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Clinical Trial Results

A Phase II Prospective, Randomized, Double-Blind, Placebo-Controlled and Multicenter Clinical Trial to Assess the Safety of 0.005% Estriol Vaginal Gel in Hormone Receptor-Positive Postmenopausal Women with Early Stage Breast Cancer in Treatment with Aromatase Inhibitor in the Adjuvant Setting

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT02413008
- **Sponsor**: ITF Research Pharma, S.L.U.
- **Principal Investigator**: Pedro Sánchez-Rovira
- **IRB Approved**: Yes

Lessons Learned

- The levels of circulating follicle-stimulating hormone, luteinizing hormone, estriol, estradiol, and estrone remained unchanged after a 12-week treatment with 0.005% estriol vaginal gel in postmenopausal women receiving nonsteroidal aromatase inhibitors for hormone receptor-positive early breast cancer.
- These results support the safety of 0.005% estriol vaginal gel for the treatment of bothering symptoms of vulvovaginal atrophy in breast cancer survivors.
- The results provide clinicians with confidence in the use of this product in women who do not experience symptom relief with nonhormonal remedies.

Abstract

Background. Symptoms of vulvovaginal atrophy associated with treatment with nonsteroidal aromatase inhibitors (NSAIs) negatively impact patients' quality of life and may affect adherence to NSAIs. Vaginal estrogens effectively improve these symptoms, although their safe use in breast cancer survivors remains unclear.

Methods. Postmenopausal women with hormone receptor-positive early breast cancer receiving NSAI and moderate-to-severe vaginal dryness were randomized to 0.005% estriol vaginal gel or placebo for 12 weeks. Circulating estrogens, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), were analyzed at baseline and at weeks 1, 3, 8, and 12. The primary safety outcome was the variation in serum FSH from baseline to week 12.

Results. Sixty-one women (mean age, 59 years) enrolled in the study. Small oscillations were observed in FSH and LH, although they were always maintained within the postmenopausal range. No significant differences were found in the variation of FSH and LH between baseline and week 12 from the physiological variation observed before treatment. Women receiving 0.005% estriol vaginal gel had slightly increased estriol levels at weeks 1 and 3, with a subsequent reduction until normalizing at week 12; estradiol and estrone remained the below limit-of-quantitation in almost all samples.

Conclusion. Ultralow-dose 0.005% estriol vaginal gel did not significantly influence estrogens, FSH, and LH levels in women with breast cancer receiving NSAI. A transient negligible absorption of estriol and a nonsignificant variation

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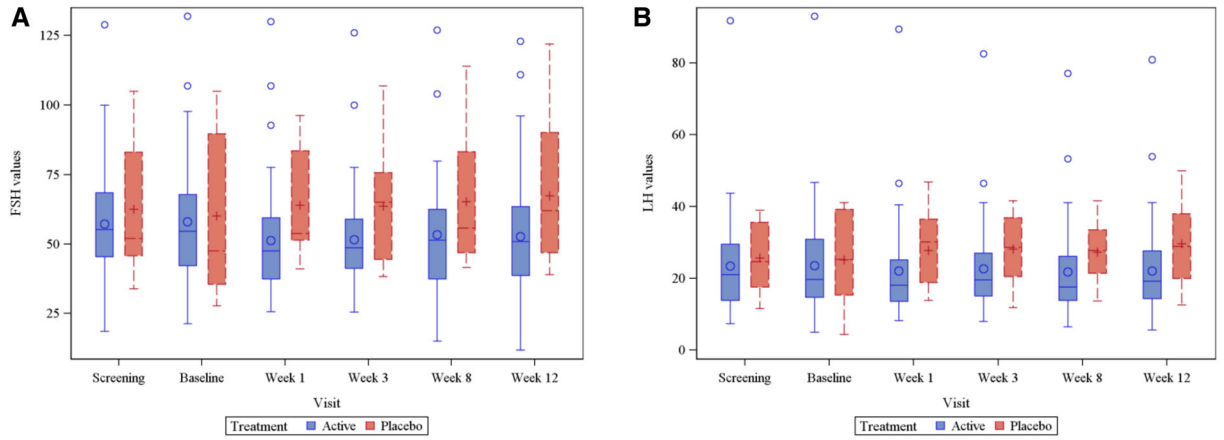

Figure 1. Box-plot of the FSH and LH values determined at each of the indicated visits in the active and placebo groups (intention-to-treat population). (**A**)**:** FSH levels. (**B**)**:** LH levels.
Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

of FSH after 12 weeks were observed. These findings provide confidence for the safe use of 0.005% estriol vaginal gel in women with breast cancer with an indication for treatment with vaginal estrogens. ***The Oncologist*** 2020;25:e1846–1854

Discussion

Breast cancer survivors who are receiving adjuvant therapy with NSAIs have to deal with a constellation of genitourinary symptoms, including but not limited to dryness, burning, and dyspareunia, associated with vulvovaginal atrophy (VVA) [1, 2]. Although not severe, the long-lasting nature of these symptoms negatively affects the patient's quality of life and may even jeopardize adherence to adjuvant endocrine therapy [3, 4]. Although moisturizers and lubricants may provide temporary relief of VVA symptoms, most women require local hormonal treatments [1–3]. These treatments have proven efficacy in reversing VVA associated with estrogen depletion; however, their use in breast cancer survivors has raised safety concerns because of the need for keeping serum estrogens depressed.

Under the hypothesis that an ultralow-dose estriol vaginal gel would not affect the serum levels of gonadotropin hormones, we randomized 61 NSAI-treated breast cancer survivors to receive either 0.005% estriol vaginal gel (n = 50) or placebo moisturizing gel (n = 11). Owing to the high variability of FSH and LH levels between screening (study enrollment) and baseline (immediately before treatment start), the primary endpoint was based on the differences between physiological variability (i.e., screening vs. baseline) and treatment variability (i.e., mean of screening and baseline vs. given time point). After 12 weeks of treatment, no significant differences were observed between physiological and treatment variability of FSH levels in the active group (median, −2.8 mIU/mL; interquartile range [IQR], −13.1 to 7.4; p = .104) or in the placebo group (median, 1.4; IQR, −5.4 to 15.7; p = .413; Fig. 1). These results were reinforced by the lack of significant differences between treatment arms in the absolute values of serum FSH: median, 51.0 mIU/mL (IQR, 38.6 to 63.5) and 62.1 (46.8 to 90.1) for active and placebo groups, respectively (p = .078). This trend was also observed in LH levels, except for week 12, where median (IQR) differences between physiological variability and treatment variability were − 0.8 (−5.3 to 2.9) and 1.3 (−1.6 to 7.1) mIU/mL for active and placebo groups, respectively (p = .025).

Consistent with the decline in absorption of vaginal estrogens with epithelium maturation [5, 6], estriol levels were higher in the active group within the first 3 weeks but decreased throughout treatment, reaching similar levels at week 12: median (IQR), 0.5 (0.5 to 7.3) and 0.5 (0.5 to 0.5) for active and placebo group, respectively (p = .140). As expected, the serum levels of estradiol and estrone remained below the limit of quantification at baseline and at all time points for both active and placebo groups.

In summary, our results provide confidence in the safe use of ultralow-dose 0.005% estriol vaginal gel in breast cancer survivors treated with NSAIs. The application of the gel has a negligible impact on the systemic levels of estrogens, FSH, and LH in these patients, whereas the proven efficacy in symptom relief may improve compliance with adjuvant treatment for breast cancer.

Trial Information	
Disease	Breast cancer
Disease	Vaginal atrophy
Stage of Disease/Treatment	Adjuvant
Prior Therapy	No designated number of regimens
Type of Study	Phase II, randomized
Primary Endpoint	Safety

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Study Design and Population

This was a phase II, randomized, double-blind, placebo-controlled, international, multicenter trial for assessing safety and efficacy of 0.005% estriol vaginal gel in the treatment of vaginal dryness in postmenopausal women with breast cancer experiencing VVA. The study included patients with hormone receptor-positive (and any HER2 status) early breast cancer (stage I–IIIA) treated with NSAIs (either anastrozole or letrozole) for at least 6 months. Participants were recruited from five Spanish sites and one site in Sweden. Patients had to report vaginal dryness, either moderate (i.e., bothersome and annoying) or severe (i.e., bothersome, annoying, and interfered with normal daily activity). Other inclusion criteria were a score 0–1 in the Eastern Cooperative Oncology Group performance status (ECOG) and an adequate bone marrow and organ function. Patients with vaginal bleeding of unknown etiology and endometrial thickness ≥ 4 mm were excluded. A full list of selection criteria is provided in supplemental Online File 1. All patients signed an informed consent before treatment. The study protocol was approved by the regulatory authorities and applicable ethics committees of the participating countries.

Intervention

The study was conducted in two phases: the safety phase and the study phase. During the safety phase, a sentinel group of 10 women were treated daily for 3 weeks with active treatment (0.005% estriol vaginal gel, study drug) or placebo (moisturizing gel) at a 4:1 ratio. After verifying no influence of treatment on either the levels of systemic estrogens or gonadotropins in sentinel participants, a minimum of 60 women (study group) were randomized to receive either active treatment or placebo at a 4:1 ratio. The study drug and placebo had identical characteristics (appearance, smell, and texture), and the investigators and patients were blinded to randomization codes.

Both treatments were administered using an intravaginal applicator at the dose of 1 g of gel per application (containing 50 mg of estriol for the active treatment) for 12 weeks: once daily during the first 3 weeks and twice weekly during weeks 4–12. The baseline visit was scheduled within 2 weeks after the screening visit. Follow-up visits were performed at weeks 1, 3, 8, and 12 of treatment and 30 $\pm$ 5 days after the last study drug dose (post-treatment visit). Treatment compliance was assessed by counting and recording the number of unused applicators.

Safety Assessments

The primary endpoint was the change in serum levels of FSH from baseline to week 12. Secondary endpoints regarding safety included the variation of serum levels of FSH, LH, and plasma levels of estrogens (estriol, estradiol, and estrone) throughout treatment. Estrogen determinations were performed at a central laboratory (Pharm-Analyt, Baden Austria) at baseline and weeks 1, 3, 8, and 12. Owing to the extremely low levels of estrogens expected, the concentration of estriol, estradiol, and estrone was determined using a newly developed and validated ultrasensitive liquid chromatography-tandem mass spectrometry method. Values below the limit of quantification (LOQ) were considered as 0.5 pg/mL for estriol, 1.5 pg/mL for estradiol, and 2.5 pg/mL for estrone. FSH and LH were determined at the same time points and additionally at screening visit to assess their physiological variability and analyzed by chemiluminescent immunoassay at Laboratorios Echevarne (Barcelona, Spain). Other safety assessments included laboratory assessments (hematology, blood chemistry, and urine tests) and a physical and gynecological examination (breast and pelvic examination) performed at baseline and at weeks 3 and 12. Endometrial examination was performed by ultrasound at baseline and week 12. All adverse events were recorded, and the causal relationship between the investigational product and the event was assessed [7].

Statistics

All the analyses were performed on the intention-to-treat population, which included all randomized patients unless otherwise specified. Categorical variables were presented as frequency and percentage, whereas quantitative variables were presented as the mean and SD or the median and interquartile range (IQR). The differences between pretreatment variability (i.e., screening vs. baseline) of hormone levels and treatment variability (i.e., mean of screening and baseline vs. given assessment point) were analyzed using the Wilcoxon signed-rank test, and the between-group differences regarding the change in hormone levels were analyzed using the nonparametric Mann-Whitney-Wilcoxon test. Based on FSH levels in patients treated with NSAIs reported by Pfeiler et al. [8], a sample size of 44 patients was considered to provide 80% power to detect a decrease of FSH levels from 75.7 to 66.0 mIU/mL, assuming an SD of 22.3 and with an α level of 0.05. All analyses were performed using the statistical software SAS Enterprise Guide 5.1 (SAS Institute, Cary, NC).

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	Ultralow-dose 0.005% estriol vaginal gel
Trade Name	Blissel, Gelistrol, or Gelisse
Drug Type	Small molecule
Drug Class	Hormone analog
Dose	50 μg per
Route	Vaginal
Schedule of Administration	1 g of gel per application (containing 50 mg of estriol for the active treatment arm) for 12 weeks: once daily during the first 3 weeks, and twice weekly during weeks 4–12

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Drug 2	
Generic/Working Name	Moisturizing gel
Trade Name	Ainara
Route	Vaginal
Schedule of Administration	1g of gel per application for 12 weeks: once daily during the first 3 weeks, and twice weekly during weeks 4–12

Patient Characteristics: Placebo	
Number of Patients, Male	0
Number of Patients, Female	11
Breast Cancer Stage	Stage I: 4 (36.4%) Stage IIA: 3 (27.3%) Stage IIB: 2 (18.2%) Stageg IIIA: 2 (18.2%)
Age	Median (range): 63 years (52–66 years)
Performance Status: ECOG	0 — 11 1 — 0 2 — 0 3 — 0 Unknown — 0
Previous Adjuvant Hormone Treatments	Aromatase inhibitors: 10 (90.9%) Aromatase inhibitors + tamoxifen: 1 (9.1%) Aromatase inhibitors + tamoxifen +luteinizing hormone-releasing hormone (LHRH) agonist: 0 (0.0%)
Cancer Types or Histologic Subtypes	Estrogen receptor-positive, 11; progesterone receptor-positive, 9; HER2-positive, 3.

Patient Characteristics: Experimental	
Number of Patients, Male	0
Number of Patients, Female	50
Breast Cancer Stage	Stage I: 18 (36.0%) Stage IIA: 23 (46.0%) Stage IIB: 7 (14.0%) Stage IIIA: 2 (4.0%)
Age	Median (range): 58.5 years (45–77 years)
Performance Status: ECOG	0 — 44 1 — 5 2 — 3 — Unknown — 1
Previous Adjuvant Hormone Treatments	Aromatase inhibitors: 41 (82.0%) Aromatase inhibitors + tamoxifen: 8 (16.0%) Aromatase inhibitors + tamoxifen + LHRH agonist: 1 (2.0%)
Cancer Types or Histologic Subtypes	Estrogen receptor-positive, 50; progesterone receptor-positive, 38; HER2-positive, 13.

Primary Assessment Method	
Title	Change in serum levels of FSH
Number of Patients Screened	86

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Number of Patients Enrolled	61
Number of Patients Evaluable for Toxicity	61
Number of Patients Evaluated for Efficacy	61
Evaluation Method	Determination of FSH
Outcome Notes	The primary outcome was the change in serum levels of FSH, shown in Table 2.

Adverse Events

The frequency of each adverse event is provided in Table 3.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

In this phase II, randomized, double-blind, placebo-controlled clinical trial, we investigated the safety of 0.005% estriol vaginal gel for the treatment of symptoms of vulvovaginal atrophy in postmenopausal women receiving nonsteroidal aromatase inhibitors (NSAIs) for hormone receptor-positive early breast cancer in terms of the impact of vaginal treatment on the levels of serum gonadotropins. The analysis included 61 women (Fig. 2), all of them with menopausal status, achieved either by spontaneous amenorrhea or because of an oophorectomy (Table 1). Patients were randomized 4:1, with 50 in the treatment group and 11 in the placebo group.

One of the major barriers for the analysis of the primary objective (i.e., the influence of estriol treatment on the serum levels of gonadotropins) was the high physiological variability of the serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in our study ranged from 18.6 to 132 mIU/mL and from 4.3 to 93 mIU/mL, respectively. This variability in serum levels was consistent with those reported previously [9] and slightly higher than the postmenopausal range typically considered for FSH and LH (21.7–153 mIU/mL and 11.3–39.8 mIU/mL for FSH and LH, respectively). Based on the physiological variability of gonadotropin levels observed in our cohort, we deemed the comparative analysis of the variation of the pretreatment and during treatment ranges the most accurate strategy to capture this variability and minimize its confounding effects. During therapy with 50 μg vaginal estriol, small differences between physiological variability and treatment variability of FSH were found at weeks 1 and 3 but not at subsequent visits (Table 2). At week 12 (primary endpoint), no significant differences were observed between physiological and treatment variability of FSH levels (p = .104; Wilcoxon signed-rank test). The variability of LH levels throughout treatment was persistently comparable to the physiological variability. These results were reinforced by the lack of significant differences between active and placebo groups regarding the changes in pretreatment and treatment variability of FSH levels (p > .1 for differences in variability changes [pretreatment vs. treatment] between active and placebo groups at all follow-up visits; Fig. 2). This trend was also observed in LH levels, except for week 12, where median (interquartile range [IQR]) differences between physiological variability and treatment variability were -0.8 (−5.3 to 2.9) and 1.3 (−1.6 to 7.1) mIU/mL for active and placebo groups, respectively (p = .025).

The serum levels of estradiol and estrone were not affected by the vaginal treatment, and both hormones remained within the expected postmenopausal ranges in both study groups. In contrast, a transient and minimal absorption of estriol was observed at the beginning of treatment. Estriol is a much weaker estrogen than estradiol and displays a preferential affinity to β (urogenital) rather than α (breast) estrogen receptors [10, 11]. Furthermore, pharmacokinetic analyses have shown very limited absorption in healthy postmenopausal women, which tend to decrease as the vaginal epithelium matures within a short time following the start of the vaginal treatment [5, 12]. Based on these pharmacodynamic and pharmacokinetic characteristics, various authors have supported vaginal estriol over estrogen in patients with adjuvant therapy for breast cancer [3]. Nevertheless, to date, the safety of this approach has only been assessed in general postmenopausal women [13] or short series (10–16 subjects) of breast cancer survivors under adjuvant therapy, who used vaginal tablets containing 0.5–0.03 mg of estriol [14, 15]. In our cohort, serum estriol transiently raised within the first 3 weeks, with the highest levels observed at week 1 after treatment start. However, estriol levels at that time point (median, 3.9 pg/mL; IQR, 0.5–12.1) were much lower than the active threshold of 288 pg/mL reported in in vitro analyses [16]. Furthermore, unlike previous experiences with higher concentrations of vaginal estriol, which reported a small and transient decrease in gonadotropin levels [14, 15], the variation of FSH and LH in our analysis remained within the physiological range and equivalent to that of patients in the placebo group. These findings, together with a lack of recurrences reported in series of women using hormone-based vaginal creams [14], suggest that the small and transient increase in estriol after the firsts weeks of ultralow-dose administration is unlikely to jeopardize the therapeutic outcomes of adjuvant therapy.

In addition to the high physiological variability observed in the serum levels of gonadotropins, which was overcome by analyzing the pretreatment and during-treatment variability, our study was limited by the unbalanced country representativeness, with all centers being Spanish except one. Of note, this did

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not affect the laboratory tests, which were performed by two central laboratories in Spain and Austria. Given that our results indicate that the 0.005% estriol gel preparation is safe, the replication of the study using a larger sample size is warranted.

In summary, our results provide confidence in the safe use of ultralow-dose 0.005% estriol vaginal gel in postmenopausal breast cancer survivors treated with NSAIs. The application of the ultralow-dose estriol vaginal gel has a negligible impact on estrogens, FSH, and LH systemic levels in these patients, whereas the proven efficacy of estriol in symptom relief may improve compliance to adjuvant therapy in patients with breast cancer.

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Disclosures

Pedro Sánchez-Rovira: Roche, Pfizer, Novartis, Daiichi (C/A), Roche, Bristol-Meyers Squibb, Merck (RF), Roche, Kern-Pharma, Pfizer (H), Roche, Kern-Pharma, Pfizer, Novartis, AstraZenca (ET, educational activities); **Angelica Lindén Hirschberg:** ITF Research Pharma (RF); **Begoña Bermejo-De Las Heras:** Pfizer, Genentech, Novartis (C/A), Pfizer, Genentech, Eisai, Novartis (H); **Concepción Nieto-Magro:** Italfarmaco (Medical Director). Miguel Gil-Gil indicated no financial relationships.

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Figure and Tables

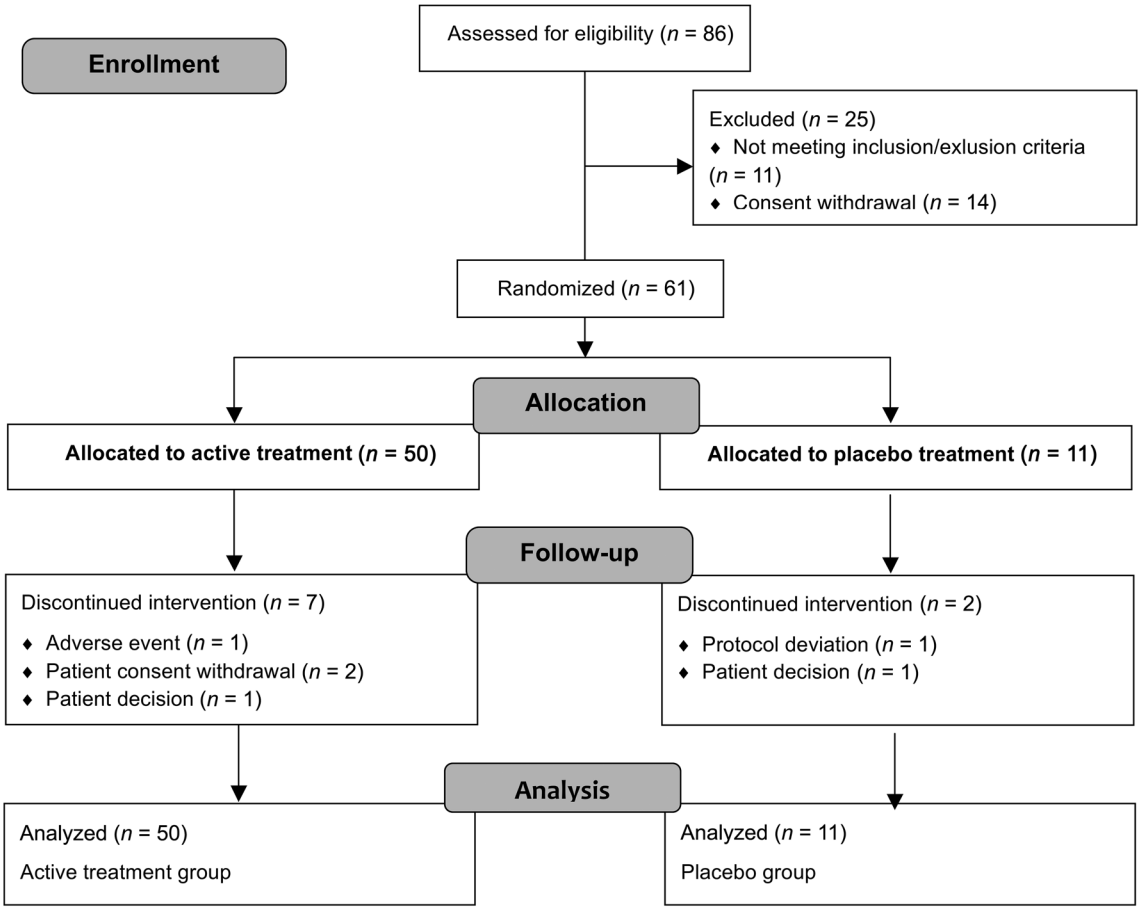

Figure 2. Flow diagram of the patients included in the study.

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Table 1. Baseline demographic, clinical, and previous treatment characteristics of the study patients, *n* (%)

Characteristics	Active (*n* = 50), *n* (%)	Placebo (*n* = 11), *n* (%)	Total (*n* = 61), *n* (%)
Postmenopausal status			
≥ 12 mo of spontaneous amenorrhea	44 (88.0)	11 (100.0)	55 (90.2)
≥ 6 wk postsurgical bilateral oophorectomy[a]	5 (10.0)	0 (0.0)	5 (8.2)
6 mo of spontaneous amenorrhea with serum FSH increased levels >40 mIU/mL	1 (2.0)	0 (0.0)	1 (1.6)
ECOG performance status			
0	44 (88.0)	11 (100.0)	55 (90.2)
1	5 (10.0)	0 (0.0)	5 (8.2)
Not available	1 (2.0)	0 (0.0)	1 (1.6)
Breast Cancer Stage			
I	18 (36.0)	4 (36.4)	22 (36.1)
IIA	23 (46.0)	3 (27.3)	26 (42.6)
IIB	7 (14.0)	2 (18.2)	9 (14.8)
IIIA	2 (4.0)	2 (18.2)	4 (6.6)
Estrogen receptor			
Positive	50 (100.0)	11 (100.0)	61 (100.0)
Progesterone receptor			
Negative	11 (22.0)	2 (18.2)	13 (21.3)
Positive	38 (76.0)	9 (81.8)	47 (77.0)
Not available	1 (2.0)	0 (0.0)	1 (1.6)
HER2			
Negative	37 (74.0)	8 (72.7)	45 (73.8)
Positive	13 (26.0)	3 (27.3)	16 (26.2)
Adjuvant hormonal treatments			
Aromatase inhibitors	41 (82.0)	10 (90.9)	51 (83.6)
Aromatase inhibitors + tamoxifen	8 (16.0)	1 (9.1)	9 (14.8)
Aromatase inhibitors + tamoxifen + LHRH agonist	1 (2.0)	0 (0.0)	1 (1.6)

[a]Including patients with and without hysterectomy.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

Table 2. Change in hormone levels between physiological variability (i.e., from screening to baseline) and treatment variability (i.e., from mean screening-baseline to a given treatment point)

Hormone	Active Δ [physiological variability vs. treatment variability]	Placebo Δ [physiological variability vs. treatment variability]
FSH		
Wk 1	−4.8 (−11.6 to 2.6)[a]	4.2 (−7.8 to 7.3)[b]
Wk 3	−4.2 (−12.0 to 3.5)[a]	−0.9 (−4.0 to 2.3)[b]
Wk 8	−2.6 (−10.1 to 7.9)[b]	5.2 (−11.8 to 9.0)[b]
Wk 12	−2.8 (−13.1 to 7.4)[c]	1.4 (−5.4 to 15.7)[c]
LH		
Wk 1	−0.6 (−3.7 to 2.8)[b]	0.2 (−1.8 to 8.1)[b]
Wk 3	−0.5 (−4.1 to 3.5)[b]	0.3 (−1.8 to 7.7)[b]
Wk 8	−0.3 (−4.9 to 3.1)[b]	−1.3 (−2.0 to 6.0)[b]
Wk 12	−0.8 (−5.3 to 2.9)[c]	1.3 (−1.6 to 7.1)[c]

Results shown as median (interquartile range).
[a]Significant difference based on the multiple comparisons Dunn's test at α cut off 0.05.
[b]Nonsignificant difference based on the multiple comparisons Dunn's test at α cut off 0.05.
[c]Nonsignificant difference based on the Wilcoxon matched-pairs signed-rank test at α cutoff 0.05.
Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

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Table 3. Patients reporting adverse events during treatment, *n* (%)

Adverse event	Active (*n* = 50), *n* (%)	Placebo (*n* = 11), *n* (%)	Total (*n* = 61), *n* (%)
Reproductive system and breast disorders			
Atrophic vulvovaginitis	1 (2.0)		1 (1.6)
Breast tenderness	1 (2.0)		1 (1.6)
Vaginal discharge	1 (2.0)		1 (1.6)
Vulvovaginal inflammation	1 (2.0)		1 (1.6)
Vulvovaginal pruritus	1 (2.0)		1 (1.6)
Musculoskeletal and connective tissue disorders			
Back pain		1 (9.1)	1 (1.6)
Pain in extremity	1 (2.0)		1 (1.6)
Nervous system disorders			
Burning sensation	1 (2.0)		1 (1.6)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (2.0)		1 (1.6)
Gastrointestinal disorders			
Diarrhea	2 (4.0)		2 (3.3)
Vomiting	1 (2.0)		1 (1.6)
Infections and infestations			
Gastroenteritis		1 (9.1)	1 (1.6)
Gastroenteritis viral	1 (2.0)		1 (1.6)
Influenza	1 (2.0)		1 (1.6)
Pharyngitis	1 (2.0)		1 (1.6)
Urinary tract infection	3 (6.0)	1 (9.1)	4 (6.6)
Viral upper respiratory tract infection	1 (2.0)		1 (1.6)
Vulvovaginal candidiasis		1 (9.1)	1 (1.6)
General disorders and administration site conditions			
Mucosal dryness	1 (2.0)		1 (1.6)
Polyp	1 (2.0)		1 (1.6)
Pyrexia	1 (2.0)		1 (1.6)
Ear and labyrinth disorders			
Vertigo positional	1 (2.0)		1 (1.6)

None of the adverse events reported was severe enough to interrupt treatment with ultralow-dose 0.005% estriol vaginal gel.
In addition to the adverse events summarized in this table, one serious, nonrelated adverse event was reported in the active group: lymphoma. The patient experienced fever and jaw pain (a sample of the lymph node was extracted to investigate the symptoms) before entering the study. The result of the analysis, which was available after assigning the patient to the active group, revealed the presence of lymphoma, and the patient was excluded from the study.

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