ORIGINAL RESEARCH

CONFIRMATION OF THE EFFICACY OF ERr 731 IN PERIMENOPAUSAL WOMEN WITH MENOPAUSAL SYMPTOMS

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Objective • In a previous study, the special extract ERr 731 of *Rheum rhaponticum* significantly reduced vasomotor and other menopausal symptoms associated with perimenopause. This trial was conducted to confirm the efficacy of ERr 731.

Design • A multicenter, randomized, placebo-controlled, clinical trial with 112 perimenopausal women with menopausal symptoms receiving either 1 enteric-coated tablet of ERr 731 (n=56) or placebo (n=56) daily for 12 weeks. Primary outcome criterion for efficacy of ERr 731 compared to placebo was the change of the Menopause Rating Scale (MRS) total score from day 0 to day 84. Other efficacy assessments analyzed included the number and severity of hot flushes, individual symptoms of the MRS, treatment outcome, and various safety parameters.

Results • By 12 weeks, ERr 731 caused a highly significant reduction of the MRS total score from 27.0 ± 4.7 points to 12.4 ± 5.3 points when compared to the placebo-induced decrease from 27.0 ± 5.3 points to 24.0 ± 6.2 points ($P<.0001$). A significant reduction in each individual MRS item score, in hot flushes and the hot flush weekly weighted score, together with a marked improvement in treatment outcome were also observed ($P<.0001$). These results confirm the efficacy of ERr 731 in alleviating menopausal symptoms in perimenopausal women. Fourteen adverse events were reported in total: 11 by 5 women receiving ERr 731 and 3 by 3 women receiving placebo. ERr 731 was well tolerated by the majority of the women.

Conclusion • ERr 731 was confirmed to be effective for the treatment of menopausal symptoms in perimenopause. (*Altern Ther Health Med*. 2009;15(1):24-34.)

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The conventional therapy for the relief of moderate to severe menopausal symptoms is hormone therapy (HT). In March 2007, the North American Menopause Society (NAMS) recommended HT as the preferred therapy but with the caveat that it should be weighed carefully against the potential risk of breast cancer and thromboembolism.[1] A recent comment on the NAMS statement recommended that postmenopausal HT should be used only for bothersome symptoms, using the lowest effective HT dose for the shortest possible time and should not be used to prevent disease (eg, osteoporosis).[2] Lower HT doses or even ultra-low doses appear to be better tolerated than standard doses and may have a better safety profile.[3,4] The risks of the long-term use of low-dose HT over extended periods (ie, several years), however, has not been clarified. The European Medicines Agency (EMEA) guidance for HT recommends the use of HT only for the treatment of menopausal symptoms in postmenopausal women,[5] and the risks of breast cancer, coronary heart disease, stroke, and thromboembolism in perimenopausal women with moderate to severe menopausal symptoms taking HT have not been established in randomized controlled trials (RCTs).

The problems with HT therefore limit the spectrum of effective measures available for women in perimenopause suffering from menopausal symptoms, and often their only option is to use herbal preparations. The special extract ERr 731 from the roots of rhapontic rhubarb (*Rheum rhaponticum*) (trade name Phytoestrol N, rebranded since September 1, 2007, Phyto-Strol and Phyto-Strol Loges, Chemisch-Pharmazeutische Fabrik Göppingen, Carl Müller, Apotheker, GmbH & Co KG, Göppingen, Germany) has been used in Germany since 1993 for the treatment of women with menopausal symptoms in both perimenopause and postmenopause.[6] The extract ERr 731 contains rhaponticin, desoxyrhaponticin, and their

aglycones, rhapontigenin and desoxyrhapontigenin.[6] Neither rhapontic rhubarb nor the special extract ERr 731 contains any of the anthraquinones such as emodin or rhein that are found in other rhubarb species.[7] Thus, this extract has no laxative effect. The absence of anthraquinones, of which some are known to be potent activators of estrogen receptors (ERs) and therefore may increase the risk of unwanted side effects in the endometrium and breast,[8] supports the use of ERr 731 in menopausal women.

It is thought that part of the reduction of menopausal complaints by HT is due to the replacement of estradiol levels, and this is consistent with the known role of estrogens in the development and functioning of the female reproductive system and their important role in the maintenance of structure and function in nonreproductive tissues and systems (eg, vasculature, smooth muscle, central nervous system, immune system).[9] It is also known that some of these effects are mediated with high specificity via the structurally and functionally different estrogen receptor-α (ERα) and ERβ systems. A recent study with ERα- and ERβ-specific activators has shown that both ERs need to be activated to alleviate hot flushes.[10] Additionally, through the use of ERβ-deficient mice, an involvement of this receptor subtype in the etiology of anxiety and depression has been demonstrated.[11] Most importantly, ERβ seems to act as a negative regulator of ERα and, where the receptors are coexpressed, protect against ERα-mediated tissue hyperproliferation and carcinogenesis.[12-15]

Recent investigations with ERr 731 and its hydroxystilbene constituents have shown that they bind and activate the ERβ with high specificity in a variety of cell lines.[16,17] In contrast, neither ERr 731 nor its aglycones rhapontigenin and desoxyrhapontigenin nor the structurally related compounds resveratrol and piceatannol activate the ERα in Ishikawa cells naturally expressing ERα. Similarly, ERr 731 showed no agonist activity when tested in the HEC-1B endometrial cancer cells transfected with ERα.[16] On ERβ, the activity of ERr 731 is comparable to that of 10^{-8} M E2, and thus, it appears likely that ERr 731 mediates its beneficial effects on menopausal symptoms such as hot flushes, depression, and anxiety at least in part via its ERβ-selective properties. Preliminary results from an uterotrophic assay in ovariectomized rats have shown that ERr 731 up to 100 mg per kg body weight per day did not display any proliferative and uterotrophic effects (submitted for publication).

In 4-week and 13-week toxicity studies in male and female dogs with continuing intake of 100 mg, 300 mg, and 1000 mg ERr 731 per kg body weight per day, it was demonstrated that even at the highest doses, ERr 731 (1000 mg per kg body weight per day) did not affect viability, induce any signs of toxicity or significant pathological changes in any organs in either male or female animals which might be related to the intake of the extract.[18] Of particular importance is the observation that the uterine weight was not changed when compared to the control animals, indicating that ERr 731 even in these high dosages given continuously had no uterus-stimulating effect. Also, no other abnormalities in the genital tracts of either female or male dogs were detected macroscopically or microscopically. Based on the animal study reports, the no-observed-adverse-effect-level has been determined to be 1000 mg per kg body weight per day.

The recommended therapeutic dose of ERr 731 for menopausal women is 4 mg extract per day (taken as 1 tablet once daily). This dose has been demonstrated to be effective in reducing menopausal symptoms in a 12-week RCT in 109 perimenopausal women[6,19] and in a 6-month postmarketing surveillance study with 252 perimenopausal and postmenopausal women.[20]

In these and other long-term (48-week and 96-week) observational studies with continuous intake of ERr 731, no clinically relevant changes due to ERr 731 in endometrial biopsies, bleeding, weight, blood pressure, pulse, and laboratory parameters were seen, whilst sustained alleviation of the menopausal symptoms was present, and there were no adverse events associated with the intake of the extract.[21] The results have confirmed that ERr 731 is a safe and effective alternative to HT in perimenopausal women for the alleviation of menopause symptoms.

In order to provide confidence to physicians, consumers, and regulatory authorities that ERr 731 is of value in alleviating the cardinal menopausal complaints such as vasomotor, psychological, and physical symptoms, the efficacy and safety of ERr 731 has been further examined using an extended battery of symptom scores and including additional safety parameters. These results are reported here. The primary outcome criterion for efficacy used was the change of the Menopause Rating Scale (MRS) total score under ERr 731 when compared with placebo after 12 weeks of treatment. Menopausal symptoms were assessed using an international version of the validated MRS score, with the subjects reporting their experiences directly using subject diaries to record the MRS, hot flushes, and other efficacy parameters independently of the investigators.[22]

METHODS

Trial Design, Participants, and Treatment

This was a 12-week, multicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled, phase III clinical trial using a multistage adaptive-sequential design with 2 interim analyses to compare the efficacy and safety of ERr 731 with placebo in women with menopausal complaints in perimenopause. The trial and the subsequent 52-week observational study were conducted at 8 gynecological outpatient departments with a Russian-speaking trial population in the Ukraine from February 2004 to April 2007. Trial and study were conducted in accordance with the ethical requirements of the Declaration of Helsinki, ICH GCP guideline, and the legal provisions of the Ukraine. Approval by the Ethics Committee, Kiev, Ukraine, and the State Pharmacological Committee of the Ministry of Health, Kiev, Ukraine, was obtained in December 2003.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) females aged 45 to 55 years; (2) perimenopause defined as a break in cycle regularity during the past 12 months or last menstruation at least 3 but no longer than 12 months ago; (3) MRS total score ≥18 points, reflecting moderate to severe menopausal symptoms[23]; (4) capability of providing written informed consent; (5) accessibility by telephone; and (6)

willingness and ability to comply with all procedures of the trial and attend all scheduled contacts at the investigational site.

Exclusion criteria included abnormalities in the endometrium and breast, presence of concomitant diseases, the concomitant use of predefined medications, pretreatment of menopausal symptoms with hormone therapies, semi-luxuries (alcohol, smoking, caffeine), and a body mass index <18kg/m^2 or >30kg/m^2.

Women who met all inclusion and no exclusion criteria and gave informed consent were enrolled into the trial and allocated to one of the treatment groups.

Trial Conduct

Baseline and all assessment parameters were recorded by the investigator in electronic case report forms. In addition, every woman was required to keep a diary during the course of the trial recording her hot flushes, menstrual bleeding, MRS, and the consumption of investigational medication. Other assessments including anxiety, depression, state of health, and quality of life also were recorded (not reported here; they will be the subject of a separate publication).

Subjects visited the investigator on days 28, 56, and 84, where the clinical status was checked, the diary reviewed, and blood and urine samples taken for laboratory analyses. The intake of investigational medication was also documented, as were any changes in concomitant medications and the appearance of any adverse events (AEs).

On day 84 (and also in the case of premature withdrawal from the trial), each participant underwent a final investigation including determination of laboratory blood and urine parameters, a tobacco test, a clinical breast examination, breast tenderness assessment, mammography, PAP and vaginal smears, a transvaginal ultrasound examination, a pelvic examination, and endometrial biopsy. Women were free to discontinue their participation in the trial at any time without any prejudice to their further treatment. In contrast to a previous RCT,[6] the protocol for the present trial did not permit nonresponders to withdraw from the trial or cross over to open active treatment during the 12-week period of the double-blind phase due to lack of efficacy of the investigational medication.

Investigational Medication

The investigational medication was administered as enteric coated tablets (400 mg) containing 4 mg *Rheum rhaponticum* dry extract as the only active ingredient (drug:extract ratio 16-26:1, extraction solvent calciumoxide:water, 1:38 [m/m]). Placebo was matched to a formulation of ERr 731 with regard to color, smell and taste, and viscosity. The medication was manufactured by Chemisch-Pharmazeutische Fabrik Göppingen, Carl Müller, Apotheker, GmbH & Co KG, Göppingen, Germany. On day 0, day 28, and day 56, women received 30 enteric coated tablets of either ERr 731 or placebo over a maximum time period of 12 weeks, according to their treatment group. Tablet intake started on day 1. Participants documented the consumption of investigational medication every day in their diaries.

Outcome Criteria

Primary outcome criterion for the efficacy of ERr 731 compared to placebo was the change of the MRS total score from day 0 to day 84:

$\Delta MRS_{day\ 84} = MRS_{day\ 0} - MRS_{day\ 84}$.

The Menopause Rating Scale (MRS) consists of 11 symptoms typically associated with the menopausal transition.[22] The individual MRS items recorded were (1) hot flushes, sweating; (2) heart complaints; (3) sleep problems; (4) depressive mood; (5) irritability; (6) anxiety; (7) physical and mental exhaustion; (8) sexual problems; (9) bladder problems; (10) vaginal dryness; and (11) joint and muscular discomfort.

These items were further categorized for analysis as "psychological," "somatic," and "urogenital." Subscales were calculated from the following item groups[23]:

- Psychological subscale: symptoms number 4, 5, 6, and 7;
- Somatic subscale: symptoms number 1, 2, 3, and 11; and
- Urogenital subscale: symptoms number 8, 9, and 10.

The MRS was recorded by both the investigators (in the eCRFs at each visit on day 0, day 28, day 56, day 84) and by the trial subjects in their diaries every week, using the following rating scale: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. The value of the total MRS score is between 0 and 44 points, with lower scores indicative of less severe menopausal symptoms.

Secondary outcome criteria used to determine efficacy were (1) the individual symptoms of the MRS, (2) the number and severity of hot flushes, (3) the Hot Flush Weekly Weighted Score (HFWWS), (4) the time until onset of treatment effect, and (5) treatment outcome according to Integrative Medicine Outcomes Scale (IMOS).[24]

The HFWWS was calculated from the daily assessment of the number and severity of hot flushes during the last week as follows: total number of slight hot flushes per week multiplied by 1, plus total number of moderate hot flushes per week multiplied by 2, plus total number of severe hot flushes per week multiplied by 3.[25]

Outcome criteria for safety were endometrial biopsy findings, transvaginal ultrasound, PAP smear, vaginal smear, mammography, breast tenderness, vital parameters, tolerability of investigational medication, adverse events, and laboratory safety parameters.

Response Criteria

The following 3 response criteria were used to determine which subjects had responded to treatment:

1. MRS total score < 24 points by the end of the trial (day 84);
2. Decrease of ≥10 points in MRS total score from baseline (day 0) to the end of the trial (day 84); and
3. Women fulfilling criterion number 1 and criterion number 2.

Trial Objective

This was a confirmatory trial to prove the superiority of ERr 731 when compared to placebo as determined using the primary outcome variable "change of the MRS from day 0 to day 84 ($\Delta MRS_{day\ 84} = MRS_{day\ 0} - MRS_{day\ 84}$)." For women who discontinued the trial, the

clinical findings at the time of discontinuation were used for the analysis of the primary outcome variable using the last observation carried forward (LOCF) method.

The null hypothesis was as follows:

H_0: Decrease of the MRS in the ERr 731 group is less than or equal to the decrease in the placebo group.

The alternative hypothesis was as follows:

$H_{1:}$ Decrease of the MRS in the ERr 731 group is larger than the decrease in the placebo group.

Statistical Methods

The trial was conducted according to a 3-stage group sequential design with adaptive sample size adjustments at the 2 interim analyses.[26] The adjusted 1-sided significance limits for the first, second, and third stages were α_i=0.00026, 0.00710, and 0.02253 (i=1, 2, 3) with the corresponding critical values 3.471, 2.454, and 2.004 and the information rates 0.333, 0.667, and 1, respectively.

The statistical evaluation was performed using the statistical software package SAS (release SAS 9.1.3, SAS Institute Inc, Cary, North Carolina). The primary efficacy comparison of the treatment groups was performed using a 2-factorial analysis of covariance with the 2 factors treatment and study site, and the baseline value as covariate. Study sites with less than 6 women (4 of 7 study sites) were pooled. Descriptive statistical methods were used to analyze baseline, secondary efficacy, and safety variables. Explorative *P* values were calculated for the comparison of ERr 731 with placebo on day 0 and day 84 (LOCF) using the 2-sample *t*-test. The data are presented as mean and standard deviation (SD) and [median] if not otherwise indicated.

RESULTS

Baseline Characteristics

In this trial, 171 women were screened for participation; 112 women were enrolled in the trial at 7 of 8 investigational sites (1 site failed to recruit any trial subjects). All enrolled trial subjects were randomized to treatment with ERr 731 (56 women) or placebo (56 women). All women in the ERr 731 and the placebo group were included in the intention-to-treat (ITT) analysis (Figure 1). Three (5.4%) women in the ERr 731 group and 2 (3.6%) women in the placebo group were excluded from the per-protocol (PP) analysis due

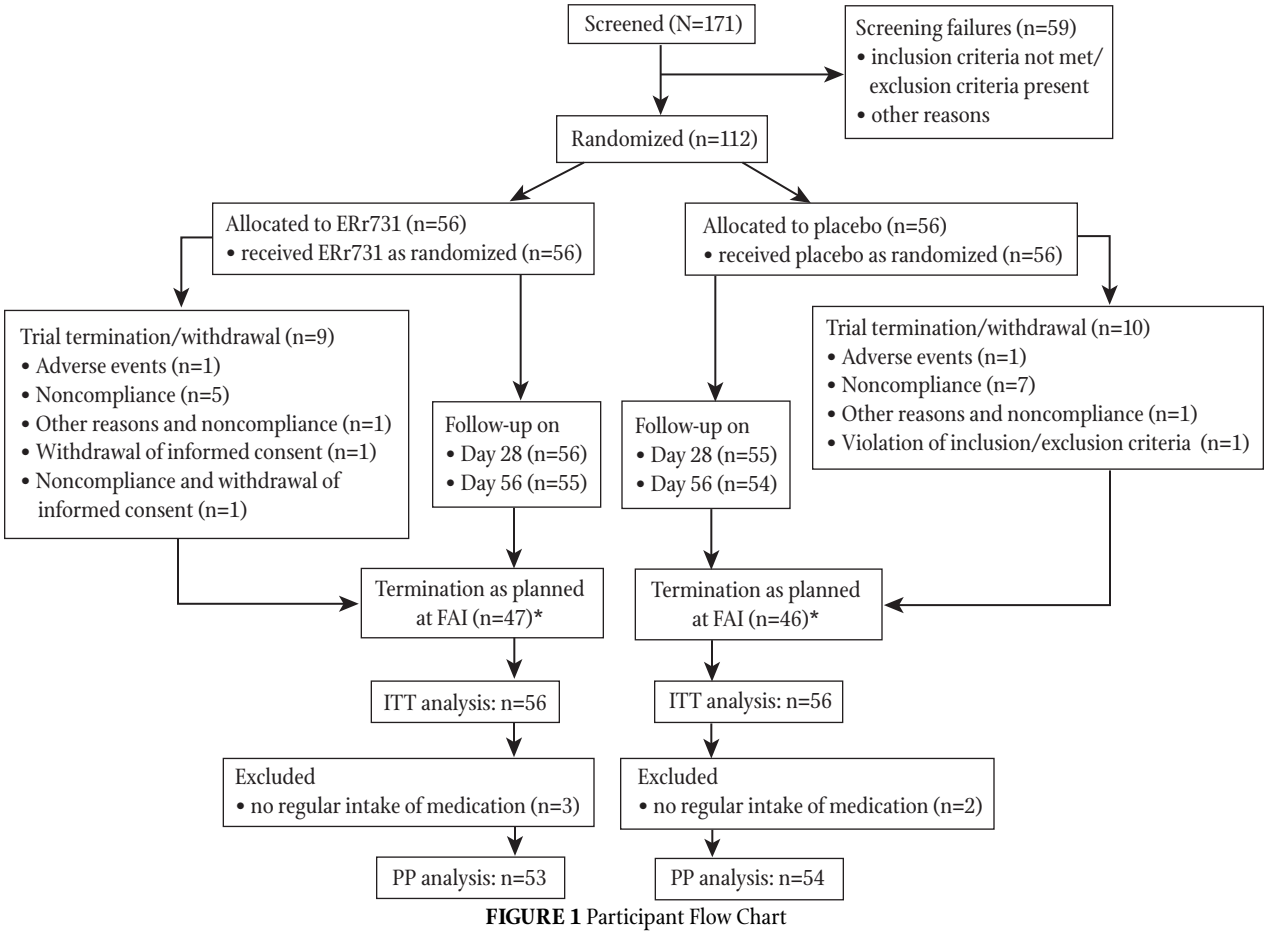

FIGURE 1 Participant Flow Chart

Individuals may have discontinued for more than one reason. For these trial subjects, all examinations and assessments were available at the Final Assessment I (FA I). Eighty-nine women who terminated the double-blind phase of the trial entered into a 52-week observational study with ERr 731. ITT indicates intention to treat.

to major protocol deviations. All planned examinations and assessments were available for 93 of 112 women at the end of the double-blind trial (FA I, Figure 1).

None of the baseline characteristics differed markedly between the treatment groups (Table 1). All women were perimenopausal when included in the trial, with their serum hormone levels showing large variations as expected during perimenopause. All women reported menstrual cycle irregularities during the previous 12 months. The time since last menstrual bleeding was slightly longer in the ERr 731 group (4.1 ± 3.6 [3.0] months) than in the placebo group (3.6 ± 3.5 [2.0] months). Previous gynecological diseases and surgeries were distributed similarly among the treatment groups (Table 1). The most frequently reported diseases and surgeries were salpingitis, uterine leiomyoma, and cervical diathermy.

TABLE 1 Demographic Data and Gynecological Findings at Screening*

Screening	ERr 731 (n=56)	Placebo (n=56)
Age, yrs (mean ± SD [median])	49.4 ± 3.6 [49.0]	49.6 ± 3.0 [49.0]
Height, cm (mean ± SD [median])	163.7 ± 5.3 [164.0]	164.0 ± 5.5 [165.0]
Weight, kg (mean ± SD [median])	68.9 ± 9.3 [70.0]	71.3 ± 8.9 [72.0]
Body mass index, kg/m^2 (mean ± SD [median])	25.7 ± 3.2 [26.0]	26.4 ± 2.7 [27.5]
Serum hormone levels (mean ± SD [median])		
17β-Estradiol, ng/L	110.3 ± 127.9 [49.4]	138.6 ± 159.2 [76.0]
FSH, IU/L	44.5 ± 36.7 [42.5]	36.2 ± 32.6 [19.3]
Polymenorrhea, n (%)	6 (10.7)	8 (14.3)
Oligomenorrhea, n (%)	20 (35.7)	23 (41.1)
Amenorrhea, n (%)	30 (53.6)	25 (44.6)
Intermenstrual bleeding, n (%)		
yes	0 (0)	1 (1.8)
no	56 (100.0)	55 (98.2)
Spotting, n (%)		
yes	0 (0)	1 (1.8)
no	56 (100.0)	55 (98.2)
Dysmenorrhea, n (%)		
yes	6 (10.7)	7 (12.5)
no	50 (89.3)	49 (87.5)
Complications concerning pregnancies, births, or abortions, n (%)		
yes	25 (44.6)	20 (35.7)
no	31 (55.4)	36 (64.3)
Previous gynecological diseases and surgeries, n (%)		
yes	38 (67.9)	39 (69.6)
no	18 (32.1)	17 (30.4)
Pretreatment of menopausal symptoms (during the past 6 months), n (%)		
yes	1 (1.8)	1 (1.8)
no	55 (98.2)	55 (98.2)

*Intention-to-treat population (N=112); FSH indicates follicle-stimulating hormone.

Duration of Treatment

The duration of treatment was comparable between the 2 treatment groups (ERr 731: 81.5 ± 9.7 [84.0] days, placebo 81.3 ± 12.4 [84.0] days).

Primary Outcome Criterion

At baseline (day 0), the MRS total score was 27.0 ± 4.7 [26.0] points in the ERr 731 group (n=56) and 27.0 ± 5.3 [26.0] points in the placebo group (n=56) (not significant, P=1.00, 2-sided t-test).

From baseline to day 84 (LOCF), the MRS total score decreased by -14.6 ± 5.1 [-15.0] points in the ERr 731 group (n=56) and -2.9 ± 4.3 [-2.0] points in the placebo group (n=56). The difference in the MRS total score between the 2 treatment groups on day 84 was highly significant (P<.0001; 95% confidence interval [-13.8 to -9.5], LOCF). The results from the PP analysis were consistent with the ITT analysis (data not shown). Figure 2 shows the change in the MRS total score in the ERr 731 group compared with the placebo group from day 0 to day 84 for those trial subjects for whom MRS assessments were available on day 84 (n=105, no LOCF).

Response Criteria

Using the response criteria defined earlier, the number of responders in the ERr 731 group (n=56, LOCF) was higher than in the placebo group (n=56, LOCF) in each category:

- response criterion 1: 54 (96.4%) women with ERr 731 vs 27 (48.2%) women with placebo;
- response criterion 2: 47 (83.9%) women with ERr 731 vs 2 (3.6%) women with placebo; and

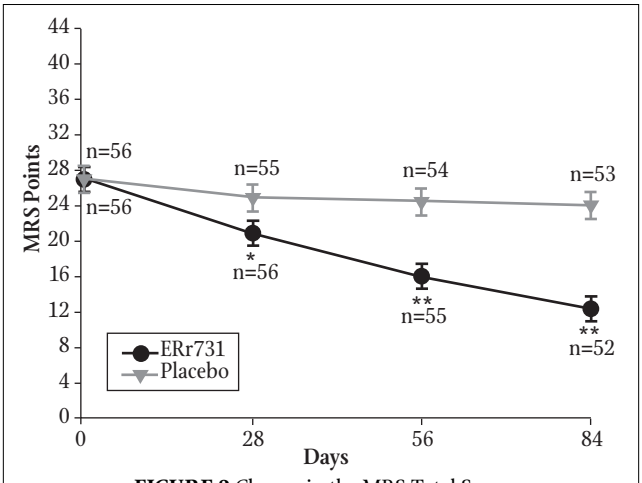

FIGURE 2 Change in the MRS Total Score

Presented is the decrease in the Menopause Rating Scale (MRS) total score from baseline to the third follow-up contact on day 84. The number of trial subjects, for whom MRS assessments in the electronic case report forms were available, is indicated for each time point. The significances were calculated for the differences between the treatment groups: *P<.001, **P<.0001.

- response criterion 3: 46 (82.1%) women with ERr 731 vs 2 (3.6%) women with placebo.

Diary-reported MRS

The diary-reported MRS total score in the ERr 731 group decreased continuously over the 84-day period, whereas the scores in the placebo group displayed a small decrease during the first week and then remained constant. This decrease (a mean of -2.4 points) was observed over the first week; scores then remained generally constant but returned to their original value before the next follow-up contact. This pattern was repeated over the next assessment periods (decreases of -1.5 points after day 28, -1.3 points after day 56, respectively [Figure 3]). The treatment success reported by the women in their diaries was consistent with that reported by the physicians at the follow-up contacts (Figure 2).

At the end of the RCT, the severity of the menopausal symptoms was significantly different in the 2 groups. The majority of the ERr 731 women reported to have no/mild (0-8 points) or moderate (9-16 points) symptoms on Day 84, while more than 80% of the placebo women still had severe (>17 points) symptoms (Figure 3).

Individual Symptoms of MRS

Analysis of the individual MRS symptoms showed that the majority of women in both treatment groups had moderate to very severe symptoms at baseline (Table 2). After 12 weeks, ERr 731 was effective in reducing symptoms, whereas the placebo group continued to report high incidences of each symptom. The difference between the groups on day 84 is highly significant for all MRS items. The analysis of the combined MRS items into the "psychological," "somatic," and "urogenital" subgroups showed that ERr 731

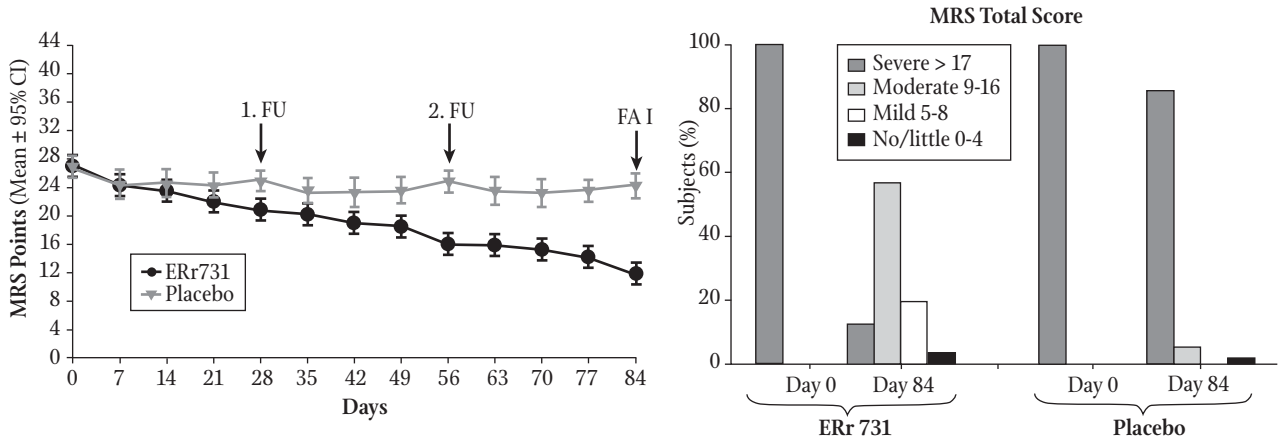

FIGURE 3 Change in the MRS Total Score as Assessed by the Women in Diary I

The Menopause Rating Scale (MRS) total score was assessed weekly by the women in diary I. Presented is the change from baseline to the third follow-up contact on day 84. The arrows indicate the time point of the scheduled visits of the women at their gynecological centers on day 28, day 56, and day 84. FU indicates follow-up contact; FA I, final assessment I.

TABLE 2 Changes in the Individual Menopause Rating Scale (MRS) Items*

MRS Item	ERr 731 (n=56) mean ± SD [median]			Placebo (n=56) mean ± SD [median]		
	Day 0	Day 84	Δ Day 0 to Day 84	Day 0	Day 84	Δ Day 0 to Day 84
1. Hot flushes/sweating‡	2.8 ± 0.9 [3.0]	1.0 ± 0.7 [1.0]	-1.7 ± 0.8 [-2.0]	2.9 ± 0.8 [3.0]	2.5 ± 1.1 [3.0]	-0.4 ± 0.9 [0.0]
2. Heart complaints‡	2.3 ± 0.9 [2.0]	1.2 ± 0.9 [1.0]	-1.1 ± 0.9 [-1.0]	2.4 ± 0.9 [2.0]	2.2 ± 0.9 [2.0]	-0.2 ± 0.9 [0.0]
3. Sleep problems‡	2.5 ± 1.1 [3.0]	1.0 ± 0.8 [1.0]	-1.5 ± 0.9 [-2.0]	2.4 ± 1.0 [2.0]	2.1 ± 0.8 [2.0]	-0.4 ± 0.9 [0.0]
4. Depressive mood‡	2.5 ± 1.1 [3.0]	0.8 ± 0.9 [1.0]	-1.8 ± 1.2 [-2.0]	2.7 ± 0.8 [3.0]	2.1 ± 0.8 [2.0]	-0.5 ± 0.7 [0.0]
5. Irritability‡	2.7 ± 0.8 [3.0]	1.1 ± 0.7 [1.0]	-1.6 ± 1.1 [-2.0]	2.9 ± 0.8 [3.0]	2.2 ± 0.7 [2.0]	-0.6 ± 0.8 [-1.0]
6. Anxiety‡	2.7 ± 1.0 [3.0]	1.1 ± 0.7 [1.0]	-1.6 ± 1.0 [-2.0]	2.7 ± 0.9 [3.0]	2.3 ± 0.9 [2.0]	-0.4 ± 0.9 [0.0]
7. Physical and mental exhaustion‡	2.7 ± 0.9 [3.0]	1.4 ± 0.6 [1.0]	-1.3 ± 0.9 [-1.0]	2.6 ± 0.9 [3.0]	2.5 ± 0.9 [3.0]	-0.1 ± 0.7 [0.0]
8. Sexual problems‡	2.4 ± 0.9 [2.0]	1.5 ± 0.7 [1.5]	-0.9 ± 1.0 [-1.0]	2.4 ± 1.0 [2.0]	2.3 ± 1.1 [2.0]	-0.1 ± 0.7 [0.0]
9. Bladder problems‡	1.9 ± 1.1 [2.0]	0.9 ± 0.8 [1.0]	-1.0 ± 0.9 [-1.0]	1.9 ± 1.0 [2.0]	1.7 ± 1.0 [2.0]	-0.2 ± 0.8 [0.0]
10. Vaginal dryness†	1.8 ± 1.2 [2.0]	1.1 ± 0.7 [1.0]	-0.7 ± 1.1 [-0.5]	1.7 ± 0.7 [2.0]	1.6 ± 0.8 [2.0]	-0.1 ± 0.6 [0.0]
11. Joint and muscular discomfort‡	2.8 ± 0.9 [3.0]	1.5 ± 0.9 [1.0]	-1.3 ± 1.1 [-1.0]	2.5 ± 0.8 [3.0]	2.6 ± 0.8 [3.0]	0.1 ± 0.6 [0.0]

*Intention-to-treat population (n=112). The significances were calculated for the difference between both treatment groups on Day 84: †P<.001, ‡P<.0001 (t-test, 2-sided, last observation carried forward).

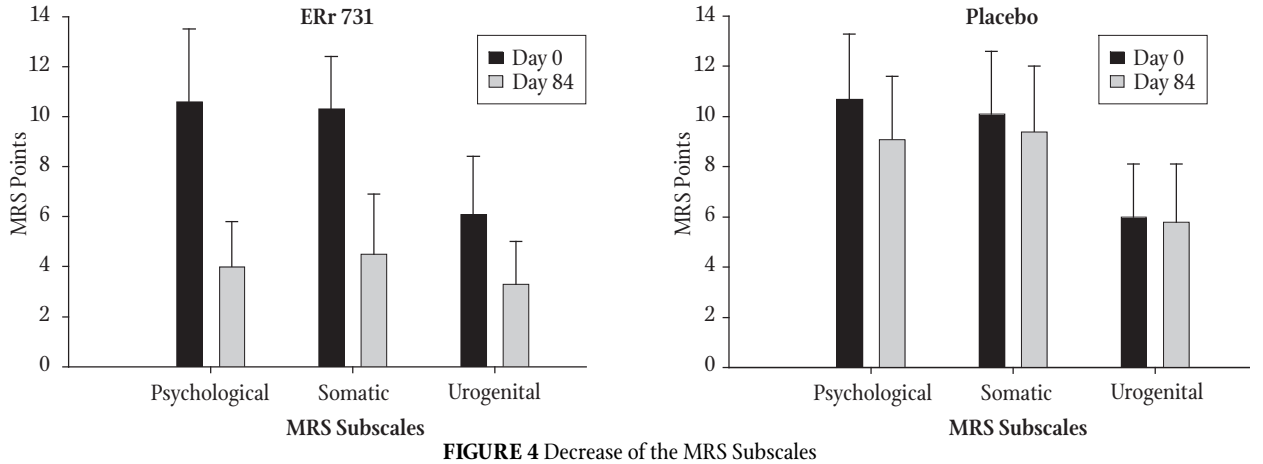

FIGURE 4 Decrease of the MRS Subscales

Presented is the decrease of the Menopause Rating Scale (MRS) subscales "psychological," "somatic," and "urogenital" with ERr 731 compared to placebo from baseline to the third follow-up contact on day 84.

was most effective in reducing symptoms in the "psychological" and "somatic" subscales (Figure 4).

Hot Flushes

On entry to the study, all women were experiencing an average of 12 hot flushes per day (Figure 5), and there was no difference between the treatment groups (ERr 731: 11.4 ± 5.8 [12.0] hot flushes, placebo: 12.1 ± 6.0 [12.0] hot flushes, Table 3).

By day 84, a significant reduction in the number of hot flushes was observed in women in the ERr 731 group when compared to placebo (Figure 5). Moderate and severe hot flushes decreased to a larger extent with ERr 731 than with placebo (Table 3). One woman did report an increase in hot flushes following ERr 731 intake, but on average, women taking ERr 731 were experiencing 2.8 ± 2.8 [2.0] hot flushes per day after 12 weeks.

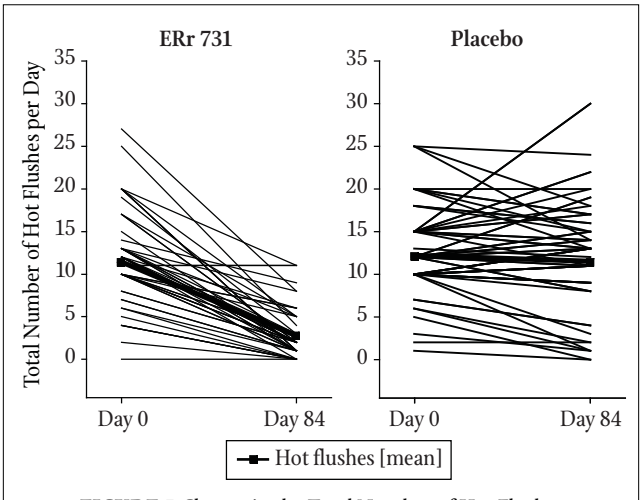

FIGURE 5 Change in the Total Number of Hot Flushes

The total number of hot flushes during the last 24 hours on day 0 and day 84 was plotted for each individual patient in the ERr 731group (n=46) and the placebo group (n=43) of the double-blind trial ERr 004-DB. The thick lines represent the change in the mean values of hot flushes per day from day 0 to day 84.

In contrast, women in the placebo group experienced variable changes in hot flushes: some reduction, some not changing, and some deterioration (Figure 5). By 12 weeks, the women in the placebo group still had an average of 11.4 ± 6.8 [13.0] hot flushes per day, most of them being moderate to severe (Table 3).

On entry to the trial, women had an average of 84 hot flushes per week, with most of the trial subjects reporting >60 moderate to severe hot flushes in this period. Thus, the HFWWS on entry was 121.83 ± 75.9 [120.5] points in the ERr 731 group and 144.96 ± 81.6 [158.0] points in the placebo group. The difference between the groups is not significant (P=.13, 2-sided t-test).

In the ERr 731 group, the HFWWS decreased to 23.9 ± 27.5 [13.0] points from day 1 to day 84, but it remained high in the placebo group (137.6 ± 95.9 [147.0] points, LOCF). The 95% CI for the differences in HFWWS between the 2 treatment groups (ERr 731 minus placebo) on day 84 (LOCF) was calculated as [-140.3 to -87.0] (P<.0001, 2-sided t-test).

Treatment Outcome

On day 84 (LOCF), 44 (78.6%) women in the ERr 731 group but only 2 (3.6%) women in the placebo group reported a major improvement. Ten (17.9%) women in the ERr 731 group and 5 (8.9%) women in the placebo group reported slight to moderate improvement, and the majority of women in the placebo group (47 of 56 [83.9%]) reported no change. In the ERr 731 group, 2 of 56 (3.6%) women reported no change following treatment. One woman in the placebo group (1.8%) and no women from the ERr 731 group reported a deterioration of their condition. The investigator-reported changes of treatment outcome confirmed the ratings given by the women themselves (data not shown).

Adverse Events

Fourteen adverse events and no serious AEs were reported during the study. Eleven AEs were reported by women in the ERr 731 group (all assessed as "moderate") and 3 by women in the placebo group (2 mild and 1 moderate, Table 4). Three AEs in the ERr

TABLE 3 Decrease in the Number and Severity of Hot Flushes from Day 0 to Day 84*

Number and Severity of Hot Flushes	ERr 731 mean ± SD [median]					Placebo mean ± SD [median]				
	Day 0	n†	Day 84	n†	Δ Day 0 to Day 84	Day 0	n†	Day 84	n†	Δ Day 0 to Day 84
Total	11.4 ± 5.8 [12.0]	53	2.8 ± 2.8 [2.0]	48	-9.3 ± 5.2 [-9.0]	12.1 ± 6.0 [12.0]	50	11.4 ± 6.8 [13.0]	49	-0.7 ± 4.6 [-1.0]
Mild	5.4 ± 2.3 [5.0]	49	2.5 ± 2.1 [2.0]	44	-2.8 ± 2.8 [-2.5]	5.3 ± 2.6 [5.0]	47	4.8 ± 3.0 [5.0]	48	-0.3 ± 2.6 [0.0]
Moderate	4.3 ± 1.7 [4.0]	48	0.7 ± 1.2 [0.0]	27	-3.8 ± 1.8 [-4.0]	4.7 ± 2.6 [5.0]	47	4.6 ± 4.4 [4.0]	45	-0.2 ± 3.2 [0.0]
Severe	4.3 ± 1.7 [4.5]	32	0.4 ± 0.8 [0.0]	7	-5.2 ± 1.1 [-5.0]	4.3 ± 1.1 [5.0]	32	3.5 ± 2.2 [3.0]	35	-0.3 ± 2.2 [0.0]

*Intention-to-treat population (N=112).
†Number of women who reported their hot flushes in their diaries.

731 group (vertigo, asthenia, and headache) were assessed as having a possible causal relationship to the intake of ERr 731. These AEs all occurred in the same woman and were reported 6 weeks after starting intake of ERr 731. They disappeared the day after the woman discontinued the intake of ERr 731. All other reported AEs were assessed as not being related to the study medication. None of the AEs in women in the ERr 731 group were associated with gynecological organs or tissues.

Liver and Hematology Parameters

Serum levels for liver and hematology parameters were measured at baseline and again at the end of the trial. The majority of women in both treatment groups had liver enzyme serum levels within the normal range, and no differences in these parameters between the groups were seen. Values outside the normal range were assessed by the investigators as not being clinically relevant (Table 5). No clinically relevant deviations from the normal range were observed for the hematological parameters (data not shown).

The results of endometrial biopsies, mammography, vaginal cytology, and other safety parameters will be reported separately, together with the results of the open observational study with ERr 731 intake for 52 weeks that followed this study (results currently being analyzed).

TABLE 4 Details on Adverse Events*

Adverse Events (AEs) per Subject	ERr 731 (n=56) 5 women with AEs			Placebo (n=56) 3 women with AEs		
	n	Intensity	Relation to study medication (cause)	n	Intensity	Relation to study medication (cause)
Vertigo Headache Depression Sleep disorder	1	Moderate Moderate Moderate Moderate	No (other known cause) No (other known cause) No (other known cause) No (other known cause)			
Asthenia Vertigo Headache	1	Moderate Moderate Moderate	Possibile Possibile Possible			
Pneumonia (chlamydial)	1	Moderate	No (concomitant illness)			
Respiratory tract infection (viral)	1	Moderate	No (unknown)			
Hypoaesthesia Sleep disorder	1	Moderate Moderate	No (other known cause) No (other known cause)			
Facial swelling				1	Mild	No (unknown)
Increase in blood pressure				1	Moderate	No (unknown)
Endometrial polyp				1	Mild	Unlikely

*Safety population n=112, "no" indicates no causal relationship to the investigational medication.

TABLE 5 Liver Parameters*

Parameter	ERr 731 mean ± SD [median]			Placebo mean ± SD [median]		
	Day 0	Day 84	Δ Day 84 to Day 0	Day 0	Day 84	Δ Day 84 to Day 0
ALT [IU/L]	21.8 ± 16.2 [16.7] n = 56	24.4 ± 25.1 [14.9] n = 50	1.9 ± 19.6 [-1.2] n = 50	17.6 ± 6.8 [16.4] n = 55	19.7 ± 7.6 [19.4] n = 52	1.7 ± 6.3 [2.0] n = 52
AST [IU/L]	21.9 ± 13.3 [18.2] n = 56	23.1 ± 14.0 [19.8] n = 50	0.7 ± 9.0 [0.5] n = 50	20.1 ± 4.1 [19.8] n = 55	21.9 ± 6.3 [21.4] n = 52	1.6 ± 5.8 [-0.1] n = 52
γ-GT [IU/L]	25.1 ± 28.5 [16.6] n = 56	30.8 ± 40.5 [18.9] n = 50	4.6 ± 29.7 [0.7] n = 50	20.6 ± 11.0 [17.6] n = 55	23.9 ± 17.7 [18.8] n = 52	3.1 ± 14.0 [0.3] n = 52
Total bilirubin [mg/dL]	0.58 ± 0.23 [0.53] n = 56	0.67 ± 0.63 [0.56] n = 50	0.10 ± 0.62 [0.02] n = 50	0.51 ± 0.20 [0.49] n = 55	0.55 ± 0.23 [0.54] n = 52	0.04 ± 0.24 [0.00] n = 52
Direct bilirubin [mg/dL]	0.11 ± 0.07 [0.11] n = 56	0.14 ± 0.06 [0.13] n = 50	0.03 ± 0.07 [0.02] n = 50	0.11 ± 0.07 [0.11] n = 55	0.13 ± 0.09 [0.13] n = 52	0.02 ± 0.10 [0.00] n = 52
Indirect bilirubin [mg/dL]	0.47 ± 0.19 [0.42] n = 56	0.46 ± 0.17 [0.44] n = 50	-0.00 ± 0.22 [-0.01] n = 50	0.40 ± 0.17 [0.38] n = 55	0.43 ± 0.18 [0.44] n = 52	0.03 ± 0.21 [0.00] n = 52

*Intention-to-treat population (N=112). Indicated is the number of trial subjects for which blood samples were taken on day 84. AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyltransferase.

Tolerability

The medication was well tolerated by the majority of women from both treatment groups. On Day 84 (LOCF), tolerability was reported to be "very good" in 25 (44.6%) and "good" in 28 (50%) women in the ERr 731 group, compared to 11 (19.6%) and 44 (78.6%) women, respectively, in the placebo group. In the ERr 731 group, 2 (3.6%) women assessed the tolerability as "moderate" and 1 (1.8%) woman as "bad."

DISCUSSION

The study was undertaken to confirm the superiority of ERr 731 when compared to placebo for the treatment of menopausal symptoms using a clinical trial design that repeated and strengthened the results of previous studies.[6,19] The data obtained has confirmed these results and the experience of practitioners over many years recommending ERr 731 for the treatment of menopausal symptoms.

The trial included only those perimenopausal women with an MRS total score of ≥18 points (≥17 is indicative of moderate to severe menopausal symptoms[22]) and thus, with a mean MRS total score of 27.0 ± 5.0 points at baseline, all the women were experiencing moderate to severe menopausal symptoms on entry. This population was selected to introduce sufficient power in the trial design to be able to (1) clearly detect any differences between the ERr 731 and placebo groups, (2) to examine the effects on the individual as well as the total MRS item scores, and (3) to investigate the effects of ERr 731 compared to placebo on hot flushes and the HFWWS as a predictor of treatment success.

The effectiveness of ERr 731 in reducing both the frequency and severity of menopausal symptoms was confirmed by all measures studied. The MRS total score (which provides a better overall measure of well-being in these women than the individual MRS items) had decreased significantly from day 1 to day 84 in the ERr 731 group, unlike the placebo group. The difference in scores at this time (ERr 731 minus placebo) was also highly significant, confirming the superiority of ERr 731 in alleviating menopausal symptoms.

These results also support the use of the total MRS score for comparing menopausal symptoms between perimenopausal and/or postmenopausal women, as this scale dampens the large variations seen in the individual parameters between individual women. This is perhaps not unexpected, since perimenopausal women are known to experience strong fluctuations in their endogenous estradiol and follicle-stimulating hormone (FSH) levels, and thus, hot flushes and other individual menopausal symptoms may undergo significant swings during these changes, unlike in postmenopausal women, where the hormonal fluctuations are less pronounced.

This may also explain in part the statistically weak placebo effects observed in the current study, despite the fact that individual placebo subjects experienced reductions, increases, or no change in their MRS scores (Figure 5). It is also likely that the severity of the symptoms (~84 hot flushes per week, of which up to 70% were classified as moderate or severe) would contribute to a lack of placebo effect, since this group of women are clearly experiencing predominately physiologically induced symptoms. This is in contrast to other trials reporting placebo effects where much lower baseline levels are reported (eg, 50 moderate to severe hot flushes per week[3]; 21 to ≥42 per week[27-29]).

The MRS subscales provide a valuable insight into the primary reasons for these improvements with ERr 731. The effectiveness of ERr 731 on vasomotor and psychological symptoms was already reported in the first published clinical trial[6,19] and is confirmed here. This study also collected data using different

assessment scales for quality of life, anxiety, and depression, and the preliminary results from these instruments also support the effectiveness of ERr 731 in reducing psychological and vasomotor symptoms (manuscript in preparation). It is also clear that similar effects are present in some individual MRS scores.

Hot flushes are significantly decreased, both in frequency and severity, by ERr 731.

After 12 weeks' treatment, women taking ERr 731 had on average 2.8 hot flushes per day, compared to 11.4 hot flushes per day in the placebo group. The reduction in frequency was proportional to the baseline frequency: women with a higher number of hot flushes (≥10 per day) experienced a more pronounced alleviation of symptoms than women with less than 10 hot flushes per day. In contrast, several women in the placebo group with baseline frequencies of ≥10 hot flushes per day reported increases in the number of hot flushes over the course of the study. This group displayed many different individual trends, however, as shown by the individual hot flush records in Figure 5. These results are similar to those observed in a previous study, where it also was reported that moderate to severe hot flushes did not change significantly following a 12-week intake of placebo.[6]

Similar results are also seen from the calculation of the HFWWS. Whereas the placebo group continued to have scores of about 135 points over the 12-week trial period, the scores for the ERr 731 treated group decreased to about 25 points, due predominately to the reduction in severe hot flushes because the HFWWS is more sensitive to changes in severe hot flushes.

The HFWWS has been used successfully to assess the efficacy of HT products and also a black cohosh extract.[25,30] This offers the possibility to compare the efficacy of ERr 731 seen here with that of HT from other trials. For example, a recent RCT investigating the effect of ultra-low-dose oral hormone therapy in postmenopausal women reported a decrease of the mean HFWWS to 35.8 points in the group receiving 0.5 mg 17β-estradiol plus 0.1 mg norethisterone acetate (NETA) and to 26.6 points in the group receiving 0.5 mg 17β-estradiol plus 0.25 mg NETA after 12 weeks.[3] These values are similar to those reported here for ERr 731 and suggest that ERr 731 may be an effective alternative to ultra-low-dose HT, particularly in perimenopausal women for whom HT is not recommended.

No gynecological AEs were reported in this RCT in any women taking ERr 731, and all of the reported AEs were classified as mild or moderate. These results are similar to those reported for ERr 731 previously.[6] Three AEs (all experienced by the same woman) were considered to have been possibly related to the intake of ERr 731, but it could not be determined how the extract may have caused these effects. The good safety profile was confirmed by the laboratory safety parameters that showed no changes of any clinically relevance, with most values remaining within the normal range throughout the trial. In contrast, the values of FSH and 17β-estradiol levels displayed large individual variations, which are expected to be found in perimenopausal women and present no safety issues. None of the participants reported problems with tolerating the product over this study period.

CONCLUSION

The results of this double-blind, placebo-controlled clinical replication trial confirm that ERr 731 is superior in efficacy when compared to placebo for the treatment of menopausal symptoms and is particularly effective at alleviating the vasomotor and psychological symptoms of menopause.

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Marianne Heger passed away on August 24, 2005, before the results of her medical and scientific contributions to this paper could be realized. Her fellow authors pay tribute to the leadership, guidance, and enthusiasm she contributed that were critical to the successful completion of these studies.

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