International multicentre study to verify the effects of applying Cicatrix® cream CATALYSIS, S. L. Madrid in patients with fresh surgical scars or traumatic wounds

Final Report

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

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

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

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Contents

Introduction:

In the period from August 1st, 2006 to April 15th, 2007 a pilot study to verify the efficacy and tolerability of the preparation Cicatrix® cream, a product developed and produced by Catalysis Madrid, in patients with keloid and hypertrophic scars and to evaluate differences in tolerability and in the final effect in individual patients was carried out at the DOST Clinic in Svidník, Slovakia.

Since the results of the study verified the expected effects of applying the topical preparation Cicatrix® cream CATALYSIS, S. L. Madrid, it has been decided that its effects be verified also in other indications. For the following trial, patients with fresh surgical scars or traumatic wounds including burns and cuts of smaller extent were selected, and a decision was passed that the trial be international and multicentre.

In the second stage, the trial was extended, the new added dimension being the application of placebo in two control groups of patients in two trial centres.

For the purposes of the trial, the preparation Cicatrix® cream CATALYSIS, produced by the company S. L. Madrid was delivered to the trial centres and applied in practice.

The said preparation had undergone prior molecular activation.

As mentioned above, in two selected trial centres also the placebo preparation was delivered and applied.

Minor surgical interventions, ways of influencing the final healing effects

When in first contact with another person, the appearance and the overall impression play an important role. Unfortunately, these attributes are in some cases disturbed by unwanted skin marks, such as moles, more or less extensive benign skin tumours or scars that occur after their excision. Hypertrophic scars and keloids are a problem both physical and mental for those people who are affected. In the end, they may have a significant influence on their ability to participate in working and social life.

The ability of the skin to repair after a trauma (mechanical or chemical injury, burn, scald, frostbite) or operation varies in every human being. The same traumatic impulse may result in totally different types of healing in individual persons. Not all people react adequately – by perfect healing of the traumatised skin (cut, or surgery). It is the role of the therapist to prevent the formation of unaesthetic scars or scars that might have an influence on the function of the skin.

It is inevitable to perform all pre-surgery tests in the affected patient (to find out whether the patient is prone to developing keloid or hypertrophic scars), go through the pre-surgery phase, perform the surgery adequately and then perform the post-surgery testing again. Operating surgeons usually select the least invasive surgical methods possible. In case there are complications and the patients develop scars, they always require that their scars be treated to achieve a final cosmetic effect, whereby the patophysiological processes of healing are usually of no importance for them at all.

The processes of healing or the subsequent corrections of developed scars, however, ought to be well known to all doctors performing surgery and all those who treat the outcomes.

The reaction of the connective tissue called **healing**, the result of which in some cases is the development of a scar, is an utmost complex process. The scar tissue is rich in collagen fibres, but contains few cells or vessels. It contains no fair follicles, sebaceous or sweat glands, since those do not renew in the process of healing. In favourable conditions the scar that develops is smooth, nearly invisible, with typical skin spots, not elevated, and blending well into the surrounding skin. The colour of fresh scars is reddish, sometimes with a slight brownish or bluish coloration. The scar matures in the course of 3 to 6 months (some authors state 8 to 18 months) and changes its colour, becoming lighter than the surrounding skin. In some cases, pigments are deposited in the scar, resulting in the scar being darker than the surrounding skin, however, sometimes the skin around the scar gets fairer, creating the well known "halo effect".

Healing "per primam" is quite usual for example in clean-cut surgical wounds. In a longer secretion phase connected with the production of rich granulated tissue and tardy epithelisation we speak about healing "per secundam". Another type of healing is present in post-inflammatory skin diseases such as acne. These scars are the so called **hypertrophic scars** or their opposite variant - atrophic scars.

Spontaneous keloids are formed as a result of uncontrollable proliferation of skin collagen structures, whereby their aetiology remains unknown. **Classic hypertrophic scars** are formed after burns, other typical scars –**irradiation** scars - develop after irradiation. There are many types of scars and their clinical differentiation is sometimes very difficult (e.g. between a hypertrophic scar and a keloid). Apart from typical localities, such as those in which **spontaneous keloids** develop (on the shoulders, above the sternum, on the neck), scars may appear on the surface of the whole body after surgical interventions. Race and genetic factors, physical influences and some serious diseases also play an important role here.

Therapeutic methods and surgical interventions in cases of minor skin defects

Surgical intervention

Nearly all excisions of skin marks and minor skin tumours are performed in outpatient departments in local infiltration anaesthesia. The cuts to remove skin moles are performed in the shape of an ellipse and in subcutaneous tumours the cuts go straight in the line of skin splitting, or a round excision is performed with a rotating knife. In special cases plastic surgery is performed, including skin moving.

After the removal of skin moles or subcutaneous tumours, in some cases (locality exposed to pressure or stretching, extensive scar etc.) the skin must be stitched with resorbable material and the edges of the wound are stitched together using the intradermal stitch to achieve the final result which is a merely visible scar. The wound is in the end covered with sterile bandage and plaster. In minor wounds skin glue is used, which is absorbed in the process of healing. In the so called „shave technique“ the small lesion is removed on the level of skin and the bleeding focus is not stitched, just covered with a secondary bandage, left to the natural process of epithelisation. Some operating surgeons use a special liquid bondage to cover the focus, the so called Novikov solution. After radio- or electrocautery (electrocoagulation) or laser treatment the superficial wounds are not stitched, but treated with sterile material.

Treatment of various types of acute wounds or burn

In traumas (cuts, more extensive abrasions and erosions, devastation wounds or burns) the selection of the therapeutic approach is the role of the therapist. In each case it is necessary to select procedures, which in the end will bring benefit for the patient, will end in an aesthetically acceptable appearance, and will not influence their life functions.

Post-surgery period

In general, the performance of any surgical interventions underlies a special set of guidelines. The surgical wound must be covered for 24 to 48 hours, after that it is possible to remove the dressing material. In case the wound is located on the face, it is possible to leave it undressed or cover it with a bio-film, or a hydrocolloid dressing material or a special liquid dressing. If the anatomy of the affected area allows it, it is possible to cover the wound with the bio-film mentioned above, (as it is transparent and allows for a very effective monitoring of the scar healing condition without restricting the normal everyday habits of the patients including bathing or taking showers). There are many clinics that use Steri-strips to support the surgical wounds. Some experts recommend that the surgical wound should be left free and not further treated by any topical preparations. Stitches are removed in the time interval of 7 to14 days following the surgical intervention (depending on the locality of the surgical wound and on how much it is strained).

In the post surgery period the scars „mature" and change from quite thick pink tissue to thin delicate merely visible marks. This process takes approximately 3 to 6 months. In the period of 1 - 2 months after surgery it is of course recommended to stay out of the sun and solarium.

The methods mentioned above are used in uncomplicated healing. Reconvalescence, however, is a process that takes a different course in every individual and very much depends on the ability of every organism to heal. Healing also very much depends on patient compliance. Of course, a crucial role is played by the operating surgeon and their experience and skills, and by their decision to apply other supplementary therapeutic approaches which accelerate the healing itself and prevent processes that may lead to unaesthetic changes on the skin.

It is necessary to take into consideration that apart from the binding guidelines, every operating surgeon has their own set of methods, which they use based on their experience and erudition.

Supplementary physical therapeutic methods are becoming more and more popular, and are employed in the post-surgery period to accelerate healing and result in a great therapeutic and aesthetic effect very much appreciated both by the therapist and the patient.

Supplementary treatment methods to prevent the formation of scars or favourably influence the condition of fresh surgical wounds

In the „Pilot Trial of applying Cicatrix® cream CATALYSIS, S. L. Madrid in patients with keloid and hypertrophic scars“ the role of the most simple conservative treatment method – light scar massage - has been verified once again. **The technique is considered very important, because the special preparation** (that is either meant to prevent scarring, or influence the appearance of a scar that has already been formed) **being just applied on the treated area does not lead to a lasting effect.** The verified system of massage movements dissolves the rigid scar fibres and has therefore great influence of the final effect.

The effective system of massage movements may be used immediately after surgery to prevent the formation of a keloid scar.

In combination with pulverization using thermal water the final effect is optimised.

Pulverisation is a special way of treating damaged or disease affected skin (for example in burnt patients, patients with atopic dermatitis or psoriasis) using thermal water and fine massage. In some diseases it is possible to increase therapeutic effect by massaging the skin with special ointments and emulsions.

Other therapeutic approaches (recommended in order to achieve optimum results) after the removal of stitches or after some time include:

Occlusion stands for the coverage of the focus with microtone foil or hydrocolloid after applying a special preparation.

Microdermabrasion is applied approximately **5 weeks after surgical intervention.** In combination with massage and pulverisation great effects can be achieved, which has been reported by many clinics that have the device at their disposal.

Class II B biostimulation laser and its employment in the prevention of keloid scar formation and their therapy has a long tradition. Many techniques may be combined to achieve optimum final effect. The most popular combinations include laser therapy and application of thin silicone or polymer bandages and occlusion.

Biolamps are the latest versions of products employed in light therapy. Their accumulator batteries allow for long application in special indications. In combination with quasi continuous (100Hz) broad spectrum pulse light (with variable frequency from 2 to 10 Hz) they have introduced a new dimension to light therapy. This modality is sometimes combined with special gels containing oxygen, and herbal extracts – such as tea tree or rosehip extract.

Satisfactory effects in the prevention and therapy of keloid and hypertrophic scars are achieved by applying topical preparations with herbal extracts (Extractum cepae, Centella Asiatica) or heparin or **Dermatix** silicone gel, or silicone strip.

Intralesional corticoids are applied in patients where the effect is still dissatisfactory after 1 to 2 months (or a longer period) of intensive therapy.

Fresh scars react better and quicker to therapy **but it is necessary to inform the patient that physical irritation is not desired. During the therapy it is necessary to protect the locality from extreme cold and especially from UV rays**. Intensive massage is not advisable!

Considering the broad variety and the number of interventions performed daily at departments of dermatosurgery, surgery and plastic surgery connected with the possible risk of scarring, and not always satisfactory reaction to therapy , every preparation is welcome that brings to the patient the desired final effect and which may be successfully used for prevention. ***One of such preparations clearly is, as the pilot trial has proven, Cicatrix® cream, a product of the company Catalysis S. L. Madrid, which has been subjected to molecular activation to potentiate the effect.***

Basic product characteristics: Cicatrix® cream, Catalysis S.L. Madrid**:**

Cicatrix® cream is a new product by Catalysis Madrid, employed to treat keloid and hypertrophic scars. The active substances contained in the cream include Centella Asiatica and Pinus Sylvestris . The said active agents and **their molecular activation** guarantee its efficacy in adequate indications.

Trial objective:

The objective of the trial was to prove the efficacy and tolerability of applying Cicatrix® cream, a product of CATALYSIS S.L. Madrid, in patients with fresh surgical scars or traumatic wounds (1 cm long the minimum, 12 cm long the maximum or in the extent of 10 - 15cm^2) and to assess differences in tolerability and the final healing acceleration effect and the effect on keloid and hypertrophic scars formation in individual patients.

To verify the validity of results in comparison with placebo in selected groups of patients in randomly selected centres.

Trial type: prospective randomised controlled open type IV trial with post-registration monitoring and continuous inclusion of patients into the trial according to set criteria

In two groups of patients a double blind trial of applying the preparation vs. placebo was performed.

Note:
Centre 04 Brno the investigator Dr. Jarmila Rulcová, Ph.D was invited to participate in the trial additionally, to follow patients with extensive fresh keloid scars after acne conglobata therapy. The results of this Centre results have been assessed separately.

Trial design:

Participating countries:	**1.**	**Slovakia**	**Svidník I and II, Žilina**
	2.	**Czech Republic**	**Prague, Brno**

Centres:

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. Jarmila Rulcová, Ph.D.)**	**04**
Prague	**(Dr. Jiřina Cabalová)**	**05**
Brno	**(Dr. Zuzana Vykutilová)**	**06**

Number of patients: the total number of patients included in Centres 01 - 06 was 132
Centres 01, 02, 03, 05, and 06 counted the total of 126 patients

Trial design: patients aged 10 – 82 years (men and women)
topical application of Cicatrix® cream CATALYSIS, S. L. Madrid
topical application of a placebo product
(in Slovakia in Centre 03, and in Czech Republic in Centre 05)

Diagnosis: fresh surgical scars or traumatic wounds (burns, cuts)
Centre 04 - patients with extensive keloid scars after acne conglobata therapy

Tested preparation: Cicatrix® cream, Catalysis S.L. Madrid
(vs. placebo in Centres 03 and 05)

Time schedule: December 2007 – January 2008 patient inclusion and exclusion
January 1st, 2008 – May 30th, 2008 performance of the trial
June 2008 assessment and processing of the results
July August 2008 handing over of the **complete** results
September - December 2008 presenting and publishing of the results

Materials and Methods

The investigators in single centres undertook to elaborate the documentation, photodocumentation and to report about any important events and circumstances occurring in the centres in connection with the trial. They used the schedule, and the protocols and **the following**:

- Basic work protocol (Annex 1)
- Inclusion and exclusion criteria (Annex 2)
- Working and assessment table (Annex 3)
- List of patients (Annex 4)
- Patient consent form (Annex 5)

Trial centres:

Slovakia		**Centre No.**	**No. of patients**
Svidník I	**(Dr. Hana Zelenková, Ph.D.)**	**01**	**30**
Svidník II	**(Dr. Júlia Stracenská)**	**02**	**30**
Žilina I	**(Dr. Alena Nejdková)**	**03**	**31 (16 placebo)**
Czech Republic			
Brno	**(Dr. Rulcová Jarmila, Ph.D.)**	**04**	**6**
Prague	**(Dr. Jiřina Cabalová)**	**05**	**25 (10 placebo)**
Brno	**(Dr. Zuzana Vykutilová)**	**06**	**10**

Trial duration: 8 months December 1st, 2007 – July 31st, 2008

Series of patients: 126 patients (22 men, 104 women) in Centres 01, 02, 03, 05, and 06
6 patients – men in Centre 04, **assessed separately**

Average age: 39.76 years (39.46 in women, 40.06 in men,
youngest patient 2 years, oldest patient 80 years

Diagnoses: fresh surgical scars or traumatic wounds (burns, cuts)
Centre 04 - extensive keloid scars after acne conglobata therapy

Note: In Centres 03 and 05 patients with two comparable scars (in locality, extent, and type) were selected randomly to compare the effects properly of the tested preparation Cicatrix® cream, Catalysis S.L. Madrid versus placebo

Extent: 1 cm long min., 12 cm long max., or in the extent of 10 - 15cm^2

Application: 2 times a day with a system of massage movements, in indicated cases accompanied with supplementary physical treatments such as microdermabrasion, biostimulation laser, intralesional corticoids, pulverization, occlusion, or bio lamp

Supplementary treatments were indicated after 2 weeks after surgery the earliest.

Start of application:
I after stitching of the operated locality
II 7 days after surgical intervention or trauma
III after the removal of stitches
IV after 2 days
(dermabrasion, shave technique, radio- and electrocautery)

The product must not be applied to fresh bleeding or secerning wounds!!!!

Application duration:	21 days (3 weeks) the minimum, 90 days (3 months) the maximum
Application information:	given by the therapist both orally and in writing
Documentation:	Working protocol, tables
Photodocumentation:	pictures taken 2 - 3 times in all patients
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
Other medication:	only the medication necessary for the basic comfort of the patient, administered exclusively based on recommendation by other medical experts
Local finding assessment:	performed 4 times, at inclusion and after week 2, 6 and 8
Final assessment:	at exclusion from the group
Used preparations:	Cicatrix® cream, Catalysis S.L. Madrid placebo
Composition:	provided by the producer, see below unknown in case of placebo preparation

Inclusion criteria

- Fresh surgical scars or traumatic wounds (burns, cuts)
- Male or female gender, Caucasian
- Inpatient or outpatient status
- Ag : 10 – 82 years
- Voluntary participation in the trial
- Written patient consent form confirmation
- One-time participation in the trial

Exclusion criteria

Specific exclusion criteria

- Bleeding wound or scar
- Open wound
- 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

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

1 healing acceleration, with healing without scarring with an excellent aesthetic and cosmetic effect

2 mild erythema and infiltration appearing around the scar to the day of application termination, however, with satisfactory aesthetic and cosmetic effect in general

3 insignificant improvement, erythema, infiltration, oedema, itching

4 dissatisfactory condition, keloid scar formation

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

1 excellent aesthetic and cosmetic effect without any undesired effects

2 satisfactory aesthetic and cosmetic effect, slight scar swelling, and reddening

3 insignificant improvement, erythema, infiltration, oedema, itching, poor satisfaction with the healing

4 scar development, irritation, and itching, dissatisfactory effect

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

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

Assessment of possible complications in connection with the application of Cicatrix® cream or placebo:

1 – irritation

2 – secernation

3 – absence of healing acceleration

4 – absence of changes in the condition

5 – keloid scar formation

Adverse effects in direct connection with the application of Cicatrix® cream or placebo:

1 – burning sensation

2 – skin dryness

3 – reddening (erythema)

4 – itching (pruritus)

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, 05, and 06**
2. **Assessment in Centre 04**
3. **Assessment of the effects of placebo preparation in Centres 03 and 05**
4. **Summary assessment of Centres 01, 02, 03, 05, and 06**
5. **Comparison of the effects and percentage assessment of Cicatrix® cream versus placebo in the whole series of patients**

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

Basic data: **30 patients – 7 men, 23 women**
gender, number of patients, age (highest, lowest age)
average application period (in days), possible complications,
application discontinuation, hospitalised patients
See Table No. 1, Graphs No. 1 to 4, Annex II, pages 74 to 76

Specific data: – scar locality and extent, start of application of Cicatrix® cream,
assessment of its effects and tolerability by the therapist and the patients
See Table No 2 Graph No. 5 to 13, Annex II, pages 77 to 82

Special data: – application of supplementary therapy
See Table No. 3, Graphs No. 14 to 16, Annex II, pages 83 to 85

Special data: – complete assessment of efficacy, tolerance, and adverse effects
See Table No. 4, Graphs No. 17 to 22, Annex II, pages 86 to 89

Diagnoses:

In the group of 30 patients (7 men and 23 women), most patients had scars on the face (15x) in the extent of less than 2 cm (20x), whereby most of them were treated 7 days after surgical intervention (20x). In two cases there were extensive burns (on the face, hand), which were not stitched. In the group there also was a child of 2 years with a burned hand. Etiological background (surgical interventions, burns) was not relevant for the therapeutic approach.

***Surgical methods*:**

Surgical interventions were performed under topical injection anaesthesia (anaesthetics: Lidocain, Supracain), the wounds were stitched with intradermal mattress stitches, adaptive stitches, treated with iodine tincture, and dressed with Inadine or Gazin. For secondary dressing sterile Sterilux bandages and Suprasorb F foil were used. In scars of greater extent Steri-strips were used. In three patients a thin layer of Cicatrix® cream was applied immediately after stitching with intradermal stitches, and then covered with Gazin, and Sterilux dressing and Suprasorb F for 7 days. After the change of dressing after 7 days, Cicatrix® cream was applied daily.

***Other medication*:** antioxidants, vitamins, other agents only if recommended by other specialists.

Recommended methods: special massages with Cicatrix® cream

Other physical therapies were used not earlier than 3 weeks after trial commencement:

II B class biostimulation laser,
microdermabrasion, pulverization, occlusion.
Intralesional corticoids were not applied in this group.
See Table No. 3, Graphs No. 14 to 16, Annex II, pages 83 to 85

Improvement of the local finding: visible in 30% already after 3 weeks,
continued until end of application of Cicatrix® cream

Note: The patients appreciated the application properties and the texture of Cicatrix® cream, and also the patients in which the effect was not final, continued with the application of Cicatrix® cream willingly.

Special data: 3 patients with keloid formation

Efficacy of topical therapy as to the day of trial completion*:*
***(*See Table No. 4, Graphs No. 17, 19 to 21, Annex II, pages 86 to 89*)*:**

Assessment performed by the therapist:

12 patients (40.00%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
10 patients (33.33%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
5 patients (16.67%)	insignificant improvement, erythema, mild oedema, itching
3 patients (10.00%)	keloid formation, dissatisfactory condition

Subjective assessment performed by the patients:

13 patients (43.33%)	excellent aesthetic and cosmetic effect, no adverse effects
10 patients (33.33%)	satisfactory aesthetic and cosmetic effect, mild oedema and skin reddening
4 patients (13.33%)	insignificant improvement, erythema, infiltration, oedema, itching, lack of satisfaction with the healing
3 patients (10.00%)	scar formation, irritation, itching, and dissatisfactory final effect

Tolerability of the therapy as to the day of trial completion:

***(*See Table No. 4, Graphs No. 18 to 21, Annex II, pages 86 to 89*)*:**

Assessment performed by the therapist:

23 patients	(76.67%)	excellent tolerance
4 patients	(13.33%)	very good tolerance
3 patients	(10.00%)	good tolerance

Assessment performed by the patients:

25 patients	(83.33%)	excellent tolerance
3 patients	(10.00%)	very good tolerance
2 patients	(6.67%)	good tolerance

***Adverse effects (*See Table No. 4, Graph 22, Annex II, pages 86, and 89*)*:**

2 patients	(6.67%)	burning sensation
3 patients	(10.00%)	skin dryness
2 patients	(6.67%)	skin reddening
1 patient	(3.33%)	itching

The adverse effects were of transient nature and were no reason for application discontinuation.

Keloid formation: three patients (one man and 2 women) – 10.00%

Excluded patients: **0**

Hospitalised patients: **0**

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

Cicatrix® cream, Catalysis S.L. Madrid was applied in the total of 30 patients.
The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, later (app. 14 days following the surgical intervention) with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods.

Before the commencement of therapy, all patients were instructed in the massage technique (see Annex), they were provided with guidelines, and they were also shown live how to perform the massage movements. **All centres considered the massage extremely important, since the application itself does not lead to lasting results.**

In practice, for more than 15 years a system of fine massage movements has been used and verified in practice, which leads to gradual deterioration of rigid scar fibres and is therefore very important in order to achieve a lasting final effect. In combination with other therapeutic possibilities (biostimulation laser, pulverization, microdermabrasion, occlusion) the optimum final effect is potentiated.

Adverse effects:

Sporadically observed adverse effects including burning sensation, skin dryness, skin reddening, and itching were of transient nature and were not a reason for therapy discontinuation.

No bacterial infection was recorded.

Most significant effects were observed in patients with scars localised on the face, since the face is not exposed to pressure or traction and when using the right system of therapy there is minimum risk of complications. In these areas it is possible to monitor in an ideal way the dynamics of healing. Very good effects were observed following the application of Cicatrix® cream Catalysis S. L. Madrid in patients with burns, that means wounds, in which stitching was not necessary.

Results: Centre 02 Svidník Dr. Júlia Stracenská

Basic data: **30 patients– 5 men, 25 women**
gender, number of patients, age (highest, lowest age)
average application period (in days), possible complications,
application discontinuation, hospitalised patients
See Table No. 1, Graphs No. 1 to 4, Annex II, pages 90 to 92

Specific data: – scar locality and extent, start of application of Cicatrix® cream,
assessment of its effects and tolerability by the therapist and the patients
See Table No 2 Graph No.5 to 13, Annex II, pages 93 to 98

Special data: – application of supplementary therapy
See Table No. 3, Graphs No. 14 to 16, Annex II, pages 99 to 101

Special data: – complete assessment of efficacy, tolerance, and adverse effects
See Table No. 4, Graphs No. 17 to 22, Annex II, pages 102 to 105

Diagnoses:

In the group of 30 patients (5 men and 25 women, most of them had scars on the faces (16x) and trunk (6x) in the extent of less than 2 cm (21x), whereby most of them were treated from day 7 after surgery (16x). In two cases the areas had not been previously stitched.

***Surgical methods*:**

Surgical interventions were performed under topical injection anaesthesia (anaesthetics, Lidocain, Supracain), the wounds were stitched using intradermal stitches, mattress stitches, adaptive stitches, treated with iodine tincture, and dressed with Inadine or Gazin, secondary dressing with sterile Sterilux bandages and Suprasorb F foil. In scars of greater extent Steri-strips were used. In patients treated with electrocautery the areas were covered using Gazin, and Sterilux dressing materials for one day and then left free to heal without bandage. In 6 patients a thin layer of Cicatrix® cream was applied immediately after stitching using intradermal stitches, and then covered with Gazin, and Sterilux dressing and Suprasorb F for 7 days. After the change of dressing after 7 days, Cicatrix® cream was applied daily.

***Other medication*:** antioxidants, vitamins,
other agents only if recommended by other specialists.

Recommended methods: special massages with Cicatrix® cream

Other physical therapies were used not earlier than 3 weeks after trial commencement:

II B class biostimulation laser,
microdermabrasion, pulverization, occlusion.
Intralesional corticoids were not applied in this group.
See Table No. 3, Graphs No. 14 to 16, Annex II, pages 99 to 101

Improvement of the local finding: visible in 30% already after 15 days, and
continued until end of application of Cicatrix® cream

Note: The patients appreciated the application properties and the texture of Cicatrix® cream, and also the patients in which the effect was not final, continued with the application of Cicatrix® cream willingly.

Special data: 4 patients –keloid formation

Efficacy of topical therapy as to the day of trial completion***:***
(*See Table No. 4, Graphs No. 17, 19 to 21, Annex II, pages 102 to 105*):

Assessment performed by the therapist:

13 patients	(43.33%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
11 patients	(36.67%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
2 patients	(6.67%)	insignificant improvement, erythema, mild oedema, itching
4 patients	(13.33%)	keloid formation, dissatisfactory condition

Subjective assessment performed by the patients:

15 patients	(50.00%)	excellent aesthetic and cosmetic effect, no adverse effects
10 patients	(33.33%)	satisfactory aesthetic and cosmetic effect, mild oedema and skin reddening
1 patient	(3.33%)	insignificant improvement, erythema, infiltration, oedema, itching, lack of satisfaction with the healing
4 patients	(13.33%)	scar formation, irritation, itching, dissatisfactory final effect

Tolerability of the therapy as to the day of trial completion:

***(*See Table No. 4, Graphs No. 18 to 21, Annex II, pages 102 to 105*)*:**

Assessment performed by the therapist:

22 patients	(73.33%)	excellent tolerance
3 patients	(10.00%)	very good tolerance
4 patients	(13.33%)	good tolerance
1 patient	(3.33%)	intolerance

Assessment performed by the patients:

24 patients	(80.00%)	excellent tolerance
2 patients	(6.67%)	very good tolerance
3 patients	(10.00%)	good tolerance
1 patient	(3.33%)	intolerance

***Adverse effects (*See Table No. 4, Graph 22, Annex II, pages 102, and 105*)*:**

2 patients	(6.67%)	burning sensation
2 patients	(6.67%)	skin dryness
2 patients	(6.67%)	itching

The adverse effects were of transient nature and were no reason for application discontinuation until 3 weeks since trial commencement.

Keloid formation: 4 patients (1 man and 3 women) – 13.33%

Excluded patients: **0**

21 days after trial commencement 1 female patient discontinued the application

Hospitalised patients: **0**

Comment: Centre 02 Svidník Dr. Júlia Stracenská

Cicatrix® cream, Catalysis S.L. Madrid was applied in the total of 30 patients.
The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, later (app. 14 days following the surgical intervention) with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods and supplementary treatments.

Before the commencement of therapy, all patients were instructed in the massage technique (see Annex), they were provided with guidelines, and they were also shown live how to perform the massage movements.

All centres considered the massage extremely important, since the application itself does not lead to lasting results.

Adverse effects:

Sporadically observed adverse effects including burning sensation, skin dryness, skin reddening, and itching were of transient nature and were not a reason for therapy discontinuation. There was only one female patient who decided to discontinue the application spontaneously after 21 days. Despite this fact, it was possible to assess a visible therapeutic effect of applying Cicatrix® cream.

No bacterial infection was recorded.

Most significant effects (similarly as in Centre 01) were observed in patients with scars localised on the face, since the face is not exposed to pressure or stretching and when using the right system of therapy there is minimum risk of complications. In these areas it is possible to monitor in an ideal way the dynamics of healing. Very good effects were observed following the application of Cicatrix® cream Catalysis S. L. Madrid after stitching the operated area.

Results: Centre 03 Žilina Dr. Alena Nejdková

In 16 patients in Centre 03 the assessment of 2 comparable scars was performed, whereby one of them was treated with Cicatrix® cream and the other with placebo. Due to that the number of scars in this group is higher than the number of patients.

Basic data: **31 patients– 6 men, 25 women**
gender, number of patients, age (highest, lowest age)
average application period (in days), possible complications,
application discontinuation, hospitalised patients
See Table No. 1, Graphs No. 1 to 4, Annex II, pages 106 to 108

Specific data: – scar locality and extent, start of application of Cicatrix® cream,
assessment of its effects and tolerability by the therapist and the patients
See Table No 2 Graph No.5 to 13, Annex II, pages 109 to 114

Specific data: – comparison of the scars treated with Cicatrix® cream and placebo,
scar locality and extent, start of application,
therapeutic effect assessed by the therapist and the patients
See Table No 2a, Graph No. 14 to 17, Annex II, pages 115 to 120

Special data: application of supplementary therapy
See Table No. 3, Graphs No. 18 to 20, Annex II, pages 121 to 123

Special data: complete assessment of efficacy, tolerance, and adverse effects
See Table No. 4, Graphs No. 21 to 25, Annex II, pages 124 to 127

Diagnoses: In the group of 31 patients (6 men and 25 women) most of them had scars on the face (40x), sporadically on the neck, upper extremity or trunk, in the extent of less than 2 cm (43x), whereby most of them were first treated on day 7 following the surgical intervention (29x). In 4 patients the treated areas were not stitched.

Surgical methods: Surgical interventions were performed under topical injection anaesthesia (anaesthetics Mesocain), the wound then was stitched with adaptive stitches, treated with Betadine, dressed with Biatain Ag, and sterile bandages Sterilux, and Omnifix. In more extensive scars Steri-strips were used. After electrocautery we used Biatain Ag for 3 days, leaving the wound free after its removal. In all patients Cicatrix® cream was applied after the removal of stitches (on the face on day 7, on the trunk and extremities on day 14).

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

Recommended methods: special massages with Cicatrix® cream

Other physical therapies were used not earlier than 3 weeks after trial commencement:

occlusion (13 patients)

intralesional corticoids were not applied in this group.

See Table No. 3, Graphs No. 18 to 20, Annex II, pages 121 to 123

Improvement of the local finding:

Visible in 30% already after 10 days of applying Cicatrix® cream, and continued until trial completion.

The same effect was observed in the placebo preparation.

At the beginning, no significant differences were observed in the application of Cicatrix® cream and placebo.

Note: The patients appreciated the application properties and the texture of Cicatrix® cream, as well as of the placebo.

Special data: 2 patients (2 men) with keloid formation

Note: In 1 woman with keloid formation the diagnostics was performed at a time when the study was completed. For this reason the data is not included in the table.

The efficacy of topical therapy in 16 women with comparative scars of the effects of Cicatrix® cream versus placebo as to the day of trial completion:

***(*See Table No. 2a, Graphs No. 14 to 16, Annex II, pages 115 to 119)**

Assessment performed by the therapist *Cicatrix® cream vs. placebo*

16 patients (100%): 6 patients (37.5%)	excellent cosmetic and aesthetic effect, accelerated healing, without scar formation
0 patients: 6 patients (37.5%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
0 patients: 4 patients (25.0%)	insignificant improvement, erythema, infiltration, mild oedema, itching

Subjective assessment by the patients ***Cicatrix® cream vs. placebo***:

16 patients (100%) : 6 patients(37.5%)	excellent aesthetic and cosmetic effect, accelerated healing, healing without visible scar formation
0 patients: 6 patients (37.5%)	satisfactory aesthetic and cosmetic effect, mild erythema and infiltration around the scar on the day of trial completion
0 patients: 4 patients (25.0%)	insignificant improvement, erythema, infiltration, mild oedema, itching

Tolerance assessment performed by the therapist and the patients: Cicatrix® cream:
***(*See Table No. 2a, Graph No.17, Annex II, pages 115, and 120*)**:

15 patients	(93.75%) :	15 patients (93.75%)	excellent tolerance
1 patient	(6.25%) :	1 patient (6.25%)	very good tolerance

Tolerance assessment performed by the therapist and the patients: placebo:

7 patients	(43.75%)	6 patients	(37.5%)	excellent tolerance
5 patients	(6.67%)	8 patients	(50.00%)	very good tolerance
4 patients	(25.00%)	2 patients	(12.5%)	good tolerance

Adverse effects recorded in the group of patients applying Cicatrix® cream vs. placebo
***(*See Table No. 4, Annex II, page 124*)**
Efficacy of topical therapy as to the day of trial completion - Cicatrix® cream and placebo (the table gives the total number of scars - 47 (100%) in 31 patients, the percentage therefore stands for the real number of scars:
***(*See Table No. 4, Graphs No. 21, 24 - 25, Annex II, pages 124 to 127*)**:

Assessment performed by the therapist:

31 scars (65.96%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
10 scars (21.28%)	satisfactory aesthetic and cosmetic effect, mild erythema and infiltration around the scar on the day of trial completion
4 scars (8.51%)	insignificant improvement, erythema, infiltration, mild oedema, itching
2 scars (4.26%)	keloid formation, dissatisfactory condition

Subjective assessment performed by the patients:

31 scars (65.96%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
10 scars (21.28%)	satisfactory cosmetic and aesthetic effect, mild erythema and infiltration around the scar on the day of trial completion
4 scars (8.51%)	insignificant improvement, erythema, infiltration, mild oedema, itching
2 scars (4.26%)	keloid formation, dissatisfactory condition

Tolerance of topical therapy as to the day of trial completion - Cicatrix® cream and placebo (the table gives the total number of scars - 47 (100%) in 31 patients, the percentage therefore stands for the real number of scars:
***(*See Table No. 4, Graphs No. 22, 24 - 25, Annex II, pages 124 to 127*)*:**

Assessment performed by the therapist:

32 scars	(68.09%)	excellent tolerance
10 scars	(21.28%)	very good tolerance
4 scars	(8.51%)	good tolerance
1 scar	(2.13%)	intolerance

Assessment performed by the patients:

31 scars	(65.96%)	excellent tolerance
13 scars	(27.66)	very good tolerance
2 scars	(4.26%)	good tolerance
1 scar	(2.13%)	intolerance

No adverse effects in the group of patients applying Cicatrix® cream or placebo were recorded (*See Table No. 4, Annex II, page 124*)

Keloid formation: 2 patients (2 men) – 4.26%
Excluded patients: **0**
Hospitalised patients: **0**

Comment: Centre 03 Žilina Dr. Alena Nejdková

Cicatrix® cream, Catalysis S.L. Madrid was applied in the total of 31 patients.
The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, later (app. 14 days following the surgical intervention) with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods and supplementary treatments.

Before the commencement of therapy, all patients were instructed in the massage technique (see Annex), they were provided with guidelines, and they were also shown live how to perform the massage movements.

Especially Centre 03 Žilina considered the massage extremely important, since the results of comparing the effects of applying Cicatrix® cream and placebo differ very slightly. Due to that the investigator believes that the mere application of the cream (with or without the content of an active ingredient), does not lead to lasting results. The question is, whether the placebo preparation contained an active ingredient, since the trial was double blind.

Adverse effects:

Adverse effects such as burning sensation, skin dryness, itching were either not observer, or were of transient nature, and it was not necessary to state them in the protocol. This was also due to the fact that Cicatrix® cream and placebo were applied (with some exceptions) after the removal of stitches.

No bacterial infection was recorded

Most significant effects (similarly as in Centres 01 and 02) were observed in patients with small extent scars localised on the face, since the skin on the face is not exposed to pressure or stretching and when using the right system of therapy there is minimum risk of complications. In these areas it is possible to monitor in an ideal way the dynamics of healing.

Results: Centre 05 Prague Dr. Jiřina Cabalová

In Centre 03 in 8 patients (1 man, 7 women) the therapy of two comparable scars was followed, whereby one was treated with Cicatrix® cream and the other with placebo. Due to that, the number of scars is higher than the number of patients in this group.

Basic data:	**25 patients– 1 man, 24 women** gender, number of patients, age (highest, lowest age) average application period (in days), possible complications, application discontinuation, hospitalised patients **See Table No. 1, Graphs No. 1 to 3, Annex II, pages 140 to 142**
Specific data:	scar locality and extent, start of application of Cicatrix® cream, assessment of its effects and tolerability by the therapist and the patients **See Table No 2 Graph No.4 to 12, Annex II, pages 143 to 148**
Specific data:	comparison of the treated scars **-** Cicatrix® cream vs. placebo, Scar locality and extent, start of application, assessment of effects and tolerability by the therapist and the patients **See Table No 2a, Graph No.13 to 16, Annex II, pages 149 to 153**
Special data:	application of supplementary therapy **See Table No. 3, Graphs No. 17 to 19, Annex II, pages 154 to 156**
Special data:	complete assessment of efficacy, tolerance, and adverse effects **See Table No. 4, Graphs No. 20 to 24, Annex II, pages 157 to 160**

Diagnoses:

In the group of 25 patients(1 man a 24 women) most of them had scars on the face (15x), sporadically on the neck, 4x on upper extremity, 7x on the trunk, and 2x on lower extremities. The two evaluated scar extent types - less than 2cm and more than 2 cm - were represented nearly equally. There also were really extensive scars up to 16 cm long, whereby most of those were treated on day 14 after surgery (24x). In five cases the treated areas were not stitched.

***Surgical methods*:**

Surgical interventions were performed under topical injection anaesthesia (anaesthetics Mesocain, Supracain, Marcain), the wounds were treated with intradermal adaptation stitches, treated with iodine or Betadine, Sterilux, and Omnifix. In scars of greater extent Steri-strips were used. In patients treated with electrocautery the areas were covered using Inadine or Bactigras for 3 days, and then left free to heal without bandage. In all patients Cicatrix® cream was applied after the removal of stitches (on day 7 on the face and on day 14 on the extremities and the trunk).

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

Recommended methods: special massages with Cicatrix® cream

Other physical therapies used not earlier than 3 weeks after trial commencement: occlusion

Intralesional corticoids were not applied in this group of patients.

See Table No. 3, Graphs No. 17 to 19, Annex II, pages 154 to 156

Improvement of the local finding:

Visible in 25% already after 12 days of applying Cicatrix® cream, and continued until end of application.

Note: The patients appreciated the application properties and the texture of Cicatrix® cream, and placebo.

Special data: keloid formation was not recorded in the group.

Efficacy of topical therapy in 8 patients (1 man, 7 women) with comparable scars as to the day of trial completion: Cicatrix® cream vs. placebo:

(*See Table No. 2a, Graphs No. 13 to 16, Annex II, pages 149 to 153*):

Assessment performed by the therapist *Cicatrix® cream vs. placebo*

3 patients (37.5%) : 0 patients - excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

4 patients (50%) : 2 patients (25%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

1 patient (12.5%) : 6 patients (75.0%) insignificant improvement, erythema, mild oedema, itching

Subjective assessment made by the patients *Cicatrix® cream vs. placebo* :

2 patients (25%) : 0 patients - excellent cosmetic and aesthetic effect, accelerated healing, and healing without visible scar formation

6 patients (75%) : 3 patients (37.5%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration

0 patients: 5 patients (62.50%) insignificant improvement, erythema, mild oedema, itching

Tolerance assessment performed by the therapist and the patients of Cicatrix® cream:

(*See Table No. 2a, Graph No.16, Annex II, page 149, and 153):

8 patients (100%) : 3 patients (37.5%) excellent tolerance

0 patient : 5 patients (62.5%) very good tolerance

Tolerance assessment performed by the therapist and the patients of the placebo:

***(*See Table No. 2a, Graph No.16, Annex II. pages 149, and 153*)*:**

7 patients (87.5%) : 3 patients (37.5%) excellent tolerance

0 patients (12.5%) : 4 patients (50%) very good tolerance

1 patients (12.5%) : 1 patient (12.5%) good tolerance

No adverse effects were recorded in the group of patients applying Cicatrix® cream or placebo (*See Table No. 4, Annex II, page 157*)

The efficacy of topical therapy as to the day of trial completion was assessed together, including Cicatrix® cream and placebo (the table shows the total number of scars 33 (100%) in 25 patients, the percentage assessment gives the real number of scars:

***(*See Table No. 4, Graphs No. 20, 22 to 24, Annex II, pages 157 to 160*)*:**

Assessment performed by the therapist:

10 scars (30.30%) - excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

15 scars (45.45%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

8 scars (24.24%) insignificant improvement, erythema, infiltration, mild oedema, itching

Subjective assessment performed by the patients:

8 scars (24.24%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
17 scars (51.52%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
8 scars (24.24%)	insignificant improvement, erythema, infiltration, mild oedema, itching

Tolerability of topical therapy as to the day of trial completion was assesses together including Cicatrix® cream and placebo (the table shows the total number of scars - 33 (100%) in 25 patients, the percentage assessment gives the real number of scars:

Tolerability of the therapy as to the day of trial completion:
***(*See Table No. 4, Graphs No. 21 to 24, Annex II, pages 157 to 160*)**:

Assessment performed by the therapist:

25 scars	(75.76%)	excellent tolerance
8 scars	(24.24%)	good tolerance

Assessment performed by the patients:

24 scars	(72.73%)	excellent tolerance
5 scars	(15.15)	very good tolerance
4 scars	(12.12%)	good tolerance

No adverse effects were recorded in the group of patients applying Cicatrix® cream or placebo (*See Table No. 4, Annex II, page 157*)

Keloid formation:	0
Excluded patients:	**0**
Hospitalised patients:	**0**

Comment: **Centre 05 Prague** **Dr. Jiřina Cabalová**

Cicatrix® cream, Catalysis S.L. Madrid was applied in the total of 25 patients.

The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, Dermacyn solution or later (app. 14 days following the surgical intervention) with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods and supplementary treatments.

Before the commencement of therapy, all patients were instructed about the massage technique (see Annex), and they were provided with guidelines, and they were also shown live how to perform the massage movements.

The massage is considered extremely important by this Centre and Centre 03 Žilina. The investigators believe that (with or without an active ingredient) the application of a product itself does not lead to lasting results.

Both the therapist and the patients assessed the effects of Cicatrix® cream clearly more significant than the effect of placebo.

Adverse effects:

No adverse effects such as burning sensation, skin dryness, or itching were observed. Cicatrix® cream and placebo were applied after the removal of stitches, in some cases as late as 3 weeks after surgery. It is possible to state that this group of patients presents the broadest variety of treated localities and scar types ranging from dog bites to knife attack cuts, breast surgery or leg bone operation, to scars in self-destructive patients.

No bacterial infection was recorded.

Most significant effects (similarly to Centre 01 and 02) were observed in patients with scars localised on the face, since the skin on the face is not exposed to pressure or stretching and when using the right system of therapy there is minimum risk of complications. In these areas it is possible to monitor in an ideal way the dynamics of healing. Good cosmetic effects were recorded in patients with extensive scars e.g. after breast surgery.

Results: Centre 06 Brno Dr. Zuzana Vykutilová

Basic data: **10 patients– 3 men, 7 women**
gender, number of patients, age (highest, lowest age)
average application period (in days), possible complications,
application discontinuation, hospitalised patients
See Table No. 1, Graphs No. 1 to 3, Annex II, pages 161 to 163

Specific data: scar locality and extent, start of application of Cicatrix® cream,
assessment of its effects and tolerability by the therapist and the patients
See Table No 2 Graph No.4 to 12, Annex II, pages 164 to 169

Special data: application of supplementary therapy
See Table No. 3, Graphs No. 13 to 15, Annex II, pages 170 to 172

Special data: complete assessment of efficacy, tolerance, and adverse effects
See Table No. 4, Graphs No. 16 to 20, Annex II, pages 173 to 176

Diagnoses: In the group of 10 patients (3 men, 7 women) most of them had scars on the face (7x), sporadically on the neck, upper or lower extremity or trunk, in the extent of over 2 cm (6x) whereby most of them were first treated on day 7 following the surgical intervention (6x). All treated areas had been previously stitched.

***Surgical methods*:** Surgical interventions were performed under topical injection anaesthesia (Lidocain, Supracain, Marcain, Mesocain), the wounds were treated with intradermal adaptive stitches, iodine tincture or Curaderm, and dressed with Inadine or Bactigras, Sterilux and sporadically with Suprasorb F foil. In scars of greater extent Steri-strips were used. In 2 patients a thin layer of Cicatrix® cream was applied immediately after stitching using intradermal stitches, dressed with Bactigras, Sterilux and Suprasorb F for 7 days, after change of dressing Cicatrix® cream was applied daily. In 6 patients Cicatrix® cream was applied at the check-up on day 7 after surgery, in 2 patients after the removal of stitches on day 14.

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

Recommended methods: special massages with Cicatrix® cream

Other physical therapy applied in 3 weeks after surgery the earliest: occlusion in 3 patients. Intralesional corticoids were not applied.

See Table No. 3, Graphs No. 13 to 15, Annex II, pages 170 to 172

Improvement of the local finding*:* was visible in 30% already after 15 days, and continued until end of application of Cicatrix® cream.

Note: The patients appreciated the application properties and the texture of Cicatrix® cream, and also those patients in which the effect was not final, continued with the application of Cicatrix® cream willingly.

Specific data: ***Adverse effects (*****See Table No. 4 Annex II, page 173*****)****:* ***0***

Keloid formation: **0**

Excluded patients: **0**

Hospitalised patients: **0**

Efficacy of topical therapy as to the day of trial completion***:***

(**See Table No. 4, Graphs No. 16, 18 to 20, Annex II, pages 173 to 176*****)****:*

Assessment performed by the therapist:

9 patients (90%) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

1 patient (10%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

Subjective assessment performed by the patients:

9 patients (90%) - excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

1 patient (10%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

Tolerability of the therapy as to the day of trial completion:

(**See Table No. 4, Graphs No. 17 to 20, Annex II, pages 173 to 176*****)****:*

Assessment performed by the therapist:

10 patients (100%) excellent tolerance

Assessment performed by the patients:

10 patients (100%) excellent tolerance

Comment: Centre 06 Brno Dr. Zuzana Vykutilová

Cicatrix® cream, Catalysis S.L. Madrid was applied in the total of 10 patients.

The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, later (app. 14 days following the surgical intervention) with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods and supplementary treatments.

Before the commencement of therapy, all patients were instructed about the massage technique (see Annex), and they were provided with guidelines, and they were also shown live how to perform the massage movements. **All centres considered the massage extremely important, since the application itself does not lead to lasting results.**

Adverse effects:

Were not recorded also due to the fact that in the group there were older patients, the skin of whose is less sensitive to external influences.

No bacterial infection was recorded.

Most significant effects (like in other Centres) were observed in patients with scars localised on the face, since the skin on the face is not exposed to pressure or stretching and when using the right system of therapy there is minimum risk of complications. Very good effects were observed in this Centre in patients who applied Cicatrix® cream Catalysis S. L. Madrid immediately after stitching. Due to this reason, the Centre preferred this system of treatment.

Results: Centre 04 Brno Doc. Dr. Jarmila Rulcová, Ph.D

Basic data: **6 patients– men**
gender, number of patients, age (highest, lowest age)
average application period (in days), possible complications,
application discontinuation, hospitalised patients
See Table No. 1, Graphs No. 1 to 3, Annex II, pages 128 to 130

Specific data: scar locality and extent, start of application of Cicatrix® cream,
assessment of its effects and tolerability by the therapist and the patients
See Table No 2, Graph No.4 to 7, Annex II, pages 131 to 133

Special data: – application of supplementary therapy
See Table No. 3, Graph No. 8, Annex II, pages 134 to 135

Special data: – complete assessment of efficacy, tolerance, and adverse effects
See Table No. 4, Graphs No. 9 to 13, Annex II, pages 136 to 139

Diagnoses: In the group of 6 patients (all men), most of them had multiple keloids after acne conglobata therapy with retinoids (Roaccutane Roche), present over 12 months on the shoulders (6x) and on the trunk (6x), in the extent over 2 cm (12x).

***Other medication*:** topical anti-acne therapy was applied to other localities, which were followed within the trial

Recommended methods: special massages with Cicatrix® cream

Other physical therapy employed in 3 weeks after therapy the earliest: none
intralesional corticoids were not applied in this group of patients.
See Table No. 3, Graph No. 8, Annex II, pages 134 and 135

Improvement of the local finding:
Was visible already after 21 days in 35% patients with scars not older than 2 months,
and continued until the application of Cicatrix® cream was completed.
In older scars improvement was visible approximately after 30 days.
Note: The patients appreciated the application properties and the texture of Cicatrix® cream, and continued with the application also when the effect was not final.

Efficacy of topical therapy as to the day of trial completion:

***(*See Table No. 4, Graphs No. 9, and 11 to 13, Annex II, pages 136 to 139*)*:**

Assessment performed by the therapist:

2 patients (33.33%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
3 patients (50%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration of the scar as towards trial completion day
1 patient (16.67%)	insignificant improvement, erythema, infiltration, oedema, itching

Subjective assessment performed by the patients:

2 patients (33.33%) -	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
4 patients (66.67%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration of the scar as towards trial completion day

Tolerability of the therapy as to the day of trial completion:

***(*See Table No. 4, Graphs No. 10 to 13, Annex II, pages 136 to 139*)*:**

Assessment performed by the therapist:

6 patients (100%)	excellent tolerance

Assessment performed by the patients:

6 patients (100%)	excellent tolerance

Adverse effects	***0***	***(*See Table No. 4, Annex II, page 136*)***
Keloid accentuation	0	
Excluded patients:	**0**	
Hospitalised patients:	**0**	

Comment: Centre 04 Brno Doc. Dr. Jarmila Rulcová, Ph.D

Cicatrix® cream, Catalysis S.L. Madrid was applied in the total of 6 patients.

The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, or with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods and supplementary treatments.

All patients were instructed in how to perform the massage (see attachment) orally and in writing. **This fact was considered very important by Centre 04 (as well as other centres), since only the application does not lead to lasting results.**

The assessment resulted in the following findings:

1. In patients with scars 2 months old the effect was present already after 3 weeks – they were softer to touch, and their colour changed, after 6 weeks they were softer and flatter.
2. After 3 weeks of application in patients with keloid scars 6 to 12 months old we observed significant improvement at touch. However, due to the short duration of the trial it is too early to make final conclusions. **The investigators recommend that in patients with old keloid scars the preparation be used for at least 3 up to 12 months.**
3. Based on the experience gained within the trial, Cicatrix® cream appears to be an excellent preventive preparation, especially in patients prone to developing inflammatory infiltrates. In such patients the preparation could be efficient in the healing phase of more extensive inflammatory lesions – i.e. in concomitant oral therapy with isotretinoin - Roaccutane. We assume this could prevent keloid formation.

No adverse effects were recorded.

No bacterial infection was recorded.

Results of scar therapy with placebo:

Centre 03 Žilina, Dr. Alena Nejdková

Centre 05 Praha Dr. Cabalová Jiřina

The centres were selected to treat patients who had two comparable scars, whereby one was treated with Cicatrix® cream and the other with a placebo preparation.

The following comment includes the summary assessment of placebo application in both centres: ***Centre 03*** **with 16 female patients**

Centre 05 **with 8 patients (1 man, 7 women)**

Basic data: **24 patients– 1 man, 23 women**

Specific data: – gender, scar locality and extent, start of application of placebo and assessment of effects and tolerability by the therapist and the patients **see Tables Placebo Centre 03, 05, No. 2A, Annex III, pages 187, 188**

Specific data: – assessment of scar therapy with placebo in percentages
scar locality and extent, start of application,
assessment of effects and tolerability by the therapist and the patients

See Tab 5: Placebo % in Centre 03, 05, Graph No.23 to 26, Annex III, pages 196 to 198

Diagnoses: In the group of 24 patients (1 man a 23 women) most of them had scars on the face (18x), sporadically on the neck, upper extremity and trunk, in the extent of less than 2 cm (19x), whereby in most cases the scar was treated from day 7 after the intervention (13x). In two cases the treated areas were not previously stitched.

***Surgical methods*:** Surgical interventions were performed under topical injection anaesthesia (using Mesocain, Supracain, or Marcain), the wounds were stitched using adaptive stitches, treated with iodine or Betadine, and dressed using Biatain Ag, or sterile dressing Sterilux, and Omnifix. In scars of greater extent Steri-strips were used. In patients treated with electrocautery the areas were covered using Biatain Ag, Inadine or Bactigras for 3 days and then left free to heal without bandage. In all patients Cicatrix® cream was applied after the removal of stitches (on day 7 on the face, and on day 14 on the extremities and trunk).

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

Recommended methods: special massages from the commencement of placebo therapy

Other therapies used not earlier than 3 weeks after trial commencement: occlusion, Intralesional corticoids were not applied in this group of patients.

See relevant Tables representing data in Centres 03 and 05

Improvement of the local finding: visible in 20% already after 20 days of placebo application

At the beginning (the first 2 weeks) no significant differences were observed between the effects of the applied Cicatrix® cream and the placebo

Note: The patients appreciated the comfortable application form and texture of the placebo.

Centre 03

Efficacy of the topical therapy in 16 women as to the day of trial completion - placebo:

***(*See Table No. 2A, placebo Centre 03, Annex III, pages 187 and 188*)*:**

Assessment performed by the therapist

6 patients (37.5%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
6 patients (37.5%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
4 patients (25.0%)	insignificant improvement, erythema, mild oedema, itching

Subjective assessment performed by the patients at trial completion:

6 patients (37.5%)	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
6 patients (37.5%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
4 patients (25.0%)	insignificant improvement, erythema, mild oedema, itching

***Tolerance assessment* performed by the therapist and the patients at trial completion:**

7 patients (43.75%)	6 patients (37.5%)	excellent tolerance
5 patients (31.25%)	8 patients (50%)	very good tolerance
4 patients (25%)	2 patients (12.5%)	good tolerance

No adverse effects in the group of 16 patients applying placebo were recorded.

Keloid formation: **0**

Excluded patients: **0**

Hospitalised patients: **0**

Centre 05

Efficacy of topical therapy in Centre 05 in 8 patients as to the day of trial completion: placebo

***(*See Table No. 2A, placebo Centre 05, Annex III, pages 187 and 188*)*:

Assessment performed by the therapist

0 patients	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
2 patients (25%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
6 patients (75.0%)	insignificant improvement, erythema, mild oedema, itching

Subjective assessment performed by the patients:

0 patients-	excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation
3 patients (37.5%)	satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion
5 patients (62.5%)	insignificant improvement, erythema, mild oedema, itching

Tolerance assessment performed by the therapist a patients*:*

7 patients (87.5%)	3 patients (37.5%)	excellent tolerance
0 patient	4 patients (50%)	very good tolerance
1 patient (12.5%) :	1 patient (12.5%)	good tolerance

No adverse effects were observed in the group of patients 05 on placebo.

Keloid formation: **0**

Excluded patients: **0**

Hospitalised patients: **0**

Centres 03 and 05 together

Efficacy of topical therapy in 24 patients as to the day of trial completion - placebo:
***(*see Tab. 5 Placebo % in Centre 03, 05; Graphs 23 to 26 Annex III, pages 196 to 198*)*:**

Assessment performed by the therapist

6 patients (25.00%) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

8 patients (33.33%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

10 patients (41.67 %) insignificant improvement, erythema, mild oedema, itching

Subjective assessment performed by the patients:

6 patients (25%) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

9 patients (37.50%) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

9 patients (37.50%) insignificant improvement, erythema, mild oedema, itching

Tolerance assessment performed by the therapist a patients*:*

14 patients (58.33%)	9 patients (37.50%)	excellent tolerance
5 patients (20.83%)	12 patients (50%)	very good tolerance
5 patients (20.83%)	3 patients (12.5%)	good tolerance

Comment: **Centres 03 Žilina** **Dr. Alena Nejdková**

Centre 05 Praha **Dr. Cabalová Jiřina**

Placebo preparation was applied in the total of 24 patients.

The following standard treatment procedure was selected, which included:

1. washing the treated area with micellar water, or, after 14 days following the surgical intervention, with preparations with a low content of Ichthamol (soap, liquid soap, and bath gel)
2. special soft massages
3. reassessing the condition after a month and introducing other combinations of treatment methods and supplementary treatments.

Before the commencement of therapy, all patients were instructed in the massage technique (see Annex), they were provided with guidelines, and they were also shown live how to perform the massage movements *and were instructed in the necessity to always treat one scar with Cicatrix® cream and the other with placebo*.

The massage system is considered extremely important especially by Centre 03 Žilina, since the results of comparing the application of Cicatrix® cream and placebo differ quite insignificantly. Due to this reason, the investigator is convinced that the application of the cream without the massage (whether it contains any active ingredients or not) does not lead to lasting results.

In Centre 05 the effect of placebo compared to Cicatrix® cream was much worse.

Adverse effects:

Adverse effects such as burning sensation, skin dryness, itching were not observed, or were of transient nature, only, and it was therefore not necessary to give them in the protocol. What contributed to this result was the fact that the placebo was applied, apart from a few exceptions, after the removal of stitches.

No bacterial infection was recorded

Most significant differences in the effects of placebo versus Cicatrix® cream were observed in patients with bigger scars under the breasts, and on upper and lower extremities. In these areas it is possible to monitor in an ideal way the dynamics of healing.

Summary results on Centres 01, 02, 03, 05, and 06

Assessment of scars treated with Cicatrix® cream

Basic data on Cicatrix® cream: 126 patients– 22 men (17.46%), 104 women (82.54%)

gender, number of patients, age (highest, lowest age)
average application period (in days), possible complications,
application discontinuation, hospitalised patients
See Table No. 1, Graphs No. 1 to 4, Annex III, pages 178 to 180

Specific data on Cicatrix® cream:

scar locality and extent, start of application of Cicatrix® cream and
assessment of effects and tolerability by the therapist and the patients
See Table No 2 Graph No.5 to 13, Annex III, pages 181 to 186

Specific data on placebo:

Scar locality and extent, start of application of placebo,
assessment of effects and tolerability by the therapist and the patients
See Table No 2A, Annex III, pages 187 to 188

Specific data on Cicatrix® cream:

Supplementary therapy
See Table No. 3, Graphs No. 14 to 16, Annex III, pages 189 to 191

Specific data on Cicatrix® cream

Complete assessment of efficacy, tolerability, and adverse effects in percentages
See Table 4, page 192; Table 6, pages 199; Graphs No. 17 to 22, pages 193 to 195; Graphs No. 27 to 30, pages 201 to 222, Annex III

Specific data on placebo

Complete assessment of efficacy, tolerability, and adverse effects in percentages
See Table No. 5, Graphs No. 23 to 26, Annex III, pages 196 to 198

Specific data: Cicatrix cream versus placebo

Comparison of % assessment of the therapeutic effect in the whole series of patients see Graphs No. 31 – 34, Annex III, pages 203-206

Diagnoses:

In the group of 126 patients (22 men and 104 women) with the average age of 39.76 years (men 40.06 years, women 39.46 years), with the lowest age in men 15, and the highest age in men 80 years; the lowest age in women was 2, and the highest age was 78 years.

The average application period was 50.4 days (47.8 days in men, and 53 days in women).

Most patients 76 - 60.32% had scars on the face (8 in men, 68 in women), followed by scars on the trunk 19x – 15.8% (5 in men and 14 in women), 11x and upper extremities – 8.73% (2x in men, 9x in women), there were less scars on the neck, shoulders, and legs.

Scars in the extent of less than 2 cm - 87x – 69.05% (12x in men, 75x in women).

Scars in the extent of over 2 cm, together 39x – 30.95% (10x in men and 29x in women).

Most patients 59 – 46.83% (12x men, 47x women) were treated from day 7 after surgery.

Preparation applied after the removal of stitches on day 14 in 33 patients – 26.19% (6x men, 27x women). In 22 patients - 17.46% (3 men, 19 women) Cicatrix® cream was applied immediately after the intervention. In 12 cases (9.52%) the treated areas on the skin were not previously stitched (1x man, 11x women).

For exhaustive data see Table No. 2 and 6, Annex III, pages 181, 189.

***Therapy efficacy in 126 patients as to the day of Cicatrix® cream application discontinuation: (*See Table 2, pages 181; Graphs No. 7 to 10, pages 183 to 184; Table 4, pages 192, Graphs 17, 19 to 21, pages 193 to 195, Table 6, pages 199 Graphs 27 to 29, pages 201 to 202 Annex III)**

<u>Assessment performed by the therapist *Cicatrix® cream*</u>

68 patients (53.97% - 13 men, 55 women) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

38 patients (30.16% - 3 men, 35 women) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

11 patients (8.73% - 2 men, 9 women) insignificant improvement, erythema, infiltration, mild oedema, itching

9 patients (7.14% - 4 men and 5 women) keloid formation, dissatisfactory condition

Subjective assessment made by the patients of *Cicatrix® cream*

69 patients (54.76% - 12 men, 57 women) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

38 patients (30.16% - 4 men, 34 women) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

10 patients (7.94% - 2 men, 8 women) insignificant improvement, erythema, mild oedema, itching

9 patients (7.14% - 4 men and 5 women) keloid formation, dissatisfactory condition

***Tolerance assessment* performed by the therapist and the patients *Cicatrix® cream* as to the day of trial completion:**

(see Table 4, page 192; Graphs No. 18 to 21, pages 193 to 195; Table 6, page 199, Graph 30, page 202 Annex III)

97 patients (76.98%)	104 patients (82.54%)	excellent tolerance
13 patients (10.32%) :	12 patients (9.25%)	very good tolerance
14 patients (11.11%) :	8 patients (6.35%)	good tolerance
2 patients (1.59%) :	2 patients (1.59%)	poor tolerance, intolerance

Adverse effects of Cicatrix® cream as to the day of trial completion

(See Table No. 4, Graph 22, Annex III, pages 192, and 195)*:*

4 patients	(3.17% - 2 men, 2 women)	burning sensation
5 patients	(3.97% - 2 men, 3 women)	skin dryness
2 patients	(1.59% - 2 women)	skin reddening
3 patients	(2.38% - 3 women)	itching

The adverse effects were of transient nature and were no reason for application discontinuation 3 weeks from start of application.

Keloid formation: 9 patients (4 men, 5 women) – 7.14%

Excluded patients: **0, after 21 days 1 female patient discontinued the application**

Hospitalised patients: **0**

Comment to the comparison of therapeutic effect assessed in percentages of Cicatrix® cream versus placebo (Tables 5, 6, pages 196, 199; Graphs No. 23 to 25, pages 197 to 198; Graphs No. 31 to 33, pages 203 to 206, Annex III)

Assessment performed by the therapist:

53.97% (68 patients) : 25.00% (6 patients) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

30.16% (38 patients) : 33.33% (8 patients) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

8.73% (11 patients) : 41.67% (10 patients) insignificant improvement, erythema, infiltration, mild oedema, itching

7.14% (9 patients) : 0 % (0 patients) keloid formation, dissatisfactory condition

Assessment performed by the patients:

54.76% (69 patients) : 25.00% (6 patients) excellent cosmetic and aesthetic effect, accelerated healing, healing without visible scar formation

30.16% (38 patients) : 37.50% (9 patients) satisfactory aesthetic and cosmetic effect, slight erythema and infiltration around the scar on the day of trial completion

7.94% (10 patients) : 37.50% (9 patients) insignificant improvement, erythema, infiltration, mild oedema, itching

7.14% (9 patients) : 0 % (0 patients) keloid formation, dissatisfactory condition

Tolerance of Cicatrix® cream vs. placebo in percentages:

(Tables No. 5, 6, pages 196, 199; Graphs No. 26, page 198, Graph No. 34, page 206, Annex III)

Assessment performed by the therapist:

76.98% (97 patients) : 58.33% (14 patients**)**	excellent tolerance
10.32% (13 patients) : 20.83% (5 patients)	very good tolerance
11.11% (14 patients) : 20.38 (5 patients)	good tolerance
1.59% (2 patients) : 0 % (0 patients)	keloid formation, dissatisfactory condition

Assessment performed by the patients:

82.54% (104 patients) : 37.50% (9 patients)	excellent tolerance
9.52% (12 patients) : 50.00% (12 patients)	very good tolerance
6.35% (8 patients) : 12.50 (3 patients)	good tolerance
1.59% (2 patients) : 0 % (0 patients)	keloid formation, dissatisfactory condition

Discussion

Cicatrix® cream, a product of the company Catalysis S. L. Madrid represents a group of preparations used to treat keloid and hypertrophic scars, and contains Centella Asiatica 1.0% and Pinus Sylvestris 0.5% (TECA extracts). The said active ingredients are responsible for its effects in adequate indication and application. The application of these ingredients is ***considered as effective as the one of other agents, including external or intralesional corticoids and comparable with the prolonged usage of pressure bandages (occlusion).***

The efficacy of Cicatrix® cream, Catalysis S. L. Madrid has been proven by the pilot study carried out in 2006 and 2007 and subsequently verified in many patients in practice. The secret behind the great efficacy is called molecular activation, which increases the potency of molecules 20–100 times.
The chemical composition of the product remains the same; however, its bioactivity is significantly increased.

In order to widen the range of indications of the product it was necessary to verify the possible preventive effects and tolerability of Cicatrix® cream, CATALYSIS S.L. Madrid in patients with fresh surgical scars and traumatic wounds (burns, cuts, stab wounds) ***and assess the final effect of accelerated healing and prevented formation of keloid and hypertrophic scars in various age groups and in wounds of various aetiology.***

The proven validity of results was verified again in comparison with a placebo preparation in selected patients in randomly appointed centres.

A part of the therapy aimed to prevent the formation of keloid scars is the elaborated system of massage movements, which has been used in practice for many years with provable results.

Conclusion

The application of Cicatrix® cream, Catalysis S. L. Madrid represents a classic conservative monotherapy or combination therapy of keloid and hypertrophic scars. The trial has proven that it also may be used as a preventive modality in those patients who are predisposed to keloid formation.

Therefore, all patients have been instructed in the technique of performing the massage prior to inclusion into the trial (see attachment), they had been provided with written guidelines and shown how to perform the movements in practice. The special soft massage movements **are considered inevitable by all trial centres, since simple application of the preparation does not lead to lasting results.**

The massage leads to gradual deterioration of the rigid scar fibres (or prevents their formation) and very much influences the final effect. In combination with other therapeutic modalities (biostimulation laser, pulverization, microdermabrasion, occlusion, biolamps) used only after 3 weeks following surgery, the optimum effect gets even more potentiated.

The results of the assessment of the therapeutic effect of Cicatrix® cream, Catalysis S. L. Madrid versus placebo performed by the therapist in a group of 126 patients speak clearly in favour of Cicatrix® cream:

53.97% patients on Cicatrix® cream **vs.** **25.00% patients on placebo**
excellent cosmetic and aesthetic effect, accelerated healing without visible scar formation

30.16% patients on Cicatrix® cream **vs.** **33.33% patient on placebo**
satisfactory aesthetic and cosmetic effect,
slight erythema and infiltration around the scar on the day of trial completion

8.73% patients on Cicatrix® cream **vs.** **41.67% patients on placebo**
insignificant improvement, erythema, infiltration, mild oedema, itching

7.14% patients on Cicatrix® cream **vs.** **0 % patients on placebo**
keloid formation, dissatisfactory condition

The investigators in single centres all agree that greatest effects are obtained when Cicatrix® cream is applied as early after the surgery as possible. In case the locality of the wound and the condition of the patient allow it, the stitched area should be treated on day 7 after surgery. In case surgical interventions are performed on the face the preparation may be used on the day when stitches are removed, in other cases on the day when dressing is changed.

Most significant effects were observed in patients with small extent scars on the face, where the skin is not as much exposed to pressure or stretching and where the right system of care is connected with minimum risk of complications. In this area it is also possible to observe the dynamics of healing very easily.

Great effects were achieved in patients with burns, where Cicatrix® cream was applied starting on day 5 or day 7 when the affected areas were no longer secerning These healed with no signs of scarring.

Similarly great effects were obtained in elderly patients, in which a catamnestic study performed 4 months after trial completion has proven that there are no scars present in the operated area.

Surprisingly good effects were observed in patients after blepharoplasty and in patients with extensive scars after breast reduction or leg surgery. Cicatrix® cream also had a clear anti-oedematous effect. Patients reported that the effect they appreciated most was the softening of the scar, less erythema and infiltration, and a satisfaction with the effect as such.

Outside the trial, the Cicatrix® cream was applied in Centre 01 in a patient with actinic keratosis, treated with Efudix® cream (5-fluorouracil). The effect of a two-week application of Efudix® cream is equal as the one of a grade II burn. Therefore, the usual therapeutic approach is to foster skin epithelisation using special agents. After the area stopped secerning in this particular patient, we started applying Cicatrix® cream. In 10 after the commencement of Cicatrix® cream application we observed complete healing and an excellent aesthetic effect. Please see the pictures enclosed in photodocumentation. Due to that, it is more than advisable to recommend the usage of Cicatrix® cream also in those indications.

We may not omit the results obtained on a small group of patients with keloid scars that accompanied the therapy of acne conglobata. It is necessary to draw attention especially to the following details:

- In patients with old keloid scars it is necessary to apply Cicatrix® cream for at least 3 to 12 months (always using the massage movements).
- Based on our experience Cicatrix® cream appears to be an *excellent preventive preparation*, especially in patients with inflammatory infiltrates. The application has proven effective already in the process of healing of extensive inflammatory lesions especially in the group of patients treated with oral isotretinoin - Roaccutane. If the indication range is extended and based on producer recommendation, targeted application of Cicatrix® cream could prevent keloid formation.

In 9 patients applying Cicatrix® cream there was keloid formation, whereas in the placebo group there were none, which is very interesting.

Adverse effects such as skin dryness, burning sensation, erythema, and pruritus were rare and did not last long; therefore application discontinuation was not necessary.

All 126 included subjects completed the trial.

Great tolerability, practically no contraindications or adverse effects, the possibility to apply the preparation safely in paediatric patients and the high success rate of the preparation applied either preventively, or to reduce the appearance of keloids in the group of 126 patients with fresh surgical scars or traumatic wounds are the attributes, that open the door to extensive usage of Cicatrix® cream.

The final satisfactory cosmetic and aesthetic effect has shown immense influence on the mental comfort of the patients.

Based on the results obtained within the trial, therapy with Cicatrix® cream, a product of Catalysis S. L. Madrid, is a very elegant and highly effective preventive and therapeutic modality. In order to potentiate the final effects, it is necessary to apply the preparation using a system of special massage movements (to accelerate the deterioration of scar fibres and start the formation of capillaries.

The preparation should not be applied in patients with a known allergy or perform an epicutaneous test prior to application.

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Massage technique applied to avoid the formation of keloid scars

Keloid scars massage technique

- Massage ought to be performed in a warm and cosy environment
- It is advisable to find some time after bath in evening hours for massage according to the extent or localisation of the scar
- It is recommended to use bath oils such as Balneum, Linola oil bad, Balmandol etc

- The idea is to deteriorate rigid fibre bundles
- it is necessary to perform single massage steps repeatedly and on a regular basis
- it is necessary to adhere to the sequence order of massage movements

it is inevitable to choose adequate massage pressure

Massage movements:

- 9 massage steps are performed using two fingers (second and third finger),
- The last massage step is performed with 3 - 4 fingers
- Every of the ten massage movements is repeated 10 times, at least 2 times a day, The optimum number of massage sessions being 3 times a day

After the massage the scar ought to be kept warm for at least half an hour, and at night it is possible to use partial biooclusive material occlusion

Keloid scars massage movements

- 1. circle clockwise
- 2. circle counter clockwise
- 3. = 1 + 2 (combine one circle clockwise and another circle counter clockwise)
- 4. zig-zag downwards
- 5. zig-zag upwards
- 6 = 4 + 5 (combine one zig-zag downwards and one zig-zag upwards)
- 7. follow number eight with your finger starting clockwise
- 8. follow number eight with your finger starting counter clockwise
- 9 = 7 + 8 (follow number eight with your finger starting clockwise, and continue counter clockwise)
- 10. apply vibrations to the scar – use slight but firm pressure

Important!!!

- Remember to repeat everything to your patients since repetition is the mother of wisdom
- It is necessary to inform the patients on the preparation and massage technique at the same time

It is advisable to organise practical lectures, use audiovisual material and distribute instructions in writing

Annex I

Trial Design

International Multicentre Trial Design

International Multicentre Trial to verify the effects of applying Cicatrix® cream, CATALYSIS, S. L. Madrid, in patients with fresh surgical scars and traumatic wounds

Version as of December 1st, 2007

Trial type: single open type IV with post-registration monitoring and continuous inclusion of patients into the trial according to set criteria

In two groups of patients the trial was double blinded and compared with placebo.

Trial objective to prove the efficacy and tolerability of applying Cicatrix® cream, a product of CATALYSIS S.L. Madrid, in patients with fresh surgical scars or traumatic wounds (1 cm long the minimum, 12 cm long the maximum or in the extent of 10 - 15cm^2) and to assess the difference in tolerability and the final healing acceleration effect and the effect of keloid and hypertrophic scars formation in individual patients
The validity of results was verified in comparison with placebo in selected groups of patients in randomly selected centres.

Number of patients included: 126 on the whole

Participating countries:

1.	**Slovakia**	**Svidník I and II, Žilina**
2.	**Czech Republic**	**Prague, Brno**

Trial centres:

Slovakia		**Centre No.**	**No. of patients**
Svidník I	**(Dr. Hana Zelenková, Ph.D.)**	**01**	**30**
Svidník II	**(Dr. Júlia Stracenská)**	**02**	**30**
Žilina I	**(Dr. Alena Nejdková)**	**03**	**31 (16 placebo)**
Czech Republic			
Brno	**(Dr. Rulcová Jarmila, Ph.D.)**	**04**	**6**
Prague	**(Dr. Jiřina Cabalová)**	**05**	**25 (10 placebo)**
Brno	**(Dr. Zuzana Vykutilová)**	**06**	**10**

Trial design: patients aged 10 –82 years (men and women) shall apply a topical preparation Cicatrix® cream CATALYSIS, S. L. Madrid

Diagnosis: fresh surgical scars or traumatic wounds

Note:
Centre 04 Brno has been invited to participate in the trial additionally, with the investigator Dr. Jarmila Rulcová, Ph.D, to trialpatients with extensive fresh keloid scars after acne conglobata therapy. The results of this Centre results are assessed separately.

Employed preparation: Cicatrix® cream, Catalysis S.L. Madrid

Product characteristics: Cicatrix® cream, Catalysis S.L. Madrid

Cicatrix® cream is a new product by Catalysis Madrid, employed to treat keloid and hypertrophic scars. The active substances contained in the cream include Centella Asiatica 1.0% and Pinus Sylvestris 0.5%

The said active agents guarantee its efficacy in adequate indications. Other ingredients include Abil B8839, Sk-Influx, Tego Alkanol 1618, Glycerine and other agents according to producer standard. The product has been subjected to molecular activation.

Centella Asiatica has been used in medicine for many centuries; however, it was only in the fifties of the previous century an adequate extraction of the active components was performed successfully.

Gotu kola extract (titred extract of Centella Asiatica – TECA), Madecassoside and Asiaticoside are the most important components of the preparation, showing activity. They all have been described many a time, including their excellent effects shown to treat venous hypertension, vessel circulation, oedema or varicose veins. They also decrease the level of cholesterol and demonstrate antibacterial activity.

TECA extracts can foster collagen synthesis in arterial walls and maintain their tonus. What is really interesting is the knowledge obtained about the changes of human fibroblasts induced by the triterpenoids of Centella Asiatica. TECA testing on animals has proven their absolute safety. Of course the advantages of its topical application have been verified and proven by many studies and documented experiments in the field of wound healing acceleration were performed, describing the ways to promote skin healing after radiodermatitis therapy and the treatment of experimental wounds and scars. TECA animal testing has also proven analgesic effects in small animals as well as the fact that some Gotu kola components may interfere with fertility in mice. TECA is alleged to act as an aphrodisiac – however, this has not been proven by research so far.

TECA has been tested in a row of clinical trials and the presumption has been proven that its application accelerates the healing of surgical wounds, leg ulcers of various aetiology, parasitic skin diseases, skin diseases of pemphigoid group and scars. The healing itself is not accompanied by any damage or scarring.

The pilot trial carried out in 2007 (DOST Svidník) has proven the excellent therapeutic parameters of the product in a variety of patients with both fresh and older hypertrophic and keloid scars..

The composition of the placebo preparation remained unknown.

Number of applications: 2 times a day using the prescribed massaging movements and pulverisation in indicated cases

Application start:

I after stitching of the operated locality
II 7 days after surgical intervention or trauma
III after the removal of stitches
IV after 2 days
(dermabrasion, shave technique, radio- and electrocautery)

Note: The product must not be applied to fresh bleeding or secerning wounds!

Application duration: 21 days (3 weeks) the minimum,
90 days (3 months) the maximum

Application information: given by the therapist both orally and in writing
Documentation: Working Protocol, tables
Photodocumentation: pictures taken 2 - 3 times in all patients
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

Other medication: only the medication necessary for the basic comfort of the patient, administered exclusively based on recommendation by other medical expert

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

1 healing acceleration, with healing without scarring with an excellent aesthetic and cosmetic effect
2 mild erythema and infiltration appearing around the scar to the day of application termination, however, with satisfactory aesthetic and cosmetic effect in general
3 insignificant improvement, erythema, infiltration, oedema, itching
4 dissatisfactory condition, keloid scar formation

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

1 excellent aesthetic and cosmetic effect without any undesired effects
2 satisfactory aesthetic and cosmetic effect, slight scar swelling, and reddening
3 insignificant improvement, erythema, infiltration, oedema, itching, poor satisfaction with the healing
4 scar development, irritation, and itching, dissatisfactory effect

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

All centres shall be provided with Cicatrix® cream by the company Catalysis S.L. Madrid
It is possible to obtain more samples upon request.

Time schedule: December 2007 – January 2008, patient inclusion and exclusion
January 1st, 2008 – May 30th, 2008 performance of the trial
June 2008 result assessment and processing
July August 2008 handing over the **complete** results
September - December 2008 – 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!

Attachments:
1. Basic Working Protocol
2. Inclusion and Exclusion Criteria
3. List of Patients
4. Patient Consent Form
5. Adverse Effects Documentation Form

Suppl. data -Centres 03 and 05 – application of placebo to comparable scars

Žilina I (Dr. Alena Nejdková)	**03**	**15 +16**
Praha (Dr. Jiřina Cabalová)	**05**	**15 + 10**

The centres above have been addressed and instructed to carry out a double blind trial of applying placebo preparation in randomly patients.

Materials and Methods:
The randomly selected patients were selected out of those with two operated or traumatised localisations.
One of them was treated by applying Cicatrix, and the other was treated with placebo.

The system of applying the preparation, monitoring the development of the condition, and performing the documentation remained unchanged.

The precondition is to take high quality pictures and perform the final assessment and comparison of the therapeutic effects of Cicatrix cream versus placebo.