THE SPECIAL EXTRACT ERr 731® IS SAVE IN ACUTE AND LONG-TERM TREATMENT OF CLIMACTERIC COMPLAINTS IN PERIMENOPAUSAL WOMEN

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Abstract

Background: ERr 731® (the special extract from the roots of *Rheum rhaponticum*) has been demonstrated as being a safe herbal extract to reduce menopausal symptoms. Results of previous publications show that ERr 731® is very well tolerated with only a few transient and mild-to-moderate adverse events (AEs). The objective of this report was to demonstrate in a confirmatory study the safety of ERr 731® in acute and long-term treatment of climacteric complaints in perimenopausal women.

Hypothesis: ERr 731® is safe and very well tolerated in acute and long-term treatment of climacteric complaints.

Study Design: A 12-week, multicenter, double-blind randomized controlled trial (DB) followed by a 1-year open-label observational phase (OS).

Methods: During the DB, 112 symptomatic perimenopausal women were randomized to receive ERr 731® or placebo for 12 weeks. For the OS, 89 women from the (44 from the ERr731® arm and 45 from the placebo arm) agreed to take ERr 731® for 1 year. Safety parameters that were investigated included endometrial biopsy, vaginal smear, mammography, and laboratory safety parameters, as well as AEs.

Results: No endometrial hyperplasia, no increase in breast density, breast tenderness, and no clinically relevant increase in liver enzymes and other safety parameters were observed in both DB and OS. Differences between the treatment groups were not found. There were no serious AEs during DB and OS. All AEs were assessed as mild to moderate. Merely one patient during the DB experienced AEs that were assessed as being possibly related to ERr 731®. By the end of OS, all AEs had stopped. No causal relationship was reported between any AE and ERr 731®.

Conclusion: The results of the DB and OS confirmed ERr 731® to be safe in the acute and long-term treatment of climacteric symptoms in perimenopausal women.

Objective

For many years Hormone replacement therapy (HRT) was applied quite casually for the treatment of climacteric complaints in perimenopause. It was regarded as efficacious and safe treatment. However, the situation has changed as a number of large randomized controlled trials have demonstrated the contrary (9). Moreover, results from several randomized controlled trials(4, 2) conducted in healthy postmenopausal women (12, 3), found HRT to be associated with an increased risk of incident and fatal breast cancer. Therefore, the number of women seeking herbal medicines as an alternative for the treatment of climacteric complaints is increasing (5). The plant Rheum rhaponticum known as Sibiric Rhubarb originates from Central Asia. In the 17th century, it was imported to Europe and has been cultivated since then in Western Europe, East Asia and the United States. A special extract from the roots of Sibiric Rhubarb named ERr 731® (**E**xtract **R**heum **r**haponticum) has been used in Germany for decades as an effective and safe herbal medication for the treatment of climacteric complaints. The principal constituent of this purified and standardized concentrated dry extract is rhaponticin. Other active constituents are rhapontigenin, desoxyrhaponticin and desoxyrhapontigenin (7). The results of a 12-week, randomized, double-blind, placebo-controlled clinical trial with ERr 731® in 109 perimenopausal women with climacteric complaints followed by a 48- and 96-week open observational study were published recently,(8,6). There were no adverse events associated with the intake of ERr 731®, endometrial biopsies, weight, blood pressure, and other laboratory parameters were not affected, indicating that ERr 731® is a safe and effective alternative to HRT in perimenopausal women for alleviating climacteric symptoms.

The objective of this present investigation was to demonstrate the efficacy and safety of ERr 731® compared to placebo in a double-blind, placebo-controlled trial (DB followed by an open-label 1 year observational phase (OS) to assess long-term efficacy and safety of ERr 731® in patients with climacteric complaints in perimenopause

Trial Design

12-week double-blind, randomized placebo-controlled, prospective phase III clinical trial (DB) followed by a 1-year open observational phase (OS). The main objects were the improvement of menopausal symptoms according to the MRS rating scale and the safety of ERr 731® in long-term application. For DB, 112 patients were enrolled and randomized to treatment with ERr 731® or Placebo (56 for each group). For OS, 89 patients were included and analyzed as treated (ITT = 44 patients from the ERr 731® , 45 patients from the placebo group). One tablet per day of the investigational medication was taken. Subjects visited the investigator on Days 28, 56, and 84. Clinical status was checked and laboratory analyses were performed. The appearance of any adverse events (AEs) were documented. After completion of the DB (Final Assessment I (FA I)), each woman was offered to participate in the 52-week OS, where all women received ERr 731 ®. At the end of OS, after 52 weeks (FA II), each participant underwent a final investigation. Figure 1 shows the course of the trial during DB and OS:

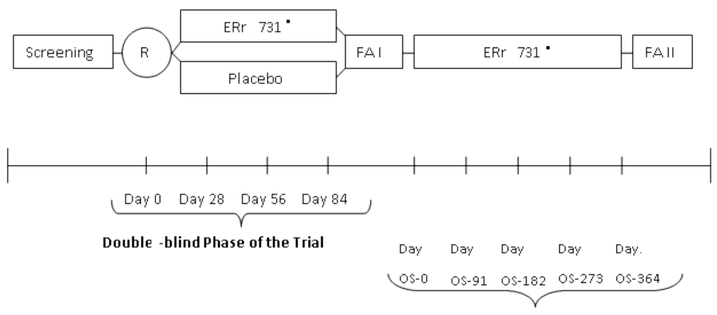

Figure 1: study flow chart, overview over planned phases and contacts during DB and OS

Investigational medication: Enteric coated tablets containing 4 mg *Rheum rhaponticum* dry extract (drug: extract ratio 16-26:1, extraction solvent calciumoxide: water, 1:38 (m/m)) and placebo. The medication was manufactured by Chemisch-Pharmazeutische Fabrik Goeppingen GmbH u. Co. KG, Goeppingen, Germany.

Outcome criteria for long-term efficacy and safety

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, and to Day 364 (end of OS). The Menopause Rating Scale (MRS) consists of eleven 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. Dryness of vagina, 11. Joint and muscular discomfort. The following rating scale was used: 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. Outcome criteria for safety were identical for both phases of the trial and included: Endometrial biopsy findings, transvaginal ultrasound findings, PAP smear findings, vaginal smear findings, mammography findings, breast tenderness, vital parameters, tolerability of investigational medication, adverse events and laboratory safety parameters.

Methods of examination

Mammography

Mammographic findings were classified according to 5 categories: negative, benign finding, probably benign finding, suspicious abnormality, highly suggestive of malignancy.

Breast density was assessed according to the Breast Imaging Reporting and Data System (BIRADS) and additionally by using the classification of Sterns and co-workers which is very similar to that of Wolfe (1, 10, 11): **BIRADS** categories were: 1 = almost entirely fat, 2 = Scattered fibroglandular tissue, 3 = Heterogeneously dense tissue,4 = extremely dense tissue. **Modified Wolfe categories were:** (0) fatty with minimal stromal or glandular tissue, (I) parenchymal density occupying <25% of the left breast, (II) parenchymal density with little or no confluence affecting ≥ 25% of the left breast, (III) confluent density obscuring detail and involving ≥ 75% of the left breast

Breast tenderness

Breast tenderness was assessed by the investigator using a 4-point verbal rating scale:

0 = no pain and/or tenderness
1 = occasional mild pain and/or tenderness but not bothersome
2 = occasional pain that is bothersome and/or tenderness to the extent that touching has to be limited
3 = pain and/or tenderness that is nearly always or always present, any degree of touching (including clothes and bra) is limited or intolerable.

Statistical Methods

Descriptive statistical methods were used to analyse baseline and secondary safety variables. For MRS, p-values were calculated for the comparison of ERr 731® with Placebo on Day 0 and Day 84 as well as on Day 84 and Day OS-364 (LOCF) using the two sample t-test (total score and single items).

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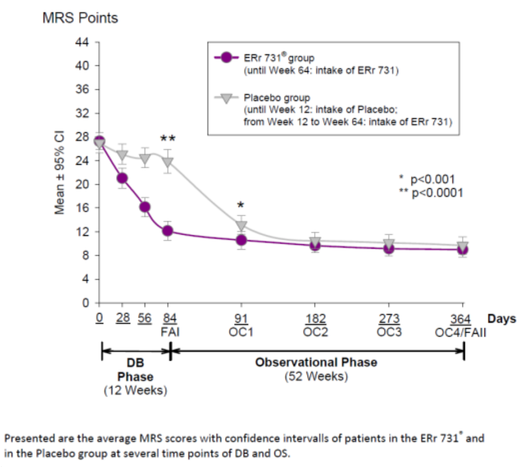
Results

Baseline Characteristics

At screening, no remarkable clinical differences (age, height, weight, BMI, blood pressure, pulse rate, family diseases, medications) were observed between the patients from both treatment groups. Out of 112 patients from DB, a total of 89 patients subsequently participated in OS and were included in the ITT analysis (ERr 731® group: n = 44 patients; Placebo group: n = 45 patients). Age ranged between 45 to 55 years. There were no considerable clinical differences between the two treatment groups of the DB phase.

MRS total score

Primary outcome criterion for the efficacy was the change of the MRS total score from Day 0 to Day 84. At baseline (Day 0), the MRS total score was rated with 27.1 ± 5.2 [26.0] points for all patients (n = 89) with no significant differences between the two treatment groups (p = 0.7897). From Day 0 to Day 84, the MRS total score decreased by -15.1 ± 4.4 [-15.0] points in the ERr 731® group (n = 44) and -3.1 ± 4.7 [-2.0] points in the placebo group (n = 45), yielding a significant difference in MRS total score between the two treatment groups (p<0.0001).



Presented are the average MRS scores with confidence intervalls of patients in the ERr 731® and in the Placebo group at several time points of DB and OS.

Figure 2: Changes of MRS total score during DB and OS

Time course	MRS total score (ITT) ERr 731® (n = 44) *(n = 43)		Placebo (n = 45) *(n = 43) **(n = 41)		Difference ERr 731® minus Placebo	
DB	mean ± SD [median]	95% CI	mean ± SD [median]	95% CI	mean ± SD	95% CI
Day 0	27.3 ± 4.8 [26.0]	25.816, 28.729	27.0 ± 5.6 [26.0]	25.303, 28.652	0.30 ± 5.20	-1.897, 2.487 n.s.
Day 28	21.0 ± 5.7 [21.0]	19.321, 22.770	25.1 ± 5.1 [24.0]	23.549, 26.629	-4.04 ± 5.40	-6.320, -1.767**
Day 56	16.2 ± 5.3 [16.0]	14.570, 17.794	24.5 ± 5.6 [24.0]	22.795, 26.183	-8.31 ± 5.48	-10.614, -6.000***
Day 84	12.2 ± 5.2 [12.0]	10.565, 13.753	23.9 ± 6.5 [24.0]	21.934, 25.844	-11.73 ± 5.92	-14.223, -9.237***
ΔDay 0 to Day 84	-15.1 ± 4.4 [-15.0]	-16.451, -13.776	-3.1 ± 4.7 [-2.0]	-4.490, -1.687	-12.03 ± 4.54	-13.936, -10.113***
OS	mean ± SD [median]	95% CI	mean ± SD [median]	95% CI	mean ± SD	95% CI
Day OS-91	10.6 ± 5.0 [10.0]	9.085, 12.097	13.2 ± 5.2 [13.0]	13.156, 5.2352	-2.57 ± 5.10	-4.713, -0.417*
Day OS-182	9.7 ± 3.9* [9.0]	8.487, 10.862	10.5 ± 4.5* [11.0]	9.118, 11.859	-0.81 ± 4.17	-2.601, 0.973 n.s.
Day OS-273	9.2 ± 4.1* [9.0]	7.910, 10.415	10.1 ± 4.3**	8.779, 11.465	-0.96 ± 4.16	-2.766, 0.848 n.s.
Day OS-364#	9.3 ± 4.7 [10.0]	7.920, 10.762	9.9 ± 4.8 [11.0]	8.501, 11.366	-0.59 ± 4.72	-2.583, 1.398 n.s.
Δ Day OS-364# to Day 84	-2.8 ± 3.9 [-2.0]	-4.019, -1.618	-14.0 ± 6.6 [-13.0]	-15.925, -11.987	11.14 ± 5.43	8.851, 13.423***

n.s. = not significant; *** = highly significant, p<0.0001; ** = significant, p<0.001, *.= significant, p<0.05
# = LOCF

Table 1: Changes in the MRS total score from Day 0 of DB to day OS-364 of OS

The difference in MRS total score between the two treatment groups (ERr 731® minus Placebo) was highly significant in favour of ERr 731® compared to placebo on Day 84 (p<0.0001, 95%CI). Table 8 shows the changes in the MRS total score from day 0 of DB to day 364 of OS. On Day 91 of OS, the MRS total score was rated with 11.9 ± 5.2 [11.0] points for all patients (n = 89), (10.6 ± 5.0 [10.0] for ERr 731®,13.2 ± 5.2 [13.0] for placebo). Thus, after 13 weeks of treatment with ERr 731®, a weak significant difference was found between the two treatment groups (p = 0.0198). At the end of OS, the MRS score was 9.6 ± 4.7 [10.0] points for all patients (n = 89) showing no significant difference between the two treatment groups (p = 0.5556). From the end of DB to the end of OS (Day 364), the MRS total score decreased by - 8.4 ± 7.8 [-7.0] points for all patients. A small decrease of -2.8 ± 3.9 [-2.0] points was observed in the ERr 731® group and a high decrease of -14.0 ± 6.6 [-13.0] points was found in the placebo group. The difference between the two treatment groups regarding decrease of symptoms from Day 84 to Day 364 was highly significant (p<0.0001).

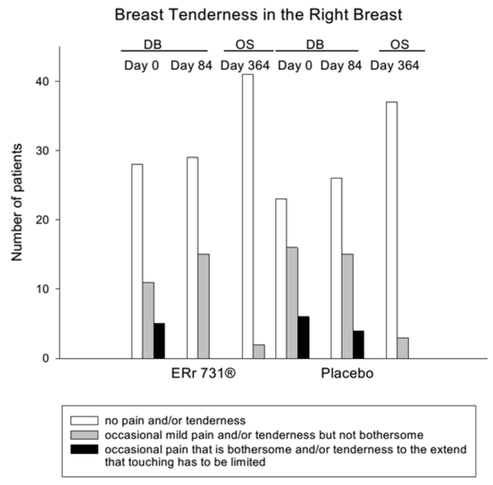


Fig. 3: Assessment of breast tenderness from baseline, to Day 84 pf DB and up to day 364 of OS

Category (1 = negative 2 = benign)	Number of Patients ERr 731® group (n = 44)			Placebo group (n = 45)		
	Screening	FA I	FA II	Screening	FA I	FA II
1....left breast	40	40	35	38	38	35
right breast	36	37	32	38	39	35
2....left breast	4	4	4	7	7	5
right breast	7	7	7	7	6	5
No remark ...						
left breast	0	0	5	0	0	5
right breast	1	0	5	0	0	5

Table 2: Mammography findings according to the categories negative (1), benign finding (2), probably benign finding (3), suspicious abnormality (4), and highly suggestive of malignancy (5) for both treatment groups from screening to FA I and FA II.

Clinical Evaluation

Breast Tenderness

The majority of all patients reported no change in breast tenderness from baseline to the end of DB (Day 84). Six patients in the ERr 731® group and 5 patients in the placebo group reported an improvement of breast tenderness. Figure 3 shows the improvement of breast tenderness from baseline until the end of the observational period (day 364). At the end of OS, no patient from either the ERr 731® group or the placebo group reported "occasional pain that is bothersome and/or tenderness to the extent that touching has to be limited".

Mammography

There was no change in the assessment of the mammography compared to screening, to FA I and FAII for the majority of all patients from both treatment groups regarding breast density assessment with BIRADS and *Modified Wolfe Assessment*. Mammographic findings were also classified according to 5 categories: negative (1), benign finding (2), probably benign finding – short interval follow-up suggested (3), suspicious abnormality – biopsy should be considered (4), and highly suggestive of malignancy – appropriate action should be taken (5) (results are shown in table2). From screening to FAI, all patients remained either in the category "negative" (ERr 731®: 40/44 (90.9%); Placebo: 38/45 (84.4%)) or "benign" (ERr 731®: 4/44 (9.1%); Placebo: 7/45 (15.6%)). From FA I to FA II there was no change in the assessment categories for all patients from the ERr 731® group and for most of the patients from the placebo group (73.3%). Overall, there was no change in the assessment to the categories 3, 4 or 5 in both treatment groups from screening to FA I and from FA I to FA II.

Adverse Events and tolerability of investigational medication

There were no serious Adverse Events (AEs) during the double blind phase or the observational phase of the trial. During the DB**,** 7 out of 112 patients experienced AEs (5 in the ERr 731® group, 2 patients in the placebo group). All AEs were assessed as "mild" to "moderate". All AEs with one exception (asthenia, headache, vertigo; causal relationship possible to ERr 731®), were assessed as not being causally related with the study medication. The reported AEs in the ERr 731® group were: pneumonia (chlamydial), respiratory tract infection (viral), hypoaesthesia, depression, sleep disorder, vertigo, asthenia and headache. The reported AEs in the placebo group were: increase in blood pressure, swelling face. In the OS, no causal relationship was reported between any AE and the investigational medication. All AEs were caused by a concomitant illness or were explained by another known reason. By the end of the observational study, all AEs had stopped.

The tolerability of the Investigational Medication during DB and OS was assessed as good to very good for all patients from both treatment groups.

Laboratory assessment

Vaginal Cytology : Vaginal smear and PAP smear (Papanocolaou) findings showed no abnormalities. From screening to the end of OS, the analysis of vaginal cytology showed no considerable changes in patients from both treatment groups.

Endometrial Biopsy: At all assessment points, no endometrial hyperplasia was found in any patient.

Hormones: Follicle stimulating hormone (FSH), 17-β-estradiol and sex hormone binding globulin (SHBG) were measured in serum. At all assessment points, the hormone levels were within normal ranges.

Liver and lipid Parameters: From baseline until the end of OS, no clinically relevant deviations from the normal range were observed for the liver parameters ALT, AST, gamma-GT, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin levels) in serum. Triglyceride, total cholesterol, LDL, and HDL levels were also not affected by the investigational medication.

Vital signs: There was no difference in weight and no changes in BMI from Day 0 to and Day 364 in both treatment groups.

Conclusion

Efficacy

The data from the double-blind trial and observational study ERr 004 presented here confirmed the results of the previous double-blind and observational study ERr 003 showing that ERr 731® is superior in efficacy compared to placebo in the treatment of climacteric complaints. The results obtained are in line with and confirm the effectiveness of ERr 731® also in the long-term treatment of climacteric complaints in every-day practice.

Safety

In the DB-phase 7 patients had AEs, all were assessed as "mild" or "moderate". Only 1 patient had 3 AEs which were assessed as being possibly related with the study medication. All other AEs were assessed by the investigators as not being causally related with the study medication. In the **52-week observational phase**, a total of 8/89 patients experienced one AE each (7/44 in the ERr 731® group and 1/45 in the placebo group). All adverse events were assessed as mild to moderate and had stopped by the end of the observational study. No causal relationship was reported between any AE and the investigational medication. No serious adverse events with relation to ERr 731® were reported in the present trial. Importantly, no endometrial hyperplasia, no increase in breast density and breast tenderness, and no clinically relevant increase in liver enzymes and other safety parameters were observed thus confirming the safety of ERr 731® in the treatment of women with menopausal symptoms.

Dr. Loges
Naturheilkunde neu entdecken