

ORIGINAL RESEARCH

EFFICACY OF THE SPECIAL EXTRACT ERr 731 FROM RHAPONTIC RHUBARB FOR MENOPAUSAL COMPLAINTS: A 6-MONTH OPEN OBSERVATIONAL STUDY

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Background • The special extract ERr 731 from the roots of rhapontic rhubarb has been in widespread use in Germany since 1993, and the current regulations have required an evaluation of its risk:benefit ratio in daily use.

Objective • To demonstrate the efficacy and tolerability of ERr 731 in menopausal women in everyday practice.

Design • Three hundred sixty-three menopausal women with menopausal symptoms were enrolled at 70 German gynecological practices and received ERr 731 for 6 months. Women visited the practices for a baseline assessment and after 3 and 6 months.

Main Outcome Measures • Primary outcome criterion was the change of the Menopause Rating Scale (MRS) total score after 6 months. Other assessments included compliance, tolerability, health-related quality of life, and occurrence of adverse events.

Results • After 6 months of treatment with ERr 731 in 252 women, there was a significant decrease of the MRS total score from 14.5 points at baseline to 6.5 points ($P < .0001$). The reduction of the MRS score was more pronounced in women with a score of ≥ 18 points at baseline. One tablet per day was sufficient to reduce the symptoms significantly in the majority of women. The health-related quality of life improved markedly. A good or very good treatment outcome was reported by the majority of the participating women. One adverse event was reported that was assessed as having no relation to ERr 731 intake.

Conclusion • ERr 731 is a well-tolerated and safe medication for the successful treatment of menopausal symptoms in peri- and postmenopausal women. (*Altern Ther Health Med*. 2008;14(6):32-38.)

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The most frequently occurring symptoms of menopause are hot flushes and psychosomatic complaints, followed by vaginal dryness, and they all exert a profound impact on the quality of life of sufferers. The special extract ERr 731 (trade name Phyto-Strol® and Phyto-Strol Loges®, Chemisch-Pharmazeutische Fabrik Göppingen, Carl Müller, Apotheker, GmbH & Co KG, Göppingen, Germany) has been an established treatment for menopausal symptoms in women in Germany since 1993.¹ ERr 731 is derived from the roots of rhapontic rhubarb (*Rheum rhaponticum*), also known as Siberian rhubarb. The constituents of the standardized extract ERr 731 (drug:extract ratio 16-26:1,

extraction solvent calcium oxide: water, 1:38 [mass/mass]) are rhaponticin, desoxyrhaponticin, rhapontigenin, and desoxyrhapontigenin. They are all-natural hydroxystilbenes and are structurally related to resveratrol, which is found in red wine.² One tablet of Phyto-Strol 400 mg contains 4 mg of ERr 731.

ERr 731 is well known as an effective and safe medication for the treatment of menopausal symptoms. The recently published results from a 12-week multicenter, prospective, randomized, double-blind, placebo-controlled, clinical trial with 109 perimenopausal women showed that ERr 731 alleviates menopausal symptoms in perimenopause quickly and effectively.¹ At the end of the trial, endometrial biopsies, bleeding, body weight, blood pressure, pulse, and laboratory parameters revealed no significant differences among the treatment groups, and there were no adverse events associated with the intake of ERr 731. Importantly, an excellent long-term efficacy, tolerability, and safety profile has been demonstrated in a subsequent open-label observational study with ERr 731 intake over 48 and 96 weeks.³

A second placebo-controlled clinical trial recently submitted for publication with ERr 731 in 112 perimenopausal women also confirmed its efficacy and safety. In summary, this medication appears to be safe and effective in perimenopausal women for

alleviating menopausal symptoms and can be recommended when hormone therapy (HT) is not indicated.⁴

Rhubarb preparations, and particularly the roots of the medicinal rhubarb plants (*R officinale*, *R palmatum*, *R polygonatum*), are traditionally used as laxatives because they contain anthraquinone glycosides such as emodin and aloë-emodin, which are the active constituents in this indication.⁵ Medicinal rhubarbs are not the same species as the garden rhubarb used for food.

Commercially available rhubarb products have marked variations in the content of their active compounds and should be used with caution. For example, rhubarb root can cause severe diarrhea and abdominal cramps and lead to potassium depletion.⁶ Therefore, treatment with laxative doses should not exceed 8 to 10 days to prevent addiction and laxative abuse.⁶ People with a history of renal stones should also avoid rhubarb due to the oxalate content. In women's health, these medicinal rhubarb species are specifically used for the treatment of constipation in pregnant women.^{7,8} In all cases, the presence of emodin or rhein in these preparations may increase the risk of unwanted side effects in the breast and endometrium due to the known potent estrogen receptor-activation properties of these compounds.^{9,10}

High-performance liquid chromatography (HPLC) analysis has confirmed that, in contrast to other medicinal rhubarb species, neither the roots of *R rhaponticum* nor the special herbal extract ERr 731 of the roots contains any emodin, aloë-emodin, or rhein. Thus, neither laxative nor other effects are associated with the plant or the special extract. Consequently, menopausal women, who often require relief over several years, can take ERr 731 in its proposed indication of "relief of climacteric symptoms" safely as a long-term therapy.

METHODS

Study Design

The study was a prospective, multicenter open observational study (PMS) of ERr 731. Data were entered into electronic case report forms (web-enabled eCRF) by the investigators at each of the 3 visits. Three hundred sixty-three menopausal women in perimenopause or postmenopause were enrolled from May 2005 to February 2006 in 70 German gynecological practices. Two hundred fifty-two of the 363 women remained in the study for the full 6-month period.

Disposition of Participating Women

Three hundred sixty-three women were enrolled into the ERr 731 PMS (intent-to-treat [ITT] population). Three hundred fifty-three of 363 women who took at least 1 tablet of ERr 731 were included in the tolerability population. The per-protocol (PP) population consisted of 191 women; 172 women were excluded due to protocol deviations. More details about the allocation of the participating women to different analysis groups are shown in Figure 1.

Inclusion Criteria

Only menopausal women were included in the PMS. The time of their last menstrual bleeding was used to categorize them

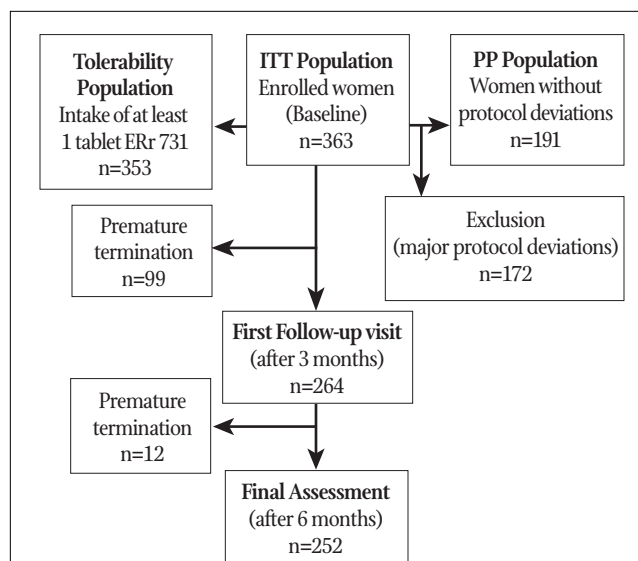


FIGURE 1 Allocation of Women to the Different Analysis Populations*

*ITT indicates intent-to-treat; PP, per-protocol.

at the baseline visit as either perimenopausal (break in cycle regularity during the past 12 months or last menstruation at least 3 but no more than 12 months ago)¹¹ or as postmenopausal (last menstruation more than 12 months ago).¹²

Exclusion Criteria

Exclusion criteria included the following:

- hormone treatment for menopausal symptoms during the past 3 months before enrollment into the PMS;
- simultaneous treatment of menopausal symptoms with other medications (eg, soy, red clover, black cohosh, hormone therapy);
- previous or present treatment with ERr 731;
- known or suspected hypersensitivity to ERr 731 or one of its components;
- pregnancy and breast-feeding;
- unsettled bleeding; and
- existing or suspected estrogen-dependent tumor.

Outcome Criteria

The primary outcome criterion for the efficacy of ERr 731 was the change of the Menopause Rating Scale (MRS)¹³ total score from baseline to final assessment. The MRS consists of 11 symptoms typically associated with the menopausal transition. Symptoms were assessed using a 5-level rating scale with a maximum of 4 points (0=none, 1=mild, 2=moderate, 3=severe, 4=very severe). The total MRS score ranges from 0 to 44 points; the lower the score, the less severe are the woman's menopausal symptoms. A decrease of the MRS total score, is therefore indicative of the relief of the menopausal symptoms.

Secondary outcome criteria were the change of the MRS total score in the following subgroups: high/low initial MRS values (≥ 18 points/ ≤ 18 points), the daily dosing and the women's

compliance, and a possible correlation between the success of therapy and the women's status at baseline (eg, decrease of symptoms depending on the initial MRS score or on previous treatment with herbal medicine or hormones). Further assessments were the tolerability of ERr 731, health-related quality of life (EuroQol Visual Analog Scale [EQ-VAS]), treatment outcome using the Integrative Medicine Outcome Scale (IMOS), and the occurrence of adverse events.

Statistical Analysis

The statistical analysis of the primary outcome criterion was based upon the ITT population (n=363 women, who took at least 1 tablet of ERr 731) and for whom data had been collected in the course of the PMS or upon the PP population (n=191). All analyses were conducted using the last-observation-carried-forward (LOCF) principle. Each woman was to be observed over a time period of 6 months, with 3 planned visits to the practice (baseline visit, follow-up visit after 3 months, and a final assessment visit after 6 months). The recommended dosage was 1 tablet ERr 731 once daily, but each patient was advised to take 1 or more tablets daily at the discretion of the gynecologist.

RESULTS

Baseline Characteristics

The Table presents an overview of the women's data concerning age, weight, height, body mass index (BMI), and gynecological anamnesis.

Pretreatment, Concomitant Illnesses and Medication, and Risk Factors

Before inclusion in the PMS, 142 of 363 women (39.1%) had

received some form of treatment for menopausal symptoms: hormone therapy (110 women, 30.3%), herbal medication (43 women, 11.9%). Seven women (1.9%) received another treatment, and 3 women (0.8%) failed to answer. Multiple responses were possible.

Concomitant illnesses and risk factors were present in 155 of 363 women (42.7%). The most prominent were smoking (63 women, 17.4%), hypertonia (56 women, 15.4%), hyperlipidemia (14 women, 3.9%), diabetes (5 women, 1.4%), and obesity (56 women, 15.4%). Other concomitant illnesses and risk factors were reported by 33 women (9.1%). Eleven (3.0%) women gave no answer. Eighty-four (23.1%) women received medication for concomitant illness over the study period. Concomitant medication included beta blockers (27 women, 7.4%), thyroid hormones (25 women, 6.9%), ACE-blocker/AT-1 antagonists (10 women, 2.8%), psycholeptics/psychoanaleptics (13 women, 3.6%), calcium antagonists (5 women, 1.4%), and analgesic (4 women, 1.1%).

Intake of ERr 731

Over the first 3 months, 243 women took 1 tablet once daily, 13 women took 2 tablets per day, and 1 woman took 4 tablets per day. Over the total study period of 6 months, 228 women took 1 tablet once daily, and 6 women took 2 tablets per day as recommended.

Duration of Treatment and Compliance

Two hundred fifty-two of 363 (69.4%) women completed the PMS as planned. One hundred eleven of 363 (30.6%) women prematurely terminated the PMS (Figure 1). The principal reasons for premature termination were lack of data entries by the investigators at the follow-up visits or a failure by the women to

TABLE Baseline Characteristics*

Baseline characteristics	Number of Women	Values	Range
Age (years)	346	53.1 ± 6.1	39-71
Height (cm)	362	165 ± 5.8	147-180
Weight (kg)	362	69.6 ± 11.1	46-132
BMI (kg/m ²)	362	25.5 ± 4.0	16.7-43.1
Number (%) of women in			
Perimenopause		145 (40.4%)	NE
Postmenopause		214 (59.6%)	NE
Menstrual bleeding			
Duration since last menstrual bleeding (years)	343	4.7 ± 6.4	0-34
Duration of last menstrual bleeding (days)	310	15 ± 2.1	1-20
Number (%) of women with spotting			
Total		14 (3.9%)	NE
Perimenopausal		12 (3.3%)	NE
Postmenopausal		2 (0.6%)	NE
Number (%) of women with			
Regular menstruation		117 (32.2%)	NE
Polymenorrhoea		26 (7.2%)	NE
Oligomenorrhoea		56 (15.4%)	NE
Amenorrhoea		154 (42.4%)	NE

*Intent-to-treat population (N=363). Values are presented as mean ± SD (%) if not otherwise indicated. BMI indicates body mass index; NE, not evaluated.

comply with the timing of the follow-up visits. Only 23 women withdrew from the PMS due to lack of efficacy, bad tolerability, or poor compliance.

The duration of treatment was 186.0 ± 33.3 days. Ninety-five percent of the women reported a regular intake of ERr 731, with more than 90% of the women demonstrating a “very good” or “good” compliance at both follow-up visits.

Change in the MRS Total Score

At baseline, a mean total score of 14.4 ± 7.5 points was assessed for all women ($n=363$, ITT). The highest individual scores were observed for hot flushes/sweating followed by irritability and sleep problems, and 42.2% of the women assessed the occurrence of hot flushes/sweating as “severe” or “very severe.” More than 50% of the women reported “none” or only “mild” symptoms for 8 of the 11 scores.

During the course of the PMS, a decrease of the mean MRS total score from 14.5 ± 7.4 points at baseline ($n=342$) to 9.0 ± 5.6 points at the first follow-up visit after 3 months ($n=263$) to 6.7 ± 4.7 points after 6 months (final assessment, $n=250$) was observed.

In the group of women who completed the study as planned ($n=252$, Figure 1), the intake of ERr 731 resulted in a highly significant decrease of the MRS total score from 14.5 ± 7.4 points at baseline to 6.9 ± 4.9 points at the final assessment (-7.9 ± 6.3 points, LOCF; $P<.0001$; Wilcoxon’s matched pairs rank test, Figure 2).

Decrease in the MRS Single Item Scores

Figure 3 shows the change from baseline to final assessment of the 3 defined MRS subscales “somatic,” “psychological,” and “urogenital.”¹⁴ In each case, a decrease in scores was observed.

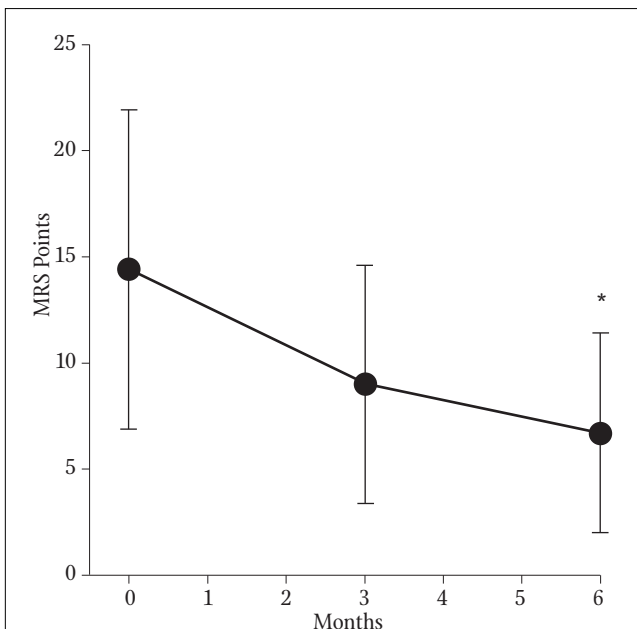


FIGURE 2 Decrease of the MRS Total Score (mean \pm SD) in All Women From Baseline to 3 and 6 Months of Treatment With ERr 731
* $P<.0001$ (highly significant)

The largest changes were observed for the symptoms “hot flushes/sweating” (-1.5 points), sleep problems (-1.1 points), irritability (-0.9 points), depressive mood (-0.8 points), and physical and mental exhaustion (-0.8 points). These items belong either to the psychological or the somatic subscale. Changes in the urogenital subscale scores were less pronounced. The decrease of each single MRS item was highly significant (LOCF; $P<.0001$; Wilcoxon’s matched pairs rank test).

Change in the MRS Total Scores in Different Subject Subgroups

Changes in menopausal symptoms also were assessed in different subject subgroups (Figure 4). The most pronounced decrease was determined for the subgroup of women who had a high baseline MRS total score (>18 points; ie, reporting “severe” to “very severe” symptoms).¹³ During the 6 months of treatment, they experienced a decrease of the MRS total score of 13.8 ± 5.8 points, which was highly significant compared to the baseline value ($P<.0001$; Wilcoxon’s matched pairs rank test).

The comparison of the mean MRS total scores in the perimenopausal ($n=145$) and postmenopausal women ($n=214$) subgroups showed a higher baseline value of 15.6 ± 7.5 points for the postmenopausal women vs 12.9 ± 7.0 points in perimenopausal women. It decreased to 6.9 ± 4.7 points in postmenopausal women and to 6.3 ± 4.8 points in perimenopausal women. Thus, the overall decrease of the MRS total score from baseline to the final assessment was more pronounced in postmenopausal than in perimenopausal women. The sample size in the other subgroups was too small to determine the statistical significance of the observed changes.

Changes in Health-related Quality of Life

The current health state was assessed using the health-related quality of life score EQ-VAS.^{15,16} At baseline, the mean EQ-VAS score was 64.1 ± 16.8 points (scale 0 to 100, whereby 0 indicates “the worst imaginable health state” and 100 “the best imaginable health state”).

Over the course of the PMS, an increase in the EQ-VAS score was observed. At the first follow-up contact, it had increased to 75.9 ± 14.5 points, and at the final assessment to 80.8 ± 13.3 points. The increase in the EQ-VAS score demonstrates an overall improvement in the reported state of health, with the maximum improvement already observable within the first 3 months following intake of ERr 731 (Figure 5).

Treatment Outcome

Treatment outcome was assessed using the IMOS, a 5-point scale that rates whether a subject has achieved “complete recovery,” “major improvement,” “slight to moderate improvement,” “no change,” or “deterioration.” After 3 months of treatment, almost half of the women reported a “major improvement” of symptoms (43.2%) or a “complete recovery” (4.9%). After a further 3 months of ERr 731 intake, the proportion of women reporting “complete recovery” had increased to 13.1%, with those reporting a “major improvement” also increasing (56.4%) (Figure

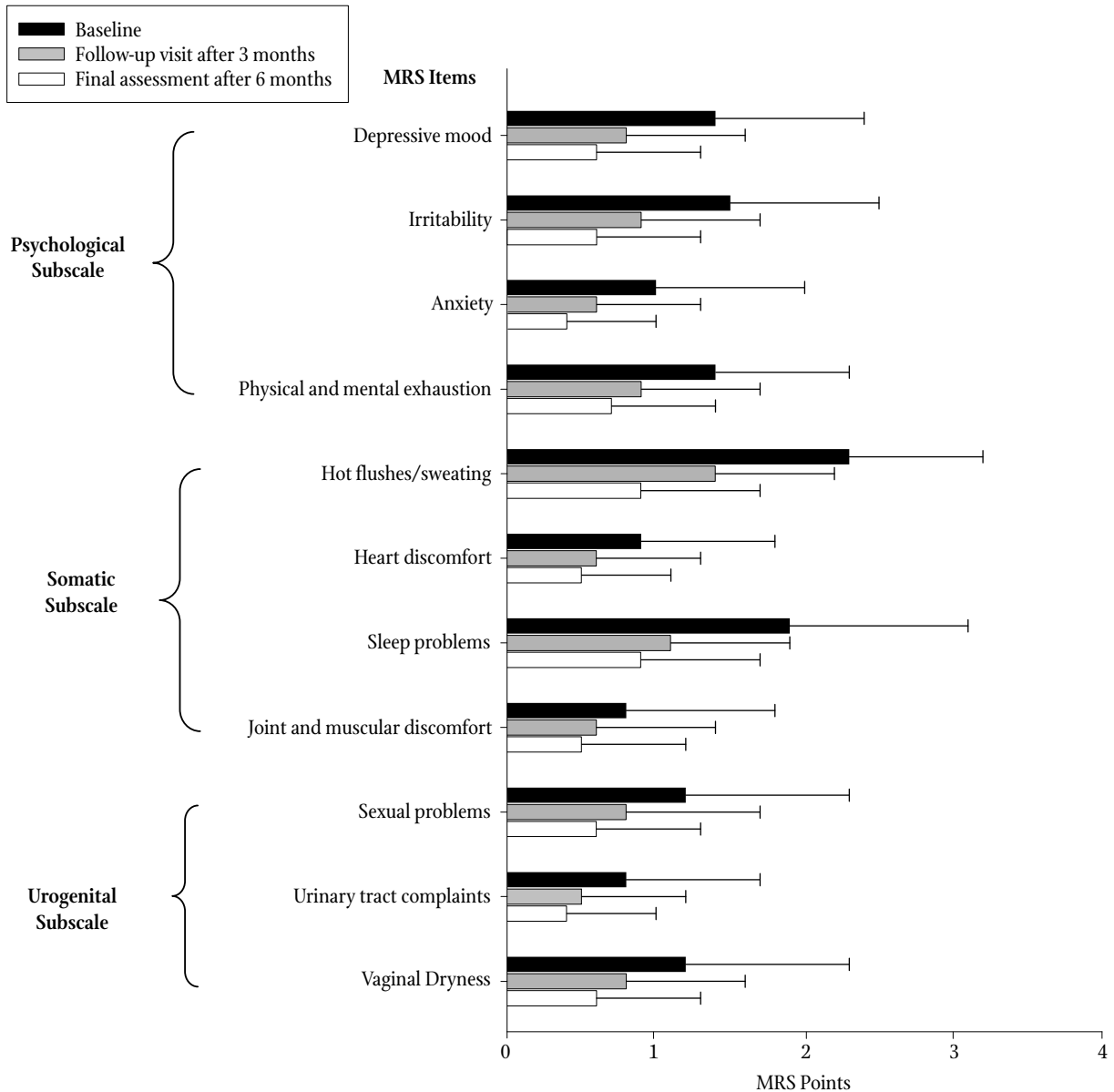


FIGURE 3 Decrease of Single MRS Items During Treatment With ERr 731*

*The single Menopause Rating Scale (MRS) item scores (mean \pm SD) from all women are presented. The bars represent the scores at baseline, first follow-up visit, and final assessment.

6). The gynecologist-reported treatment success rates after 3 and 6 months were similar (at 3 months, “major improvement,” 49.2%; “complete recovery,” 4.6%; at 6 months, “major improvement,” 54.4%, “complete recovery,” 18.3%).

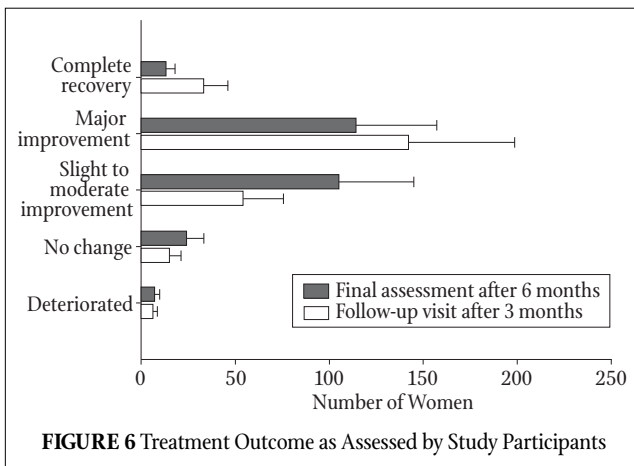
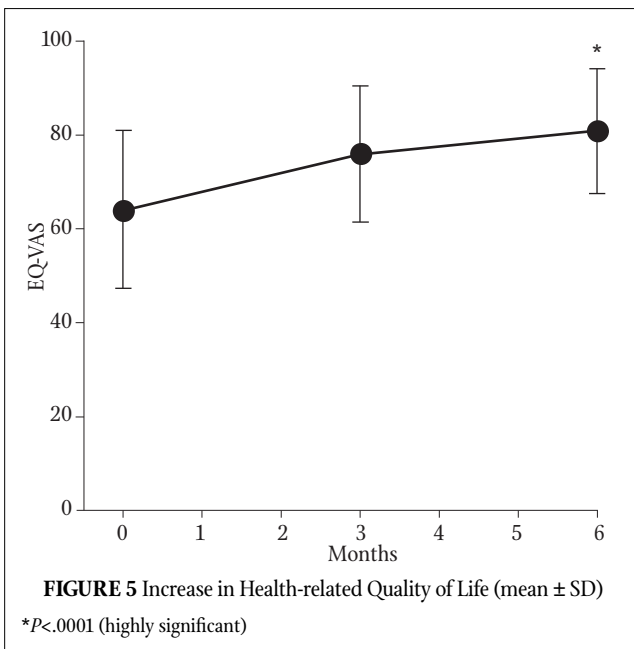
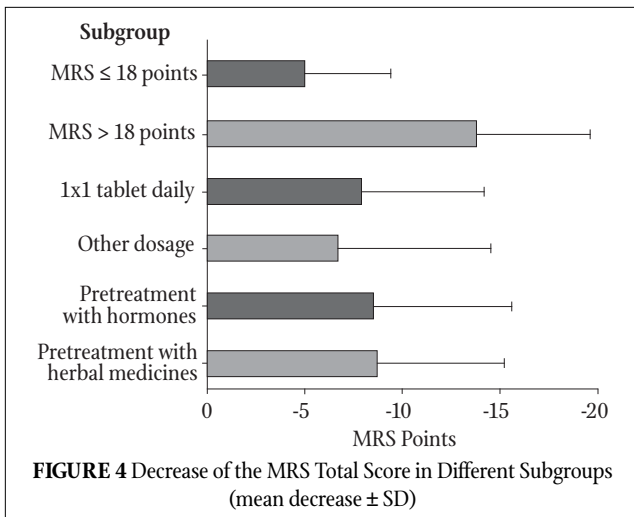
Adverse Events and Tolerability

Only one adverse event was documented in the PMS: after 8 days of ERr 731 intake, one woman developed vascular collapse of mild intensity. The gynecologist assessed it as not causally related to ERr 731. No therapeutic measures for this problem were initiated, and the woman continued with her intake of ERr 731.

Both the gynecologist and the subjects assessed the tolerability of the treatment with ERr 731 after 3 and 6 months’ intake of ERr 731. Most of the women reported “very good” (>60%) or “good” (about 30%) tolerability at both visits. Only 6.4% of the women reported “moderate” tolerability at the first follow-up visit, and this percentage decreased to 1.6% of the women at the final assessment. The observations by the gynecologists were comparable (data not shown).

DISCUSSION AND OVERALL CONCLUSIONS

The efficacy and tolerability of a 6-month treatment with ERr



731 was assessed in 363 peri- and postmenopausal women with menopausal symptoms during an open observational study that was conducted at 70 German gynecological practices. The study is the first to examine the use of ERr 731 in everyday practice and was designed to recruit a study population broadly representative of that found in normal practice. Therefore, in contrast to the stringently defined inclusion criteria required by controlled clinical trials, a markedly broader spectrum of women was included in the PMS: 17.4% were smokers, one-third had received hormone therapy prior to therapy with ERr 731, 43% of the women had concomitant diseases, and 24% had previous gynecological diseases.

Six months of treatment with ERr 731 reduced the menopausal symptoms significantly. This was shown by the highly significant decrease of the MRS total score from an average 14.7 points at baseline to 6.9 points after 6 months (LOCF) (decrease of 7.8 points, *P*<.0001). The most pronounced effect occurred within the first 3 months of intake of ERr 731, and the overall treatment success was also observed in several of the individual MRS items.

Over the 6-month treatment period, no loss of efficacy was observed. This result is consistent with the results of a long-term observational clinical study demonstrating a sustained efficacy of ERr 731 for up to 2 years (submitted for publication). This feature of ERr 731 may be of value when compared to long-term therapy with other herbal preparations.

The most pronounced improvements were observed for the symptoms "hot flushes/sweating," "irritability," "sleep problems," "depressive mood," and "physical and mental exhaustion" belonging either to the psychological or somatic subscale.¹⁴ This reflects the results of a previous clinical trial showing a marked improvement particularly in hot flushes and anxiety accompanied by an improvement in general well-being.¹⁷ In particular, postmenopausal women with a higher initial MRS total score at baseline (15.6 points) experienced a greater decrease (-8.7 points) than perimenopausal women with a lower initial score of 12.9 points (-6.6 points).

The health-related quality of life was influenced in a similar way: in women with more severe menopausal symptoms (initial MRS score >18 points), a more pronounced improvement than in women with less severe symptoms (initial MRS score ≤18 points) was observed. There was no correlation between the dosage and the increase of the EQ-VAS score or the decrease of the MRS score. The intake of more than 1 tablet once daily did not enhance the change of either score, indicating that this dose is sufficient for an optimal reduction of menopausal symptoms in the majority of women. The effects of ERr 731 were comparable irrespective of whether the women had pretreatment of their menopausal symptoms.

More than half of the gynecologists as well as participating women assessed the treatment outcome as positive with a pronounced decrease of symptoms. The vast majority of women took ERr 731 regularly. Even by the end of the 6-month study, the compliance in 90% of the women was "very good" or "good." Most of the women (90%) indicated that they want to continue to take ERr 731. Only 23 terminated the intake of ERr 731 after the final assessment, 16 of them due to lack of efficacy and 1 due to intolerability. When considering the total number of patients (*n*=252) who participated in

the PMS for 6 months as planned, this represents a small proportion.

No breakthrough bleeding, as is often reported for HT due to an estrogen-dependent stimulation of the endometrium,¹⁸ occurred in postmenopausal women in this PMS. In only 7 postmenopausal women was spotting documented during the PMS; however, none terminated the treatment for this reason. No adverse events that were considered to be related to ERr 731 occurred. One woman suffered from a vascular collapse, which did not require further treatment, and she continued to take ERr 731. Most importantly, no adverse effects similar to those described in patients using HT occurred with ERr 731.

This study has confirmed that ERr 731 as used in everyday practice is an effective and well-tolerated medication for the treatment of menopausal symptoms. It is an effective and safe alternative to HT during perimenopause for the treatment of menopausal symptoms,¹⁹ particularly hot flashes.

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