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Clinical trial paper

# Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: A randomized, double blind, parallel-controlled study versus tibolone

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**Abstract**

*Objective:* To investigate the efficacy-safety balance of the isopropanolic extract of *Actaea* (=*Cimicifuga*) *racemosa* (iCR, Remifemin®) in comparison with tibolone in Chinese women with climacteric complaints.
*Method:* The randomized, double-blind, controlled 3-month study in 5 centers of 3 cities in China enrolled 244 menopausal patients aged 40–60 years and with a Kupperman Menopause Index (KMI) ≥ 15. The participants were assigned to either iCR corresponding to 40 mg crude drug/day ($N = 122$) or tibolone 2.5 mg/day ($N = 122$) orally. The primary endpoint was the combination of the Mann–Whitney values (MWV) of the KMI and the frequency of adverse events (benefit-risk balance) at end of treatment (MWV > 0.5 shows superiority; MWV > 0.36 shows non-inferiority).
*Results:* KMI decreased from $24.7 \pm 6.1$ to $11.2 \pm 6.2$ and $7.7 \pm 5.8$ (iCR) and to $11.2 \pm 7.2$ and $7.5 \pm 6.8$ (tibolone) at 4 and 12 weeks. This remarkable and clinically relevant improvement was similar in both treatment groups (MWV = 0.47; 95% CI = 0.39–0.54; $p_{\text{non-inferiority}} = 0.002$) showing statistical significant non-inferiority of iCR to tibolone. The KMI-responder rate

*Abbreviations:* CR, *Cimicifuga racemosa*; iCR, isopropanolic extract of *Cimicifuga racemosa*; $TTSE_2$, transdermal therapeutic system for estradiol; QD, once per day; KMI, Kupperman Menopause Index; AE, adverse event; MWV, Mann–Whitney value

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was similar in both groups (84% and 85%). The safety evaluation showed for both groups a good safety and tolerability profile, however, there is a significant lower incidence of adverse events ($p < 0.0001$) in favor of the herbal treatment. None of the postmenopausal iCR patients experienced vaginal bleeding in contrast to tibolone (17 cases). Breast and abdominal pain as well as leukorrhea was mostly observed in the tibolone group ($p = 0.015$, $p = 0.008$, $p = 0.002$). No serious adverse event was observed in the iCR-group, however, two occurred in the tibolone-group. The benefit-risk balance for iCR was significantly ($p = 0.01$) superior to tibolone (MWV = 0.56; 95% confidence interval [0.51–0.62]).

*Conclusion:* The efficacy of iCR (medicinal product Remifemin®) is as good as tibolone for the treatment of climacteric complaints, even for moderate to severe symptoms, whereby iCR is clearly superior regarding the safety profile. This iCR containing medicinal product is an excellent option for treatment of climacteric complaints which has now for the first time been verified in Asian women.



*Keywords:* Black cohosh; Tibolone; Menopausal symptom

## 1. Introduction

Not only in Western world but also in the Asian region, menopause is regarded as a major event in women's life [1,2]. Many Asian women are symptomatic but there are huge differences between individuals and across cultures [1]. In regard to menopause symptom treatment many Chinese climacteric women prefer alternative approaches to hormone therapy (HT). The medicinal plant *Cimicifuga racemosa* (vernacular name black cohosh) was widely used traditionally and nowadays continues to be utilized as evidence-based herbal medicine for a variety of conditions including menopausal vasomotor symptoms, anxiety, depression [3]. This rational assessment of benefits and risks based on randomized, controlled trials was performed with a standardized isopropanolic extract of the rootstock of *Actaea* (=*Cimicifuga*) *racemosa* (iCR) demonstrating to be efficacious in alleviating climacteric symptoms such as hot flushes, associated sleep disturbances, depressive mood swings, nervousness, sexual dysfunction, etc. [4–7]. Comprehensive reviews on the safety of *C. racemosa* support the good safety profile of extracts from this herbal drug, few and mild side effects and good tolerability [8,9]. In particular, the isopropanolic CR-extract iCR has been widely studied and shown not to induce cytotoxic, mutagenic, carcinogenic or teratogenic effects even at doses much higher than the therapeutic dose [8]. The objective of this randomized, double-blind, parallel-controlled study has been to investigate the efficacy-safety balance of Remifemin® in comparison with tibolone in Chinese peri- and postmenopausal women with climacteric complaints. It was shown frequently that tibolone reduces effective menopausal symptoms [10,11]. This clinical study has been a pivotal trial for approaching the Chinese market under the regulations of the SFDA (Chinese Food and Drug Administration).

## 2. Materials and methods

The trial was conducted as randomized, double-blind, tibolone-controlled, parallel designed clinical study in five centers of three cities in China. With permission of the local ethics committee, women between 40 years and 60 years in age with menopausal complaints for at least 4 weeks were included after written informed consent if they met the following criteria:

Inclusion criteria: (1) spontaneous amenorrheic interval ≥5 months since the last regular menstruation, (2) baseline level of $E_2 \leq 30$ pg/ml if amenorrheic interval <12 months, (3) Kupperman Menopause Index (KMI) ≥15.

Exclusion criteria: (1) hormone therapy (HT) in or after the last 4 weeks before study entry, any drug, nutritional supplement or food and Traditional Chinese Medicine against climacteric complaints, (2) psychoactive drugs, (3) body mass index > 28 kg/m$^2$, (4) endometrial thickness ≥5 mm if amenorrhea ≥12 months or ≥15 mm if amenorrhea <12 months, (5) irregular gynecological bleeding in the last 4 weeks before start of study medication, cervical smear examination (ASCUS) with any intraepithelial pathologic change, hysterectomy, amenorrhoea >8 years, (6) con-

traindication of tibolone, (7) cancer, (8) severe or current disease which could interfere with the climacteric complaints or the actual or expected treatment of which could interfere with the study objectives, (9) drug abuse, alcohol addiction, etc. Further, participation in another clinical trial of phases I, II during the last 180 days or of phases III, IV during the last 90 days before initiation of trial, or simultaneous participation in another clinical trial.

At the first visit, women underwent a general and gynecological anamnesis, physical examination, an ultrasound evaluation endometrial thickness and breast, cervical smear and a clinical interview for menopausal symptoms. The same day patients provided blood samples for the determination of FSH, E2, standard hematology and biochemistry. Urine samples served for urinalysis.

All eligible subjects were randomly allocated to the two treatment groups at a ratio of 1:1. In this clinical trial an isopropanolic extract of *C. racemosa* rootstock (Remifemin®) and tibolone (Zi Zhu Awei®) were used in tablets for oral administration.

Concerning the active ingredients in each tablet, 0.018–0.026 ml liquid extract of *Cimicifuga* rootstock (0.78–1.14:1) is corresponding to on average 2.5 mg dry extract and to 20 mg herbal drug (extraction agent isopropanol 40% (v/v); bulk-batch number 422450; manufactured by Schaper & Bruemmer, Germany), and Zi Zhu Awei® contains 2.5 mg tibolone (produced by Zizhu Pharm, Beijing, China, bulk-batch number 20040416). A double dummy design was used: the Remifemin®-group patients applied two Remifemin® tablets (1-0-1) and one tibolone-matching placebo per day, and the tibolone-group applied two Remifemin®-matching placebos and one tibolone tablet per day.

The contract research organization Excel Pharma Studies, China, was responsible for organizing the study, monitoring, quality assurance, data management, statistical analysis and study report according to ICH-regulations. They kept the data base in a blind fashion. Unblinding was activated after all queries had been resolved and after irreversible archiving of the clean data file. This study was registered at http://www.clinicaltrials.gov/ and approved by the Chinese regulatory authority SFDA.

Twelve weeks of treatment with trial medication were planned for each patient. Scheduled study visits were: visit 1 at study entry, visit 2 after 4 weeks, visit 3 after 12 weeks of treatment. On each follow-up visit clinical variables as Kupperman Menopause Index (KMI), vital signs, body weight, concomitant diseases, and adverse events, respectively, and concomitant medication were documented in the CRF. Blood sampling for standard hematology (leucocytes, erythrocytes, haematocrit, haemoglobin, thrombocytes) and biochemistry (AST, ALT, gamma-GT, AP, total protein, albumin, C-reactive protein, creatinine, uric acid, total bilirubin, glucose, prothrombin time), and an ultrasound evaluation of endometrial thickness were conducted after 12 weeks (at the end of treatment).

The primary endpoint was the benefit-risk balance. This was estimated by the combination of the Mann–Whitney values (MWV) of the efficacy dimension (KMI at the end of treatment as covariance analytically adjusted to baseline), and the safety dimension (the number of adverse events per patient) according to Wei and Lachin [12]. As first step, the MWV of the primary endpoint was tested for non-inferiority of iCR (MWV > 0.36) at one-sided test level of 0.025. Subsequently, as to the principle of ordered hypotheses, the MWV of the primary endpoint was tested for superiority of iCR (MWV > 0.5) at two-sided test level of 0.05.

Secondary endpoints were: total score of Kupperman Menopause Index (KMI) and each individual item, KMI-responder rate, Clinical Global Impression Item 1 (CGI 1, the severity of climacteric syndrome) at each visit, Clinical Global Impression Item 2 (CGI 2, global improvement of climacteric complaints) at visit 2 and 3, Clinical Global Impression Item 3 (CGI3.1, therapeutic effect) at visit 3, subject's global assessment of efficacy at week 12.

SAS Version 6.12 was used for all analyses. Data were summarized with descriptive statistics, frequency tables, and data listings. Nominal categorical variables were analyzed using Wei–Lachin–Mann–Whitney *U*-test, Fisher's exact test, Pearson's Chi-square test, or Cochran–Mantel–Haenszel (CMH) methods where appropriate. The site effect was incorporated, where applicable. Continuous variables were analyzed using the Wei–Lachin–Mann–Whitney *U*-test with or without preceding adjustment for covariates. Within-group changes from baseline at each follow-up visit were analyzed using the Wilcoxon signed-rank test.

Table 1
Demographic and other baseline characteristics in the full analysis set FAS and the per protocol set PPS (mean ± S.D.)

| | FAS ($N=238$) | | | PPS ($N=213$) | | |
|---|---|---|---|---|---|---|
| | Remifemin® ($N=118$) | Tibolone ($N=120$) | $p$ | Remifemin® ($N=107$) | Tibolone ($N=106$) | $p$ |
| Age (years) | 51.8 ± 3.7 | 51.5 ± 3.5 | 0.398 | 51.6 ± 3.6 | 51.6 ± 3.5 | 0.982 |
| Body height (cm) | 160.2 ± 4.9 | 161.1 ± 4.5 | 0.123 | 160.1 ± 4.7 | 161.3 ± 4.5 | 0.076 |
| Body weight (kg) | 59.5 ± 6.9 | 61.1 ± 7.6 | 0.079 | 59.2 ± 6.6 | 61.6 ± 7.5 | 0.02* |
| BMI (kg/m$^2$) | 23.2 ± 2.3 | 23.5 ± 2.4 | 0.208 | 23.1 ± 2.2 | 23.6 ± 2.4 | 0.072 |
| Amenorrhea duration (month) | 32.2 ± 24.6 | 35.4 ± 25.3 | 0.301 | 31.6 ± 24.5 | 36.1 ± 25.1 | 0.143 |
| Number of hot flush episodes per week at screening | 30.0 ± 26.1 | 30.1 ± 20.1 | 0.182 | 29.9 ± 26.3 | 29.8 ± 19.7 | 0.221 |
| Duration of climacteric complaints history (month) | 44.3 ± 32.8 | 47.2 ± 34.2 | 0.536 | 43.9 ± 32.8 | 47.5 ± 33.6 | 0.403 |
| Former HRT use | 44 (37.3%) | 48 (40.0%) | 0.580 | 42 (39.3%) | 42 (39.6%) | 0.761 |
| Baseline E2 (pmol/L) | 60.8 ± 36.3 | 69.9 ± 74.2 | 0.732 | 59.6 ± 37.3 | 67.5 ± 74.9 | 0.712 |
| Baseline FSH(IU/L) | 76.8 ± 28.5 | 78.2 ± 30.5 | 0.554 | 76.9 ± 29.3 | 78.9 ± 28.8 | 0.48 |

## 3. Results

### 3.1. Subjects

The trial was conducted in five investigation centers between September 2004 and May 2005: Department of Gynaecology of The First Hospital of Peking University ($N=60$), the General Hospital of PLA ($N=48$), the Third Hospital of Peking University ($N=44$), West China Second Hospital of Sichuan University ($N=32$), Jiangsu Province People's Hospital ($N=60$).

Out of 316 screened subjects 244 were enrolled and randomized, 122 per treatment group. Two hundred and eighteen subjects (89.3%) completed this trial. Twenty six (10.7%) prematurely withdrew from the trial, 12 in the iCR group and 14 in the tibolone group. iCR: five because of adverse events, two because of major protocol violation, four due to the request of the subject, and one case was lost to be followed up. Tibolone: nine cases dropped out for adverse events, two due to major protocol violation, two were lost to be followed up, and one case dropped out due to the request of the subject.

Two hundred and forty three of randomized subjects were included in the safety population set and one subject was excluded who did not take any dosage. Six subjects were excluded from the full analysis set (FAS, $N=238$) for discontinuing the trial for any reasons except for lack of efficacy before visit 2. Thereof, 213 subjects came into the per protocol set (PPS) with 107 cases in the iCR group and 106 cases in the tibolone group.

Table 1 reports the baseline characteristics of the two groups in FAS and PPS. Almost all baseline demographic data were comparable between the two treatment groups. The only statistically significant imbalance was the baseline body weight in the PPS, while in the FAS and safety population there was no statistically significant difference ($p>0.05$). All enrolled subjects were Asian.

### 3.2. Compliance and concomitant treatment

In FAS and PPS, the treatment compliance of subjects was very good in this trial. It was comparable in both groups ($p \geq 0.5$). The compliance was evaluated for the first treatment period (day 0 to week 4) separately from the more important second period (week 5 to week 12). The proportion of patients with compliance ≥80% was 95.7% and 96.4% in the Remifemin® group and 94.2% and 95.5% in the tibolone group from baseline to week 4 and from week 5 to week 12 ($p=0.64$ and 1.00) not revealing any statistical significant difference.

The concomitant treatment during the treatment was generally the same as compared between the two groups ($p \geq 0.86$). The reasons for these concomitant treatments were concomitant diseases.

### 3.3. Primary endpoint (benefit-risk-balance)

An efficacy-safety-composite variable defined from the frequency of adverse events and the total score of

Table 2
Primary endpoint: benefit-risk-balance: Mann–Whitney value (MWV) combination of KMI and the frequency of adverse events including the 95% CI adjusted with baseline

| | Mann–Whitney statistic | | | | |
|---|---|---|---|---|---|
| | Mann–Whitney value | | | *p*-Value | |
| | $p(X<Y)+0.5p(X=Y)$ | Lower limit of 95% CI | Upper limit of 95% CI | Superiority test | Non-inferiority test |
| FAS | | | | | |
| Composite of KMI and AE | 0.5623 | 0.5069 | 0.6177 | 0.0137 | <0.00005 |
| Baseline adjusted KMI | 0.4666 | 0.3936 | 0.5396 | 0.8152 | 0.0021 |
| Rate of AE | 0.6580 | 0.5886 | 0.7273 | <0.00005 | <0.00005 |
| PPS | | | | | |
| Composite of KMI and AE | 0.5708 | 0.5123 | 0.6293 | 0.0088 | <0.00005 |
| Baseline adjusted KMI | 0.4771 | 0.3999 | 0.5542 | 0.7199 | 0.0015 |
| Rate of AE | 0.6646 | 0.5920 | 0.7371 | <0.00005 | <0.00005 |

The MWV gives the probability that a randomly selected patient given Remifemin® responds better than a randomly selected patient given tibolone. MWV = 0.36 denotes the threshold of non-inferiority. KMI: Kupperman Menopause Index; AE: adverse events.

the Kupperman Menopause Index was used as the primary target parameter for risk-benefit evaluation after 3-month treatment compared to baseline.

In the PPS, the Mann–Whitney value for this combined efficacy-safety endpoint after treatment is 0.5708 (95% CI: 0.5123, 0.6293) with $p_{\text{superiority}} = 0.009$. Hence, the efficacy-safety-balance of iCR is non-inferior and even superior to tibolone. There is a significant trend (57.08%) that a randomly selected patient given Remifemin® responds better than a randomly selected patient given tibolone in terms of efficacy-risk balance. The results of the FAS are in accordance (Table 2).

### 3.4. Secondary efficacy endpoints

The total score of KMI declined from $24.7 \pm 6.1$ at baseline to $11.2 \pm 6.2$ and $7.7 \pm 5.8$ after iCR-treatment for 4 and 12 weeks and to $11.2 \pm 7.2$ and $7.5 \pm 6.8$ after tibolone-treatment. Hence, the total score of KMI had declined remarkably in each group (Fig. 1) without any relevant differences between the two groups at each time-point (significant non-inferiority, Table 2). The same result counts for the single items of KMI (hot flush, profuse sweating, insomnia, nervousness, depressive mood, vertigo, weakness and fatigue, joint pain, headache and palpitation), except for significant differences in the insomnia item score between the two groups at baseline ($p = 0.006$). This was accounted for by adjusting the results to baseline.

Regarding the distribution of KMI-response there was no statistical difference between the two treatment groups ($p > 0.05$) and similar for both the FAS and PPS population. In the FAS population, 39%, 42.4%, 13.6% and 5.1% of the subjects in the iCR group and 47.5%, 35%, 13.3%, and 4.2% of the subjects in the tibolone group can be classified as very much improved, much improved, improved, and no change. In the PPS population, the figures were 41.1%, 43.1%, 12.1% and 3.7% for the Remifemin® group, and 49.1%, 37.7%, 12.3% and 0.9% in the tibolone group.

The Clinical Global Impression of the severity (CGI 1) of psychovegetative complaints at baseline, week 4

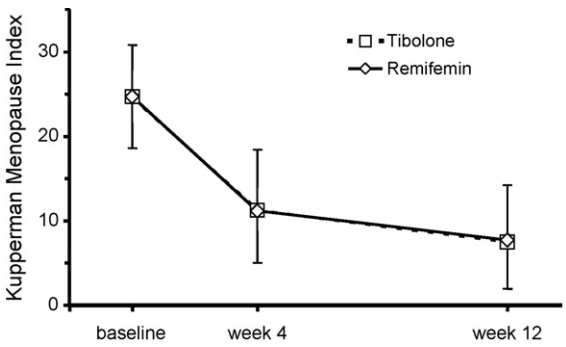


Fig. 1. Time course of the Kupperman Index in the full analysis set, baseline-adjusted data. Mean ± S.D. are shown.

and the end of treatment at week 12 revealed remarkable score reductions in each group. There are no significant differences between the two groups at each timepoint, and non-inferiority of the herbal treatment was significant. The clinical global impression of the therapeutic effect (CGI 3.1) and the patients' global assessment of efficacy at week 12 did not significantly differ between the two groups, and non-inferiority of Remifemin® was again significant.

### 3.5. Safety evaluation

Three hundred and ninety two adverse events (AE) occurred in 154/243 subjects. Thereof, 139 AE occurred in 64 (52.9%) subjects in the iCR group and 253 AE occurred in 90 (73.8%) subjects in the tibolone group. There is a significant difference between the two groups regarding the rate of patients with any adverse event ($p = 0.001$) in favor of iCR.

Of the 243 subjects, 130 patients (53.5%) experienced 281 possibly drug related adverse events: 86 in 49 patients (40.5%) in the iCR group, and 195 in 81 patients (66.4%) in the tibolone group. The incidence of possibly drug related adverse events was very much lower in the herbal group compared to the one in the tibolone group ($p < 0.0005$). All adverse events were either known climacteric symptoms or listed adverse drug reactions.

Adverse events that might have been interpreted as sign of a liver dysfunction did not occur.

Gynecological adverse events were of particular interest. They are listed in Table 3. The iCR therapy demonstrated lower incidences in comparison with tibolone with respect to any vaginal bleeding, vaginal bleeding or spotting, breast pain, abdominal pain, leucorrhea, and any of these gynecological adverse events.

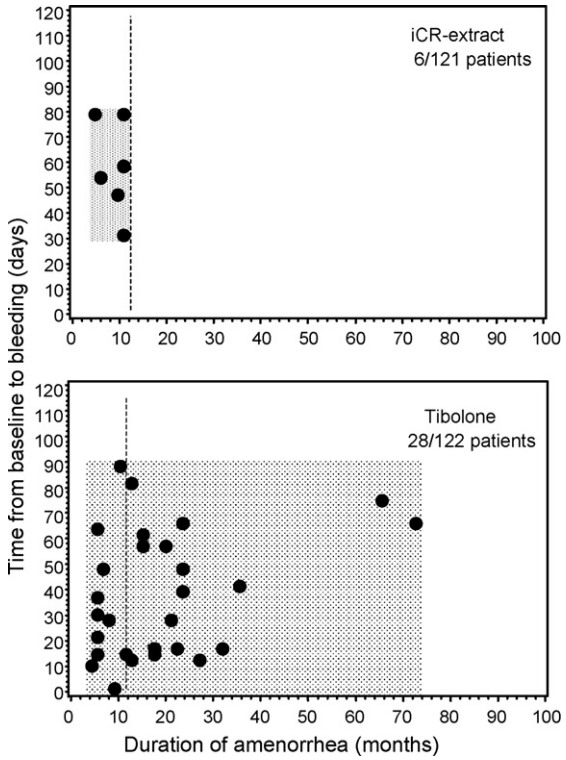


Fig. 2. Scatter plots of the occurrence of an adverse gynecological bleeding over the duration of amenorrhea before onset of therapy.

The time profile of the occurrence of adverse gynecological bleedings was analyzed in detail (Fig. 2). Most of the subjects experiencing bleeding were perimenopausal as they had been amenorrhoeic for less than 12 months. None of the postmenopausal

Table 3
Gynecological adverse Events

| | REMIFEMIN® ($N = 121$) | | | TIBOLONE ($N = 122$) | | | Fisher's exact test |
|---|---|---|---|---|---|---|---|
| | $N$ events | $N$ subjects[a] | % subjects | $N$ events | $N$ subjects[a] | % subjects | ($p$-Value) |
| Vaginal bleeding or spotting | 17 | 13 | 10.7 | 61 | 41 | 33.6 | <0.0005 |
| Vaginal bleeding | 6 | 6 | 5.0 | 40 | 28 | 23.0 | <0.0005 |
| Vaginal spotting bleeding | 11 | 9 | 7.4 | 21 | 16 | 13.1 | 0.205 |
| Edema | 7 | 6 | 5.0 | 17 | 15 | 12.3 | 0.066 |
| Leucorrhea | 7 | 7 | 5.8 | 27 | 22 | 18.0 | 0.005 |
| Abdominal pain | 12 | 12 | 9.9 | 30 | 29 | 23.8 | 0.006 |
| Breast pain/enlargement | 32 | 25 | 20.7 | 48 | 43 | 35.2 | 0.015 |
| Any of these gynecological AE | 75 | 47 | 38.8 | 183 | 84 | 68.9 | <0.0005 |

[a] Subjects with at least one event.

iCR-patients experienced a vaginal bleeding in contrast to tibolone (17 cases).

The average thickness of the uterine intima slightly increased from $2.8 \pm 1.3$ mm at baseline to $3.3 \pm 2.0$ mm at week 12 when analyzed together for peri- and postmenopausal patients in the iCR group ($p = 0.012$), $2.9 \pm 1.2$ mm at baseline to $3.4 \pm 2.0$ mm at week 12 in the tibolone group ($p = 0.005$). However, such low increase is without clinical relevance. A subgroup analysis showed that in the iCR group this increase was found only in perimenopausal but not in postmenopausal patients (from $2.7 \pm 1.1$ to $2.9 \pm 1.4$ mm; $p = 0.148$). In contrast, the mean endometrial thickness significantly increased also in postmenopausal tibolone patients (from $2.8 \pm 1.1$ to $3.4 \pm 2.0$ mm; $p = 0.01$).

The intra-group comparison of the mean body weight demonstrates a clinically irrelevant increase at week 12 as compared to baseline and week 4 ($p < 0.01$). The inter-group comparison shows that the body weight in the tibolone group at week 12 was significantly higher than that in the iCR group ($p = 0.027$), while the body weight at baseline and week 4 was similar in the two groups.

In this trial 2 serious adverse events occurred. One was related to tibolone (spotting for 28 days with an endometrial thickness of 9.1 mm; the endometrial biopsy indicated endometrial polyps and complex hyperplasia). The other one also occurred in the tibolone group but without any causal relationship to the study medication (traffic accident).

Premature dropouts of 14 subjects were registered due to adverse events (5.8%): 5 subjects in the iCR group who experienced 10 AEs (4.1%) and 9 subjects in the tibolone group who experienced 12 AEs (7.4%). The group-difference between the incidence of adverse events leading to premature withdrawal was not statistically significant.

### 3.6. Laboratory parameters

No clinically significant findings were found from the results of hematology, blood chemistry, urinalysis during treatment in both groups. In particular, neither AST, nor ALT nor gamma-GT nor AP revealed any suspicion of liver dysfunction. Only C-reactive protein slightly increased, but only in the tibolone group ($p = 0.06$) in contrast to the iCR-group. Regarding the Clinical Global Impression (Item 3.2) for side effects the women given the herbal treament responded significantly better than those given tibolone (week 4: $p = 0.002$; week 12: $p = 0.033$). However, the difference in the patient's global assessment of tolerability between the two groups in favor of Remifemin® was not statistically significant ($p = 0.13$).

## 4. Discussion

The results of this randomised and double-blind clinical study once more demonstrate that the special isopropanolic *C. racemosa* extract (iCR), beneficially improves the menopausal climacteric complaints effectively and safely, even moderate to severe symptoms. This is the first-time proof of iCR in Chinese peri- and postmenopausal women with climacteric complaints that the benefit-risk-balance of this herbal medication is clearly superior to a treatment with tibolone.

Literature describes the therapeutic efficacy and safety of iCR in more than 11,000 patients, especially pointing out the excellent efficacy inherent with its good tolerability [9,13]. For any medicinal product to be used in climacteric complaints, adequately powered trials with a double-blind, randomized, placebo-controlled design should be available as well as comparison with hormonal treatment (HT) as gold standard. However, the major disadvantages of HT are the known contraindications and an increase in risk of various diseases. Up to 2006, more than 1500 women were included in several randomized controlled trials comparing the therapeutic suitability of *C. racemosa* for climacteric complaints with placebo [5–7,14–18] or an active medication [4,7,14,19]. They unanimously showed a significant superiority of black cohosh to placebo if

- only naturally climacteric women were investigated
- and the treatment duration was at least 12 weeks
- and the frequency and intensity of investigations and questionnaires was reduced to an absolute minimum
- and the black cohosh medication was a medicinal product with a certified pharmaceutical quality as approved by medical regulatory authorities.

These preconditions hold for four independent double-blind placebo-controlled studies on black cohosh [5–7,14]. Only efficacy on tamoxifen-induced

vasomotor symptoms seems to be inconclusive [15,16], however, a major vasomotor symptom "sweatings" was beneficially treated with black cohosh in patients having a history of breast cancer. The positive clinical efficacy of CR on climacteric symptoms has recently been shown to be similar to that of conjugated estrogens in a 3-month, placebo-controlled study [14]. Another clinical trial shows that iCR (40 mg/day) may be a valid alternative to low-dose transdermal estrogen-patch ($TTSE_2$) in the management of climacteric complaints in those women who cannot be treated with or just refuse hormonal strategies [4]. However, a recently published randomized, double-blind and controlled trial in 351 peri- and postmenopausal patients for 1 year comparing various botanicals including black cohosh to placebo and HT contradicts the findings of efficacious menopause symptom treatment seen in the majority of black cohosh trials [20]. The authors' overall statement that black cohosh shows only little potential as an important therapy for vasomotor symptom relief caused a scientific debate whether this is really a valid conclusion, especially in the light of this study's several pitfalls regarding, e.g. randomization, partial unblinding and dubious stability of study medication [21,22].

The results of our trial show a remarkable reduction in the total score and the individual items of KMI in the iCR group. The significance of these changes was as strong as in the tibolone group, a substance which is accepted as powerful treatment for menopausal symptoms. From our results, it is concluded that the efficacy-safety balance (a composite of the Kupperman Menopause Index and the frequency of adverse events) of Remifemin® (2.5 mg extract twice daily corresponding to 20 mg herbal drug twice daily) is non-inferior and even superior to tibolone 2.5 mg once daily. Remifemin® was similar to tibolone in alleviating the KMI-symptoms and superior to tibolone regarding the frequency of adverse events, particularly of gynecological adverse events. Recently, the endometrial safety of *Cimcifuga racemosa*—extract has been proven in a 12-month trial in postmenopausal patients with menopausal complaints [23], demonstrating no case of hyperplasia or other serious adverse endometrial outcome.

The effects of black cohosh are believed to be the result of complex synergistic actions of triterpene glycosides (actein, 27-deoxyactein, cimicifugoside) and cinnamic acid esters [24]. The American Herbal Pharmacopoeia has recognized the clinical research on black cohosh, mainly conducted on the product Remifemin® (Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany) [25]. The exact mode of action of black cohosh in alleviating menopausal symptoms is still not fully understood. In pharmacological studies, the special iCR extract possesses, however, unique features that propose two parallel pathways for its therapeutic effects. The concomitant estrogen-receptor-mediated, but tissue-specific estrogen-agonistic (e.g., on bone: [26]) or estrogen-antagonistic (at the breast or the endometrium: [27,28]) properties are paralleled by CNS-actions [29] via neuroreceptor-mediated and/or -modulatory effects. As newly published epidemiological data demonstrate, women having had an iCR treatment, compared to women not treated with iCR, do not show an increase of breast cancer recurrence, but rather a reduced risk [28], this medication is particularly useful in women with estrogen-dependent malignancies.

Tibolone is characterized as a selective tissue estrogenic activity regulator (STEAR) expressing estrogenic, progestogenic and androgenic activity. It is administered as an effective alternative to HT in treating, e.g. climacteric symptoms. According to the literature and our results, we deem that black cohosh is as efficacious as synthetic alternatives including estrogen and tibolone in alleviating climacteric symptoms, however, at a better safety profile.

Climacteric complaints are characterized by somatic and psychological symptoms. Vasomotor symptoms are a major quality of life concern for women and clinicians likewise. They can be improved significantly and to a similar extent by standard doses of conjugated equine estrogen, oestradiol or tibolone. The results of our study demonstrably show that the black cohosh extract has a similar efficacy on vasomotor symptoms as tibolone.

Also psychological symptoms are frequent in the climacteric, particularly in Chinese peri- and postmenopausal women, the most prevalent being nervousness, depressive mood swings, sleep disturbances and vertigo. Black cohosh has a moderate efficacy in the reduction of psychological symptoms during menopause [5]. In our study, the score of such items at day 0 indicated that these symptoms are mild or moderate. After 12 weeks treatment, the score was

significantly reduced, similar to the improvement of psychological symptoms achievable by tibolone. Interestingly, improvement of psychological symptoms can be further enhanced by combining iCR with St. John's Wort [6,30].

During the climacteric treatment, unscheduled spotting and bleeding is the main side effect. It may be influenced by such factors as age at menopause and the time elapsed since onset of menopause [31–33], BMI and the levels of endogenous estrogens [31,33], the estrogen/progestin dose ratio and the duration of treatment [34–36]. Tibolone induces a lower incidence of adverse gynecological bleedings compared to estrogen–progestin treatment (EPT), ranging from 3% to 27.7% [33,37,38], with only Bennink [39] reporting a high 51% rate. Our results (33.61%) are more than that of Doeren et al. [37], who reported a 27.7% spotting and bleeding rate for tibolone, but less than that of Bennink [39]. Notably, none of the postmenopausal Remifemin® patients experienced a vaginal bleeding in contrast to tibolone (17 cases, 16.8%). Moreover there were only very few subjects (five cases, 5.5%) in the Remifemin® group who experienced postmenopausal spotting in contrast to tibolone (27 cases with bleeding or spotting, 26.7%). No matter peri- or post-menopausal subjects, the incidence or risk of vaginal bleeding or spotting in the Remifemin® group was clearly and significantly lower than that in the tibolone group.

Endometrial thickness, as assessed by TVS, is a highly reliable predictor of endometrial pathology and a dependable index for monitoring the effect of HT in the endometrium. Tibolone is associated with the least effect on endometrial thickness compared to routine EPT regimens [40]. In the two groups at week 12, although the uterine intima thickness slightly increased, it was still within the physiological range of 5 mm for postmenopausal women. This slight increase was at least in part due to the patients with less than 12 months amenorrhea. They have a distinct probability to experience another regular vaginal bleeding by chance that is physiologically preceded by an increase in endometrial thickness. Therefore this analysis was repeated for the subgroup of cases who had been amenorrhoeic for at least 12 months at baseline. In these postmenopausal patients, the mean endometrial thickness significantly increased in the tibolone group but not in the Remifemin® group. The body weight increased significantly but slightly which was possibly related with seasonal change and spontaneous body mass increase of menopausal women. Tibolone is limited to postmenopausal women, preferably patients with more than 1 year since menopause. In contrast, the isopropanolic extract of black cohosh is already suitable for patients with climacteric symptoms before menopause. It has to be pointed out that in this trial the laboratory parameters, including liver enzymes did not reveal any suspicion of liver dysfunction. This is in good agreement with the results of other randomised and controlled clinical studies performed with this special iCR-extract [4,5]. There have been reports on the alleged hepatotoxicity of black cohosh world wide (EMEA 2006). When profoundly assessing the available 42 cases only 16/42 of the cases were found to be sufficiently documented: 5 were classified as "not related" to black cohosh, 7 were classified as "unlikely" and only in 4 cases the causal relation was either "possible" (2) or "probable" (2). However, one of these as "probable" classified cases [41] has been inaccurately reported in the literature and therefore has to be re-assessed as "unlikely" [42,43]. In none of these as "probable" or "possible" classified cases the special isopropanolic CR-extract Remifemin® has been used.

In conclusion, our randomized, double blind, parallel-controlled trial confirms the results of other studies of the clinical efficacy of black cohosh in the treatment of climacteric complaints. The benefit-risk-balance is clearly not inferior and even superior to tibolone in Chinese women with peri- and postmenopausal climacteric symptoms. Bearing in mind newly upcoming long-term data [28,30] beyond our 3 months data, iCR is an effective and safe therapeutic option for climacteric symptoms.

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