments, special massages or cosmetic treatments were prohibited as well.

Undesirable effects :

Undesirable effects such as burning sensation, erythema of the face, neck and décolleté were observed in 1 patient, who discontinued the trial. The said woman applied placebo on the left side of her face. She developed symptoms within 10 days , whereby her erythema was developing gradually, affecting the treated area and later her whole face neck and décolleté. Her condition was assessed as irritative dermatitis.

Most significant effects were observed in women with class I and II wrinkles on the face, and in practically all localities (severe and moderate level 50%). In this area the monitoring possibilities of the effects are ideal. In 11 cases the structure of the skin and its aesthetic parameters improved objectively. As regards the neck and décolleté better results were observed on the décolleté. In case of placebo results were insignificant (see Graphs).

Smoothness improved most significantly (7 women), suppleness improved in all women and elasticity improved more or less in 7 women. On the neck and décolleté the results were less significant than on the décolleté. In placebo those results were less significant (see the graphs).

In applying Retorna® cream on the face, in 10 women (71%) sebum production improved significantly or satisfactorily, in 4 cases the skin changed from very greasy to normal, in 2 cases dry skin changed to normal. In placebo changes in sebum production were observed in 8 (58%) cases.

In monitoring the hydration levels following the application of Retorna® cream on the faced the changes were most notable, and hydration improved in practically all women, with excellent results on 4 women (29%), satisfactory results in 7 women (50%) and slight improvement in 3 women (21%). Placebo results were as follows – excellent in 2 women (14%), satisfactory in 5 women (36%) and insignificant in 7 women (50%). The same results were observed on the neck and décolleté. The tables and graphs do not show a difference in the quality of skin (smoothness, suppleness a elasticity) in Retorna cram and placebo, since it was clinically insignificant. However, we made an exact assessment and comparison of sebum production ad hydration, comparing Retorna® cream and placebo.

Comparing the efficacy and tolerability of Retorna® cream versus placebo, the application of Retorna® cream was assessed as better in all areas by both the investigators and the patients.

All women cooperated very well and followed the recommended application and drinking regimen and avoided sun and UV exposure.

Results: Centre 03 – Žilina Dr. Alena Nejdková

Basic data: **15 women** number of patients, age (lowest and highest age)
average application time (in days),
possible complications, application discontinuation, hospitalisation
see Table 1, Graph 1 to 2, Annex II, p. 208 -209

Specific data: skin phototype
see Table 2 Graph 3, Annex II, p 99

Specific data: quality of skin and wrinkling
visit 1 to 4, condition at the end of trial, improvement
see Table 3 Graph 3-6, Annex II, p 210 – 212

Specific data: quality of skin on the face - smoothness, suppleness, elasticity,
visit 1 to 4, condition at the end of trial, improvement
see Table 4 Graph 7-10, Annex II, p. 213 – 215

Specific data: skin fat content – forehead, chin, visit 1 to 4,
condition at the end of trial, improvement
see Table 5 Graph 11-12, Annex II, p. 216 -217

Specific data: skin hydration, standardly measured on the left cheek, visit 1 to 4,
condition at the end of trial, improvement
see Table 6 Graph 13-14, Annex II, p 218 - 219

Specific data: skin elasticity, visit 1 to 4, condition at the end of trial, improvement

see Table 7 Graph 15-16, Annex II, p 220 – 221

Specific data: complete assessment of efficacy and tolerability,

undesirable effects on the face

see Table 13, Graph 17-21, Annex II, p. 222 – 224

Specific data: undesirable effects on the face

see Table 13, Annex II, p. 222,

Specific data: Multi Skin Test Center® measurement data compared at trial inclusion and trial conclusion, sebumetry and hydration level

see Table 15 a 16,Graph 22-23, Annex II, p. 225 – 226

Diagnosis: in the group of 15 women Class I and II wrinkles were found

Class III wrinkles were found around the eyes and mouth in 4 women.

Concomitant application or administration of other preparations:

In emergency cases exclusively and based solely on recommendation of other medical experts.

Administration of systemic antioxidants was strictly prohibited during the trial

Recommended regimen: Retorna ® cream was applied 2 times a day

in the morning and evening by rubbing or patting

Other physical therapy: ***0***

Condition improvement: Was observed in 35% women after 4 weeks and continued slightly until Retorna® cream application termination.

Note: The women appreciated the application form ad texture of Retorna ® cream, and continued applying the cream spontaneously also after the trial.

Therapy efficacy at trial conclusion on the face:

see Table 13, Graph 17, 19-21, Annex II, p. 222 – 224

Assessment made by the investigator:

2 women (13,33%)	significant wrinkle reduction excellent cosmetic and aesthetic effect
5 women (33,33%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
5 women (33,33%)	insignificant improvement
3 women (20,00%)	dissatisfactory condition without visible improvement

Subjective assessment made by the patients:

4 women (26,67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
4 women (26,67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
5 women (33,33%)-	insignificant improvement
2 women (13,33%)	dissatisfactory condition without visible improvement

Therapy tolerance at trial conclusion on the face:

***(*see Table 13, Graph 18-21, Annex II, p. 222 - 224 *)**:*

Assessment made by the investigator:

9 women (60,00%)	excellent tolerability
6 women (40,00%)	very good tolerability

Subjective assessment made by the patients:

9 women (60,00%)	excellent tolerability
6 women (40,00%)	very good tolerability

Undesirable effects (*see Table 13, p. 222*)

Comment **Centre 03 Žilina** **Dr. Alena Nejdková**

Retorna® cream by Catalysis S.L.Madrid was applied in the total of 15 women aged 42.79 years on the average, whereby the youngest woman was 36 and the oldest woman was 60 years of age. The average application duration comprised 86 days. In this group of women the dominant skin phototype was type II present in 12 women, there were 2 women with skin phototype I and 1 with woman skin phototype III. The application regimen consisted of the following steps:

1. The area of the face, neck, and décolleté was washed with micellar water and preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. Retorna® cream was gently rubbed or patted on the treated area
3. The condition was assessed at every visit, based on which further application was either continued or discontinued

Before the commencement of therapy, all women were instructed in the technique of applying Retorna® cream and were informed about the strictly prohibited usage of other creams and systemic antioxidants (such as Evelle, Innéov, Pycnogenol and others.). During the duration of the trial rejuvenation treatments, special massages or cosmetic treatments were prohibited as well.

Undesirable effects:

No undesirable effects such as burning sensation, skin dryness, reddening or itching, which could cause application discontinuation, were observed.

Most significant effects were observed in women with class I and II wrinkles on the forehead and around the eyes in 7 cases (46% moderate and insignificant level). In this area the monitoring possibilities of the effects are ideal. Skin smoothness improved most significantly (u5 women), followed by suppleness (most significant in 7 women) and elasticity (in 4 women) and aesthetic parameters. In 8 (53%) women sebum content changed, in 4 cases the skin changed from very greasy to normal. Hydration changed very slightly, only in 3 women.

The final assessment of the investigator differed slightly from the assessment made by he patients. While the investigator observed significant improvement and improvement in 7 women (46,66%), the women observed improvement in 8 cases (53,34%).

Multi Skin Test Center® measured in all women positive changes in sebum production and skin hydration (Graphs 22 – 23).

In general, the group consisted of well disciplined women who adhered strictly to the application and drinking regimen and avoided sun exposure and solariums.

Results: Centre 04 BrnoDr. Zuzana Vykutilová

Basic data : **15 women** number of patients, age (lowest and highest age)
average application time (in days),
possible complications, application discontinuation, hospitalisation
see Table 1, Graph 1 to 3, Annex II, p. 227 - 229

Specific data: skin phototype
see Table 2 Graph 3, Annex II, p. 99

Specific data: quality of skin on the neck and wrinkling
at visit 1 to 4, condition at the end of trial, improvement
see Table 8, Graph4, Annex II, p 230 - 231

Specific data: quality of skin on the neck and smoothness, suppleness, elasticity
at visit 1 to 4, condition at the end of trial, improvement
see Table 9 Graph 5-7, Annex II, p 232 - 234

Specific data: elasticity of skin on the neck
at visit 1 to 4, condition at the end of trial, improvement
see Table 12 Graph 8-9, Annex II, p 235 - 236

Specific data: complete assessment of efficacy and tolerability,
undesirable effects on the face
see Table 14, Graph 10, 12-14, Annex II, p. 237 - 240

Specific data: undesirable effects on the face
see Table 14, Annex II, p. 237,

Diagnosis: in the group of 15 women class I and II were found,
class III wrinkles appeared sporadically (2 women).
1 woman discontinued the trial after 3 days due to adverse effects.

Concomitant application or administration of other preparations:
In emergency cases exclusively and based solely on recommendation of other medical experts.

Administration of systemic antioxidants was strictly prohibited during the trial

Recommended regimen: Retorna ® cream was applied 2 times a day
in the morning and evening by rubbing or patting

Other physical therapy: ***0***

Condition improvement: Was observed in 30% of women after 4 weeks,
continued until termination of Retorna® cream application

Note: The women appreciated the application form ad texture of Retorna ® cream, and continued applying the cream spontaneously also after the trial.

Therapy efficacy at trial conclusion on the neck:

see Table 14, Graph 10, 12-14, Annex II, p. 237 -240

Assessment made by the investigator:

9 women (60,00%)	significant wrinkle reduction excellent cosmetic and aesthetic effect,
4 women (26,67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
1 woman (6,67%)	insignificant improvement
1 woman (6,67%) -	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

9 women (60,00%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
4 women (26,67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	**undesirable effects, exclusion from the trial**

Therapy tolerance at trial conclusion on the face:

***(*see Table 13, Graph 11-14, Annex II, p. 237 - 240*)*:**

Assessment made by the investigator:

10 women (66,67%)	excellent tolerability
4 women (26,67%)	very good tolerability
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

10 women (66,67%)	excellent tolerability
4 women (26,67%)	very good tolerability
1 woman (6,67%)	undesirable effects, exclusion from the trial

***Undesirable effects (*see Table 13*)*:**

1 woman developed symptoms of burning, erythema, and irritative dermatitis after three days and discontinued the trial.

Comment **Centre 04 Brno** **Dr. Zuzana Vykutilová**

Retorna® cream by Catalysis S.L.Madrid was applied in the total of 15 women aged 53,86 years on the average, whereby the youngest woman was 47 and the oldest woman was 60 years of age. The average application duration comprised 64,8 days. In this group of women the dominant skin phototype was type II present in 11 women, there were 3 women skin phototype I and 1 woman with skin phototype III. The application regimen consisted of the following steps:

1. The area of the face, neck, and décolleté was washed with micellar water and preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. Retorna® cream was gently rubbed or patted on the treated area
3. The condition was assessed at every visit, based on which further application was either continued or discontinued

Before the commencement of therapy, all women were instructed in the technique of applying Retorna® cream and were informed about the strictly prohibited usage of other creams and systemic antioxidants (such as Evelle, Innéov, Pycnogenol and others.). During the duration of the trial rejuvenation treatments, special massages or cosmetic treatments were prohibited as well.

Undesirable effects:

1 trial participant developed undesired symptoms such as burning sensation, leading to irritative dermatitis, which resulted in application discontinuation after 3 days.

Most significant effects were observed in all women. Class II and III wrinkles on the neck improved as well, the results were actually most significant in this group. The neck was ideal as regards the monitoring of the effects, whereby significant improvement of skin tone was observed, with satisfactorily improved smoothness, suppleness, and elasticity. Skin fat content and hydration were monitored clinically, without computer measurement and assessment.

There were no differences between the assessment by the investigator and the trial participants.

The group consisted of extremely disciplined women who adhered strictly to the application and drinking regimen and avoided sun exposure and solariums.

Placebo results: Centre 02 Svidník Dr. Júlia Stracenská

The following comment includes the summary assessment of placebo application:

Basic data: **15 women** number of patients, age (lowest and highest age)
average application time (in days),
possible complications, application discontinuation, hospitalisation
see Table 1, Graph 1 to 3 X, Annex II, p. 142 - 144

Specific data: skin phototype
see Table 2, Graph 3, Annex II, p 99

Specific data: condition of facial skin and wrinkle severity assessment
visit 1 to 4, condition at the end of trial, improvement
see Table 3, Annex II, p 145-148

Specific data: quality of skin on the face - smoothness, suppleness, elasticity,
visit 1 to 4, condition at the end of trial, improvement
see Table 4, Annex II, p 149-151

Specific data: skin fat content of the left cheek, forehead, and chin,
visit 1 to 4, condition at the end of trial, improvement
see Table 5 Graph 14, 15, 17, Annex II, p. 152, 154 - 155

Specific data: skin hydration on the left cheek,
visit 1 to 4, condition at the end of trial, improvement
see Table 6 Graph 19, 21, Annex II, p 156 - 158

Specific data: skin elasticity, visit 1 to 4, condition at the end of trial, improvement
see Table 7, Annex II, 159

Specific data: condition of the skin on the face and on the neck, condition of wrinkles, visit 1 to 4, condition at the end of trial, improvement
see Table 8, Graph 24-26 Annex II, 161-163

Specific data: quality of skin on the neck and décolleté,
smoothness, suppleness, elasticity,
visit 1 to 4, condition at the end of trial, improvement
see Table 9, Annex II, p.164

Specific data: skin fat content – on the neck and décolleté, on the left side
visit 1 to 4, condition at the end of trial, improvement
see Table 10 Graph 37, 38, 41, 42, Annex II, p 169, 171, 173

Specific data: skin hydration on the left side of the neck and décolleté,
visit 1 to 4, condition at the end of trial, improvement
see Table 11 Graph 44, 46, 49, 50, Annex II, p 174 -176, 178

Specific data:– complete assessment of efficacy and tolerability,
Undesirable effects on the left side of the **face**
see Table 13 Placebo, Graph 60-65, Annex II, p. 183, 187 - 189

Specific data: complete assessment of efficacy and tolerability,
undesirable effects on the left side on the **neck** and **décolleté**,
see Table 14 PLACEBO, Graph 71-75, Annex II, p. 191, 195 - 197,

Specific data: Undesirable effects on the face, neck and décolleté
see Table 14 PLACEBO, Annex II, p. 191

Specific data: Multi Skin Test Center® measurements at trial inclusion and trial conclusion, sebumetry and hydration level
see Table 15, 16, Graph 79-81, 85-87, Annex II, p. 198, 201-202, 203, 206-207

Placebo therapy efficacy at trial conclusion on the face

see Table č. 13 Graph 60, 62-65, Annex II, p. 183, 187-189

Assessment made by the investigator:

1 woman (6,67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
5 women (33,33%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
8 women (53,33%)	insignificant improvement
1 woman	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

1 woman (6.67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
6 women (40.00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
7 women (46.67%)	insignificant improvement
1 woman (6.67%)	undesirable effects, exclusion from the trial

***Therapy tolerability at trial conclusion: (*see Table 13, Graph 61-65, Annex II, s. 183, 187-189*)*:**

Assessment made by the investigator:

11 women (73,33%)	excellent tolerability
2 women (13,33%)	very good tolerability
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

11 women (73,33%)	excellent tolerability
2 women (13,33%)	very good tolerability
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

***Undesirable effects (*see Table 13, Graph 65, p. 183, 189*)**:*

1 woman developed a burning sensation and severe erythema after 10 days of application (whereby her manifestations stared on the left side of the face where she applied the placebo preparation and gradually spread all over the treated area). She gradually developed irritative dermatitis on the whole face and discontinued the trial.

Placebo therapy efficacy at trial conclusion on the neck and décolleté:

see Table 14 Graph 71, 73-75 , Annex II, p. 191, 195 - 197

Assessment made by the investigator:

1 woman (6,67%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
6 women (40,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
6 women (40,00%)	insignificant improvement
1 woman (6,67%)	dissatisfactory condition without visible improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

2 women (13.33%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
7 women (46.67%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
4 women (26.67%)	insignificant improvement
1 woman (6.67%)	dissatisfactory condition without visible improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Placebo therapy tolerability at trial conclusion on the neck and décolleté:

***(*see Table 14 Graph 72-75, Annex II, p. 191, 195 - 197*)*:**

Assessment made by the investigator:

9 women (60,00%)	excellent tolerability
4 women (26,67%)	very good tolerability
1 woman (6,67%)	good tolerability
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

9 women (60,00%)	excellent tolerability
4 women (26,67%)	very good tolerability
1 woman (6,67%)	good tolerability
1 woman (6,67%)	undesirable effects, exclusion from the trial

***Undesirable effects (*see Table 14, p.191*)*:**

1 woman developed *a* burning sensation, severe erythema (which started on the left side of the face where she applied the placebo preparation, and gradually spread all over the face, neck and décolleté

Comment **Centre 02 Svidník** **Dr. Júlia Stracenská**

In this group of patients there were women who applied Retorna® cream, Catalysis S.L.Madrid on the right and placebo on the left side of the face. The basic data (age, average application time, undesirable effects) were assessed in Centre 02 in tables, including the Multi Skin Test Center® measurements of sebum production and skin hydration.

Percentage assessment, clinical results and exact device measurements support the effects of Retorna® cream, Catalysis S.L.Madrid versus placebo. The result was verified by the final percentage assessment of the whole series of patients.

9 Summary results in Centres 01, 02, 03, 04

Retorna ® cream applied on the face, neck and décolleté

In the group of 60 women 45 treated their faces and 15 women (Centre 04) treated their neck and décolleté.

In order to compare the effect of Retorna ® cream versus placebo , Centres 01-03 were assessed, in which the area of the face was treated and the results were documented by Multi Skin Test Center® measurements.

Basic data: **60 women in Centres 01 to 04**

number of patients, age (lowest and highest age)

average application time (in days),

possible complications, application discontinuation, hospitalisation

see Table 1, Graph 1 to 3, Annex II, p. 242-244

Specific data: skin phototype in all Centres – skin phototype

see Table 2 Graph 4, Annex II, p. 245-246

Specific data: quality of skin on the face and wrinkles in Centres 01 to 03

at visit 1 to 4, condition at the end of trial, improvement

see Table 3, Graph 5-7, Annex II, p. 247-249

Specific data: skin fat content on the right cheek in Centres 01 to 03

at visit 1 to 4, condition at the end of trial, improvement

see Table 4, Graph 8,10, Annex II, p. 250-252

Specific data: skin fat content on the right cheek and chin in Centres 01 to 03
at visit 1 to 4, condition at the end of trial, improvement
see Table 4 A PLACEBO , Graph 9, 10, Annex II, p. 250-252

Specific data: skin hydration on the right cheek
at visit 1 to 4, condition at the end of trial, improvement
see Table 5, Graph 11, 13, Annex II, p. 253-255

Specific data: skin hydration on the left cheek
at visit 1 to 4, condition at the end of trial, improvement
see Table 5A PLACEBO, Graph 12-13, Annex II, P. 253-255

Specific data: quality of skin on the neck - elasticity, with Retorna ® cream
at visit 1 to 4, condition at the end of trial, improvement
see Table 6 Graph 14, Annex II, p. 256-257

Specific data: complete assessment of efficacy and tolerability,
undesirable effects with Retorna ® cream applied on the face
see Table 7, Graph 15-19, 24-27, Annex II, p. 258, 260-262, 265-266

Specific data: complete assessment of efficacy and tolerability,
undesirable effects with placebo applied on the face
see Table 13, Graph 20-23, Annex II, p. 259, 263-264

Specific data: undesirable effects on the face

see Table 7,13, Annex II, p. 258, 259,

Specific data: percentage assessment and comparison of therapy effect
Retorna ® cream versus placebo in the whole series of patients
Centres 01-03
see Graph 28-31, Annex II, p. 267-270

Diagnosis: In the group of 60 females most had class I and II wrinkles on tghe face, neck and décolleté. In groups 01-03 (45 women) there were more Class II wrinkles on the glabella and forehead and class III wrinkles in the periocular and perioral areas (Table 3, p. 247).

***Other medication*:** Only if recommended by other specialists.

Administration of systemic antioxidants was strictly prohibited during the trial

Application regimen: Retorna ® cream applied 2 times a day on the right
by rubbing or patting,
placebo applied 2 times a day on the right
by rubbing or patting

Other physical therapy: ***0***

Condition improvement: visible in 35% of women after 4 weeks of applying Retorna ® cream

Continued slightly until application terminated

The effect of placebo was not so significant,

irritative dermatitis occurred with placebo after 10 days, with skin dryness and burning sensation affecting also the contralateral side.

Retorna ® cream efficacy at trial conclusion on the face (Centres 01-03)

See Table 7 Graphs 15, 17-19, 24-27 Annex II., p. 258, 260-262, 265-266

Assessment made by the investigator:

6 women (13,00%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
17 women (38,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
15 women (33,00%)	insignificant improvement
6 women (13,00%)	without changes
1 woman (2,00%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

10 women (22,00%)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
12 women (27,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
18 women (40,00%)	insignificant improvement

4 women (9,00%)	without changes
1 woman (2,00%)	undesirable effects, exclusion from the trial

Therapy tolerability of Retorna ® cream at trial conclusion on the face– (Centres 01-03) -

***(*see Table 7, p. 259, Graph 15-19, 24-27, Annex II., p. 260-262, 265-266*)**:*

Assessment made by the investigator:

29 women (64,00%)	excellent tolerability
14 women (31,00%)	very good tolerability
1 woman (2 00%)	insignificant improvement
1 woman (2,00%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

29 women (64,00%)	excellent tolerability
14 women (31,00%)	very good tolerability
1 woman (2 00%)	insignificant improvement
1 woman (2,00%)	undesirable effects, exclusion from the trial

Placebo therapy efficacy at trial conclusion on the face – Centres 01-03

See Table 13, p. 259, Graphs 20-23, Annex II, p. 263-264

Assessment made by the investigator:

1 woman (6,67%) -	significant wrinkle reduction, excellent cosmetic and aesthetic effect
5 women (33,33%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
8 women (53,33%)	insignificant improvement
1 woman	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

1 woman (6,67)	significant wrinkle reduction, excellent cosmetic and aesthetic effect
6 women (40,00%)	moderate wrinkle reduction, satisfactory cosmetic and aesthetic effect
7 women (46,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Placebo therapy tolerability at trial conclusion on the face – Centres 01-03:

***(*see Table 13, p. 259, Graphs 20-23, Annex II, p. 259, 263-264*)**:*

Assessment made by the investigator:

11 women (73,33%)	excellent tolerability
2 women (13,33%)	very good tolerability
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Subjective assessment made by the patients:

11 women (73,33%)	excellent tolerability
2 women (13,33%)	very good tolerability
1 woman (6,67%)	insignificant improvement
1 woman (6,67%)	undesirable effects, exclusion from the trial

Undesirable effects Centres 01 – 03 *1 woman* developed *a* burning sensation, severe erythema (which started on the left side of the face where she applied the placebo preparation, and gradually spread all over the face. She was excluded from the trial subsequently.

Comment to percentage assessment and comparison of therapy effect

Retorna® cream versus placebo by the investigator in Centres 01-03)
(Table 7, p. 258, Table 13, p. 259; Graphs 28, 30-31, p. 267, 269-270, Annex II)

13.33% women : 6,67%

- significant improvement in wrinkling, hydration, elasticity and sebum content

37.78% women : 33,33%

- moderate improvement in wrinkling, hydration, elasticity and sebum content

33.33% women : **53,33%** insignificant improvement of the monitored parameters

13.33% women : 0,00%condition without visible improvement

2.22%% women : **6,67%** exclusion from the trial

Comment to percentage assessment and comparison of therapy effect

Retorna® cream versus placebo by the patients in Centres 01-03

(Table 7, p. 258, Table 13, p. 259; Graphs 29-31, p. 268-270, Annex II)

22.22% of women: 6,67%

- significant improvement in wrinkling, hydration, elasticity and sebum content

26.67% of women: 40,00%

- moderate improvement in wrinkling, hydration, elasticity and sebum content

40.00% of women: **46,67%** insignificant improvement of the monitored parameters

8.89% of women: 0,00% condition without visible improvement

2.22%% of women: **6,67%** exclusion from the trial

Comment to percentage assessment and comparison of tolerability

Retorna® cream versus placebo by the investigator and patients
(Tab. 7 p. 258, Tab. 13, p. 259; Graph 30, p. 270; p. Annex II.)

64.44 % : 73,33%	excellent tolerability
31.11 % : 13,33%	very good tolerability
2.22 % : 6,67%	insignificant improvement
2.22 % : 6,67%	undesired effects, exclusion from the trial

10 Discussion

Retorna® cream, Catalysis S. L. Madrid is a product used to treat ageing and damaged skin with Class I to III wrinkles. It contains active ingredients such as Mimosa Extract 0.25 %, Aloe Vera 5.0%, and Glycyrrhizinic Acid 0.1 %. The active agents are responsible for the activity of the product in adequate indications under daily application regimen. The cream may be considered equally effective compared to ***other anti-aging preparations.***

The efficacy of Retorna® cream, Catalysis S. L. Madrid was verified in a pilot trial carried out in 2006 – 2007 and subsequently proven in many women in practice. The increased efficacy was achieved by molecular activation, increasing the activity of molecules 20 to 100 times. *The composition of the preparation remained unchanged, only biological activity of the product was increased.*

In order to verify the indication range of the preparation it was necessary to test the prophylactic effect and the tolerability of Retorna® cream, CATALYSIS S.L.Madrid versus placebo (in a group of patients applying placebo on the other side of the face, neck, and décolleté) in a randomly selected centre ***and assess the final effect on skin hydration and elasticity and sebum production, and to assess the depth of wrinkles in women aged 35 to 60 years. The changes were verified by exact measurement using the Multi Skin Test Center® in Centres 01-03. In all centres photodocumentation was used as well.***

The tables and graphs representing Centres 01-03 assess the input and output values in the measurement of sebum, hydration and elasticity.

The results obtained verified the efficacy of Retorna® cream, Catalysis S. L. Madrid and showed that the product is comparable to anti ageing products produced by other renowned companies.

The percentage assessment determined that:

- **51,11 women applying Retorna® cream** (*versus 40 % of women applying placebo*) - in 3 months observed significant or moderate improvement in wrinkling, skin hydration and sebum production

  33, 33% women applying Retorna® cream (*versus 53,33% of women applying placebo*) in 3 months observed insignificant improvement in the said monitored parameters

Conclusion

Retorna ® cream by Catalysis S. L. Madrid represents a modern anti-aging preparation with positive influence on wrinkling. It helps achieve youthful with good cosmetic and aesthetic parameters.

Retorna® cream, Catalysis Madrid, S.L.was applied in 60 women with average age of 47 years; the oldest patient was 35 and youngest 60 years. Average application time comprised 78,33 days. Most women in the group were of skin phototype II (46 women). There were 10 women with skin phototype I. and 4 women with skin phototype III. Women of other ethnicity with skin phototype IV were not included. Most frequently they presented class I and II wrinkles on the forehead, around the eyes and mouth, and on the neck. Class III wrinkles usually appeared around the eyes and mouth.

All women were instructed in the system of application, and the prohibited use of similar products and systemic antioxidants, as well as the necessity to use sunscreens (the preparation contains no UV filters).

All women were provided with information in writing and were offered personal consultancy. The women were informed of the possibility to use Retorna® cream as a make-up base, which was done by 45% women.

All 60 women applied Retorna® cream for at least 12 weeks (the shortest application period comprised 10 days, and the longest application period comprised 86 days) without discontinuation. 1 patient applying placebo developed an adverse reaction and was excluded from the trial after 10 days. In Centre 04 there was 1 adverse reaction as well and the patient discontinued her participation after 3 days.

58 women terminated the trial according to schedule (%), and 2 women discontinued (%).

Following the application of Retorna® cream, Catalysis Madrid, P.L., the skin was smoother and slightly stretched. In the course of the first 4 weeks we observed reduction in fine wrinkles and in some women also improvement of inflammatory manifestations, for example in those patients suffering from acne menstruationis. The texture (as well as packing) Retorna® cream, Catalysis Madrid, P.L was appreciated by all women. Those women with dry skin would apply the cream three times a day, which is the application regimen some of them actually followed after trial termination.

Skin comfort and overall moderate improvement of aesthetic parameters were observed in some patients also 5 weeks after trial termination. Catemnestic monitoring in three months after trial conclusion has not been possible so far, it was thus impossible to assess whether the parameters returned to the original condition. It was also impossible to follow the prolonged effect of applying Retorna® cream, Catalysis Madrid, S.L.

Retorna® krém, Catalysis P.L., Madrid was assessed (clinically and by measurements) **as the more effective product.**

Most significant effects were observed in women who have not used any special products prior to trial inclusion and whose skin had been previously exposed to sun, weather and aggressive influences

Many women were glad t find out that the application of Retorna® cream, Catalysis Madrid, S.L.had a positive influence on puffy eyes and periocular hyperpigmentation (11 women). The skin around the eyes lightened visibly during the application of Retorna® cream, Catalysis P.L., Madrid,. and its aesthetic parameters improved. All 11 women with periocular hyperpigmentation appreciated this fact more than the general effects of Retorna® cream.

The results were assessed objectively by the Multi Skin Test Center®. **The patients and the investigators in Centre 01 and 02 very much appreciated the recommendations following the computer programme assessment made by the Multi Skin Test Center® which they were provided with at the end of trial**.

During the trial no rejuvenation modalities and no physical treatments were applied, including microdermabrasion, laser scanner, Biostimulation laser etc.

The trial was carried out in winter and spring, however, this fact seemed to have no influence on the final effect.

The results of comparing the therapeutic effect of Retorna® cream, Catalysis S. L. Madrid and placebo in a group of 60 patients promote the usage Retorna® cream:

Adverse effects during the application including burning sensation, erythema, or pruritus were observed only in 1 patient applying placebo and 1 patient applying Retorna® cream, Catalysis S. L. Madrid:

Excellent tolerability, practically no adverse effects and the possibility of applying the cream in women aged 30 to 35 years and high efficacy percentage in older women in preventing and reducing class II and III wrinkles are attributes which advocate wider usage of Retorna® cream Catalysis Madrid, S.L.

The final aesthetic effect influences the mental comfort of the patients indeed.

According to the results obtained, the application of Retorna® cream, Catalysis S. L. Madrid represents an efficient preventive dermatocosmetics modality. In order to potentiate the effect it is necessary to apply Retorna® cream two times a day for at least 3 months, protect the skin from UV rays or potentiate the effect by using systemic antioxidants.

Application is not recommended in patients with known skin allergies. Epicutaeous testing should be performed in such cases prior to application

Bibliographical reference is with the trial coordinator:

1. Konkoľová, R.: Korektivní dermatologie. In: Korektivně dermatologické metody. Maxdorf Jessenius 2001. p. 11.
2. Zelenková, H.: Predbežné závery z klinickej štúdie: Aplikácia Retorna® cream a Retorna® solutio oral ako anti-aging prírpavkov, apríl 2007

13. Annex I

13. Annex I

Trial design

Annex I

Trial Design Draft – Version as of September 18th, 2008

Application of Retorna® cream (Catalysis S.L. Madrid) as an anti-aging preparation in women aged 35 to 60 years with ageing or damaged skin and Class I to III wrinkles

Trial objective:

To verify the efficacy and tolerability of applying Retorna® cream, Catalysis Madrid in female trial participants with ageing or damaged skin on the face, neck and décolleté and assess the differences in the final effect and individual tolerability.

trial coordinator: Dr. Hana Zelenková, Ph.D., DOST Svidník

Trial type: type IV with post-registration monitoring,
Double or single blind (the producer decides),
randomised open trial with continuous inclusion of patients according to set criteria

Number or patients: 60, 4 Centres with 15 females each

Trial centres:

Slovakia		**Centre**	**Patients**
Svidník I	**(Dr. Hana Zelenková, Ph.D.)**	**01**	**15**
Svidník II	**(Dr. Júlia Stracenská)**	**02**	**15**
Žilina I	**(Dr. Alena Nejdková)**	**03**	**15**
Czech republic			
Brno	**(Dr. Zuzana Vykutilová)**	**04**	**15**

Diagnosis: ageing and damaged skin with class I – III wrinkles (see notes**)

Participants: women aged 35 to 60 years

Local finding assessment: performed 4 times, at inclusion, and after 4, 8, and 12, weeks

Note * : *the patients shall be followed 3 months after trial conclusion*

At least three Centres shall work with the Multi Skin Test Center® by Courage + Khazaka to measure:

- **skin elasticity**
- **skin hydration**
- **skin type according to sebum production and the changes in sebum production**

and objectively assess the condition of wrinkles and skin quality (hydration, tone) in all patients. Other centres shall use photodocumentation or imprinting methods.

The assessment shall be made 3 times: at inclusion, after 4 and 12 weeks

Time schedule:

October -November 2008	continuous inclusion and exclusion of the patients
December 2009 – March 2009	performance of the trial
April - May 2009	assessment and processing of obtained results
June 2009	handing over the completely processed results
July - December 2009	presenting and publishing of the results

It is important to start the trial in autumn in order to minimise the effects of sun exposure and spare the trial participants of using sunscreens!!

Tested preparation: **Retorna® cream Catalysis Madrid S.L. Madrid**

Innovation: **molecular activation**

Composition (presumed):

The qualitative and quantitative composition of RETORNA CREAM is as follows:

ACTIVE PRINCIPLE:		
Mimosa Extract	0.25	%
Aloe Vera	5.0	%
Glycyrrhizinic Acid	0.1	%
EXCIPIENTS:		
C12-C15 Alkyl Benzoate	6.4	%
Caprylic/Capric Triglyceride	3.0	%
Salicyloyl Phytophingosine; PPg-3Myristyl Ether	3.0	%
Glycerin	3.0	%
Glyceryl Stearate	2.0	%
Stearyl Alcohol	2.0	%
Polyglyceryl-3-Methylglucose Distearate 1.5	%	
Decyl Oleate	1.5	%
Stearic Acid	1.0	%
Euxyl K300	1.0	%
Ceteareth -25	0.5	%
Tecopheryl Acetate	0.5	%

Creatine	0.5	%
Panthenol	0.2	%
Sodium Hydroxide	0.2	%
Allantoin	0.1	%
Carbomer 134	0.1	%
Parfum	0.1	%
Aqua	62.3	%

Patient information: given by the therapist both orally and in writing,

also about the possible adverse effects

Inclusion criteria

- Aging or damaged skin on the face, neck and décolleté
- **wrinkles of class I to III (see wrinkle classification system**)**
- Outpatient status
- Age: 35 years and more
- Voluntary participation in the trial
- Written patient consent form confirmation
- One-time participation in the trial

Exclusion criteria

Specific exclusion criteria

- Known allergies to the tested preparation
- Disease focus infection manifestations (superinfection requiring therapy)
- Immunosuppressive therapy
- Cancer
- Malignancies
- Employment of other drug/s and /or preparation/s in therapy

General exclusion criteria:

- Alcohol and drug abuse
- Painkiller abuse
- Participation in another clinical trial within the past 30 days
- Simultaneous participation in any other clinical trial
- Other reasons excluding the patient from the trial
- Restricted ability of the patient to follow therapy instructions
- Other physical or mental disorders disturbing the trial plan
- Possible consent withdrawal, presumed patient unreliability

Application regimen: Retorna® cream applied 2 times a day for 12 weeks (3 months)

on the face, neck and décolleté

Concomitant application or administration of other preparations:

In emergency cases exclusively and based solely on recommendation of other medical experts

Drinking regimen:

All women have been instructed in the necessity to adhere to a drinking regimen

Laboratory screening:

Performed 2 times - before therapy commencement and upon therapy termination

Documentation: Work Protocol. Multi Skin Test Center® measurements

Photodocumentation: pictures taken during every check-up to assess the condition of single patients

Note: At inclusion, it is inevitable to adhere to the following Wrinkle classification system**

Class I	Very superficial wrinkles. No specific treatment or intervention (using filling material injection) is required.
Class II	Superficial wrinkles and lines. It is advisable to treat such wrinkles once in a time using semi-permanent filling materials.
Class III	Moderately deep wrinkles – It is advisable to treat such wrinkles once in a time using absorbable, semi-permanent and/or permanent filling materials.
Class IV	Deep wrinkles. Recommended semi-permanent and permanent filler injections, with reduced frequency of interventions.
Class V	Very deeps wrinkles fixed in connective tissue. Filler injections are not recommended

Class IV and V wrinkles are not subject of the trial and inclusion criteria!!!

Therapy effect assessment made by the therapist: scale 1 – 4

1 significant reduction in wrinkling with great aesthetic and cosmetic effect
2 slight reduction in wrinkling with satisfactory aesthetic and cosmetic effect
3 insignificant improvement
4 dissatisfactory effect, without visible changes or with undesired effects

Therapy effect assessment made by trial participants: scale 1 – 4

1 excellent aesthetic and cosmetic effect with no undesired effects
2 satisfactory cosmetic effect
3 insignificant improvement, lack of satisfaction on the side of the patient
4 dissatisfactory effect with progressive wrinkling and other ageing symptoms

Therapy tolerability assessment made by the therapist and the patients: scale 1 – 4
(1- excellent, 2 – very good, 3 – good, 4 – intolerance)

The Centres shall receive Retorna® cream Catalysis Madrid, S.L. for the given number of patients to be used within 12 weeks (at least 3 tubes for every patients)

It is possible to obtain more samples upon request.

Time schedule (based on agreement with the management of Catalysis Madrid, S.L.)

October -November 2008	continuous inclusion and exclusion of the patients
December 2008 – March 2009	performance of the trial
February 2009	coordination meting at Catalysis in Madrid
April - May 2009	assessment and processing of results, pre-report
June 2009	handing over the completely processed results
July - December 2009	presenting and publishing of the results

It is not possible to publish the results without prior written consent obtained from the company Catalysis S.L. Madrid, Spain

The company shall send all documentation and the products necessary to carry out the clinical trial in a group and number of selected patients to all trial performing teams.

Annexes:

1. Basic Working Protocol plus tables for investigators
2. Inclusion and Exclusion Criteria
3. List of Patients
4. Patient Consent Form
5. Adverse Effects Documentation Form

13.1. Annexes 1 - 5

Basic set of documents

Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin and class I - III wrinkles

Visit 1 – inclusion parameters

Date of Visit 1: 1111/1111/11111111
day month year

Basic Patient Data:

Age: 1111 years

Sex: 11 male 11 female

Height: 111111 cm

Weight: 111111 kg

Anamnesis:

Signed Patient Consent	□yes	□no
Provided Patient Information	□yes	□no

Application regimen:

Retorna® cream	applied 2 times in the morning and evening on the face
Retorna® cream	applied 2 times in the morning and evening on the neck and décolleté

Skin type: skin phototype I: ☐

skin phototype II : ☐

skin phototype III : ☐

skin phototype IV : ☐

Notes:

stamp date signature

Acute or chronic skin diseases, causing skin manifestations: ☐ yes ☐ no

If YES, state _____

_____

Known allergies to the active or other Retorna® cream ingredients: ☐ yes ☐ no

If YES, state _____

_____

Other diseases causing skin manifestations: ☐ yes ☐ no

If YES, state _____

_____

Usage of drugs or cosmetics, causing skin manifestations: ☐ yes ☐ no

If YES, state _____

_____

Pregnancy/lactation? ☐ yes ☐ no

Any YES answer excludes the patient from participation in the trial

Notes:

stamp date signature

Visit plan

Date of Visit 2: 1111/1111/11111111

(Week 2– Day 14) day month year

Were there any changes in application regimen? □yes □no

If YES, state: _____

Pictures of the lesion □yes □no □number

Date of Visit 3: 1111/1111/11111111

(Week 8– Day 56) day month year

Were there any changes in application regimen? □yes □no

If YES, state: _____

Pictures of the lesion □yes □no □number

Date of Visit 4: 1111/1111/11111111

(Week 12– Day 84) day month year

Were there any changes in application regimen? □yes □no

If YES, state: _____

Pictures of the lesion □yes □no □number

Notes:

stamp date signature

Summary assessment tables:

Quality of skin on the face:

Tab. 1: Pathological manifestations on the face

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
macule					
papule					
vesicle					
pustule					
excoriation					
scales					
node					
atrophy					
Total					

Manifestation assessment and the condition at trial conclusion:

0 = none
1 = slight
2 = moderate
3 = severe

Tab. 2: Condition of the skin on the face

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
wrinkling					
class I wrinkles					
class II wrinkles					
class III wrinkles					
Total					

Wrinkling and condition at trial conclusion:

0 = none
1 = slight
2 = moderate
3 = severe

A - forehead B – glabella C – periocular area D - perioral area

The assessment in the table must include the number and locality in brackets – e.g.: 1 (A), 2 (C)
Improvement: must give the X/Y – figure with X being the number of patients
Y being the assessment score e.g.: 4/

This is valid for all tables

Note: Class IV and V wrinkles result in patient exclusion

Notes:

stamp date signature

Tab. 3: Quality of skin on the face

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Smoothness					
Suppleness					
Elasticity					
Total					

Description:

Smoothness – 1 dissatisfactory, 2 satisfactory, 3 very good
Suppleness - 1 dissatisfactory, 2 satisfactory, 3 very good
Elasticity - 1 very decreased, 2 decreased, 3 satisfactory

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Tab. 4: Sebum content in the skin (Sebumeter Courage & Khazaka) – forehead/chin

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Very dry (<100)					
Normal (100-220)					
Greasy (> 220)					

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Tab. 5: Skin hydration (Corneometer Courage & Khazaka) – left cheek

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Very dry (<50)					
Dry (50-50)					
Hydrated (> 220)					

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Notes:

stamp date signature

Tab. 6.: Skin elasticity on the face

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Very decreased					
Decreased					
Satisfactory - normal					

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Tab. 7: Assessed efficacy of the cream applied on the face - investigator/patient

	Visit 1 (test) date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion:
Very good					
Good					
Satisfactory					
Without changes					
Dissatisfactory					

Tab. 8: Assessed tolerability of the cream applied on the face - investigator/patient

	Visit 1 (test) date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion:
Very good					
Good					
Satisfactory					
Without changes					
Dissatisfactory					

Photodocumentation:

Face: ☐yes ☐no

Notes:

stamp date signature

Assessment of the quality of skin on the neck and décolleté:

Tab. 9: Pathological manifestations on the neck and décolleté

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
macule					
papule					
vesicle					
pustule					
excoriation					
scales					
node					
atrophy					
Total					

Manifestation assessment and condition at trial conclusion:

0 = none
1 = slight
2 = moderate
3 = severe

Tab. 1: Condition of the skin on the neck (x) and décolleté (y) – x/y

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
wrinkling					
class I wrinkles					
class II wrinkles					
class III wrinkles					
Total					

Wrinkling and condition at trial conclusion:

0 = none
1 = slight
2 = moderate
3 = severe

Note: class IV and V wrinkles result in trial exclusion

Notes:

stamp date signature

Patient No.: **Initials:** **Centre:** **Page:**

Tab. 11: Quality of skin on the neck (x) and décolleté (y) – x/y

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Smoothness					
Suppleness					
Elasticity					
Total					

Description:

Smoothness – 1 dissatisfactory, 2 satisfactory, 3 very good
Suppleness - 1 dissatisfactory, 2 satisfactory, 3 very good
Elasticity - 1 very decreased, 2 decreased, 3 satisfactory

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Tab. 12: Sebum content in the skin (Sebumeter Courage & Khazaka) – on the neck (x) and the central part of décolleté (y) - x/y

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Very dry (<100)					
Normal (100-220)					
Greasy (> 220)					

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Tab. 13: Skin hydration (Corneometer Courage & Khazaka) – on the neck (x) and the central part of décolleté (y) - x/y

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Very dry (<50)					
Dry (50-50)					
Hydrated (> 220)					

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Notes:

stamp date signature

Tab. 14: Skin elasticity on the neck (x) and décolleté (y) – x/y

	Visit 1 date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion: Improvement:
Very decreased					
Decreased					
Satisfactory - normal					

Assessment of condition at trial conclusion:

0 = no improvement
1 = slight
2 = satisfactory
3 = excellent

Tab. 15: Assessed efficacy of Retorna® cream applied on the neck and décolleté – by investigator/patient

	Visit 1 (test) date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion:
Very good					
Good					
Satisfactory					
Sufficient					
Dissatisfactory					
Insufficient					

Tab. 16: Assessed tolerability of Retorna® cream applied on the neck and décolleté – by investigator/patient

	Visit 1 (test) date	Visit 2 day 28 date	Visit 3 day 56 date	Visit 4 day 84 date	Condition at trial conclusion:
Very good					
Good					
Satisfactory					
Sufficient					
Dissatisfactory					
Insufficient					

Photodocumentation:

Neck and décolleté: ☐yes ☐no

Notes:

stamp date signature

Table 16: Retorna® cream assessed by the trial participant:

	Visit 1 date	**Visit 2 day 28 date**	**Visit 3 day 56 date**	**Visit 4 day 84 date**	**Condition at trial conclusion:**
Does the cream smell nice?					
Is it easy to apply?					
Do you like the texture?					
Easy to penetrate?					
How does your skin feel upon application?					
Does the cream stain?					

Assessment:
1 = very good
2= good
3= satisfactory
4= sufficient
5= dissatisfactory
6= insufficient

Does the cream have pleasant properties? □yes □no

If YES, state _____

_____

Application regimen:
Retorna® cream applied 2 times in the morning and evening on the face

□yes □no

Retorna ® cream applied 2 times in the morning and evening on the neck and décolleté

□yes □no

Notes to final assessment:

stamp date signature

Table 17 **Visits and final assessment**

	Visit 2 after 4 weeks *	Visit 3 after 8 weeks *	Visit 4 after 12 weeks *	Final assessment
Date				
Compliance	yes no	yes no	yes no	yes no
Exclusion from the trial	yes no	yes no	yes no	yes no
Changes in inclusion criteria and supplementary medication	yes no	yes no	yes no	yes no
Healing and reduction of manifestations ** none, ¼, ½, ¾, total				
Complete reduction of manifestations	yes no	yes no	yes no	yes no
Record of supplementary parameters (dry skin, burning sensation, pruritus, erythema)				
Picture of the affected area (whole body, close-up) + number of pictures taken				
Tested preparation tolerability assessment made by the therapist++				
Tested preparation tolerability assessment made by the patient ++				
Tested preparation therapy success assessment made by the therapist++				
Tested preparation therapy success assessment made by the patient++				
Notes Cream quality Photodocumentation				
Next visit				
Notes				

Notes:

***** **Deviation: +/- 2 days at the maximum**

****** **Healing and reduction in manifestations: none, ¼, ½, ¾, total**

+ **The identification card must be seen on all pictures**

++ **1 - very good, 2 - good, 3 - satisfactory, 4 – moderate improvement, 5 - aggravation**

+++ **1- excellent, 2 – very good, 3 – good, 4 – intolerance)**

Date and stamp of the investigator

Annex 2 Retorna

Patient No: **Initials:** **Centre:** **Page:**

Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin and class I - III wrinkles

Version as of October 20th, 2008

CATALYSIS, S. L. MADRID

Inclusion criteria

Inclusion criteria

• Aging or damaged skin on the face, neck and décolleté	yes	no
• **wrinkles of class I to III (see wrinkle classification system**)**	yes	no
• Outpatient status	yes	no
• Age: 35 years and more	yes	no
• Voluntary participation in the trial	yes	no
• Written patient consent form confirmation	yes	no
• One-time participation in the trial	yes	no

Exclusion criteria

Exclusion criteria

Specific exclusion criteria

• Known allergies to the tested preparation	yes	no
• Disease focus infection manifestations	yes	no
(superinfection requiring therapy)	yes	no
• Immunosuppressive therapy	yes	no
• Cancer	yes	no
• Malignancies	yes	no
• Employment of other drug/s and /or preparation/s in therapy	yes	no

General exclusion criteria:

• Alcohol and drug abuse	yes	no
• Painkiller abuse	yes	no
• Participation in another clinical trial within the past 30 days	yes	no
• Simultaneous participation in any other clinical trial	yes	no
• Other reasons excluding the patient from the trial	yes	no
• Restricted ability of the patient to follow therapy instructions	yes	no
• Other physical or mental disorders disturbing the trial plan	yes	no
• Possible consent withdrawal, presumed patient unreliability	yes	no

Annex 2 Retorna

Patient No: **Initials:** **Centre:** **Page:**

Initial examination:

FACE **Class I – III. Wrinkles (Wrinkle classification system)**

Forehead	**Class I:** yes	no	**Class II:** yes	no	**Class III:** yes	no
Glabella	**Class I:** yes	no	**Class II:** yes	no	**Class III:** yes	no
Periocular area	**Class I:** yes	no	**Class II:** yes	no	**Class III:** yes	no
Perioral area	**Class I:** yes	no	**Class II:** yes	no	**Class III:** yes	no
DÉCOLLETÉ	**lass I:** yes	no	**Class II:** yes	no	**Class III:** yes	no

Duration: weeks months years

„ Wrinkle classification system “

Class I	Very superficial wrinkles. No specific treatment or intervention (using filling material injection) is required.
Class II	Superficial wrinkles and lines. It is advisable to treat such wrinkles once in a time using semi-permanent filling materials.
Class III	Moderately deep wrinkles – It is advisable to treat such wrinkles once in a time using absorbable, semi-permanent and/or permanent filling materials.
Class IV	Deep wrinkles. Recommended semi-permanent and permanent filler injections, with reduced frequency of interventions.
Class V	Very deeps wrinkles fixed in connective tissue. Filler injections are not recommended

Class IV and V wrinkles are not subject of the trial and inclusion criteria!!!

Included	excluded

date/stamp/signature

Annex 3 Retorna :

List of Patients

Title: **Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin and class I - III wrinkles**

Version: ..... as of October 21st, 2008

Investigator: **Address:**

Initials (max. 3 letters)	Full name	Year of birth	Sex. f m	Consultation and Instruction Sheet provided (obligatory)	Patient Consent signature obtained (obligatory)	Patient No.: (in case of inclusion only)	Date	Signature

Centre:

List of Patients

Initials (max. 3 letters)	Full name	Year of birth	Sex. f m	Consultation and Instruction Sheet provided (obligatory)	Patient Consent signature obtained (obligatory)	Patient No.: (in case of inclusion only)	Date	Signature

Trial Centre:
Investigator:

I..... (full name) have been fully and comprehensibly instructed in and advised on the nature, purpose and potential contribution of the trial titled

Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin and class I - III wrinkles

by:

and I have been given enough time to decide upon my participation in this clinical trial. I have been influenced or by any means forced neither by my therapist nor any other clinic staff member. I have received patient information in writing and I have read it carefully and understood it thoroughly.

I have been instructed in the principles of health insurance as well as in my obligations resulting thereof.

I agree to my participation in this trial and understand that I am free to withdraw my consent at any time without having to give a reason.

I give my permission for other experts to carry out examinations with the consent of my therapist exclusively, except in case of evident emergency, and understand that I am not allowed to participate in any other clinical trial.

I understand that any adverse effects or health damage that may result from this clinical trial must be reported to my therapist without unreasonable delay.

1. Confirmation of Consent:
I hereby give and confirm my consent for the information gained in the course of this trial, including information about the disease, to be recorded on the forms as well as digital media and submitted without my name attached:

a) to the party ordering this study, the company CATALYSIS, S. L. Madrid, for further scientific evaluation

Apart from that, I give my permission for the pictures of the affected skin to be taken

Moreover, I give my consent for the publication of anonymous photo documentation to be performed.

I have received a copy of Patient Consent Form to keep. The other copy remains with my therapist responsible for the trial. I have received a copy of the patient information sheet as well as the insurance conditions forms to keep.

_____ _____
place, date Patient signature

_____ _____
place, date **Investigator** signature

Patient No.: **Initials:** **Centre:** **Page:**

Adverse and Undesired Effects Documentation

DOCUMENTATION FORM
Undesired effects

Date: . .

Date of first occurrence of the undesired effect: . .

Brief description of the undesired effect:_____

Therapy duration from _____to ___

Brief description of the measures taken _____ _____

Trial discontinuation: yes no

Please fill in the form on undesired effects and enclose it to the patient protocol

Notes:

date/stamp/signature

Date of discontinuation: . .

Tested preparation therapy duration: from _____to: _____

Trial plan carried out until_____ including check-up on _____

Discontinuation cause:

- Patient Consent withdrawal
- Occurrence of adverse effect *****
- Missing therapy effects
- Compliance with any of the exclusion criteria
- Failure to comply with the inclusion criteria
- Missing patient compliance or cooperation
- Serious failure to comply with the protocol
- Other personal reasons stated by the patient (change of address)
- Other reasons stated by the therapist

Notes:

date/stamp/signature

14. Annex II

Tables and graphs -

Single centres 01, 02, 03, 04

Centre 01 MUDr. Zelenková Hana, PhD.

Tab 16

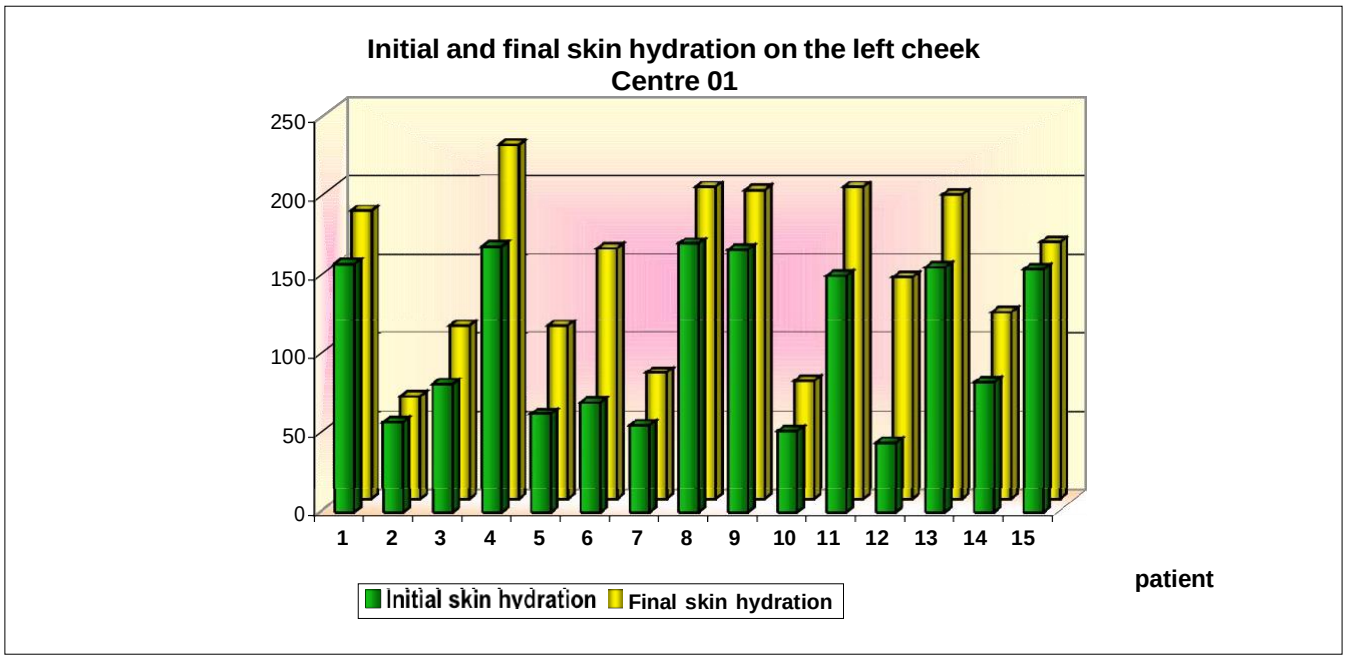
Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles

Multiskin Khazaka Courage

Number of patient	Initial skin hydration on the left cheek	Final skin hydration on the left cheek	Initial skin hydration on the neck	Final skin hydration on the neck	Initial skin hydration on the décolleté	Final skin hydration on the décolleté
1.	157	183	174	188	181	196
2.	57	65	86	200	87	220
3.	81	110	67	180	87	190
4.	168	225	177	221	187	230
5.	62	110	167	198	183	228
6.	69	159	80	226	88	230
7.	55	80	60	92	70	104
8.	170	198	77	190	86	202
9.	166	196	180	190	195	215
10.	51	75	75	178	84	195
11.	150	198	150	180	180	222
12.	44	141	171	222	160	197
13.	155	193	65	110	73	129
14.	82	119	75	85	82	110
15.	154	163	171	203	165	178

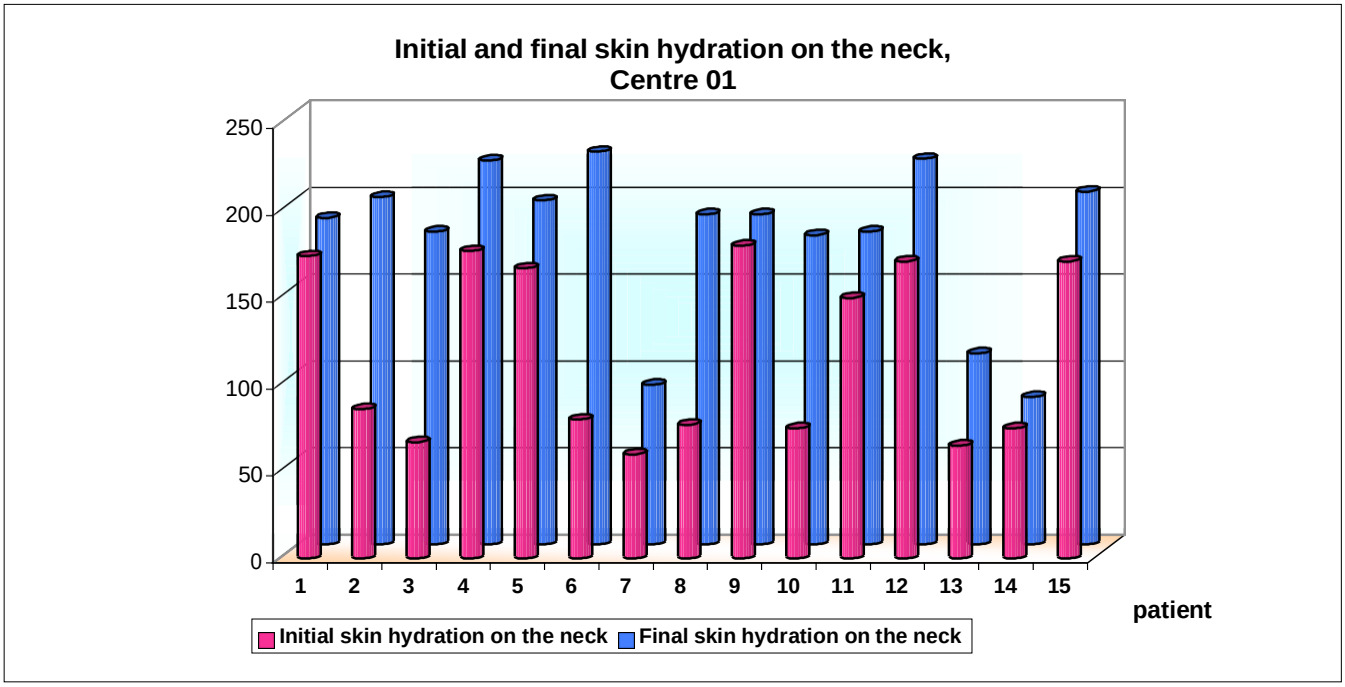
Graph 54

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles
Multiskin Khazaka Courage



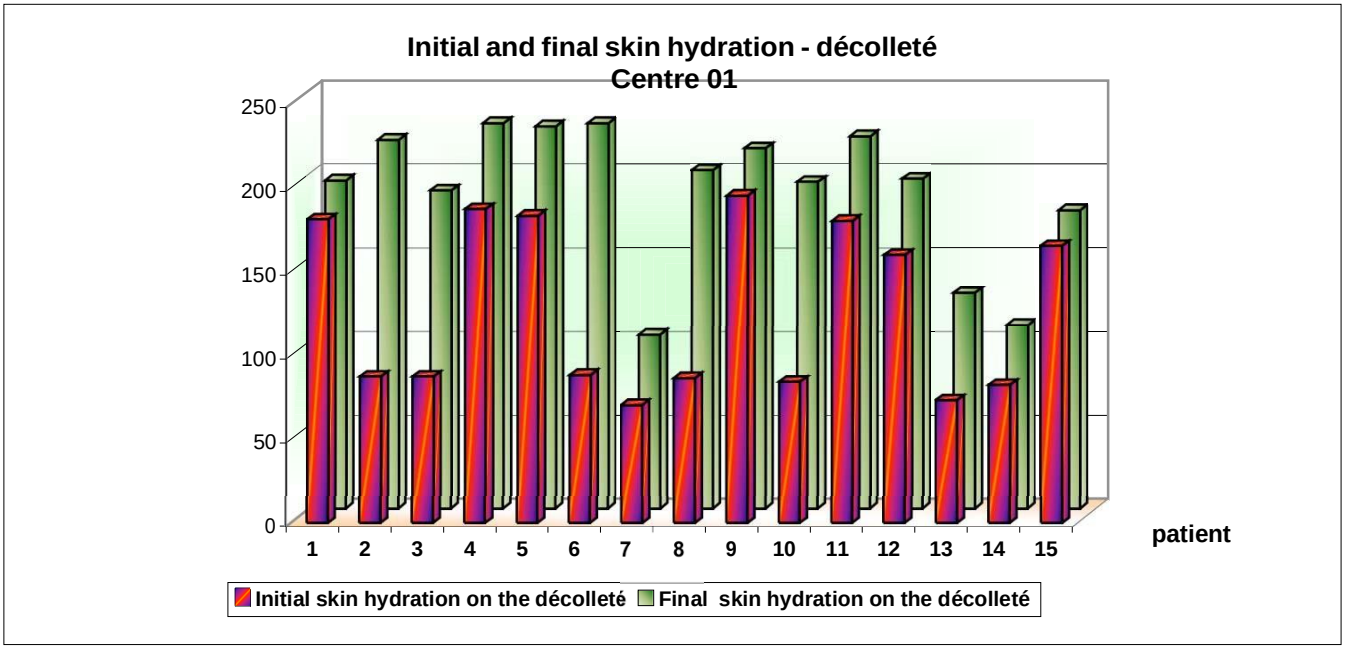
Graph 55

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles
Multiskin Khazaka Courage



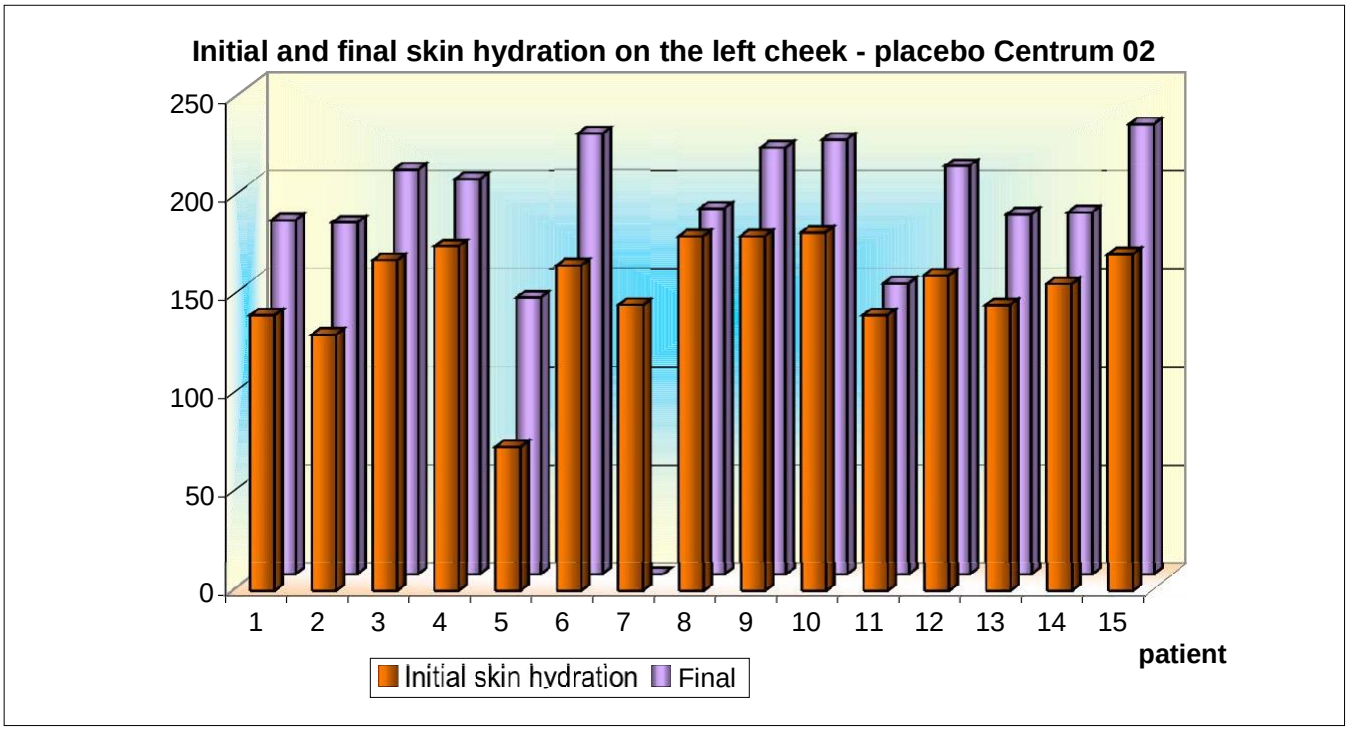
Graph 56

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles
Multiskin Khazaka Courage



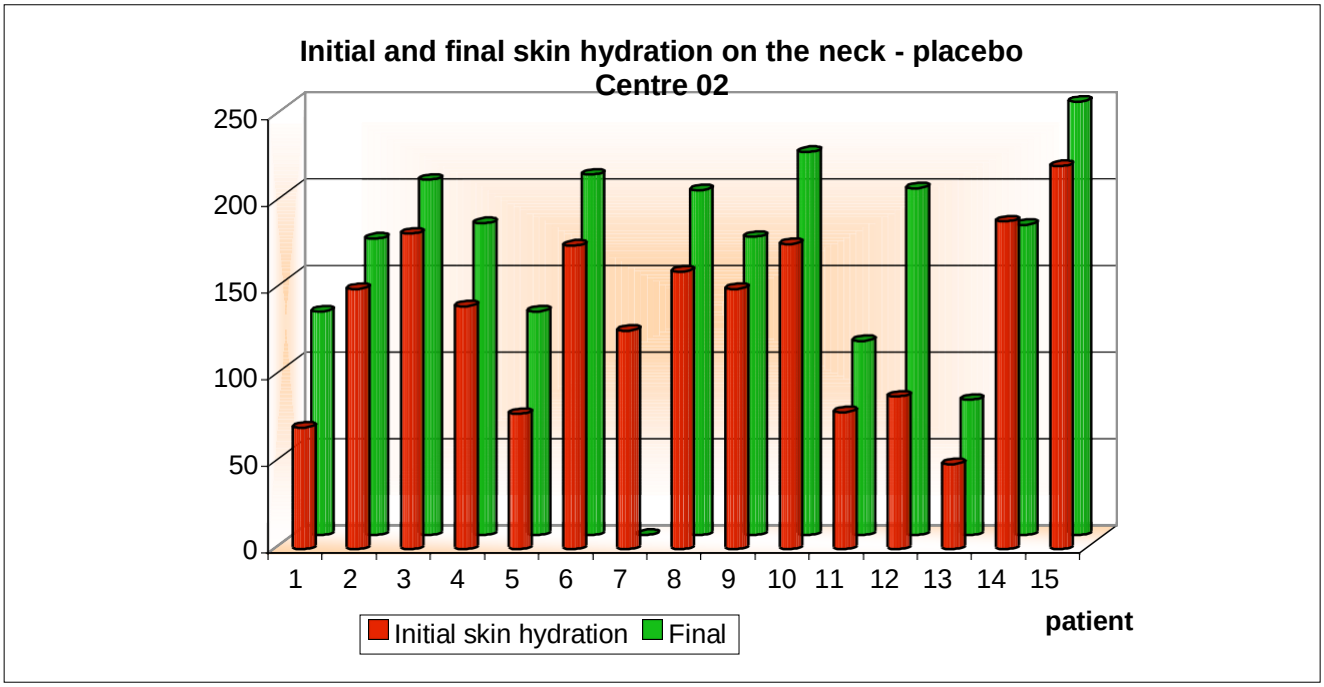
Graph 85

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - Multiskin Khazaka Courage



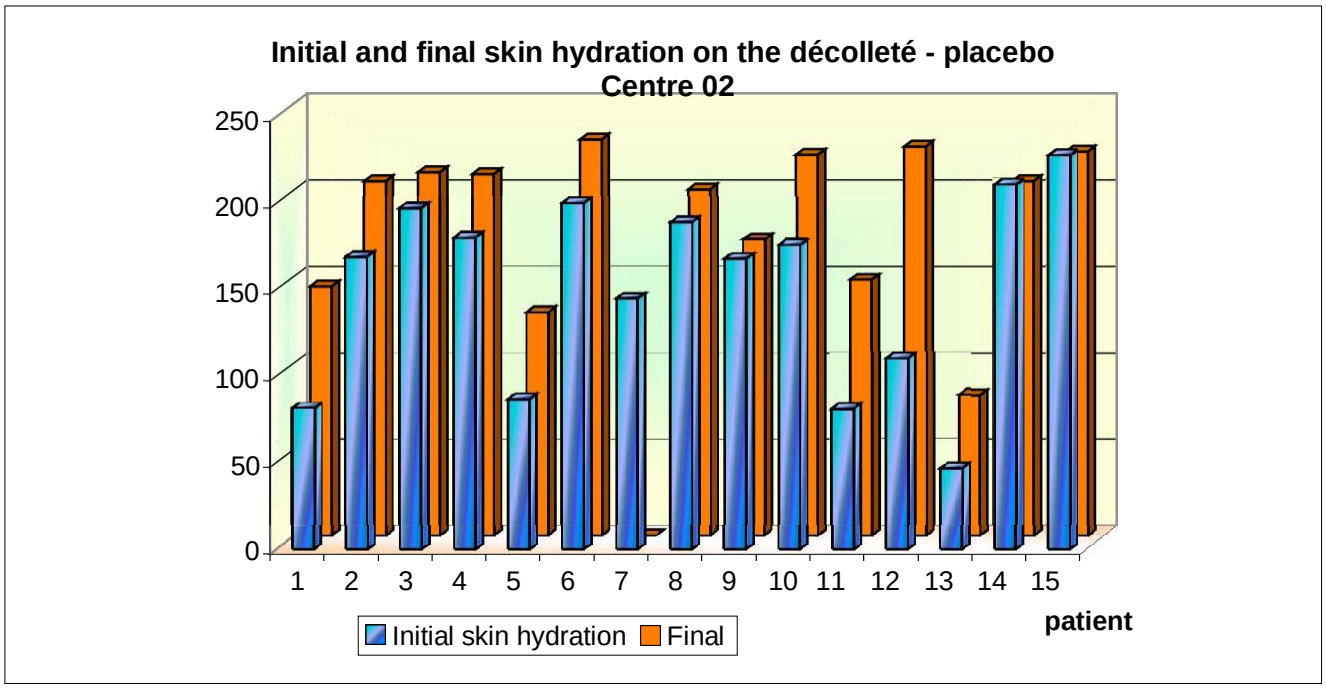
Graph 86

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - Multiskin Khazaka Courage



Graph 87

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - Multiskin Khazaka Courage



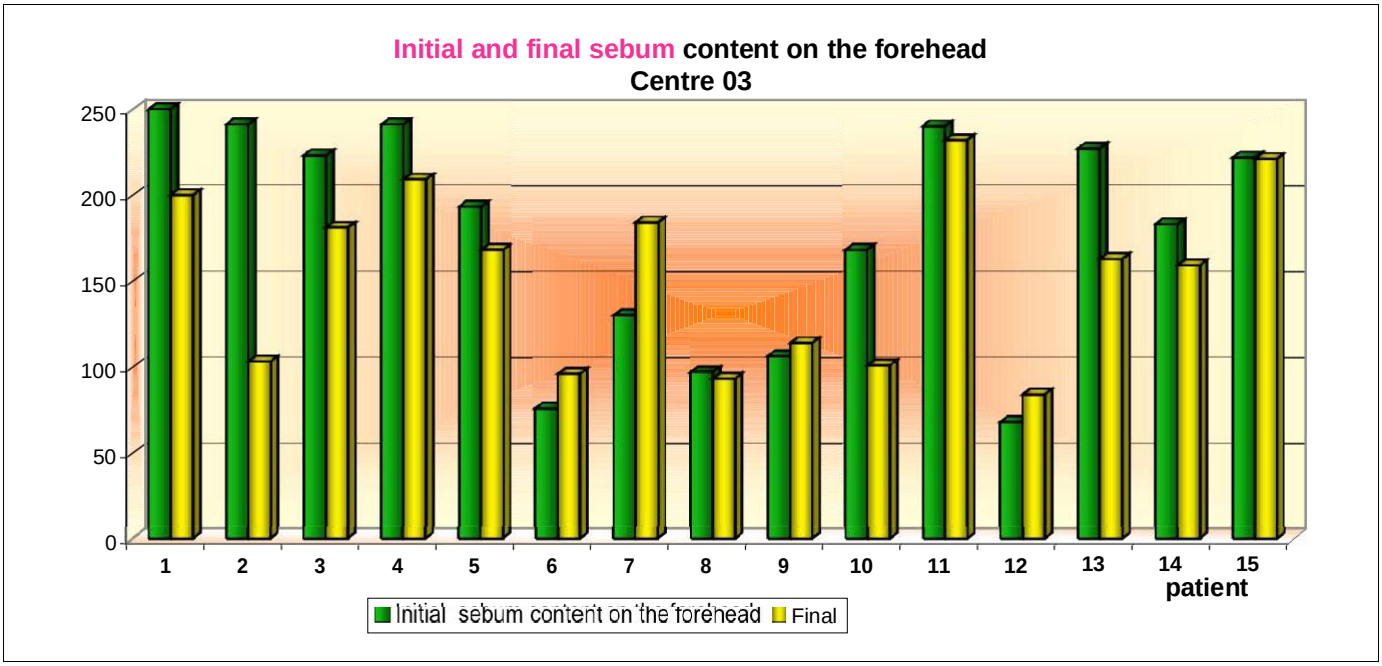
Tab15, 16

Specific data and group assessment - International Multicentre Trial of Retorna® crea (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 ye with ageing and damaged skin with class I – III wrinkles - Multiskin Khazaka Courage

Number of patient	Initial	Final	Initial	Final
	sebum content on the forehead		skin hydration on the left cheek	
1.	250	200	156	182
2.	241	103	56	65
3.	223	181	80	110
4.	241	209	168	226
5.	193	168	61	111
6.	76	96	68	159
7.	130	184	56	80
8.	97	93	171	199
9.	106	114	164	195
10.	168	101	51	76
11.	240	232	151	198
12.	68	84	45	141
13.	227	163	156	192
14.	183	159	81	119
15.	222	221	154	162

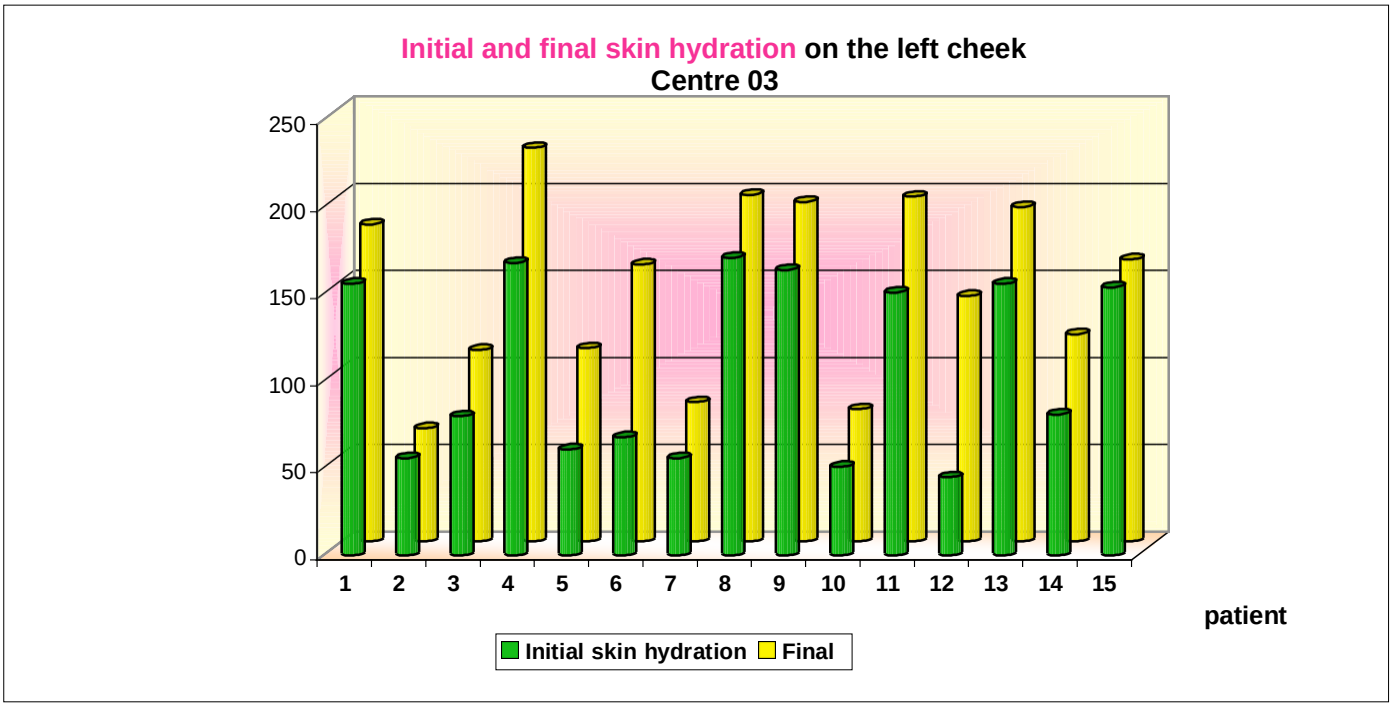
Graph 22

Specific data and group assessment - International Multicentre Trial of Retorna® crea (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 ye with ageing and damaged skin with class I – III wrinkles - Multiskin Khazaka Courage



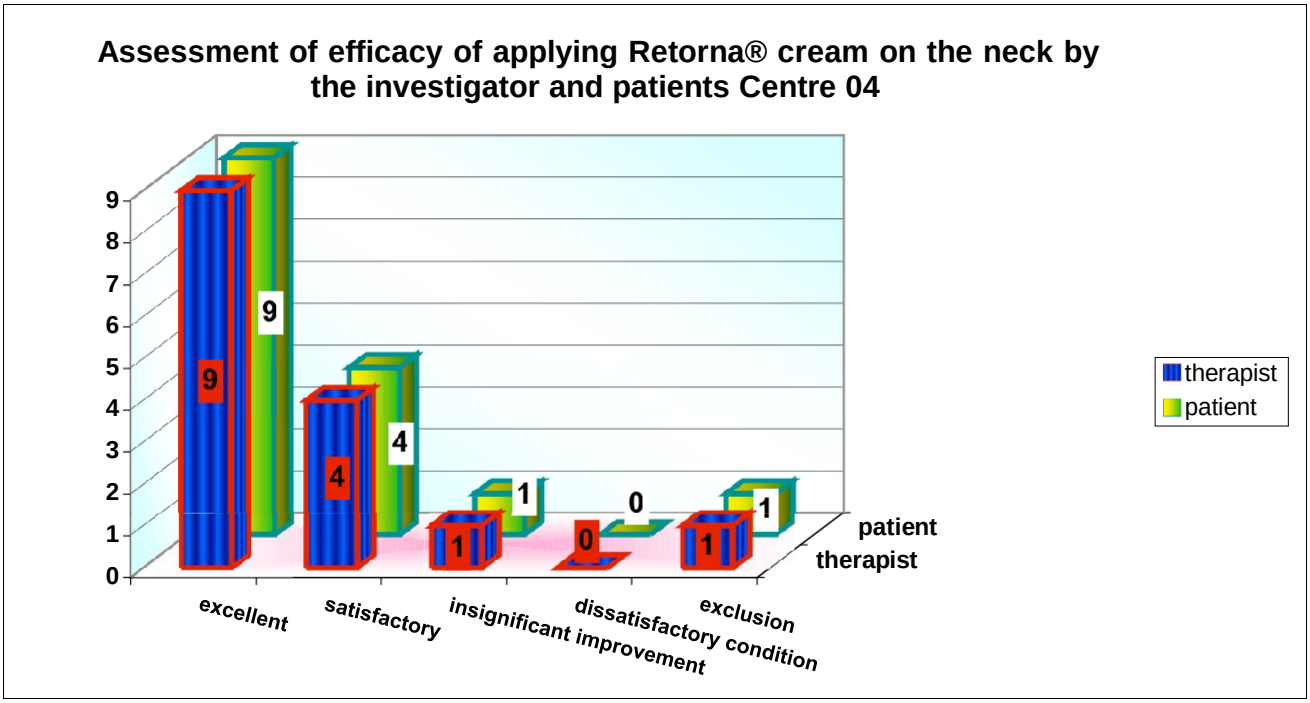
Graph 23

Specific data and group assessment - International Multicentre Trial of Retorna® crea (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 ye with ageing and damaged skin with class I – III wrinkles - Multiskin Khazaka Courage



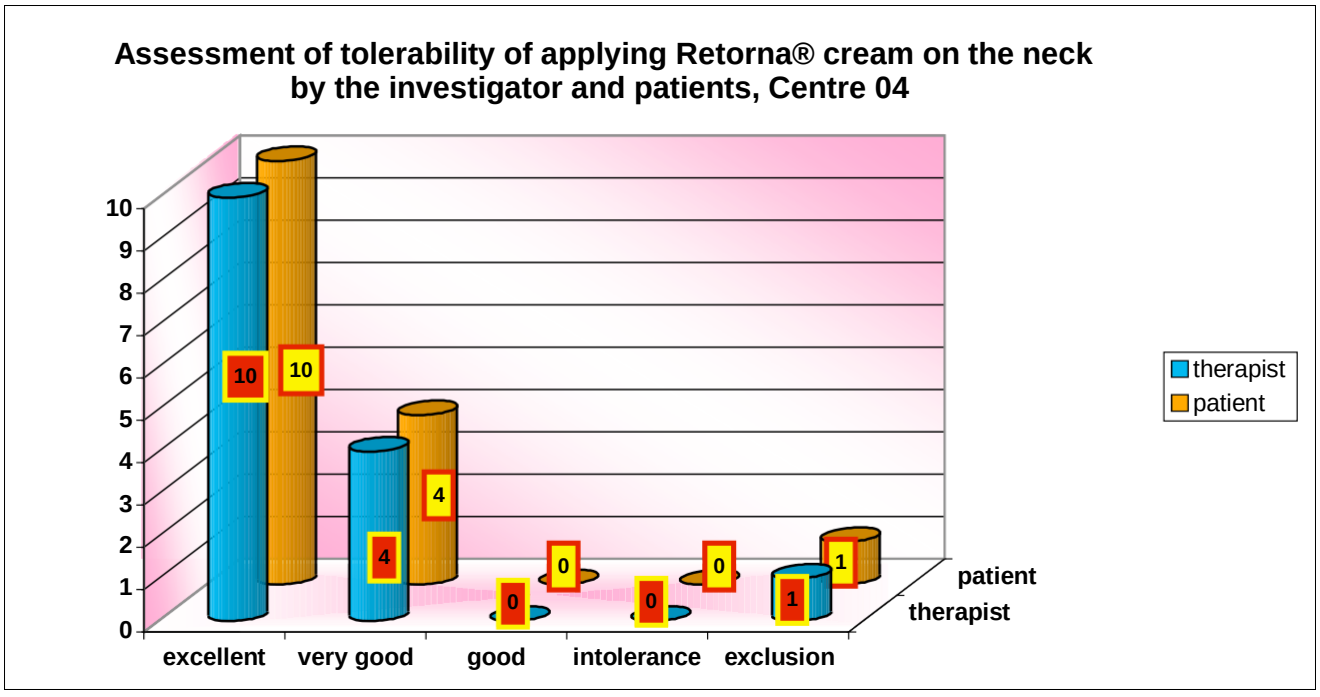
Graph 10

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - area of neck



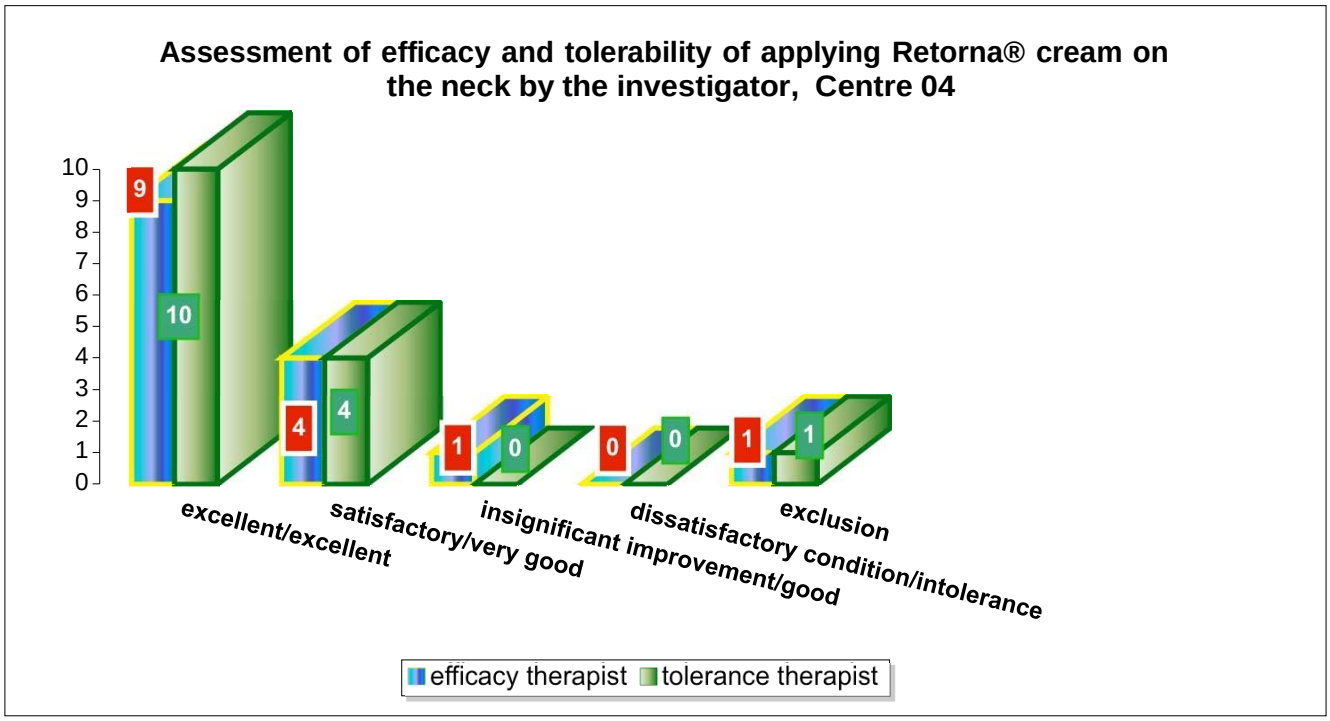
Graph 11

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - area of neck



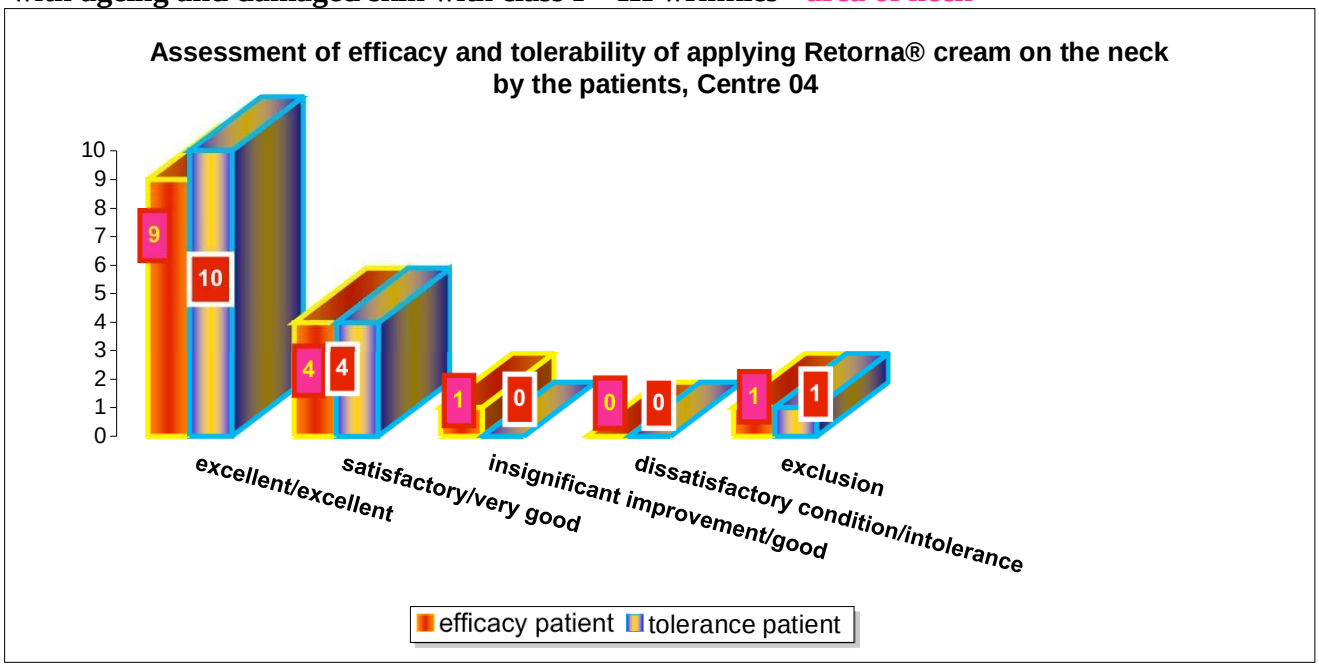
Graph 12

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - area of neck



Graph 13

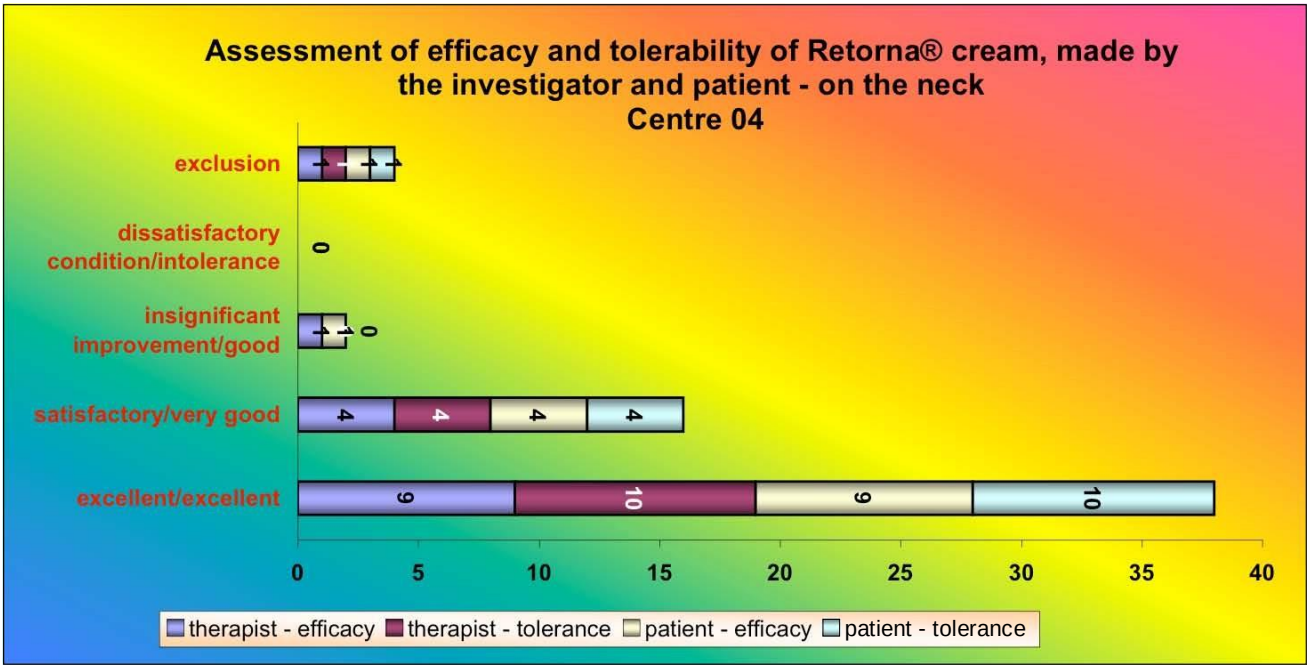
Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - area of neck



Graph 14

Specific data and group assessment - International Multicentre Trial of Retorna® cream

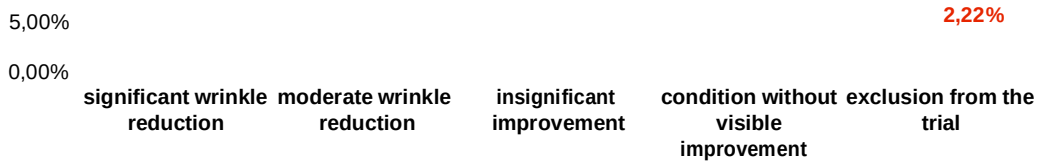
(Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - area of neck



15. Annex III

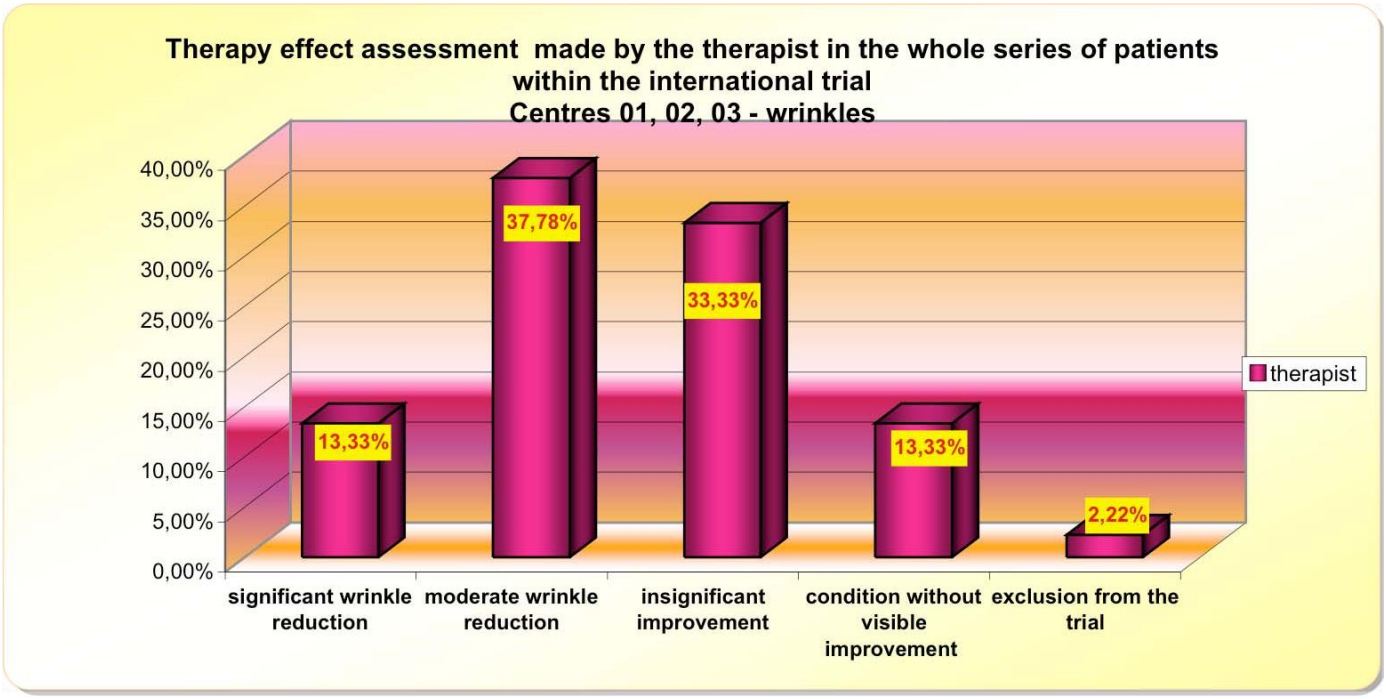
Tables and graphs

Centre 02 –placebo



Graph 24

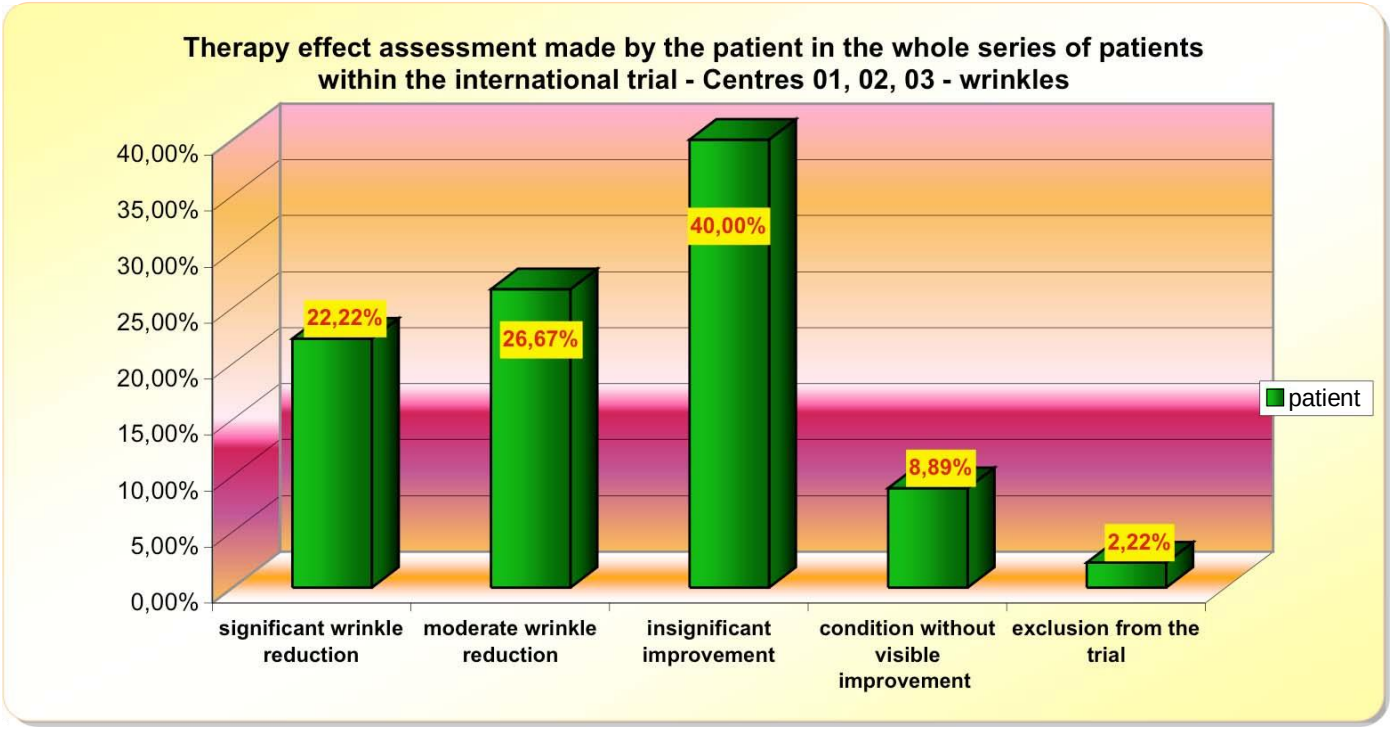
Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - on the face



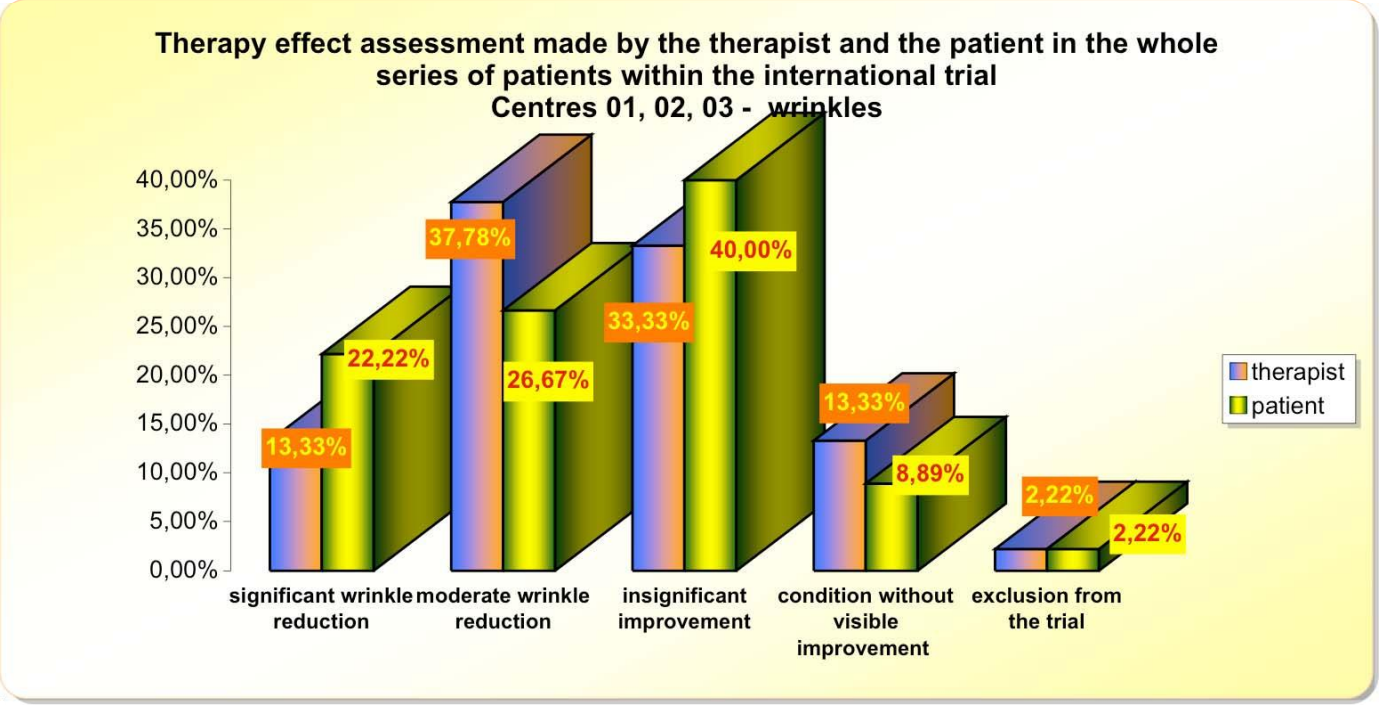
improvement

Graph 25

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - on the face

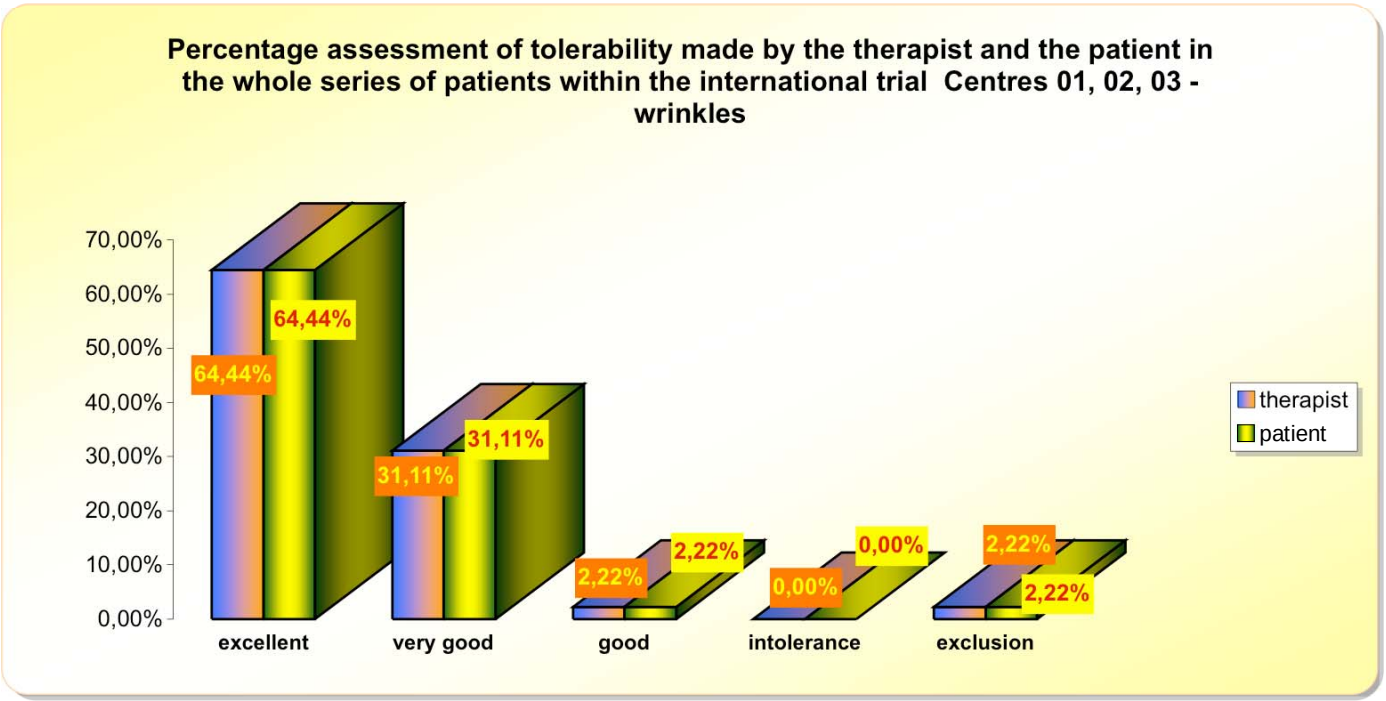


Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - on the face



Graph 27

Specific data and group assessment - International Multicentre Trial of Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I – III wrinkles - on the face

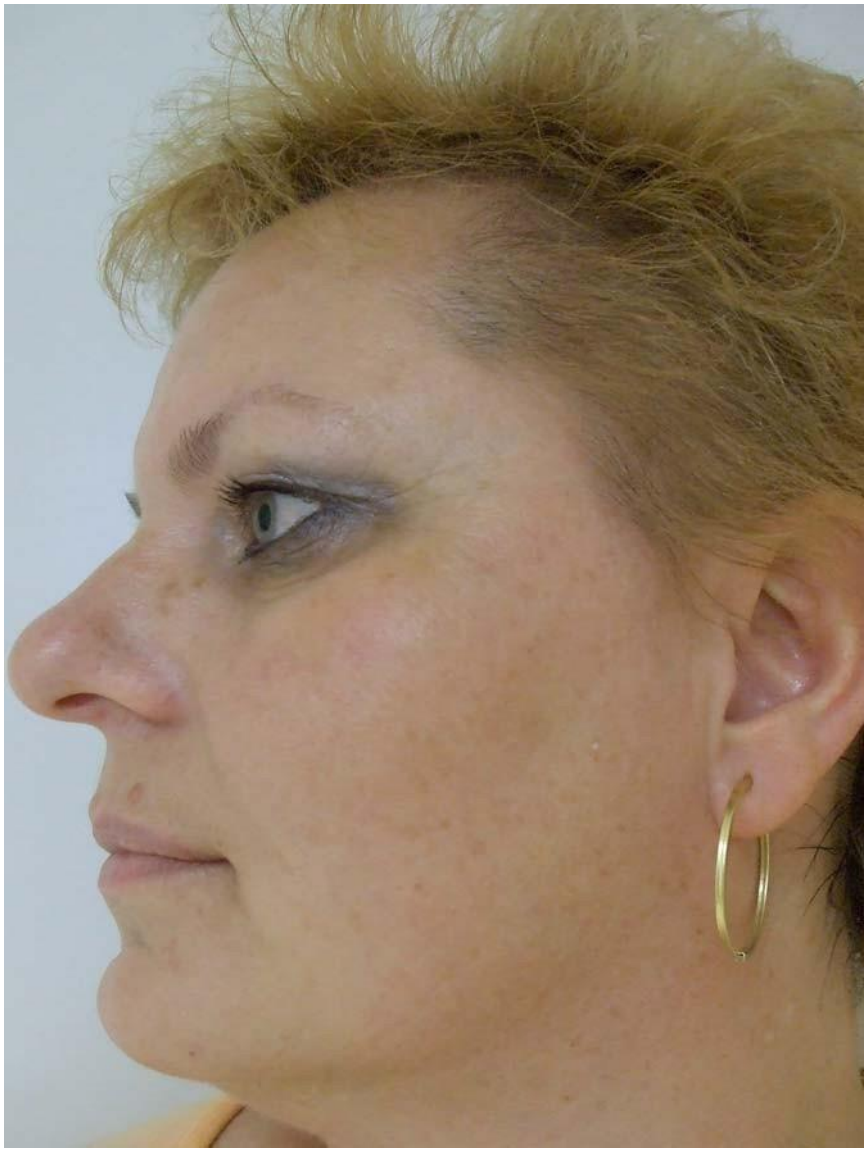


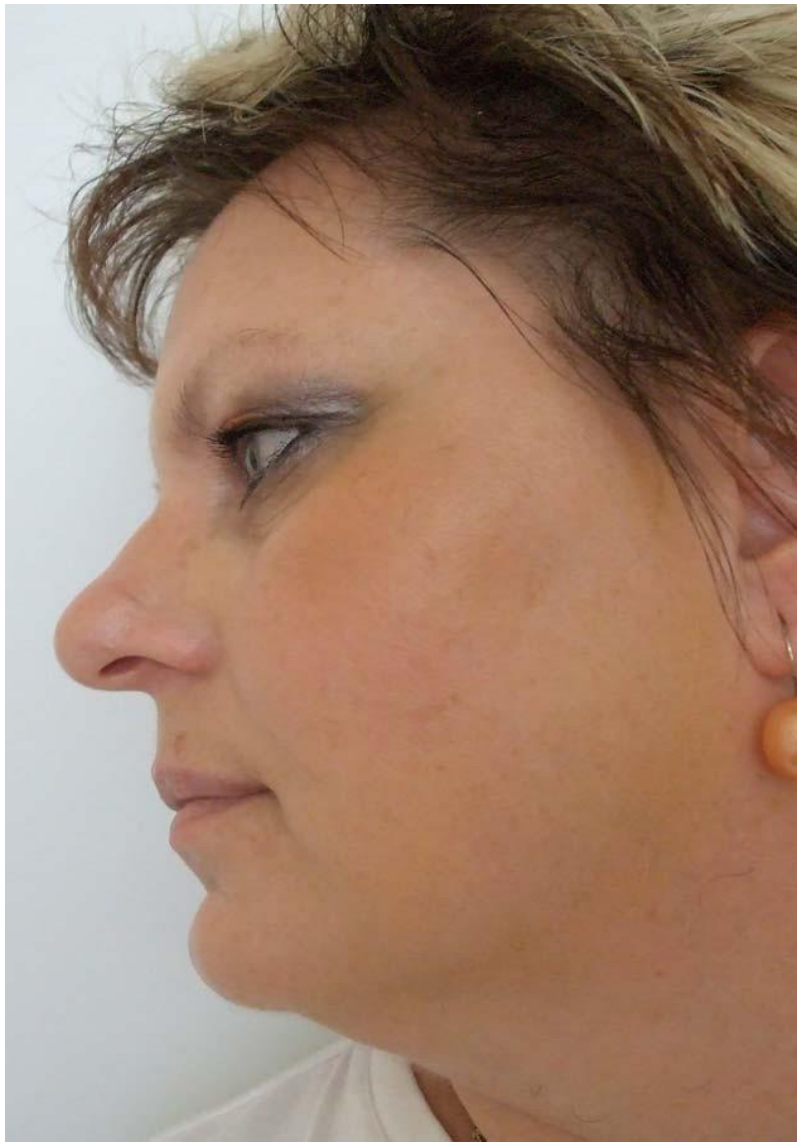
16. Annex IV

Photodocumentation in Centres 01, 02, 03, 04

Centrum 01 MUDr. Zelenková Hana, PhD.

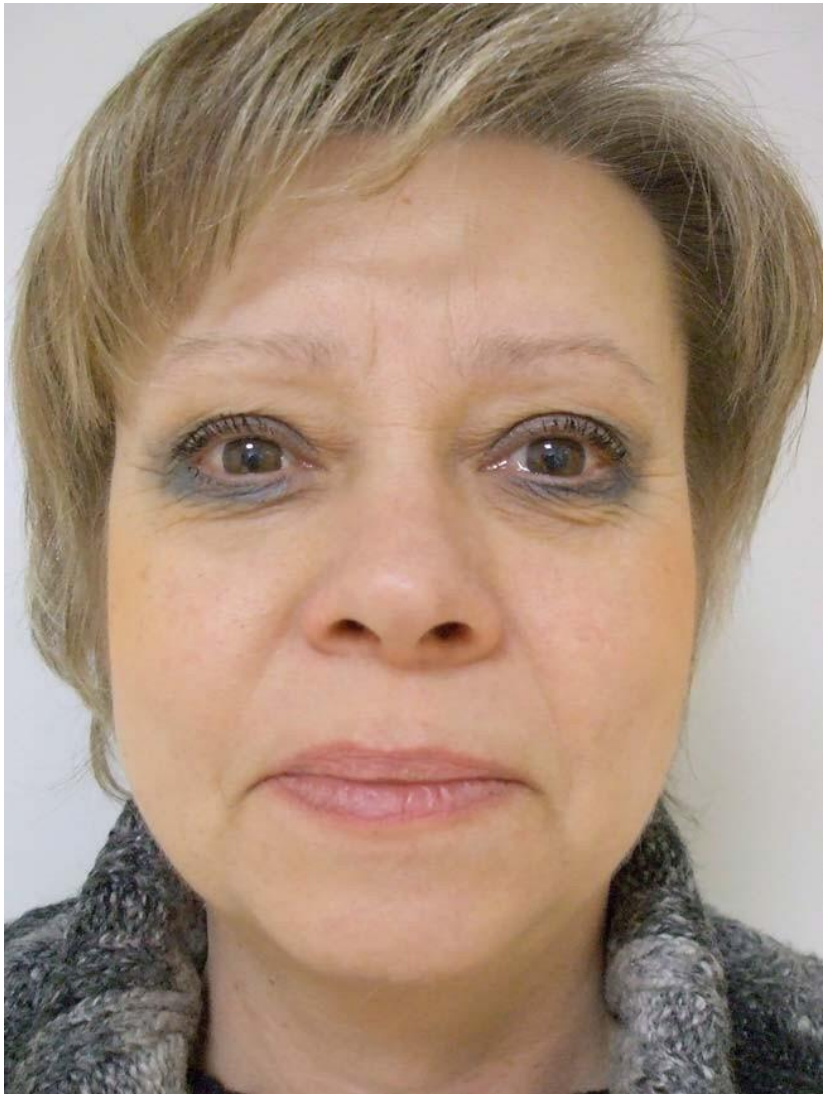
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream, Improved hydration and aesthetic parameters, improved condition of wrinkles around the eyes

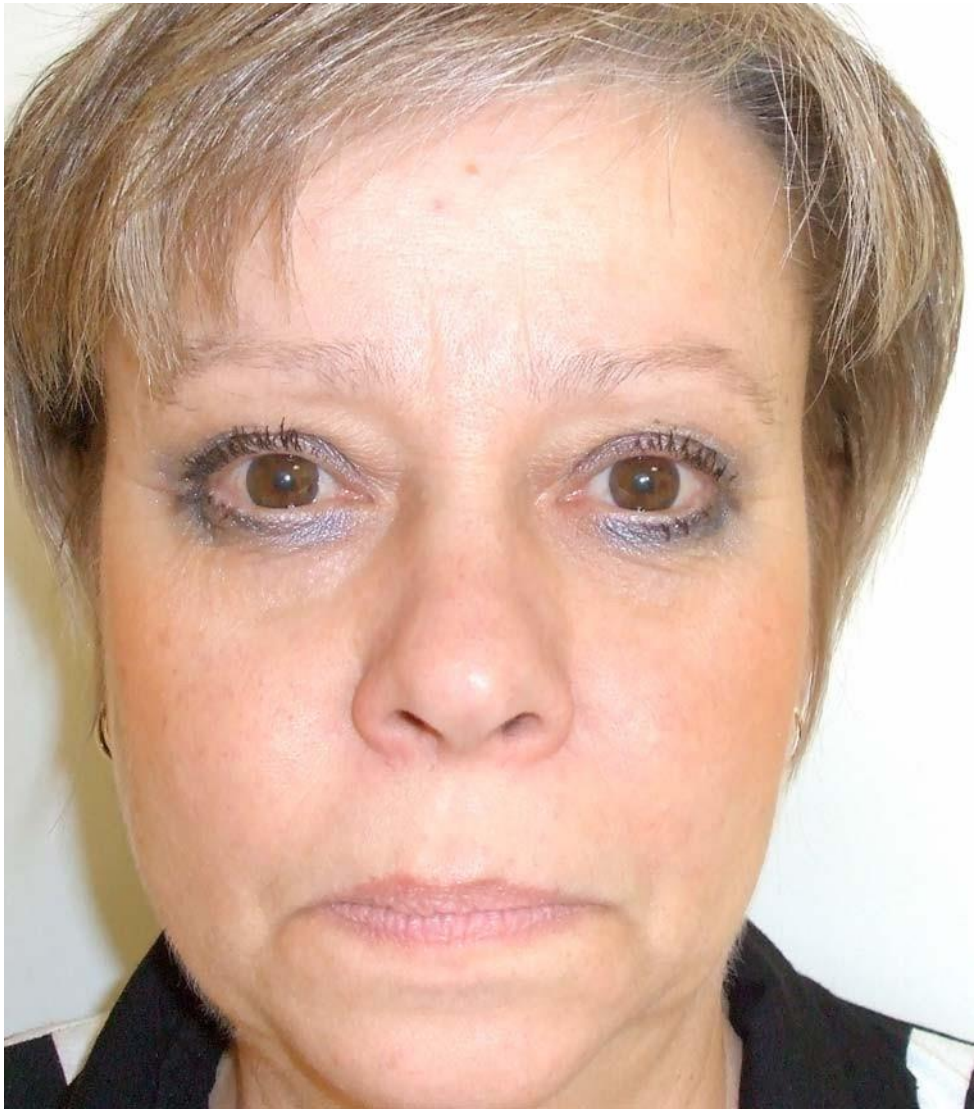




Centrum 01 MUDr. Zelenková Hana, PhD.

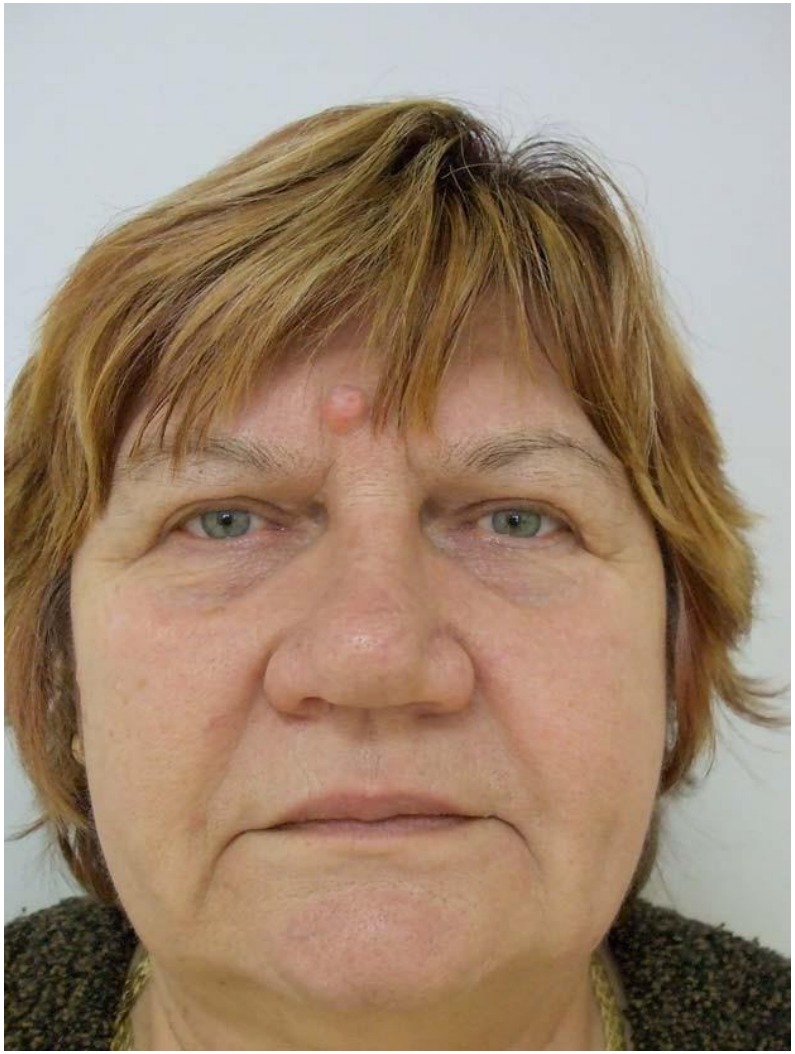
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream –changes in the area around the eyes with brighter skin

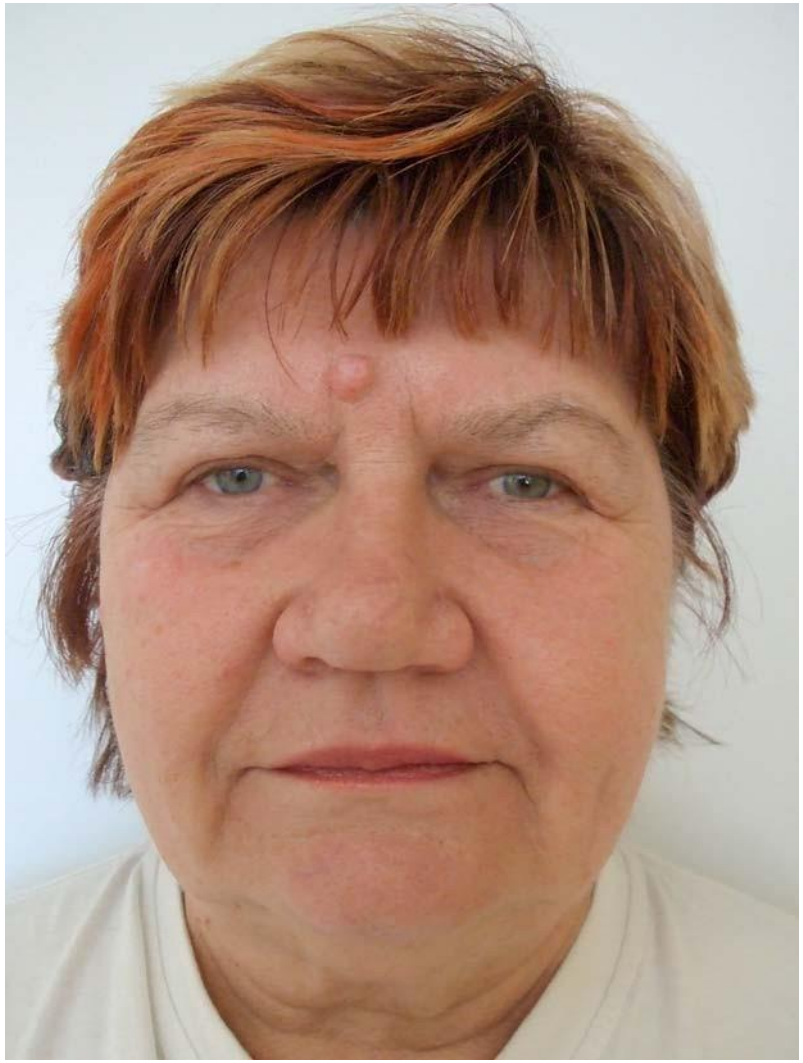




Centrum 01 MUDr. Zelenková Hana, PhD.

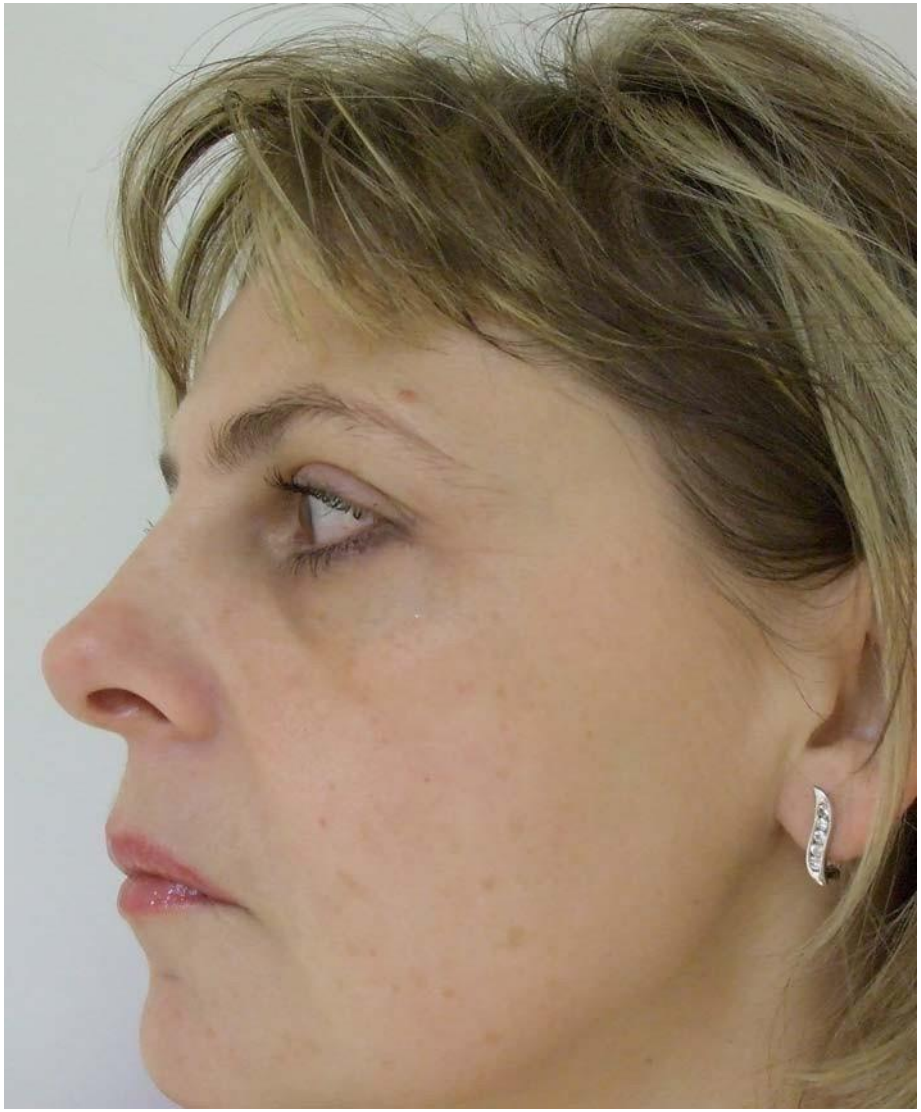
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream – improved wrinkling, brighter skin and significantly improved aesthetic parameters

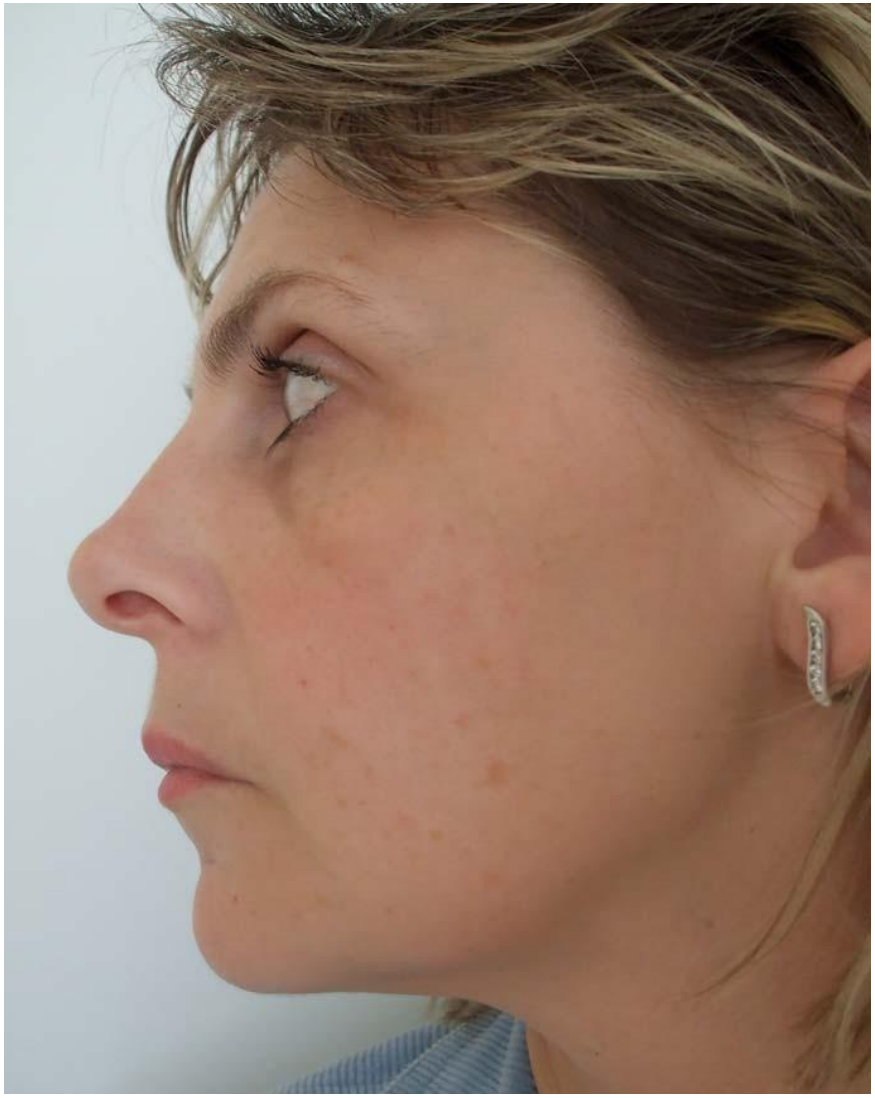




Centrum 01 MUDr. Zelenková Hana, PhD.

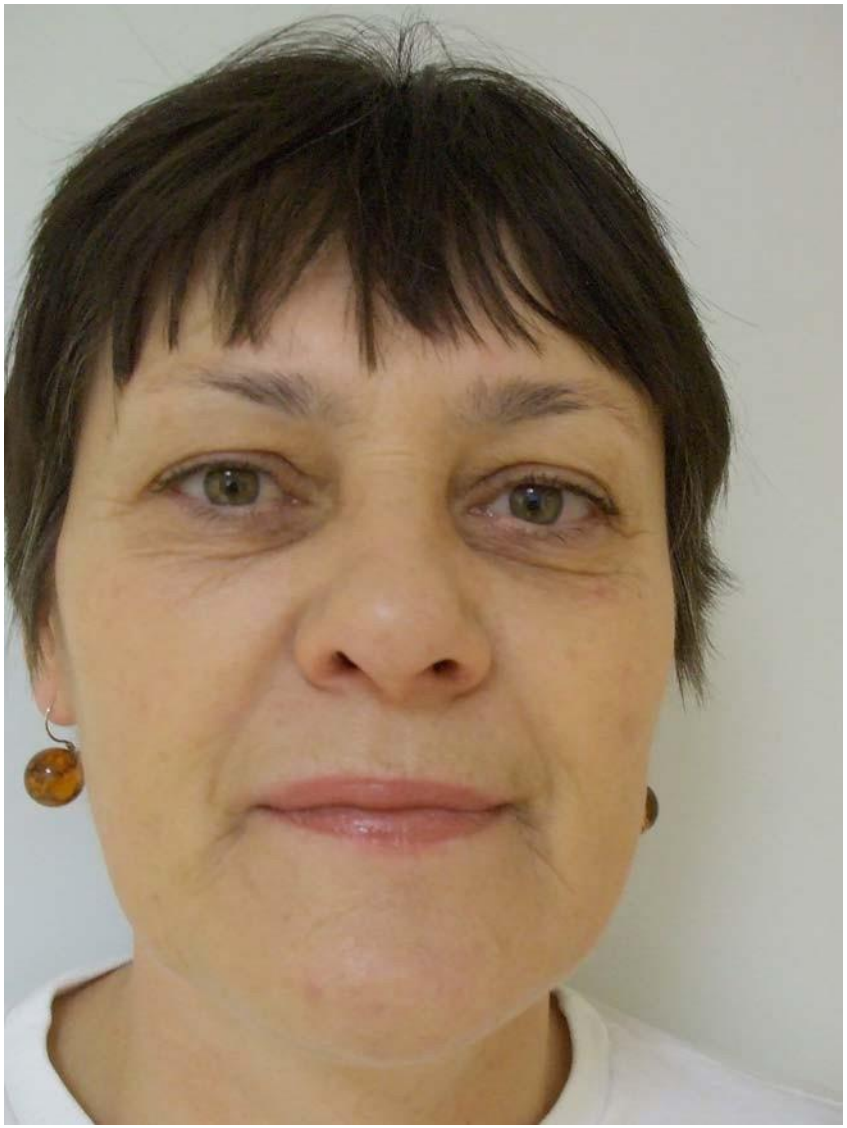
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream – changes in the area around the eyes, significantly improved aesthetic parameters, improved periocular hyperpigmentation

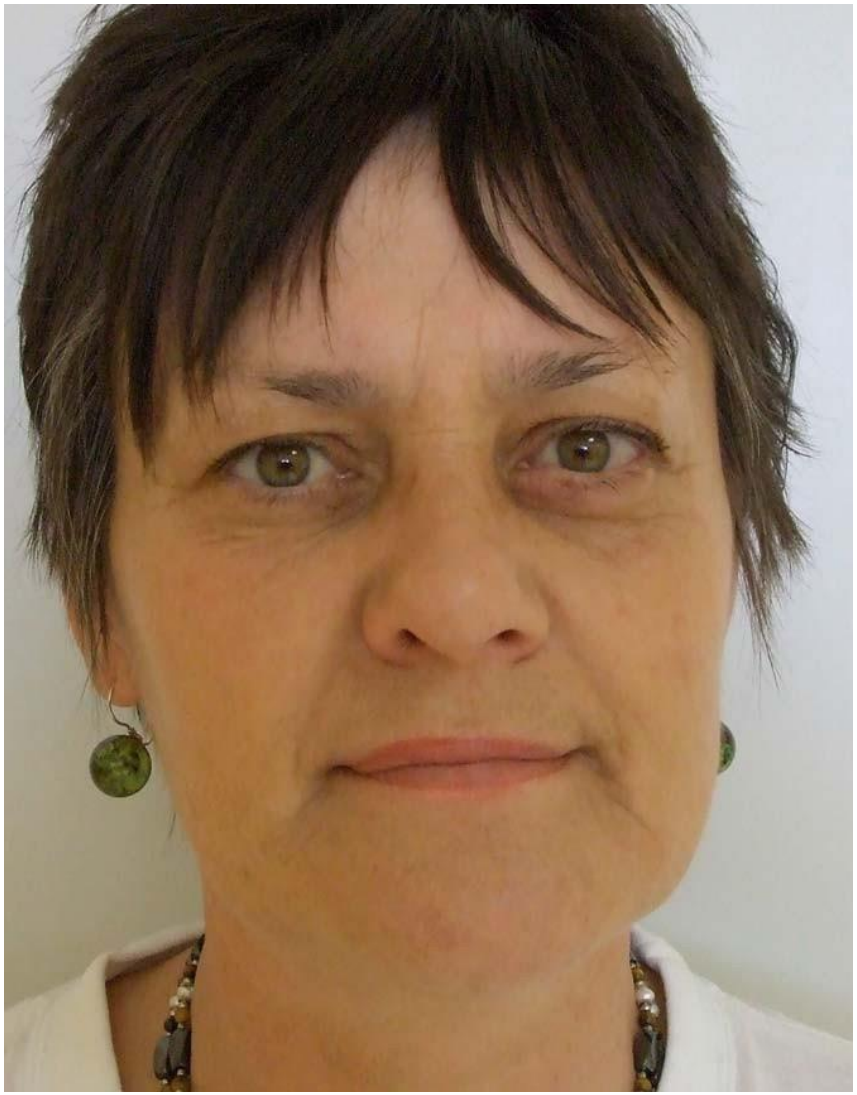




Centrum 02 MUDr. Stracenská

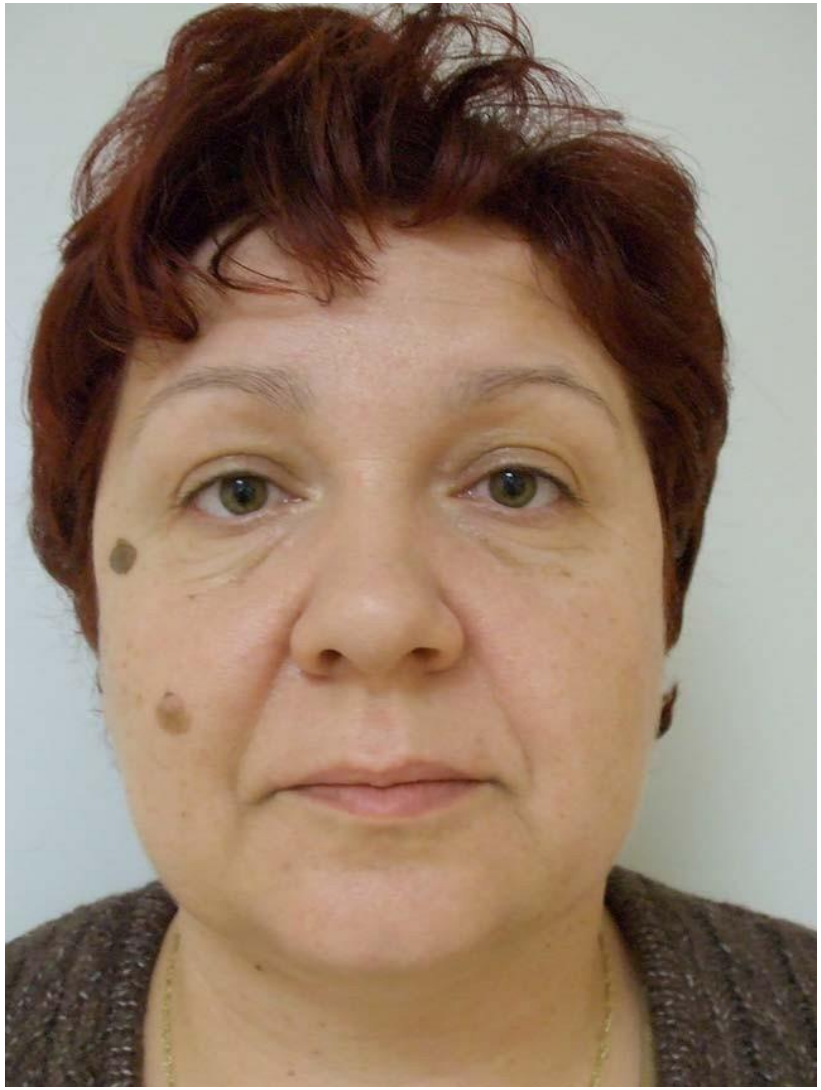
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the right (visible effect) versus placebo on the left without changes in aesthetic parameters and wrinkling

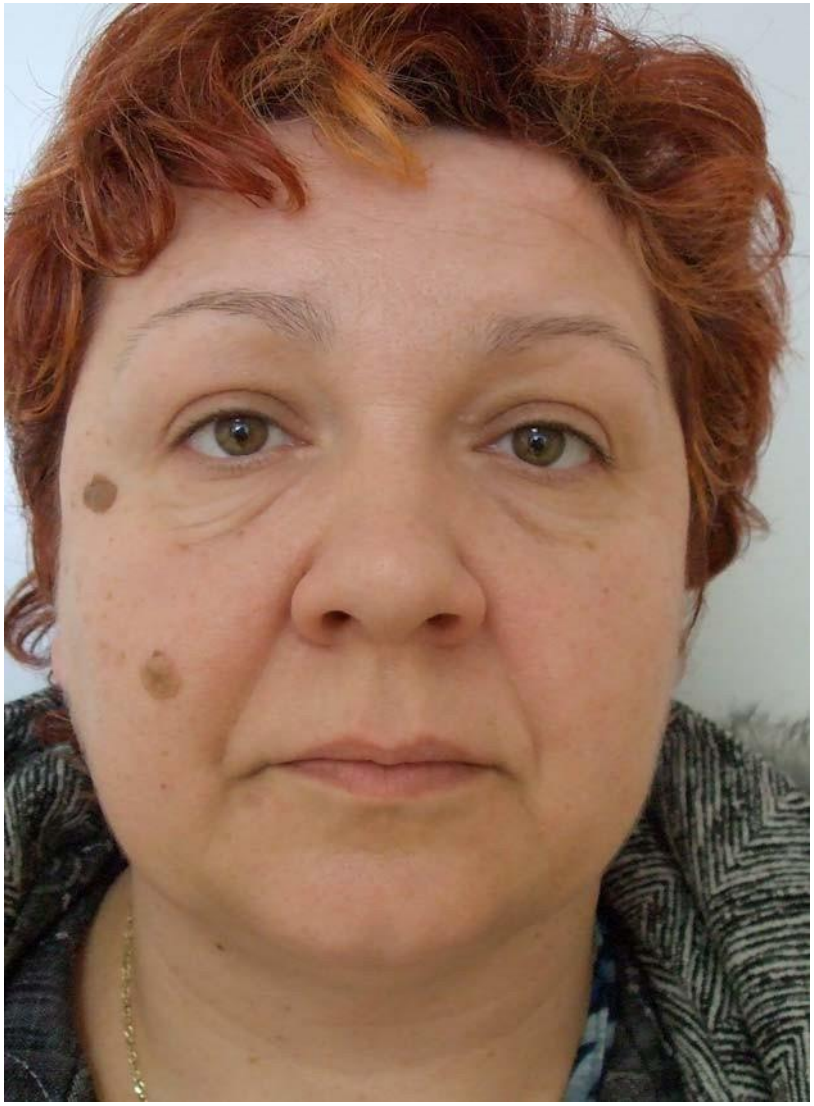




Centrum 02 MUDr. Stracenská

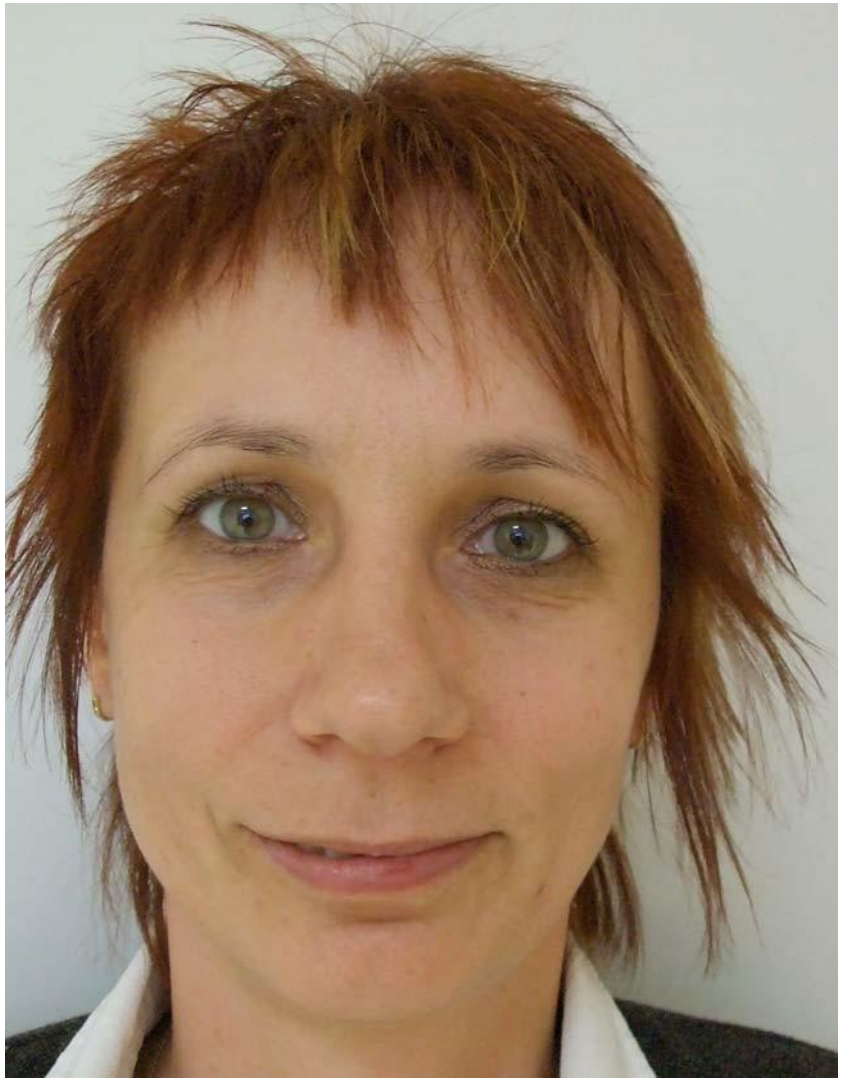
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the right (moderate effect) versus placebo on the left without changes in aesthetic parameters

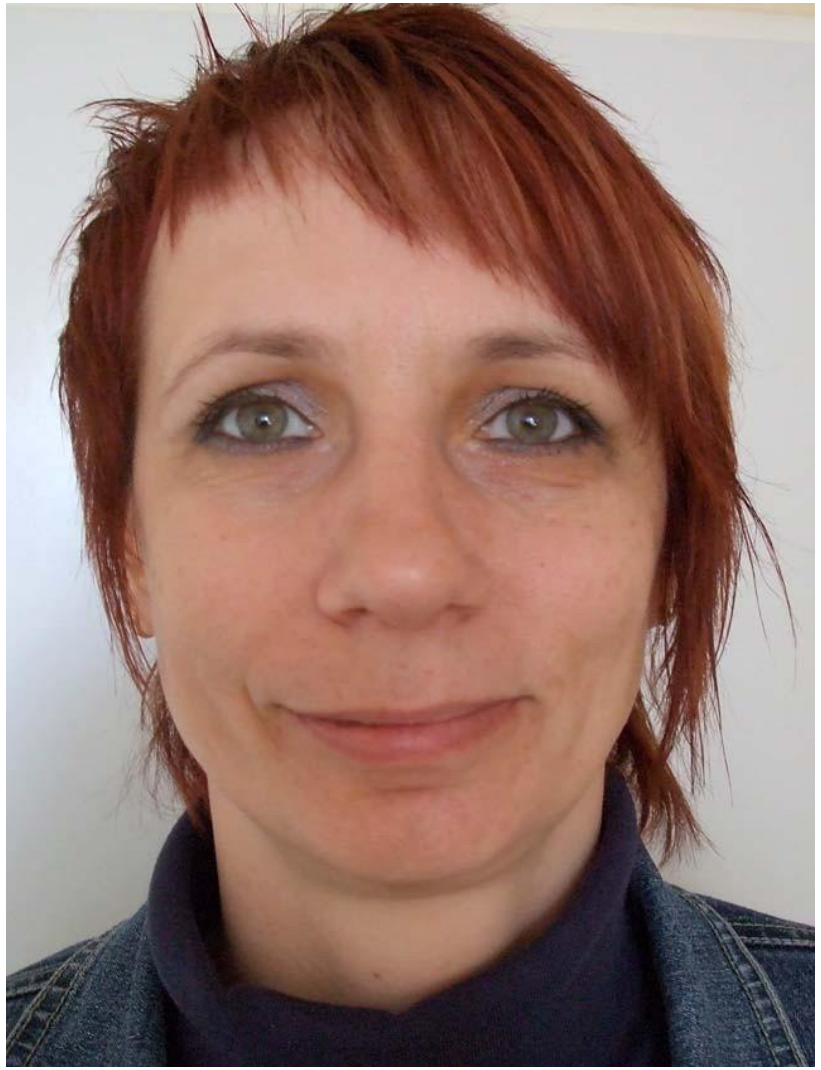




Centrum 02 MUDr. Stracenská

International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the right (visible effect) versus placebo on the left without changes in aesthetic parameters



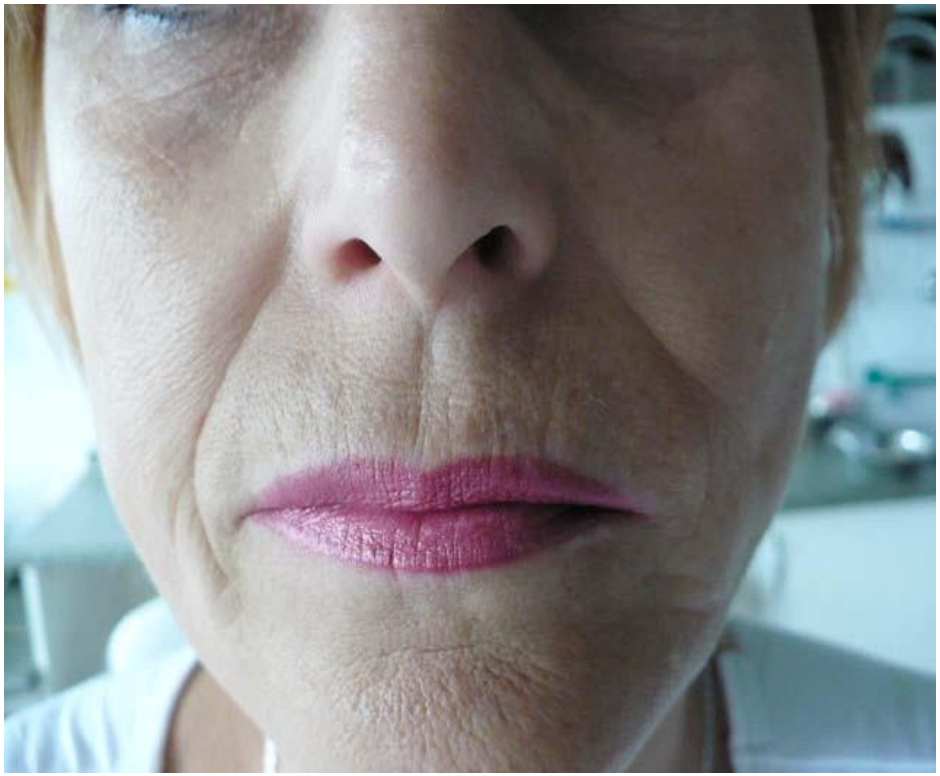


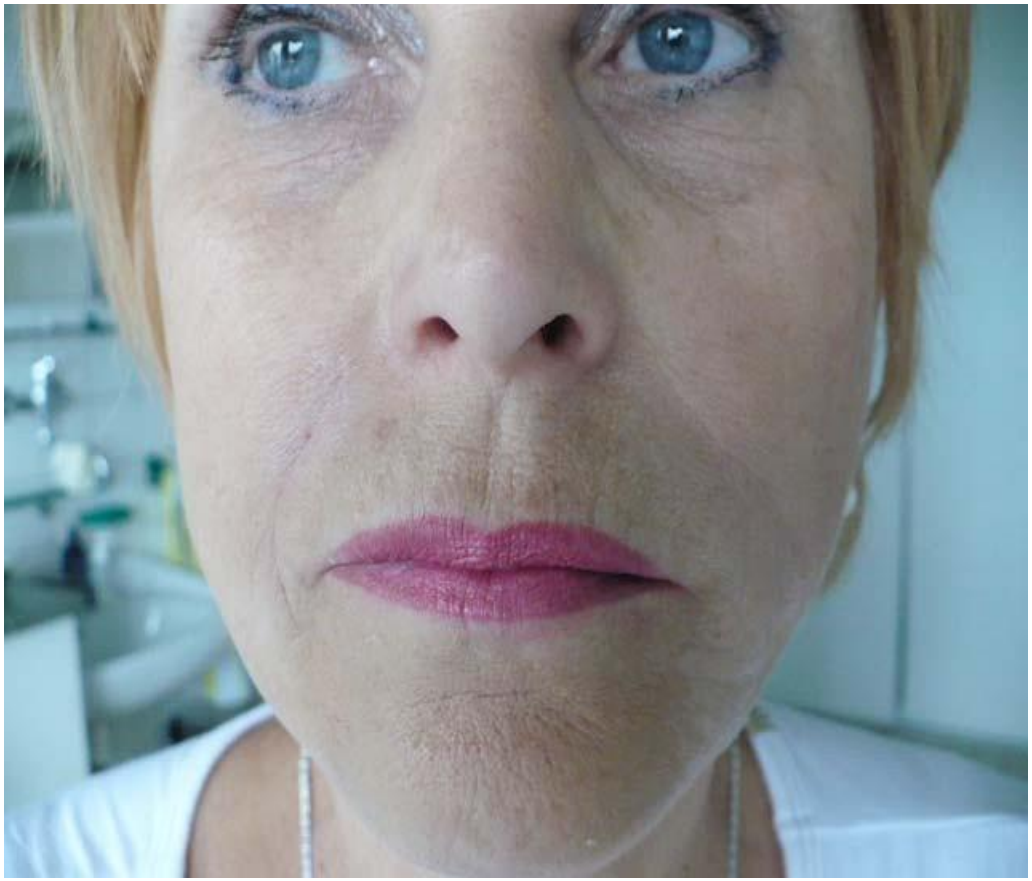
Centrum 02 MUDr. Stracenská

International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the right (visible effect) – slight improvement of periocular oedema and hyperpigmentation versus placebo on the left without changes in aesthetic parameters

Centrum 03 MUDr. Nejdková Alena

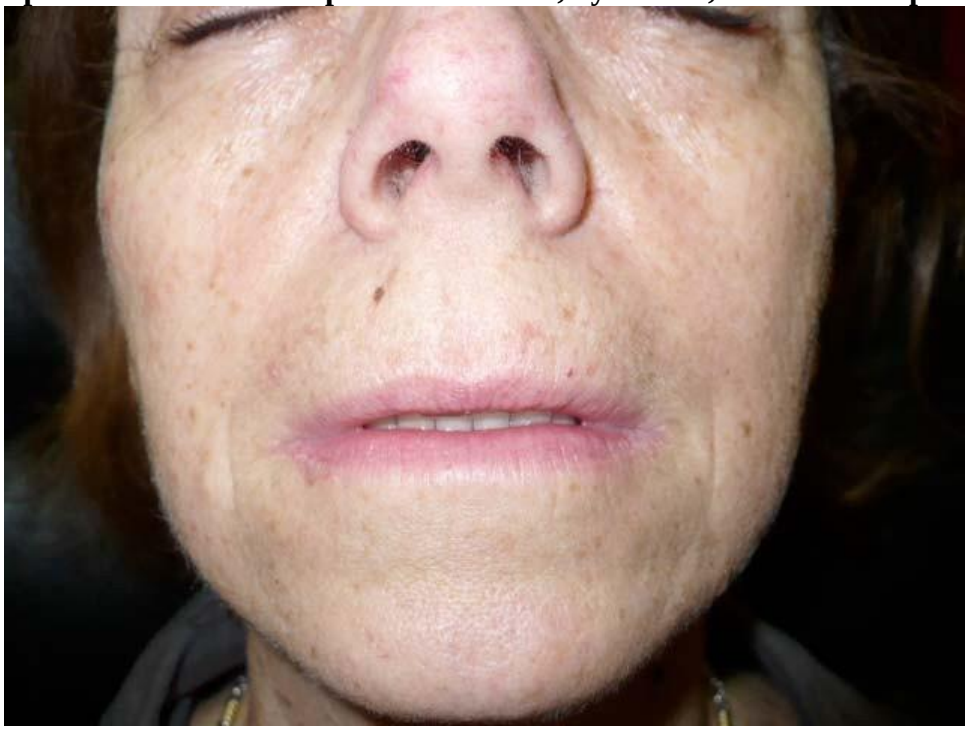
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream
- perioral wrinkles – improved condition, hydration, and aesthetic parameters

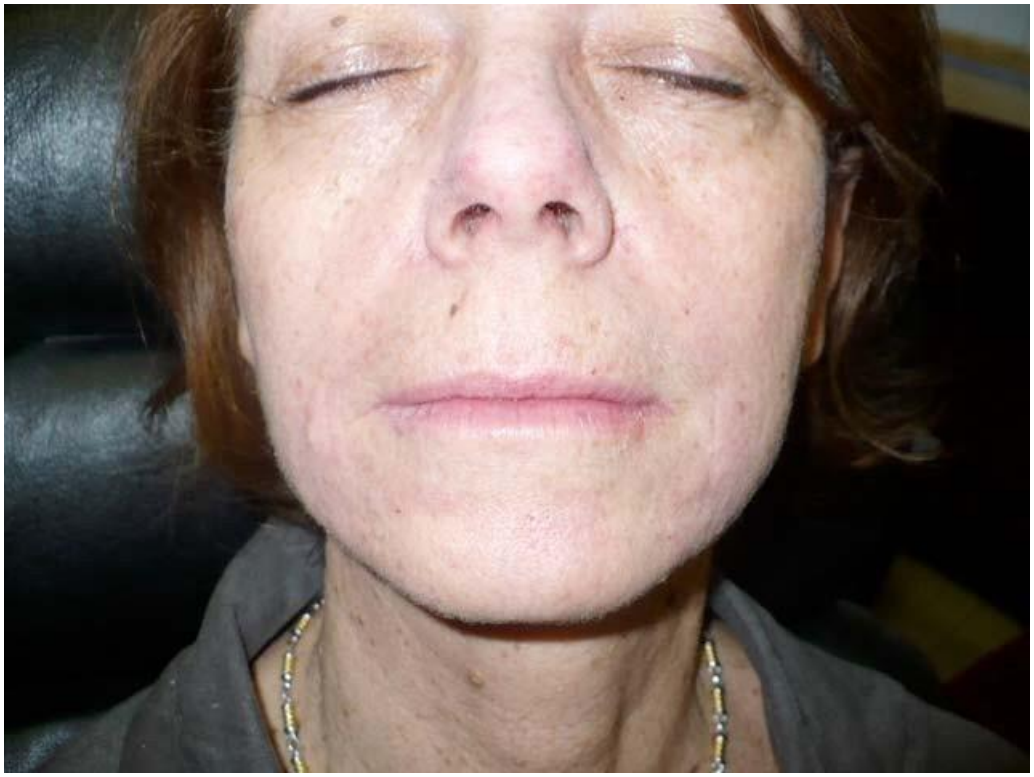




Centrum 03 MUDr. Nejdková Alena

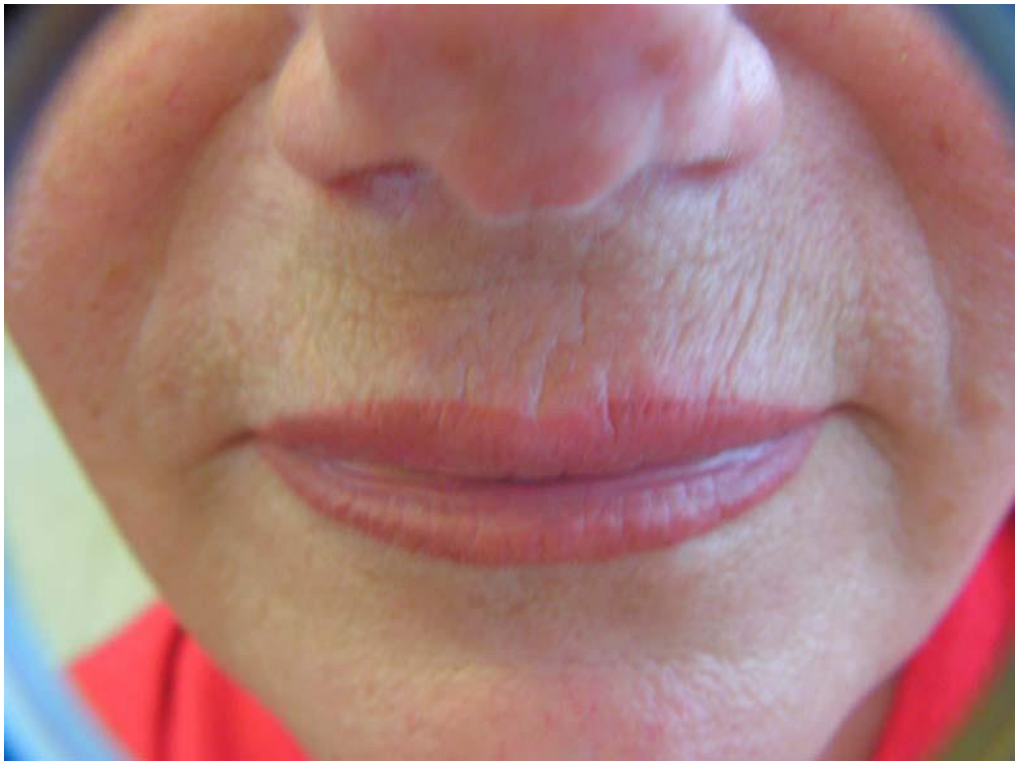
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream
- perioral wrinkles – improved condition, hydration, and aesthetic parameters

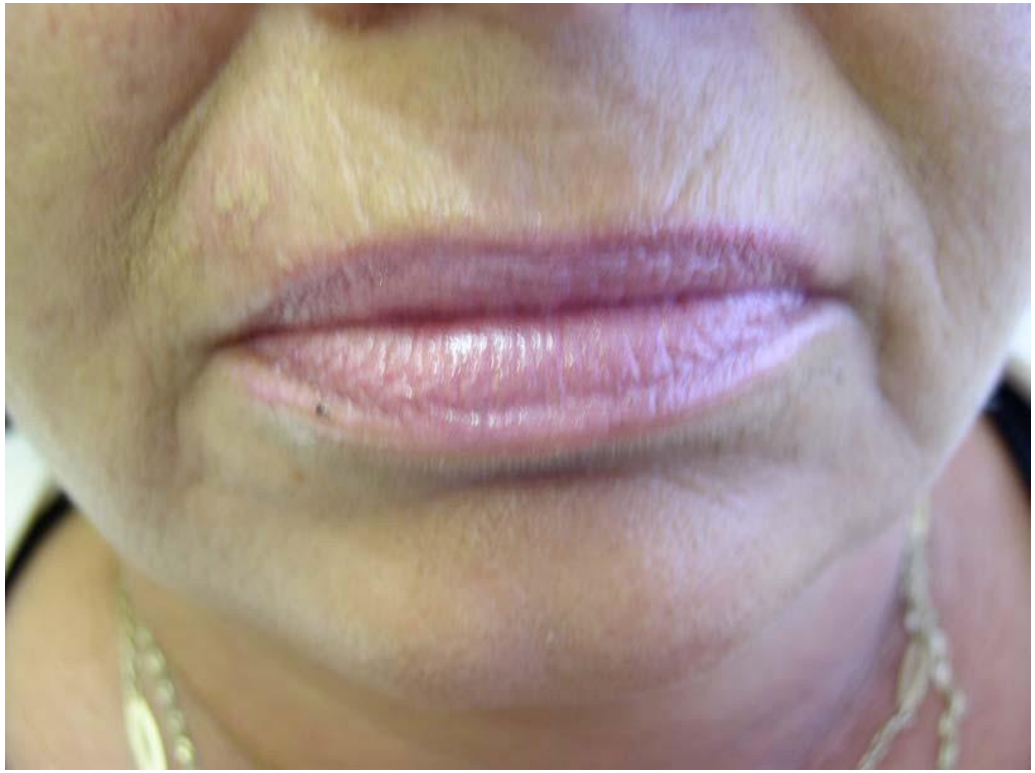




Centrum 03 MUDr. Nejdková Alena

International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream
- perioral wrinkles – improved condition, hydration, and aesthetic parameters

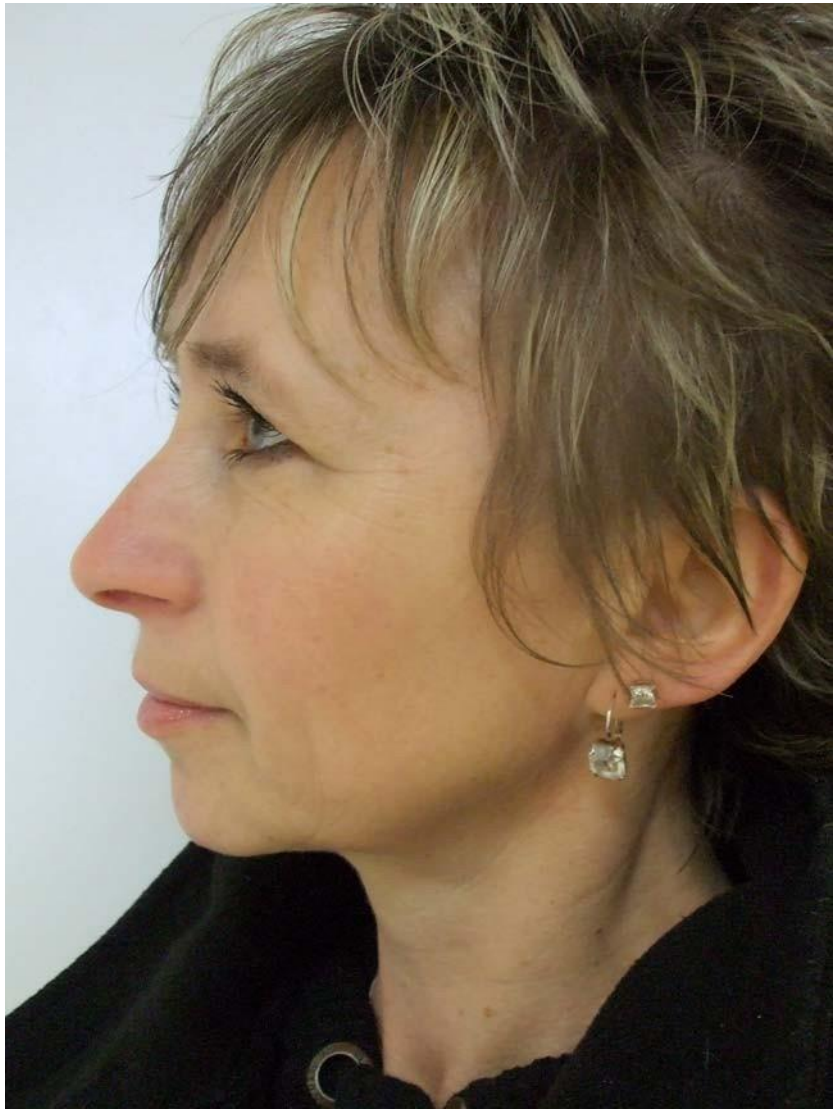




Centrum 03 MUDr. Nejdková Alena

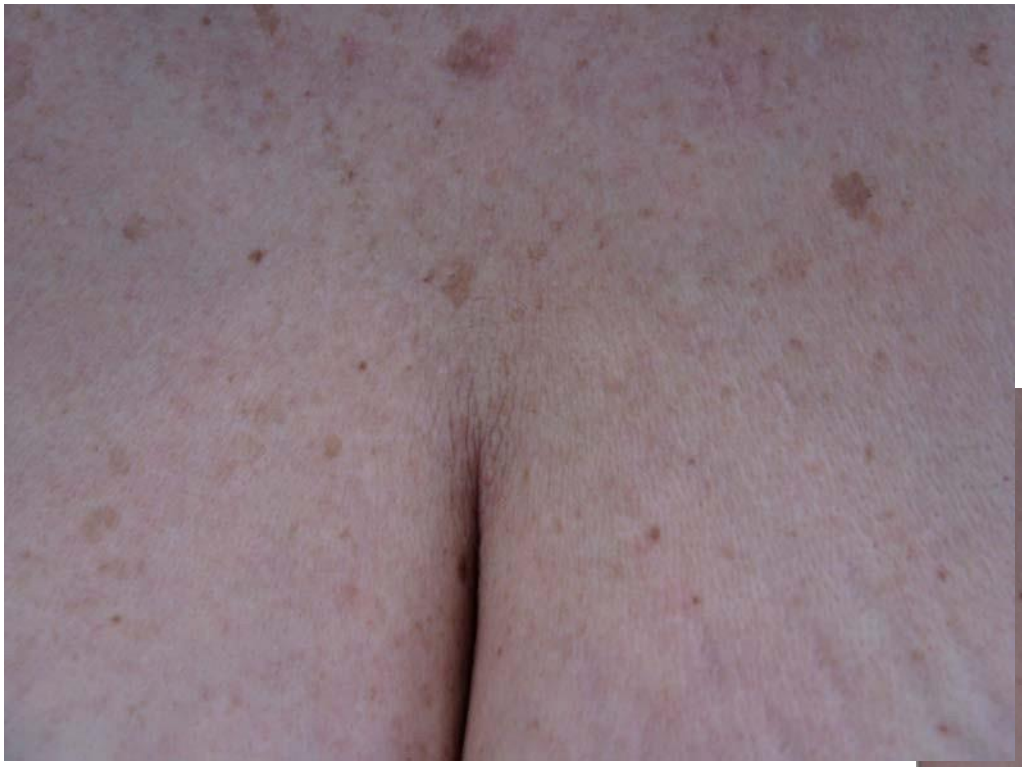
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream

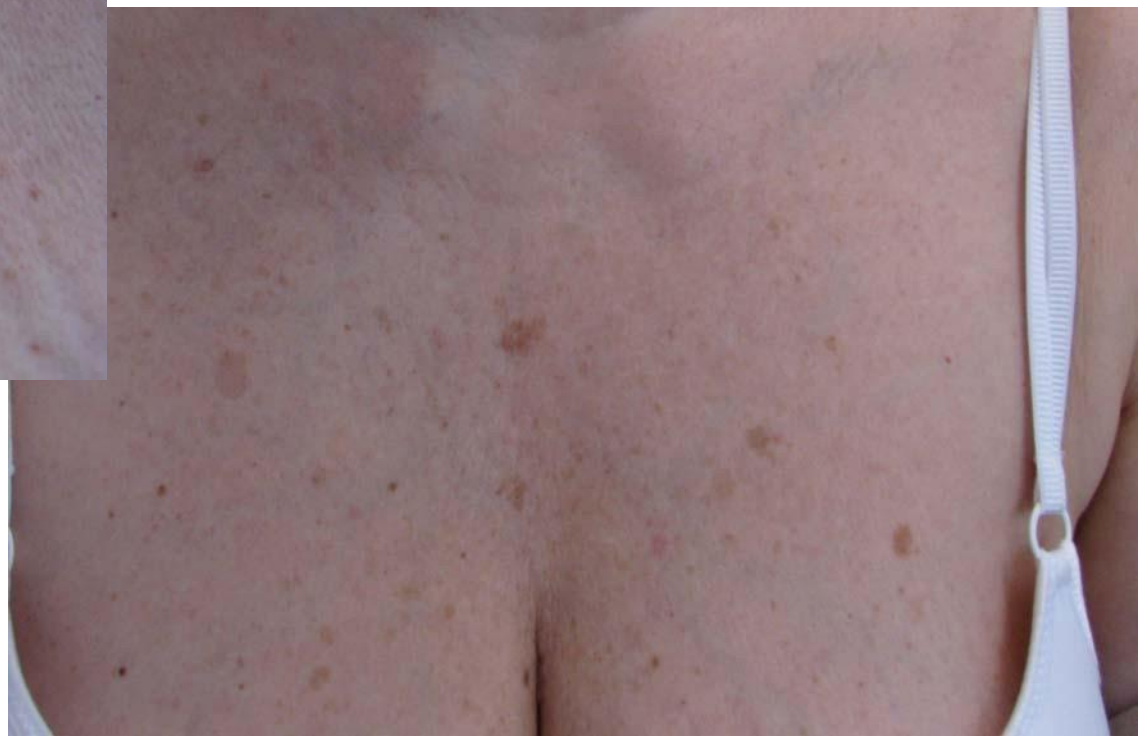
- **periorbital wrinkles – improved condition, hydration, and aesthetic parameters**



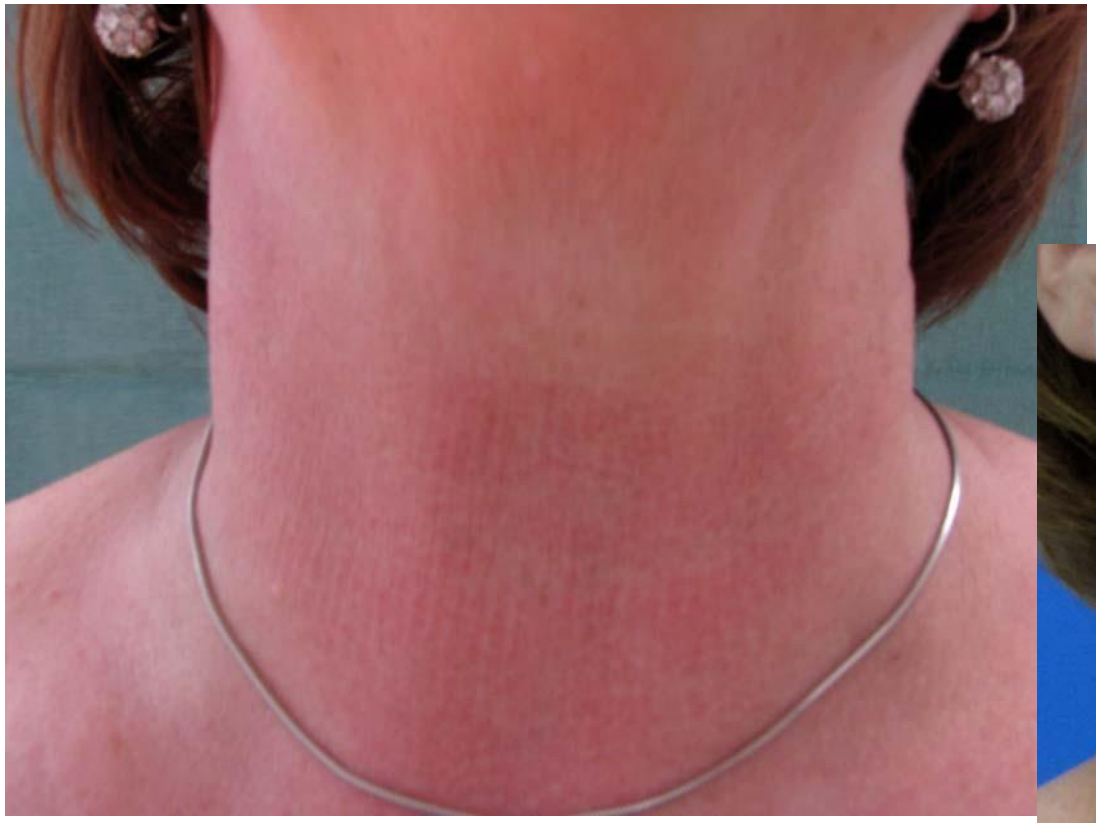
Centrum 04 MUDr. Vykutilová Zuzana

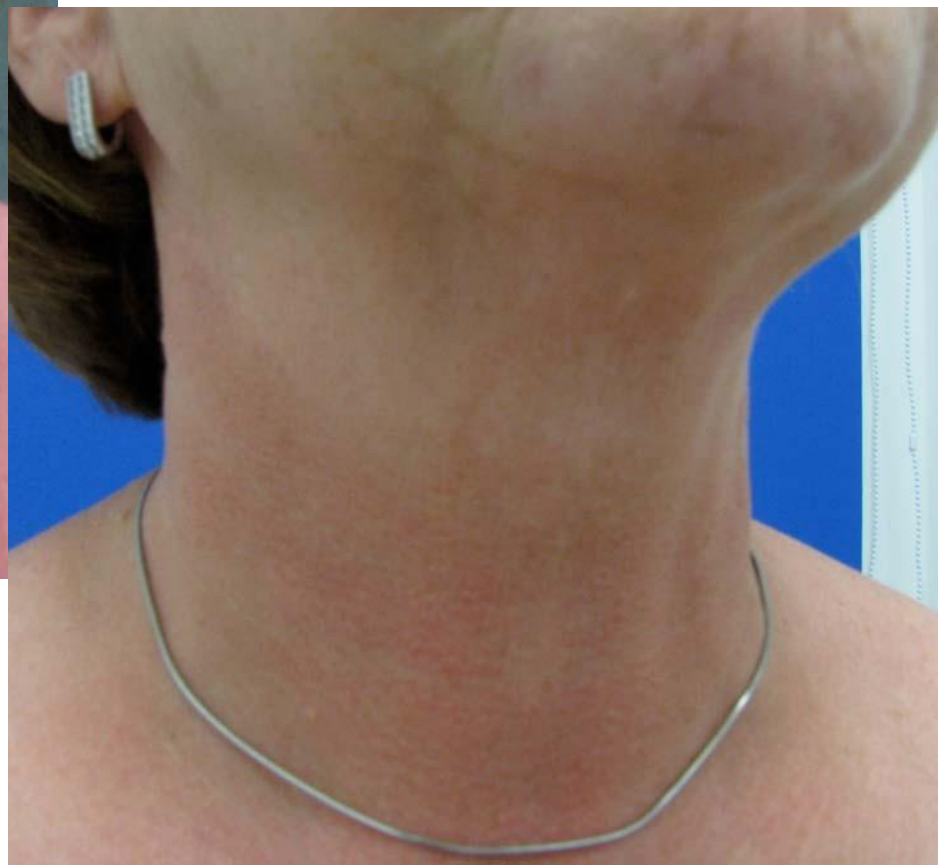
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the décolleté with visible effects and improved wrinkling



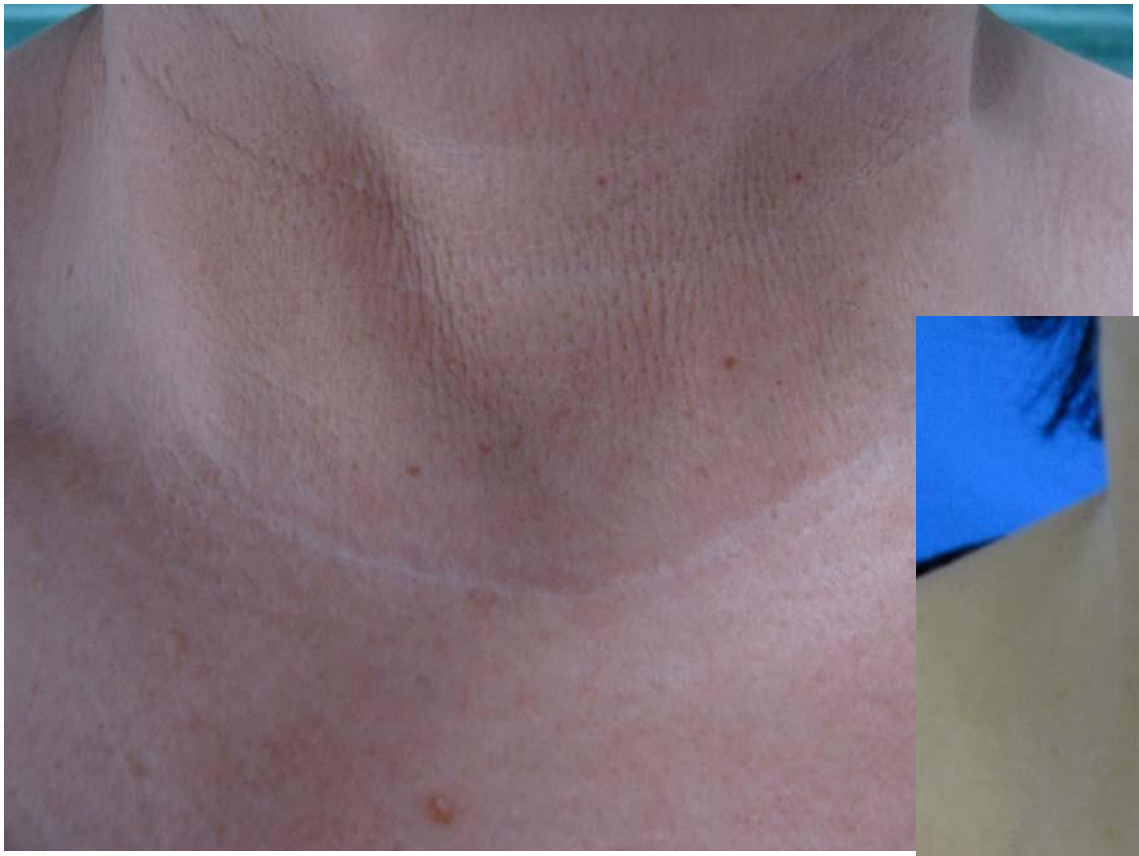


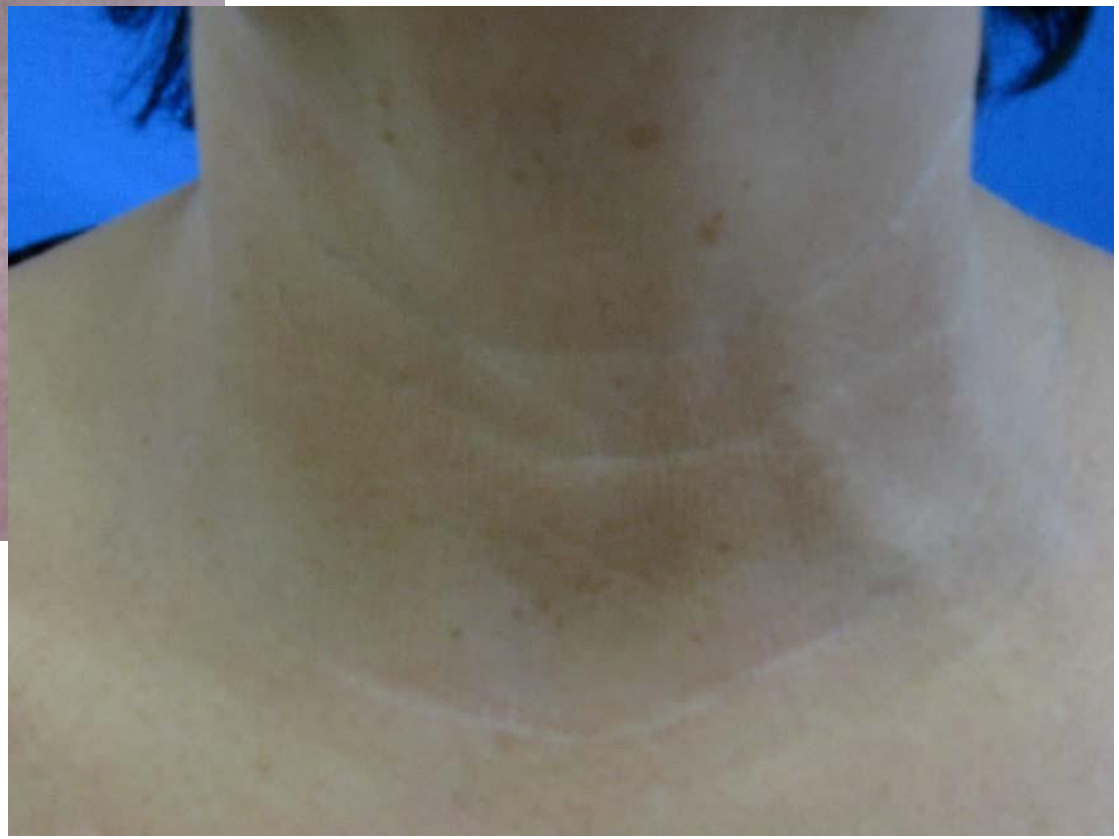
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the neck with visible effects and improved wrinkling





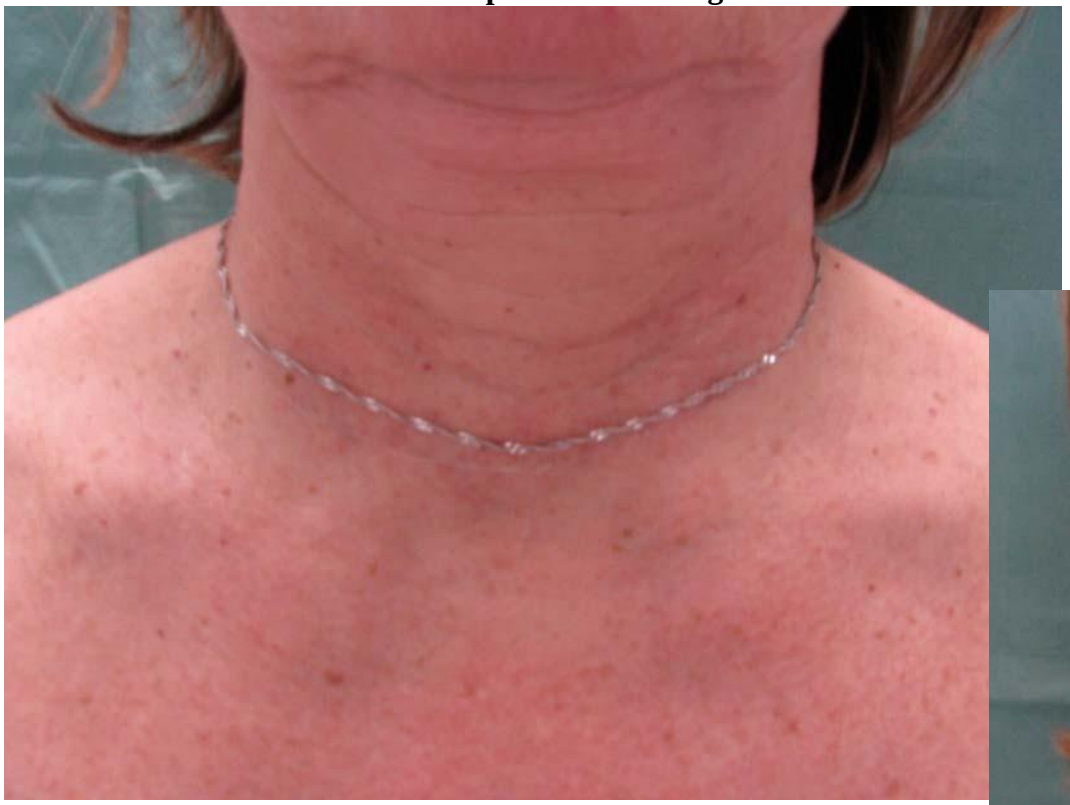
International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream on the neck with visible effects and improved wrinkling

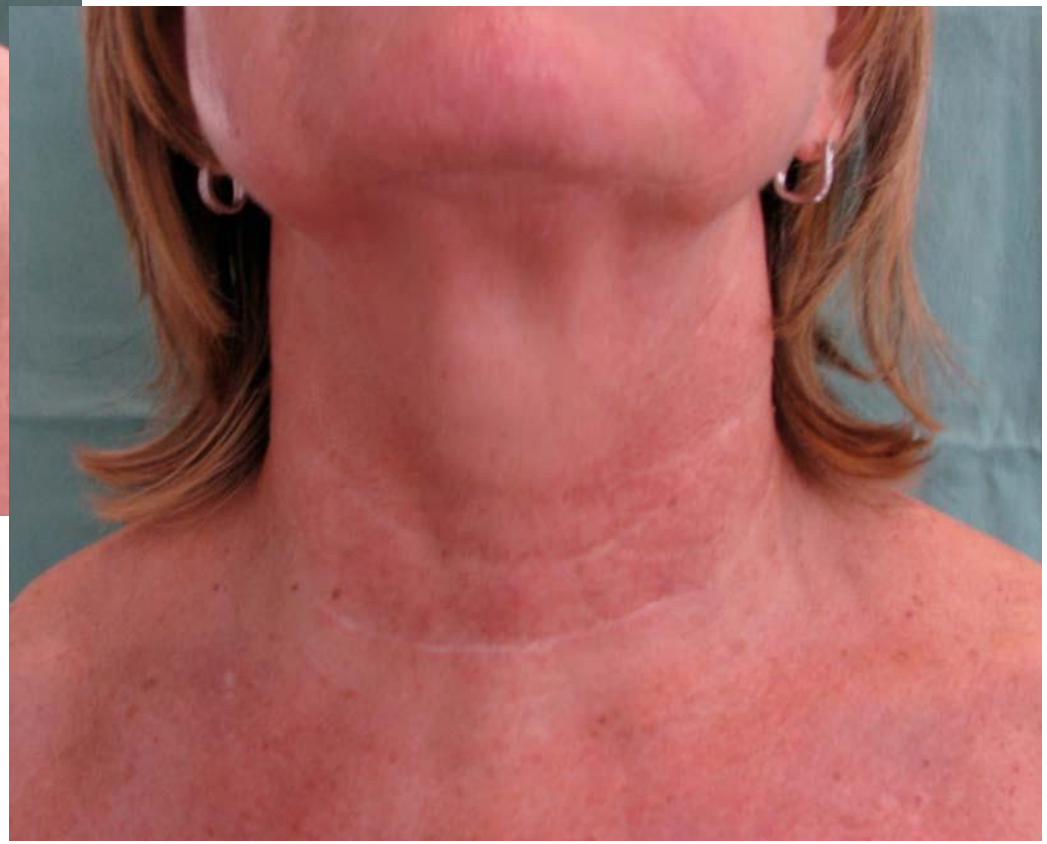




Centrum 04 MUDr. Vykutilová Zuzana

International Multicentre Trial „Retorna® cream (Catalysis S.L. Madrid) applied as an anti-ageing preparation in women aged 35 to 60 years with ageing and damaged skin with class I. – III wrinkles“ – patient before therapy and after 3 months of applying Retorna® cream, on the neck and décolleté with visible effects and improved wrinkling





CERRAR