ORIGINAL RESEARCH ARTICLE

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Efficacy of a Non-Hormonal Treatment, BRN-01, on Menopausal Hot Flashes

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Homeopathic medicines have a place among the non-hormonal therapies for the treatment of hot flashes during the menopause.

Objective: The objective of this study was to evaluate the efficacy of the non-hormonal treatment BRN-01 in reducing hot flashes in menopausal women.

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled study carried out between June 2010 and July 2011.

Setting: The study was conducted in 35 active centers in France (gynecologists in private practice).

Patients: One hundred and eight menopausal women, ≥50 years of age, were enrolled in the study. The eligibility criteria included menopause for <24 months and ≥5 hot flashes per day with a significant negative effect on the women's professional and/or personal life.

Intervention: Treatment was either BRN-01 tablets, a registered homeopathic medicine containing *Actaea racemosa* (4 centesimal dilutions [4CH]), *Arnica montana* (4CH), *Glonoinum* (4CH), *Lachesis mutus* (5CH), and *Sanguinaria canadensis* (4CH), or identical placebo tablets, prepared by Laboratoires Boiron according to European Pharmacopoeia standards. Oral treatment (2 to 4 tablets per day) was started on day 3 after study enrollment and was continued for 12 weeks.

Main Outcome Measure: The main outcome measure was the hot flash score (HFS) compared before, during, and after treatment. Secondary outcome criteria were the quality of life (QoL) [measured using the Hot Flash Related Daily Interference Scale (HFRDIS)], severity of symptoms (measured using the Menopause Rating Scale), evolution of the mean dosage, and compliance. All adverse events (AEs) were recorded.

Results: One hundred and one women were included in the final analysis (intent-to-treat population: BRN-01, n = 50; placebo, n = 51). The global HFS over the 12 weeks, assessed as the area under the curve (AUC) adjusted for

baseline values, was significantly lower in the BRN-01 group than in the placebo group (mean ± SD 88.2 ± 6.5 versus 107.2 ± 6.4; p = 0.0411). BRN-01 was well tolerated; the frequency of AEs was similar in the two treatment groups, and no serious AEs were attributable to BRN-01.

Conclusion: BRN-01 seemed to have a significant effect on the HFS, compared with placebo. According to the results of this clinical trial, BRN-01 may be considered a new therapeutic option with a safe profile for hot flashes in menopausal women who do not want or are not able to take hormone replacement therapy or other recognized treatments for this indication.

Trial registration number (EudraCT): 2009-016959-21.

Introduction

Menopausal women frequently complain about hot flashes because of the embarrassment they cause socially and professionally and their impact on the quality of life (QoL).[1-3] During the perimenopause and the menopause proper, up to 80% of women may experience this climacteric problem.[3] In 50% of women, this problem tends to resolve spontaneously within 4 years,[4] but around 30% of women >60 years of age continue to suffer from hot flashes.[5] The number, intensity, and duration of hot flashes and night sweats varies considerably from one woman to another and even individually.[3-5] Hot flashes have a mean duration of between 3 and 4 minutes, but some can last up to 1 hour.[3] Hot flashes can occur spontaneously at any time or may be triggered by certain factors such as emotion, a sudden change in temperature, stress, or consumption of alcohol, coffee, or a hot drink.[4]

Hormone replacement therapy (HRT) is the reference treatment for this climacteric problem,[6,7] and for women who are able and willing to use estrogen, it will successfully relieve hot flashes by about 80–90%.[8] Until recently, the benefit/risk ratio of HRT was considered to be largely favorable as long as the contraindications were respected. However, several large-scale studies, including the American Women's Health Initiative (WHI)[9-11] and the British Million Women Study (MWS),[12,13] have recently challenged this benefit/risk ratio by showing that women taking HRT have an increased risk of breast cancer (odds ratio = 1.25 in the WHI study). This has led to a large number of women discontinuing or not wanting to take HRT. In the US, the number of prescriptions for HRT, which was 91 million in 2001 (treating approximately 15 million women per year) prior to publication of the WHI study in 2002, fell to 56.9 million in 2003.[8] In France, the WHI findings prompted the health authorities to carry out and publish the results of a public hearing on the place of HRT in the menopause.[2] Faced with the increased risk of breast cancer with HRT, there has been new interest in non-hormonal treatments from medical bodies and from women themselves.[14-17]

The development of non-hormonal treatments has evolved in two ways: first, toward existing drugs such as selective serotonin/norepinephrine reuptake inhibitors (SSRIs/SNRIs) or antiepileptics such as gabapentin, which have been shown to have some benefits against hot flashes; and second, toward 'natural medicines' ranging from phytotherapy to acupuncture, although the evidence base for such complementary therapies remains weak.[18-26]

Homeopathic medicines have a place among these non-hormonal treatments, and several of them are indicated for the treatment of hot flashes, following their traditional use by homeopathic practitioners.[27,28] The efficacy of these homeopathic medicines in the management of hot flashes has been described in large-scale observational studies.[29,30] In France, the agent BRN-01 (Acthéane®) is commercially available as a homeopathic combination for this indication. As such, it seemed important to evaluate its efficacy and safety in a randomized, double-blind, placebo-controlled therapeutic trial.

Patients and Methods

Study Design

This multicenter, randomized, double-blind, placebo-controlled study was carried out in 35 active centers in France (gynecologists in private practice) between June 2010 and July 2011. Investigators were randomly selected from a French database of private gynecologists and were contacted by mail and telephone. The principal objective of the study was to evaluate the efficacy of BRN-01 versus placebo on the reduction of the hot flash score (HFS) in menopausal women. The study was authorized by a regional French ethics committee (Comité de Protection des Personnes EST I) and by the French Medicine Agency (on February 19, 2010), and was conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The study was registered with the EU Clinical Trials Register (EudraCT no.: 2009-016959-21).

Study Sample

Women going through the menopause were enrolled in the study if they were aged ≥50 years; if they had experienced amenorrhea for >12 months; and if, during a routine gynecologic consultation, they had spontaneously complained of hot flashes that had started <2 years previously and had significant repercussions on their social and/or professional life of ≥40 mm on a Visual Analog Scale (VAS) ranging from 0 to 100 mm, with a mean frequency of ≥5 hot flashes per day during the 48 hours preceding study enrollment. Women were excluded if they were receiving or had ever received HRT; if they were receiving or had received (within 2 weeks prior to enrollment) β-alanine (Abufène®), food supplements (phytoestrogens, etc.), vitamin E, or courses of acupuncture aimed at relieving hot flashes; or if they were receiving or had received (within 1 week prior to enrollment) other homeopathic treatments aimed at relieving hot flashes. Other exclusion criteria included menopause induced artificially by surgery, chemotherapy, or radiotherapy; hot flashes that could be iatrogenic in origin or could be caused by an associated pathology; receiving treatments that could reduce the frequency of hot flashes, such as antihypertensive treatment with clonidine, antidepressant treatment with SNRIs (venlafaxine), SSRIs (citalopram, paroxetine), mirtazapine (a noradrenergic and specific serotonergic antidepressant), or antiepileptic treatment with gabapentin; and a risk of not complying with the protocol. All patients were able to understand, read, and write French, were affiliated with a social security plan, and gave their written informed consent to participate in the study.

Study Treatments

The treatment evaluated in this study, BRN-01 (Acthéane®, a homeopathic medicine registered in France for menopausal hot flashes and manufactured by Laboratoires Boiron, Sainte Foy-lès-Lyon, France), was in the form of tablets consisting of dilutions of the following five homeopathic medications: *Actaea racemosa* (4 centesimal dilutions [4CH]), *Arnica montana* (4CH), *Glonoinum* (4CH), *Lachesis mutus* (5CH), and *Sanguinaria canadensis* (4CH). The placebo tablets were identical in appearance to the active tablets but included only saccharose (75%), lactose (24%), magnesium stearate E572 (1%), and purified water without any homeopathic dilutions. All treatments were in the same packaging. Laboratoires Boiron provided BRN-01, its matching placebo, and financial support for the study.

Randomization and allocation were carried out centrally by Laboratoires Boiron and generated using the random function of SAS (version 9.2) software. Patient allocation was equilibrated by blocks of six in that each investigator/center was allocated three active treatment units and three placebo treatment units assigned in a double-blind, randomized fashion. In practical terms, each center received a randomization list containing the numbers of six patients and the treatment they should receive, indicated by the letter 'A' or 'B', and treatments were dispensed according to the randomization list. Laboratoires Boiron held the key to the randomization list in a sealed envelope, which was not opened until the end of the study. The key was used only after freezing of the database and finalization of the statistical analyses. Both treatments (BRN-01 and placebo) were

dispensed by Laboratoires Boiron in strictly identical (primary and secondary) packaging.

Treatment was not started until the morning of the third day after enrollment in the trial, in order to allow collection of baseline data for the patients over the preceding 2 days, using a self-administered questionnaire. Treatment was then started for 12 weeks at a dose of 2 tablets per day (taken at least 15 minutes before or after food). Patients were informed that they had the possibility to increase intake to a maximum of 4 tablets per day as needed, depending on the severity of vasomotor symptoms – for instance, when hot flashes were the most bothersome (in terms of the daily number, intensity, or duration).

Primary Evaluation Criterion

The primary evaluation criterion was the effect of BRN-01 on the HFS, compared with placebo. The HFS was defined as the product of the daily frequency and intensity of all hot flashes experienced by the patient, graded by the women from 1 to 4 (1 = mild; 2 = moderate; 3 = strong; 4 = very strong). These data were recorded by the women on a self-administered questionnaire, assisted by a telephone call from a clinical research associate. Data were collected (i) during the first 2 days after enrollment and before any medication had been taken; (ii) then every Tuesday and Wednesday of each week until the 11th week of treatment, inclusive; and (iii) finally, every day of the 12th week of treatment.

Secondary Evaluation Criteria

The secondary objectives were to evaluate variations between enrollment and after 12 weeks of treatment in (i) QoL, measured using the Hot Flash Related Daily Interference Scale (HFRDIS);[31] (ii) severity of symptoms, measured using the Menopause Rating Scale (MRS);[32] and (iii) the effect of hot flashes on the professional and personal life of the patients, measured using a VAS ranging from 0 to 100 mm. Compliance with treatment was measured using the Morisky-Green score, taken at the end of week 12. This score measures treatment adherence on a 4-item self-reported 'yes/no' questionnaire: (i) Do you ever forget to take your medicine? (ii) Are you careless at times about taking your medicine? (iii) When you feel better, do you sometimes stop taking your medicine? (iv) Sometimes if you feel worse when you take the medicine, do you stop taking it? One point was scored for every affirmative answer, and compliance was graded as follows: 0 points = high adherence; 1–2 points = intermediate, moderate adherence; 3–4 points = low adherence or non-adherence.

Safety

All adverse events (AEs) occurring during the study were recorded, and their possible link to the study treatment was assessed.

Statistical Analysis

The statistical analysis was carried out on the intent-to-treat (ITT) population, defined as all patients who took at least one dose of the study treatment and had a least one post-enrollment evaluation. In the case of missing data, the analysis took into account the last evaluation available according to the last-observation-carried-forward (LOCF) technique. The safety analysis was carried out on all patients who took at least one dose of the study treatment.

The sample size for the primary outcome was calculated on the basis of data from previous hot flash studies, as described by Sloan et al.[33] In these, data from the placebo arms showed differences in hot flash activity (between baseline and the end of the first treatment period) of a standard deviation (SD) of two hot flashes and 5 score units per patient per day. From this, it was shown that 50 patients per group provided 80% power to detect differences in average hot flash activity of 0.58 SDs, and that 50 patients per treatment arm provided 80% power to detect an average shift of 1.2 hot flashes per day or an HFS of 3 units per day.[33] With this approach and our hypothesis that there would be a (clinically relevant) difference of 3 points in the HFS in favor of the active (BRN-01) arm and an SD of 5, sample size estimates were calculated using nQuery Advisor (version 6.01) software. We found that a sample size of 49 in each group was required to show this outcome with an α error rate of 5% in a unilateral situation and with a power of 90%.

Quantitative data are described as the number, mean, and SD. Qualitative data are described as the absolute and relative frequencies with 95% confidence intervals (CIs). Comparisons of means were carried out by analysis of variance (ANOVA) or by using the Kruskal-Wallis test if the distribution was not normal. Comparisons of percentages were carried out using the χ^2 test or Fisher's exact test if the conditions for use of the χ^2 test were not fulfilled. Where appropriate, comparisons over time were performed using the Student's t-test. The evolution of the HFS in the two groups was assessed by analysis of the area under the curve (AUC) of the mean scores recorded weekly from each patient in each group over the duration of the study, including those at enrollment (before any treatment). From these data, the mean AUC for each group was calculated for each week (using the rectangular method, which draws non-overlapping rectangles down from the data points) and used as follows, where Sc is the score for any given week (ranging from 1 to 12):

$$\begin{aligned}\text{Area} = &[(Sc1 + Sc2) \times 1/2] + [(Sc2 + Sc3) \times 1/2] + [(Sc3 + Sc4) \times 1/2] \\ &+ [(Sc4 + Sc5) \times 1/2] + [(Sc5 + Sc6) \times 1/2] + [(Sc6 + Sc7) \times 1/2] \\ &+ [(Sc7 + Sc8) \times 1/2] + [(Sc8 + Sc9) \times 1/2] + [(Sc9 + Sc10) \times 1/2] \\ &+ [(Sc10 + Sc11) \times 1/2] + [(Sc11 + Sc12) \times 1/2]\end{aligned}$$

In this method, as each AUC value is unique, comparisons of mean AUCs between the two groups was made using ANOVA. Analysis of covariance (ANCOVA) was used for comparisons adjusted for the baseline HFS between the two groups.

Secondary evaluation criteria were compared by ANOVA on series matched for two factors: time and treatment, and also their interaction. A comparison with baseline values was carried out using the Student's t-test. The percentage of patients who presented with at least one AE was compared between the two groups, using Fisher's exact test. The Morisky-Green score was compared between the two groups at the end of the 12 weeks of treatment, using the χ^2 test, and the number of tablets remaining in the boxes returned by the patients (as a measure of treatment compliance) was compared using the Student's t-test.

All statistical analyses were carried out using SAS (version 9.2) software, with a level of statistical significance fixed at alpha = 0.05.

Results

Study Protocol

One hundred and eight patients were enrolled in this study between June 2010 and July 2011: 54 in each group (BRN-01 and placebo). The ITT analysis included 101 patients: 50 in the BRN-01 group and 51 in the placebo group. Figure 1 summarizes the reasons for patients being excluded from the analysis.

Description and Comparison of Symptoms in the Two Treatment Groups at Enrollment

The mean (± SD) age of the patients was 54.5 ± 4.4 years. There was no statistically significant difference between treatment groups in any of the sociodemographic characteristics or lifestyle habits of the patients (table I). The first signs of the menopause appeared at 50.8 ± 2.9 years and the first hot flashes appeared 2.5 ± 2.9 years before enrollment in the study. Previous treatments for the menopause were homogeneous between the groups: 42.0% of patients in the BRN-01 group and 31.4% in the placebo group had already been treated for the menopause (p = 0.2677): 23.8% versus 18.8%, respectively, had received phytoestrogens (p = 1.0000); 52.4% versus 56.3%, respectively, had received non-hormonal allopathic treatment (Abufene®; p = 0.8150); 14.3% versus 37.6%, re-

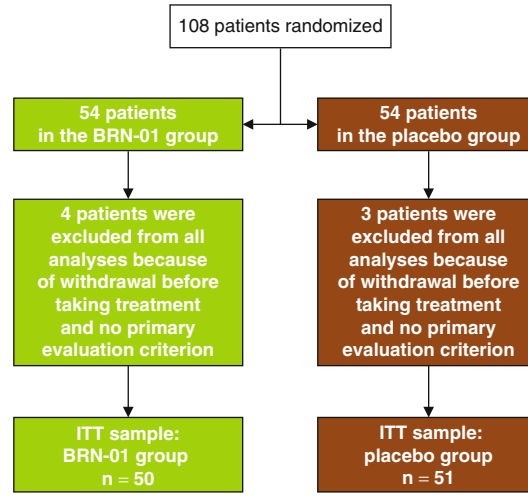

Fig. 1. Distribution of patients in the BRN-01 and placebo treatment groups (CONSORT diagram).

Table I. Sociodemographic characteristics and lifestyle habits of the patients in the two treatment groups

Characteristics	BRN-01 (n = 50)	Placebo (n = 51)
Age (years; mean ± SD)	54.3 ± 4.4	54.6 ± 4.4
Bodyweight (n [%])[a]		
Underweight	1 [2.1]	1 [2.0]
Normal weight	30 [63.8]	32 [65.3]
Overweight	13 [27.7]	12 [24.5]
Obese	3 [6.4]	4 [8.2]
Urban residence (n [%])	34 [68.0]	30 [58.8]
Engaged in professional activity (n [%])	36 [72.0]	41 [80.4]
Non-smoker (n [%])	41 [82.0]	44 [86.3]
Alcohol consumption <1 glass of wine per day (n [%])	45 [90.0]	45 [88.2]
Sedentary lifestyle (n [%])[b]	25 [50.0]	21 [41.2]
Hypocalorific diet (n [%])[c]	3 [6.0]	2 [3.9]
Homeopathic treatment (n [%])[d]	32 [64.0]	32 [62.7]

a Based on the body mass index ($kg \cdot m^{-2}$). The bodyweight data were missing for 3 patients in the BRN-01 group and 2 patients in the placebo group.

b Reported <30 minutes per day of walking, or <30 minutes of jogging or <1 hour of cycling 3 times per week.

c Daily calorie intake below the standard level for a given subject.

d Regular or occasional use of over-the-counter homeopathic medicine to self-treat for general health (not specific to hot flashes or other menopausal symptoms).

SD = standard deviation.

spectively, had received homeopathic treatment (p = 0.1357); and 19.0% versus 25.0%, respectively, had received other food supplements for the menopause (p = 0.7048).

The characteristics of the vasomotor symptoms were also comparable in the two groups at enrollment (table II). Similarly, the distribution of other symptoms of the menopause was comparable in the two groups (figure 2). In association with hot flashes, the women experienced insomnia (79.2% on average in the two groups); nervousness, irritability, and palpitations (68.3%); asthenia (60.4%); skin or mucocutaneous dryness (46.5%); problems with libido (35.6%); problems with memory (20.8%); migraines (15.8%); and mastodynia and mastopathy (12.9%). The mean HFS at enrollment was 12.7 ± 9.5 in the BRN-01 group compared with 15.3 ± 14.7 in the placebo group (p = 0.2902). QoL evaluated using the HFRDIS score (ranging from 0 = not affected to 10 = extremely affected) was also comparable between the groups (4.6 ± 1.9 in the BRN-01 group versus 4.8 ± 2.2 in the placebo group; p = 0.7327), as were all of the ten individual dimensions of QoL (figure 3). When evaluated using a VAS (ranging from 0 mm = no effect to 100 mm = a significant effect), the repercussions of hot flashes and night sweats on professional life were 58.6 ± 23.2 mm in the BRN-01 group versus 61.7 ± 24.7 mm in the placebo group (p = 0.5390) and the repercussions on personal life were 63.6 ± 16.0 mm versus 65.8 ± 18.4 mm, respectively (p = 0.5349).

The MRS score (ranging from 0 = no symptoms to 44 = very strong symptoms) was 20.3 ± 7.5 in the BRN-01 group versus 22.0 ± 8.4 in the placebo group (p = 0.3126). The values were also comparable between the two groups for the three dimensions of the MRS: 7.5 ± 3.5 in the BRN-01 group versus 8.3 ± 3.8 (p = 0.2997) in the placebo group for the psychic dimension; 8.8 ± 2.7 versus 9.3 ± 3.2, respectively (p = 0.4137), for the somatic dimension; and 4.1 ± 3.2 versus 4.4 ± 3.3, respectively (p = 0.5646), for the urogenital dimension.

Evolution of Symptoms on Treatment

Primary Evaluation Criterion: the Hot Flash Score

The comparison of the global HFS over the 12 weeks of treatment, using the AUC, showed that it was significantly lower in the BRN-01 group (82.3 ± 49.4 [95% CI 68.3, 96.4]) than in the placebo group (113.0 ± 88.2 [95% CI 88.2, 137.8]; p = 0.0338). This translates into a decrease in the HFS of 37.3% in favor of women treated with BRN-01.

To accommodate the fact that the baseline HFS was higher in the placebo group, the AUCs for each group were adjusted using Cole's least mean square method, to provide normalized baseline values for the HFS at week 1 (before treatment) for each treatment group, with the corresponding baseline level as the covariance, and compared again. This analysis also showed that the HFS was significantly lower in the BRN-01 group than in the placebo group over the 12 weeks of treatment (88.2 ± 6.5 versus 107.2 ± 6.4; p = 0.0411). This translates into a relative decrease in the HFS of 21.5% in favor of women treated with BRN-01. Furthermore, a clinically relevant decrease of

Table II. Vasomotor symptoms reported at enrollment in the two treatment groups

Symptoms	BRN-01 (n = 50)	Placebo (n = 51)
Symptoms occurring during the last 48 hours before enrollment (n [mean ± SD])		
Night sweats	47 [8.2 ± 10.0]	48 [6.4 ± 4.6]
Hot flashes	48 [15.3 ± 6.2]	51 [15.7 ± 8.4]
Maximum intensity of hot flashes		
Weak	0 [0.0]	0 [0.0]
Moderate	16 [32.0]	13 [25.5]
Strong	26 [52.0]	31 [60.8]
Very strong	8 [16.0]	7 [13.7]
HFS at enrollment, post-randomization (score [mean ± SD])	50 [12.7 ± 9.5]	51 [15.3 ± 14.7]
HFRDIS at enrollment (score [mean ± SD])	47 [4.6 ± 1.9]	48 [4.8 ± 2.2]
MRS at enrollment (score [mean ± SD])	47 [20.3 ± 7.5]	49 [22.0 ± 8.4]
VAS scores at enrollment (mm [mean ± SD])		
Effect of hot flashes and night sweats on personal life	49 [63.6 ± 16.0]	51 [65.8 ± 18.4]
Effect of hot flashes and night sweats on professional life	44 [58.6 ± 23.2]	48 [61.7 ± 24.7]

HFRDIS = Hot Flash Related Daily Interference Scale; **HFS** = hot flash score: self-administered questionnaire on days 1–2 following randomization (after enrollment and before starting treatment); **MRS** = Menopause Rating Scale; **SD** = standard deviation; **VAS** = Visual Analog Scale (ranging from 0 to 100 mm).

3 points in the HFS was obtained after 3.2 ± 1.5 weeks in the BRN-01 group versus 3.6 ± 2.5 weeks in the placebo group, although with no inter-group difference (p = 0.3632). The evolution of the HFS over the course of the study is shown in figures 4 and 5.

Secondary Evaluation Criteria

After 12 weeks of treatment, the HFRDIS score for QoL was not significantly lower in the BRN-01 group than in the placebo group (2.3 ± 1.9 versus 2.8 ± 2.4, respectively; p = 0.2430). The re-

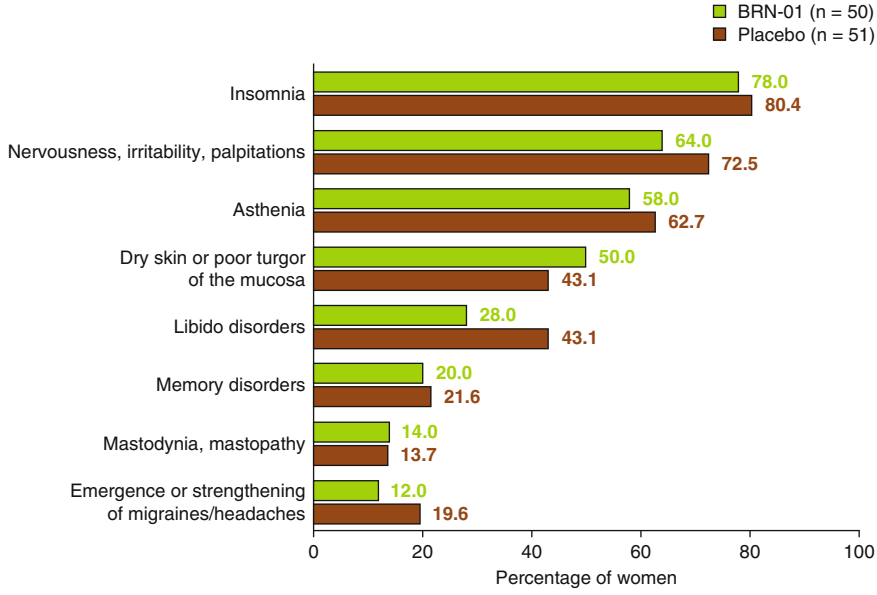

Fig. 2. Comparison of symptoms of the menopause (other than hot flashes) experienced by the women in the BRN-01 and placebo treatment groups.

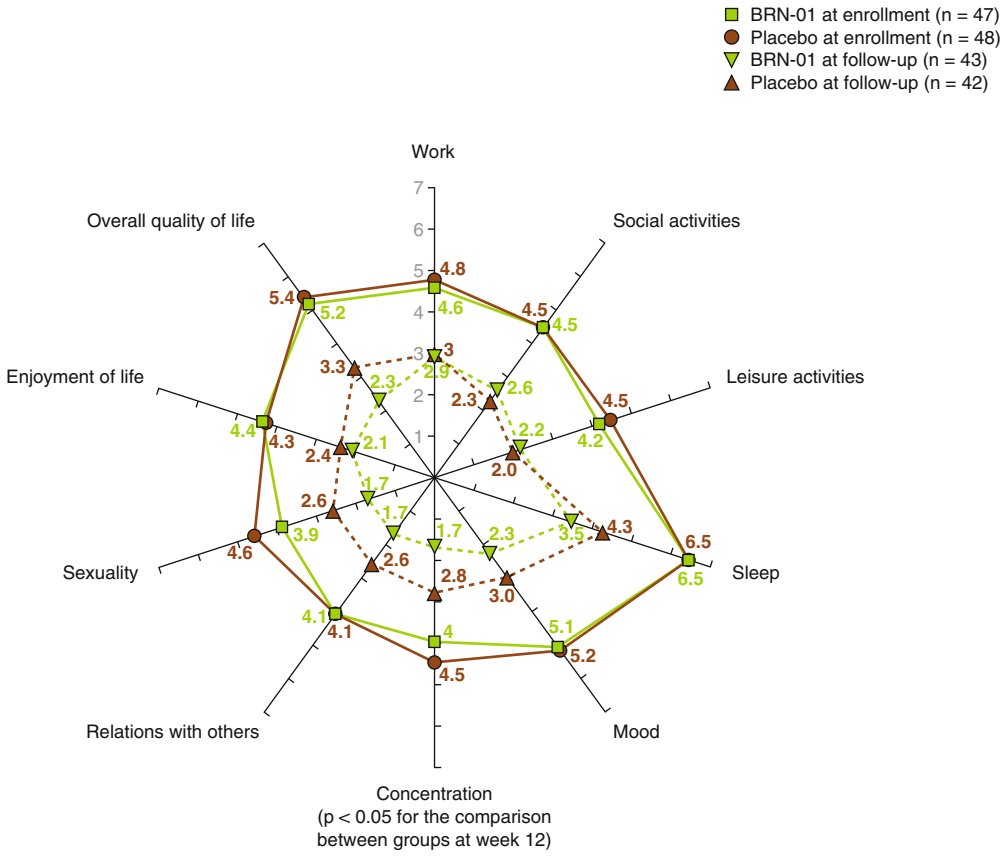

Fig. 3. Comparison of the ten individual dimensions of the Hot Flash Related Daily Interference Scale score in the BRN-01 and placebo treatment groups at enrollment (day 0, before treatment), at the final follow-up visit after 12 weeks of treatment, and from day 0 to week 12. For each dimension, there was a significant reduction in the mean scores from day 0 to week 12 in both treatment groups. The only dimension that differed significantly between groups was the 'Concentration' dimension at week 12 ($p < 0.05$); all other between-group differences at day 0, at week 12, and from day 0 to week 12 were non-significant.

duction in the HFRDIS score was significant in each group but did not differ significantly between the two groups (2.3 ± 2.3 [95% CI 1.7, 3.0] for BRN-01 versus 2.0 ± 2.7 [95% CI 1.2, 2.8] for placebo; p = 0.5121). A similar result was obtained for each of the ten dimensions of the HFRDIS score (figure 3). The reduction in the MRS score at week 12 was also significant for each group but did not differ significantly between the two groups (5.1 ± 5.9 [95% CI 3.1, 7.2] for BRN-01 versus 7.8 ± 9.5 [95% CI 4.7, 10.8] for placebo; p = 0.1774). A similar reduction in distress in the patients' professional and/or personal life and in the number of night sweats between week 1 and week 12 (as measured using a VAS) was also found (data not shown).

Compliance

Calculation of the Morisky-Green score showed that there was poorer compliance with treatment in the placebo group than in the BRN-01 group, although the difference was not statistically significant (figure 6). This was confirmed by the greater number of unused tablets returned by patients in the placebo group (185.5 ± 98.4 for placebo versus 167.0 ± 98.2 for BRN-01; p = 0.3773).

Safety

BRN-01 was well tolerated. There were five AEs in the BRN-01 group and four in the placebo

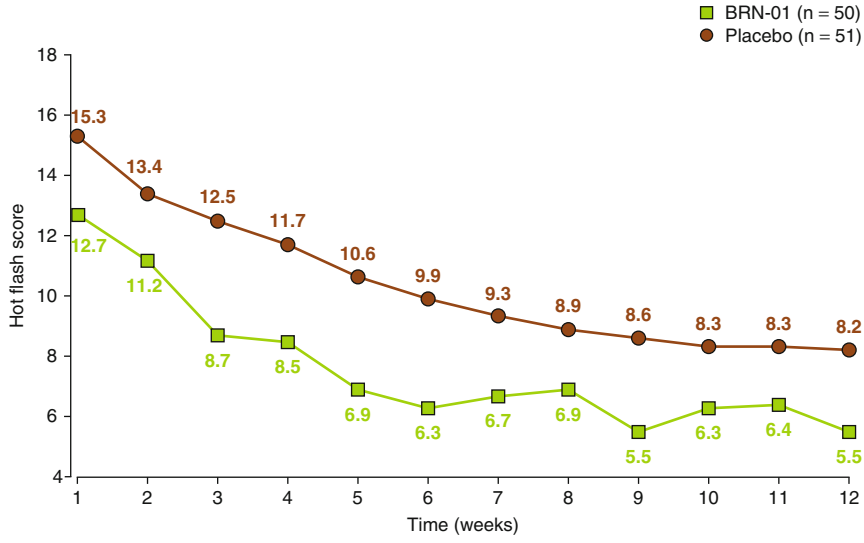

Fig. 4. Evolution of hot flash scores over 12 weeks in the BRN-01 and placebo treatment groups.

group, including one severe AE in each group. These latter AEs were not considered to be related to the study treatment. There was no statistically significant difference between treatment groups in the number of patients experiencing an AE or a serious AE ($p = 0.7409$). Details of the AEs are shown in table III.

Discussion

This randomized, double-blind, placebo-controlled study was carried out in two groups of menopausal women with similar sociodemographic, clinical, and therapeutic characteristics. The characteristics of these women were also similar to

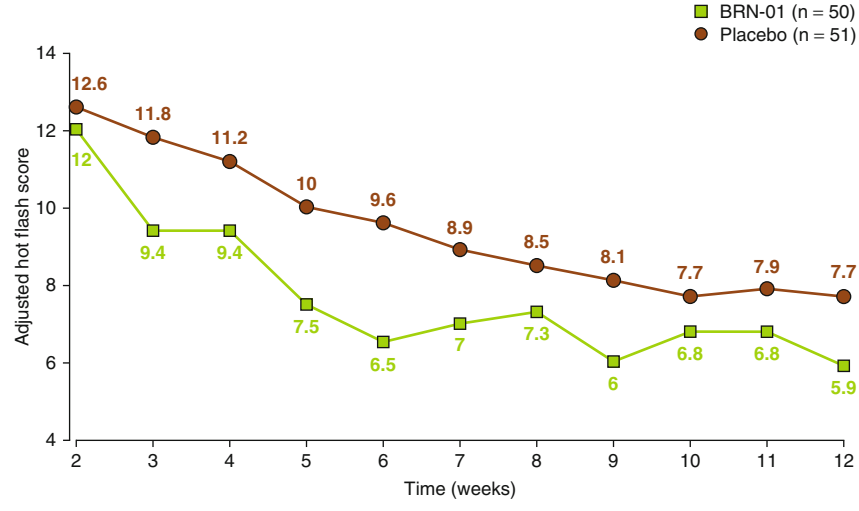

Fig. 5. Evolution of hot flash scores over 12 weeks, adjusted for baseline values (at week 1), in the BRN-01 and placebo treatment groups.

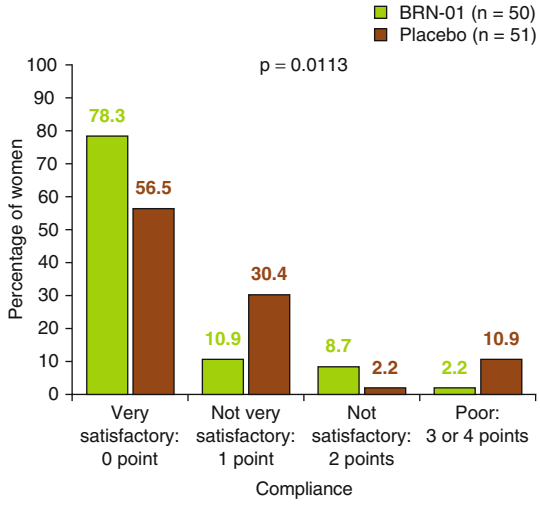

Fig. 6. Morisky-Green scores for compliance in the BRN-01 and placebo treatment groups.

those described in other studies of the management of menopausal hot flashes.[8,18,34] We chose to carry out a comparison of the evolution of the HFS in the two groups, using AUC analyses. This allowed quantification of the evolution of hot flashes over the duration of the study rather than limited estimations, which are subject to important fluctuations from one day to another, and may be particularly relevant, as the prevalence of vasomotor symptoms in menopausal women varies according to the climate, diet, and way of life.[3,35] In contrast to a comparison of limited daily values, the AUC method can provide an overall view of the evolution of individual patients' symptoms over a given period. A similar approach is used in the research of pain,[36] where sequential measurement is subject to similar fluctuations. Our results show that, in terms of the reduction in the HFS, the evolution of the HFS over the period of the study was significantly better in the BRN-01 group than in the placebo group.

The mean reduction in the HFS observed with BRN-01 was 56.7%, or around three-quarters of that obtained with HRT, described as being between 75% and 79% in a review of the Cochrane database.[34] While the reported reductions in the frequency and intensity of hot flashes obtained with BRN-01 are less than those obtained with HRT, they are comparable to the reductions obtained with SSRIs and noradrenaline, evaluated at between 50% and 60% in a meta-analysis by Nelson et al.[18] In this context, BRN-01 has a place in the therapeutic management of hot flashes in women who do not want or are unable to take HRT.

As demonstrated in the literature, the placebo effect is important in the treatment of hot flashes. In our study, the mean reduction in hot flashes with placebo was 46.4% (without adjustment for baseline values), which is less than the 57.7% reduction reported in the Cochrane database,[34] but well within the range of 20–50% established by Kelley and Carroll.[8] The close similarity in the MRS results between BRN-01 and placebo in our study could be due to the fact that this scale includes clinical elements of menopausal symptoms that BRN-01 is not thought to act on.

This is the first randomized, double-blind, placebo-controlled study of the efficacy of BRN-01 to be performed. However, two observational studies have supported the use of homeopathic medicines in women experiencing menopausal hot flashes. In 2004, the National Health Service in Sheffield, UK, carried out an observational study in menopausal women who did not want or were unable to receive HRT. Homeopathic treatment was proposed. Among the 124 patients aged 53 years

Table III. Adverse events occurring in the two treatment groups[a]

Adverse events	BRN-01 (n = 50)	Placebo (n = 51)
No (n [%])	45 [90.0]	47 [92.2]
Yes (n [%])	5 [10.0]	4 [7.8]
Diverticular intestinal abscess[b]	1	
Sensation of thirst at night	1	
Removal of cyst under the left foot[b]	1	
Pruritus	1	
Migraine	1	
Gastritis		1
Headaches		1
Fracture of the wrist (fall)[b]		1
Recurrence of hot flashes		1

a There was no statistically significant difference between treatment groups in the number of patients experiencing an adverse event or a serious adverse event (Fisher's exact test: p = 0.7409).

b These adverse events were not considered to be related to treatment.

who were included in the study, 83 (67%) described an improvement in their vasomotor symptoms.[29] In 2008, a prospective observational study was carried out by 99 doctors in eight countries to evaluate the clinical effectiveness of homeopathic treatments prescribed in daily practice for hot flashes and their impact on QoL of menopausal women. That study, carried out on 438 patients with a mean age of 55 years, showed decreases in the frequency and number of daily and nightly hot flashes ($p < 0.001$) between the enrollment visit and the follow-up visit 2–6 months later. Among those women, 19.4% reported the disappearance of their hot flashes and 70.3% felt an improvement from the first 15 days of treatment onward. They also described a decrease in their daily discomfort and sleep disturbances ($p < 0.001$).[30] Most of the components found in the composition of BRN-01 were present in the different homeopathic treatments described in those studies, at different homeopathic dilutions: *A. racemosa*, *A. montana*, *Glonoinum*, *L. mutus*, and *S. canadensis*. *L. mutus* is traditionally used for its effects in vascular phenomena such as hot flashes, metrorrhagia, palpitations, and throbbing headaches; *Glonoinum* is traditionally used for its effects on hot flashes with redness of the face, palpitations, sweating, and congestive headaches; *S. canadensis* is used for its effects against hot flashes predominantly of the face, with blushing and congestive headaches with throbbing pain; *A. racemosa* is used in menstrual cycle dysfunction with pelvic heaviness, mastodynia, and sleep problems (as observed in the perimenopause); *A. montana* is used for its general action on the vascular system and in hemorrhagic manifestations such as metrorrhagia. In these observational studies, some degree of a placebo effect, as discussed earlier, must be considered. However, our results with BRN-01 (which contains these agents in combination) show a greater reduction in the activity of hot flashes compared with placebo, and suggest that BRN-01 is effective in reducing the severity of hot flashes.

Conclusion

In conclusion, this randomized, double-blind, placebo-controlled study shows that the homeopathic medicine BRN-01 had a greater effect than placebo on the frequency and intensity of hot flashes experienced over a 12-week period, as quantified by AUC analysis. The reductions in the HFS and other measures observed with BRN-01 were smaller than those reported for HRT or, to a lesser extent, antidepressant therapy. However, it remains that BRN-01 could be a new therapeutic option for climacteric syndrome, with an interesting benefit/risk profile, notably in women who do not want or are unable to receive HRT (because of a history of breast cancer, perimenopause, etc.) or other recognized treatments for this indication. Further investigations, which could include controlled and observational studies with BRN-01, would be welcome, to further validate these promising findings.

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