PEER REVIEW

in the matter of

Regumed GmbH

Client:

Regumed GmbH
Herr Rudolf Moyses
Hans-Cornelius-Straße 4
D-82166 Gräfelfing

Consultants:

Dr. Volker W. Rahlfs, C. Stat. (RSS)
Certificate 'Biometry in Medicine' (GMDS)

Dr. med. Andreas Rozehnal
Head Clinical Research

Translator:
Thomas van Sant, (M.Sc)

idv
Data Analysis & Study Planning
Dr. Volker W. Rahlfs
Wessobrunner Str. 6, D-82131 Gauting
Tel.: +49 (089) 8508001, Fax: +49 (089) 8503666

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1. Introduction

Eight publications were to be discussed in this peer review and were to be evaluated with regard to their scientific evidence. Also considered is a report of the Ukrainian Children's Scientific and Applied Centre of Clinical Toxicology (Ukrainisches Zentrum für Forschung und für angewandte klinische Toxikologie bei Kindern) concerning the clinical testing of BICOM in children with acute or chronic renal disease, as well as in children with leukemia.

2. Methodology

The degree of scientific evidence of the 8 Chinese publications was again considered following an 8 step scheme, which is also applied in the guidelines for cardiopulmonale reanimation [modified in accordance with: Dick, 2000; for further clarification also see our peer review of December 2005].

In the peer review at hand all newly presented studies are considered and discussed, even those which, in our opinion, do not have sufficiently evidence regarding the question of interest. Only by a complete description of all studies we can be sure that a possible distortion of the results is avoided. Such a distortion could arise if only studies with positive results were included, while at the same time those with negative results were excluded (see for example Bulpit [1988] on the comparable situation in meta-analyses: "in particular we must take care to avoid selection of papers that support one view").

Because of frequent misunderstandings, even among professionals, it must be clearly stated at this point that a study not showing sufficient evidence in a statistical sense does not permit *any* assertions with a satisfactory degree of certainty. Such a study is surely not evidence of efficacy, but, by the same token, it may not be interpreted as evidence for a lack of efficacy.

We follow the principle of evidence based medicine as described by Rosenberger und Donald [1995]: "Evidence-based medicine follows four steps: formulate a clear clinical question from a patient's problem; search the literature for relevant clinical articles; evaluate (critically appraise) the evidence for its validity and usefulness; implement useful findings in clinical practice." [Rosenberg W., Donald A. (1995)].

All of the 8 papers with which we are concerned are scientific publications that appeared in different Chinese medical journals for professionals between September 2004 and September 2005. That basically the investigations in these studies were scientifically serious can be deduced from the fact that otherwise they would not have been accepted for publication in established medical journals for professionals.

All papers are available in certified translations into German. Grammatical and verbal errors, as well as uncommon grammatical constructions and verbal usage in the translations, have been reproduced uncorrected in this peer review.

In particular the publications being investigated are:

1. Du X. et al., Klinische Beobachtung über 79 Behandlungsfälle gegen allergische Hautkrankheiten mittel Bioresonanzgerät

   (English translation: Du X. et al., Clinical observation of 79 treatment cases of allergic skin disorders by means of the bioresonance device)

   Chinese Journal of Practical Medicine 3 (2005), 259)

2. Feng Y. et al., Die neulich klinische Beobachtung der Heilwirkung mit Bioresonanztherapiegerät in 150 Fällen der Kinder-Allergiekrankheit

   (English translation: Feng Y. et al., New clinical observation of the healing effect of the bioresonance device in 150 cases of children with allergic disorders)

   Chinese Journal of Contemporary Pediatrics 3 (2005), 257-258)

3. Huang S. et al., Klinische Beobachtung der Behandlung vom allergischen Schnupfen und Bronchialasthman der Kinder mit dem Bioresonanztherapiegerät

   (English translation: Huang S. et al., Clinical observation of the treatment of allergic rhinitis and bronchial asthma of children with the bioresonance device)

   Zhejiang Medical Journal 6 (2005), 457-458)

4. Liu X. et al, Die Anwendung der Bioresonanz-Technik in allergischen Krankheiten – die Analyse von häufigen Allergien in der Stadt Xiamen

   (English translation: Liu X. et al, The application of the bioresonance-technique in allergic disorders – the analysis of frequent allergies in the city of Xiamen)

   China Journal of Leprosy and Skin Disease 9 (2005), 727-728)

5. Xu M. et al., Klinische Beobachtung der Behandlung vom chronischen Nesselausschlag mit dem Bioresonanztherapiegerät

   (English translation: Xu M. et al., Clinical observation of the treatment of chronic urticaria with the bioresonance device)

   China Journal of Leprosy and Skin Disease 7 (2005), 533-534)

6. Yang J., Zhang L., 300 Behandlungsbeispiele gegen Asthma mittels BICOM Gerätes für Kinderpatienten

   (English translation: Yang J., Zhang L., 300 examples of treatment of asthma with the BICOM device in child patients)

   Maternal and Child Health Care of China 9 (2004), 126-127)

7. Yang X., Liu Q., Untersuchung der Bioresonanztechnik in der Allergieprüfung der Atopikdermatitis

   (English translation: Yang X., Liu Q., Investigation of the bioresonance technique in the allergy testing of atopic dermatitis)

   Shanxi Medical Journal 10 (2004), 900)

8. Zhang X et al., Klinische Beobachtung über 54 Behandlungsfaelle gegen Nesselausschlag mittels BICOM Bioresonanztherapiegerät

   (English translation: Zhang X et al., Clinical observation of 54 treatment cases of urticaria with BICOM bioresonance therapy device)

   China Journal of Leprosy and Skin Disease 8 (2005), 651)

The sequence of evaluation is alphabetic, based on the names of the main (first) author.

The exact specifications of the literature for these publications can be found in Section 6 of this peer review. In accordance with the international usage, the medical journals for professionals in China are cited using their English language titles insofar as these are known to us. Otherwise the certified translations are used.

The report of the Ukrainian Children's Scientific and Applied Centre of Clinical Toxicology on the experience with BICOM treatment in children having acute and chronic renal disease, as well as in children with leukemia, has the character of a medical opinion rather that a publication and treats other indications as the Chinese publications. This is the reason for this report being presented in a separate chapter.

3. Describing and Evaluation the Study in Detail:

Du X. et al., Klinische Beobachtung über 79 Behandlungsfälle gegen allergische Hautkrankheiten mittel Bioresonanzgerät

(English translation: Du X. et al., Clinical observation of 79 treatment cases of allergic skin disorders by means of the bioresonance device)

Design: One group cohort study

Degree of Evidence: 5

Duration of the treatment and observation: Desensibilisation treatment with the bioresonance device, 1 to 2 times every week with a total of 7 to 8 sessions, duration of the follow-up observations: 1 year.

Indication: Allergic skin diseases, 79 Patients (27 patients with eczema, 20 patients with contact dermatitis, 30 patients urticaria, 2 patients with psoriasis)

Efficacy criteria: A 4-point scale is used:

1. Healing: The rash disappears completely and does not return for a year despite allergic contact.
2. Remarkably effective: The rash disappears completely, but there is a mild reaction to allergic contact after a year.
3. Effective: Number and expansion of the rashes decrease, itching is less intense.
4. Ineffective: Rash improves only slightly, returns during the treatment.

Results: Healing in 74.7 %, at least a remarkable effect in 89.9 % of the cases.

Evaluation of the results by the author(s): "The treatment was effective, especially with child patients having eczema". [The device] ... "can replace the traditional method of testing and treating allergies. Patients have a high tolerance for this treatment. Long term treatment effect must yet be observed".

Biometrical-medical evaluation within the scope of the peer review: The trial is a one group cohort study with an unambiguously defined efficacy criterion. A control group is in fact missing, but it is generally acknowledged that spontaneous healing occurs very seldom in this indication, so that the results clearly distinguish themselves in a positive way from the expectations in untreated courses. With 79 patients the study is sufficiently large. The subsequent observation period of one year is remarkably long and increases confidence in the study results. The efficacy of the BICOM therapy is demonstrated very convincingly within the framework of evidence-based medicine [compare our peer review from December 2005].

The design is similar to the common "observational study" (Anwendungsbeobachtung) according to German drug law (AWB). To be better able to assess the scientific evidence of the study of *Du X. et al.* it shall be compared with the German AWB:

The AWB will now be briefly explained (all citations [BAnzNr.229, 1998]). We cite from the definition "a AWB can be designed without a comparison group ..." and from the general requirements "a AWB is to be performed prospectively ... and orients itself in equipment and performance on a cohort study". Moreover the AWB serves, among other things, "to expand knowledge of efficacy", but "the demonstration of the efficacy with AWB alone ... except for some justified exceptions [is] not possible", "a carefully planned AWB, however, ... can enable the acceptance of indication statements if there is comprehensive, reproducibly documented, plausible experience with known medicines."

The standard of the AWB is, in fact, not required of the study by *Du X. et al.* (among other reasons, because the AWB refers to pharmaceuticals and not to medical devices), but it can be stated with confidence that the study of *Du X. et al.* would be recognized as AWB in the area of pharmaceuticals with all the above-mentioned consequences. Although there is no requirement to do so, applying the same standard to medical devices we come again to the conclusion that the study considered *alone* is at least a suitable tool for acquiring knowledge of the efficacy of BICOM and must be considered at least as a strong indication of efficacy.

The summary evaluation of several individual studies with strong indications of efficacy is to be found in Chapter 5.

Feng Y. et al., Die neulich klinische Beobachtung der Heilwirkung mit Bioresonanztherapiegerät in 150 Fällen der Kinder-Allergiekrankheit

(English translation: Feng Y. et al., New clinical observation of the healing effect of the bioresonance device in 150 cases of children with allergic disorders)

Design: One group cohort study

Degree of evidence: 5

Duration of treatment and observation: Desensibilisation treatment with bioresonance device once weekly with 5 to 8 sessions altogether. The treatment is terminated when all allergens are tested negative in a follow-up test. The duration of the observation is 5 sessions.

Indication: Allergic diseases, 150 patients (95 patients with asthma plus rhinitis, 20 patients with asthma alone, 25 patients allergic rhinitis, 5 patients with skin eczema, 5 patients with other allergies, all diagnosed with the diagnostic criterion of the Chinese work group for prevention and therapy of child asthma [1998].

Efficacy criterion: A 3-point scale is used:

1. Clear healing effect: Allergies at new exposure negative, allergy symptom disappears or heavy breathing and coughing clearly improve.
2. Improvement: Allergen at new exposure negative, Symptoms clearly relieved when compared to those before the desensibilisation treatment.
3. No healing effect: No improvement after 5 sessions.

Result: Efficacy rate ("clear improvement" or "improvement") in 94.6% of the cases. Furthermore for 21 asthma patients diagnoses with BICOM were compared with diagnoses through skin test and agreement was found in 78.2%of the cases.

Result evaluation by the author(s): "A short treatment time and a quick effect have opened a new path in clinical therapy for allergy diseases of children." "The long term healing effect is yet to be observed."

Biometrical-medical evaluation within the scope of the peer review: The trial design is a one group cohort study with an unambiguously defined efficacy criterion. The design is similar to the common observational studies in Germany (AWB) with conclusions as described above for the study of *Du X. et al.* Despite the missing comparator group, the efficacy is presented in a convincing way, as the successes are far more than those to be expected by chance. The credibility of the inclusion diagnoses is supported by reference to relevant criteria. With 150 patients included the study has a sufficiently large sample size. With reference to long term success, the study of *Feng Y. et al.* is less scientifically persuasive, the study of *Du X. et al.* is much more convincing.

The evaluation of the suitability of BICOM as a diagnostic device has weaknesses because the selection criteria for the 21 patients included in the comparison are not clarified.

Huang S. et al., Klinische Beobachtung der Behandlung vom allergischen Schnupfen und Bronchialasthma der Kinder mit dem Bioresonanztherapiegerät

(English translation: Huang S. et al., Clinical observation of the treatment of allergic rhinitis and bronchial asthma of children with the bioresonance device)

Design: Randomized controlled prospective parallel group study

Degree of evidence: 1-2

Indication: Allergic rhinitis (97 patients) and allergic bronchial asthma (84 patients), 181 patients altogether, of whom 9 discontinued the study because of a change of schools or moving to a new location. The diagnoses were determined in accordance with standardised criteria [Haikou, 1997][Med. Association China, 2003].

Duration of treatment and observation: The patients are divided into three groups. Group 1: BICOM treatment for children with a first-time diagnosis; Group 2: BICOM treatment for children for whom earlier medication therapy was not successful; Group 3 (control group): children with a first-time diagnosis, medication "hormone" (from the context it is clear that glucocorticoid is meant) plus antihistaminic.

BICOM treatment: Desensibilisation treatment with bioresonance device, once daily for acute cases with 5-6 sessions, once weekly for chronic cases with 4 to 5 sessions; duration of follow-up observations is 6 months. The way in which the therapy of the control group is administered is not reported in detail.

Efficacy criterion: A three point scale is used:

1. "Clearly effective": The symptoms of the allergy disappear completely and do not return for 6 months.
2. "Effective": Symptoms of the allergy disappear but return after the treatment is terminated. The complaints, however, are mild.
3. "Ineffective": Symptoms of the allergy do not clearly improve.

Result: Rate of success (clearly effective and effective are combined) for allergic rhinitis: Group 1 (BICOM, first-time treatment) 85.4%, Group 2 (BICOM, earlier medication was not successful) 81.9%, Group 3 (medical treatment) 76.7%.

The test result of the comparison group 1 plus group 2 versus group 3 of $P > 0.05$ is interpreted as "no clear difference".

Result evaluation by the author(s): "This therapy is especially suited to chronic patients." It is explained that serious side effects from the BICOM treatment, as appear with the medication, can be avoided. The authors refer to the fact that their results are almost identical to those of other researchers [Yang J., Zhang L., 2004]. We also discuss these results further along in this paper.

Biometrical-medical evaluation within the scope of the peer review: The trial design is a randomized controlled prospective parallel group study with unambiguously defined efficacy

criterion. The sample size of 181 patients distributed among three groups seems to be sufficiently large. The observation period of 6 months is satisfactory.

The control group implemented in the study (parallel group comparison) together with the random allocation of the patients (randomization) provides very good scientific evidence. A statistical evaluation using the chi-square test is available. This is an established procedure which is appropriate for the available data (categorical data). The authors point out that their results agree with the results of other research groups (so-called "external validation") and thus decrease even more the possibility of a result being cause by chance.

A blinding is missing, but this could only be achieved with a very large expense when comparing a device and a pharmaceutical so that in fact also many other researchers would also dispense with blinding. The statistical demonstration of the equivalence of BICOM therapy and the comparator therapy does not satisfy the more modern requirements ("demonstration of equivalence" by P-value > 0.05); the equivalence among the study patients is, however, convincingly demonstrated by the descriptive statistic.

Summarizing, we conclude that the study represents a high degree of evidence. Because of the aforementioned (rather unimportant) deficiencies we have downgraded the degree of evidence from 1 to 2. In practice this means that the scientific community would regard this study *alone* as already "borderline proof". With this expression it is meant that, within the scope of discretion, some reviewers would recognize the study *alone* as proof of efficacy (so-called confirmative demonstration), whereas others would dispute the scientific evidence of the study's evidence *alone* and demand additional information.

Remark: There is a small discrepancy in this publication between Table 1 and the text regarding the percentages in the control group. For this peer review we have used those percentages that strengthen the comparison group and thereby disadvantage the BICOM group. If the alternative were considered correct, the result would be even more favourable for BICOM.

Liu X. et al, Die Anwendung der Bioresonanz-Technik in allergischen Krankheiten – die Analyse von häufigen Allergien in der Stadt Xiamen, China Journal of Leprosy and Skin Disease 9 (2005), 727-728

(English translation: Liu X. et al, The application of the bioresonance-technique in allergic disorders – the analysis of frequent allergies in the city of Xiamen)

Design: One group cohort study

Degree of evidence: 8

Duration of treatment and observation: No treatment, the BICOM device is used for allergy testing.

Indication: Allergic diseases, 1079 patients (374 patients with urticaria, 363 patients with eczema, 85 patients with contact dermatitis, 79 patients with allergic rhinitis, 46 patients with asthma, 132 patients with other allergies).

Efficacy criterion: not applicable

Result: The frequencies of different diagnosed allergens are presented.

Result evaluation by the author(s): The accuracy of the test with BICOM ... among allergy patients is 80%.

Biometrical-medical evaluation within the scope of the peer review: The study is designed to use the BICOM device to test allergies and to investigate common allergies in the city of Xiamen. Conclusions concerning therapeutic efficacy are not planned and cannot be drawn (the result doesn't provide evidence either for or against efficacy).

Regarding the suitability of BICOM for testing allergies, the evaluation of results is unfounded. The method of comparison is not described. We do not know which methods were used in order to determine that the accuracy of the test with BICOM was 80%. Furthermore, there are no numerical results for the comparator method for allergy testing, so that the result cannot be verified.

The study is not suitable for making scientifically founded statements about BICOM.

Xu M. et al., Klinische Beobachtung der Behandlung vom chronischen Nesselausschlag mit dem Bioresonanztherapiegerät

(English translation: Xu M. et al., Clinical observation of the treatment of chronic urticaria with the bioresonance device)

Design: One group cohort study

Degree of evidence: 5

Duration of treatment and observation: Desensibilisation treatment with bioresonance device, twice weekly for a total of 5 weeks. Duration of follow-up after treatment is one month.

Indication: 56 patients with chronic urticaria, all age groups

Efficacy criterion: A 4-point scale is used:

1. Healing: Skin impairment and itching disappear completely without recurrence for a period of one month after treatment.
2. Remarkably effective: Skin impairment and itching disappear completely, but recur after the treatment has ended, but the complaints are milder.
3. Effective: Skin impairment and itching are reduced but return after the treatment has ended.
4. No effect: Skin impairment and itching do not improve.

Result: Efficacy rate (healing or remarkably effective): For 0 to 15 year old children, 90%; for 16 to 30 year old patients, 69.2% of the cases. Efficacy rate for patients of all age groups 60.7% of the cases.

Result evaluation by the author(s): "[the BICOM device] displays clear clinical efficacy without side effects." "We determine that the healing effect decreases with increasing age." In the opinion of the authors the precision and long term effects require more investigation. The authors also state that "reason" has to be investigated more into detail. Considering the above assertion of positive efficacy, the term "reason" is perhaps to be understood as "theoretical background". In fact the translator from Chinese is repeatedly unsure considering wording, see below as well.

Biometrical-medical evaluation within the scope of the peer review: The trial design is a one group cohort study with unambiguously defined efficacy criterion. The design is again similar to the common observational study in Germany (AWB) with conclusions as for the study of *Du X. et al.* considered above. Despite the fact that a comparator group is absent, the efficacy is demonstrated convincingly (at least for younger patients) as the successes are far in excess of those to be expected by chance. With 56 patients the study is sufficiently large. As stated by the authors themselves, the study shows the efficacy of this treatment, but the long term effect requires more investigation (for long term evaluation see study *Du X. et al.* above).

Remark: There is a translation error: The repeatedly used word "gunwale" or in German "Dollbord" comes from nautical science and is not present in medical terminology. It is clear from the context, however, that skin impairment is meant.

Yang X., Liu Q., Untersuchung der Bioresonanztechnik in der Allergieprüfung der Atopikdermatitis, Shanxi Medical Journal 10 (2004), 900

(English translation: Yang X., Liu Q., Investigation of the bioresonance technique in the allergy testing of atopic dermatitis)

Design: One group cohort study

Degree of evidence: 8

Duration of treatment and observation: No treatment, the BICOM device is used for testing allergies.

Indication: 168 patients with atopic dermatitis

Efficacy criterion: not applicable

Result: The frequencies of different diagnosed allergies are presented.

Result evaluation by the author(s): Omitted, no comparisons were performed

Biometrical-medical evaluation within the scope of the peer review: The study uses the BICOM device for testing allergies without discussing the suitability of the device for this application. The investigation should be interpreted as a pilot study. A further allergy testing study is planned to compare BICOM and the established method of blood IgE analysis, but details are not described in the report being considered.

Statements about therapeutic efficacy are not planned and cannot be taken from such a study. (No evidence either for or against efficacy.)

The study is not suitable for making scientifically founded assertions concerning BICOM, as it should rather be considered a preparatory work for a following, more comprehensive study.

Yang J., Zhang L., 300 Behandlungsbeispiele gegen Asthma mittels BICOM Gerätes für Kinderpatienten

(English translation: Yang J., Zhang L., 300 examples of treatment of asthma with the BICOM device in child patients)

Design: Controlled perspective parallel group study

Degree of evidence: 2-3

Indication: 300 patients (children with asthma according to "International Prevention of Asthma 2002"according to GINA[1]) with 213 patients in the BICOM group and 87 patients in a control group that is treated with a pharmaceutical.

Duration of treatment and observation: The patients were divided into two groups. Group 1: received BICOM treatment once every week, mostly 7 to 10 sessions. Group 2: received antiallergics and corticoids in accordance with the GINA concept of the "International Prevention of Asthma 2002". Observations were made for 7 months.

Efficacy criterion: A 4-point scale is used:

1. "Remarkably effective": Allergic symptoms disappear and do not recur within 6 months.
2. "Effective": Allergic symptoms are reduced, the number of recurrences is smaller, symptoms are mild.
3. "Improvement": Allergic symptoms are reduced, the number of recurrences is smaller, in-patient treatment is less frequent.
4. "Ineffective": Allergic symptoms occur after the treatment as they did previously, no effect is observed in comparison to the conditions prior to the treatment.

Result: The rate of success (the translation uses the expression "rate of healing" instead of "rate of success" which we have discarded because the meaning does not apply and is surely not intended by the authors) is computed from "remarkable efficacy", "efficacy", and "improvement". The rate of success is 84.5% for the BICOM treatment and 75.8% for the control group with pharmaceutical treatment according to the GINA concept.

Result evaluation by the author(s): "The therapeutic efficacy is very reliable and shows in particular efficacy in children who have asthma.", "[the device]...can also be used as an effective means of reducing medicine ... and sinking the costs". "No noticeable negative effects were observed by any of the patients". Furthermore, the authors indicate that their results correspond essentially to those of comparable studies. They believe that the prospects of success are greater when treatment starts in childhood or youth, but they are also of the opinion that adults can profit from the therapy (in this regard compare previously mentioned study of *Xu M. et al.*).

[1] Global Initiative for Asthma

Biometrical-medical evaluation within the scope of the peer review: The trial design is a controlled perspective parallel group study with an unambiguously defined efficacy criterion. The sample size of 300 patients with the previously described distribution is satisfactory as is also the 6-7 month observation period. The implementation of a control group (parallel group comparison) gives the study higher scientific evidence than one-group studies have. The authors show that their results agree with those of another research group (so-called "external validating") and thereby reduce the risk of a result being due to chance.

The authors proceed in accordance with the "GINA concept" in finding the diagnoses as well as in choosing the comparator therapy. GINA was founded in 1993 in cooperation with the American National Heart Lung and Blood Institute, the National Institute of Health, USA, and the World Health Organization (WHO) and is dedicated to asthma research. The use of such common international standards for diagnosis and therapy makes the study even more convincing.

The evaluation is, however, only descriptive. Statistical testing was not applied. A description of the methods used to assign patients to groups would have been desirable.

Blinding has again not been introduced, but, as mentioned above, the introduction of blinding in a comparison between a device and a pharmaceutical would involve very high costs so that in practice many other researchers would also dispense with blinding.

In summary, we judge the study to have an overall acceptable level of evidence. Because of the aforementioned deficiencies, in particular the missing description of the way in which patients were assigned to treatment groups and the missing test statistics, the degree of evidence is determined to be between 2 an 3. If these deficiencies were not present, the appropriate degree of evidence would have been 1. This study should not be used by itself as confirmatory proof of efficacy, but together with other studies – even those having a lower degree of evidence – it may be considered as convincing evidence of efficacy.

Zhang X et al., Klinische Beobachtung über 54 Behandlungsfaelle gegen Nesselausschlag mittels BICOM Bioresonanztherapiegerät

(English translation: Zhang X et al., Clinical observation of 54 treatment cases of urticaria with BICOM bioresonance therapy device)

Design: One group cohort study

Degree of evidence: 5

Duration of treatment and observation: Desensibilisation treatment with a bioresonance device, where acute cases receive treatment every 2 days with 3 sessions in total, and chronic cases receive treatment every 5 to 7 days with 5 to 6 sessions, after improvement there are 2 additional sessions. Duration of treatment was 3 months.

Indication: 54 patients with urticaria, all age groups

Efficacy criterion: An index of 5 criteria is used:

- Number of efflorescences (4 point scale)
- Size of efflorescences (4 point scale)
- Itching (4 point scale)
- Frequency of occurrences (4 point scale)
- Duration of the wheals (4 point scale)

The percentage change in the index is computed with the following ratings:

1. Healing: 100 %
2. Remarkbale efficacy: 60 % ≤ index value < 100 %
3. Effective: 20 % ≤ index value < 60 %
4. Ineffective: index < 20 %

The efficacy rate refers to the combination of the categories of healing and remarkable efficacy.

Result: Efficacy rate (healing or remarkable efficacy) 66.66 % of the cases.

Result evaluation by the author(s): The results were compared with the results of other researchers and the efficacy rate of the study under consideration was found to be rather low when compared to other investigations. The long-term effect requires more investigation.

Biometrical-medical evaluation within the scope of the peer review: The trial design is a one-group cohort study with a well-defined efficacy criterion (not all steps of the computations for the index are reproducible with the available information). Again the design is similar to the

common German observational study (AWB) with conclusions as those described above for the study of *Du X. et al.* Despite the fact that the comparator group is missing, there are clear indications for efficacy. With 54 patients the study is large enough. As the authors themselves remark, the duration of the study is not sufficiently long to permit a long-term evaluation.

Remark: There is an error in the translation: The word "Dollbord" refers to a nautical concept and is not contained in the medical vocabulary. It is clear from the context that "efflorescence" is meant. Within this peer review the word "Dollbord" is always replaced correspondingly.

4. Report of the Ukrainian Children's Scientific and Applied Centre of Clinical Toxicology on the experience with BICOM treatment in children having acute and chronic renal disease, as well as in children with leukaemia

Design of the studies being discussed: Each is a prospective controlled parallel group comparison.

Degree of evidence of the studies being discussed: Each has a degree of evidence of at least 3 (a higher degree is possible, but cannot be attested to from the available reports).

Indication:

Study 1: 82 children with serious renal disorders (77 children with acute renal insufficiency, 5 children with chronic renal insufficiency).

Study 2: 68 children with leukaemia (60 children with acute lymphoblastic leukaemia und 8 children with acute myeloblastic leukaemia).

Treatment:

Study 1, renal insufficiency: test group (46 patients) receiving routine treatment with pharmaceuticals plus BICOM, comparator group (36 patients) receiving routine treatment with pharmaceuticals only.

Study 2, Leukemia: test group (33 patients) receiving routine treatment with pharmaceuticals plus BICOM, comparator group (35 patients) receiving routine treatment with pharmaceuticals only.

Duration of treatment: The studies were performed between June 15, 1993 and August 7, 1993. There is no information concerning the observation time of individual patients.

Efficacy criteria:

- Follow-up controls of numerous laboratory variables
- Presence and extent of different clinical symptoms
- General condition

Results: Tables and individual values are added to the report, allowing judgements to be made at the level of individual cases. The results, however, have not been prepared statistically.

Result evaluation by the author(s):

Study 1, renal insufficiency: There was a decrease in urea and creatinine (i.e. improvement of the renal function) 7 to 8 days after beginning of treatment for children with BICOM treatment. An improvement occurred in children without BICOM treatment only after 10 to 12 days. High body temperature, blood pressure, urine flow, arrhythmia und immune status showed a clear advantage of the BICOM therapy when compared to the control group without BICOM therapy.

Study 2, leukaemia: Most children in the group with BICOM therapy experienced an increase in weight, appetite, and showed improved sleep together with an increase in physical activity, as well as a swift reduction of the "symptoms of poisoning" [Remark by the peer reviewers: probably the serious side effects of the chemotherapy are being referred to]. The analysis of the laboratory values shows a quick normalisation of the liver enzymes and of bilirubin in the BICOM group, as well as a larger immune modulating effect in the BICOM group. In summary, the researchers state that „ ...the treatment methods with the BICOM device can be used in the complex therapy of children with renal disorders and leukaemia. The method can also be used together with the usual treatments for children with mild or medium severe degrees of the disorder."

Biometrical-medical evaluation within the scope of the peer review: A summary of the results of 2 prospective controlled parallel group comparisons is submitted for consideration. For each study at least a degree of evidence 3 can be assigned. However, there are no detailed data for the individual studies available, so that the criterion of detailed verifiability of the individual statements by an expert is not satisfied.

In summary, an empirical report from doctors and research centres for clinical toxicology of children is at hand for consideration. The satisfactory scientific preparation is the result of a very precise medical representation of the diagnoses, an exact description of the number of patients in each treatment group, a satisfactory representation of each therapy scheme, as well as a description of the results, which is satisfactory at least as a summary.

The scientifically prepared study report of the research group describes the efficacy of BICOM for serious renal disorders and leukaemia using control groups and thus extends beyond the requirements of simple case reports.

5. Summarizing Evaluation

Eight studies were considered. All referred to allergic disorders. Two studies [Liu X. et al, 2005] [Yang X., Liu Q., 2004] were excluded from the consideration because they had methodological weaknesses or different objectives. From the description of these two studies in chapter 3 it can be concluded that their exclusion from this study does not lead to an unwarranted advantage for BICOM.

Thus there remain 6 studies to be evaluated. The study of Huang S. et al. [2005] was evaluated as 1 to 2 on an evidence scale [modified in accordance with Dick, 2000] from 1 (very good) to 8 (deficient). The study of Yang J., Zhang L [2004] received an evaluation of 2 to 3 on the same scale. The four remaining studies were given degree of evidence 5 being one-group cohort studies.

Within the framework of the usual scope of discretion a part of the scientific community would consider the study of Huang S. et al [2005] alone, in and of itself, as an acceptable demonstration of efficacy. More conservative researchers would consider the study to be indicative but not confirmatory and would require further positive results that confirm the study findings.

These additional positive results (in so-called "supportive studies") may have a lower degree of evidence. When discussing the study of *Du X. et al. [2005]* in chapter 3, we first referred to the similarity of these studies with degree of evidence 5 and the German AWB and cited that "insofar as the empirical knowledge is comprehensively and understandably documented and plausible ... a carefully planned AWB ... can justify the acceptance of statements based on indications." [BAnzNr. 229, 1998]. We pointed out that AWB regulations entail no legal obligations for medical devices. It seems to us, however, that in accordance with the quality norms enunciated there, it is appropriate for the present peer review to assign a degree of evidence 5 to the studies under consideration.

Therefore, in our opinion, a sufficient demonstration efficacy is achieved with the study of Huang S. et al [2005] together with the studies having degree of evidence 5, whereby the study of Yang J., Zhang L [2004] with degree of evidence 2 to 3 has not yet been considered and can only further support confidence in the efficacy of the BICOM treatment.

For a further clarification of the scientific value of even those studies assigned the relatively low degree of evidence 5 we would like to cite Letzel [2005]: "RCTs [Remark of the peer reviewers: randomized controlled study with degree of evidence of 1 to2] can only amount to a part of the overall evaluation because they do not include the application of a therapeutic procedure under everyday conditions ... For this reason the research in the field of everyday medical care (German term "Versorgungsforschung") has become so important." This concept can be interpreted in this connection as "AWB", or more generally also as "one-group cohort study".

It is also true that the scientific evidence of the 8 studies under consideration is not lower than found in most of the other university studies or studies by research groups outside universities (teaching hospitals, institutes, etc.) where controlled double-blind studies of high quality with degree of evidence 1 must remain the exception because of the limited resources at the disposal of the researchers. It is worldwide standard to publish results even with low degrees of evidence and to deduce the scientific evidence from reproducibility– as has been done in the studies now under consideration. In practice, this means that even studies with scientifically weak evidence may be seen as scientifically convincing if other researchers also come to the same conclusions – this so with studies also having scientifically weak evidence.

This generally recognized technique of external validation is already to be seen in the peer reviewed studies of Huang S. et al.[2005], Yang J., Zhang L.[2004], and Zhang X et al.[2005] where the aforementioned authors compare their results with the results of other authors - each in her/his own publication.

As already mentioned in the foregoing peer review of December 2005, it must be clearly stated that a degree of evidence of 1 is presently only required in pharmacological research. The documents under consideration adhere to the requirements for medical devices.

Summarizing we come to the conclusion that, according to the requirements currently applicable and appropriate for these studies, the efficacy of BICOM in allergic disorders has been sufficiently demonstrated by the studies under consideration.

Furthermore a report of Ukrainian Children's Scientific and Applied Centre of Clinical Toxicology on the experience with BICOM treatment in children having acute and chronic renal disease, as well as in children with leukaemia is appraised. The scientifically prepared study of this research group goes beyond the requirements of a simple case report with the use of control groups. This study also describes the efficacy of BICOM in cases of serious renal disorders and leukaemia.

6. Reviewed Studies

Du X. et al., Klinische Beobachtung über 79 Behandlungsfälle gegen allergische Hautkrankheiten mittel Bioresonanzgerät

(English translation: Du X. et al., Clinical observation of 79 treatment cases of allergic skin disorders by means of the bioresonance device)

Chinese Journal of Practical Medicine 3 (2005), 259

Feng Y. et al., Die neulich klinische Beobachtung der Heilwirkung mit Bioresonanztherapiegerät in 150 Fällen der Children-Allergiekrankheit

(English translation: Feng Y. et al., New clinical observation of the healing effect of the bioresonance device in 150 cases of children with allergic disorders)

Chinese Journal of Contemporary Pediatrics 3 (2005), 257-258)

Huang S. et al., Klinische Beobachtung der Behandlung vom allergischen Schnupfen und Bronchialasthman der Children mit dem Bioresonanztherapiegerät

(English translation: Huang S. et al., Clinical observation of the treatment of allergic rhinitis and bronchial asthma of children with the bioresonance device)

Zhejiang Medical Journal 6 (2005), 457-458)

Liu X. et al, Die Anwendung der Bioresonanz-Technik in allergischen Krankheiten – die Analyse von häufigen Allergien in der Stadt Xiamen

(English translation: Liu X. et al, The application of the bioresonance-technique in allergic disorders – the analysis of frequent allergies in the city of Xiamen)

China Journal of Leprosy and Skin Disease 9 (2005), 727-728)

Xu M. et al., Klinische Beobachtung der Behandlung vom chronischen Nesselausschlag mit dem Bioresonanztherapiegerät

(English translation: Xu M. et al., Clinical observation of the treatment of chronic urticaria with the bioresonance device)

China Journal of Leprosy and Skin Disease 7 (2005), 533-534)

Yang X., Liu Q., Untersuchung der Bioresonanztechnik in der Allergieprüfung der Atopikdermatitis

(English translation: Yang X., Liu Q., Investigation of the bioresonance technique in the allergy testing of atopic dermatitis)

Shanxi Medical Journal 10 (2004), 900)

Yang J., Zhang L., 300 Behandlungsbeispiele gegen Asthma mittels BICOM Gerätes für Kinderpatienten

(English translation: Yang J., Zhang L., 300 examples of treatment of asthma with the BICOM device in child patients)

Maternal and Child Health Care of China 9 (2004), 126-127)

Zhang X et al., Klinische Beobachtung über 54 Behandlungsfaelle gegen Nesselausschlag mittels BICOM Bioresonanztherapiegerät

(English translation: Zhang X et al., Clinical observation of 54 treatment cases of urticaria with BICOM bioresonance therapy device)

China Journal of Leprosy and Skin Disease 8 (2005), 651)

further:

Sheiman, B.S. et al., Bericht des Ukrainian Children's Scientific and Applied Centre of Clinical Toxicology über die klinische Prüfung von BICOM bei Children mit akutem oder chronischen Nierenerkrankungen und Leukämie. Unveröffentlicht. Eine Kopie des Berichts kann bei idv Datenanalyse und Versuchsplanung angefordert werden.

(English translation: Sheiman, B.S. et al., Ukrainian Children's Scientific and Applied Centre of Clinical Toxicology on the experience with BICOM treatment in children having acute and chronic renal disease, as well as in children with leukaemia. Unpublished. A copy of the report can be obtained when requested from idv Data Analysis and Study.)

7. Literature

Bulpitt, C.J.: Meta-Analysis, Lancet, July 9th (1988), 93-94

Chinesischen Arbeitsgruppe für Vorbeugung und Therapie des Kinderasthmas, Allgemeine Vorschriften für Vorbeugung und Therapie des Kinderasthmas

(English translation: Chinese working group for the prevention and therapy of asthma in children, general rules for the prevention and therapy of asthma in children)

Chinese Journal of Contemporary Pediatrics 12 (1998), 747-751)

Dick, W.F.: Evidence based emergency medicine, Circulation (2000), 102, 1-4

Empfehlungen zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen vom 12. November 1998, BAnzNr. 229, S. 16884 v. 4.12.98

(English translation: Recommendations for planning, performing, and evaluating observational studies, November 12, 1998, BAnzNr. 229, S. 16884 v. 4.12.98)

Gruppe Beatmung vom Kinderzweigverein des medizinischen Verein Chinas – Allgemeine Norm der Vorsorge und Heilung vom Bronchailasthman der Children (Probeausgabe).

(English translation: Group [concerned with] ventilation from the children's branch society of the medical society of China – General norm for prevention and healing of bronchial asthma in children [Test edition])

Journal of the Children's Department of China 42 (2), 2004, 100)

Letzel, H., Das deutsche „Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen" (IQWig) im Spiegel seines Auftrags und seiner Aktivitäten, Pharm. Ind. 67 (12) (2005),1399-1412

(English translation: Letzel, H., The German "Institute for quality and economy in health care" (IQWig) reflected in its assignments and its activities")

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Rahlfs, V.W.: Gutachten in Sachen Regumed GmbH, Dezember 2005

(English translation: Rahlfs, V.W.: Peer Review in the matter of Regumed GmbH, December 2005)

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(English translation: Society of the ear-nose-throat department of the medical society of China – norms for diagnosis and appraisal of the treatment effects of allergic rhinitis).

Journal of the National Ear-Nose-Throat Department 33 (3) (1998), 134)

Gauting, 20 January 2006,

Dr. med. Andreas Rozehnal
Reviewer
Head, Clinical Research
idv Data Analysis & Study Planning

Dr. Volker W. Rahlfs, C.Stat.(RSS)
Certificate 'Biometry in Medicine' (GMDS)
Senior Biometrician
idv Data Analysis & Study Planning