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ORIGINAL ARTICLE

Does a homeopathic medicine reduce hot flushes induced by adjuvant endocrine therapy in localized breast cancer patients? A multicenter randomized placebo-controlled phase III trial

Pierre-Etienne Heudel[1,2] · Isabelle Van Praagh-Doreau[3] · Bernard Duvert[4] · Isabelle Cauvin[5] · Anne-Claire Hardy-Bessard[6] · Jean-Philippe Jacquin[7] · Laetitia Stefani[8] · Lionel Vincent[9] · Dominique Dramais[10] · Jean-Paul Guastalla[1] · Ellen Blanc[11] · Aurélie Belleville[11] · Emilie Lavergne[11] · David Pérol[1]

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Abstract

Purpose Endocrine therapy (ET) used to reduce the risk of recurrence in hormone receptor-expressing disease (75% of breast cancers) is associated with worsening of climacteric symptoms with a negative impact on quality of life (QoL). Homeopathy might allow a better management of hot flushes (HF).

Methods In this multicenter randomized double-blind placebo-controlled phase III study (ClinicalTrials.gov NCT01246427), we enrolled ≥ 18 years old women with histologically proven non metastatic localized breast cancer, with Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) ≤ 1, treated for at least 1 month with adjuvant ET, and complaining about moderate to severe HF. Patients should not be scheduled for chemotherapy or radiotherapy, and had no associated pathology known to induce HF. After a 2- to 4-week placebo administration, we randomly assigned (1:1) patients with HFS ≥ 10 using an interactive web-based centralized platform to BRN-01 homeopathic medicine complex (Actheane®) in arm A or Placebo (Arm P). Randomization was stratified by adjuvant ET (taxoxifen/aromatase inhibitor) and recruiting site. HF scores (HFS) were calculated as the mean of HF frequencies before randomization, at 4, and at 8 weeks post-randomization (pre-, 4w,- and 8w-) weighted by a 4-level intensity scale. Primary endpoint was assessed at 4-week post-randomization, as the variation between pre- and 4w-HFS. Secondary endpoints included HFS variation between pre- and 8w-HFS, compliance and tolerance assessed 8 weeks after randomization, and QoL and satisfaction assessed at 4- and 8-week post-randomization.

Results Two hundred ninety-nine patients were included, and 138 (46.2%) randomized (A, 65; P, 73). Median 4w-HFS absolute variation (A, − 2.9; P, − 2.5 points, $p = 0.756$) and relative decrease (A, − 17%; P, − 15%, $p = 0.629$) were not statistically different. However, 4w-HFS decreased for 46 (75%) in A vs 48 (68%) patients in P arm. 4w-QoL was stable or improved for respectively 43 (72%) vs 51 (74%) patients ($p = 0.470$).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-018-4449-x) contains supplementary material, which is available to authorized users.

✉ Pierre-Etienne Heudel
PierreEtienne.HEUDEL@lyon.unicancer.fr

[1] Department of Medical Oncology, Centre Léon Bérard, 28 rue Laennec, 69373 Lyon Cedex 08, France

[2] Centre Léon Bérard, 28 rue Laennec, 69008 Lyon, France

[3] Centre Jean Perrin, 58, Rue Montalembert, 63011 Clermont-Ferrand, France

[4] Centre Hospitalier, 3 Rue Adhémar, 26200 Montélimar, France

[5] Centre Hospitalier, BP1125, 73011 Chambéry, France

[6] Clinique Armoricaine de Radiologie, 21 rue du Vieux Séminaire, 22000 Saint Brieuc, France

[7] Institut de Cancérologie Lucien Neuwirth, 108, avenue Albert-Raimond, 42270 Saint-Priest-en-Jarez, France

[8] Centre hospitalier de la région d'Annecy, 1 avenue de l'hôpital, BP90074, 74374 Annecy, France

[9] Centre hospitalier de Roanne, 28, Rue de Charlieu, 42300 Roanne, France

[10] Centre hospitalier, 179, Boulevard Maréchal Juin, 26000 Valence, France

[11] Department of Clinical Research and Innovation, Centre Léon Bérard, 28 rue Laennec, 69373 Lyon Cedex 08, France

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Conclusions The efficacy endpoint was not reached, and BRN-01 administration was not demonstrated as an efficient treatment to alleviate HF symptoms due to adjuvant ET in breast cancer patients. However, the study drug administration led to decreased HFS with a positive impact on QoL. Without any recommended treatment to treat or alleviate the HF-related disabling symptoms, Actheane® could be a promising option, providing an interesting support for better adherence to ET, thereby reducing the risk of recurrence with a good tolerance profile.

Keywords Early breast cancer · Hot flushes · Homeopathy · Quality of life

Abbreviations

ET	Endocrine therapy
QoL	Quality of life
HF	Hot flushes.
HFS	HF score
HFRDIS	Hot Flash Related Daily Interference Scale

Introduction

Locally advanced breast cancer is a potential curative disease. Local therapy alone, adjuvant systemic chemotherapy alone, or endocrine therapy (ET) whether combined with chemotherapy or not, and anti-HER2-directed therapy substantially reduce the risk of distant recurrence and breast cancer mortality. ET whether combined with chemotherapy or not, is the adjuvant treatment for 75% of breast cancer patients whose tumors express estradiol or progesterone hormone receptors [1]. The side effects of ET depend on the drugs used and therapeutic strategy. The side effects of the widely prescribed tamoxifen are similar to menopausal symptoms: hot flushes (HF), vaginal dryness or leukorrhea, nausea, irregular menstruation, benign ovarian cyst and, less frequently, weight gain [2]. Aromatase inhibitors induce similar side effects, even if the frequency and the intensity of the symptoms are less noticeable [3, 4]. The HF incidence rate with adjuvant treatment in menopausal women with localized breast cancer is 60 to 65%; severe disabling reactions are observed in one third of these women. Nevertheless, HF management is not systematic, and there is currently no supportive strategy with proven efficiency. Hershmann and colleagues reported that non adherence to ET in women with hormone sensitive stages I–III breast cancer was associated with a 49% increase in all-cause mortality. Promoting interventions to help such patients to comply with the full course of adjuvant ET may impact breast cancer survival [5]. Besides, vasomotor symptoms in breast cancer should be better managed [6].

A growing interest in comprehensive, integrative approaches of cancer has emerged, and physical but also psychological and spiritual well-being should be considered [7–9]. A significant proportion of cancer patients—almost two-third of them—report that they turn towards complementary and alternative medicine at some point in their treatment [10]. Complementary and alternative medicine belong to diverse group of medical and health-care systems, practices, and products and are not yet integrated into conventional medicine [7]. Homeopathy is currently in use to alleviate menopausal symptoms and HF and could reduce this frequent ET's side effect. BRN-01 (Actheane®) is registered in France for the treatment of menopausal HF and functional disorders. BRN-01 is composed of five homeopathic medications in one tablet (*Actaea racemosa* 4CH, *Arnica Montana* 4CH, *Glonoinum* 4CH, *Lachesis mutus* 5CH, and *Sanguinaria Canadensis* 4CH. Mechanism of action hypothesized, in particular, the involvement of the hypotensive activity of *Actaea racemosa*, the cardiovascular activity of *Arnica Montana, Glonoinum*, *Lachesis mutus and Sanguinaria Canadensis*, and neuroendocrine activity of *Lachesis mutus*. The constitutive components are homeopathic drugs indicated for the management of menopausal HF [11, 12]. A placebo-controlled trial reported the efficacy of BRN-01 on the frequency and intensity of menopausal HF experienced over a 12-week period. No statistically significant difference in the number of patients experiencing adverse events or serious adverse events had been reported, and any adverse event was considered to be related to treatment. [13].

The main objective of the present study was to evaluate the efficiency of the homeopathic medicine complex on the HF intensity in women with breast cancer receiving adjuvant hormonal treatment.

Patients and methods

Patients

This multicenter, randomized, double-blind, placebo-controlled, phase III study was carried out in nine authorized centers in France (Online Resource 1). Eligible patients were women ≥ 18 years with histologically proven non metastatic localized breast cancer, treated for at least 1 month with adjuvant ET (aromatase inhibitor, or tamoxifen ± ovarian suppression [LH-RH agonist, surgical menopause…]), with Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) ≤ 1, and complaining about moderate to severe HF and/or bothersome night sweats. Patients with ongoing or scheduled chemotherapy or radiotherapy, with associated pathology (such as hyperthyroidism, diabetes, adrenal tumor, enteric carcinoid tumor, or mastocytosis...) known to induce HF, with severe renal or

hepatic failure, cardiovascular disease, known as hypersensitivity to one of the components of the homeopathic medicine, galactose or fructose intolerance, Lapp lactase or isomaltase invertase deficiency, or with glucose or galactose malabsorption syndrome were ineligible. Enrolment of patients who could not be followed up for social, familial, geographical, or psychological reasons or patients suspected of poor compliance with protocol or treatment was not allowed.

The protocol was approved by Ethics Committee Lyon Sud-Est IV, conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization on Good Clinical Practices guidelines (GCPs). All patients provided written informed consent before enrolment. This study was registered on 2010, Nov 16th with ClinicalTrials.gov, NCT01246427.

Randomization

Randomization was stratified by recruiting site and adjuvant ET (taxoxifen vs aromatase inhibitor ET) and randomly assigned patients in a 1:1 ratio to receive BRN-01 in arm A or Placebo (Arm P) during 8–10 weeks using an interactive web-based centralized registration platform. The randomization list was generated via a computer-generated system, using a permuted block design of size 4 within each stratum. Double-blind randomization was performed, so that neither the patients nor the investigators knew which was the treatment administrated.

Treatment and procedures

BRN-01 (Actheane®) (Laboratories Boiron, Sainte Foy-les-Lyons, France), is a homeopathic medicine registered in France for menopausal HF. BRN-01 is composed of five homeopathic medications in one tablet/*Actaea racemosa* (4 centesimal dilutions [4CH]), *Arnica Montana* (4CH), *Glonoinum* (4CH), *Lachesis mutus* (5CH), and *Sanguinaria Canadensis* (4CH). The placebo tablets were identical to BRN-01 but inert. Treatments were provided by Laboratoires Boiron, in identical primary and secondary packaging.

We performed a baseline assessment within a 2- to 4-week run-in period before randomization. All patients received, a single-blinded HF evaluation kit for a 4-week treatment period exclusively including placebo (two boxes including tablets for twice daily oral intake -morning and evening, between meals-) and a diary for HF self-reporting. After this run-in period, only patients displaying a hot flushes score (HFS) ≥ 10 were randomized to receive experimental treatment, five boxes of either BRN-01 or placebo for the ten following weeks. Masked study drug administration was continued until ET discontinuation, sponsor or investigator-reasoned decision, death, or consent withdrawal. The HFS was calculated at pre-randomization, 4w-, and 8w- post-randomization, and subsequent variations assessed. The Hot Flash Related Daily Interference Scale (HFRDIS) was applied for QoL assessment at each study time. A self-reported patient satisfaction questionnaire had to be filled at 4 and 8 weeks post-randomization. Safety and tolerance were assessed by physical examinations, vital signs, ECOG-PS, and adverse events (AEs) analysis graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4. Confounding factors were collected (BMI, tabagism, alcohol, relaxation practice, regular sport practice, acupuncture, psychological care, homeopathic support, prior moderate to severe HF for menopausal women, antidepressant drugs…). Alternative therapeutic strategies were authorized when initiated prior to study treatment, but patients were not allowed to start another treatment after enrolment (Fig. 1).

Outcome

The primary endpoint was the hot flushes score (HFS) variation between the randomization and the fourth week post-randomization (4w-HFS). Secondary endpoints included the HFS variation between the randomization and the 8th week post-randomization (8w-HFS), compliance, tolerance, quality of life (QoL), and satisfaction.

HFS was calculated as the mean of HF frequencies, weighted by a 4-level intensity scale (1[mild] to 4[very severe]) over a 1-week period [14]. HF were evaluated before randomization (pre-), during the fourth (4w-), and the eighth week (8w-) post-randomization; thanks to a HF self-reported diary to daily report over a 1-week period the number of HF experienced and their intensity. A maximum of 3 days with missing data was tolerated to perform HFS calculation, otherwise HFS was not assessable.

QoL was measured at each study time with the Hot Flash Related Daily Interference Scale (HFRDIS) score ranging from of 1 to 10 where 0 was not affected and 10 was extremely affected [15]. A self-reported patient satisfaction questionnaire had to be filled at 4- and 8-week post-randomization, including satisfaction with treatment efficacy for HF based on a 1 to 5 scale where 1 was inefficient and 5 was very efficient firstly, and secondly satisfaction with HF global management based on a 1 to 5 scale where 1 was very unsatisfied and 5 was very satisfied. Adverse events (AEs) occurring during the study were recorded and their imputability to the study treatment was assessed.

Statistical analysis

The trial design aims to detect a 5-point (± 8.6) difference of HFS variation between arms with 5% two-sided alpha and 90% power. The HFS threshold (≥ 10) was used according to Sloan et al. [14]. Assuming that 49% patients will have a HFS < 10 after the run-in period, a total of 280 patients had to be enrolled to ensure the randomization of a total of 138 patient (69 per arm) for the final analysis.

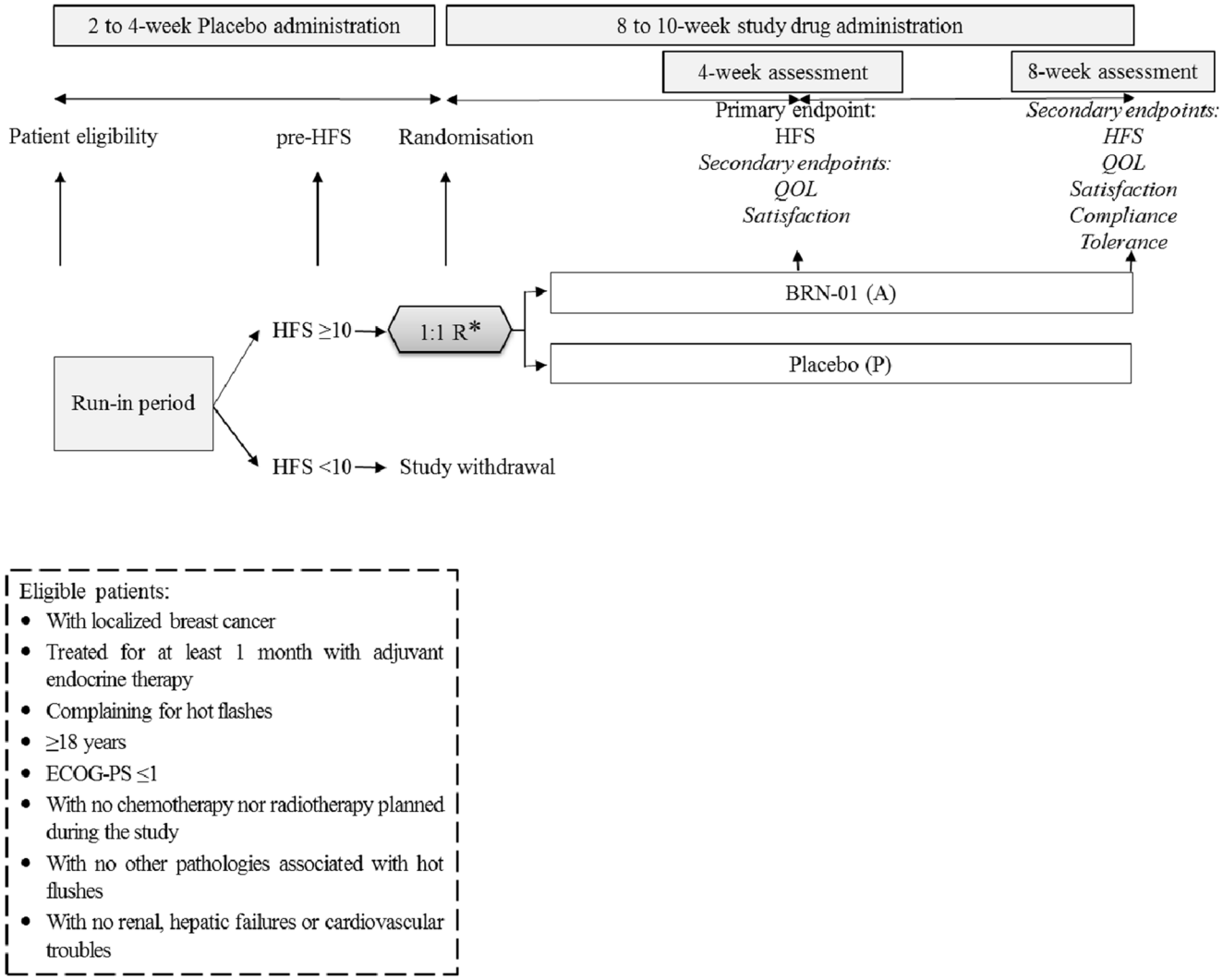


Fig. 1 Treatment and procedure. HFS hot flushes score, assessed after the run-in period, just before randomization (pre-HFS), assessed after the administration of the study drug during 4 week (4w-HFS), or 8 weeks (8w-HFS). R randomization. *Stratification factors were centers and adjuvant endocrine therapy

Based on the intention-to-treat principle, efficacy (HFS variation) analysis was performed on all randomized patients. The primary endpoint was calculated as the intra-individual HFS variability between the fourth week and the randomization date and compared between arms using Wilcoxon test. The HFS relative variation was calculated between the fourth week and the randomization, and compared between treatment arms. Secondary endpoints were HFS variation between the eighth week and the randomization date, and compared between treatment arms. HFS mean daily intensity and frequency were evaluated separately at the fourth and the eighth week, and evolution since the randomization was evaluated by Fisher exact test and Wilcoxon test respectively. Absolute or relative variations from randomization were calculated in each treatment arm and expressed as improved, stable, or decrease. Each dimension of the HFRDIS QoL questionnaire was independently studied at each timepoint, and a global score was inferred. A decreased HFS impact on QoL led to an increased QoL level (increased QoL). Evaluation of the global satisfaction was assessed by determining the rate of patients who were satisfied with the HF management or who required a consultation for HF management during the study. Compliance was evaluated by counting the leftover tablets, and the patient was considered as compliant when the difference between the theoretical and the experimental number was less than 20%. When no packaging was returned, the patient was considered as non evaluable for compliance.

Safety analysis included all patients who received at least one dose of study drug. The number of patients with at least one adverse event related to study drug, or leading to study drug discontinuation were presented in each arm. We did statistical analysis with SAS version 9.3.

Results

From February 2010 to April 2014, nine French centers (three cancer centers, five hospital centers, and one private clinic) enrolled 299 patients, including 138 (46.2%) patients who were randomly assigned after a 2- to 4-week run-in period to receive either the experimental medicine BRN-01 in the arm A, or placebo in the arm P (A, 65 [47%]; P, 73 [53%]; Fig. 2). This population was analyzed following the intent-to-treat principle. One hundred sixty-one patients were not randomized. Six patients although HFS > 10, 142 patients with HFS < 10, and 13 patients with a lack of compliance in reporting data in the HF self-evaluation diary during the run-in period (not assessable HFS, missing booklet for ten patients, and more than 3 days with no HF information collected in the booklet for three patients). Demographic and baseline characteristics were similar between arms (Table 1). Randomized patients had an infiltrating breast tumor diagnosed for 1.5 (0.5–28.2) year in median, and already undergone a surgery − 84 (61%) patients with tumor resection, 36 (26%) with mastectomy, or 18 (13%) with tumor resection followed by mastectomy with a median duration of 15 (2.6–67.1) months since surgery and inclusion date. Median age at inclusion was 63 years (27–85), median BMI was 24 (17–49), and 108 (86%) patients had ECOG-PS = 0. One hundred twenty-eight (93%) patients have been treated by radiotherapy, and 111 (80%) by chemotherapy. Eighty-two (62%) patients were postmenopausal. Twenty-eight (21%) patients did already receive a prior hormone-replacement therapy with a median delay of 3.2 (1–21.3) years since discontinuation. At the inclusion, 79 (57%) patients were treated by tamoxifen and 59 (43%) by aromatase inhibitor with a median delay since ET initiation of 8.3 (0–57) months. To note, median delay since the ET initiation was greater in BRN-01 group (A, 9.9 [1.1–

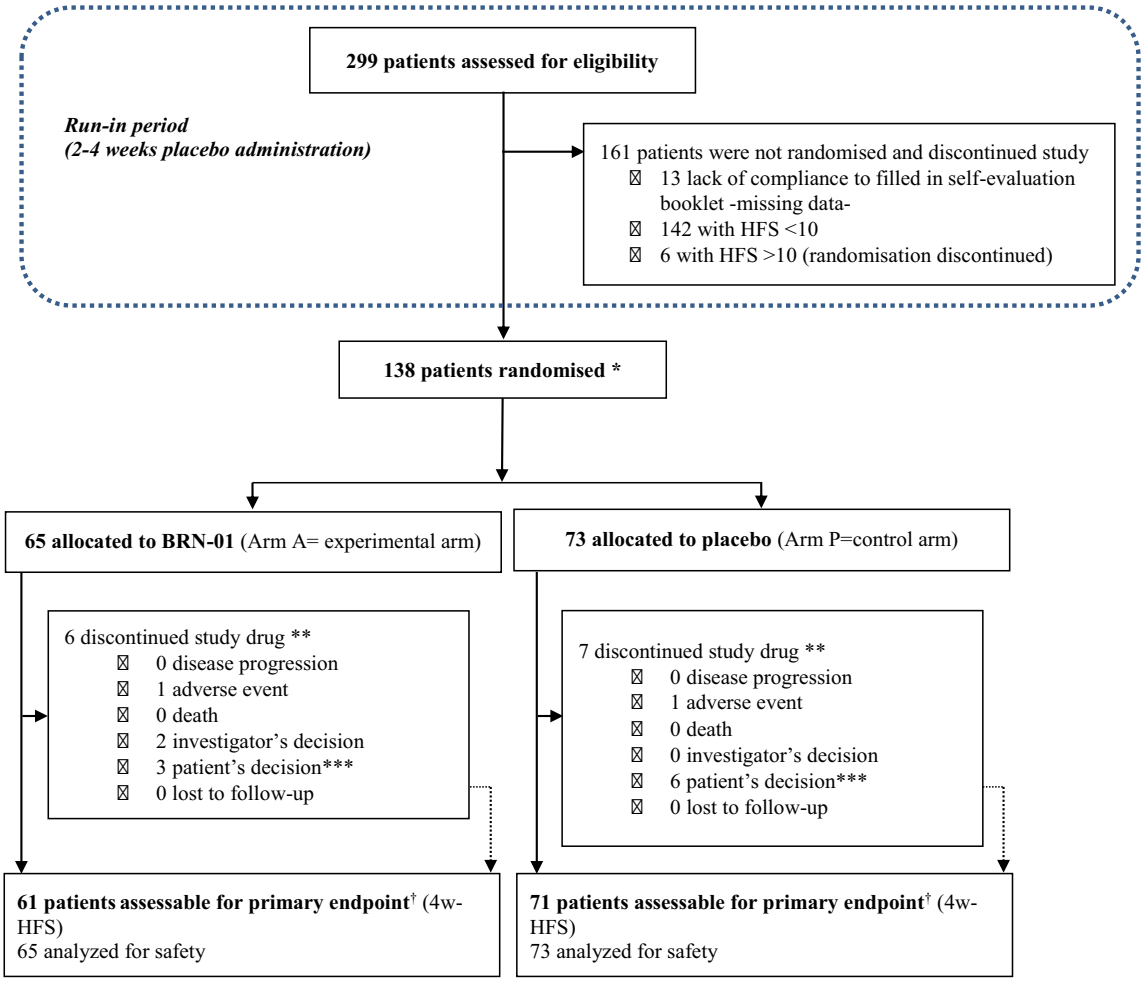


Fig. 2 Trial profile (*treated patients ($N = 138$); **non-exclusive reasons for discontinuation; ***Nine patients decided to prematurely stop the study drug for lack of treatment efficacy (7 patients), too extensive treatment (1 patient), and disappearance of HF even without any study drug administration (1 patient). †6(A, 4; P, 2) patients were non evaluable for the primary endpoint: no booklet at 4 weeks for five patients, and one patient completed the booklet 1 day after randomization. NB per-protocol analysis excluded five randomized patients (one modification in hormono-therapy, two treatment misadministrations during the run-in phase, two treatment misadministrations after randomization). 4w-HFS, hot flushes score at 4 weeks

Table 1 Main demographics and baseline characteristics

	Arm A BRN-01 $N = 65$	Arm P Placebo $N = 73$
Median age at inclusion, years (range)	51.7 (37.6–72.2)	59 (27–81)
Median body mass index	24.45 (17.20–36.2)	23.90 (17.80–48.8)
ECOG performance status		
0	54 (90.0%)	54 (83.1%)
1	6 (10.0%)	11 (16.9%)
Missing data	5	8
Postmenopausal status	39 (61.9%)	43 (62.3%)
Missing data	2	4
Prior hormone-replacement therapy	17 (27.4%)	11 (15.5%)
Missing data	3	2
Median delay since the discontinuation of hormone-replacement therapy (years)	3.0 (1–21.3)	4.0 (1.0–9.2)
Median delay since diagnosis (years)	1.60 (0.50–28.2)	1.50 (0.50–16.0)
Previous treatment		
Chemotherapy	48 (73.8%)	63 (86.3%)
Median delay since the last chemotherapy, months	13.0 (2.8–62.5)	10.9 (3.6–186.7)
Radiotherapy	61 (93.8%)	67 (91.8%)
Median delay since the last radiotherapy, months	12.7 (1.6–338.3)	8.5 (0.2–174.2)
Surgery	65 (100%)	73 (100%)
Mastectomy	16 (24.6%)	20 (27.4%)
Tumorectomy	41 (63.1%)	43 (58.9%)
Mastectomy and tumorectomy	8 (12.3%)	10 (13.7%)
Median delay since the last surgery, months	15.8 (4.4–67.1)	14.9 (2.6–59.5)
Ongoing endocrine therapy		
Tamoxifen	36 (55.4%)	43 (58.9%)
Aromatase inhibitor	29 (44.6%)	30 (41.1%)
Median delay since the initiation of ongoing endocrine therapy (months)	9.6 (1.2–46.8)	0.6 (0.0–4.7)
Prior hormonotherapy	12 (18.5%)	10 (13.7%)

ECOG Eastern Cooperative Oncology Group. Data are median (min-max) or *n* (%)

47]; P, 7.6 [0–57] months). Twenty-two (16%) patients already received a previous hormonotherapy.

As of the cut-off date for data analysis (2014, Dec 1st), the primary endpoint was evaluable for 132 (95.7%) patients (A, 61; P, 71). Six patients were not evaluable because their self-evaluation booklet was missing (no 4w-booklet for five patients, and one patient completed the booklet 1-day post-randomization). No statistical difference was observed in the median (range) 4w-HFS variation (A, − 2.9 [− 16.9; 16.5]; P, − 2.5[− 21.8; 19.4] points; $p = 0.756$), corresponding to a relative decrease of − 17% (− 98.0; 76.7) in A, and − 15% (− 99.6; 171.5) in P group ($p = 0.629$) (Fig. 3). However, 4w-HFS decreased in most patients (A, 46 [75%]; P, 48 [68%]; ($p = 0.323$)) whatever the treatment arm was. 4w-HFS exceeded the < 10 points threshold for 35 (26%) patients without any significant difference between arms (A, 16 [26%], P, 19 [27%]; $p = 0.945$).

No statistical difference was observed in median 8w-HFS variation (A, − 3.9 [− 27.3–17.3]; P, − 3.3 [− 30.4–17.7] points; $p = 0.775$), nor in relative decrease of 28% (− 100.0; 87.1) vs 25% (− 100.0; 156.4) ($p = 0.773$). However, 8w-HFS decreased for 94 (75%) patients (A, 43 (72%) patients, P, 51 (77%); $p = 0.470$). 8w-HFS decreased beyond the threshold of 10 points, identified as clinically significant, for 50 (40%) patients without any significant difference between arms (A, 23 [38%]; P, 27 [41%]; $p = 0.768$). To note, 12 patients were not evaluable for the 8w-efficacy endpoint.

No significant difference between arms was observed neither in the mean daily HF frequency reported as mild/moderate and severe/very severe in 111 (80%) and 27 (20%) patients before randomization, in 104 (79%) and 28 (21%) patients at 4w-, and in 104 (83%) and 22 (18%) at 8w-, nor in mean daily HF 4w−/8w intensity, increased in 80 (61%) and 79 (62.7%) patients respectively. No differences in the 4w- or 8w-variation of the relative or absolute HF frequencies between arms were observed. However, 4w- and 8w-HF mean daily frequency decreased in 94 (71%) and 93 (74%) patients respectively. The 4w- and 8w-HF mean daily intensity was stable in 88 (67%) and 78 (62%) and decreased in 28 (21%) and 34 (27%) patients respectively.

Compliance to the study treatment was similar in arms (A, 82%; P, 85%; $p = 0.606$). During the double-blind period, one assessable patient in A arm and two in P arm had grade ≥ 3 adverse events. Joint pain for one patient in each arm, and one cholecystitis reported as a SAE in the placebo arm 1 month after randomization leading to treatment discontinuation. None of the three grade 3 adverse events were related to treatment. Thirteen (A, 6; P, 7) patients discontinued the treatment. To note, seven patients experienced ET modifications (A, 4 [1 permanent, and 3 temporary discontinuations]; P, 3), and even before randomization for two of them.

The quality of life (QoL) measured using the Hot Flash Related Daily Interference Scale (HFRDIS) reported on Fig. 4 showed either a stable or a mostly reduced HF impact on different QoL item, 4w-, and 8w-post-randomization, whatever the treatment arm considered. The HF impact on QoL was stable or decreased in 33 (26%) and in 61 (47%) patients respectively after 4 weeks and in 33 (27%) and in 61 (50%) patients after 8 weeks. The 4w- and 8w-evaluation of the self-reported satisfaction regarding the global care management was improved in 28 (24%) and in 33 (28%) patients respectively (Table 2).

The requirement to concomitant treatment concerned 20 (15%) patients at randomization, and was similar in both arms, with 11 (8%) patients concerned after 4 weeks and 15 (12%) after 8 weeks. At least one confounding factor at randomization was observed in 115 (84%) patients and several ones in 64 (47%) patients. The most common ones were regular sportive practice (61%) and requirement to homeopathy (31%).

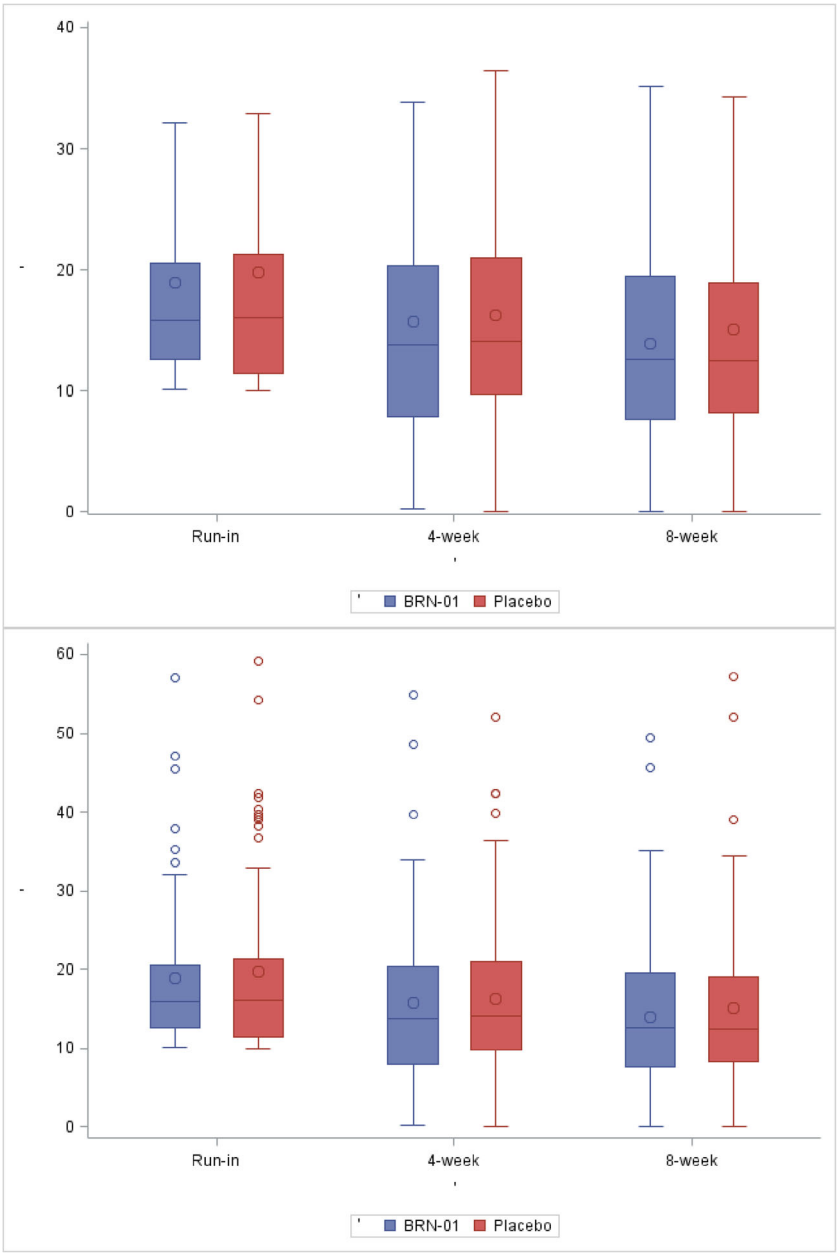
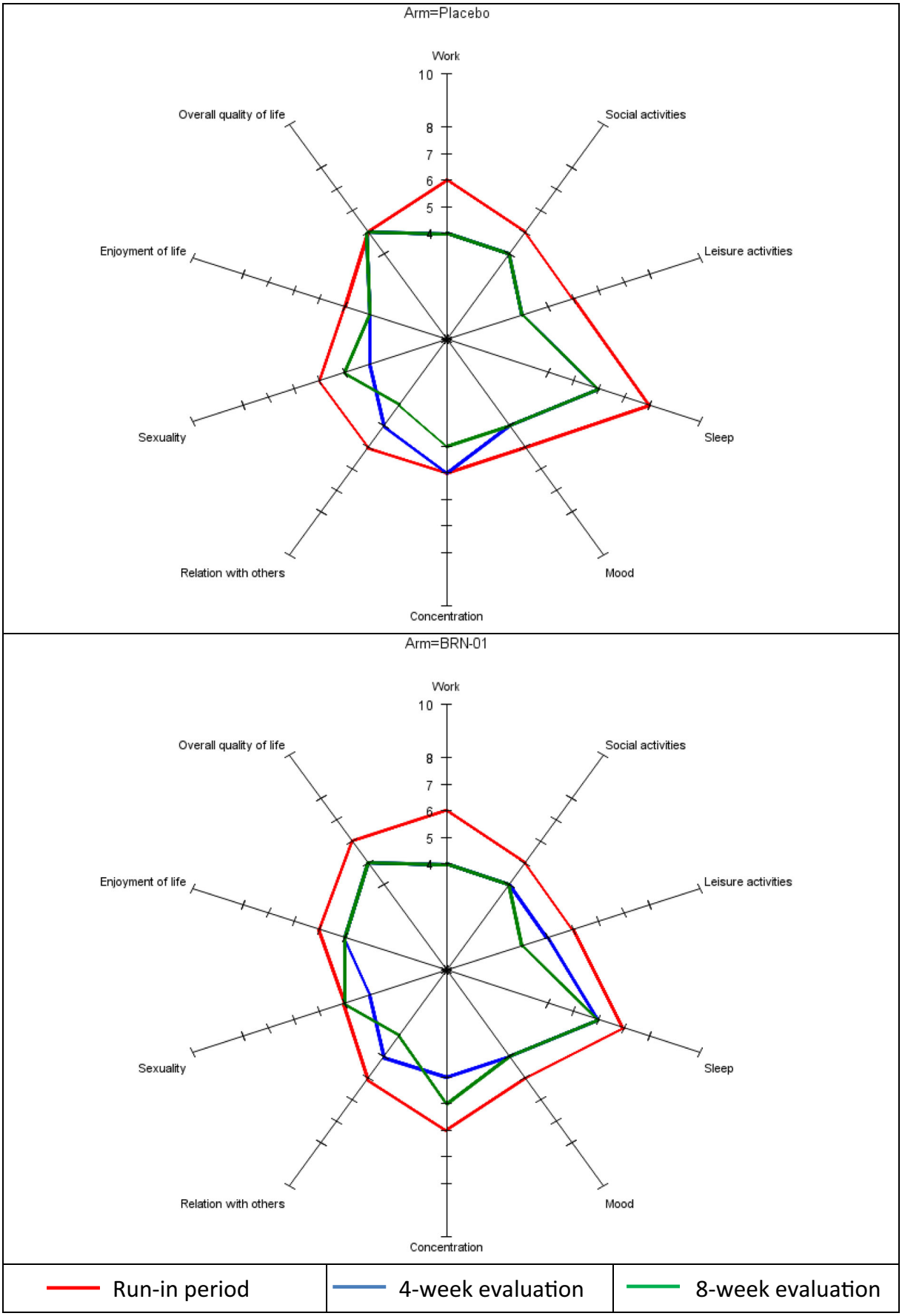


Fig. 3 Evolution of the median HFS in BRN-01 (A) and placebo (P) treatment groups

Discussion

This randomized double-blinded placebo-controlled phase III study failed to demonstrate BRN01 efficacy. Indeed, the efficacy endpoint was not reached, and no significant difference in hot flushes score (HFS) variation was observed between arms in patients with breast cancer. This trial demonstrated that the efficacy of BRN-01 to alleviate hot flushes (HF) was not better than placebo. However, the administration of a study drug (BRN-01 or placebo) led to a clinically significant HF score (HFS) reduction in patients with breast cancer. The HFS was reduced for 75% of the patients in the experimental arm and 68% in the placebo arm ($p = 0.323$), and a 16% HFS decrease was observed in the global population.

The results in our series contrast with the greater effect of BRN-01 on the HF severity in terms of frequency and intensity reported in a randomized double-blind placebo-controlled trial [13] in menopausal women experiencing > 12-month duration amenorrhea and spontaneously complaining of HF with significant repercussion on their social and professional life. We focused on breast cancer women having received at least a 1-month period of endocrine therapy (ET); we used HFS variation as primary outcome and reported as a classical measurement tool in many publications as presented in the recent meta-analysis on hot flushes in breast cancer [16], and a threshold of 10 as defined by Sloan et al. [14]. In addition, we designed a placebo run-in period to minimize the influence of a dreaded placebo effect. Despite no difference between treatment arms, the global patient


Arm=Placebo
Work
10
8
7
6
5
4
Social activities
Leisure activities
Sleep
Mood
Concentration
Relation with others
Sexuality
Enjoyment of life
Overall quality of life
Arm=BRN-01
Work
10
8
7
6
5
4
Social activities
Leisure activities
Sleep
Mood
Concentration
Relation with others
Sexuality
Enjoyment of life
Overall quality of life
Run-in period
4-week evaluation
8-week evaluation

◀ **Fig. 4** Comparison of the ten individual dimensions of the Hot Flash Related Daily Interference Scale (HFRDIS) score in the placebo and in the BRN treatment groups after the 2 to 4w- run-in period, at 4-week, and at 8-week post-randomization

satisfaction was improved. The significant HFS decrease observed in both treatment groups could translate a consequence of a placebo effect from receiving an intervention or another aspect of taking part of a clinical trial as reported in some trials with other highly subjective symptoms like fatigue [17]. Physicians could have not properly addressed the issue of HF in the context of cancer therapy if a related improvement in ET adherence was not expected. We were aware and concerned

Table 2 Concomitant treatment requirement, confounding factors, patient satisfaction – HFRDIS and self-perception satisfaction at randomization (run-in), and at 4w- and 8w- post-randomization

	Arm A BRN-01 *N* = 65	Arm P Placebo *N* = 73
Concomitant treatment requirement		
Requirement at randomization	10 (15.4%)	10 (13.7%)
4w-requirement	4 (6.6%)	7 (9.7%)
8w-requirement	6 (10.0%)	9 (13.0%)
Evolution in the requirement of concomitant treatment		
Missing data	5	4
Continued without any concomitant treatment	50 (83.3%)	56 (81.2%)
Continued with concomitant(s) treatment(s)	4 (6.7%)	5 (7.2%)
Introduction of concomitant(s) treatment(s)	2 (3.3%)	4 (5.8%)
Discontinuation of concomitant(s) treatment(s)	4 (6.7%)	4 (5.8%)
Confounding factors		
At least one confounding factor at randomization	52 (80.0%)	63 (87.5%)
Median number of confounding factor at randomization	1.0 (0.0–4.0)	1.0 (0.0–6.0)
At least one confounding factor at 8w-evaluation	40 (72.7%)	50 (82.0%)
8w-median number of confounding factor	1.0 (0.0–4.0)	1.0 (0.0–5.0)
Variation of the HF impact on perceived quality of life (HFRDIS score): Global mean score		
Missing data at 4w-, 8w- post-randomization	5, 7	4, 8
4w- decrease	28 (46.7%)	33 (47.8%)
4w- stable	15 (25.0%)	18 (26.1%)
4w- increase	17 (28.3%)	18 (26.1%)
8w- decrease	26 (44.8%)	35 (53.8%)
8w- stable	16 (27.6%)	17 (26.2%)
8w- increase	16 (27.6%)	13 (20.0%)
Global self-perception satisfaction:		
Overall care management satisfaction (consultations, follow-up)		
Missing data at the end of run-in, at 4w-, at 8w- post-randomization	5, 6, 8	6, 8, 7
Satisfied/very satisfied at the end of the run-in	36 (60.0%)	41 (61.1%)
Satisfied/very satisfied at 4w	43 (72.9%)	43 (66.2%)
Satisfied/very satisfied at 8w	40 (70.1%)	41 (62.1%)
Evolution of overall care management satisfaction		
Missing data at 4w-, at 8w- post-randomization	10, 11	12, 11
4w- decrease	8 (14.5%)	10 (16.4%)
4w- stable	35 (63.6%)	35 (57.4%)
4w- increase	12 (21.8%)	16 (26.2%)
8w- decrease	9 (16.7%)	12 (19.4%)
8w- stable	32 (59.3%)	30 (48.4%)
8w- increase	13 (24.1%)	20 (32.3%)

Concomitant treatment requirement, confounding factors, global satisfaction regarding overall care management, and evolution of the satisfaction through the study period. Data are median (min-max) or *n* (%)

about a potential placebo effect, and we planned an enrolment of 30% more patients in the run-in phase to reach the expected sample size but almost half of the enrolled population experienced HF improvement in the run-in phase and was consequently withdrawn. Such a high rate of patients with placebo effect was unexpected and a result in itself. However, the subjectivity was not erase in each arm. To note, the 4w- and 8w-HFS even exceed the HFS ≤ 10, score pre-identified as a disabling limit, for respectively 35 (26%) and 50 (40%) patients in the global population with no difference between arms. HF related to ET's side effects appeared to be better tolerated when clinicians were allocating adequate time though clinical consultations to acknowledge and discuss HF. Thus, patients benefit from this kind listening and this attentive relationship with the oncologist might correlate with a higher patient's satisfaction regarding the global care management. Patients would be more likely to support ET-related inconvenience, and an improved adherence might consequently be expected. This relationship with the oncologist may also be perceived as emotionally supportive, and even if positive therapeutic outcomes are still to be explored, the global patients support network appeared as a key component; its effect on health could not be ignored and should contribute to the evolution of the patient care management. The importance of listening to patient complaints might also lead to a survival benefit through support by a palliative care team as soon as cancer is diagnosed [18], and patient symptom evaluation self-reporting on web application [18, 19].

The question whether homeopathic intervention differs from placebo awaits decisive answers and despite important growth activity in homeopathic research in the last decades, concerns about study quality limit the interpretation of available randomized controlled trials data [20, 21]. Homeopathy, as other complementary and alternative medicine like phytotherapy and acupuncture might represent an active coping strategy for the management of cancer-related symptoms and distress, through greater understanding of biopsychosocial approaches to cancer treatment regimens [22], and might facilitate the growth of benefit finding.

The main limitation of this study is based on the measures issued from a health-related quality of life questionnaire classically used to evaluate health-related concerns. Moreover, we reported self-reporting questionnaire data, which may provide a high variability, with subjective measures such as hot flush rates. Even though retrospective measures were avoided, self-reported over a 1-week diary data were collected, and no follow-up was provided neither through a telephone call assistance of a clinical research associate nor a link to a sentinel web application follow-up [19]. Self-reporting questionnaire data were used intentionally in this study to avoid potential biases due to extra-attention through a phone call provided to enrolled patients [23]. The high variability of data with subjective measures such hot flush rates may have deserved to be followed-up through a sentinel web application, but such follow-up was not frequent at the time of study conception, it would probably be carefully studied nowadays in a study design.

Conclusions

Although efficacy endpoint was not reached, the management of HF globally decreased HFS, with a positive impact on QoL in patients with breast cancer. Without any validated treatment to alleviate disabling symptoms such as HF, Actheane® could be a well-tolerated therapeutic option contributing to overcome the related endocrine therapy side effects, enhance adherence to endocrine therapy, and thereby improve treatment efficacy and survival. Further studies will be required to evaluate more accurately the impact of care management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent An informed consent was obtained from all individual participants included in the study.

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