Efficacy and Safety of Isopropanolic Black Cohosh Extract for Climacteric Symptoms

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OBJECTIVE: Several clinical studies suggest that black cohosh may be effective in climacteric complaints. However, evidence of its efficacy based on current quality standards has been limited.

METHODS: This randomized, multicenter, double-blind clinical trial compared the efficacy and tolerability of the isopropanolic black cohosh extract in the treatment of climacteric complaints compared with placebo. A total of 304 patients were randomly allocated to receive tablets corresponding to 40 mg drug or matching placebo daily for 12 weeks. The primary efficacy measure was the change from baseline on the Menopause Rating Scale I; secondary measures included changes in its subscores and safety variables.

RESULTS: Patient groups did not differ in baseline characteristics. The isopropanolic black cohosh extract was more effective than placebo ($P < .001$) depending on time from symptom onset ($P = .014$) and follicle-stimulating hormone level ($P = .011$). The effect size was 0.03 to 0.05 Menopause Rating Scale units which is similar to recent hormone replacement therapy study results (0.036 Menopause Rating Scale units) and may therefore be considered clinically relevant. Women in the early climacteric phase benefited more than in the late phase. The hot flush subscore was the most effective measure of the isopropanolic black cohosh extract's efficacy. There were no relevant group differences in adverse events, laboratory findings, or tolerability.

CONCLUSION: This isopropanolic extract of black cohosh root stock is effective in relieving climacteric symptoms, especially in early climacteric women. (Obstet Gynecol 2005;105:1074–83. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

The medicinal use of black cohosh (*Actaea racemosa*, formerly *Cimicifuga racemosa*) has a long tradition. Since the end of the 1950s numerous clinical trials have been conducted on black cohosh for the treatment of various gynecologic conditions. The main target of clinical research has been the indication "climacteric symptoms." Meanwhile, the therapeutic efficacy and drug safety of black cohosh has been investigated in more than 3,800 climacteric women,[1] and the drug has been approved by independent expert committees for use in climacteric symptoms.[2,3] 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) in liquid or tablet form.[4]

Most of the clinical studies on *Cimicifuga racemosa* suggesting its efficacy in the therapy of climacteric symptoms were conducted in the 1980s or 1990s.[2,3] However, clinical research methods in this indication have changed. Therefore, this clinical study aimed to supply new evidence-based efficacy and safety data by assessing the isopropanolic extract of the root stock of *Cimicifuga racemosa* (iCR) in the recommended daily dosage of 40 mg of the drug each day in comparison with placebo.

MATERIALS AND METHODS

This randomized, double-blind study was conducted according to Good Clinical Practice (ICH-E6)[5] and the declaration of Helsinki[6] at 24 gynecologic or gynecologically experienced private practices in Germany. The study commenced after registration with the regulatory authorities (4018732) and approval by the ethics committee of the General Medical Council of Lower Saxony (February 18, 2002) responsible for the coordinating investigator. Subsequently, the ethical review boards of the study centers were consulted.

The patients were recruited among the routine clientele of the practices. Each patient was informed about the study verbally and in writing according to Good Clinical Practice and gave her written informed consent. Patients could withdraw from the study at any time or be withdrawn for safety and inefficacy reasons.

After written informed consent, each patient was randomly assigned to receive one blinded Remifemin tablet

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or matching placebo twice daily for 12 weeks (batch 114210). Each active medication contained 2.5 mg isopropanolic extract of *Cimicifuga Racemosa* corresponding to 20 mg of root stock. Placebo medication corresponded to the active medication without iCR. The medication was prenumbered using a 1:1-randomization block size of 4. New patients should receive the next possible number in ascending order per study center. Unblinding for the statistical analysis occurred after all relevant implausibilities of the data were cleaned, all individual decisions about the data sets of the analysis were made, and data base was closed.

The Institute for Applied Statistics, Bielefeld, was responsible for the study's coordination, monitoring, data analysis, and report. An independent audit of the protocol, case report forms, study centers, and the final report was conducted by Medical Control, Leese, Germany.

Inclusion criteria were postmenopausal women (interval of ≥ 12 months since the last regular menstruation or an interval ≥ 6 months since the last regular menstruation plus follicle-stimulating hormone [FSH] ≥ 50 U/L), age at least 45 years, climacteric complaints as defined by Menopause Rating Scale (MRS) ≥ 0.4 in at least 3 items. Exclusion criteria were body mass index (BMI) more than 28 kg/m^2 (amended to > 35 kg/m^2), cancer, diseases that could interfere with the assessment of climacteric symptoms, drug abuse, participation in another clinical trial including the recent 180 days. Concomitant hormone replacement therapy (HRT) was not allowed throughout the study including a 4-week wash-out before study entry. None of the following medications were allowed including a 1-week wash-out phase before study entry: nonhormonal climacteric drug, including homeopathics and nutritional supplements (eg, soy, red clover) (Anatomic therapeutical classification (ATC code G02C), antiepileptics (N03), psycholeptics (N05, especially N05C = hypnotics and sedatives), psychoanaleptics (N06, especially N06A = antidepressants) including phytotherapeutics.

Clinical examinations and interviews were performed before commencement of treatment, and at 4 and 12 weeks later. The intensity of the climacteric symptoms was assessed by means of the Menopause Rating Scale according to Hauser et al (MRS I)[7,8,9] which was applied as investigator-assessed rating scale. The MRS comprises 10 items (Fig. 1), each ranging from 0 (no complaints) to 1 (severe symptoms) in increments of 0.1. The MRS was formally standardized according to psychometric rules.[10] The MRS enables for comparing profiles of climacteric symptoms, severity of symptoms over time, and the changes between pretreatment and posttreatment. The majority of women demonstrated sufficient reliability of MRS scores.[11] The comparison with

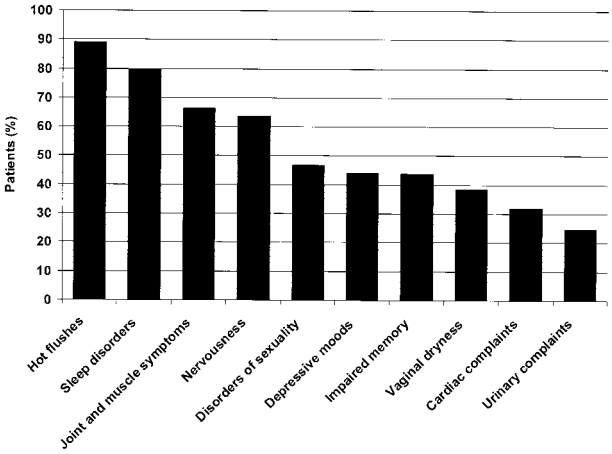

Fig. 1. Severity of climacteric complaints at baseline. The bars indicate the percentage of patients with intensities of 0.4 or greater in Menopause Rating Scale I.
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other scales for menopausal symptoms (Kupperman Index) showed sufficiently close association and correlation coefficients, ie, illustrating a good criterion-oriented validity. The same holds for the comparison with the Medical Outcomes Study Short Form 36[11] The primary endpoint was defined as change from baseline in the MRS mean score, analyzed in a linear regression model considering the following cofactors and covariates: age at study onset, MRS at baseline, FSH at baseline, pooled centers (2 center groups: large and small), interaction treatment by FSH, and interaction treatment by pooled centers (primary model). As a variant, we omitted all insignificant parameters in stepwise fashion (advanced primary model).

Secondarily, the advanced primary model was used for analyzing the changes from baseline in the 4 subscores (factors) of the MRS according to Schneider et al[12] (mean score of the items) in the following hierarchical a priori fixed order:

HOT FLUSHES, items 1 (hot flushes, sweating) and 3 (sleep disorders),
PSYCHE, items 4 (depressive mood), 5 (nervousness, nervous irritability) and 6 (generally impaired performance and memory),
SOMA, items 2 (cardiac complaints) and 10 (joint and muscle symptoms), and
ATROPHY, items 7 (disorders of sexuality), 8 (urinary complaints), and 9 (vaginal dryness).

The predefining of the confounders in the confirmatory statistical procedure avoids alpha-inflationary multiple testing. However, too many statistically irrelevant covariates or cofactors will jeopardize the power of the

study. If the list of confounders is too short, this puristic way might entail a medically important confounder being overlooked.

A more pragmatic procedure is to not predefine a list of confounders but rather predefine an algorithm how to select the relevant ones from a list of putative confounders[13,14] that might have a medically reasonable influence on the primary endpoint: age at study onset, MRS at baseline, FSH at baseline, pooled centers, FSH × treatment, center × treatment, body mass index, HRT last 3 months, pregnancy in the history, contentment with partnership, ovariectomy in the history, hysterectomy in the history, age at menarche, duration of climacteric complaints, number of hot flushes at baseline, clinical global impression item 1 at baseline, 17-β-estradiol at baseline, pretreatment, duration of climacteric complaints × treatment. Accordingly, we additionally performed a stepwise backward selection procedure (exclusion of confounders at $P > .15$, significance threshold for the treatment factor at $P = .05$), and the results of this medically most relevant model are reported in Table 5. The expected values of the treatment differences and the corresponding P values of the significance tests were calculated by means of the regression model reported in Table 5 using the observed patients characterized by the limits which are marked on both axes. Numerous outcomes of "Duration of Climacteric Complaints" (x-axis) and "FSH" (y-axis) were used to estimate the areas shown in Figure 2 (ESTIMATE statement of the SAS PROG REG procedure).

Safety and tolerability of the study medication were monitored by adverse events, clinical laboratory evaluation (central laboratory Becker; Munich), including liver enzymes, vital signs, body weight, and physical examination. Exploratory χ^2 test, Wilcoxon test and analysis of covariance were used for comparing the treatment groups. Analyses were conducted using SAS 82 (SAS Institute Inc., Cary, NC).

Sample size estimation relied on MRS I data from open uncontrolled HRT studies.[12] The inclusion of approximately 300 patients with balanced frequentation of the treatment groups iCR and placebo and 8–40 patients per center was planned assuming $\alpha = 0.05$, $\beta = 0.20$, standardized treatment difference 0.35, and 13% dropouts.

The primary efficacy analysis used the intention-to-treat population consisting of all randomly assigned patients who took the study medication at least once and at least once reported about efficacy, including dropout due to inefficacy. Missing values were handled by last observation carried forward.

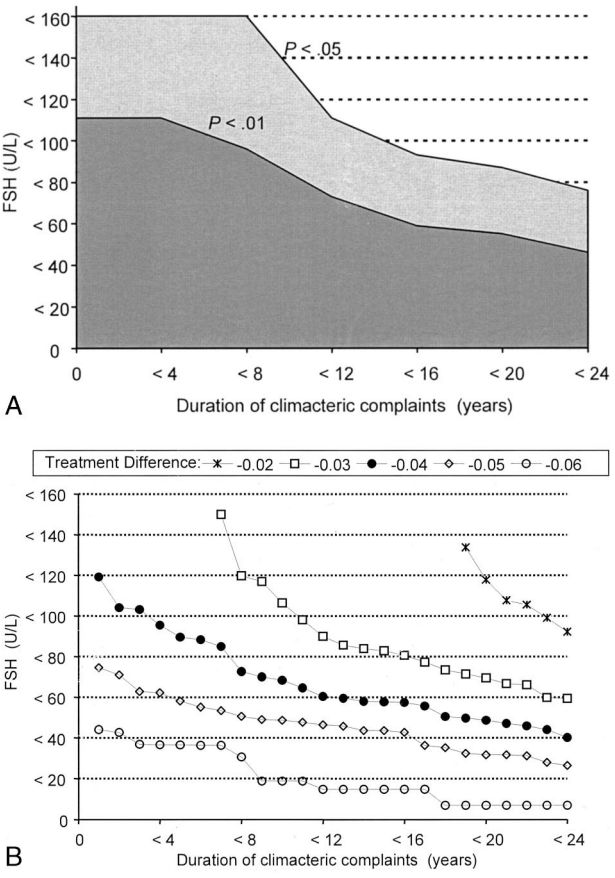

Fig. 2. A. Predictors for efficacy significance. The P value for the treatment difference in Menopause Rating Scale I of iCR minus placebo depends on baseline follicle-stimulating hormone level and duration of climacteric complaints (intention-to-treat population). **B.** Predictors for the size of efficacy. The lines show the treatment difference in Menopause Rating Scale I of iCR minus placebo dependent on follicle-stimulating hormone and duration of climacteric complaints (intention-to-treat population). FSH, follicle-stimulating hormone; iCR, isopropanolic extract of *Cimicifuga racemosa*.

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RESULTS

Patients were recruited at 24 centers for this randomized, double-blind, placebo-controlled parallel-group study. A total of 309 patients were enrolled into the study screening period of which 304 were randomized to one of the two treatment groups. The intention-to-treat and per-protocol populations are shown in Figure 3. This clinical trial focused on the confirmatory analysis of the intention-to-treat patients. The per-protocol population was derived from the intention-to-treat population by excluding patients with major protocol violations or who dropped out for reasons not related to the study drugs. A

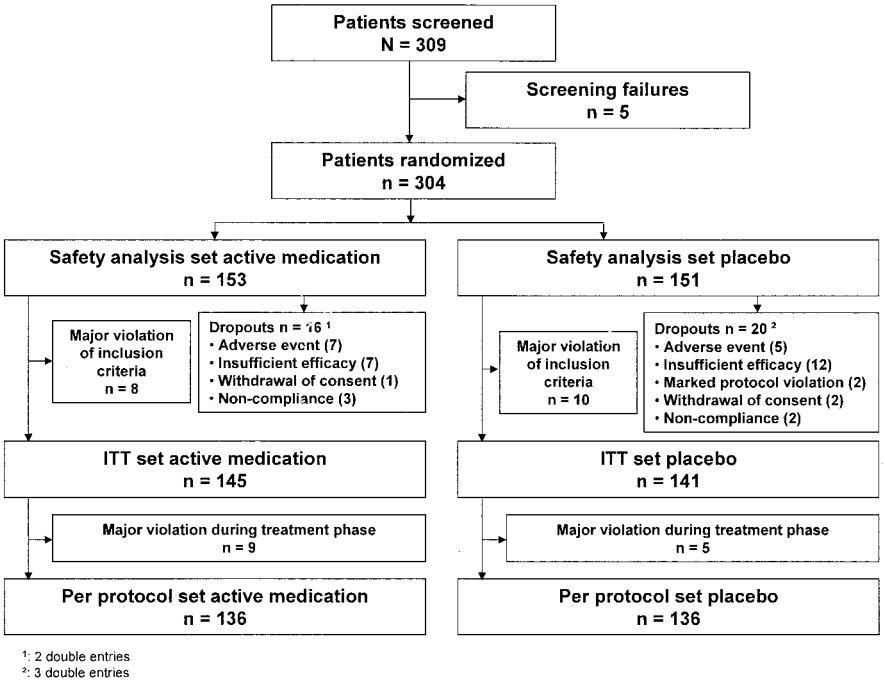

Fig. 3. Disposition of patients and analysis populations. ITT, intention to treat.

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total of 268 (88%) patients completed the study in a regular fashion.

The demographic and other baseline characteristics are listed in Table 1. The baseline data were comparable in the 2 groups, showing a median of 28 hot flushes per week. Figure 1 shows the severity of climacteric complaints at baseline in the intention-to-treat population. The MRS score and factors were evenly distributed in the intention-to-treat and per-protocol population at baseline.

The confirmatory analysis of the MRS score at the end of therapy was carried out on the 2 groups using predefined covariates in a linear regression model (Table 3, intention-to-treat population). This revealed a statistically significant difference in treatment ($P = .027$) in favor of iCR. Thus, the efficacy of iCR is basically proven. In addition, a statistically relevant increase in the treatment difference (and hence iCR therapeutic benefit) with declining baseline FSH level was registered. Even after statistically irrelevant covariates were eliminated (advanced primary model, Table 4), the difference in treatment remained significant ($P = .026$) indicating iCR efficacy again.

The medically most relevant regression model (Table 5) was generated by a predefined algorithm (details in MATERIALS AND METHODS). This also produced a statistically significant treatment factor ($P < .001$), demonstrating iCR efficacy even when considering all significant confounders. Large centers tended to show a higher change from baseline than small centers (Table 5). Additionally, a statistically relevant decline of the treatment difference with increasing baseline FSH level and the duration of climacteric complaints at baseline was obtained (Table 5). Figure 2 shows how these predictors influenced the significance of the treatment's efficacy (Figure 2A) and the size of the treatment's efficacy

Table 1. Demographic and Other Baseline Characteristics

	Remifemin	Placebo
Age (y)		
Median	53	54
Mean	54 ± 6	55 ± 6
Body mass index (kg/m^2)	25.5 ± 3.0	24.9 ± 2.7
Age at menarche (y)	13.5 ± 1.5	13.3 ± 1.4
Age at onset of complaints (y)	48 ± 5	49 ± 6
Median number of pregnancies	2	2
Contentment with partnership (% of patients indicating "yes")	84	76
Hysterectomy (% of patients indicating "yes")	33	39
Median number of hot flushes per week	28	28
Median duration of climacteric complaints (y)	4.4	5.1
Menopause Rating Scale	0.35 ± 0.12	0.35 ± 0.12
Median follicle-stimulating hormone level(U/L)	60 (median)	60 (median)
Hormone replacement therapy in last 3 months (%)	20	19

Values are mean ± standard deviation unless otherwise stated.

Table 2. Incidences of Adverse Events

System Organ Class	Remifemin	Placebo	P*
Number of patients	153	151	
Any symptom	50 (32.7)	47 (31.1)	.771
Blood–blood and lymphatic system disorders	1 (0.7)	1 (0.7)	.993
Card–cardiac disorders	2† (1.3)	0	.159
Ear–ear and labyrinth disorders	0	1 (0.7)	.313
Gastr–gastrointestinal disorders	8 (5.2)	7 (4.6)	.811
Genrl–general disorders and administration site conditions	1 (0.7)	1 (0.7)	.993
Infec–infections and infestations	13 (8.5)	19 (12.6)	.246
Inj&P–injury, poisoning and procedural complications	2 (1.3)	0	.159
Inv‡–investigations	6 (3.9)	5 (3.3)	.776
Metab–metabolism and nutrition disorders	2 (1.3)	0	.159
Musc–musculoskeletal and connective tissue disorders	15 (9.8)	10 (6.6)	.313
Nerv–nervous system disorders	4 (2.6)	5 (3.3)	.720
Psych–psychiatric disorders	2 (1.3)	5 (3.3)	.244
Renal–renal and urinary disorders	1 (0.7)	0	.320
Repro–reproductive system and breast disorders	4 (2.6)	4 (2.6)	.985
Resp–respiratory, thoracic and mediastinal disorders	0	1 (0.7)	.313
Skin–skin and subcutaneous tissue disorders	3 (2.0)	3 (2.0)	.987
Vasc–vascular disorders	1 (0.7)	1 (0.7)	.993

Values are n (%).
* *P* value from χ^2 test.
† Tachycardia.
‡ Isolated investigational results without detailed diagnosis.

(Figure 2B). Medically relevant values of the predictors lie within the area of significance below $P < .05$ or even below $P < .01$ (Figure 2A) and reveal effect sizes ranging from 0.03 to 0.05 MRS units (Figure 2B). In general, the difference in the changes in the primary efficacy measure was most pronounced in the first years after menopause.

Analysis of the MRS subscores showed that "hot flushes" ($P = .007$), "atrophy" ($P = .012$), and "psyche" ($P = .019$) decreased statistically significantly in the cimicifuga compared with the placebo group. The efficacy estimates (parameter estimates for the treatment factor) were −0.127 (standard error of the mean = 0.047), −0.053 (0.021), and −0.071 (0.030) MRS units, respectively. The increase of the treatment difference with declining baseline FSH level was less pronounced as compared with the total MRS score ($P = .044$, .051, and .147). The other confounders remained important ($P < .10$). No relevant treatment effect was observed for the MRS subscore "soma."

The treatment differences and 95% confidence intervals obtained for specific FSH levels and duration of climacteric complaints are plotted for early climacteric women (FSH = 20 U/L and 1 year duration of climacteric complaints, Figure 4) and for later climacteric women (FSH = 40 U/L and 3 years duration of climacteric complaints, Figure 5).

All 304 randomly assigned patients were included in the safety analysis. In the iCR group, 50 (32.7%) patients reported 71 adverse events and 47 (31.1%) in the placebo group reported 67 adverse events ($P = .771$). A causal relationship with the study medication was judged[15] to be at least "possible" in 6 adverse events (3.9%) that

Table 3. Primary Model

Variable	Parameter Estimate	Standard Error	P	95% Confidence Interval
Intercept	$\beta_0 = -0.0837$	0.0578	.148	−0.197, 0.03
T = treatment	$\beta = -0.0663$	0.0298	.027	−0.125, −0.00765
x_1 = age at study onset	$\beta_1 = 0.00239$	0.000899	.008	0.000623, 0.00417
x_2 = MRS at baseline	$\beta_2 = -0.312$	0.0484	< .001	−0.407, −0.217
x_3 = FSH at baseline	$\beta_3 = -0.0000632$	0.000269	.815	−0.000593, 0.000467
x_4 = pooled centres	$\beta_4 = -0.0523$	0.0166	.002	−0.085, −0.0196
x_5 = FSH × treatment	$\beta_5 = 0.000664$	0.000377	.079	−0.0000784, 0.00141
x_6 = center × treatment	$\beta_6 = 0.031$	0.0234	.186	−0.015, 0.077

iCR, isopropanolic extract of *Cimicifuga racemosa*, Menopause Rating Scale; FSH, follicle-stimulating hormone.
Changes in the Menopause Rating Scale I score from baseline to end of treatment (12 weeks) (Intention-to-Treat Group); confirmatory analysis of the treatment difference between iCR and placebo using a linear regression model taking into account the listed variables.

Table 4. Advanced Primary Model

Variable	Parameter Estimate	Standard Error	*P*	95% Confidence Interval
Intercept	$\beta_0 = -0.0978$	0.0526	.064	−0.201, 0.00584
T = treatment	$\beta = -0.0439$	0.0195	.026	−0.0825, −0.00539
x_1 = age at study onset	$\beta_1 = 0.00244$	0.000895	.007	0.000676, 0.0042
x_2 = MRS at baseline	$\beta_2 = -0.312$	0.0483	< .001	−0.407, −0.217
x_4 = pooled centers	$\beta_4 = -0.0368$	0.0118	.002	−0.0601, −0.0135
x_5 = FSH × treatment	$\beta_5 = 0.000555$	0.00026	.034	0.000042, 0.00107

iCR, isopropanolic extract of *Cimicifuga racemosa*, MRS, Menopause Rating Scale; FSH, follicle-stimulating hormone.

Changes in the Menopause Rating Scale I score from baseline to end of treatment (12 weeks) (Intention-to-Treat Group); analysis of the treatment difference between iCR and placebo using a linear regression taking into account the listed variables–this model resulted from a backward procedure starting with the variables listed in Table 3 eliminating the statistically irrelevant covariates.

occurred with iCR and 7 (4.6%) adverse events with placebo ($P = .758$). Further details are described in Table 2. Cardiovascular or menstruational adverse event rates were inconspicuous. Stomach complaints were almost equally distributed to both treatment groups (Table 2). No serious adverse events were observed.

No clinically relevant differences from baseline between the treatment groups were registered for laboratory measures. Use of iCR did not elevate liver enzyme activity in peripheral blood. There were no statistically significant differences between groups. The rate of changes in enzyme levels was equal in both groups: 4 patients each with iCR and placebo. The maximum increase in liver enzyme activity and the posttreatment ranges for aspartate amino transferase, alanine amino transferase and γ-glutamyl-transpeptidase were very similar when the groups were compared. Weight, heart rate, and blood pressure remained constant throughout the study in both groups. Good compliance (intake of study medication 80–120%) was reported in 91.3% of the patients in the iCR and 91.8% in the placebo group ($P = .923$).

DISCUSSION

This randomized, multicenter double-blind, placebo-controlled clinical trial investigated the efficacy and some safety aspects of an isopropanolic extract of black cohosh (Remifemin) in a population of women who are representative of patients presenting to gynecologists, especially in terms of age (median 53 years).[16] The average age at menopause is 52 years.[16] This study was conducted in accordance with Good Clinical Practice European Medicines Agency Guideline,[5] the Food and Drug Administration Guidelines for Industry,[17] and the Helsinki Declaration.[6] Study quality was assured by Good Clinical Practice monitoring and an independent audit of study centers and the study report.

Clinical efficacy was measured using the well-accepted and validated Menopause Rating Scale I (MRS).[7] The 10 MRS I items may be grouped into 4 subscores[12] that identify the main target symptoms of any climacteric medication. This score can accurately profile a patient's individual climacteric syndrome while guiding the physician's treatment decisions.

Table 5. Medically Most Relevant Model

Variable	Parameter Estimate	Standard Error	*P*	95% Confidence Interval
Intercept	$\beta_0 = 0.0317$	0.0195	.105	−0.0067, 0.0702
T = treatment	$\beta = -0.0788$	0.0210	< .001	−0.12, −0.0374
x_2 = MRS at baseline	$\beta_2 = -0.301$	0.0476	< .001	−0.395, −0.207
x_4 = pooled centers	$\beta_4 = -0.0351$	0.0117	.003	−0.0581, −0.0121
x_5 = FSH × treatment	$\beta_5 = 0.000659$	0.000257	.011	0.000153, 0.00116
x_8 = HRT last 3 months	$\beta_8 = 0.0455$	0.0148	.002	0.0164, 0.0746
x_{12} = hysterectomy	$\beta_{12} = -0.02$	0.0120	.104	−0.0432, 0.00405
x_{23} = duration × treatment	$\beta_{23} = 0.00387$	0.00156	.014	0.000801, 0.00694

iCR, isopropanolic extract of *Cimicifuga racemosa*, MRS, Menopause Rating Scale; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy.

Changes in the Menopause Rating Scale I score from baseline to end of treatment (12 weeks) (Intention-to-Treat group); analysis of the treatment difference between iCR and placebo using a linear regression taking into account the listed variables–the model resulted from a backward procedure starting with all putative confounders (see Material and Methods) that might have a medically reasonable influence on the primary endpoint and eliminating the statistically irrelevant variables.

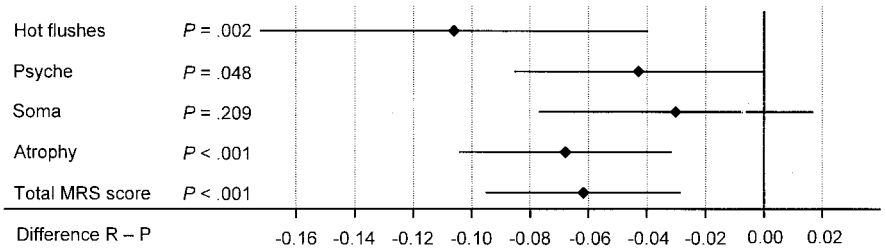

Fig. 4. Treatment differences and 95% confidence limits of active medication (iCR) minus placebo based on Menopause Rating Scale I and the subscores "hot flushes," "psyche," "soma," and "atrophy" determined for "early" climacteric women (assuming follicle-stimulating hormone = 20 U/L and 1-year duration of climacteric complaints). MRS, Menopause Rating Scale; R, active medication; P, placebo; iCR, isopropanolic extract of *Cimicifuga racemosa*.

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The incidence of adverse events and measurements of laboratory measurements were evaluated. This study was not powered for these exploratory safety variables. We did not examine long-term data beyond 3 months. This is the subject of a currently ongoing study. Nevertheless, the results are consistent with the safety data from all studies on iCR (data on file), which demonstrate the drug's harmlessness.

A patient's climacteric syndrome may be influenced by her individual environment.[18,19] Even large-scale clinical trials investigating risk factors for coronary heart disease in patients on HRT have been criticized for neglecting important confounders.[20] Therefore, any statistical evaluation of the primary endpoint in a clinical study measuring climacteric symptoms should also consider all relevant confounders as we did in the present study. Our statistical analysis took both statistical probability and medical rationale into account. The clinical multivariate situation demanded multivariate regression procedures. However, the lack of a crossover design might allow for an overestimated placebo effect. Thus, the true therapeutic benefit of the iCR may even be higher than the group difference obtained with our parallel group design. The time frame was sufficient for assessing efficacy.

The efficacy data of the iCR obtained in this clinical trial agree with those of numerous other studies.[21–26] Our results were obtained in accordance with current quality standards for clinical trials and provide new evidence. The statistical evaluation of the primary efficacy measure, ie, the total MRS score ($P = .027$), as well as of the supportive statistical models ($P = .026$; $P < .001$) consistently demonstrated the treatment factor being significant. The efficacy of iCR was most pronounced during early menopausal years. The therapeutic efficacy of black cohosh has also been investigated by a previous estrogen- and placebo-controlled pilot study: Their design was similar to ours, their patient characteristics and treatment duration identical, but their population was smaller (N = 62).[27] After a treatment period of 12 weeks, the authors likewise observed the statistical trend that black cohosh leads to a reduction in total MRS score ($P = .051$) compared with placebo. Their estrogen group[27] serves as a reference for placebo-controlled MRS I data in patients on estrogen. They reported that the average of all 10 MRS items decreased from baseline

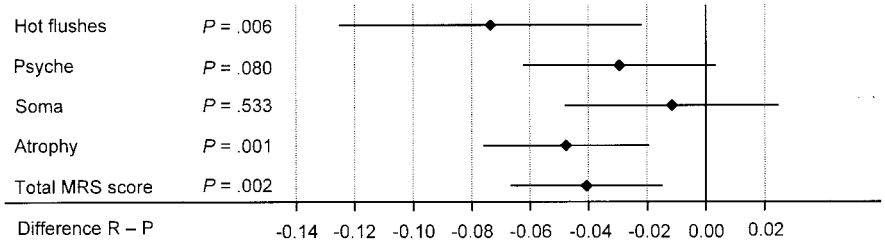

Fig. 5. Treatment differences and 95% confidence limits of active medication (iCR) minus placebo based on Menopause Rating Scale I and the subscores "hot flushes," "psyche," "soma," and "atrophy" determined for "late" climacteric women (assuming follicle-stimulating hormone = 40 U/L and 3-year duration of climacteric complaints). MRS, Menopause Rating Scale; R, active medication; P, placebo; iCR, isopropanolic extract of *Cimicifuga racemosa*.

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by −0.147 and −0.183 in the placebo group and in the estrogen group, respectively. The corresponding group difference was −0.036 in favor of estrogen.

In our study iCR's efficacy was similar to that achievable with conjugated estrogens when the group-specific influence of both FSH at baseline and duration of climacteric complaints are considered. Implying reality-relevant thresholds of the duration of climacteric complaints, group differences between −0.03 and −0.05 (Fig. 2B) were seen in favor of iCR. This is in the same order of magnitude as the −0.036 reported for conjugated estrogens.[27] Our study provides further evidence of iCR's clinically relevant efficacy in climacteric patients, confirming the results of previous randomized clinical trials with this extract in which the Kupperman Index was used.[2]

Climacteric complaints represent a polysymptomatic disorder. The occurrence of somatic and psychic symptoms depends on the climacteric phase and endocrine level.[28]

The treatment of neurovegetative climacteric symptoms is the main indication for iCR. The hot flush MRS subscore identifies the most prominent symptoms (Fig. 1). In our study, the iCR's effect size in the hot flush MRS subscore was approximately 1.7 times as high as in the total MRS score (Fig. 4 and Fig. 5) and also greatest in the early climacteric phase.

Efficacy may be related to a modification of climacteric overactivation of the gonadotropin-releasing hormone (GnRH) pulse generator[29] which is closely related to central nervous system (CNS) regions regulating body temperature. A CNS effect of black cohosh also discussed in the literature is a dopaminergic effect in the brainstem that can relieve hot flushes (Löhning et al. 23. Int. LOF Symposium "Phyto-Estrogens," Ghent, Belgium, 1999). Our study results confirm the general evidence that black cohosh is effective in reducing neurovegetative symptoms like hot flushes.[2,3]

In early climacteric women there was a statistically significant difference in psychic complaints in favor of iCR in comparison to placebo ($P = .048$), whereas the improvement was not statistically significant in women who had been climacteric for more than 3 years. Black cohosh thus appears to relieve psychological climacteric symptoms insufficiently. In patients with more severe psychological symptoms, some authors have recommended the adjuvant use of St. John's Wort.[30]

Earlier clinical studies on climacteric women have shown that *Cimicifuga racemosa* can alleviate their anxiety/depressive syndromes.[21,22,31–33] These findings can be explained by the age of the climacteric women who were in the early climacteric stages.

Preclinical data have also shown *Cimicifuga racemosa* to have antidepressant activity.[34] Screening experiments with various human CNS receptors showed that black cohosh binds to serotonin and dopamine receptors.[35] These transmitter systems are involved in emotional and anxiety behavior.

The MRS subscore "atrophy" shows beneficial effects for iCR, confirming recent data by Wuttke et al.[27] Human pharmacologic studies that investigated both hormone level and effects on female reproductive organs demonstrated no systemic estrogenic effects of iCR.[32] Preclinical data suggest a tissue-selective mechanism for black cohosh, referred to as selective estrogen receptor modulator activities.[36] The MRS subscore "atrophy" comprises vaginal dryness, sexuality, and urinary tract symptoms, modifiable by emotion. Thus, the total effect measured for this subscore may indicate a primarily neuronal effect. Indeed, vaginal cytology even tends to improve slightly under placebo.[21] A meta-analysis of an estrogen therapy of climacteric urinary incontinence has not provided strong evidence that estrogen affects urodynamic variables in hypoestrogenic women.[37] By contrast, other data suggest an exacerbation of urinary incontinence.

The few, mild and transient adverse events observed in this clinical trial are consistent with the data of numerous other studies (overview: 2, 3). Reviews of the safety of black cohosh extracts state that *Cimicifuga racemosa* is safe and its adverse events are rare, mild, and reversible.[38,39,40]

We also evaluated a putative hepatotoxic potential of black cohosh. Other authors concluded that case reports of Whiting et al[41] show no causal relationship to black cohosh.[42,43] Acute liver failure was described in one case report, but the author concluded that "it is not possible to determine the individual ingredient or mixture of ingredients that resulted in acute liver failure in this patient."[44] Our study does not show clinically relevant changes in the primarily important hepatic enzymes (γ-glutamyltranspeptidase, aspartate amino transferase, and alanine amino transferase) in comparison to placebo. Neither the analysis of variance group comparison nor cross tables nor the assessment of clinical relevance of shifts to abnormal nor the adverse events tables revealed any statistically significant group difference. Especially, the rate of adverse events on changes in enzyme activity was equal in both treatment groups (iCR: 4 patients; placebo: 4 patients). Even in a 3-times higher therapeutic dose, no clinically relevant changes were observed.[32]

The present randomized controlled trial confirms the results of other studies of the clinical efficacy of iCR in the treatment of climacteric complaints. Women in the early climacteric phase appear to benefit more than those

in later postmenopause. The hot flush MRS subscore proved the most iCR-responsive symptom group. There was neither a statistically significant nor a clinically relevant difference in drug safety between the isopropanolic black cohosh extract and placebo. In conclusion, from all the numerous studies, the isopropanolic black cohosh extract shows a favorable benefit–risk ratio. Further randomized controlled trials compared with HRT would be valuable for the future.

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