

## Therapy of Climacteric Complaints with *Cimicifuga racemosa*: Data on Effect and Efficacy from a Randomized Controlled Double-Blind Study

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### ► Introduction

Neurovegetative and psychical symptoms are reported by a great number of women during their 50s and 60s within the context of climacteric syndrome. Currently in Germany approx. 6 - 8 million women are affected by climacteric symptoms [11]. Approx. 70 % of these women describe their complaints as more than "mild" in their intensity; this means that an appropriate therapy is necessary.

As therapeutic options hormone replacement therapy (HRT) as well as of recently the therapy with Tibolon as chemical-synthetic alternatives are to be named. Without a doubt these are effective strategies, nevertheless one has to note that the motivation among patients to subject themselves to a long-term therapy with these pharmaceuticals is rather small [4, 17]. Reasons for this are found in the fear of weight gain, reoccurrence of menstrual bleedings, fear of increasing the risk of breast cancer and a general aversion to hormonal preparations [10, 18]. Therefore both patients and doctors include therapeutic alternatives such as herbal preparations into their therapy strategies.

The Black Cohosh, *Cimicifuga racemosa*, is of exceptional importance. For more than 40 years clinical experience reports, observational cohort studies, uncontrolled as well as controlled studies have been published that prove the efficacy for the therapy of neurovegetative and psychical complaints without a doubt [1]. Validated scales such as the Kupperman Menopause Index, the Hamilton Anxiety Scale and the Self Depression Scale (SDS) were employed as objective criteria.

These positive experiences have been expressed in the positive monograph on *Cimicifuga racemosa* from 1989 [2]. It recommends a daily dose of 40 mg herbal drug equivalent. The question of a dose dependency of efficacy and tolerability, i. e. a possibly increased effect under a higher dosage has not been examined up to now, however. This was the primary objective of the subject randomized controlled double-blind study.

With regard to the *mode of action* up to now an estrogen-like effect of the Black Cohosh had been assumed. The absence of estrogenic effects onto estrogen receptor-positive mamma carcinoma cell lines [15], however, appeared to be at odds with the assumed mode of action so that the subject study was supposed to obtain additional human

pharmacological data on the mode of action by means of investigating the influence on estrogen-sensitive parameters such as different hormones as well as vaginal cytology.

## ► **Methods**

### **Study objective**

The objective of the subject study was a comparison of the efficacy and tolerability of two dosages of an isopropanolic Black Cohosh extract in patients with vegetative climacteric symptoms. They were examined and treated over a period of up to 6 months. For obtaining data on the mode of action furthermore hormone assays were carried out and the vaginal cytology (eosinophilic index, karyopyknotic index and examination of the proliferation as per Schmitt) was monitored.

### **Patients**

Volunteering women from every stage of the climacteric (pre- and postmenopausal) were included after verbal and written information and after rendering their written consent. Their Kupperman index had to be at least 20, i. e. at least a moderate degree of complaints.

### **Exclusion criteria**

The exclusion criteria comprised more serious gynecological, internistic or psychiatric illnesses as well as circumstances, which could have interfered with the objective parameters

### **Medication**

An isopropanolic *Cimicifuga* rhizome extract (40 % V/V) in tablet form was used. The patients received either an amount of herbal drug of 127.3 mg per day ("CH") or 39.0 mg ("CN"). As inactive compounds the preparation contained cellactose, potato starch, magnesium stearate and peppermint oil. The medication of both study arms could neither be distinguished by patients nor investigators.

### **Study design and randomization**

The study corresponded to the national and international standards for clinical investigations, in particular to Good Clinical Practice (GCP) and to the declaration of Helsinki including quality assurance and quality control measures. The patients received one of the two investigational products via double-blind randomization allotment over an initial period of three months at first and where appropriate for a further three months (validated program RANCODE, idv). For this purpose the medication was pre-numbered, new patients received the next higher free number available in the respective study center. The examination dates are shown in table 1.

**Table 1.** Schematics of the Study Course

| Visits  | 1      | 2     | 3 | 4 | 5 | 6     | 7  | 8  | 9     |
|---|--------|-------|---|---|---|-------|----|----|-------|
| Week  | -1 (a) | 0 (b) | 2 | 4 | 8 | 12    | 16 | 20 | 24    |
| Clinical examination for selection                      | X      |       |   |   |   |       |    |    |       |
| General anamnesis,<br>anamnesis of the menstrual cycle  | X      |       |   |   |   |       |    |    |       |
| Information and written consent                         | X      |       |   |   | O |       |    |    |       |
| Logbook record with patient number                      | X      |       |   |   | O |       |    |    |       |
| Clinical investigation by means of<br>Kupperman and SDS | X      |       | X | X | X | X     | O  | O  | O     |
| Global evaluation of the efficacy<br>(CGI 3.1)          |        |       | X | X | X | X     | O  | O  | O     |
| Global evaluation of the tolerability (CGI<br>3.2)      |        |       | X | X | X | X     | O  | O  | O     |
| Physical examination / EKG                              | X      |       |   |   |   | X     |    |    | O     |
| Clinical chemistry/hematology                           | X      |       |   |   |   | X     |    |    | O     |
| Hormones  | X      |       |   | X |   | X     |    |    | O     |
| Colpocytology/vaginal cytology                          | X      |       |   | X |   | X     |    |    | O     |
| Recruitment   |        | X     |   |   |   | O     |    |    |       |
| Concomitant medication                                  | X      |       | X | X | X | X     | O  | O  | O     |
| Adverse events  |        |       | X | X | X | X     | O  | O  | O     |
| Handout of the investigational product                  |        | X     | X | X | X | O     | O  | O  | O     |
| Return of the investigational product                   |        |       | X | X | X | X     | O  | O  | O     |
| Final examination                                       |        |       |   |   |   | X (c) |    |    | O (d) |

a) Day - 4 to -1 prior to the study beginning (ingestion of the first medication)

b) immediately before the ingestion of the first medication and/or in the time prior to that

c) at the end or before (in case of early dropout from the study)

d) at the end or before (in case of early termination of the study)

## Objective Parameters

### ► Efficacy

The Kupperman menopause index, a generally recognized and validated scale for recording the severity of climacteric symptoms and/or a possible therapeutic effect, was used as a primary objective criterion. For this purpose 10 different climacteric symptoms were evaluated by the investigator during the interview with the patient on a 4-step scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). These were multiplied with a factor proportional to the weighting of the single symptom and finally the products were totalled. These symptoms are (weighting factor in brackets): Hot flushes (4), profuse sweating (2), sleeping problems (2), nervousness/irritability (2), depressive moods (1), vertigo (1), inability to concentrate (1), joint pains (1), headaches (1), palpitation (1).

A classification of the severity of these climacteric symptoms by means of the index is as follows: severe (> 35), moderate (20 - 35) and mild (15 - 19) complaints; a score below 15 is not considered as requiring therapy. As secondary objective criteria the Zung Self Depression Scale (SDS) as well as the Clinical Global Impression Scale (CGI) were applied. For recording the human pharmacological parameters vaginal cytological examinations

(karyopyknotic, eosinophilic-index and degree of proliferation as defined by Schmitt) were carried out and the hormones SHBG, LH, FSH, prolactin and 17- $\beta$ -estradiol were determined.

### ► Safety Criteria:

The tolerability was assessed globally (very good, good, moderate, poor) and the usual safety laboratory tests were carried out. Adverse events were registered and amongst others were assessed with regard to their intensity and their causal relationship with the investigational product. For this purpose the suggestions of Karch and Lasagna [9] were used as algorithm.

### Biometrics

The sample size estimate showed 140 patients as necessary for proving a standardized group difference of 0.5 ( $\alpha = 0.05$  one-sided,  $1 - \beta = 0.9$ ). Considering possible study dropouts a sample size of 150 patients was scheduled. As primary analysis a test for the superiority of

**Table 2:** Patient Distribution

| Main study:                            | Cimicifuga<br>High-dose | Cimicifuga<br>Low-dose | Total |
|--|-------------------------|------------------------|-------|
| scheduled                              | 75                      | 75                     | 150   |
| randomized                             | 76                      | 76                     | 152   |
| study dropouts                         | 10                      | 9                      | 19    |
| lack of efficacy                       | 5                       | 3                      | 8     |
| adverse events                         | 1                       | 2                      | 3     |
| non-compliance with the study protocol | 1                       | 1                      | 2     |
| administrative reasons                 | 1                       | 0                      | 1     |
| others                                 | 2                       | 3                      | 5     |

Note: 4 of 19 withdrawals occurred after the 12th week and thus are available for all data evaluations up to that week.

| Records | Cimicifuga<br>High-dose | Cimicifuga<br>Low-dose | Total |
|---------|-------------------------|------------------------|-------|
| Safety  | 75                      | 75                     | 150   |
| ITT     | 75                      | 74                     | 149   |
| PP      | 62                      | 61                     | 123   |

Note: 1 patient of the high-dose group was excluded from the ITT record, since she discontinued the study after 3 days of application (reason: lack of efficacy), 2 patients were excluded from the low-dose group because they did not return after the first doctor's consultation.

| Extension study:                | Cimicifuga<br>High-dose | Cimicifuga<br>Low-dose | Total |
|---------------------------------|-------------------------|------------------------|-------|
| not included into the extension | 7                       | 10                     | 17    |
| normal, no reason               | 6                       | 7                      | 13    |
| administrative reason           | 1                       | 1                      | 2     |
| lack of efficacy                | 0                       | 2                      | 2     |
| at the start of the study:      | 59                      | 57                     | 116   |
| study withdrawals               | 2                       | 3                      | 5     |
| lack of efficacy                | 1                       | 1                      | 2     |
| administrative reasons          | 0                       | 1                      | 1     |
| others                          | 1                       | 1                      | 2     |

ITT: Intention-to-treat; PP: Per Protocol; "normal, no reasons" describes patients that did not want to participate in the extension study without naming further reasons.

the higher dosage for the decrease in the Kupperman index at week 2, 4 and 8 on a multiple alpha-level of 0.05 according to the method of Wei and Lachin [21].  $H_0$ : Mann-Whitney parameter (MWP < 0.05);  $H_A$ : MWP > 0.5 was used. The subject primary analysis was based on the intention-to-treat-population with missing values being replaced as per the LOCF method. The results were repeated for the patients who had been treated per protocol. On the one hand the relevancy of detected differences was estimated by means of classic ratings (mean, median, responder rate difference) and by means of Mann-Whitney parameters (MWP). The latter indicates the probability that any random patient of one group does better than any random patient of the other group. Standard values for the interpretation of the MWP are 0.5 = no difference, 0.56 = small difference, 0.64 = medium difference, 0.71 = large difference [3]. For the further improvement of the interpretation additionally a responder analysis was carried out (Responder = Kupperman index < 15).

## ► Results

### Patient Characteristics

Table 2 shows the assignment of the patients to the different evaluation collectives. Table 3 contains important demographic and anamnestic data. It shows that the patients of both study arms were well comparable concerning these demographic data.

Table 3 : Demographic and Anamnestic Data

|                           |                                    | High-dose  | Low-dose   |
|---------------------------|------------------------------------|------------|------------|
| Age<br>[Years]            | Mean/SD                            | 50.2/4.45  | 49.7/4.39  |
|                           | Median                             | 49.0       | 48.0       |
|                           | min./max.                          | 42/60      | 42/60      |
| Weight<br>[kg]            | Mean/SD                            | 67.6/9.72  | 66.6/10.73 |
|                           | Median                             | 66.0       | 66.0       |
|                           | min./max.                          | 50/90      | 45/99      |
| Height<br>[cm]            | Mean/SD                            | 163.1/5.86 | 162.0/4.97 |
|                           | Median                             | 164.0      | 163.0      |
|                           | min./max.                          | 150/176    | 151/175    |
| Duration of<br>Complaints | up to 1 month                      | 0          | 1          |
|                           | > 1 to 6 months                    | 10         | 11         |
|                           | > 6 months to 2 years              | 34         | 34         |
|                           | > 2 years                          | 31         | 28         |
| Type of<br>Menopause      | premenopause                       | 35         | 28         |
|                           | early postmenopause<br>(< 2 years) | 18         | 18         |
|                           | late postmenopause<br>(≥ 2 years)  | 22         | 28         |
|                           |                                    |            |            |

## Kupperman Menopause Index

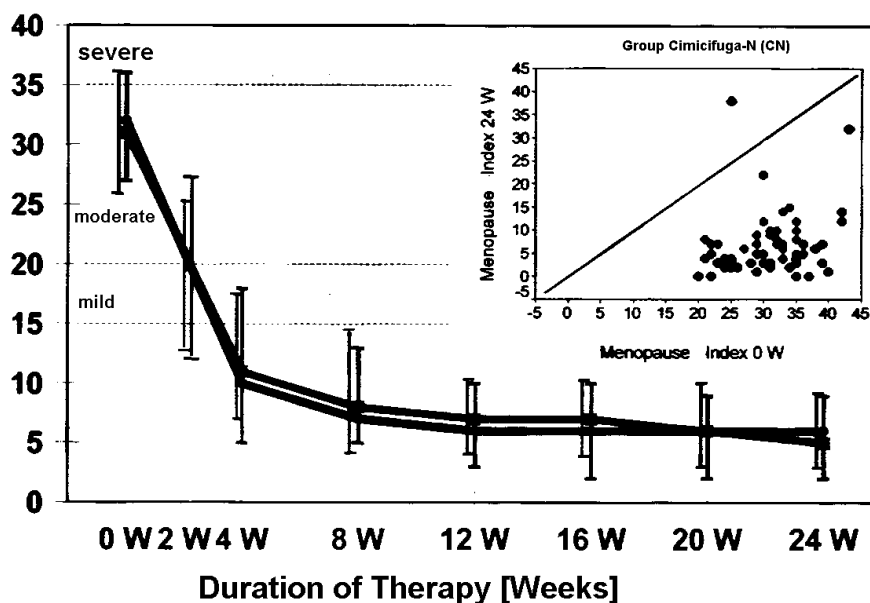


Fig. 1. The course of the Kupperman score with 40 mg herbal drug or 127 mg herbal drug as well as the response scheme for 40 mg/d. The medians and quartiles are depicted.

## Efficacy

### ► Kupperman Index

The baseline values for the Kupperman index were 31.0 (median) for the high-dose and/or 31.5 for the low-dose. After a 3-month treatment period the scores could be lowered to 7.0 and/or 8.0. This favourable result could be maintained during a further 3 months. After 2 weeks already a therapeutic effect was evident (fig. 1).

Patients with a Kupperman index below 15 were defined as responders. After 3 months 54 of 75 patients (high-dose) and 52 of 74 patients (low-dose) fulfilled the responder criterion [72 %; 95 % confidence interval: 59 % - 80 % resp. 70 %; 95 % confidence interval: 61 % - 82 %] (fig. 1).

Checking the Kupperman index values at time points 2, 4 and 8 for a superiority of the higher dose produced no statistically significant result ( $p = 0.7271$ ; combined test for 3 variables, one-sided). The Mann-Whitney parameter was 0.47. Thus an equivalence of the two dosages for the primary objective parameter could be verified.

Even if an additional subgroup analysis with regard to the menopause type produced a statistical superiority for the high-dose for *premenopausal* patients ( $p = 0.0322$ ), the results must be interpreted in the sense of a dose equivalence and thus a justification of the low-dose of 40 mg drug per day.

### ► Self Depression Scale

The analysis of the values, which were determined with the Zung Self Depression Scale, showed a similar result. Based on score values of 44.0 ("CH") and 44.5 ("CN") this median could be lowered to 36.0 and/or 37.0. Values of 41 to 47 are considered as a mild

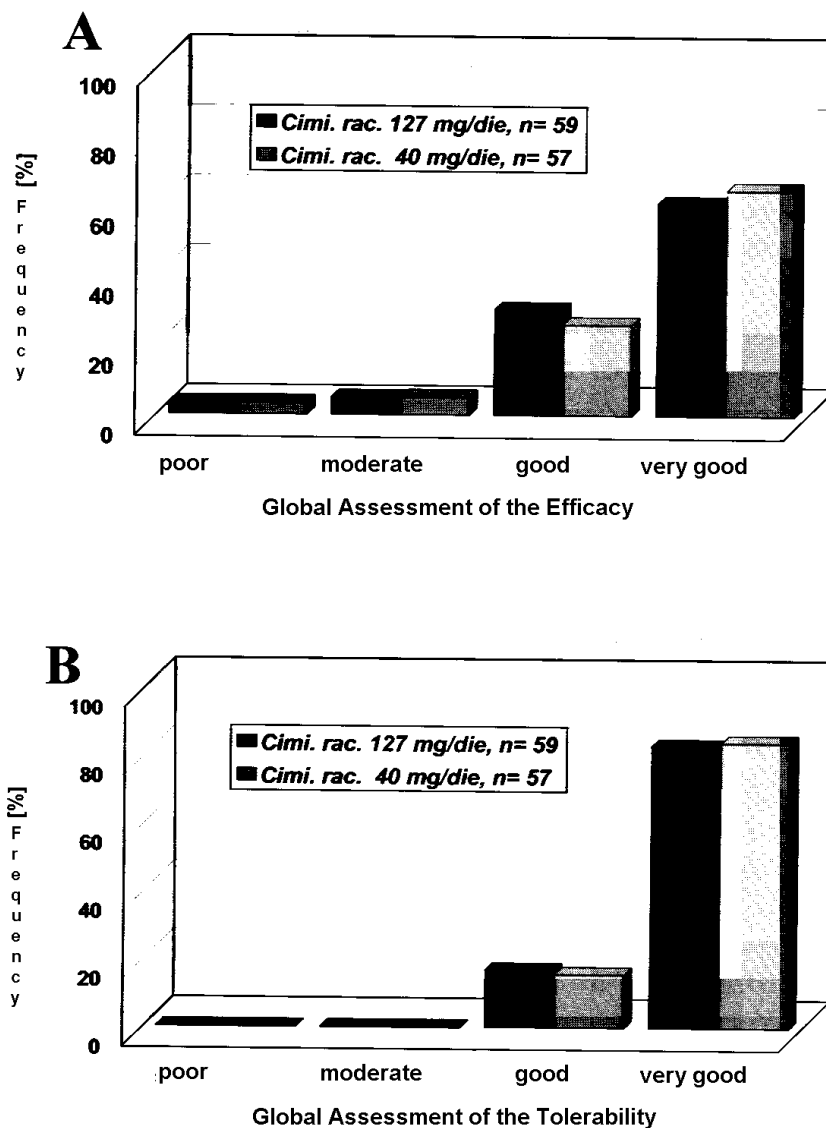


Fig 2. Global assessment of efficacy and tolerability by the investigator after 6 months.

depression, below 41 "normal". Here, too, there was no indication of a superiority of the high-dose ( $p = 0.19$ ; MWP = 0.54).

The classification of the global efficacy through the investigators after 3 months showed good to very good results in approx. 80 % in both groups.

### Effect (Human Pharmacological Data)

#### ► Vaginal cytology

#### ► Degree of proliferation as per Schmitt

Both for pre- and postmenopausal patients the 10-step Schmitt proliferation scale showed a baseline value of 4 (Median;  $n = 59$ ) (Mean  $\pm$  SD:  $4.5 \pm 1.99$ ) in the high-dose- and 4 (Median;  $n = 57$ ) (MV  $\pm$  SD:  $4.8 \pm 2.19$ ) in the low-dose group. After 6 months the values had increased slightly to 5 in both groups (MV<sub>H</sub>  $\pm$  SD:  $5.2 \pm 1.89$  and/or MV<sub>N</sub>  $\pm$

SD:  $5.6 \pm 1.88$ ), which was neither significant nor clinically relevant. A subdivision into pre- and postmenopausal patients showed similar results. (4 = degree 2; 5 degree = 2 - 3)

► Karyopyknotic index

The karyopyknotic index in the high-dose group (n = 59) had a median of 10.0 (Mean  $\pm$  SD:  $16.5 \pm 16.72$ ) at the beginning and 20.0 (MV  $\pm$  SD:  $22.0 \pm 18.49$ ) after 6 months. In the low-dose group (n = 57) the median was 10.0 (MV  $\pm$  SD:  $16.2 \pm 17.07$ ) at the beginning and 20.0 (MV  $\pm$  SD:  $23.7 \pm 18.43$ ) after 24 weeks. There was no significant increase in karyopyknotic index as an expression of an estrogenic effect.

► Eosinophilic-index

The eosinophilic-index was 15.0 (Median) at the beginning of the therapy (MV  $\pm$  SD:  $18.6 \pm 18.39$ ) in the high-dose group, and after 6 months 20.0 (MV  $\pm$  SD:  $22.6 \pm 18.82$ ) (n = 59). In the low-dose group these values were 14.0 (MV  $\pm$  SD:  $18.1 \pm 19.3$ ) and/or 20.0 (MV  $\pm$  SD:  $24.6 \pm 18.58$ ). Here, too, there was no significant increase.

The investigations of all three parameters for group differences showed that there were no significant differences between the dose groups.

► Hormonal parameters (Fig. 3)

► 17- $\beta$ -estradiol

In the subgroup of the postmenopausal patients (n = 37) no changes of the estradiol level were observed for 6 months either in the CH- or in the CN-group: Median 9.1 pg/ml (Mean  $\pm$  standard deviation:  $36.8 \pm 94.3$  pg/ml) to 16.2 pg/ml ( $70.3 \pm 143.6$  pg/ml)

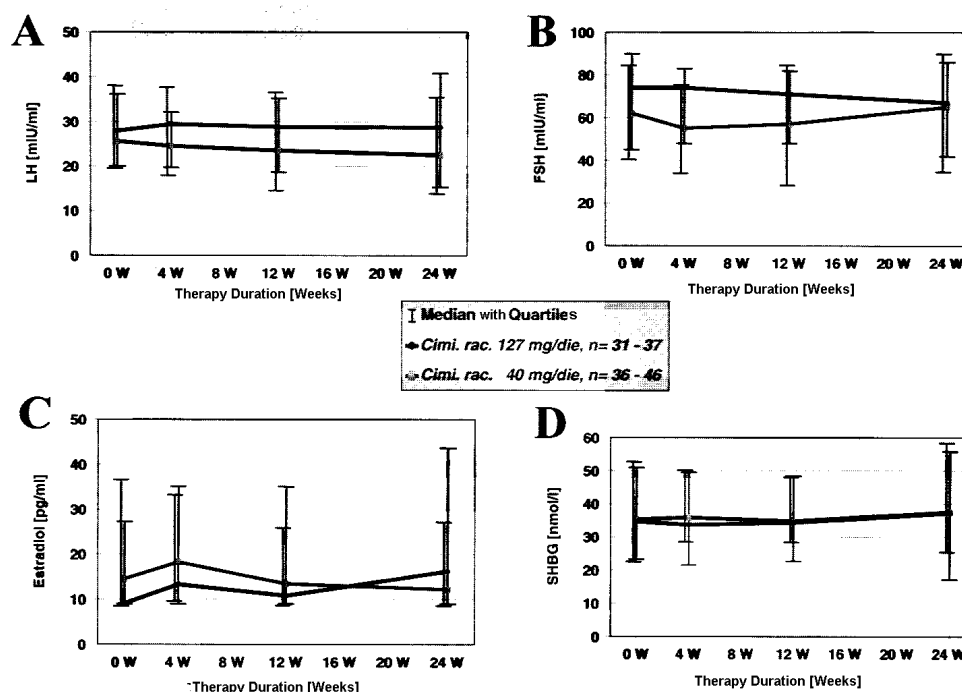


Fig. 3. Hormonal/serological parameters of the subgroup postmenopausal patients

for the high-dose and 14.5 pg/ml ( $30.0 \pm 43.4$  pg/ml) to 12.2 pg/ml ( $24.7 \pm 28.4$  pg/ml) in the low-dose group ( $n = 46$ ). There was no indication of a relevant influence of the Black Cohosh on the estradiol level.

► **Luteinizing Hormone**

In the postmenopausal patient group the following changes were found: Median: 27.9 mIU/ml (MV SD  $\pm$ :  $28.6 \pm 14.1$  mIU/ml) to 28.7 mIU/ml ( $27.8 \pm 15.7$  mIU/ml) [CH-group over 6 months] and/or. 25.6 mIU/ml ( $30.7 \pm 19.7$  mIU/ml) to 22.5 mIU/ml ( $26.3 \pm 17.5$  mIU/ml) in the low-dose group. Here, too, there was no indication of an LH-suppression.

► **Follicle Stimulating Hormone**

In the high-dose group there was a median value of 74.7 mIU/ml at the beginning (MV  $\pm$  SD:  $70.4 \pm 33.3$  mIU/ml), after 24 weeks 67.5 mIU/ml ( $62.5 \pm 34.0$  mIU/ml), in the low-dose group a median value of 62.1 mIU/ml ( $64.4 \pm 35.0$  mIU/ml) and/or 65.6 mIU/ml ( $65.6 \pm 37.8$  mIU/ml).

For prolactin, too, and the sex hormone binding globulin (SHGB) there were no significant changes between the groups and/or for the process of the therapy.

## **Drug safety**

In the global assessment the tolerability was evaluated as "good" or "very good" at all timepoints in 82 - 100 % (fig. 2). After half a year these values were 100 % in both groups. The statistical test for all 7 visits showed an MWP = 0.49 (95 % confidence interval: 0.44 - 0.54), which corresponds to an equivalence of the two therapy groups with regard to global assessment of the tolerability. Here, too, no dose dependence could be recorded.

No serious adverse events occurred during the entire observation phase.

In the first three months 19 adverse events, where a relationship with the investigational product could be suspected, occurred, (12 in the high and 7 in the low-dose group). The observed adverse events were mainly mild or moderate. There was no certain relationship in any case. 5 adverse events were subsumed in the organ class "gastrointestinal tract", 5 in the class "central nervous system", 5 in the organ class "breast and feminine genital organ system" and 4 under "other".

In one patient an endometrial biopsy had to be carried out because of a metrorrhagia. This showed the existence of an inactive endometrium. Most of the reported AEs represent symptoms which are generally known for occurring in climacteric women. In months 4 - 6 no AEs occurred, which were causally related with the medication.

## **Safety lab**

There were no conspicuous findings with regard to biochemical or hematological controls.

## ► Discussion

The basic efficacy of Black Cohosh extracts for the therapy of vegetative symptoms has been proven by extensive clinical data [6, 12, 13, 14, 19, 20] and found consideration in the positive monograph on *Cimicifuga racemosa*-rootstock of the former German federal health authorities (BGA) (1989). The dose recommended in the monograph is 40 mg drug (dried rhizome per day).

The question whether an increase in the amount of herbal drug can affect the efficacy or tolerability as opposed to the monograph recommendation was the objective of this study. Estrogen-sensitive parameters were determined to further evaluate the mode of action in order to obtain data regarding the "estrogen-like" mode of action previously presumed.

With regard to the efficacy and tolerability both dosage groups proved as equivalent. In both groups a high responder rate became evident after a relatively short therapy duration already. These therapeutic effects could still be increased in the further process of the therapy and retained over the entire observation period of 6 months. The unambiguous equivalence of both therapy groups in the end proves that the dose of 40 mg recommended by the monograph drug/day is sufficient in accordance with the therapeutic basic principle of "as little as possible, as much as necessary". Also with regard to the tolerability, measured by means of the global assessment, the number and kind of adverse events as well as the safety lab data, showed no difference of both dosages so that under this aspect, too, 40 mg can be considered as a suitable dose.

The human pharmacological data showed, that the hormonal parameters estradiol, prolactin, LH, FSH and SHBG do not change in the course of the therapy, either under the high or under the low dose. This opposes the theory of an estrogenic effect involving the entire system, in the same way as the observation, that there had been no estrogenic stimulation of vaginal cytologic parameters during this observation period lasting up to six months. Thus as opposed to former opinions an estrogen-like effect can be excluded.

Regarding the exact mode of action of Black Cohosh extracts there is no definitive clarity at the present time yet. Current discussions favour specifically an effect in the sense of a selective estrogen receptor modulation, which, in particular, is supported by estrogen antagonistic/absent agonistic effects onto estrogen receptor-positive breast cancer cells [7, 15] as well as at the uterus [5, 8]. For agonistic effects, for instance at the bone, first experimental data [8] have been obtained already. For the isopropanolic extract which was used in this clinical study first positive results [16] have been obtained, too.

*In conclusion* this study confirms the fundamental efficacy of *Cimicifuga racemosa* for the therapy of climacteric complaints and the dose of 40 mg/day recommended by the monograph is supported. Not only an effective, but also well tolerable dosage. The human pharmacological data match the context of the nonestrogenic mode of action.

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