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French multicentre randomised phase III trial evaluating the efficacy and safety of vaginal radiofrequency in the management of vulvovaginal atrophy and dryness in patients treated for breast cancer (RF-Vaginale): trial protocol

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ABSTRACT

Introduction Symptoms associated with vulvovaginal atrophy affect up to 73% of patients with breast cancer, whether menopausal or non-menopausal, because certain breast cancer treatments are responsible for oestrogen deprivation on the genital tract. These symptoms are currently underdiagnosed and undertreated but can significantly impair the quality of life and can be a cause of premature discontinuation of adjuvant hormone therapy. Treatment of vulvovaginal atrophy in patients managed for breast cancer should be the first-line treatment with non-hormonal local moisturising therapy. However, this treatment is often insufficient. Systemic menopause hormone treatment is not indicated and local oestrogen treatment is not a first-line treatment in this neoplastic context. Therapeutic alternatives, such as vaginal radiofrequency (RF) treatment, could be considered. Vaginal RF increases collagen synthesis by stimulating fibroblasts. However, the vaginal RF has not been sufficiently evaluated in the literature. We hypothesised that vaginal RF can improve a patient's experience of vaginal dryness after breast cancer treatment when first-line local moisturising treatment is insufficient.

Methods and analysis The RF-Vaginale trial will be a multicentre randomised phase III trial in two parallel groups until the 6-month assessment comparing a reference treatment with local moisturising (hyaluronic acid-based treatment, three times a week) versus the experimental treatment combining reference treatment+vaginal RF treatment. The vaginal RF treatment will consist of three sessions spaced 4–6 weeks apart (MATMATECH, GynWave 360). The primary outcome will be vaginal dryness, assessed at 6 months using a patient-rated 0–10 numerical scale. The secondary outcomes will be dyspareunia and Vaginal Health Index Score (VHIS). Dyspareunia will be assessed by the patient using a patient-rated 0–10 numerical scale, in patients reporting a sexual life with a male partner engaged in vaginal intercourse. The VHIS will be assessed by a physician blinded to the treatment group. All outcomes will also be evaluated at 3 and 12 months.

This trial will be proposed to a population receiving an adjuvant treatment for breast cancer with an aromatase inhibitor ±luteinising hormone-releasing hormone (LHRH) agonist.

The primary analysis will focus on the evaluation of the mean difference in vaginal dryness score at 6 months between arms, adjusted for baseline value, patient age (<50 vs 50–54 vs 55–64 vs ≥65) and type of hormone therapy (anti-aromatase with vs without LHRH agonist), estimated using an analysis of covariance model. Assuming a SD of 4.5 for the score at 6 months, 71 patients need to be analysed to ensure an 80% power if the difference between the groups is 3, the test being performed at the two-sided alpha threshold of 0.05. Assuming a 5% rate of non-evaluable patients at 6 months, we plan to recruit a total of 75 patients.

Ethics and dissemination The study protocol has been approved by the ethics committee (CPP Sud Est I, 12 November 2024), complied with the Declaration of Helsinki and French laws and regulations, and followed the International Conference on Harmonisation E6 Guideline for Good Clinical Practice (reference number EMA/CHMP/

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multicentre academic trial.
⇒ Randomised controlled design.
⇒ Primary estimand based on patient-reported outcome, evaluated on the intention-to-treat population, with a blinded assessment of secondary physician-evaluated outcomes.
⇒ The eligibility criteria lead to a rather homogeneous study population, and consequently, external validity is limited to this specific target population.

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ICH/135/1995). The trial results, even if inconclusive, will be presented at international oncology congresses and published in peer-reviewed journals.

Trial registration number NCT06900374.

INTRODUCTION

Vulvovaginal atrophy and dryness are caused by oestrogen deprivation of receptors in the genital tract. Symptoms generated by atrophy have been defined as Genitourinary Menopause Syndrome (GUMS), and in the literature, they concern up to 70% of the menopausal population.[1–3] The GUMS has an impact on sexual health and quality of life.[4 5]

Symptoms associated with vulvovaginal atrophy affect up to 73% of patients with breast cancer, whether menopausal or non-menopausal, as breast cancer treatments (chemotherapy, hormone therapy, ovarian suppression by luteinising hormone-releasing hormone (LHRH) agonists and surgical ovarian suppression) are responsible for oestrogen deprivation.[6 7] Symptoms associated with vaginal dryness in patients with breast cancer are currently underdiagnosed and undertreated.[3 8] These symptoms, which significantly impair quality of life, can cause premature discontinuation of treatment, particularly adjuvant aromatase inhibitor therapy.[9] With new indications for extended hormone therapy beyond 5 years, the management of side effects is essential.[10–12]

First-line treatment for vulvovaginal atrophy in patients managed for breast cancer should be non-hormonal local moisturising therapy.[13–18] However, this treatment is often insufficient. Due to their temporary action, moisturising or lubricating treatments (composed of water, silicone, glycerin, mineral or vegetable oil) do not improve vaginal trophicity in the long term and are less effective than local oestrogen therapy.[19 20] Treatments based on hyaluronic acid are effective for GUMS symptoms compared with no treatment but are less effective than local oestrogen therapy.[21 22] Systemic menopause hormone treatment is contraindicated in the context of breast cancer.[23–25] Among postmenopausal women with a history of oestrogen-dependent malignancy, including breast cancer, the use of local vaginal oestrogen continues to raise clinical concerns. Current data indicate that it may be considered for carefully selected patients who do not respond to non-hormonal strategies, provided that the decision is made jointly with the patient and, in particular, when they are not receiving aromatase inhibitors.[26] However, the absence of robust long-term randomised evidence and the inconsistency of available results lead to substantial differences in clinical practice.

As a result, non-hormonal therapeutic alternatives are increasingly being investigated for women who are advised to avoid, or who prefer to avoid, hormonal treatments. However, the literature is still limited for evaluating these methods, particularly in a population of patients treated for breast cancer.[27–53]

Vaginal radiofrequency (RF) for the management of vulvovaginal atrophy has not yet been sufficiently evaluated. However, this therapy, which is possible in a neoplastic context, is attracting attention because it offers an alternative to first-line treatment, which is often insufficient. Vaginal RF increases collagen synthesis by stimulating fibroblasts.[40–42] It has positively affected the vaginal microbiome, vaginal pH and Vaginal Health Index Score (VHIS).[43] Current studies have a low level of evidence as they are mainly observational and involve a small number of participants.[44–50] Moreover, they do not always study the symptoms of vulvovaginal dryness and atrophy, but sometimes vaginal laxity,[42] urinary symptoms[49] or vulvar atrophy alone.[46] Two recent randomised trials conducted outside the cancer setting compared vaginal RF with local oestrogen therapy and found their efficacies to be comparable.[51 52] One randomised trial failed to show efficacy of RF versus Cetomacrogol gel, in the setting of postmenopausal GUMS.[53] However, the trial included lacked power as only 48 patients of the planned 112 were recruited, the study population included only 19 patients with breast cancer. Non-hormonal local moisturising therapy remains the first line of treatment in patients suffering from GUMS after breast cancer. New approaches, such as vaginal RF, should be compared with the reference therapy.

We hypothesise that vaginal RF can improve vaginal dryness in patients treated for breast cancer when first-line local moisturising treatment is insufficient. Thus, the primary objective of this study, called RF-Vaginale, is to evaluate the effect of vaginal RF in combination with a reference treatment compared with the reference treatment alone in terms of patient-reported vaginal dryness at 6 months. The secondary efficacy objectives are to evaluate the effect of vaginal RF in terms of patient-reported dyspareunia and the VHIS evaluated by a gynaecologist. We will also evaluate the side effects of vaginal RF and the use of local treatments in the first 6 months and beyond. As an exploratory objective, we plan to assess the correlation between the different measurements reported by the patient and doctor at different assessment times and the concordance in terms of response to treatment (improvement, stability, worsening of the score) according to the type of measurement. Finally, we will estimate and compare the frequency of premature discontinuation of the initially prescribed hormone therapy due to gynaecological symptoms in both groups.

METHODS AND ANALYSIS

Trial design

We will conduct a randomised phase III superiority trial comparing two parallel groups until the 6-month assessment:

- The control group will consist of the reference treatment only, combining local moisturising

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(hyaluronic acid-based treatment, three times a week) with the possibility of using associated measures at the investigator's discretion (physiotherapy, vaginal dilators).
- The experimental group will consist of vaginal RF (three sessions spaced 4–6 weeks apart) in combination with the reference treatment.

RF may be offered after the evaluation at 6 months to patients in the control group who are insufficiently relieved.

This academic trial is sponsored by the Oscar Lambret Cancer Centre (contact information: promotion@o-lambret.fr). It has been designed by the study coordinator, the investigators, the methodologist, and the sponsor team who will also be responsible for the conduct, data analysis and reporting of trial results.

The Patient Committee of the National League against Cancer (Ligue Nationale Contre le Cancer) has examined the protocol, paying particular attention to the quality of the information letter, monitoring plan and suggestions implemented in the protocol to improve patient comfort.

The trial will be conducted in five comprehensive cancer centres or university hospitals in France. This trial has been approved by the appropriate institutional review boards.

This trial has been registered at ClinicalTrials.gov in March 2025 (https://clinicaltrials.gov/study/NCT06900374).

Inclusion and exclusion criteria

The eligibility criteria for the patients will be as follows:
- Age >40 years.
- Adjuvant treatment for breast cancer with an aromatase inhibitor ±LHRH agonist (for at least 3 months with a planned remaining duration of at least 12 months).
- Disabling vaginal dryness symptoms (attested by a vaginal dryness score ≥3) despite well-administered local moisturising treatment.
- Affiliation with a social security organisation and signature of an informed consent form for the present study.

The exclusion criteria will be as follows:
- Contraindications related to the RF technique (ongoing urinary tract infection, pacemaker, intrauterine device, pregnancy).
- Mucocutaneous disease with vulvovaginal localisation: infection, sore, lichen sclerosus, psoriasis and eczema.
- Neurodegenerative disease with perineal involvement.
- Current or recent local treatment (within the last 12 months) with other physical methods, including vaginal laser, photobiomodulation, platelet-rich plasma injection, hyaluronic acid injection or lipomodelling.
- Pregnancy or breastfeeding.
- Under guardianship or trusteeship.

Treatment

Interventions

The reference treatment will be prescribed by the investigating physician (non-observer) for all randomised patients, regardless of the assigned treatment group. This treatment combines local moisturisation with hyaluronic acid-based treatment three times a week.

The investigating physician (non-observer) will prescribe vaginal RF treatment to the patients allocated to the experimental arm. This treatment will include three sessions of 20 min, spaced 4–6 weeks apart (M0, M1, M2) ±1 maintenance session between 8 and 12 months (M8–M12). The medical device is a class 1 medical device (CE-marked device, certificate of conformity, and user manual attached in the online supplemental appendix) by MATMATECH with a RF generator type Gynwave 360+ non-sterile RF probe (product references: Gynwave generator: GW/vaginal probes: V01, V03 and V04; control pedal: TGW/conductor plate: PGW). The investigating physician will be trained to use the device before participating in this study.

During the treatment session, the patient will be placed in the gynaecological position. After inserting the endovaginal probe, the temperature of the probe will be gradually increased to between 42°C and 48°C. The treatment session will last for approximately 20 min. If, during the session, the patient experiences pain or burning, the session can be continued by reducing the temperature or interrupted before 20 min have expired. The session will be suspended if, for any reason, the patient wishes to stop the session before 20 min have expired.

Criteria for treatment discontinuation

The study treatment may be discontinued on the participant's request. In the case of discontinuation of the initially planned hormone therapy (for whatever reason), the study treatment should be continued as far as possible.

Strategies to improve adherence to intervention protocols and any procedures for monitoring adherence and plans to promote participant retention and complete follow-up

The possibility of RF treatment after the 6-month evaluation should limit the risk of consent withdrawal in the control group. In both groups, all gynaecological treatments will be recorded to monitor adherence to the study procedures.

Study visits and interventions will be scheduled at the same time as standard medical visits to limit the burden related to the study protocol. In addition, the sponsor will cover the transportation costs.

The gynaecological follow-up will be maintained within the framework of the study in all cases, even if the study treatment is prematurely discontinued, except if the patient withdraws consent for any study evaluation.

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Table 1 Vaginal Health Index Score

	1	2	3	4	5
Elasticity	None	Poor	Fair	Good	Excellent
Fluid volume	None	Scarce amount, vault not entirely covered	Superficial amount, vault entirely covered	Moderate amount	Normal amount
Vaginal pH	≥6.1	5.6–6.0	5.1–5.5	4.7–5.0	≤4.6
Epithelial Integrity	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	Not friable, thin epithelium	Normal
Moisture	None (surface inflamed)	None (surface non-inflamed)	Minimal	Moderate	Normal

Relevant concomitant care and interventions that are permitted or prohibited during the trial

There is a possibility of using associated measures at the investigator's discretion, such as physiotherapy and vaginal dilators, which is part of the standard of care, similar in both treatment groups.

Physical treatments (vaginal laser, photobiomodulation, platelet-rich plasma injection, hyaluronic acid injection or lipomodelling) will be excluded. We believe that the risk of using these treatments is limited, as they are not widely used in France, apart from specialised centres that do not participate in this study.

Outcomes

The primary outcome will be vaginal dryness, assessed by the patient using a 0–10 numerical scale at 6 months (M6).[30] This endpoint will also be assessed at baseline (M0) and at 3 and 12 months (M3, M12).

The secondary efficacy outcomes will be dyspareunia and VHIS assessed at M0, M3, M6 and M12. In patients reporting a sexual life with a male partner engaged in vaginal intercourse, dyspareunia will be assessed by the patient using a patient-rated 0–10 numerical scale. The VHIS will be assessed by a gynaecologist blinded to the treatment group. The VHIS is a composite score; for each of the five components, a score from 1 to 5 is determined, and the overall score is calculated by summing the scores for the five criteria (table 1).[54]

The side effects classified as possibly related to RF treatment will be assessed by the patients and physicians during and after each RF session, over the whole study duration. The type of side effect (sensation of heat, redness, erythema, hypersensitivity, dyspareunia), time of onset (during the session, immediately after or >24 hours after the session), intensity (graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events version 6.0 scale), and consequences of the treatment (need to interrupt the session, reduce the RF temperature) will be registered.

As an exploratory criterion, we will assess any discontinuation of initially prescribed hormone therapy, change in hormone therapy, other changes in oncological treatment, and reasons for these changes (related to gynaecological symptoms or not) at each medical visit.

Time schedule

The time schedule is described in figure 1.

Sample size

Assuming an SD of 4.5 for the score at 6 months,[55] 71 patients need to be analysed to ensure an 80% power if the difference between the groups is 3 (difference

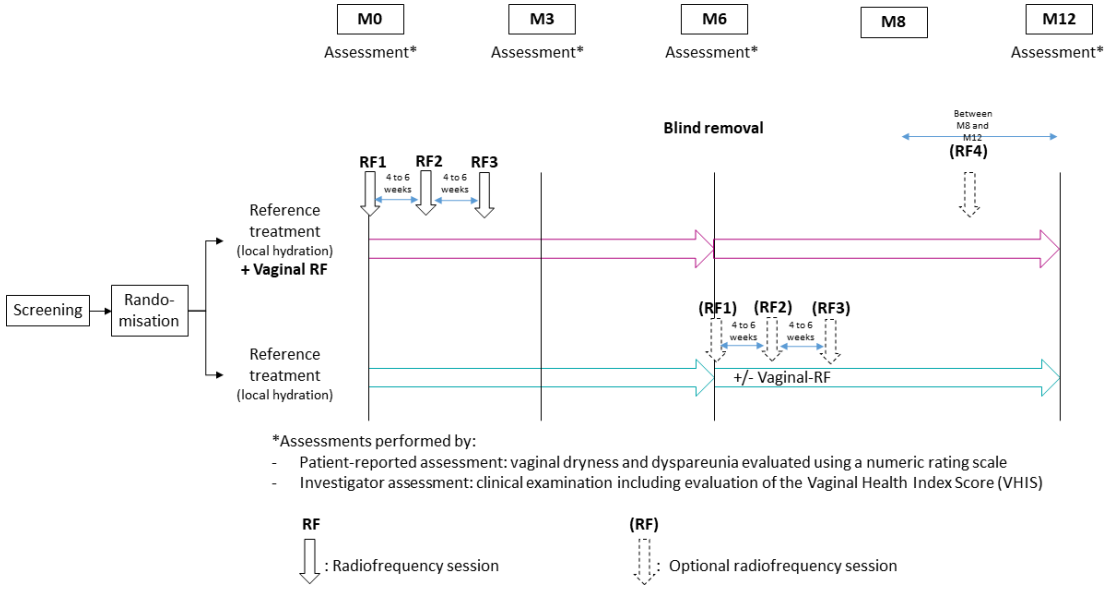


Figure 1 Trial scheme. RF, radiofrequency.

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considered clinically relevant and achievable according to the data in the literature), with the test being performed at the two-sided alpha threshold of 0.05. Assuming a 5% rate of non-evaluable patients at 6 months, we plan to recruit a total of 75 patients. This number of participants seems achievable over a 36-month recruitment period, given the recruitment capacity of the participating centres.

No interim analysis of efficacy or futility is planned, given the relatively short recruitment period and the absence of the expected risk associated with the intervention. However, given the uncertainty surrounding the parameters required to calculate the sample size (variance uncertainty), an interim analysis is planned to estimate the residual variance of the primary endpoint when data from approximately 35 patients are analysed to re-estimate the number of participants required if the variance is greater than anticipated.

Recruitment

The oncologists will routinely screen for gynaecological symptoms that occur during breast cancer treatment. Dedicated visits by gynaecologists are already planned in the participating centres to offer the best supportive care in this setting. This study will be introduced and proposed by the study gynaecologist to patients with debilitating symptoms of vaginal dryness despite well-managed local moisturising treatment.

Before signing the consent form, the patients will be informed about this study, including its aim, randomised design, duration, and schedule. An information note will be provided to the patient, and written consent will be obtained. The patients will be provided with sufficient time to decide whether to participate and given the opportunity to ask any questions they may have. The patients will be enrolled in this study by the investigator after verifying the eligibility criteria.

Assignment of interventions

Randomisation will be performed centrally by the Northwest Cancéropôle Data Treatment Centre, using an online randomisation software (CS-Rando module of Ennov Clinical software), ensuring concealment of upcoming allocations. Randomisation will be balanced 1:1 using a minimisation algorithm (with a random factor set at 0.8) based on the following stratification factors:

- Intensity of vaginal dryness symptoms 3–5 vs ≥6.
- Treatment with antiaromatase without LHRH agonist versus combination of antiaromatase with LHRH agonist.
- Age: <50 vs 50–54 vs 55–64 vs ≥65 years.

The patient will be enrolled online in the study using the electronic case report form (eCRF). Each patient will be assigned a treatment arm and an inclusion number. This number will be maintained, even if the patient withdraws from this study before the start of treatment. The patient will be informed of her assigned arm.

Masking

The patient and investigating physicians who will perform the vaginal RF sessions will not be blinded to the treatment allocation. The physician assessor in charge of the clinical assessments up to 6 months (M0, M3, and M6) will be blinded to the treatment assignment (different physicians for treatment and endpoint evaluation). Unblinding will be planned after the 6-month evaluation, with the possibility of RF treatment for patients in the control group who are insufficiently relieved.

Data collection and data management

Data management will be conducted by the data management team at the Data Management Centre Cancéropôle Nord-Ouest, located in Caen at the François Baclesse Cancer Centre.

A database specific to the study will be created, tested and validated before the initial inclusion. This database will be developed using Ennov Clinical, a software package designed for the global management of clinical studies and which meets the regulatory requirements of clinical trials and General Data Protection Regulation. A data validation plan, including an annotated CRF with a list of checks for each variable, will be defined.

An eCRF will be used for data entry by the investigating centres participating in this study. Access to the eCRF will be restricted to individuals working in the investigation department with a personal login and password. At least once a year, data will be checked by the data management team using error messages from the validation programmes (online queries) and the monitor (data clarification forms).

Once the database has been corrected and validated, it will be frozen and exported to the statistical analysis software using a standardised procedure.

Committees

The Study Steering Committee is composed of the study coordinator, the sponsor's project manager, the methodologist, and a representative from the pharmacovigilance unit. The committee will provide overall supervision of the trial, ensuring that it is conducted in accordance with the protocol, regulatory requirements and Good Clinical Practice. It will safeguard participant safety and rights, monitor recruitment progress, data quality and adherence to timelines, and offer assurance to the funders that the trial is being conducted appropriately and remains viable.

We do not plan to establish an endpoint adjudication committee as the primary outcome is a patient-reported outcome (PRO).

We also do not plan to establish an Independent Data Monitoring Committee given the relatively short recruitment period and the absence of the expected risk associated with the intervention.

Statistical considerations

The primary analysis of the treatment effect in terms of the patient-reported vaginal dryness score at 6 months

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(M6) will consider the baseline value (M0) using a covariance analysis. In addition to the treatment effect and baseline value, the linear regression model will include the type of hormone therapy (aromatase inhibitor with vs without LHRH agonist) and the patient's age (<50 vs 50–54 vs 55–64 vs ≥65). The treatment effect will be tested using a two-sided 5% alpha threshold.

This analysis will be completed by the following:

- An estimate of the distribution of scores at M0 and M6, with a comparison of the distribution of scores at M6 between the two groups using a test for comparison of means
- In each group, an estimate of the M6–M0 score difference, with the following:
  - A paired comparison of scores at M0 and M6 using the zero-difference test.
  - A qualitative description of treatment response (improvement/stability/worsening of score).
- Between the two treatment groups
  - An intergroup comparison of the M6–M0 score difference.
  - Intergroup comparison of the response distribution (improvement/stability/worsening).

The main analysis will be performed on an intention-to-treat basis and will include all informative patients, regardless of the actual treatment. A patient will be considered non-informative at 6 months if consent to participate in this study is withdrawn before the 6-month assessment, or if the patient is lost to follow-up before 6 months. A sensitivity analysis will be performed by excluding patients with a major deviation from the inclusion criteria and patients who stopped hormone therapy with an aromatase inhibitor or LHRH agonist >2 months before the evaluation at M6 (per-protocol analysis).

A similar approach to the analysis of the primary endpoint (vaginal dryness score at 6 months) will be followed for the analysis of the dyspareunia score at 6 months and VHIS scores at 6 months.

Measurements of the various scores will be described at different time points (M0, M2, M6, M12), and a graphical representation will illustrate the longitudinal results according to treatment group.

The side effects of vaginal RF treatment (type, grade) and the consequences of RF treatment will be described.

Associated local treatments during the first 6 months for each group and treatments performed beyond M6 (recourse to RF in the control group, performance of an additional session in the experimental group) will be described.

A correlation study will be conducted between the different scores, in pairs (vaginal dryness score vs dyspareunia score, vaginal dryness score vs VHIS score, dyspareunia score vs VHIS score), at different measurement times.

The concordance of the response to treatment (improvement, stability, worsening between M0 and M6) will be studied for each pair of criteria (vaginal dryness score vs dyspareunia score, vaginal dryness score vs VHIS score, dyspareunia score vs VHIS score) using a weighted kappa.

Finally, we will estimate the frequency of premature discontinuation of the initially prescribed hormone therapy in each treatment group and any changes in hormone therapy due to gynaecological symptoms. This frequency will be compared between the groups using the χ^2 test.

Statistical analysis will be planned when the 12-month assessment will be conducted for the last recruited patient.

Planned timeline of the trial

The trial was authorised on 12 November 2024. Accrual in the trial was initiated on 16 June 2025. The planned end of accrual is May 2028, with a last patient last visit planned in May 2029 and a planned date of statistical analysis and results publication in January 2030.

ETHICS AND DISSEMINATION

This clinical trial will be conducted in accordance with the Declaration of Helsinki. This study follows the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice (reference number EMA/CHMP/ICH/135/1995). The participant consent form is provided as online supplemental material. The study protocol has been approved by the ethics committee (Comité de protection des personnes Sud Est I, No 24.04974.000509 on 12 November 2024). This is the initial version of the study protocol (Version 1.0, dated 13 September 2024). Any substantial modification to the protocol will require an amendment to be submitted to the ethics committee. All participating teams will be informed of any study amendments.

This study is registered at ClinicalTrials.gov (NCT06900374).

The trial results, even if inconclusive, will be presented at international oncology congresses and will be published in a peer-reviewed journal. We also plan to share the results through a summary in lay language.

Patient and public involvement

Patients were involved in the study design through the Patient Committees of the French National Cancer League. They reviewed and revised the patient information sheet and consent form, and provided suggestions regarding the wording of these documents. They did not participate in the conduct of the study. The results of the study will be shared with participants through a summary disseminated after study completion.

DISCUSSION

The choice of a PRO as the main endpoint is justified by the recommendations of academic societies regarding the use of this type of endpoint in oncology and by the frequent observation of discrepancies in the assessment of symptoms experienced by the patient between the patient's own assessment and that of the physician, particularly for treatment side effects.[56 57]

In most studies evaluating treatments for vulvovaginal atrophy and dryness, the assessment is based on clinical evaluation by a healthcare professional and patient evaluation

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using PROs.[15 17 18 21 22 28 29 32 33 39 43 45–49] Similarly to these studies, the clinical objective endpoint used in our trial will be the VHIS, a composite score measuring vaginal trophicity and hydration, which is a standardised and validated objective tool commonly used to assess the severity of vulvo-vaginal atrophy and response to treatment.[54]

Our study population comprises female patients receiving adjuvant hormone therapy with an aromatase inhibitor, with or without an LHRH agonist. It is well established that symptoms are particularly frequent in patients treated with aromatase inhibitors, which led us to focus our study on this population in order to ensure greater homogeneity.

One of the limitations of this study is the absence of a sham group. In our proposal, the specific effect of RF may be confounded by other factors, including the insertion of a vaginal probe and the heat generated by the RF. We also cannot disentangle the placebo effect from the measured effect of the intervention. When designing the trial, we consulted the local ethics committee, which alerted us to the fact that a sham group involving the intravaginal insertion of a probe with no therapeutic effect would be difficult to justify ethically. Additionally, the characteristic thermal sensation of RF raises concerns about the feasibility of maintaining blinding in a sham arm. Lastly, our trial plans blinding of assessors for the clinical evaluation and standardisation of follow-up and other procedures. We believe this approach remains scientifically robust and clinically relevant. These results can lead to changes in clinical practice, improve patient quality of life, reduce the side effects of adjuvant hormone therapy and improve compliance to oncological treatments.

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Contributors DJ is the guarantor. JD: study design, funding acquisition, writing–original draft, review and editing and final version. MV: study design, funding acquisition, review final version. CM: study design, review final version. FBO: funding acquisition, project administration, review final version. NA: study design, review final version. CL: study design, methodology, formal statistical analysis plan, review final version. NP: study design, funding acquisition, review final version. M-PC: study design, review final version. MCLD: study design, methodology, formal statistical analysis plan, funding acquisition, writing–original draft, review and editing and final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement De-identified individual participant data (IPD), the study protocol, and statistical analysis plan may be shared with academic researchers upon justified request. Data will be made available after publication of the main results and following approval of a data-sharing agreement. Access will be granted only for research purposes consistent with the original study objectives and in compliance with GDPR and institutional policies.

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