Original Article

Quality of life and Satisfaction With Ospemifene for Treating Vulvovaginal Atrophy in Breast Cancer Survivors: Six-Month Results From the PatiEnt SatisfactiON StudY (PEONY)

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Abstract

This study evaluated ospemifene in postmenopausal breast cancer survivors with moderate to severe vulvovaginal atrophy. After 6 months, women reported higher treatment satisfaction, fewer symptoms (dryness, pain, infections), and better physical health and daily functioning. Sexual distress decreased, though overall sexual function did not change. Ospemifene proved effective and well-tolerated.

Objective: Breast cancer (BC) survivors often experience vulvovaginal atrophy (VVA) due to endocrine therapies, affecting quality of life (QoL) and well-being. We aimed to evaluate impact of ospemifene treatment in postmenopausal women with history of BC and moderate to severe VVA. **Methods:** PEONY is a real-world, prospective, multicenter study. Participants completed questionnaires at baseline, after 3 and 6 months. Treatment satisfaction score was the primary outcome. As secondary outcomes, symptoms severity, day-to-day impact of vaginal aging scale, female sexual function index, female sexual distress scale-revised, and SF-12® Health survey were investigated. **Results:** Sixty-four women with a mean age of 56.4 ± 7.2 years (41.9% with severe VVA) either initiated (35.9%) or continued (64.1%) ospemifene. Treatment satisfaction significantly improved over 6 months, with mean score rising from 7.1 to 7.8 ($P = .047$). The odds of moderate to severe symptoms, such as vaginal dryness, pain and bleeding during sexual intercourse, genital discomfort during physical activity, burning, and itching, decreased by 70% to 90% at 6 months, as well as recurrent urinary tract

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infections and cystitis associated with sexual intercourse (by 80% and 90%). QoL measurements showed significant improvements in physical health and daily functioning, although mental health improvements were not statistically significant. Likelihood of sexual distress decreased by 40%. Although overall sexual function remained unchanged, specific domains such as lubrication and pain showed improvement. **Conclusion:** Ospemifene is effective and well-tolerated for treating moderate to severe VVA of women with history of BC. However, a comprehensive and multidisciplinary approach is needed to improve sexual function of BC survivors treated for VVA.

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Introduction

Globally, 2.3 million women are diagnosed with breast cancer (BC) each year, with a survival rate of almost 90% at 5 years from diagnosis.[1] Improving survival requires proactive management of short and long-term side effects of oncological therapies. For estrogen-receptor positive BC, the standard of care involves the use of oral endocrine therapies (tamoxifen and aromatase inhibitors) along with gonadotropin-releasing hormone agonists (GnRH) for premenopausal women with high-risk tumors. Antiestrogen therapy induces or exacerbates signs and symptoms of vulvovaginal atrophy (VVA), affecting up to 90% of BC survivors,[2] with a detrimental effect on quality of life (QoL).[3] Optimal management of these side effects is crucial for compliance, as up to 20% of BC survivors consider stopping endocrine therapies due to menopausal symptoms.[4] This represents a critical aspect, since early discontinuation and nonadherence to hormonal therapies are associated with increased mortality.[4] International guidelines and scientific societies advise that healthcare providers (HCPs) should inform women about menopausal-related symptoms of endocrine therapy and their consequences, including sexual problems.

Postmenopausal BC survivors are at greater risk of VVA and symptoms linked to sexual dysfunction compared to their counterparts without a history of BC, particularly following adjuvant hormone therapy.[5] Therefore, it is essential to prioritize the preservation of both current and future sexual function, along with a satisfying sexual life, as an integral component of the care and overall experience of breast cancer patients.[6] The impact of VVA symptoms on QoL is comparable to other chronic conditions for which there is a greater awareness.[3] Unfortunately, VVA issues during oncologic follow-up often receive little attention due to patients' reluctance to report symptoms and HCPs' barriers in addressing this sensitive topic.

Vaginal estrogen administration is the most effective treatment of VVA in the general postmenopausal population,[7] whereas the optimal management of VVA in BC survivors remains challenging due to safety concerns regarding the use of local hormonal treatment. Indeed, current international guidelines recommend local moisturizers and lubricants as the first-line choice.[8] Furthermore, according to the best evidence available, fractional CO2 laser treatment for VVA is another effective and safe therapeutic option for gynecological cancer survivors, improving sexual life and quality of life (QoL).[9] However, these options typically offer only temporary and limited relief, making it important to consult with the oncologist to carefully weigh the risks and benefits of using hormonal compounds.[8] Ospemifene is the sole oral nonsteroidal selective estrogen receptor modulator (SERM) approved for treating moderate to severe symptomatic VVA in postmenopausal women.[10] The European Medicines Agency has limited its indication to those patients who are not candidates for local vaginal estrogen treatments but an expert opinion based on recent real-world data indicates that there is no additional thrombotic risk and that ospemifene can be used also as first choice.[11] Being a SERM derived from a tamoxifen metabolite, ospemifene acts as a weak antiestrogen on breast tissue.[12] Although its clinical trial program did not specifically investigate the use of ospemifene in women with BC, subsequent preclinical and clinical studies have shown no increased risk for BC or breast-related safety concerns among patients taking ospemifene.[13-16] However, real-world data regarding the efficacy and tolerability of ospemifene in BC survivors are still lacking.

The Patient Satisfaction Study (PEONY) is an Italian real-world study providing a comprehensive overview of treatment strategies for postmenopausal women with moderate to severe VVA,[17] including those with history of BC. Here we present longitudinal data about treatment satisfaction, symptoms severity, treatment persistence and patient reported outcomes (PROs) of women with history of BC.

Methods

PEONY is a prospective, longitudinal, observational study conducted in 17 gynecology centers across Italy. The primary aim of the present analysis was to assess treatment satisfaction after 6 months of therapy with ospemifene in women with history of BC. Secondary aims were to evaluate the impact of treatment on symptoms severity, treatment persistence, and PROs in sexuality and QoL. The study design was previously described in details.[17] Briefly, data were collected at baseline (T0), after 3 months (T3), 6 months (T6), and at a planned 12-month follow-up visit. Inclusion criteria were: age $\geq$ 18 years, no ongoing oncological treatment, postmenopausal state, moderate to severe VVA based on clinical judgment, and already treated with or initiating ospemifene at study entry, irrespective of other nonhormonal concomitant treatments for VVA (moisturizers, lubricants, laser, and radiofrequency).

Baseline information included demographic and anthropometric data, BC history and related treatments, relevant comorbidities, reproductive history, postmenopausal state, and prescribed treatment for VVA. The vaginal health index (VHI) and the vulvar health index (VuHI) were used to evaluate the severity of VVA

Table 1 Baseline Patient Characteristics

	BC with Ospemifene
N group	64
Socio-demo characteristics:	
Age (years)	56.4 ± 7.2
Age at BC diagnosis (years)	47.6 ± 6.5
Nationality (%):	
Italian	100
Other	-
Education (%):	
< high school	10.2
≥ high school	89.8
Marital status (%):	
Married	75.9
Single	6.9
Widow	-
Relation	17.2
Employment (%):	
Employed	68.4
Unemployed/housewife	17.5
Retired	14.0
Clinical characteristics	
Age at menopause (years)	48.0 ± 4.9
Menopause type (%):	
Physiological	26.7
Surgical	21.7
Treatment-related	51.7
BMI (kg/m^2)	23.3 ± 3.3
At least 1 abortion (%)	26.7
Deliveries type (%):	
No	21.9
Spontaneous	56.3
Cesarean	32.8
History of breast cancer (%)	
Years from BC diagnosis	9.0 ± 4.9
Surgery (%)	93.8
Treatment (%):	
Chemotherapy (%)	35.9
Anti-hormonal treatment—Tamoxifen (%)	40.6
Anti-hormonal treatment—Aromatase inhibitors (%)	26.6
Radiotherapy (%)	51.6
Comorbidities (%):	
Hysterectomy	6.7
Urinary incontinence	32.8
Other chronic diseases	22.4
Chronic therapies (%):	
None	37.5
Antihypertensive drugs	15.6
Lipid-lowering drugs	14.1
Glucose-lowering drugs	3.1
Osteoporosis treatment	23.4
Other	28.1
Lifestyle	
Smoke (%):	
No	75.0
Ex	16.7
Yes	8.3
If yes, number of cigarettes/day	5.4 ± 2.2
Alcohol (%):	
No	54.2
Sometimes	39.0
Regularly	6.8
Coffee (%):	
No	21.7
≤ 3 cups a day	63.3
> 3 cups a day	15.0
Physical exercise (%):	
No	28.8
1-2 times a week	47.5
≥ 3 times a week	23.7
Severity degree at enrolment by physician judgement (%):	
Mild	4.8
Moderate	53.2
Severe	41.9
Vaginal Health Index (VHI):	
Score	11.6 ± 2.5
VHI < 15	88.7
Vulvar Health Index (VuHI):	
Score	12.9 ± 4.7
VuHI > 8	85.2
VVA treatments	
Treatment (%):	
Naïve	35.9
Already treated with any VVA treatment	64.1
Concomitant treatments at T0 (%):	
Lubricants	3.13
Hydrating	1.56
Laser	-
Radiofrequency	-

Data are means and standard deviations or frequencies and proportions.

at baseline.[18-21] The VHI assesses vaginal elasticity, secretions, pH, presence of petechiae on the epithelial mucosa, and hydration, with a total score ranging from 5 to 25 and a cut-off < 15 indicating an atrophic vagina. The VuHI assesses vulvar inflammation, musculature contraction, pain at speculum insertion, and epithelial integrity, with a total score between 0 and 24 and a cut-off >8 indicating an atrophic vulva.

Each enrolled woman completed self-reported questionnaires at T0, T3, and T6 including socio-demographic characteristics, lifestyle, satisfaction with VVA treatment, and persistence in therapy or reasons for discontinuation. Satisfaction with VVA

treatment was assessed using a numeric rating scale ranging from 0 (very low) to 10 (very high). Symptoms of VVA were evaluated using a specific section of the European Vulvovaginal Epidemiological Survey (EVES).[19,20] Participants rated their VVA symptoms, based on a list of 19 potential complaints, on a 4-point severity scale (absent = 0, mild = 1, moderate = 2, or severe = 3). Vaginal symptoms included internal dryness, pain during intercourse (internal and at penetration), bleeding during intercourse and sexual contact, internal burning or irritation, internal itching, and vaginal discharge. Vulvar symptoms included external dryness, external burning or irritation, external itching, and pain during exercise. Urinary symptoms included incontinence, urgency, frequency, urinary difficulties, recurrent infections, and postcoital cystitis.

The following questionnaires administered at T0, T3, and T6 assessed QoL and sexual function and distress: the Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire,[22] the Female Sexual Distress Scale-Revised (FSDS-R),[23] the Female Sexual Function Index (FSFI),[24] the SF-12® Health Survey (SF-12).[25] A description of the questionnaires is reported in Supplemental Table 1.

The study protocol received approval from local ethics committees, and informed consent was obtained from all participants. All procedures adhered to the ethical standards set by the responsible committee on human experimentation (both institutional and national), as well as the Helsinki Declaration of 1964, revised in 2013.

Statistical Analysis

All consecutive eligible women seen over 12 months were enrolled, irrespective of the ongoing treatment for VVA. Descriptive data were summarized as mean and standard deviation or proportion. Treatment satisfaction changes from T3 to T6 were assessed, because most of the patients were not treated with ospemifene at T0. For all other questionnaires, changes in scores from T0 to T6 were assessed using mixed models for repeated measurements. Results are expressed as estimated mean or estimated mean difference from T0 with their 95% confidence interval (95% CI). Paired t-test derived from linear mixed models for repeated measurements was applied for within-group comparisons. As categorical secondary outcomes, the proportions of patients with FSDS-R score $\geq$ 11, FSFI score $\leq$ 26.55, and moderate or severe VVA symptoms were evaluated using mixed effects models. The results are expressed as prevalence and Odds Ratio (OR) with relative 95%CI. *P*-values $<$ .05 were considered as statistically significant.

In accordance with guidelines of the present journal, we will provide our data for independent analysis by a selected team of the Editorial Team, if requested.

Results

Out of 385 women enrolled in the PEONY study, 64 had a history of BC and either initiated (93.8%) or continued (6.2%) ospemifene at study entry. Baseline characteristics are summarized in Table 1. Women with a history of BC had a mean age of 56.4 $\pm$ 7.2 years, with average age at BC diagnosis of 47 years. Most participants had a high level of education (89.8%) and were married (75.9%), while 68.4% were employed. The mean age at menopause was 48.0 $\pm$ 4.9 years, one-fourth of patients experienced menopause before 45 years of age. The diagnosis of BC had occurred on average 9.0 $\pm$ 4.9 years prior to study enrollment. Almost all women (93.8%) had undergone breast surgery, 35.9% had received chemotherapy, and 51.6% radiotherapy. Adjuvant hormone therapy was previously prescribed to over two-thirds of the women (tamoxifen: 40.6%, aromatase inhibitors: 26.6%). Among comorbidities, there was a high prevalence of urinary incontinence (32.8%), and nearly 1 in 4 women (23.4%) were receiving treatment for osteoporosis. At enrollment, 41.9% of participants had severe VVA. A VHI score $<$ 15 was reported in 88.7% of participants, and a VuHI score $>$ 8 was reported in 85.2%. Among patients with available 6-month follow-up data, 85.7% remained on ospemifene treatment. The main reason for discontinuation was the need for treatment intensification.

Primary endpoint results are reported in Figure 1. Satisfaction with VVA treatment significantly improved from 7.1 (95% CI: 6.4-7.8) at T3 to 7.8 (95% CI: 7.1-8.5) at T6 (P = .047).

Results from the longitudinal analyses are presented in Tables 2–4 . The prevalence of various moderate to severe symptoms of VVA decreased, including vaginal dryness, pain during sexual intercourse, genital discomfort during physical activity, bleeding during sexual intercourse, burning or irritation, and itching (Table 2). Odds of moderate to severe levels of these symptoms decreased by 70% to 90% at 6 months follow-up, as indicated by ORs ranging from 0.1 to 0.3. Additionally, the likelihood of recurrent urinary tract infections (RUIs) and cystitis associated with sexual intercourse decreased by 80% and 90%, respectively (Table 2).

All DIVA questionnaire scores significantly improved after 6 months (Table 3). For general QoL, there was a significant improvement in the physical component summary (PCS) score of SF-12, while the improvement in the mental component summary (MCS) score did not reach statistical significance (Table 3).

Sexual distress FSDS-R total score significantly decreased, with an average reduction of 8.6 points (95% CI: $-$11.9 to $-$5.2) (Table 3). The prevalence of FSDS-R $\geq$ 11 (indicative of distress) decreased from 84.4% (95% CI: 73.1%-91.5%) to 75.3% (95% CI: 62%-85%) (Table 4). This change corresponded to a 40% lower likelihood of experiencing sexual distress at 6 months (T6) compared to baseline (T0), although statistical significance was not reached (OR = 0.6; 95% CI: 0.3-1.0; P = .07). Time trend of the individual items of the FSDS-R is shown in Figure 2, confirming a statistically significant improvement for most of them, except being stressed about sex and feeling inferior because of sexual problems.

Regarding overall sexual function, FSFI total score did not change significantly. However, the domains related to lubrication and pain significantly improved, whereas arousal and orgasm did not change, and desire and satisfaction worsened (Table 3). The prevalence of FSFI $\leq$ 26.55 (indicative of sexual dysfunction) was very high at T0 (84.4%) and T6 (93.6%), without any significant difference (Table 4).

Table 2 Changes in the Likelihood of Moderate/Severe VVA Symptoms From Study Entry to 6 Months

VVA Symptom	Visit	BC With Ospemifene		
		Probability Estimates and 95% CI	OR and 95% CI	*P*-Value*
Dryness (Inside the vagina)	T0	90.3 (79.8;95.6)		
	T3	70.8 (56.6;81.8)	0.3 (0.1;0.7)	**.01**
	T6	53.7 (39.8;67)	0.1 (0.0;0.4)	**.0002**
Dryness (Outside/external genitalia)	T0	90.3 (79.8;95.7)		
	T3	69.2 (55;80.5)	0.2 (0.1;0.7)	**.009**
	T6	53.3 (39.4;66.6)	0.1 (0.0;0.3)	**< .0001**
Pain during sexual intercourse (Inside the vagina)	T0	87.1 (76;93.5)		
	T3	62.8 (48.7;75.1)	0.3 (0.1;0.6)	**.0009**
	T6	42.2 (29.3;56.3)	0.1 (0.0;0.2)	**< .0001**
Pain during sexual intercourse (On penetration)	T0	90.2 (79.8;95.6)		
	T3	63.6 (49.4;75.8)	0.2 (0.1;0.4)	**.0001**
	T6	47.5 (34;61.4)	0.1 (0.0;0.2)	**< .0001**
Genital discomfort during physical activity	T0	33.5 (22.7;46.3)		
	T3	22 (12.8;35.3)	0.6 (0.3;1.1)	.08
	T6	11.9 (5.4;24.2)	0.3 (0.1;0.7)	**.007**
Bleeding during sexual intercourse	T0	33.6 (22.8;46.3)		
	T3	20.9 (11.7;34.5)	0.5 (0.3;1.1)	.07
	T6	10.1 (4.3;21.7)	0.2 (0.1;0.5)	**.0006**
Bleeding during sexual contact	T0	14.3 (7.5;25.6)		
	T3	11.4 (5.2;23.3)	0.8 (0.3;1.9)	.57
	T6	9.5 (4.1;20.4)	0.6 (0.3;1.4)	.23
Burning or irritation (Inside the vagina)	T0	62.3 (49.6;73.6)		
	T3	47.7 (34.5;61.3)	0.6 (0.3;1.0)	.06
	T6	18 (9.6;31.1)	0.1 (0.1;0.3)	**< .0001**
Burning or irritation (On the outside/external genitalia)	T0	65.7 (53;76.5)		
	T3	43.5 (30.6;57.3)	0.4 (0.2;0.8)	**.006**
	T6	23.9 (14.1;37.6)	0.2 (0.1;0.4)	**< .0001**
Itching (Inside the vagina)	T0	32.1 (21.5;44.9)		
	T3	17.6 (9.3;30.7)	0.5 (0.2;1.0)	.06
	T6	9.8 (4;21.8)	0.2 (0.1;0.7)	**.007**
Itching (On the outside/external genitalia)	T0	35.3 (24.3;48.1)		
	T3	20.5 (11.4;34.1)	0.5 (0.2;1.0)	**.04**
	T6	7.9 (3;19.5)	0.2 (0.0;0.5)	**.003**
Vaginal discharge	T0	12.9 (6.5;24)		
	T3	9.3(3.6;21.7)	0.7 (0.2;2.2)	.53
	T6	4.3 (1.2;14.5)	0.3 (0.1;1.4)	.13
Urinary incontinence	T0	11.3 (5.4;22.2)		
	T3	4.6 (1.3;14.6)	0.4 (0.1;1.4)	.13
	T6	6.5 (2.2;17.3)	0.5 (0.2;1.8)	.32
Urinary urgency	T0	14.5 (7.6;25.9)		
	T3	9.8 (4.1;21.7)	0.6 (0.2;2.0)	.44
	T6	9.8 (4.1;21.7)	0.6 (0.2;2.0)	.44
Urinary frequency	T0	19.3 (11.1;31.2)		
	T3	9.6 (3.9;21.6)	0.4 (0.2;1.3)	.12
	T6	13 (6.1;25.4)	0.6 (0.2;1.6)	.33
Difficult urination	T0	4.8 (1.5;14.4)		
	T3	-	-	-
	T6	-	-	

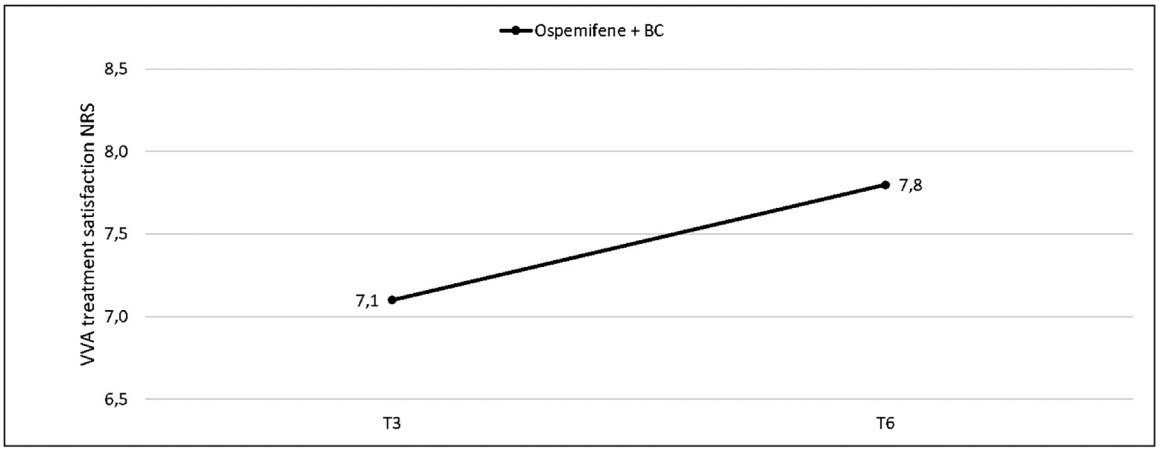
(*continued on next page*)

Table 2 (*continued*)

VVA Symptom	Visit	BC With Ospemifene		
		Probability Estimates and 95% CI	OR and 95% CI	*P*-Value*
Recurring urinary tract infections	T0	22.5 (13.6;34.7)		
	T3	2.2 (0.4;11.9)	0.1 (0.0;0.4)	**.004**
	T6	4.3 (1.2;14.1)	0.2 (0.0;0.5)	**.003**
Cystitis associated with sexual intercourse	T0	27.3 (17.5;39.8)		
	T3	7.7 (2.8;19.3)	0.2 (0.1;0.6)	**.0057**
	T6	1.9 (0.2;13.4)	0.1 (0.0;0.4)	**.005**
Abdominal pain	T0	3.2 (0.8;12.3)		
	T3	2 (0.3;13.1)	0.6 (0.1;7.3)	.69
	T6	2 (0.3;13.1)	0.6 (0.1;7.3)	.69

Abbreviations: 95% CI = confidence intervals; OR = odds ratio.
[a] Results from mixed effects models for repeated measurements. Statistically significant p-values ($P < .05$) are in bold.

Figure 1 Primary endpoint: Satisfaction with VVA treatment



Score	Visit	*Estimated mean (95%CI)*	*Estimated mean difference from T3 and 95% CI*	*p-value**
VVA treatment satisfaction NRS	T3*	7.1 (6.4;7.8)	-	-
	T6	7.8 (7.1;8.5)	0.7 (0.01;1.4)	**0.04**

NRS= numerical rating scale

**Paired t-test derived from linear mixed models for repeated measurements. Statistically significant p-values (p<0.05) are in bold.*

Discussion

Summary of Main Results

The PEONY study provides the first longitudinal data on patients with a history of BC treated with ospemifene for moderate-severe VVA. To the best of our knowledge, this is the largest analysis of real-world data involving a BC population ($N = 64$) and assessing patient satisfaction with ospemifene treatment.

Results in the Context of Published Literature

In a post-hoc analysis of an administrative claims database from the U.S. population, Cai et al[13] showed similar BC incidence rates in a large cohort of ospemifene treated and not treated patients. No difference in recurrence rate was observed also in additional analyses matched 1:1 (14 vs. 21 $P = .13$), 1:2 (10 vs. 25 $P = .44$), and 1:3 (7 vs. 24 $P = .69$) with controls. However, end-points associated with QoL were not considered. In the only other study by Pingarrón Santofímia et al.[26] prospectively evaluating the effectiveness of ospemifene in clinical practice for the treatment of VVA, only 5 women with history of BC were included, none of whom experienced a recurrence during 12 months. In line with these findings, we did not observe any cancer recurrence or severe adverse events over the PEONY study period. Our BC popula-

Table 3 Changes in Treatment Satisfaction and Quality of Life and Sexual Scores From Study Entry to 6 Months

Score	Visit	BC With Ospemifene		
		Estimated Mean Levels (95% CI)	Estimated Mean Difference From T3 and 95% CI	*P*-Value[a]
DIVA activities of daily living	T0	0.9 (0.7;1.0)		-
	T3	0.7 (0.5;0.8)	−0.2 (−0.4;0.0)	**.03**
	T6	0.5 (0.3;0.6)	−0.4 (−0.6;−0.2)	**< .0001**
DIVA emotional wellbeing	T0	1.9 (1.6;2.2)		**-**
	T3	1.5 (1.2;1.8)	−0.4 (−0.7;−0.1)	**.01**
	T6	1.4 (1.1;1.6)	−0.5 (−0.8;−0.2)	**.0003**
DIVA sexual functioning	T0	2.6 (2.3;2.8)		**-**
	T3	2.1 (1.7;2.4)	−0.5 (−0.8;−0.2)	**.0004**
	T6	1.7(1.5;2)	−0.8 (−1.2;−0.5)	**< .0001**
DIVA self-concept and body image	T0	2.5 (2.2;2.8)		**-**
	T3	2.1 (1.8;2.4)	−0.4 (−0.7;−0.2)	**.0012**
	T6	1.9 (1.5;2.2)	−0.7 (−1.0;−0.4)	**< .0001**
SF-12 (PCS)	T0	46.0 (44.0;48.0)		-
	T3	48.6 (46.5;50.7)	2.6 (1.0;4.2)	**.0015**
	T6	48.6 (46.7;50.6)	2.7 (0.9;4.4)	**.0035**
SF-12 (MCS)	T0	41.8 (39.1;44.4)		-
	T3	42.6 (40.2;45.0)	0.8 (−1.3;3.0)	.44
	T6	44.1 (41.6;46.5)	2.3 (−0.3;5.0)	.09
FSDS-R	T0	29.2 (25.7;32.8)		**-**
	T3	23.8 (19.9;27.7)	−5.5 (−8.0;−2.9)	**< .0001**
	T6	20.7 (16.7;24.6)	−8.6 (−11.9;−5.2)	**< .0001**
FSDS-R (item 13)	T0	2.6 (2.3;2.9)		
	T3	2.1 (1.7;2.5)	−0.5 (−0.9;−0.2)	**.005**
	T6	1.8 (1.4;2.2)	−0.8 (−1.2;−0.4)	**< .0001**
FSFI total score	T0	19.0 (17.4;20.7)		-
	T3	19.1 (17.4;20.8)	0.1 (−1.7;1.9)	.94
	T6	20.6 (19.4;21.9)	1.6 (−0.4;3.6)	.11
FSFI desire	T0	4.9 (4.7;5.2)		-
	T3	4.5 (4.2;4.9)	−0.4 (−0.8;−0.1)	**.02**
	T6	4.2 (3.9;4.5)	−0.7 (−1.0;−0.4)	**< .0001**
FSFI arousal	T0	3.3 (2.7;3.8)		-
	T3	3.1 (2.5;3.6)	−0.2 (−0.8;0.4)	.54
	T6	3.4 (2.9;3.9)	0.1 (−0.5;0.8)	.70
FSFI lubrication	T0	2.7 (2.2;3.2)		-
	T3	2.9 (2.5;3.4)	0.2 (−0.2;0.7)	.29
	T6	3.3 (3.0;3.7)	0.6 (0.1;1.2)	**.03**
FSFI orgasm	T0	2.7 (2.2;3.1)		-
	T3	2.7 (2.3;3.2)	0.1 (−0.4;0.5)	.81
	T6	3.2 (2.8;3.5)	0.5 (−0.1;1.1)	.09
FSFI satisfaction	T0	3.9 (3.6;4.2)		-
	T3	3.4 (3.1;3.8)	−0.4 (−0.8;−0.1)	**.02**
	T6	3.3 (3.0;3.6)	−0.5 (−0.9;−0.2)	**.0015**
FSFI pain	T0	1.6 (1.2;2)		-
	T3	2.3 (1.8;2.9)	0.8 (0.3;1.2)	**.0021**
	T6	3.2 (2.6;3.7)	1.6 (1.0;2.1)	**< .0001**

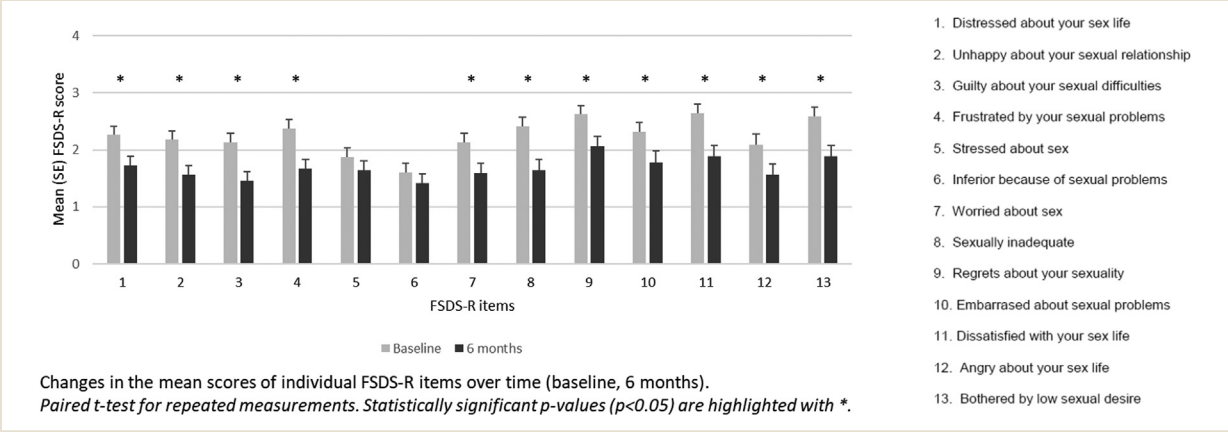
Statistically significant p-values ($P < .05$) are in bold.
DIVA: range 0-4, the higher scores, the greater impact of vaginal symptoms.
FSFI: range 2-36, the higher the score, the less severity of sexual dysfunction.
Female Sexual Distress Scale – Revised
(FSDS-R): range 0-52, the higher the score, the higher the level of sexual distress. Score $\geq$ 11 discriminates women with sexual distress.
SF-12: normalized to 50 $\pm$ 10, the higher the score, the higher the level of mental or physical health.
[a] Paired t-test derived from linear mixed models for repeated measurements.

Table 4 Changes in Categorical Sexual Score

Categorical Endpoints		Overall		
	Visit	Probability Estimates and 95% CI	OR and 95% CI	*P*-Value*
FSDS-R ≥ 11	T0	84.4 (73.1;91.5)		
	T3	79.2 (66.5;88)	0.7 (0.4;1.2)	.23
	T6	75.3 (62;85)	0.6 (0.3;1)	.07
FSFI ≤ 26	T0	84.4 (73.1;91.5)		
	T3	88.8 (76.5;95.1)	1.5 (0.6;3.9)	.43
	T6	93.6 (82.8;97.8)	2.7 (0.8;9.3)	.11

Abbreviations: 95% CI = confidence intervals; OR = odds ratio.
* Results from mixed effects models for repeated measurements. Statistically significant *P*-values ($P < .05$) are in bold.

Figure 2 Time trend of the individual items of the FSDS-R



Changes in the mean scores of individual FSDS-R items over time (baseline, 6 months).
*Paired t-test for repeated measurements. Statistically significant p-values (p<0.05) are highlighted with *.*

tion was relatively young (mean age 56 years), with a mean age at menopause of 47 years and with iatrogenic menopause in over 70% of the cases. In this scenario, we expected a high prevalence of VVA symptoms and sexual dysfunction as compared to previous survey data.[27,28] Indeed, the phenotype of VVA was particularly severe in the PEONY BC population, with almost 9 out of 10 women having VHI and VuHI scores indicating atrophic vulvovaginal changes and FSFI and FSDS-R scores indicating sexual dysfunction/distress. Moreover, 1 in 3 women reported urinary incontinence. It is therefore not surprising that both SF-12 and DIVA scores reflected poor quality of life, highlighting compromised physical and mental well-being overall, and more specifically, the negative impact of VVA symptoms. Our data confirmed the evidence of the EVES study[20] which highlighted the negative impact of VVA on several domains of personal and relational well-being in BC survivors. In our study, ospemifene provided a significant reduction in the number of women reporting moderate to severe symptoms of VVA after 6 months, with improved satisfaction with treatment and high therapy adherence. Indeed, almost 9 out of 10 women remained on ospemifene treatment at 6 months follow-up. We observed a significant improvement also in the urinary cluster of symptoms, with a substantial reduction in the likelihood of recurrent urinary infections and postcoital cystitis.

This is highly relevant in light of their association with dyspareunia, sexual distress, and poor emotional and self-concept wellbeing.[29,30] Our data suggest that an effective treatment of VVA could also reduce the burden of the urinary component of GSM,[31,32] a concept that awaits further well-designed studies.[33] Indeed, there is an urgent need to assess the natural history of urinary symptoms that are severe in 23% of BC survivors,[34] and it seems important to explore their effective management in cancer patients.[35]

Longitudinal evaluation of PROs highlighted the positive effect of 6 months of ospemifene treatment on the impact of VVA on daily life, sexual distress and ultimately general QoL. All items of the DIVA significantly improved, including those related to self-concept and body image, which are particularly critical in BC survivors. VVA is one of the main determinants of female sexual dysfunction at menopause, which may include a wide range of diagnoses, that is, hypoactive sexual desire disorder (HSDD), female orgasmic disorder, and genito-pelvic pain/penetration disorder.[36] In our sample of BC survivors, we used validated psychometric questionnaires to capture the effect of treating VVA with ospemifene, both on sexual

function (FSFI) and distress (FSDS-R). Our study showed that the likelihood of sexual distress significantly decreased when considering both the overall FSDS-R score and the individual items. The likelihood of having HSDD (distress related to low sexual desire, as measured by item 13 of the FSDS-R questionnaire)[23] also declined. Improvement in this item, along with the majority of the other items, may reflect a broader positive impact of ospemifene treatment on the subjective experience of VVA associated with sexual dysfunction. However, as far as sexual function was concerned, ospemifene positively affected domains of lubrication and pain that are likely to be more influenced by the improvement of functional and anatomical changes associated with the VVA condition. On the other hand, the treatment was unable to improve overall sexual functioning with a significant decline in desire and sexual satisfaction. Arousal and orgasm remained stable throughout the study. These findings should not be surprising in light of the complexity of dealing with sexual dysfunction in BC survivors.[37] Indeed, subjective variables, such as changing both priority for sexual activity and intimacy in the relationship, along with other physical and mental issues associated with the experience of cancer may play a crucial role in reporting information about sexual function.[37] Other data suggest that long term BC survivors often report normalization of physical and emotional functioning but continue experiencing troubles with sexual functioning and satisfaction even years after treatments.[38] We speculate that high expectations from the treatment along with a relatively short follow-up may be responsible for the lack of sexual changes measured by the FSFI questionnaire. The mental and psychological impact of cancer often intersects with the challenges of sexual dysfunction, particularly during the initial phases of the disease. Moderate to severe atrophy represents a chronic physical condition that frequently leads to a cessation or significant reduction in sexual activity. The persistence of sexual dysfunction further complicates improvements across all domains measured by the FSFI, especially arousal and orgasm, as these aspects require substantial psychological involvement and emotional support to enhance women's sexual well-being. Overall, our results reinforce the need for a comprehensive and multidisciplinary approach to the care of both women and, whenever possible, of their partner including not only the use of pharmacological interventions but also psycho-sexual and cognitive-behavioral therapies.

Strengths and Weaknesses

Our study shows both strengths and limitations. Among the latter, we cannot exclude selection bias, being the population recruited from specialized centers for the treatment of oncological menopause, which may not be fully representative of the general population. Additionally, data were collected at a relatively short follow-up period (6 months), but a further analysis at 12 months has been preplanned. Among the strengths, this study represents the largest cohort of women with a history of BC treated with ospemifene and followed longitudinally to assess satisfaction, efficacy, and adherence.

Implications for Practice and Future Research

The evaluation of PROs highlighted the importance of effectively treating VVA symptoms for improving the overall well-being of women with a history of BC. Furthermore, the high rate of adherence to treatment confirmed the importance of a comprehensive assessment of both subjective and objective variables associated with VVA for a long-lasting successful care.

Conclusions

Ospemifene is an effective treatment in women with a history of BC reporting moderate to severe vulvovaginal atrophy. It also displays a high rate of satisfaction. However, a comprehensive and multidisciplinary approach is needed to improve sexual function of BC survivors.

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Data availability

Data will be made available on request.

Compliance With Ethics Standard

The study protocol was approved by local ethics committees and all patients signed the informed consent. All procedures were conducted in compliance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Disclosure

Paola Villa has received consultancy fees from Shionogi, has served on advisory board panels for Astellas, and has received speaker fees from Bromatech and Theramex. Chiara Cassani has received consultancy fees from Astrazeneca, GSK, has served advisory board panels for Astrazeneca, GSK and received speaker fees from Astrazeneca, GSK, Pharmamar . Rossella Nappi has received consultancy fees from Abbott, Fidia, Merck & Co, Vichy Laboratories, has received funding for research from Gedeon Richter, has served on advisory board panels for Abbott, Astellas, Bayer HealthCare AG, Besins Healthcare, Biocodex, Fidia, Shionogi Limited, and received speaker fees from Abbott Bayer HealthCare AG, Fidia, Novo Nordisk, Organon & Co, Theramex, Viatris, and Vichy Laboratories. Valentina Elisabetta Bounous has served on advisory board panels for Astellas Pharma SPA, and received speaker fees from PharmaExtracta. Maurizio Guida has served on advisory board panels for MSD, Exeltis and received speaker fees from Shionogi. Luca Cova and Valentina Trionfera are employees of Shionogi. Maria Cristina Meriggiola has received consultancy fees from Shionogi, Theramex, Sandoz, Bayer, and received speaker fees from Shionogi and Theramex,

Dorella Franchi, Amar Inbal Dona, Alessandra Di Lelio, and Giusi Graziano have nothing to disclose.

CRediT authorship contribution statement

Paola Villa: Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Chiara Cassani:**

Writing – original draft, Investigation, Data curation. **Rossella E. Nappi:** Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Valentina E. Bounous:** Investigation, Data curation. **Dorella Franchi:** Investigation, Data curation. **Maurizio Guida:** Investigation, Data curation. **Inbal Dona Amar:** Investigation, Data curation. **Luca Cova:** Supervision, Data curation. **Alessandra Di Lelio:** Supervision, Data curation. **Giusi Graziano:** Formal analysis, Data curation. **Valentina Trionfera:** Supervision, Data curation. **Maria Cristina Meriggiola:** Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization.

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Supplementary material

Supplemental Table 1 List of Patient Questionnaires Adopted in the PEONY Study

Questionnaire	Abbreviation	Domain	Brief Description	No. of Items	Scoring	Ref
European vulvovaginal epidemiological survey	EVES	Vaginal and vulvar health	Symptoms of VVA are assessed using the specific section of the European Vulvovaginal Epidemiological Survey (EVES). Women are asked to score their symptoms of VVA, based on a list of 19 potentially VVA-related complaints on a 4-point severity scale (absent, mild, moderate or severe). Vaginal symptoms include vaginal dryness (internal), pain during intercourse (internal), pain during intercourse at penetration, bleeding during intercourse, bleeding during sexual contact, burning or irritation (internal), itching (internal), vaginal discharge; vulvar symptoms include vaginal dryness (external), burning or irritation (external), itching (external) and pain during exercise; urinary symptoms include urinary incontinence, urinary urgency, urinary frequency, urinary difficulties, recurrent urinary tract infections and postcoital cystitis. In addition, a single question investigates the presence and severity of abdominal pain.	19	absent to severe	18,19
The day-to-day impact of vaginal aging	DIVA	Impact of vaginal aging	The Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire is a structured, validated, self-administered instrument assessing the multidimensional impact of vaginal symptoms on functioning and well-being. The DIVA instrument consists of 4 multi-item domain scales addressing major dimensions of functioning and well-being affected by postmenopausal vaginal symptoms: (1) activities of daily living (5 items), (2) emotional wellbeing (4 items), (3) self-concept and body image (5 items), and (4) sexual functioning (9 items for a long version appropriate for sexually active women, and 5 items for a shorter version appropriate for women without a recent history of sexual activity). The questionnaire addresses symptom impact in the 4 weeks prior to survey self-administration. Each scale is designed to be scored from 0 to 4, with higher scores indicating greater impact of symptoms on the relevant domain.	23	0-4	21
The female sexual distress scale-revised	FSDS-R	Female sexual distress	The Female Sexual Distress Scale-Revised (FSDS-R) is a self-administered questionnaire consisting of 13 items that relate to different aspects of sexual distress. Every item requires an answer that is then rated as 0–4 (never [0], rarely [1], occasionally [2], frequently [3], always [4]). The total score, ranging from 0 to 52, provides a measure of sexual distress, in which the higher the score, the higher the level of sexual distress. The FSDS-R is identical to the FSDS except for the addition of 1 question that asks women to rate their level of distress related to low sexual desire.	13	0-48	22

(*continued on next page*)

Supplemental Table 1 (*continued*)

Questionnaire	Abbreviation	Domain	Brief Description	No. of Items	Scoring	Ref
The Female Sexual Function Index	FSFI	Female sexual function	The Female Sexual Function Index (FSFI) is a brief, 19-item self-report measure of female sexual function over the past 4 weeks. The instrument provides scores on 6 domains of sexual function as well as a total score. The domains include: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). The full-scale score ranges from 2.0 to 36.0, where a higher score is associated with less severity of sexual dysfunction.	19	2.0-36.0	23
SF-12 Health Survey	SF12	Physical and mental functioning	The SF-12® Health Survey (SF-12) is a 12-item questionnaire used to assess generic health outcomes from the patient's perspective. The SF-12 consists of a subset of 12 items from the SF-36® Health Survey (SF-36) covering the same 8 domains of health outcomes, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. A Physical Component Summary Score (PCS) and a Mental Component Summary Score (MCS) can also be calculated. PCS and MCS are standardized so that in the normal population a value of 50 with a standard deviation of 10 is expected. SF-12 scales and summary measures are scored so that a higher score indicates a better health state.	12	0-100	24