Available online at www.sciencedirect.com
ScienceDirect
Maturitas 58 (2007) 31–41
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

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

Wenpei Bai [a], Hans-Heinrich Henneicke-von Zepelin [b,*], Shuyu Wang [c], Shurong Zheng [a], Jianli Liu [d], Zhonglan Zhang [d], Li Geng [e], Lina Hu [f], Chunfeng Jiao [g], Eckehard Liske [b,1]

[a] *The First Hospital of Peking University, Department of Gynecology, Beijing, China*
[b] *Schaper & Brümmer, Clinical Research and International Medical Department, Salzgitter, Germany*
[c] *Jiangsu Province People's Hospital, Department of Gynecology, Nanjing, China*
[d] *The General Hospital of PLA, Department of Gynecology, Beijing, China*
[e] *The Third Hospital of Peking University, Department of Gynecology, Beijing, China*
[f] *West China Second Hospital of Sichuan University, Department of Gynecology, Chengdu, China*
[g] *Excel Pharma Studies, Biometrical Department, Beijing, China*

Received 24 November 2006; received in revised form 26 March 2007; accepted 22 April 2007

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 ± 6.1 to 11.2 ± 6.2 and 7.7 ± 5.8 (iCR) and to 11.2 ± 7.2 and 7.5 ± 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

* Corresponding author. Tel.: +49 5341 307 511; fax: +49 5341 307 524.
E-mail addresses: wenpeibai@bjmu.edu.cn (W. Bai), eckehard.liske@schaper-bruemmer.de (E. Liske).
[1] Tel.: +49 5341 307 810; fax: +49 5341 307 524.

0378-5122/$ – see front matter
doi:10.1016/j.maturitas.2007.04.009

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-