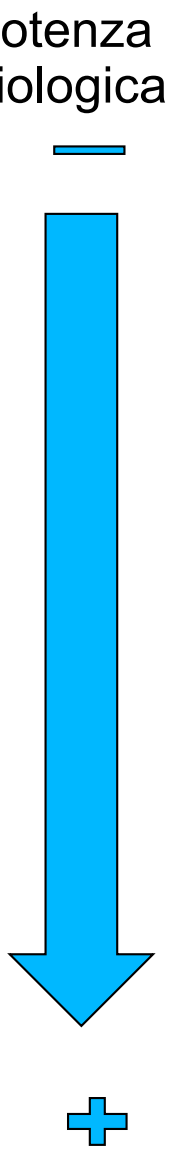
Estrogeni vaginali

Formulazione	Somm.	Principio attivo	Dose principio attivo/die
Crema	vaginale	Promestriene	3 - 6 mg
Capsule	vaginale	Promestriene	10 mg
Crema	vaginale	Estriolo (E3)	0.5 mg
Ovuli	vaginale	Estriolo(E3)	1 mg -0.5 mg - 0.03 mg
Gel	vaginale	Estriolo (E3)	0.05 mg
Ovuli	vaginale	Estriolo (E3)	3.5 mg rilascio graduale
Compresse vaginali	vaginale	Estradiolo (E2)	10 mcg - 25 mcg
Anello vaginale	vaginale	Estradiolo (E2)	2 mg (7.5mcg/24h)



Vaginal Atrophy in Breast Cancer Survivors: Attitude and Approaches Among Oncologists

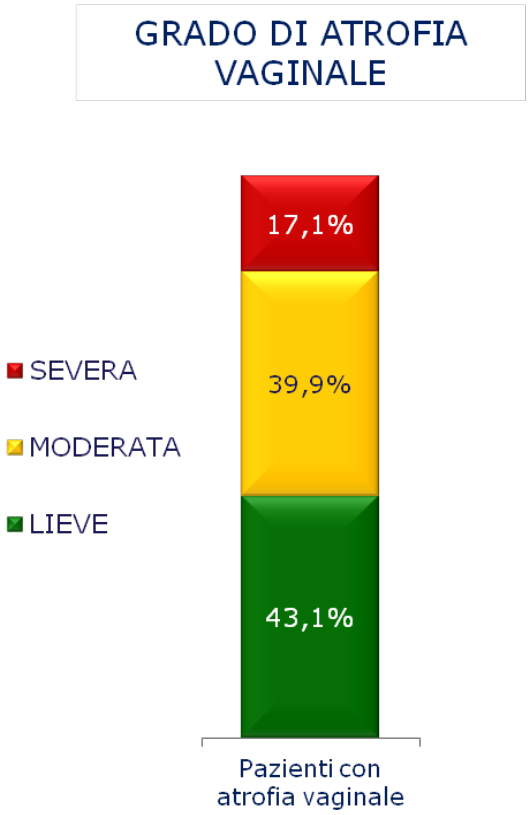
Nicoletta Biglia,[1] Valentina Elisabetta Bounous,[1] Marta D'Alonzo,[1] Laura Ottino,[1] Valentina Tuninetti,[1] Elisabetta Robba,[1] Tania Perrone[2]

Clinical Breast Cancer 2017

Oncologists are aware **that VVA is a frequent problem among BCSs**

Furthermore, oncologists know that **VVA** is an important issue for BCSs, being of **moderate or severe grade** in most of the cases.

The oncologists are conscious **that VVA strongly affects women's sexual health** and that it can increase probability of urinary tract infections.



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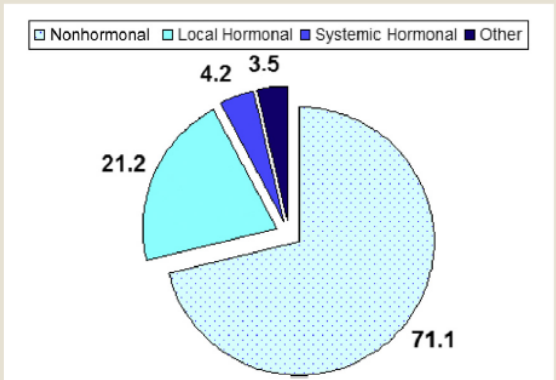
Clinical Breast Cancer December 2017

Figure 1 Treatments Prescribed to Treat Vulvovaginal Atrophy. Nonhormonal, Local, or Systemic Hormonal Drugs, and Other (Mainly Alternative Medicine Products)



- Only 50% of the oncologists directly illustrates VVA to the patients as a possible consequence of premature menopause induced by adjuvant treatments.
- Only around 1/3 of the oncologists self-manages VVA treatment, while 40% refers BCSs to a gynaecologist to define VVA treatment.

- **Non-hormonal treatments** such as lubricants or moisturizers are preferred by most the oncologists.
- The main reason not to prescribe vaginal oestrogen therapy in BCSs is the **fear of increased cancer recurrence**, the **possible interference with tamoxifen or AI**s and the fear of medical litigation.
- In **selected cases** (for non-hormone dependent breast cancer or for hormone dependent tumors, after the completion of anti-hormone adjuvant treatment), ¼ of the oncologists considers using vaginal oestrogens.
- Only 50% of the respondents know **low-dose and gel formulation** of vaginal estrogens.

Reference	Type of Study	Study Population	Main Outcome	Treatment	Study Period	Results
O'Meara et al, 2001[48]			Recurrence and mortality	LET (CEE and dienestrol)	457 person-years	Risk of recurrence or mortality not increased
Dew et al, 2003[49]			Recurrence	36 BCSs vaginal estriol creams and pessaries; 33 BCSs estradiol 25-mg tablets	1 year (median time; range, 0.1-5)	No increase in the recurrence rate
Kendall et al, 2006[47]	Prospective clinical study	7 Postmenopausal BCSs treated with AIs	Serum E2, FSH, LH levels	Vaginal estradiol 25 mg tablets	12 weeks	Serum E2 levels increase from baseline levels <5 pmol/L to a mean 72 pmol/L at 2 weeks; however, a decrease to a mean of 16 pmol/L was observed after 1 month; significant further increases were seen in 2 BCSs
Biglia et al, 2010[50]	Prospective clinical study	26 Postmenopausal BCSs using SERMs or AIs (BCSs receiving AIs were excluded from LET administration)	• Efficacy: improvement of VVA evaluated using the Vaginal Symptoms Score, Profile of Female Sexual Function, Vaginal Health Index, and Karyopycnotic Index • Safety: endometrial thickness and serum FSH, LH, E2, E1, TT and SHBG levels	10 Women, vaginal estriol cream 0.25 mg; 8 women, vaginal estradiol tablets 12.5 mg; 8 women, nonhormonal polycarbophil-based vaginal moisturizer (2.5 g)	12 weeks	• Efficacy: low-dose LET is effective for VVA relief, and nonhormonal moisturizer only provides transient benefit • Safety: minimal increase of serum hormone levels with LET
Wills et al, 2012[51]	Prospective study	48 Postmenopausal BCSs and women at risk of breast cancer during AI or SERM treatment	Serum E2 levels	24 Control participants (receiving AIs only); 14 women, intravaginal 25 mg estradiol tablet; 10 women intravaginal estradiol ring (7.5 mg/d)		
Donders et al, 2014[52]	Phase I clinical study	16 Postmenopausal BCSs who were receiving AIs	Serum E1, E2, E3 levels	Ultra—low-dose estriol 0.03 mg and *Lactobacillus acidophilus* vaginal tablets		
Pfeiler et al, 2011[53]	Prospective randomized clinical study	10 BCSs who were receiving AIs	Serum E2 or E3 levels	Vaginal 0.5 mg estriol	2 Weeks	Serum levels of E3 and E2 were not increased

Vecchi studi con risultati rassicuranti sulla prognosi di malattia

Low-dose vaginal ET improves vaginal symptoms in the majority of treated women, with plasma E2 levels remaining in the range of postmenopausal levels.

Estrogeni vaginali

Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 7, pp. 767-794
DOI: 10.1097/GME.0000000000002028

NAMS Position Statement

The 2022 hormone therapy position statement of The North American Menopause Society

BREAST CANCER

- Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe VMS unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. (Level III)
- For survivors of breast cancer with GSM, low-dose vaginal ET or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal ET for women on AIs. (Level III)

Vaginal DHEA

Prasterone is biochemically and biologically identical to the **endogenous human DHEA**, a precursor steroid which is inactive by itself and it is **converted into oestrogens and androgens**.

Menopause: The Journal of The North American Menopause Society
Vol. 23, No. 3, pp. 243-256
DOI: 10.1097/GME.0000000000000571

Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause

Fernand Labrie, MD, PhD,[1] David F. Archer, MD,[2] William Koltun, MD,[3] Andrée Vachon, MD,[4] Douglas Young, MD,[5] Louise Frenette, MD,[6] David Portman, MD,[7] Marlene Montesino, MD,[1] Isabelle Côté, BSc,[1] Julie Parent, PhD,[1] Lyne Lavoie, MSc,[1] Adam Beauregard, BSc, MBA,[1] Céline Martel, PhD,[1] Mario Vaillancourt, BSc, MBA,[1] John Balser, PhD,[8] Érick Moyneur, BSc, MA,[9] and the members of the VVA Prasterone Research Group

Randomized double blind trial (**prasterone 6.5 mg/die** per via vaginale vs **placebo)**

Results: After daily intravaginal administration of 0.50% DHEA for 12 weeks, when compared to baseline by the analysis of covariance test, the percentage of parabasal cells decreased by 27.7% over placebo ($P < 0.0001$), whereas the percentage of superficial cells increased by 8.44% over placebo ($P < 0.0001$), vaginal pH decreased by 0.66 pH unit over placebo ($P < 0.0001$), and pain at sexual activity decreased by 1.42 severity score unit from baseline or 0.36 unit over placebo ($P = 0.0002$). On the other hand, moderate to severe vaginal dryness present in 84.0% of women improved at 12 weeks by 1.44 severity score unit compared to baseline, or 0.27 unit over placebo ($P = 0.004$). At gynecological evaluation, vaginal secretions, epithelial integrity, epithelial surface thickness, and color all improved by 86% to 121% over the placebo effect ($P < 0.0001$ for all comparisons with placebo). Serum steroid levels remained well within the normal postmenopausal values according to the involved mechanisms of intracrinology. The only side effect reasonably related to treatment is vaginal discharge due to melting of the vehicle at body temperature and this was reported in about 6% of the participants.

Intent-to-treat population
157 placebo vs
325 women DHEA

Prasterone in healthy women

ADIS DRUG EVALUATION

Prasterone in healthy women

Prasterone: A Review in Vulvovaginal Atrophy

Young-A Heo[1]

REVIEW

Published online: 9 July 2019

Abstract

Vulvovaginal atrophy (VVA) is a progressive condition commonly seen in postmenopausal women. The cessation of ovarian estrogen secretion and a fall in serum levels of dehydroepiandrosterone (DHEA), the remaining source of estrogens and androgens, are thought to promote the development of VVA in this population. Intravaginal prasterone (Intrarosa®) is a synthetic form of DHEA indicated for the treatment of VVA in postmenopausal women presenting with moderate to severe symptoms in the EU; prasterone is also approved in the USA for the treatment of dyspareunia due to menopause. Approval for the treatment of VVA was based on the results of the phase III ERC-231 and -238 trials in which intravaginal prasterone 6.5 mg/day significantly improved the signs and symptoms of VVA (as assessed by the percentage of parabasal and superficial cells, vaginal pH and the severity of dyspareunia) compared with placebo. The beneficial effects of prasterone were also evident during 52 weeks' treatment in the phase III ERC-230 safety trial. Prasterone was generally well tolerated, with the most common treatment-emergent adverse event being application site discharge. During 52 weeks of treatment with prasterone, changes in serum concentrations of estrogenic and androgenic metabolites of DHEA increased from baseline but remained within the normal postmenopausal ranges. Thus, intravaginal prasterone is an effective and generally well-tolerated option for the treatment of VVA in postmenopausal women.

Prasterone in gynaecologic cancer survivors

Support Care Cancer (2018) 26:643–650
DOI 10.1007/s00520-017-3878-2

ORIGINAL ARTICLE

Evaluating the efficacy of vaginal dehydroepiandosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance)

Debra L. Barton[1] · Jeff A. Sloan[2] · Lynne T. Shuster[3] · Paula Gill[3] · Patricia Griffin[4] · Kathleen Flynn[5] · Shelby A. Terstriep[6] · Fauzia N. Rana[7] · Travis Dockter[2] · Pamela J. Atherton[2] · Michaela Tsai[8] · Keren Sturtz[9] · Jacqueline M. Lafky[3] · Mike Riepl[10] · Jacqueline Thielen[3] · Charles L. Loprinzi[3]

N=464

Abstract

Background Women with estrogen deficiencies can suffer from vaginal symptoms that negatively impact sexual health. This study evaluated vaginal dehydroepiandrosterone (DHEA) for alleviation of vaginal symptoms.

Methods This three-arm randomized, controlled trial evaluated DHEA 3.25 mg and DHEA 6.5 mg, each compared to a plain moisturizer (PM) over 12 weeks, to improve the severity of vaginal dryness or dyspareunia, measured with an ordinal scale, and overall sexual health using the Female Sexual Function Index (FSFI). Postmenopausal women with a history of breast or gynecologic cancer who had completed primary treatment, had no evidence of disease, and reported at least moderate vaginal symptoms were eligible. The mean change from baseline to week 12 in the severity of vaginal dryness or dyspareunia for each DHEA dose was compared to PM and analyzed by two independent *t* tests using a Bonferroni correction.

Results Four hundred sixty-four women were randomized. All arms reported improvement in either dryness or dyspareunia. Neither DHEA dose was statistically significantly different from PM at 12 weeks (6.25 mg, $p = .08$; 3.25 mg, $p = 0.48$), although a significant difference at 8 weeks for 6.5 mg DHEA was observed ($p = 0.005$). Women on the 6.5 mg arm of DHEA reported significantly better sexual health on the FSFI ($p < 0.001$). There were no significant differences in provider-graded toxicities and few significant differences in self-reported side effects.

Conclusion PM and DHEA improved vaginal symptoms at 12 weeks. However, vaginal DHEA, 6.5 mg, significantly improved sexual health. Vaginal DHEA warrants further investigation in women with a history of cancer.

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Baseline Demographic and Treatment Characteristics

Demographic Characteristics	Treatment Arm			P Value
	Plain Moisturizer N=147	3.25 mg DHEA N=147	6.5 mg DHEA N=149	
Age in years (SD)	58 (7.3)	56.8 (6.7)	57.3 (8.2)	0.63
Race (%):				
White	137 (93%)	142 (97%)	142 (95%)	
Black/AA	7 (5%)	3 (2%)	5 (4%)	0.63
Asian	1 (1%)	0	0	
Missing	2 (1%)	2 (1%)	2 (1%)	
Menopause-natural	95 (65%)	98 (67%)	88 (59%)	0.37
Bilateral oophorectomy	48 (33%)	43 (30%)	55 (37%)	0.38
Weight in kg (SD)	75 (16.6)	77 (14.7)	73 (14.8)	0.06
Height in cm (SD)	163.2 (6.6)	164.4 (6.0)	163.1 (6.8)	0.20
TREATMENT CHARACTERISTICS:				
Breast	142 (97%)	143 (97%)		
Ovarian	3 (2%)	4 (3%)	3 (2%)	0.70
Endometrial	2 (1%)	0	2 (1%)	
Tamoxifen current	23 (16%)	22 (15%)	24 (16%)	0.96
AI current:				
Anastrozole/Letrozole	72 (49%)	71 (48%)	72 (48%)	1.0
Exemestane	9 (6%)	11 (8%)	10 (7%)	
Months on current therapy (SD)	22 (18.7)	21.1 (17.1)	24.5 (18)	0.31

FSFI Subscale	Plain Moisturizer Mean (SD) (95% CI) N=118	3.25 mg DHEA Mean (SD) (95% CI) N=123	6.5 mg DHEA Mean (SD) (95% CI) N=112
Overall Total			
Baseline	12.2 (7.5) (11.0, 13.5)	12.5 (7.9) (11.2, 13.8)	11.6 (7.3) (10.4, 12.8)
12 week	16.2 (9.3) (14.5, 17.9)	17.9 (9.6) (16.2, 19.7)	19.1 (8.7) (17.5, 20.7)
Change	3.8 (7.4) (2.4, 5.1)	5.5 (7.5) (4.2, 6.8)	7.1 (7.3)*** (5.8, 8.5)
QOL			
Baseline	7.6 (2.0)	7.3 (1.8)	7.5 (1.8)
12 week	7.4 (2.3)	7.5 (1.7)	7.8 (1.7)
Change	−0.3 (2.2)	0.2 (1.7)	0.3 (1.9)**

Significant difference versus Plain Moisturizer :

* p≤.05,

** p ≤.01,

*** p ≤.001

Prasterone in gynaecologic cancer survivors

Ospemifene

4.1 Therapeutic indications

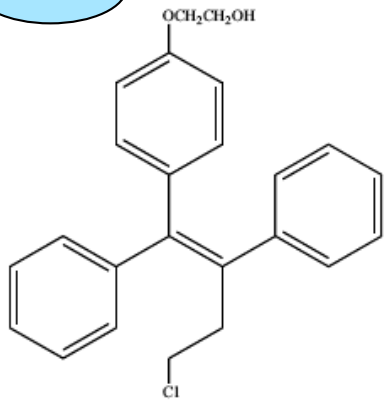
Senshio is indicated for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VVA) in post-menopausal women.

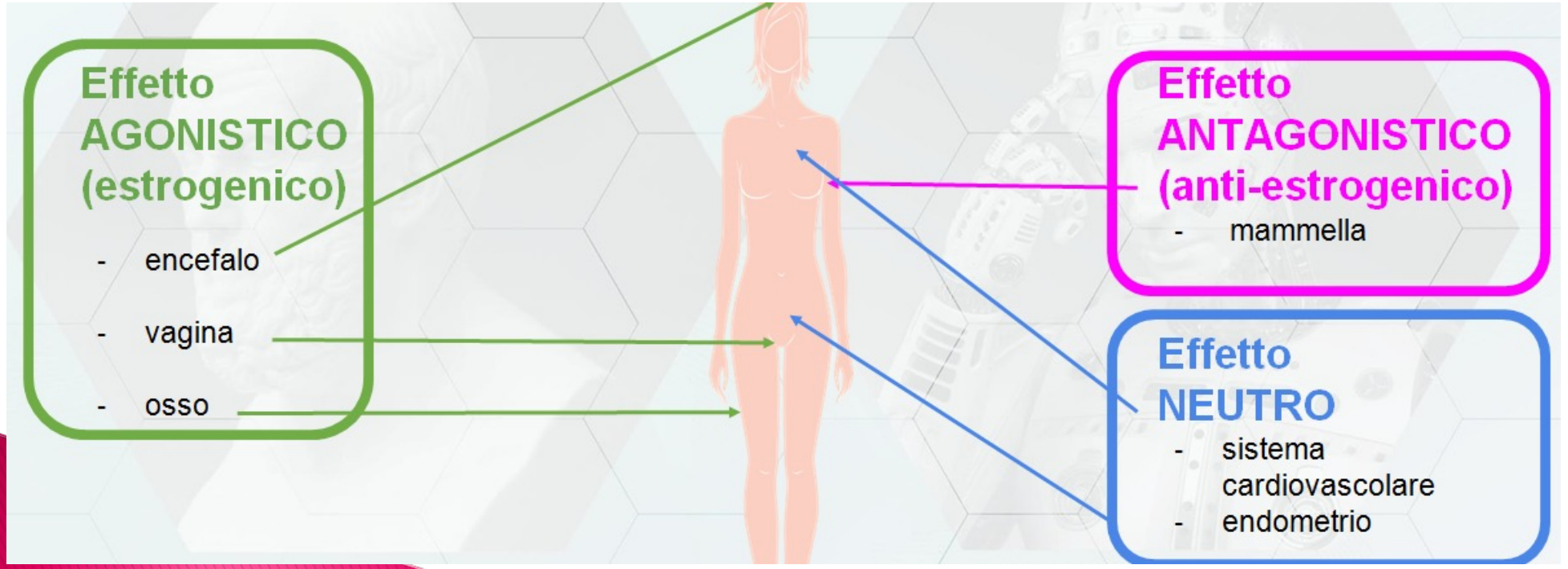
4.2 Posology and method of administration

Posology

The recommended dose is one 60 mg tablet once daily with food taken at the same time each day.

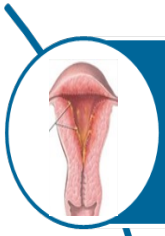
Ospemifene Drug Summary

Drug Name:	Ospemifene
Phase of Development:	NDA Submitted April 2012
Indication:	Postmenopausal Vulvovaginal Atrophy
Pharmacology/Mechanism of Action:	Selective Estrogen Receptor Modulator (SERM) (estrogen receptor agonist/antagonist)
Route of Administration:	Oral
Chemical Structure:	



Ospemifene

Safety:



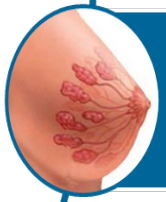
. Non increase in bleeding or spotting

. Endometrial hyperplasia incidence 0.3% (without atypia)

Constantine et al. 2015; Goldstein et al; Bachman 2010

No VTE increase

Nodstrom et al. 2022 (PASS STUDY)



No increase in recurrence of breast cancer

Cai et al. 2020

Protective effect on bone loss

De Villiers et al.2019; Maffei et al. 2023

Ospemifene: sicurezza a livello del tessuto mammario

1-Dati biologici da studi **preclinici** *(in vitro ed in modelli animali)*

2-Dati da studi **clinici**

3- Effetto di classe dei **SERM** sulla mammella *(studi clinici con tamoxifene e raloxifene hanno mostrato effetti* ***antiestrogenici o neutrali*** *sulla mammella)*

Burich et al. Menopause 2012

G.T. Wurz et al.
Journal of Steroid Biochemistry & Molecular Biology 2005

Berga Slet al. *Reprod Sci*. 2013

Table 2. Overview of Preclinical Data for Ospemifene in the Breast.

Study	Experimental Model	Key Results
Qu et al[14]	MCF-7 ERα$^+$ breast cancer cells grown in vivo in nude mice	Ospemifene suppressed expression of pS2, an estrogen marker
Taras et al[9]	MCF-7 ERα$^+$ breast cancer cells grown in vivo in nude mice	Ospemifene inhibited the growth of ER-dependent MCF-7 cells; no effect on ER-independent MDA-MB-231 cells
Qu et al[14]	DMBA-induced mammary carcinoma in intact and ovariectomized rats	Ospemifene inhibited tumor growth in a dose-dependent manner (by 12%, 59%, and 79%-88% in the 1-, 10-, and 50-mg/kg groups, respectively)
Wurz et al[10]	DMBA-induced mammary carcinoma in Sencar mice	Ospemifene significantly reduced DMBA-induced mammary carcinomas, similar to tamoxifen
Namba et al[8]	DCIS mouse model	Growth of transplanted cells and incidence of tumors were significantly reduced in mice treated with either ospemifene or tamoxifen compared with untreated mice
Burich et al[33]	MTag.Tg mouse breast cancer model	Ospemifene delayed the development of breast tumors, and average tumor volumes were smaller

Abbreviations: DMBA, dimethylbenzanthracene; DCIS, ductal carcinoma in situ; ER, estrogen receptor.

"Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study".

Bachmann, Menopause 2010

826 postmenopausal women were randomized to receive treatment with ospemifene 30 or 60 mg/day or placebo orally for 12 weeks was conducted.

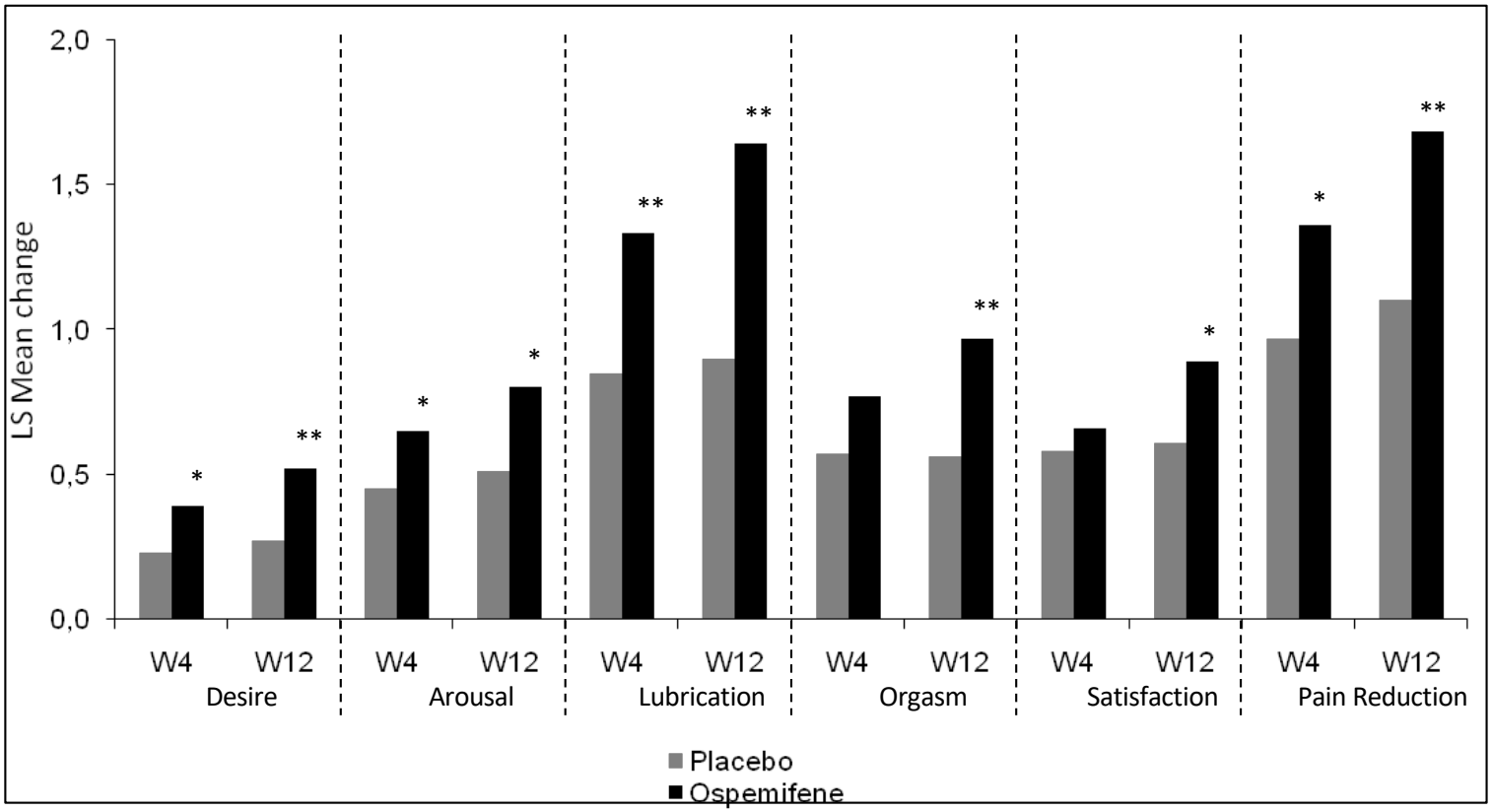
RESULTS. Ospemifene was **statistically significantly superior to placebo** in each of the **coprimary endpoints** (vaginal pH, vaginal dryness or dyspareunia) at the **60 mg** dose. Statistically significant results were achieved for all coprimary endpoints with the **30 mg** dose except for dyspareunia. Ospemifene was **well tolerated at both doses and demonstrated a favorable safety profile**.

No cases of endometrial hyperplasia or cancer (3 ospemifene participants reported vaginal bleeding or spotting).

No cases of venous thromboembolism.

CONCLUSIONS. Ospemifene was shown to be **effective and well tolerated for the treatment of the symptoms of vaginal dryness and dyspareunia associated with vulvovaginal atrophy** over and above the use of provided lubricants.

Ospemifene: significant improvement of sexual functions after 12 weeks compared to placebo



* p<0.05 vs. placebo
**p<0.001 vs. placebo

Constantine G, *et al. Climacteric* 2014; 18: 226-32.

Ospemifene

Controindicazioni:

- Ipersensibilità al principio attivo
- Eventi di tromboembolismo venoso (TEV)
- Emorragia vaginale di origine sconosciuta
- Pazienti con sospetto **carcinoma mammario** o pazienti **sottoposte a trattamento attivo** (inclusa terapia adiuvante) per carcinoma
- Tumore maligno dipendente dagli ormoni sessuali sospetto o attivo (ad es. carcinoma endometriale).
- Iperplasia endometriale

Pertanto **puo' essere impiegato per il trattamento dell'atrofia in pazienti con pregresso carcinoma mammario al termine dei trattamenti adiuvanti**