International, prospective, controlled multicentre study to prove the efficacy and tolerability of a preparation containing glycyrrhizinic acid in patients with acne vulgaris

(Cook’s acne severity grading scale 1-4)

Final Report

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Submitted by : Hana Zelenková, M.D., Ph.D.

For : Catalysis, S.L., Madrid
Contents:

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Introduction

In 2005 (from 1 February 2005 to 30 May 2005) a pilot study was carried out at the Private Department of Dermatology DOST in Svidnik to prove the efficacy and tolerability of a preparation containing glycyrrhizinic acid in patients suffering from mild and moderate acne vulgaris (grade 2 - 4 acc. to Cook’s acne severity grading scale). The study was an open trial of type IV with post registration monitoring. The conclusions of this study introduced quite surprising results demonstrating 77.77% efficacy of the preparation in a group of 18 patients, whereby the tolerability of the preparation was excellent in all patients included.

Taking into consideration that the trial was dealing with inventive therapeutic employment of a preparation containing glycyrrhizinic acid resulting from practical experience, and that there was no information described in literature on a similar group of patients with the same diagnosis to compare the therapy, the company Catalysis S.L. Madrid decided to carry out an extensive international multicentre study.

The study was defined as an: “International, prospective, randomized, controlled multicentre study to prove the efficacy and tolerability of a preparation containing glycyrrhizinic acid in patients with acne vulgaris (Cook’s acne severity grading scale 1-4)”.

11 Clinics and departments from Slovakia and the Czech Republic (Study Design, see Annex No I) participated in the study. The project monitoring was designed taking into consideration the possibility to study clinical efficacy and safety of the preparation in question and the possibilities of its employment in everyday practice.

For the purposes of this study, the preparation used and delivered to the clinics and employed in practice was Granex®, a product of the company Catalysis, S.L., Madrid, Spain.
Acne vulgaris. Its definition and therapy.

Acne vulgaris – is one of the most common diseases, and as for its therapy, also one of the conditions that are the hardest to influence therapeutically. The number of patients aged 12 – 25 affected by this disease is growing constantly. Dermatologists daily encounter a number of cases of acne, from the mildest up to the most significantly complicated ones. Apart from having to justify the therapy they choose and employ, they also have to answer the questions asked by unhappy and dissatisfied patients concerning „the preparations that really work“, which are continuously being introduced to the market by various cosmetic companies. Pharmaceutical companies are not lagging behind them and also seek to produce a variety of preparations to be used both topically and systemically. The approach adopted towards acne therapy differs in various countries of Europe. For example, in Western Europe, the patients first go to the drug-stores, chemists and pharmacies and the person that happens to be their first advisor on the matter is the pharmacists, whereas in Eastern Europe young people apply to dermatologists for advice from the beginning.

Within the past few years there have been significant changes in the approach towards acne vulgaris therapy. Of course the therapeutic approach depends on the severity grade of acne and the extent of the condition, with the sex of the patient playing a decisive role. In order to design a targeted individual therapy plan, it is absolutely necessary to elaborate and assess clear pathogenetic principles.

In acne vulgaris therapy, it is basically necessary to adhere to the following scheme: mechanic cleansing, topical therapy (alcohol solutions containing 1-2% erythromycin or other macrolide antibiotics, preparations containing salicylic acid, resorcinol, Ichthamol, azelaic acid, retinoids and other), physical therapy (cryotherapy, dermabrasion, laser, laser scanner etc.), systemic drug therapy (antibiotics, anti-androgens, isotretinoin, vaccines), individual diet plan (the opinions adopted on this matter vary in different authors) and counselling.

Acne vulgaris develops in puberty in 100% of teenagers in its either mildest and transient or complicated forms causing scarring. Primarily during the period of hormonal changes the activity of sebaceous glands increases accompanied by abnormal cornification of the skin surrounding the opening of the hair follicles.
The comedone mechanically restricts the excretion of excessive sebum or makes it literally impossible. The pressure of the accumulated sebum around the hair follicle and sebaceous gland acts like a foreign body and causes an inflammatory response. Sebum decomposition may be caused or accelerated also by the colonisation of rapidly multiplying microbial flora, most of all anaerobic Corynebacteria/cornybacteria (Corynebacterium acnes I. and II., Corynebacterium granulosum, Propionibacterium acnes) and Staphylococcus epidermidis, Staphylococcus pyogenes, yeasts – Pityrosporum ovale and others. Local inflammation and other changes reflecting the intensity of the condition are specified in various schemes.

According to Plewig, acne macroscopically most often develops into the following forms:

- Acne comedonica
- Acne papulopustulosa
- Acne conglobata

<table>
<thead>
<tr>
<th>Table No 1</th>
<th>Primary, secondary and tertiary efflorescence in acne</th>
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<tbody>
<tr>
<td>normal sebaceous gland follicle follicle filament in a sebaceous gland follicle</td>
<td>primary non-inflammatory efflorescence</td>
</tr>
<tr>
<td>microcomedo</td>
<td>secondary inflammatory efflorescence</td>
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<tr>
<td>closed comedone</td>
<td></td>
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<tr>
<td>open comedone</td>
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<tr>
<td>papule</td>
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<tr>
<td>pustule</td>
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<tr>
<td>indurate node</td>
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<tr>
<td>abscessed node</td>
<td></td>
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<tr>
<td>abscessed fistula duct</td>
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<tr>
<td>fistula comedones</td>
<td>tertiary post-inflammatory efflorescence</td>
</tr>
<tr>
<td>cyst</td>
<td></td>
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<tr>
<td>vernicular scar</td>
<td></td>
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<tr>
<td>cyst scar</td>
<td></td>
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<tr>
<td>closed comedo scar</td>
<td></td>
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<tr>
<td>small node scar</td>
<td></td>
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<tr>
<td>keloid scar</td>
<td></td>
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<tr>
<td>atrophic scar</td>
<td></td>
</tr>
</tbody>
</table>
For the purposed of this study we used *Cook’s acne severity grading scale*.

**Table No 2  Cook’s acne severity grading scale 0 - 8:**

<table>
<thead>
<tr>
<th>grade</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>the skin does not have to be absolutely clear. Single comedones or papules may remain on the skin surface, however, visible only on closer inspection on approximately 1/4 of the facial area small papules (6-12) and comedones may occur (small number of larger comedones or 20-30 small closed comedones). Isolated pustules or prominent papules are observed.</td>
</tr>
<tr>
<td>2</td>
<td>1/2 of the face is affected with small papules and large or small comedones. There are usually a few pustules or large papules present on the face. In case the lesions are quite extensive, the patient is graded with the grade &quot;4&quot;, despite the fact that the area affected represents less than ½ of the whole face on 3/4 of the facial area there are papules or large open comedones (less extensive areas of the face may also be affected, depending on the extent of inflammatory lesions). There usually are also numerous pustules of various sizes</td>
</tr>
<tr>
<td>4</td>
<td>disease lesions (of highly inflammatory type) present on the whole area of the face. Usually clearly visible large pustules. Other acne types such as acne conglobata, acne cystica or acne abscensens may also be present.</td>
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<tr>
<td>6</td>
<td></td>
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<tr>
<td>8</td>
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</table>

**Note:**

The acne severity grading scale 0 - 8 was designed as a linear scale, which means that the difference between the grades 0 and 2 ought to be the same as the difference between the grade 2 and 4, 4 and 6 etc. Grades 1, 3, 5, and 7 represent intermediary conditions. The scale is seen as a scale with an open end to assess extraordinarily severe acne conditions. In exceptional cases patients may be diagnosed with acne graded 9 or 10.

In more serious forms of acne papulopostulosa it is inevitable to use topical therapy combined with the employment of systemic antibiotics. The most frequently employed antibiotics are tetracyclines and in case they are contraindicated, it is suitable to use azithromycin, erythromycin or other macrolide antibiotics, chinolones or in exceptional cases, metronidazol. Antibiotics are administered orally for weeks or even months. Following the improvement of the condition, the initial loading dose is gradually decreased until finally replaced by the maintenance dose. The therapy effect is visible after approximately 4 weeks. Isotretinoin is administered to patients suffering from severe acne forms. Other possibilities include the employment of estrogens and anti-androgens administered in the form of oral contraceptives to women, and the employment of the products STAVA and Polystafana.
In **topical therapy** new approaches are sought constantly and what has been evident within the past few years is the comeback of preparations that had been used for centuries in traditional medicine. Quite often a new therapeutic range is discovered of preparations that had been applied only to a certain group of skin diseases. In this light it is very positive to state that in topical therapy of mild and moderate acne forms (Cook 1-4) it is possible to successfully employ a preparation containing glycyrrhizinic acid called **Granex®, produced by the company Catalysis, S.L., Madrid.**

**Basic preparation information :**

Granex® represents a unique preparation produced by the company Catalysis, S.L., Madrid, Spain

**Product description:**

The main active agent contained in the preparation Granex®, Catalysis, S.L., Madrid, Spain is a water extract of glycyrrhizinic acid Glycyrrhizin, GL) 0,1g in 100g of vehicle and 5% of Aloe Vera.

**Glycyrrhiza glabra** – especially its root– radix liquiritiae – radix glycyrrhizae glabrae - has been widely used in pharmacy. Glycyrrhizinic acid (Glycyrrhizin, GL) is a substance of glycosidic character. Aglycon is represented by glycyrrhetinic acid (glycyrrhetin). The pentacyclic triterpene acid glucuronide is of steroid character. The sugar component is represented by two molecules of glucuronic acid. The following split of the sugar component results in the loss of sweetness.

One of the basic properties of Glycyrrhizinic acid is the water foaming property and its low haemolytic efficacy. Glycyrrhizinic acid causes the inhibition of prostaglandin E2 in the affected tissue and stops the replication of viruses as the result of virus P Kinase activity inhibition. The induction of interpherone formation results in the activation of macrophages and potentiation of their phagocytary and bactericidal property. Interpherones exhibit antiviral and antiproliferative effect. Laboratory experiments in vitro have proven its inhibitory effect. Animal testing has proven the zero mortality index as well as the minimal ocular and dermal irritation.
Numerous clinical trials of Granex®, Catalysis, S.L., Madrid, Spain, performed at departments of dermatovenerology and gynaecology have proven its excellent properties, such as the ability to heal viral as well as bacterial infections. Granex®, Catalysis, S.L., Madrid, Spain, was without any problems administered also to pregnant women. Excellent effects following the application of the preparation in the initial stage of infections have been described.

The effects of glycyrrhizin are as follows:

- anti-ulcerous
- anti-inflammatory
- reducing the number of comedones
- antiviral (exhibiting the ability to inhibit virus DNA and RNA) – varicella zoster, HIV, influenza A,B, herpes simplex, hepatitis, HPV

Aloe Vera is a nutrient containing vitamin B1, B2, B6, C, niacin amide, choline and 18 amino acids, as well as many other active substances. The extract of Aloe Vera has been used in many kinds of cosmetic products (creams, lotions, shampoos). In the preparation Granex®, Catalysis, S.L., Madrid, Spain, Aloe Vera is used as an auxiliary substance.

Granex®, Catalysis, S.L., Madrid, Spain is distributed in form of a set consisting of 200 ml of cleansing lotion and a 50 ml spray packed in a box.

Granex®, Catalysis, S.L., Madrid, Spain – other properties:

* neutral fragrance
* no risk of stains in case the preparation gets into contact with clothing
* the preparation can be applied without any problems during pregnancy and lactation

Study objectives

Application of a set of preparations including Granex®, lotion and spray developed by Catalysis, S.L., Madrid, Spain within the performed study was supposed to prove the following effects:
• significant reduction in the development of comedones and inflammatory lesions
• reduction in sebum production by more than 20%
• permanent reduction in the development of comedones
• in comparison with other orally administered tetracycline antibiotics, it is necessary to accentuate the advantages of Granex®, Catalysis, S.L., Madrid, Spain such the elimination of the risk of systemic adverse effects development (diarrhoea, vaginal candida infections, photosensitivity)

**Study characteristics, type and schedule**

International, prospective, randomized, controlled multicentre study

**Study type:** open trial of type IV, with post-registration monitoring.

**Study schedule:**
- January 2006 - selection and exclusion of the patients
- February – April 2006 – carrying out the study
- May 2006 – assessment and processing of the results
- June – December 2006 – presentation and publishing of the results of the study

**Participating countries and towns:**

1. Slovak Republic – Svidník, Žilina, Bratislava
2. Czech Republic – Praha, Brno, Otrokovice

**Clinics and departments: (The Slovak and Czech Republics)**

<table>
<thead>
<tr>
<th>Slovak Republic</th>
<th>clinic/department</th>
<th>Clinic No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svidník I –</td>
<td>Hana Zelenková, M.D., Ph.D.</td>
<td>1</td>
</tr>
<tr>
<td>Svidník II –</td>
<td>Júlia Stracenská, M.D.</td>
<td>2</td>
</tr>
<tr>
<td>Žilina I –</td>
<td>Alena Nejdková, M.D.</td>
<td>3</td>
</tr>
<tr>
<td>Žilina II –</td>
<td>Bohdan Hollý, M.D.</td>
<td>4</td>
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<tr>
<td>Bratislava –</td>
<td>Eva Škutilová, M.D.</td>
<td>5</td>
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<tr>
<th>Czech Republic</th>
<th>clinic/department</th>
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<tbody>
<tr>
<td>Brno I –</td>
<td>Advisor doc. Jarmila Ručcová, M.D., Ph.D.</td>
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<tr>
<td>Brno II –</td>
<td>Zuzana Vykutilová, M.D.</td>
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<tr>
<td>Brno III –</td>
<td>Sandra Vykutilová, M.D.</td>
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<td>Praha I –</td>
<td>Jiřina Cabalová, M.D.</td>
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<tr>
<td>Praha II –</td>
<td>Jiřina Cabalová, M.D.</td>
<td>10</td>
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<tr>
<td>Otrokovice –</td>
<td>Anna Raková, M.D.</td>
<td>11</td>
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</tbody>
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Material and methodology

Prior to the commencement of the trial all participants at all clinics and departments were given instructions and information on the design of the study, the processing of documentation and photodocumentation as well as other relevant issues by the main study coordinator.

Every participant was provided with the basic set of documents:

- Basic Working Protocol (Annex 1)
- Inclusion and Exclusion Criteria (Annex 2)
- Working and Evaluation Sheet (Annex 3)
- Number of patients (Annex 4)
- Patient Consent Form (Annex 5)

Number of patients in each clinic: 10
Documentation: Working Protocol, tables
Photodocumentation: pictures taken 2 - 4 times
Basic laboratory screening: performed in every single patient
Therapeutic effect assessment made by the therapist: scale 1 - 5 (1 - healing, 2 - significant improvement, 3 - improvement, 4 - no improvement, 5 - aggravation)
Evaluation made by the patient: scale 1 - 5 (1 - excellent, 2 – very good, 3 - good, 4 – without any changes, 5 – aggravation, irritation)

Information on preparation application: shall be provided by the therapist upon inclusion into the study prior to the application

Result processing: single clinics represented by the national coordinators shall provide the main coordinator of the study with results for further processing or publishing
Every patient was entered into a special protocol upon inclusion into the study. Apart from basic data concerning the patient (name, surname, date of birth, habitus etc.) the protocol included basic laboratory screening results, examination of focal infection or a microbiologic examination – swabs taken from the pustules (the last three groups of parameters were not subject of the clinical study, which is why they are not separately assessed in the Report), local finding at the inclusion and after certain time intervals, efficacy of therapy, photodocumentation, adverse effects and final assessment made by the therapist as well as the patients themselves.

The monitoring of patients as such was performed at single clinics and departments during the period from 1 February 2006 to 30 April 2006. 110 patients were included into the series (37 (33.64%) male, 73 (66.36% female), their mean age being 18.13 years men, 20.16 women (whereby the youngest patient was a 12 year-old boy and the oldest a woman aged 46).

Monitored diagnosis: Acne vulgaris – papulopustulosa (Cook 0-4)

Local finding assessment: was performed prior to inclusion into the study and after 4 and 8 weeks of therapy according to Cook’s acne severity grading scale 0 – 8 (Tab. No 2). The assessment reflects the impression the patient makes on a strange person within the distance of, 1 - 2 m. The morphs counted included open comedones, closed comedones, papules and pustules.

The guidelines for study of Granex®, Catalysis, S.L., Madrid, Spain, recommended inclusion of patients with acne severity grade 1-4, only. Any exceptions made had to be justified.

Protocol: recorded monitored morphs typical of acne vulgaris

Assessment of facial manifestations and the grading of the severity of the disease (entered into a table):

number of non-inflammatory lesions: on the right/on the left
* open comedones
* closed comedones

*number of inflammatory lesions: on the right/on the left
* papules
### Tab. No 4  Assessment of facial manifestations

<table>
<thead>
<tr>
<th>Monitored morphs</th>
<th>Status localis at therapy commencement</th>
<th>Status localis after 2 weeks</th>
<th>Status localis after 4 weeks</th>
<th>Status localis after 6 weeks</th>
<th>Status localis after 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>open comedones</td>
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<tr>
<td>(on the right/on the left)</td>
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<td>closed comedones</td>
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<td>(on the right/on the left)</td>
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<tr>
<td>papules</td>
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<td>(on the right/on the left)</td>
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<tr>
<td>pustules</td>
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<td>(on the right/on the left)</td>
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<tr>
<td>nodules</td>
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<tr>
<td>(on the right/on the left)</td>
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* Note: Neither pustules nor nodules ought to be present in patients included into the study of the preparation Granex

### Tab. No 5  Status localis after therapy termination graded according to Cook’s scale

open comedones (on the right/on the left)
closed comedones (on the right/on the left)
closed comedones (on the right/on the left)
pustules (on the right/on the left)
nodules (on the right/on the left)
Granex®, Catalysis, S.L., Madrid, Spain - application

The product used was a topical preparation Granex®, produced by the company Catalysis, S.L., Madrid, Spain.

Every clinic was provided with 10 sets of Granex®, (consisting of lotion and spray). There was a possibility to obtain more samples upon request.

The patients were applying the preparation to predefined areas such as the cheeks, the forehead and the nose. To sum it up, the whole facial area was treated in all patients.

Granex® – application instructions

* Granex® is applied 3 times and day during the first 10 days and after that 2 times a day on the whole facial area:

1. the face was cleansed with Granex® lotion
2. which was followed by the application of Granex® spray

* the preparation is to be used continuously until the resolution of the symptoms and significant improvement of the condition of inflammatory lesions as well as reduction in the number of comedones

- the preparation is applied for the minimum of 4 weeks (and the maximum of 6 weeks or until significant improvement of the condition of inflammatory lesions and reduction in the development of comedones, which needs to be marked)
- the evaluation of facial skin lesions is performed (at the inclusion into the group of patients and after 2, 4 and 8 weeks
- the patients are followed-up for 4 weeks following the termination of the application of Granex in order to verify the continuous improvement of the clinical picture of acne

Inclusion and exclusion criteria:

* Inclusion criteria:
- activation of the basic condition, insignificant manifestations of a bacterial infection (pustules,)
- absence of oral therapy with antibiotics, chemotherapeutics or retinoids one month prior to inclusion into the study

**Exclusion:**
- known hypersensitivity to any of the product’s ingredients
- pregnancy
- lactation
- other serious skin diseases

**Warning:**

The patients were at the same time using indifferent topical such as thermal water to wash their faces. The preparations forbidden to use included other anti-acne preparations, (salicyl-bor-resorcin alcohol, Acnemycin sol, paste, Acnefug EL, Dalacin sol, Eryfluid, Acneroxid, Acnecolor and others). During the course of the therapy with Granex, **neither physical treatment nor chemical peeling was applied.**

**Results**

All basic data are to be inspected in Tables 1-4 and Graphs 1-21 annexed thereto. Classification according to Cook’s acne severity grading scale: Grade 0-2. - 9 (8,18%) patients, Grade 3. - 19 (17,27%) patients, Grade 4. - 82 (74,55%) patients. The mean disease duration period counted 16 months (with the shortest period of 4 months and the longest of 9 years). The mean duration of the present episode counted 4.2 months .

**Assessment of facial manifestations:** the number of non-inflammatory lesions was counted at inclusion into the series of patients and after 2 weeks. In 75 (68,18%) patients there was a 75% reduction in that number. The number of inflammatory lesions was reduced by 2/3 after 8 days, and in 79 (72,48%) patients there was full clearing of all inflammatory manifestations towards the end of the monitoring period, 24 (22,02%) patient stage very improved.
Laboratory screening was performed at inclusion into the study 96 patients, whereby all monitored parameters were within the normal range. In 12 patients there was a slightly elevated ASLO level and hypercholesterolemia was detected in 2 patients. The laboratory screening performed at the end of the monitoring period in 100 patients revealed that all monitored parameters were within the normal range, there was elevated ASLO level in 8 patients and hypercholesterolemia in 2 patients.

Presence of focal infection - otorhinolaryngology: infection proven in 12 patients (9 women, 3 men). Microbiologic examination of the pustules demonstrated 9 cases of Staphylococcus epidermidis, 5 cases of Staphylococcus aureus, 1 case of Staphylococcus pyogenes, (Note: u 2 patients there was mixed flora), and 1 case of Corynebacterium.

The **tolerability of Granex®, Catalysis, S.L., Madrid, Spain** was excellent or very good in 109 patients. One patient discontinued the therapy.

**Adverse effects of Granex®, Catalysis, S.L., Madrid, Spain** (however, not representing a reason to discontinue the therapy) were observed in 22 patients and included slight erythema, scaling and development of open comedones at the beginning of therapy. In one female patient the application of Granex® caused an allergic reaction (verified via testing later on).

**The success of therapy with Granex®, Catalysis, S.L., Madrid, Spain** was assessed as very good in 100 (90.91%) patients and considered good in 9 (9.09%) patients by all the therapists. In one patient the therapy showed no effect and caused slight aggravation resulting in therapy discontinuation. In patients with significant sebum overproduction the effect was observed to be less outstanding.

**Patient satisfaction:** 95 (87.16%) patients were very satisfied with the therapy due to the rapid effect onset and the comfort of application, 14 (12.84%) patients considered the therapy satisfactory, or effect indifferent and one female patient discontinued the therapy. The therapy success is photodocumented. What the patients assessed most positively were the quality and the application properties of Granex® spray, which, according to their words is the only product on the market that neither dries out nor irritates the skin and makes it feel fine and smooth.
Discussion

Based on the clinical condition of the patients as well as the achieved therapeutic results, the efficacy and tolerability as well as the occurrence of adverse effects of the product Granex®, Catalysis, S.L., Madrid, Spain were assessed.

Clinical finding: The results obtained are remarkable mainly in Table 4. At inclusion examination there were 9 (8,18%) patients suffering from acne of grade 0 – 2 and grade 3.-4. was observed in 101 (91,82%) patients. The assessment performed the termination of application (Tab.No. 3,4) revealed that there were 103 (94,5%) patients with grade 0 – 2, and 6 (5,5%) patients with grade 3. Compared with the situation at the inclusion into the study, the assessed facial manifestations (according to Cook’s acne severity grading scale) there was healing or significant improvement in 79 (72,48%) patients and improvement in 24 (22,02%) patients. There was slight improvement in 6 (5,50%) patients. In one patient there was aggravation of the local finding due to allergy. As for the manifestations of the disease, six patients were suffering from acne of severity grade 5-6 and in order to achieve satisfactory results the employment of systemic therapy would be necessary. Systemic therapy was commenced in those patients upon their exclusion from the study due to its termination, and what needs to be stated is that improvement of the local finding was achieved. What was really interesting in this light was the fact that those patients required to be treated with Granex®, Catalysis, S.L., Madrid, Spain even after the termination of the study.

In 79 patients there was extensive clearance of inflammatory lesions (72,48%) and in 24 patients (22,02%) there was significant reduction in the manifestations with only small residues left. In order to achieve total clearance of inflammatory as well as non-inflammatory morphs, the application duration of Granex®, Catalysis, S.L., Madrid, Spain would have to be prolonged to at least 3 months.

In 6 patients with significant sebum overproduction the effect was less significant and as has already been mentioned above, systemic agents would have to be employed to achieve better results. On the average, there was reduction in the number of inflammatory lesions by more than 3/4.
Since the patients were undergoing topical therapy with Granex®, Catalysis, S.L., Madrid, Spain, only, we attribute the betterment of the disease to the application of this product. Control swabs taken from residual foci of papulopustules and pustules only showed Staphylococcus epidermidis in one case. In the rest of the patients there was no colonisation.

The therapy was well tolerated by the patients and the adverse effects were only of transient nature (slight erythema, burning sensation, skin scaling) and did not represent a reason for the therapy to be discontinued, which also was stated by the patients themselves. Only in one case a female patient discontinued the therapy and was excluded from the series.

One of the every positive characteristics of the preparation employed is the fact that there was significant improvement of the quality of skin visible nearly in all patients within a very short period of time. Within 10 days there was improvement in the relief of the skin (which is the proof of the fact that glycyrrhizinic acid and aloe vera exhibit a very soothing effect and eliminate skin irritation). In this light the preparation seems excellent for the use in patients with acne papulopustulosa according to Plewig – since there really is clearing of the manifestations of the disease.

Excellent effects were observed (in all trial centres) especially in patients with atopic constitution. It would be of benefit to take advantage of this observation in the future, especially as regards the possible use of the preparations containing glycyrrhizinic acid and aloe vera in main or topical supplementary therapy of eczema atopicum.

At all clinics and departments and in all patients there was rapid improvement and significant reduction in primary non-inflammatory efflorescence, especially the closed comedones. At the beginning of therapy the development of open comedones was slightly increased in some patients, however, followed by significant improvement of the condition and healing of the morphs.

After a month of therapy (4 weeks) there were some residual foci left on the faces of some patients, which did not change significantly after 8 weeks (Tab. No 3 with slight disease activation in 22 patients, 20,18%)
Ideally, in order to achieve total clearance of both inflammatory and non-inflammatory morphs all the participating therapists recommend the preparation be used for 3 months (which has been mentioned above).

The therapists also univocally claim that **Granex®, Catalysis, S.L., Madrid, Spain** represents a unique supplementary topical preparation that can be used in more serious acne conditions requiring the employment of systemic therapy with antibiotics or retinoids. This was also supported by the expert consultant doc. MUDr. Jarmila Rulcová, Ph.D.

**Granex®, Catalysis, S.L., Madrid, Spain** was optimally applied as follows: following the success obtained by employing the initial therapeutic dose (with the preparation applied 3 times a day) it was recommended to use the product 2 times a day, only (in the morning and in the evening). The difference in the duration of application within single clinics and departments is a result of the different amount of preparation used as well as the extent of the areas treated by the patients. Patients that were applying the preparation to less extensive areas were using smaller amounts of the preparation and were thus able to use it for a longer period of time.

Nearly all of the patients stated that the therapy was comfortable, not time consuming and brought about a very pleasing cosmetic effect. Many of them underwent unsuccessful long-term therapies with other preparations, based on which they considered the treatment with **Granex®, Catalysis, S.L., Madrid, Spain** very successful and required to be treated with the product in question even after therapy termination. The only thing they together with the therapists considered a disadvantage of the set was the disproportion between its two components. It should be recommended that the content of **Granex®** Spray be adjusted (to the 200ml content of **Granex®** lotion).

**Conclusion**

The study performed has proven the declared positive therapeutic efficacy and tolerability of the preparation **Granex®, Catalysis, S.L., Madrid, Spain** employed in topical therapy of mild up to moderate forms of acne vulgaris. The results in full extent prove the
results of the pilot study carried out in 2005 and in comparison with the results of the pilot study represent data more valid due to the number of patients included.

Taking into consideration the number of patients as well as the fact that 11 clinics participated in the study (clinics, departments of dermatology in cities, towns and villages), we presume that the efficacy of therapy of 93% may be considered extraordinarily satisfactory.

**Granex®, Catalysis, S.L., Madrid, Spain** represents a modern preparation taking advantage of the experience of traditional medicine. As for the therapy of acne vulgaris, it represents a new and effective alternative form of treatment for an extensive group of the persons affected by moderate acne forms (Cook’s grading scale 0-4). **It is possible to recommend the preparation** be employed as supplementary topical therapy in patients with severe acne papulopustulosa treated systemically with antibiotics or retinoids. The application form of lotion and spray is well tolerated, causes minimal irritation of transient nature in exceptional cases, but no adverse effects. The allergic reaction present in one female patient is considered an exception.

It is possible to apply the preparation concomitantly with other systemically administered agents and support the effect by employing mechanical or physical treatment possibilities.

**Excellent effects were observed especially in patients with atopic constitution. It would be of benefit to take advantage of this observation in the future, especially as regards the possible use of the preparations containing glycyrrhizinic acid and aloe vera in main or topical supplementary therapy of eczema atopicum.**

An experienced dermatologist can take advantage of this preparation to treat other unpleasant indications such as acne vulgaris, which often is a disease bringing about serious mental distress.
Bibliography:


