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# Vaginal tamoxifen – A potential treatment option for vaginal atrophy symptoms in postmenopausal women who cannot use estrogen

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ABSTRACT

*Background:* There is a great need for non-estrogenic treatment of vulvovaginal atrophy (VVA) symptoms affecting sexual function and quality of life. Women with breast cancer on anti-estrogenic therapy are particularly vulnerable and in need of help. The primary aim of this proof-of-concept trial was to evaluate the efficacy of vaginal tamoxifen in reducing the most troublesome VVA symptom.

*Methods:* In this randomized, double blind, placebo-controlled study, 115 postmenopausal women, with or without breast cancer, were randomized to 20 mg vaginal tamoxifen once weekly or placebo (1:1). Follow-up after one and three-months of treatment, included self-reported VVA symptoms on the Endocrine Symptom Subscale of FACT-B, and gynecologic exams for VVA score and measurement of vaginal pH and endometrial thickness.

*Findings:* After three months, 37 (68.6 %) of women on vaginal tamoxifen reported their most troublesome VVA symptom to be mild or not present at all, whereas corresponding number in the placebo group was 5 (9.1 %), $p < 0.001$. Expressed as odds, women on vaginal tamoxifen were more likely to report no or minor symptoms after three-months, OR 21.76 (95 % CI 7.36 – 64.3). The improvement in self-reported outcomes was accompanied by improvements in VVA scores and vaginal pH, $p < 0.001$.

*Interpretation:* This study has demonstrated that more than two-thirds of the women on vaginal tamoxifen improved in their most troublesome VVA symptom. This is likely due to a tamoxifen-induced estrogen agonistic effects in vagina in a low-estrogen environment. While findings are promising, further studies on improved vaginal administration and endometrial safety concerns are needed.

## 1. Introduction

After menopause, whether spontaneous, surgical or induced by chemotherapy, more than half of women experience vulvovaginal atrophy (VVA) symptoms such as painful sex and vaginal dryness [1,2]. Further, the sexual discomforts associated with VVA greatly impact sexual function and quality of life [3]. For the majority of postmenopausal women, symptoms are reversed by use of vaginal estrogen therapy (ET) including either estradiol or estriol, and sometimes relieved by over the counter lubricants [2]. However, some women worry about using vaginal ET and for others, even the low dose of vaginal estrogen may be contraindicated [2,4]. Although not an absolute contraindication, breast cancer (BC) survivors and BC patients on adjuvant anti-estrogenic therapy are particularly vulnerable in this respect.

According to the World Health Organization, more than 2 million women worldwide are diagnosed with BC each year. Approximately 75 % of these have an estrogen sensitive cancer and are treated with adjuvant anti-estrogenic therapy, i.e. either tamoxifen or aromatase inhibitor (AI) treatment. Of these two options, women treated with AIs

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more often report painful sex, vaginal dryness and associated sexual dysfunction [5,6].

Vaginal ET may lead to a small but significant increase in systemic levels of estrogens [7], also in women treated with AIs [8]. As a consequence, current international guidelines suggest that vaginal estrogen therapy should be used with caution for all women with an history of estrogen sensitive BC [2,4]. This results in poor support for the women with history of BC or those on treatment with AIs. Therefore, it is of utmost importance to identify good treatment options to improve troublesome VVA symptoms in women with low estrogen levels, including women treated with AIs.

Previous studies in our group have shown that postmenopausal women treated with oral tamoxifen, in contrary to women treated with AIs, resemble healthy postmenopausal women using vaginal estrogen in all VVA measures. This includes objective vaginal atrophy scores, measurements of vaginal pH (typically low in estrogen-stimulated vaginas), and vaginal cell maturation index as a result of the estrogenic effect in vaginal tissue by tamoxifen in women with lower estrogen levels [5,7,9].

The primary aim of this proof-of-concept clinical trial was to evaluate the efficacy of *vaginal* tamoxifen in reducing the most troublesome VVA symptom in women with low estrogen levels as a result of menopause and women treated for BC with AI, evaluated by use of the Endocrine Symptom Subscale of the FACT-B. The hypothesis was that once weekly *vaginal* tamoxifen would alleviate the most troublesome VVA symptom in women with low systemic estrogen levels in comparison with placebo treatment.

## 2. Material and methods

### 2.1. Participants

The study was carried out at the Departments of Obstetrics and Gynaecology at Uppsala University Hospital, the Karolinska University Hospital and Danderyd Hospital between April 21, 2022 and December 18, 2024. We recruited participants by clinical referrals and advertisements in social media.

Women were eligible if they were healthy, 40 – 65 years of age, postmenopausal with at least 12 months of spontaneous amenorrhea or bilateral oophorectomy or follicle stimulating hormone (FSH) levels $>40$ mIU/mL and suffered from VVA. Vulvovaginal atrophy was defined as vaginal pH $>5.0$ at screening, and at least one moderate to severe VVA symptom, identified as being the most troublesome, on the Endocrine Subscale of the FACT-B [10].

Women with history of BC were included in the study if they were considered in good health and not currently on adjuvant oral tamoxifen therapy. Women with current AI treatment were included in the study.

We excluded women with endometrial thickness of $\geq 4$ mm, history of endometrial hyperplasia, endometrial polyps, and endometrial or ovarian cancer, hysterectomy was however not an exclusion criterion. On the other hand, women who had used vaginal or systemic oestrogen, hormonal contraceptives or oral tamoxifen within 12 weeks prior to the screening visit were not included. Further, women with history of cardiovascular disease, hypertension, thromboembolic events, any ongoing severe disease (with the exception of BC) were not allowed to participate. Finally, women currently using CYP2D6-inhibiting drugs such as fluoxetine, paroxetine and bupropion were excluded.

The women received oral and written information and had the opportunity to ask questions before signing informed consent in the presence of an investigator. The study was approved by the Swedish Ethical Review Authority reference number 2020–04782 with the amendment 2022–00381–02. The clinical trial was also approved and pre-registered by the Swedish Medical Product Agency with the clinical trial identifier EUDRA-CT 2021–004536–28 (later transferred to the European Clinical Trial Information System (CTIS), identifier 2024–517315–69–00).

### 2.2. Study design and procedures

The study was an investigator-initiated, multicenter, randomized, double-blind, parallel group clinical trial where participants were treated with either vaginal tamoxifen 20 mg once weekly or placebo once weekly during three 28-day treatment cycles. Women were randomized to these treatments at a 1:1 ratio.

Preliminary eligible women attended a screening visit ($n=157$, Figure 1), during which demographic data and information on previous, recent, and ongoing medical history and medication were collected. Subjective endocrine symptoms were assessed by the FACT-B Endocrine Subscale [10]. A gynaecologic examination, including transvaginal ultrasound examination was performed and routine blood tests were taken (haemoglobin, electrolytes, kidney and liver function tests). FSH levels were checked if there was any ambiguity concerning the postmenopausal status.

Following randomisation, participants attended two follow-up visits; after one month and three months. At each of these visits a gynaecologic examination was performed and women filled out the FACT-B Endocrine Subscale, and reported on the severity of their most troublesome VVA symptom. Any adverse events or change in concomitant medication were queried and registered at each visit. At the final visit, a transvaginal ultrasound was performed to reassess the endometrial thickness.

### 2.3. Study drug

We purchased tamoxifen tablets from Sandoz AS, Denmark and near identical placebo tablets from Sharp Clinical, UK (both were white, of similar size and shape, with break line but tamoxifen tablets had film-coated surface and the placebo tablet had a matt surface). The oral tamoxifen tablets were used vaginally without any modification. Treatment started with a three-day run in, where patients applied the vaginal tablet daily, after which they continued with tamoxifen of placebo tablets once weekly for 12 weeks. Patients were instructed to insert tablets as far in into the vagina as possible, using their fingers.

The rationale for the vaginal tamoxifen dose was based on the relationship between systemic and vaginal estradiol treatment, where one fifth of the systemic estradiol dose (systemic use; 50 microgram transdermal vs vaginal use 10 microgram), given twice weekly, is sufficient to improve VVA symptoms. The rationale for the vaginal tamoxifen regimen, given once weekly, was further based on the much longer half-life of tamoxifen in comparison with estradiol. Whereas the half-life of estradiol is merely 6–8 h due to rapid first-pass metabolism in the liver, the half-life of tamoxifen is seven days [11]. The chosen dose and regimen had also been piloted in a case report of four patients [12].

A randomization list was prepared (random-number generated in blocks of four) and the study drugs were packaged and labelled. At randomization, the participants were distributed the numbered package with the lowest available number at each site. During the study, participants and study personnel were blinded to treatment and randomisation codes were kept confidential from clinical staff until completion of the study.

Outcomes

Primary efficacy outcome for the study was patient-reported severity of the most troublesome VVA symptom, captured at each visit. For this purpose, we used the FACT-B Endocrine Subscale. Answers were provided on a 5-point response scale (not at all/minor/somewhat/quite a bit/very much) developed and validated for BC research [10]. Only items reflecting systemic and local oestrogen deficiency symptoms were included. Prior to randomisation, participants were asked to identify their most troublesome VVA symptom on this scale (i.e. pain at sex, vaginal dryness, vaginal irritation/itching and vaginal discharge).

Secondary efficacy outcomes were vaginal atrophy scores, vaginal pH and symptoms reflective of estrogen deficiency (i.e. pain at sex, vaginal dryness, vaginal irritation/itching and vaginal discharge) on the FACT-B Endocrine Subscale at each time-point. The same experienced

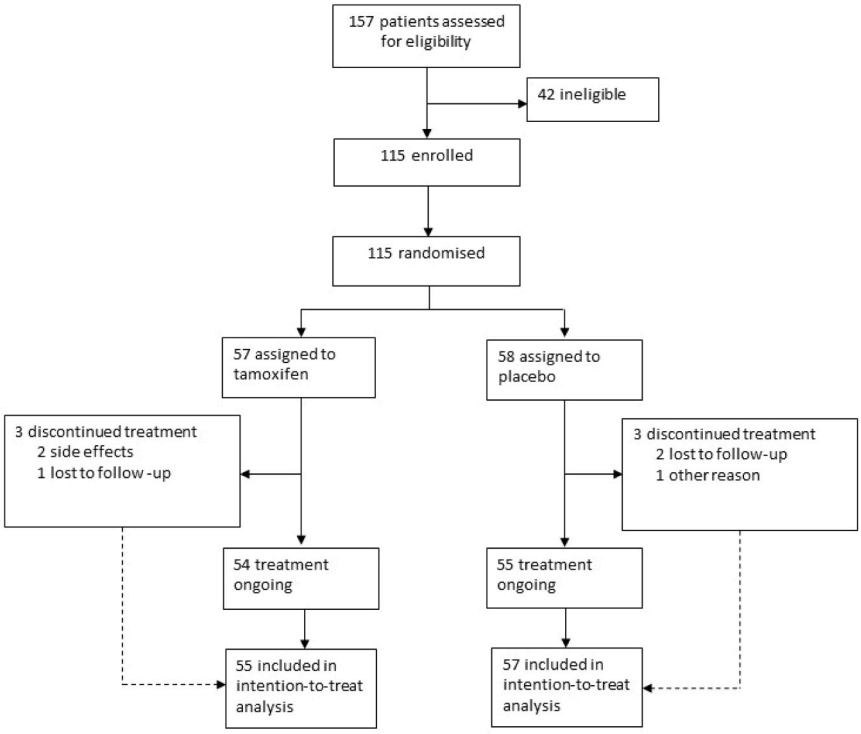


**Fig. 1.** Flow chart of the study population.

gynaecologist or a trained midwife at each department performed all gynaecologic examinations. The examiner determined the degree of vaginal atrophy by assessing the epithelium for thickness, colour, flour, and presence of petechial bleeding and rated the vaginal atrophy score as mild, moderate or severe. Vaginal pH was measured in the lateral wall of the vagina.

Safety endpoints included side effects captured at each visit (graded as mild, moderate or severe), and change in endometrial thickness from baseline to the three-months follow-up (where a significant increase was considered a safety issue).

## 3. Statistical analyses

### 3.1. Power analysis

In order to pursue clinical implementation, we decided that a *clinically relevant* effect of vaginal tamoxifen was needed, i.e. in the order of at least 30 % more women improving their most troublesome VVA symptom than in the placebo group. We also assumed that both groups would improve; by at least 20 % in the placebo group and by 50 % in the active treatment group. The possibility to find such improvement was substantiated by prior cross-sectional findings of BC patients on tamoxifen treatment and healthy controls [5,6]. Thus, the number of fully evaluable subjects needed in each treatment group to reach 90 % power using a two-sided test at 5 % significance level, were 48, i.e. 96 women in total. As we expected a drop-out rate of approximately 20 %, the objective was to include a final sample size of 120.

An intention to treat approach was applied and the outcomes, including the most troublesome VVA symptom, were compared using Chi-square and Mann-Whitney U-tests at baseline, after one month and after three months of treatment between treatment groups.

Logistic regression, for estimation of Odds ratio and 95 % confidence interval (CI) was used to estimate the odds of improvement (defined as no or minor problems with the most troublesome VVA symptom) and deterioration (defined as quite a bit of very much of the most troublesome VVA symptom).

## 4. Results

### 4.1. Study population

Between April 21, 2022 and December 18, 2024, 115 postmenopausal women with moderate to severe VVA symptoms were randomized to either vaginal tamoxifen (n = 57) or placebo (n = 58), Figure 1. The most common reasons for screen failure were low vaginal pH (vaginal pH<5, n = 10) and high blood pressure (n = 7). Three women dropped out in the vaginal tamoxifen group, two due to side effects (mental symptoms and vaginal irritation, respectively) and one was lost to follow-up. Three women dropped out in the placebo group, none due to side effects. As three of the drop outs occurred after the one-month assessment, 55 women in the tamoxifen group and 57 women in

**Table 1**
Baseline characteristics of the study population.

| | Tamoxifen (n = 57) | Placebo (n = 58) | P-value |
|---|---|---|---|
| Age (years) | 59.6 (4.6) | 58.7 (4.9) | 0.2 |
| Postmenopausal years | 7 (4–10) | 6 (5–11) | 0.8 |
| BMI (kg/m$^2$) | 25.8 (3.9) | 25.9 (3.3) | 0.8 |
| Civil status | | | 0.9 |
| Married/cohabiting/in relationship | 45 (78.9 %) | 45 (77.6 %) | |
| Single | 12 (21.1 %) | 13 (22.4 %) | |
| Educational level | | | 0.4 |
| University | 38 (66.7 %) | 34 (58.6 %) | |
| Not university | 19 (33.3 %) | 24 (41.4 %) | |
| Health status | | | 0.6 |
| Healthy women | 45 (81.8 %) | 44 (77.2 %) | |
| Women with breast cancer | 12 (21.1 %) | 15 (25.9 %) | |
| Sexually active (last month) | 32 (56.1 %) | 32 (55.2 %) | 1.0 |
| Previous treatment for vulvovaginal atrophy | | | |
| Vaginal estrogen | 24 (42.1 %) | 26 (44.8 %) | 0.8 |
| Vaginal moisturizer | 10 (17.2 %) | 6 (10.5 %) | 0.5 |

Data are n (%), median (IQR), or mean (SD). Statistical comparisons by Mann-Whitney U-test or Chi-square tests.

the placebo group were available for the intention-to-treat analyses on the primary outcome, Figure 1. Due to a lower drop-out rate than expected (5.2 %, in comparison to expected 20 %) the study inclusion closed when 96 women had finalized the study protocol and the remaining women were allowed to continue the whole study protocol.

Baseline characteristics of the treatment groups are presented in Table 1. The majority of women participating in the trial were healthy, married or cohabiting, had high educational level and were 6–7 years postmenopausal (vaginal tamoxifen treatment group 7 years postmenopausal and placebo group 6 years postmenopausal). More than half had been sexually active in the previous month, and more than 40 % had previously used vaginal estrogen treatment.

All in all, 27 (23.5 %) women with BC were included. Of these, 14 were currently on adjuvant treatment with AI, whereas the remaining 13 had stopped or never needed adjuvant anti-estrogenic treatment.

Baseline VVA symptoms and indices of vaginal atrophy are displayed in Table 2. The most common troublesome VVA symptom was pain at sex, followed by vaginal dryness. By chance, women who were later randomized to vaginal tamoxifen more often had severe vaginal atrophy and higher vaginal pH at gynecologic examination, $p < 0.05$ and $p < 0.01$, respectively. Women randomized to vaginal tamoxifen also reported more severe vaginal dryness and more lost interest in sex at baseline than women randomized to placebo, supplementary table 1.

### 4.2. Primary and secondary efficacy outcomes

The treatment effects on primary and secondary outcomes at one-month and three-month follow-ups are presented in Table 3 and Figure 2. Already by the one-month follow-up a difference in severity of the patient-reported most troublesome VVA symptom was noted, primarily driven by fewer patients in the vaginal tamoxifen treatment group who reported 'very much' symptoms (vaginal tamoxifen: 2 (3.8 %) vs. placebo: 15 (30.0 %), $p = 0.011$). This minor change was accompanied by a lower number of patients with severe vaginal atrophy at gynaecologic examination and lower vaginal pH in the vaginal tamoxifen-treated women compared to placebo-treated women, $p < 0.001$ and $p < 0.001$, respectively, Table 3.

After three months of treatment, one (1.9 %) patient in the vaginal tamoxifen group and 32 (58.2 %) women in the placebo group reported that they had 'quite a bit' or 'very much' of their most troublesome VVA symptom, Table 3. Conversely, a greater proportion of women on vaginal tamoxifen reported their most troublesome VVA symptom to be mild ('a little bit') or not present at all (vaginal tamoxifen: 37 (68.6 %) vs. placebo: 5 (9.1 %), $p < 0.001$). Expressed as odds, women on vaginal tamoxifen were more likely to report no or minor symptoms at the three-month follow-up, OR 21.76 (95 % CI 7.36 – 64.3), and less likely to report quite a bit or very much of their most troublesome VVA symptom OR 0.014 (95 % CI 0.002 – 0.105).

The vaginal atrophy score and vaginal pH continued to improve in the vaginal tamoxifen group at the three-months follow-up, whereas these indices remained almost unchanged from baseline in the placebo group, $p < 0.001$ and $p < 0.001$, respectively.

These findings were also corroborated by the responses to the FACT-B Endocrine Subscale, where women treated with vaginal tamoxifen reported less vaginal irritability, less vaginal dryness, less pain at sex and more interest in sex at the three-month follow-up in comparison with

**Table 2**
Baseline vulvovaginal atrophy symptoms and indices of vaginal atrophy of the intention-to-treat population.

| | Tamoxifen (n = 57) | Placebo (n = 58) | P-value |
|---|---|---|---|
| Most troublesome vulvovaginal atrophy symptom | | | 0.8 |
| Pain at sex | 32 (56.1 %) | 32 (55.2 %) | |
| Vaginal dryness | 23 (40.4 %) | 22 (37.9 %) | |
| Vaginal irritation/itching | 2 (3.5 %) | 3 (5.2 %) | |
| Vaginal discharge | 0 | 1 (1.7 %) | |
| Degree of most troublesome vulvovaginal atrophy symptom | | | < 0.05 |
| Very much | 24 (42.1 %) | 19 (32.8 %) | |
| Quite a bit | 29 (50.9 %) | 25 (43.1 %) | |
| Somewhat | 4 (7.0 %) | 14 (24.1 %) | |
| Vaginal atrophy score | | | < 0.05 |
| Severe | 34 (59.6 %) | 21 (36.2 %) | |
| Moderate | 19 (33.3 %) | 29 (50.0 %) | |
| Minor | 4 (7.0 %) | 8 (13.8 %) | |
| Vaginal pH | 6.8 (5.8 – 7.0) | 5.8 (5.6–6.6) | < 0.01 |

Data are n (%) or median (IQR). Statistical comparisons by Mann-Whitney U-test or Chi-square tests.

**Table 3**
The most troublesome vulvovaginal atrophy symptom and indices of vaginal atrophy at one-month and three-months follow-up.

| | One-month follow-up[a] | | | Three-months follow-up | | |
|---|---|---|---|---|---|---|
| | Tamoxifen (n = 55) | Placebo (n = 57) | p | Tamoxifen (n = 54) | Placebo (n = 55) | p |
| Degree of most troublesome vulvovaginal atrophy symptom | | | 0.011 | | | < 0.001 |
| Very much | 2 (3.8 %) | 15 (30.0 %) | | 0 | 18 /32.7 %) | |
| Quite a bit | 23 (43.4 %) | 16 (32.0 %) | | 1 (1.9 %) | 14 (25.5 %) | |
| Somewhat | 20 (37.7 %) | 13 (26.0 %) | | 16 (29.6 %) | 18 (32.7 %) | |
| A little bit | 6 (11.3 %) | 4 (8.0 %) | | 28 (51.9 %) | 1 (1.8 %) | |
| Not at all | 2 (3.8 %) | 2 (4.0 %) | | 9 (16.7 %) | 4 (7.3 %) | |
| Vaginal atrophy score | | | < 0.001 | | | < 0.001 |
| Severe | 2 (3.8 % | 19 (35.3 %) | | 0 | 19 (34.5 %) | |
| Moderate | 36 (67.9 %) | 25 (46.3 %) | | 11 (20.4 %) | 25 (45.5 %) | |
| Minor | 12 (22.6 %) | 10 (18.5 %) | | 30 (55.6 %) | 10 (18.2 %) | |
| None | 3 (5.7 %) | 0 | | 13 (24.1 %) | 1 (1.8 %) | |
| Vaginal pH | 5.5 (5.0–5.8) | 5.8 (5.5–6.7) | < 0.001 | 5.0 (4.7–5.0) | 5.8 (5.6–6.8) | < 0.001 |

Data are n (%) or median (IQR). Statistical analyses by Chi-square tests and Mann-Whitney U-test.

[a] Two patients did not attend the one-month follow-up. Three patients did not consent to gynaecologic exam. Seven patients who had reported pain at sex as most troublesome vulvovaginal atrophy symptom at baseline had not had sex during the first month of treatment and could not report on any change.

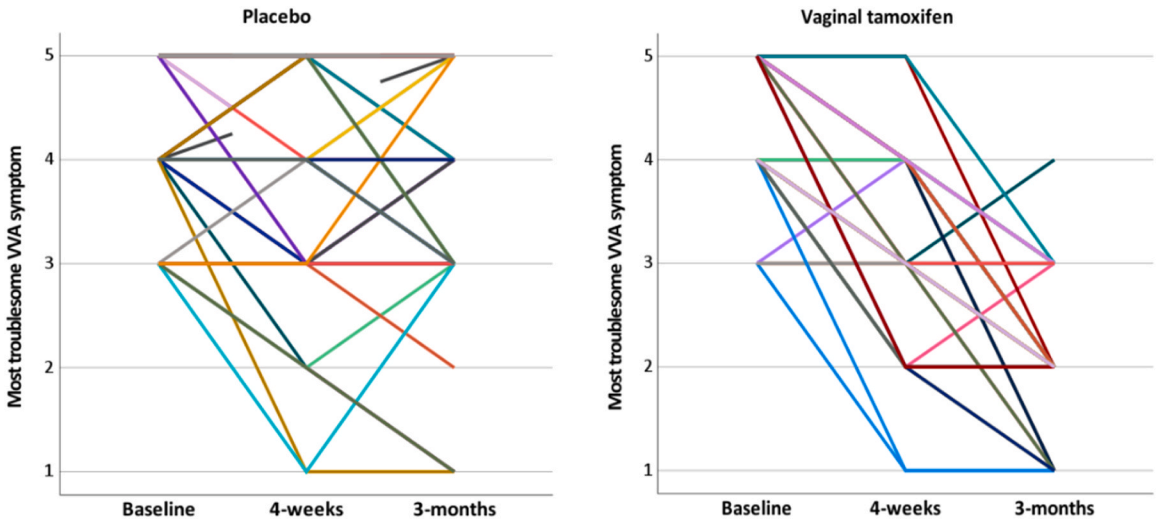


**Fig. 2.** Individual changes in the most troublesome vulvovaginal atrophy (VVA) symptom during the trial (1 = not at all, 2 = a little bit, 3 = somewhat, 4 = quite a bit, 5 = very much).

**Table 4**
Side effects reported during the trial.

| | One-month follow-up[b] | | | Three-months follow-up | | |
|---|---|---|---|---|---|---|
| | Tamoxifen (n = 55) | Placebo(n = 57) | p | Tamoxifen (n = 54) | Placebo (n = 55) | p |
| Vaginal burn at application | 12 (21.8 %) | 7 (12.3 %) | 0.2 | 9 (16.7 %) | 2 (3.6 %) | 0.024 |
| Vaginal discharge | 10 (18.2 %) | 3 (5.3 %) | 0.033 | 9 (16.7 %) | 0 | 0.002 |
| Vaginal itching | 2 (3.6 %) | 2 (3.5 %) | 1.0 | 1 (1.9 %) | 1 (1.8 %) | 1.0 |
| Vasomotor symptoms | 6 (10.9 %) | 3 (5.3 %) | 0.3 | 4 (7.4 %) | 2 (3.6 %) | 0.4 |
| Other | 5 (9.1 %) | 3 (5.3 %) | 0.5 | 2 (3.7 %) | 2 (3.6 %) | 1.0 |

Data are n (%). Statistical analyses by Chi-square tests.
[b] Two patients did not attend the one-month follow-up

women on placebo treatment, supplementary table 2.

### 4.3. Safety outcomes

Side effects of treatment were mild and are reported in Table 4. Vaginal burn (or discomfort) in conjunction or during first day/days after tablet placement was common in both groups, especially at the one-month follow-up (vaginal tamoxifen: 12 (21.8 %) vs. placebo: 7 (12.3 %). This side effect persisted in the vaginal tamoxifen users at the three-month follow-up (vaginal tamoxifen: 9 (16.7 %) vs. placebo: 2 (3.6 %), $p = 0.024$. As expected, women randomised to vaginal tamoxifen more often reported vaginal discharge in comparison with the placebo users, Table 4.

No serious adverse events occurred during the trial. Vaginal tamoxifen treatment was not associated with increased endometrial thickness throughout the trial (baseline 1.6 (0.5) mm vs. three-months follow-up 1.6 (0.6) mm, $p = 0.6$. No participant had endometrial thickness $\geq 4$ mm at the end of the trial.

## 5. Discussion

This randomized, double blind, placebo-controlled trial on the usefulness of vaginal tamoxifen once-weekly for treatment of VVA symptoms clearly demonstrates superiority of vaginal tamoxifen. At the end of the trial, more than two-thirds of the women randomized to vaginal tamoxifen reported that their most troublesome VVA symptom was mild or not present at all. Moreover, the self-reported improvement was accompanied by signs of tamoxifen-induced oestrogenic effects on the vaginal mucosa, such as improved vaginal atrophy score and lowered vaginal pH.

Tamoxifen is a selective estrogen receptor modulator (SERM) and it has long been known that it exerts both agonistic and antagonistic properties, depending on target tissue [13]. For instance in the immature rat uterine model, tamoxifen have both agonistic and antagonistic effects to estradiol, with agonistic effects most noticeable at low concentrations of estradiol [13]. Moreover, tamoxifen clearly has agonistic, i.e. estrogen-like, effects on the vaginal mucosa. We have previously demonstrated that women treated with oral tamoxifen resemble the healthy estrogen users in all VVA measures, including objective vaginal atrophy scores, measurements of vaginal pH (typically low in estrogen-stimulated vagina), and vaginal cell maturation index [5]. Further, expression of proliferative markers, estrogen-, and progesterone receptors in the vaginal mucosa were similar in women on tamoxifen and women using local estrogen [9]. Even more importantly, women on oral tamoxifen reported similar rates of vaginal dryness and pain at sex as healthy women on local estrogen [5,6]. All of these findings are in line with previous studies of tamoxifen in postmenopausal women with BC, suggesting estrogen agonism on the vaginal mucosa [14].

Our findings are in line with a small case report of vaginal tamoxifen [12] and a recent small randomized controlled trial on gel capsules with tamoxifen for vaginal use [15]. The latter study employed twice weekly treatment regimen and tested four different doses of tamoxifen (1, 5, 10 and 20 mg). Because of the small number of participants (n = 17), no differences in symptom relief across the vaginal tamoxifen doses was noted, but the 20 mg dose was associated with greater improvement in vaginal maturation index [15].

Or findings are also in line with previous studies on SERM for VVA symptoms. Ospemifene, which is an oral systemic drug, has been tested in at least 7 RCT for the treatment of VVA-induced dyspareunia in

healthy postmenopausal women. The treatment results in improvement of vaginal maturation index and relief of most VVA symptoms, as well as improvement in measures of sexual wellbeing [16], but is still contraindicated for use in patients with ongoing treatment for BC.

### 5.1. Limitations

There are a number of limitations of this trial. First, the over-arching safety issue with the proposed treatment is if it has consequences for endometrial safety. Oral tamoxifen, in doses of 20 mg daily, is associated with a small increased risk of endometrial cancer, with a prevalence of 1.6/1000 women years [17]. In analogy with vaginal estrogen use, we expected that a low, local dose of tamoxifen would have minimal impact on the endometrium. The reason local estrogen does not influence the risk of endometrial hyperplasia and cancer is hypothetically due to counter-current transfer of estrogens from vagina to the arterial blood supplying the urethra instead of the uterus [18]. Indeed, we found no increase in endometrial thickness, and no individual patient with endometrium $\geq$ 4 mm at the end of the trial. Nevertheless, endometrial safety is a continued concern, especially as this study was a short-term proof-of concept trial, and was underpowered to detect endometrial hyperplasia or other pathology.

Secondly, while our study showed clear improvement in the most troublesome VVA symptom of participants, we also noted complaints of burning and irritation in relation to the oral tablet application. Clearly, a more suitable vaginal application system for tamoxifen administration is warranted before this treatment option is implemented in the clinic.

### 5.2. Clinical implication

While vaginal tamoxifen should be safe in patients with breast cancer, we like to stress that the treatment is likely not as effective as vaginal oestrogen, although no formal comparison has been performed. Ultra-low estriol treatment has been tested in healthy postmenopausal women and in women with BC and findings demonstrate minimal impact on gonadotrophin and estradiol levels and complete normalization of VVA symptoms and vaginal pH. Thus, for BC survivors in need of treatment for VVA symptoms, ultra-low estriol treatment may still be a much more viable option [19,20].

Further, vaginal tamoxifen is most likely not a remedy for premenopausal women. In the immature rat uterine model, the agonistic (estrogen-like) effect of tamoxifen was most noticeable at low concentrations of estradiol [13], which would correspond to the postmenopausal status of the women included in this study. While still not tested, this dual effect depending on estrogen environment could mean that tamoxifen would have antagonistic effects to estradiol in the vaginal mucosa of premenopausal women, i.e. in women with maintained estradiol levels. In line with this reasoning, tamoxifen appears not to have estrogen agonistic properties on the premenopausal endometrium [21–23]. Further studies, evaluating the vaginal tamoxifen effect in relation to patients' endogenous estradiol concentrations is warranted. At the same time, estrogen concentration may not be the only driver for the tamoxifen effect in premenopausal women. Premenopausal women with BC on gonadotropin release hormone (GnRH) agonists and adjuvant tamoxifen reported more severe VVA symptoms than women on tamoxifen-only [24]. Abrupt loss of ovarian function, whether by chemotherapy or GnRH agonists have significant effects on the sexual function, well-being and quality of life of women [2].

### 5.3. Conclusion

This study has demonstrated that more than two-thirds of the women randomized to vaginal tamoxifen reported significant relief of their most troublesome VVA symptom. This effect is most likely due to estrogen agonistic effects on the vaginal mucosa in a low-estrogen environment. While findings are promising, studies with better vaginal administration systems are needed, and endometrial safety concerns need to be addressed in the future. Needless to say, greater emphasis and more research on VVA symptoms in postmenopausal women and BC survivors is warranted.

## CRediT authorship contribution statement

**Anna Wikman:** Writing – review & editing, Supervision, Formal analysis. **Angelica Lindén Hirschberg:** Writing – review & editing, Resources, Investigation. **Helena Kopp Kallner:** Writing – review & editing, Resources, Investigation. **Inger Sundström Poromaa:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Henrik Lindman:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Sara Nyback:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis. **Theodora Kunovac Kallak:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Inger Sundström Poromaa has received an unrestricted grant from Gedeon Richter for studies on hormonal contraceptives. In addition, she has received lecture fees from Gedeon Richter and Astellas. These relationships had no influence on the content, design, analysis, or interpretation of the work. Sara Nyback, Henrik Lindman, Angelica Lindén Hirschberg, Helena Kopp Kallner, Anna Wikman and Theodora Kunovac Kallak report no competing financial interests.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116261.

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