Effects of Progesterone on Vasomotor Symptoms in Postmenopausal Women (PROGEST) – a Prospective Multi-Center Randomized Double-Blind Placebo-Controlled Trial (RDPCT)

Auswirkungen von Progesteron auf vasomotorische Symptome in postmenopausalen Frauen (PROGEST): eine prospektive multizentrische randomisierte placebokontrollierte Doppelblindstudie (RDPCT)

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Authors

Sissi Valentina Beinert, Frauke Kleinsorge, Julia Worm, Katharina Victoria Tropschuh, Vanadin Seifert-Klauss

Affiliation

AG Gynäkologische Endokrinologie, Klinik und Poliklinik für Frauenheilkunde im Klinikum rechts der Isar, School of Medicine and Health der TU München (TUM), München, Germany

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Correspondence

Prof. Vanadin Seifert-Klauss

Technische Universität München Fakultät für Medizin, Klinik und Poliklinik für Frauenheilkunde, Klinikum rechts der Isar Ismaninger Str. 22, 81675 München, Germany

Vanadin.Seifert-Klauss@mri.tum.de

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ABSTRACT

Introduction Monotherapy with progesterone for treatment of vasomotor symptoms (VMS) was more effective than placebo treatment of postmenopausal healthy women in a Canadian trial. The PROGEST-trial was initiated to fulfill FDA-approval criteria for the indication of treatment of postmenopausal VMS.

Methods This prospective randomized, double-blind placebo-controlled clinical trial studied three doses of oral micronized progesterone (200 mg, 300 mg, 400 mg) and placebo for 12 weeks. Postmenopausal women with moderate to severe VMS (> 50 per week) were screened for one week for VMS frequency, then randomized to 200, 300 or 400 mg progesterone daily or placebo for a double-blinded trial of 12 weeks duration.

Results 74 women were recruited in 12 study centers. 44 terminated the study as per protocol (PP). Moderate to severe hot flushes decreased by 7.4/d in the placebo arm, 7.7 VMS/d with 200 mg/d progesterone (P4), 8.3 VMS/d on 300 mg/d and 9.0 VMS/d on 400 mg/d P4, respectively by week 12. 32 treatment emergent adverse events were documented in 18 participants, mostly minor AEs. The only SAE was a syncope requiring hospitalization on the day after treatment initiation, leading to discontinuation of the drug.

Discussion Baseline VMS frequency was much higher in the German than in the Canadian study and the course of the placebo group had a markedly stronger decrease in VMS-frequency during the PROGEST study (−7.4/d) than in the Canadian trial (−1.4/d). Trial populations differed by age, BMI, the number of women with natural menopause, and comorbidities, mainly hypertension.

Conclusion Premature discontinuation of the trial due to insufficient subject accrual rate led to only 55 randomized participants for analysis, therefore the study results lack statistical power. Still, a slight dose-dependent improvement in VMS was seen for all doses, while AE frequency did not increase with progesterone dose.

ZUSAMMENFASSUNG

Einleitung In einer kanadischen Studie war eine Monotherapie mit Progesteron effektiver zur Behandlung vasomotorischer Symptome (VMS) bei postmenopausalen gesunden Frauen als eine Placebobehandlung. Die PROGEST-Studie wurde initiiert, um die Kriterien der FDA für die Akzeptanz der Indikation „postmenopausale VMS“ zu erfüllen.

Methoden Diese prospektive randomisierte, doppelblinde, placebokontrollierte klinische Studie untersuchte die Auswirkungen von oralem mikronisiertem Progesteron in verschiedenen Dosierungen (200 mg, 300 mg, 400 mg) bzw. eines Placebos über 12 Wochen. Postmenopausale Frauen mit moderaten bis starken VMS (> 50 pro Woche) wurden nach 1 Woche Aufzeichnung der Frequenz ihrer VMS in einer Doppelblindstudie randomisiert, wo sie über 12 Wochen täglich 200, 300 oder 400 mg Progesteron oder Placebo-Kapseln erhielten.

Ergebnisse Es wurden 74 Frauen in 12 Studienzentren rekrutiert. 44 dieser Frauen haben die Studie gemäß dem Studienprotokoll beendet. Bis Woche 12 nahmen die moderaten bis schweren Hitzewallungen um 7,4/d im Placeboarm, 7,7 VMS/d mit 200 mg/d Progesteron (P4), 8,3 VMS/d mit 300 mg/d und 9,0 VMS/d mit 400 mg/d P4 ab. Es wurden 32 therapiebedingte unerwünschte Ereignisse bei 18 Teilnehmerinnen registriert, wobei die meisten nicht schwerwiegende UE waren. Das einzige ernsthafte unerwünschte Ereignis war eine Synkope, die eine Einweisung ins Krankenhaus am Tag nach Behandlungsbeginn erforderte und zu einem Absetzen des Medikaments führte.

Diskussion Die Ausgangsfrequenz der VMS war in der deutschen Studie deutlich höher als in der kanadischen Vorläufer-Studie, und bei der Placebogruppe in der PROGEST-Studie zeigte sich ein merklich stärkerer Abfall der VMS-Frequenz (−7,4/d) verglichen mit der kanadischen Studie (−1,4/d). Die Studienkohorten unterschieden sich hinsichtlich des Alters, des BMI, der Anzahl von Frauen mit natürlicher Menopause und der Begleiterkrankungen, vor allem Hypertonie.

Schlussfolgerung Die Studie wurde vorzeitig abgebrochen, da die Rekrutierungsrate zu gering war und nur 55 randomisierte Teilnehmerinnen für die Analyse zur Verfügung standen. Es fehlt daher die statistische Aussagekraft. Dennoch stellte sich eine geringfüge dosisabhängige Verbesserung der VMS bei allen Dosierungen ein, und die Erhöhung der Progesterondosis führte nicht zu einer Erhöhung der UE-Frequenz.

Introduction

Vasomotor symptoms (VMS) associated with menopause are observed in up to 80 % of menopausal women [1] and are the main reason for seeking hormone therapy. VMS are considered the most frequent menopause-associated symptoms and refer to hot flashes that may be associated with sweating [2]. These symptoms can affect the women's quality of life, impact their daily activities and cause sleep disturbances [3]. In addition, recent work suggests an association of VMS with adverse health outcomes, such as increased cardiovascular risk [4]. Ethnicity and social factors may affect the prevalence and severity of hot flashes. Further relevant risk factors include obesity, tobacco smoking and low physical activity [5, 6].

While approximately 50 % of women do not experience hot flashes at all, or only for short periods of time, VMS prevalence has been shown to have increased two-fold in recent decades [6], and in the majority of cases the mean duration is much longer than previously published [7]. In a sample of > 1400 women with VMS, the SWAN study showed a median duration of VMS persistence of more than seven years [7].

The pathophysiological processes leading to hot flashes are still debated. The currently accepted view is that menopausal estrogen withdrawal leads to a hypothalamic thermoregulatory dysfunction which causes a narrowing of the so called thermoneutral zone. This means that in menopausal women heat-regulating mechanisms are triggered at a lower threshold of the body temperature than in pre-menopausal women [2, 8]. VMS can also occur at night during sleep and can cause sleep disturbance and disruption, which may be associated with increased daytime sleepiness and tiredness [9]. However, sleep disturbance and disruption may also occur without VMS [10]. Menopausal hormone therapy (MHT) improves sleep in women with concomitant VMS. Progesterone acts as a “physiologic” regulator in case of sleep disturbances by modulating γ-aminobutyric acid (GABA)-ergic transmission rather than as a hypnotic drug in aging and postmenopausal women, where sleep is fragmented and of lower quality [11]. 30 % of the women who suffer from VMS decide on hormone therapy in the absence of contraindications, since proven alternatives, such as changes in lifestyle, diet or herbal preparations had insufficient effects on their VMS [12].

A previous Canadian randomized placebo-controlled study [13] had indicated that 300 mg micronized progesterone once daily reduced VMS frequency after 12 weeks. However, no study thus far had investigated the efficacy of different doses of micronized progesterone in women with moderate to severe VMS frequency and severity. The present study therefore aimed to test whether micronized progesterone is efficacious and safe in reducing VMS frequency and severity in symptomatic postmenopausal women, and to identify the optimal effective dose.

Methods

This prospective multicenter randomized, double-blind placebo-controlled clinical trial studied three doses of oral micronized progesterone (200 mg, 300 mg, 400 mg) against placebo for

▶ **Table 1** Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Adult (≥ 18 years), postmenopausal women, where post-menopause is defined as	Use of any hormone replacement therapy (including phytoestrogens and other plant-derived sex hormones)
a. at least 12 months of spontaneous amenorrhea, or b. 6 months of spontaneous amenorrhea and follicle stimulating hormone (FSH) levels > 40 mIU/ml, or	Endometrial thickness ≥ 5 mm at screening visit Breast cancer or history thereof, including carcinoma in situ and other pre-cancerous conditions Ongoing or history of venous thromboembolic event
c. status at least 6 weeks after bilateral oophorectomy with or without hysterectomy, or	History of myocardial infarction, stroke or transient ischemic attack or severe cardiac disease
d. subject post hysterectomy without oophorectomy with documented FSH level > 40 mIU/ml and estradiol level < 20 pg/ml	Liver diseases or a history thereof with liver enzymes having not normalized, severe disturbances of hepatic function
Non-smoker	Vaginal bleeding
Mammography without pathological findings obtained within routine medical care no longer than 12 months prior to screening visit	Active malignant disease (except for localized basal cell carcinoma of the skin) or history thereof in the last 5 years prior to screening visit
Cervical smear (Papanicolaou test) without pathological findings (i.e. < III) obtained no longer than 12 months prior to screening visit	History of icterus or generalized pruritus during a previous pregnancy
	Rotor syndrome or Dubin-Johnson syndrome
	Ongoing major depression
	Use of SSRI, SNRI for any reason
	Acupuncture for VMS
	Diabetes mellitus
	Hypersensitivity to progesterone or excipients (e.g. soy) of the study medication
	Medical history of HIV infection
	Concomitant diseases or therapies that may cause VMS
	Known or suspected drug or alcohol abuse
	Known severe renal insufficiency at screening visit

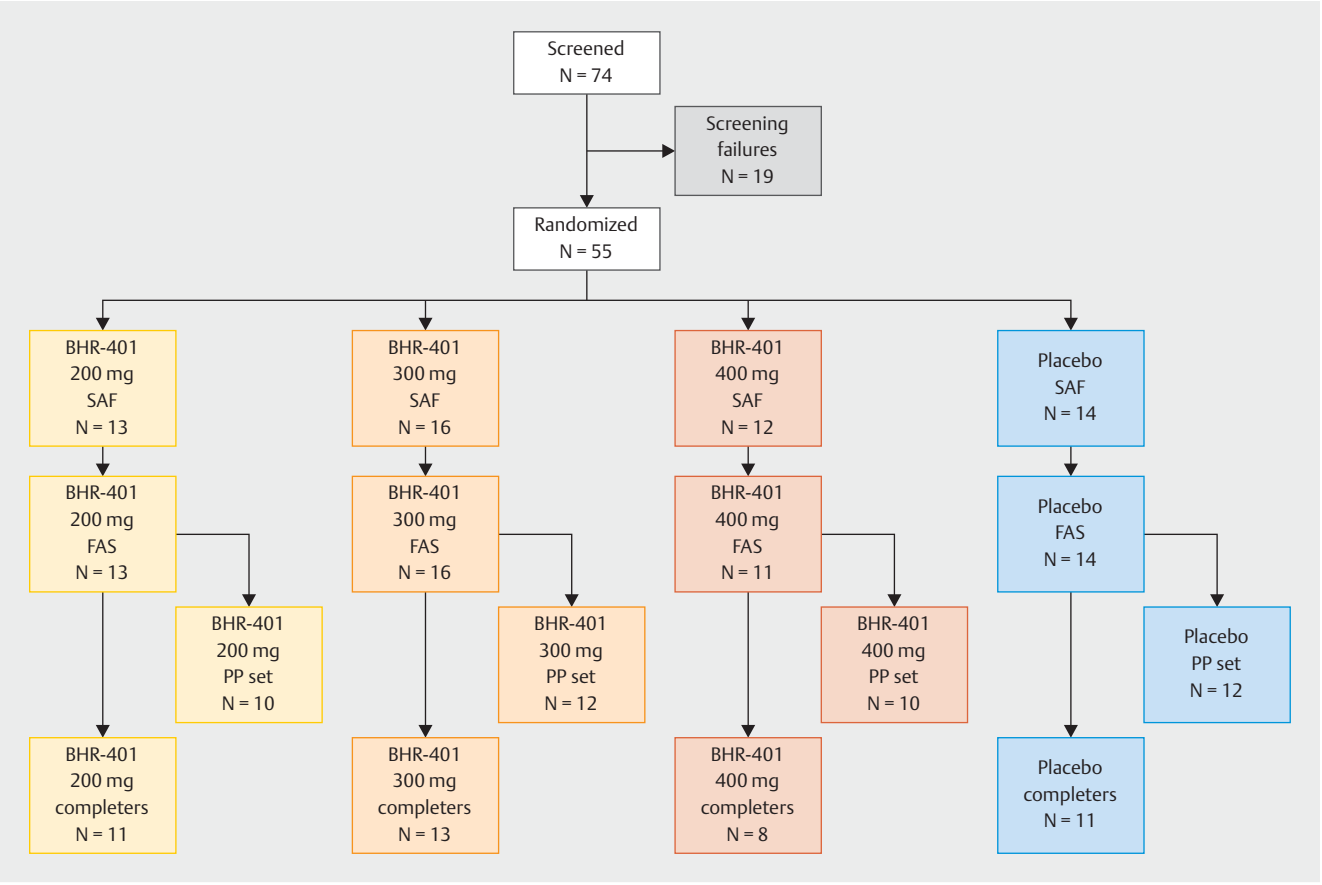
12 weeks. The PROGEST Trial was registered with protocol number BHR-401-301 and EudraCT-Number: 2016-004386-12.

The primary objective was to test progesterone versus placebo as a monotherapy for moderate to severe VMS in postmenopausal women. VMS were graded as mild (hot flashes, not associated with sweating), moderate (hot flashes leading to increased perspiration, but not causing interference with normal daytime activity or awakening from night sleep) or severe (hot flashes leading to increased perspiration and interfering with normal daytime activity or awakening from night sleep). The secondary objectives were the effect of progesterone treatment on VMS frequency and severity at treatment week 4 and week 12. Further secondary objectives of the study were the effects of the different progesterone doses on symptom severity and sleep quality over 12 weeks, and the safety and tolerability of different progesterone doses compared to placebo. All participants provided written informed consent. The ethics committee of the Technical University Munich (TUM) approved the study (Votum 184/17 Af; 2017). The study was performed from August 2017 (first patient, first visit) until December 2018 (last patient, last visit).

Participants, Randomization and Treatment

▶ **Table 1** summarizes the eligibility and exclusion criteria. The participating women were recruited in 12 study sites in Germany and had to have a minimum of 50 moderate to severe VMS episodes documented over seven consecutive days prior to the baseline visit in the subject diary, in order to be randomized. Use of any hormone replacement therapy (including phytoestrogens and other plant-derived sex hormones) within 12 weeks prior to screening was one of the exclusion criteria.

After a one-week screening phase with diary-documentation of hot flushes, patients were randomized in a 1:1:1:1 ratio to one of four treatment groups. Three groups received active progesterone treatment at daily doses of either 200 mg, 300 mg or 400 mg, available in strengths of either 100 mg or 200 mg capsules (the 400 mg dose was given by intake of two 200 mg capsules). All participants took two capsules per day, the 200 mg dose group received one, the placebo group two placebo capsules. All study medications were administered orally, once daily before bedtime.



▶ **Fig. 1** Flowchart (Consort diagram) of study participants. Abbreviations: SAF: Safety Analysis; FAS: Full Analysis Set; PP set: per protocol set.

Menopause Rating Scale and Pittsburgh Sleep Quality Index were documented three times per week. All adverse events (AEs) during the study were documented. Further safety variables, e.g. clinical and ultrasound parameters were recorded at screening (visit 1) and after 12 weeks (visit 5).

Statistical Methods

All safety and tolerability data were analyzed for the safety analysis set (SAF). SAF comprises all randomized subjects who were administered the study medication at least once. The Full analysis data set (FAS) includes all subjects of the SAF who provided any post-baseline data related to efficacy. Demographic and other baseline characteristics were evaluated for the full analysis set (FAS). The primary endpoint and key secondary endpoints were analyzed primarily for the FAS, with secondary (supportive) analysis for the per-protocol (PP) data set. The per-protocol (PP) data set included all subjects from the FAS who did not exhibit a major protocol deviation, e.g. protocol deviations that might have an influence on the outcome of the study.

The treatment effect was tested in hierarchical order between each of the three dosages of progesterone and placebo using analysis of covariance (ANCOVA) with the baseline value (i.e. VMS episodes per day prior to baseline) as a covariate. The level of significance was set to $\alpha = 5\%$ (two-sided). All other analyses were based on the FAS only.

In general, all analyses were stratified by treatment group. Analyses for the FAS and the PP data set were also performed for the respective total population.

Quantitative data were analyzed by the statistical parameters valid N, missing N, mean, standard deviation (SD), median, minimum and maximum. Qualitative and categorical variables were presented by frequency distributions. If proportions of subjects were calculated, the denominator was the number of subjects for which the variable can be assessed. However, also N missing was provided for these tables. For all efficacy endpoints two-sided 95% confidence intervals were provided. Results of statistical tests were provided in terms of p values of the respective test statistics.

Results

74 subjects were recruited in 12 study centers, of which 55 subjects were randomized to one of the four treatment arms (progesterone 200 mg: 13, progesterone 300 mg: 16, progesterone 400 mg: 12, placebo: 14) and included in the safety analysis set (SAF). For the remaining 19 subjects, the most frequent reason for screening failure was insufficient VMS frequency (14 cases). Premature discontinuation of the trial due to insufficient subject

▶ **Table 2** Baseline demographic characteristics – FAS (Full Analysis Set).

Variable	Statistic	Progesterone 200 mg N = 13	Progesterone 300 mg N = 16	Progesterone 400 mg N = 11	Placebo N = 14	Total N = 54
Age at screening (years)	Mean	54.6	57.2	57.4	56.6	56.5
	SD	2.57	6.79	6.74	5.84	5.72
Comorbidities	Valid N (%)	9 (69.2)	10 (62.5)	7 (63.6)	10 (71.4)	36 (66.7)
BMI (kg/m^2)	Mean	30.5	26.5	27.0	27.9	27.9
	SD	7.34	4.31	5.40	5.42	5.71
Smoking history, N (%)	Never smoked	9 (69.2)	16 (100.0)	9 (81.8)	12 (85.7)	46 (85.2)
	Previous smoker	4 (30.8)	0 (0.0)	2 (18.2)	2 (14.3)	8 (14.8)
Hypertension	Valid N (%)	6 (46.2)	6 (37.5)	5 (45.5)	6 (42.9)	23 (42.6)
Co-Medication	Valid N (%)	9 (69.2)	12 (75.0)	7 (63.6)	9 (64.3)	37 (68.5)
Beta-blockers	Valid N (%)	2 (15.4)	2 (12.5)	2 (18.2)	6 (42.9)	12 (22.2)

▶ **Table 3** Gynecological examination and endometrial thickness – FAS (BHR-401 = progesterone).

Variable	Visit	Statistic	BHR-401 200 mg N = 13	BHR-401 300 mg N = 16	BHR-401 400 mg N = 11	Placebo N = 14	Total N = 54
Pathological findings during gynecological examination, n (%)	V1	Yes	0 (0.0)	1 (6.3)	1 (9.1)	1 (7.1)	3 (5.6)
		No	13 (100.0)	15 (93.8)	10 (90.9)	13 (92.9)	51 (94.4)
		Missing	0	0	0	0	0
	V5	Yes	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	2 (4.3)
		No	11 (100.0)	14 (100.0)	9 (90.0)	11 (91.7)	45 (95.7)
		Missing	2	2	1	2	7
Endometrial thickness (mm)	V1	Valid N	9	13	8	10	40
		Mean	2.4	2.1	2.0	2.0	2.1
		SD	1.04	1.19	1.08	0.70	1.00
	V5	Valid N	8	12	7	10	37
		Mean	2.1	2.3	2.1	1.7	2.0
		SD	0.91	1.29	1.38	0.58	1.06

accrual rate led to only 55 randomized participants for analysis, therefore the study results lack statistical power.

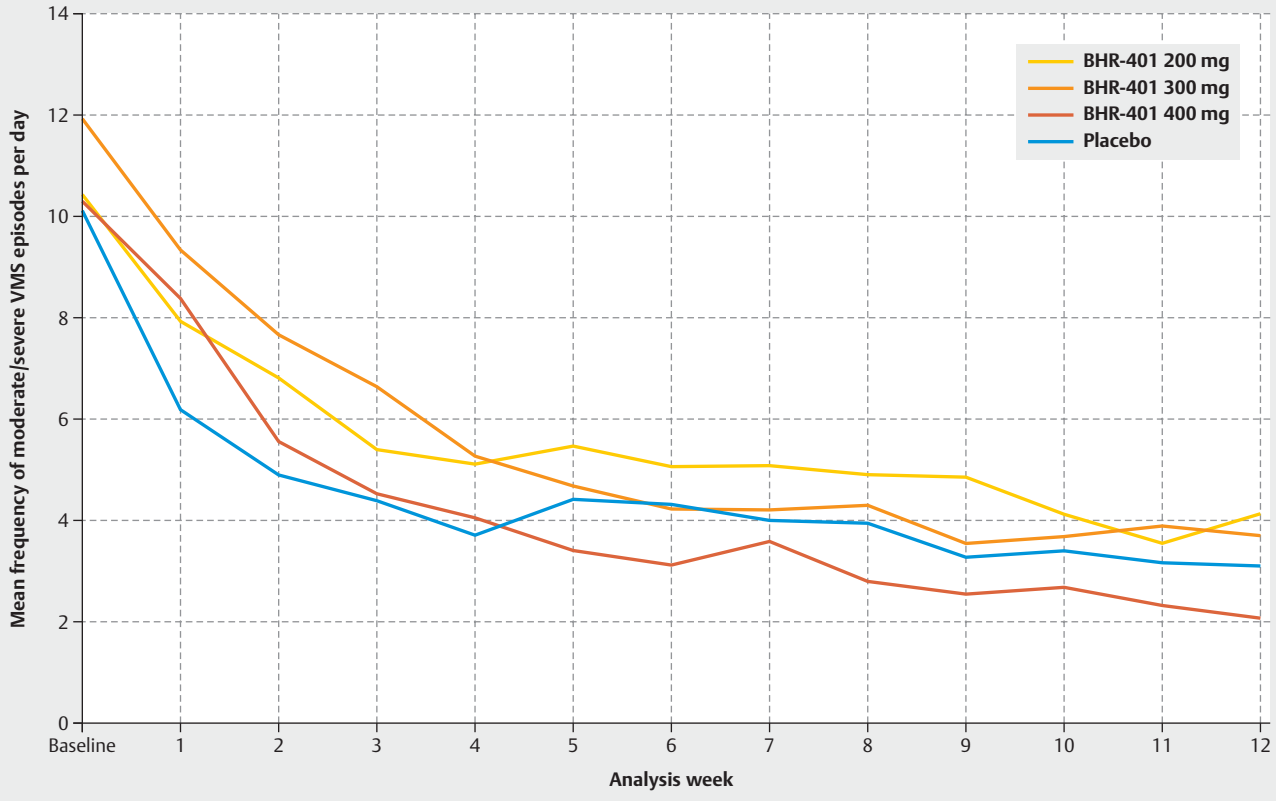
55 subjects comprised the SAF dataset. One subject from the SAF had no post-baseline data related to efficacy and therefore was excluded from FAS which finally comprises 54 subjects. 44 remained in the study as per protocol (PP). Flow through the study is shown in ▶ **Fig. 1**.

Demographic characteristics

A summary of the demographic characteristics is displayed in ▶ **Table 2**. According to the eligibility criteria, none of the subjects were current smokers. All subjects were of Caucasian race and the vast majority was currently employed (85.2%) or already retired (13.0%). The mean age was 56.5 years and the mean body mass index (BMI) was 27.9 kg/m^2. 37 participants took additional medication, e.g. 12 (22.2%) beta-blockers. Two thirds of the subjects had relevant current comorbidities. The most frequently observed comorbidity was hypertension (▶ **Table 2**).

Physical and gynecological examination

Safety variables, e.g. physical and gynecological examinations as well as measuring of endometrial thickness were scheduled at the start (visit 1: screening) and end (visit 5: week 12) of the study. No pathological findings based on physical examinations were reported. Gynecological examinations yielded pathological findings for three subjects (5.6%) at visit 1 and for two subjects (4.3%) at visit 5. The findings were vaginal bleeding (n = 3), ovarian cyst (n = 1) and endometrial thickening (n = 1). The mean endometrial thickness measured at visit 1 was 2.1 mm and 2.0 mm at visit 5 (▶ **Table 3**).



▶ **Fig. 2** Course of daily frequency of moderate or severe VMS episodes in weekly intervals from baseline – FAS (BHR-401= progesterone).

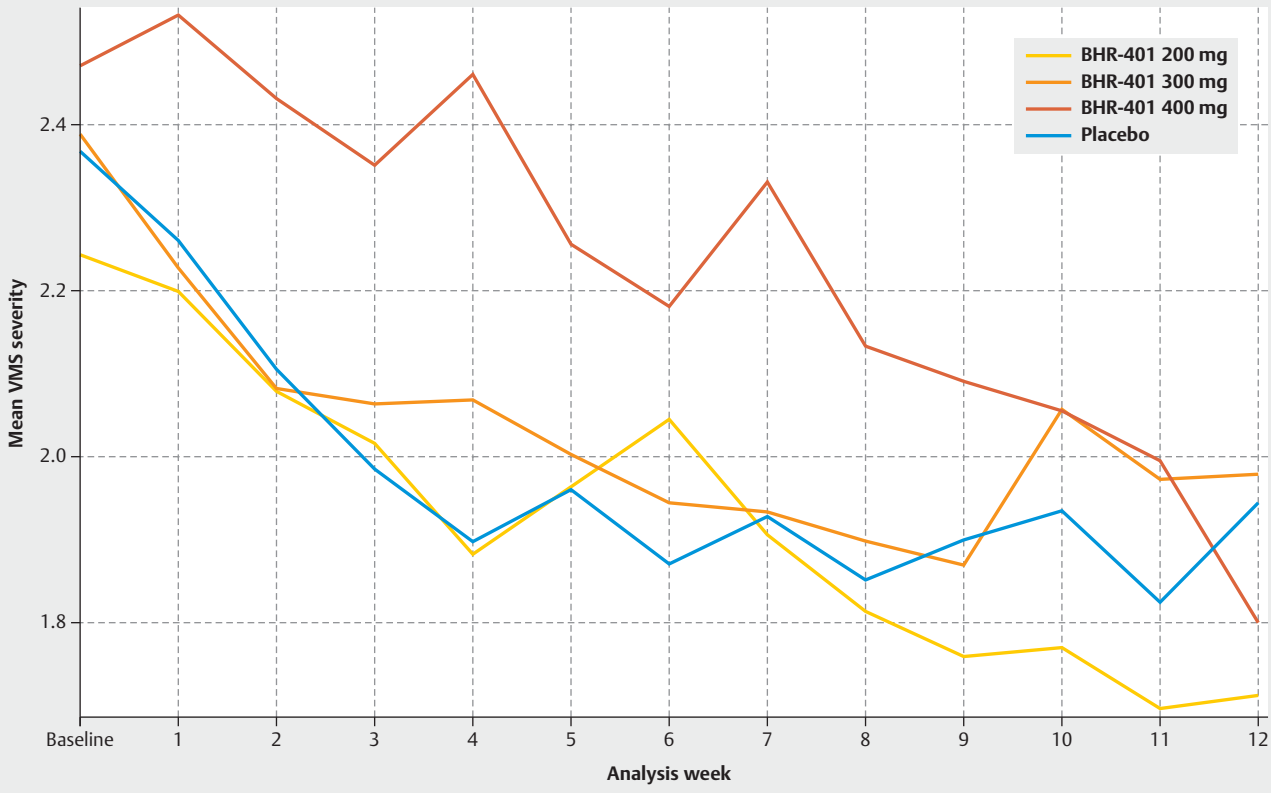
Vasomotor symptoms

The average number of moderate or severe VMS episodes per day decreased from an average of 10 (placebo group) to 12 (progesterone 300 mg) at baseline to week 12 in all four treatment groups (progesterone 200 mg: −7.7 episodes/day, progesterone 300 mg: −8.3 episodes/day, progesterone 400 mg: −9.0 episodes/day, placebo: −7.4 episodes/day). Due to the low number of subjects, the ANCOVA models did not show any significant differences in the amount of VMS reduction between placebo and any dose of progesterone (▶ **Table 4**). Results of the sensitivity analyses for the primary efficacy variable in the PP data set did not differ considerably from the primary analysis in the FAS. Details on the course of frequency of moderate or severe VMS episodes and on the course of VMS severity in weekly intervals from baseline to week 12 are shown in ▶ **Figs. 2** and **3**. In line with the primary and key secondary efficacy variables no significant differences between the treatment groups could be detected with respect to the course over time.

▶ **Table 4** Primary efficacy evaluation – FAS (BHR-401 = progesterone).

Variable	Statistic	BHR-401 200 mg N = 13	BHR-401 300 mg N = 16	BHR-401 400 mg N = 11	Placebo N = 14
Absolute change in moderate or severe VMS frequency per day between baseline and week 12	Valid N	12	16	10	13
	Mean	−7.70	−8.29	−9.00	−7.40
	SD	4.913	7.725	4.046	3.579
	L 95 % CI	−10.82	−12.40	−11.89	−9.57
	U 95 % CI	−4.57	−4.17	−6.11	−5.24
Test vs. placebo	p value*	0.8798	0.7457	0.1397	–

* P value results from ANCOVA model with baseline VMS frequency as covariate



▶ **Fig. 3** Course of severity of VMS in weekly intervals from baseline – FAS (BHR-401 = progesterone).

Safety and tolerability, adverse events

Overall, 18 subjects (32.7%) experienced 32 treatment emergent adverse events (TEAEs) in this study. TEAEs were defined as any adverse event (AE) with a start date occurring on or after baseline or, if pre-existing, worsening after baseline, and occurring within the period of treatment with the study drug.

Most of the TEAEs were minor (i.e. non-serious) AEs and were observed in the placebo group (12 TEAEs in five subjects). The incidence rate, i.e. the number of subjects with at least one TEAE was highest in the progesterone 300 mg group (37.5%) and lowest in the progesterone 400 mg group (25.0%). ▶ **Table 5** illustrates the most frequently observed TEAE with respect to system organ class (SOC). Due to the low number of subjects, the following descriptions of TEAEs will be based on the overall SAF, without focusing on any group differences. Six subjects (10.9%) experienced at least one drug-related TEAE. The most frequent drug-related TEAE in this study was vaginal bleeding (four subjects, 7.3%), followed by breast pain (two subjects, 3.6%). Four adverse events led to the withdrawal of study drug in three subjects (progesterone 400 mg: two subjects, placebo: one subject). the events were nausea, syncope, vaginal bleeding and paroxysmal tachycardia. Nausea and syncope were experienced by the same subject in the progesterone 400 mg group. Syncope of this subject was the only documented serious adverse event (SAE) and required hospitalization on the day after the initiation of progesterone, which lead to discontinuation of the drug. It was judged to be drug unrelated by the local investigator.

Discussion

In Germany, micronized progesterone is licensed at a daily dose of 100 mg or 200 mg for endometrial protection during menopausal estrogen hormone therapy. The PROGEST study tested progesterone as a monotherapy for menopausal vasomotor symptoms. Due to premature stopping of the trial for non-medical reasons, the study results summarized here are based on approximately one third of the planned sample size. This was due to insufficient subject accrual rate and led to only 55 randomized participants for analysis. Because of the low number of randomized subjects, comparisons between treatment groups lack statistical power. Therefore, findings and differences between the treatment groups are interpreted with caution. Nevertheless, the results of this study bear some interesting findings which broaden our understanding of menopausal complaints and their treatment, the most striking feature being the marked and unexpected high improvement of VMS in the placebo group.

The average number of moderate or severe VMS episodes per day decreased from an average of 10 (placebo group) to 12 (progesterone 300 mg) at baseline to week 12 in all four treatment groups (progesterone 200 mg: −7.7 episodes/day, progesterone

▶ **Table 5** Incidence of TEAEs by System Organ Class (SOC) and Preferred Term – SAF (BHR-401 = progesterone).

SOC PT	BHR-401 200 mg N = 13	BHR-401 300 mg N = 16	BHR-401 400 mg N = 12	Placebo N = 14	Total N = 55
	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	2 (3.6)
▪ Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.8)
▪ Paroxysmal tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.8)
General disorders and administration site conditions	2 (15.4)	2 (12.5)	0 (0.0)	0 (0.0)	4 (7.3)
▪ Influenza-like illness	1 (7.7)	1 (6.3)	0 (0.0)	0 (0.0)	2 (3.6)
▪ Malaise	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.8)
▪ Peripheral edema	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Infections and infestations	2 (15.4)	4 (25.0)	0 (0.0)	1 (7.1)	7 (12.7)
▪ Bronchitis	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.8)
▪ Cystitis	2 (15.4)	2 (12.5)	0 (0.0)	0 (0.0)	4 (7.3)
▪ Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.8)
▪ Sinusitis	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.8)
Musculoskeletal and connective tissue disorders	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.1)	2 (3.6)
▪ Arthralgia	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
▪ Back pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.8)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	2 (3.6)
▪ Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.8)
▪ Restlessness	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (1.8)
Reproductive system and breast disorders	0 (0.0)	1 (6.3)	2 (16.7)	1 (7.1)	4 (7.3)
▪ Breast pain	0 (0.0)	0 (0.0)	1 (8.3)	1 (7.1)	2 (3.6)
▪ Endometrial thickening	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.8)
▪ Ovarian cyst	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.8)
▪ Vaginal hemorrhage	0 (0.0)	1 (6.3)	2 (16.7)	1 (7.1)	4 (7.3)

300 mg: −8.3 episodes/day, progesterone 400 mg: −9.0 episodes/day, placebo: −7.4 episodes/day). Even though a dose-dependent tendency was observed between the progesterone groups, as well as in comparison to placebo, no statistically significant differences between the dosage groups were detected, likely due to the insufficient number of randomized subjects. Similarly, for the key secondary efficacy variables, no significant differences nor any dose-dependent trends between progesterone groups or the placebo group were detected.

Still, the magnitude of the reduction of VMS found in this trial is comparable with the precedent trial of Hitchcock et al., where in a 1 : 1 trial design, the average difference in reduction of VMS with the only dose of progesterone studied in that trial (300 mg/d) vs. placebo was −1.9 per day [13]. Another comparator is the newly approved treatment for VMS in postmenopausal women, fezolinetant. The effects of two doses of this drug in the 1 : 1 : 1 placebo-controlled three-arm Skylight 2 trial for the daily reduction of VMS were −1.82 to −2.55 per day compared to placebo [18] while −1.6 VMS was the average difference in the VMS reduction (compared with placebo) observed in the PROGEST trial with the maximum dose of progesterone studied (400 mg/d), reported here (▶ **Table 4**). In contrast to the previously published Canadian trial from 2012 [13] the present results of the PROGEST study did not confirm that 300 mg micronized progesterone once daily reduces VMS frequency substantially better than placebo after 12 weeks.This was mainly due to the unexpected, high placebo effect in the PROGEST trial. In the Canadian PCRT, only one dose of progesterone 300 mg was studied versus placebo. Particularly striking is the decline in VMS frequency with placebo, which was much greater in the PROGEST trial than in the Canadian study [13].

Caliskan EB, Bingel U et al. and others have found that placebo effects are stronger in trials with multiple treatment arms, and reasoned that this could be due to the positive expectation of trial participants, since their chance of receiving a verum drug is higher and this positively impacts on the placebo effect [14, 15].

For a better comparison of the Canadian trial and the PROGEST study, and since the previous study had not applied the FDA-required entry criteria for hot flushes (> 50 moderate to severe/week), we concentrated our comparison with the Canadian study on their sub-cohort of 46 participants with “severe” VMS (n = 29 on progesterone versus n = 17 on placebo), which met those criteria, out of the whole cohort of 114 women (68 women on proges-

terone and 46 on placebo) of the Canadian trial [13]. Both trials show differences in the characteristics of the studied populations, participants conditions and comorbidities. Study participants in the PROGEST trial were older (56.5 years) than the Canadian trial (55.5 years in the progesterone and 54.4 years in the placebo group). As serum levels of estradiol may remain at an intermediate range intermittently for up to two years after menopause, induction of nuclear progesterone receptors by endogenous estradiol may become less with time after menopause, reducing effects of progesterone mediated by nuclear receptors.

Time since the final menstrual period in the Canadian trial averaged 3.9 years in the progesterone group and only 2.5 years in the placebo group.

Participants in the Canadian trial were all without cardiovascular system disease, non-smoking, BMI below 35, without diabetes mellitus or hypertension and having a normal electrocardiogram (ECG), normal fasting lipids and regular glucose. They were taking neither antihypertensive, lipid-lowering nor other cardiovascular or diabetes therapies and were otherwise healthy [13].

In the PROGEST study, two thirds of the participants had any type of comorbidity, mainly (42.6%) hypertension, which is known to be a frequent comorbidity in postmenopausal women [16].

Since women with hypertension carry an elevated risk of stroke with estrogen only or estrogen-progestin-combined MHT [17], this may have led to recruiting bias by a preference to offer the PROGEST study to women with elevated blood pressure in the participating study centers.

68.5% of the participants in the full analysis set of the PROGEST trial took any kind of concomitant drug therapy. 22.2% were on beta-blockers, with a coincidental difference between the placebo group and the progesterone groups (placebo group 42.9%, progesterone 200 mg group 15.4%, progesterone 300 mg group 12.5%, progesterone 400 mg group 18.2%).

If the concomitant medication and the coincidental high percentage of beta-blocker treatment in the placebo group would explain why the drop in VMS in the PROGEST placebo group was so much more pronounced than in the Canadian sample, one could presume that such women might profit from placebo interventions.

The Canadian cohort was also leaner and healthier than the average of middle-age women and required strict entry criteria, e.g. low density lipoprotein cholesterol and fasting glucose [13].

On the other hand, the effect of higher attention to the patient population on the trial could have also led to relief from VMS and could explain the high response to placebo, as the participants received nonmedication benefits such as support, self-monitoring, and reduction in stigma by participating in the trial.

The most frequent single reason for dropout was lack of efficacy (4 participants; progesterone 200 mg: 1, progesterone 300 mg: 1, progesterone 400 mg: 2), followed by lack of tolerability/AE (progesterone 400 mg: 1, placebo: 1). The trial noted 32 treatment emergent adverse events (TEAE) in 18 participants. The majority of the TEAEs observed in this study (93.8%) were mild or moderate. Bleeding episodes and mastodynia have been reported with progesterone treatment, particularly in women with still ongoing endogenous estradiol production, e.g. in late perimenopause.

Conclusions

Due to the low number of randomized subjects and therefore premature termination of the trial, not based on a safety concern, the study results lack statistical power. Therefore, no validated conclusion can be drawn, but a positive trend for elevating progesterone daily dose appeared to lead to decreasing VMS in postmenopausal women. This biological gradient in efficacy would need to be confirmed in a well powered randomized placebo-controlled double-blinded trial with a participant population reflecting the average of postmenopausal women with co-morbidities and co-medication in order to meet the initial objectives of the PROGEST study.

A recent systematic review and network meta-analysis by Morga et al. compared changes in VMS frequency between 27 HT regimens and fezolinetant. They found no significant differences for the reduction of VMS versus placebo between the 300 mg dose of progesterone (−1.79), the ET regimen E2 1 mg oral (−4.0), synthetic CE (−5.17) or combined E2/drospirenon (−4.07) and fezolinetant 45 mg (−2.78). Tibolone 2.5 mg (the only HT regimen evaluable for severity) significantly reduced VMS severity compared with fezolinetant 45 mg (VMS reduction vs. placebo was −3.38 for the 2.5 mg dose) [19].

As a clinical comment on the data, it should be kept in mind that many trials exclude patients with comorbidities, which leads to insufficient study data that are applicable to real world patients, often presenting with comorbidities. This may either result in withholding treatment from patients with complaints or in treating patients for whom no study data have been generated, and for whom therefore knowledge on effects and risks is limited. The high placebo effect in the trial reported here points to the importance of acknowledging VMS as a relevant complaint, and offering sympathy and help – be it medical or placebo. Whether this is even more relevant in patients with comorbidities than in healthy women, and whether – in case of patient preferences for non-medical treatments –, these could be employed for three months and effects monitored before other therapies are initiated is beyond the scope of this trial, but should be evaluated in the future. Because of the low number of participants, subgroups were not analyzed in this study, but an exploration of the influence of concomitant medication, particularly blood pressure lowering drugs, e.g. beta-blockers, on the effectiveness of progesterone or other treatments for VMS would be worthy of further research.

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Conflict of Interest

VSK was Principal Investigator (LKP) of the PROGEST trial and mentor in the Besins program “Campus Gynäkologische Endokrinologie”.

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