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Polycarbophil vaginal moisturizing gel versus hyaluronic acid gel in women affected by vaginal dryness in late menopausal transition: A prospective randomized trial

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ABSTRACT

Objectives: During menopausal transition, women are frequently affected by vulvovaginal atrophy (VVA), due to the decline of estrogen levels. Resulting symptoms are itching, burning, dyspareunia, and vaginal dryness (reported in up to 85%). The aim of this trial was to verify if medical device polycarbophil vaginal (PCV) moisturizer gel is not less effective than hyaluronic acid (HA) gel in treating vaginal dryness.

Material and methods: This was a multicenter, open label, randomized, parallel group, comparative study with non-inferiority design. Female included were ≥45 to ≤55 years in the menopausal transition, with subjective dryness, any objective sign of VVA, pH > 5, and body mass index of ≥18.5 to ≤36 kg/m^2. Subjects were randomized to 1 g of PCV gel twice a week for 30 days or 3 g of HA vaginal gel every 3 days for 30 days.

Results: 53 subjects (mean age 49.45 ± 2.96 years) were analyzed. Vaginal health index showed an improvement ($p < 0.001$) in both groups (from 12.54 ± 1.37 to 16.36 ± 2.66 for PCV, from 12.00 ± 1.91 to 16.60 ± 2.50 for HA), but the difference between final means (95%CI: −1.66 to 1.18) evidenced that PCV is non-inferior to HA treatment. Similarly, an improvement was evidenced in vaginal maturation index ($p = 0.005$ for PCV, ns. for HA), female sexual function index ($p < 0.001$ for PCV, $p < 0.001$ for HA), and SF-12 ($p < 0.001$ for PCV, $p < 0.001$ for HA), with no difference between groups. Safety was optimal and no adverse events were reported.

Conclusions: The use of HA gel does not give additional benefits to those that are already provided by the moisturizing PCV.

Introduction

The menopausal transition (MT) can be divided in an early and late phase [1]; the first characterized by skipped cycles, and the second by periods of amenorrhea up to 11 months. In this period symptoms of vulvovaginal atrophy (VVA), particularly vaginal dryness, affects almost 1/3 of the population [2,3]. Vaginal dryness profoundly influences woman sexuality and quality of life [4–7] and it increases from the early to the late perimenopause, and in the post-menopause [3,6,8]. In the perimenopausal period already 40 to 60% of women suffer from vaginal dryness [3]. According to international guidelines, non-hormonal vaginal lubricants and moistures represent first-line treatment for VVA symptoms, ospemifene or local hormones being considered second line remedies [9–10].

The need of daily vaginal applications may hamper adherence to treatment for a chronic condition such as VVA [11]. Advantages may derive by remedies with a twice per week posology such as mucoadesive polycarbophilic vaginal (PCV) gel [12]. PCV is a safe treatment that moisturizes the vagina and increases epithelial fluid content without affecting vaginal pH [13]. Hyaluronic acid (HA) also moisturizes and lubricate the vagina [14,15], but it was

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claimed that it also reduces epithelial atrophy, vaginal pH and favors vaginal maturation, similarly to estrogens [16].

In this post marketing clinical follow up (PMCF) study we compared the effect of PVC to that of HA. The trial was performed, following in the Instruction for Use (IFU) of tested products by actual medical device legislation. For both products IFU defines posology and length of treatment (30 days).

Materials and methods

The study, previously approved by the local Ethics Committees, was performed in three private clinics specialized in gynecology located in Timisoara (Romania): the Fizio Center, the SCM Dr. Rosu, and the Materna Care. Data monitoring, management and statistics were performed by Opera CRO (Timisoara, Romania), an independent Contract Research Organization (CRO). Randomization was performed by the CRO using an online web service (https://edc.operacro.com:448), available 24 h a day and the list was generated using block size of 4 by the block-rand package (General Public License. $\geq$ 3) from R statistical software v 3.5. The Investigators enrolled the subjects and assigned them to interventions.

Study population

Participants were women between 45 and to 55 years of age, with a BMI between 18.5 and 36 kg/m^2. Inclusion criteria were having signed an informed consent, being non-pregnant and in the late menopausal transition, with a diagnosis of VVA, and willing to use lubricated condoms or intra-uterine device as contraceptive methods during the full duration of the study. Late menopausal transition was identified following the STRAW + 10 criteria [2]. VVA was diagnosed by the contemporaneous presence of subjective sensation of vaginal dryness, any objective sign of VVA (mucosa dryness, pallor, fragility, thinness, or presence of petechiae) and a pH > 5 [17]. In addition, a Vaginal Health Index (VHI) < 15 was necessary [18]. The VHI score evaluates 5 parameters: overall elasticity, type and consistency of fluid secretions, pH, epithelial mucosa, and vaginal moisture, assigning to each of them a score from 1 to 5 (Table 1). Sum of the five scores defines total VHI score.

Women were excluded if they were in post-menopause (amenorrhea $\geq$ 1 year), had suffered from malignancy (also leukemic infiltrates) within 5 years prior to day 0 (except for treated basal cell/squamous cell carcinoma of the skin), had non investigated genital bleeding, were on systemic or vaginal estrogen treatment (permitted only if terminated at least 6 months before study), suffered from acute infection requiring treatment, had clinical evidence or history of chronic infectious disease (i.e., tuberculosis), psychiatric disorders (except for intermittent anxiety), suicide attempt or suicidal ideation, drug or alcohol abuse in the last 12 months, were allergic to the tested medical devices or their excipients, had participated in clinical studies or had received any investigational agent in the previous 30 days.

Interventions

Eligible subjects were randomized 1:1 to one of the two following treatments:

- Arm A: 1 g of PCV gel (Ainara - Italfarmaco, Milano, Italy) twice a week for 30 days.
- Arm B: 3 g of HA gel (Hyalo Gyn - Fidia Farmaceutici, Abano Terme, Italy) every 3 days for 30 days.

According to IFU approved by Competent Authorities for the two medical devices, as specifically requested by the ISO 14,155 and MEDDEV 2.12/1 for PMVF studies, dosage of PCV could be increased to 1 g of gel every day from day 8 to day 30, if symptoms persisted at the 7-day phone call. Vice versa no dose modification is allowed by IFU for HA administration.

In both groups the gel was applied by inserting the applicator in the vagina while assuming a crouching or supine (laying down) position.

Five visits were planned during the study period: V1 Baseline Visit, V2 Final Visit at Day 30 (±2 day) and three intermediate phone contact visits at Day 3, Day 7 (±1 day), and Day 21 (±1 day), respectively.

Outcomes measures

The choice of outcomes was performed following international recommendations for the clinical evaluation of products to treat VVA [19] and using the experience of previous trials on the prevalence and management of these symptoms [3,20].

The primary outcome was the performance evaluation in terms of improvement of VHI assessed by the Investigator.

Several secondary outcomes were evaluated as follows.

Variations of subjective symptoms such as vaginal dryness, local irritation, and vaginal pain during sexual intercourse were rated by women on a 100 mm visual analogue scale (VAS) at baseline and at day 3, 7, 21, and 30 of treatment. Subjective symptoms of VVA [17] such as itching, burning, dyspareunia, and dysuria were evaluated at baseline and day 3, 7, 21 and 30 of treatment by patient diary; objective signs such as thinning rugae, mucosa pallor, mucosa fragility, and presence of petechiae were evaluated at baseline and day 30 of treatment by the Investigator. Subjective symptoms and objective signs were both scored as follows: 0 = absence, 1 = slight, 2 = moderate, and 3 = severe intensity [17].

The Vaginal Trophism Maturation Value (MV) was obtained from the cellular count of the vaginal smears at Baseline and at the Day 30 visit. MV was calculated as follows: MV = [1x (% superficial cells)] + [0.6x (% intermediate cells)] + [0.2x (% parabasal cells)] [21].

Sexual health was evaluated at baseline and after 30 days of treatment by the Romanian validated translation of the female sexual function index (FSFI) [22], a self-report instrument consisting of 19 items that assess sexual function over the past 4 weeks in six areas: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain [23].

Table 1
Vaginal Health Index (modified from Bachmann et al) (18).

Score	Overall elasticity*	Fluid secretion type and consistency	pH	Epithelial mucosa	Moisture
1	None	None	6.1	Petechiae noted before contact	None, mucosa inflamed
2	Poor	Scant, thin yellow	5.6–6.0	Bleeds with light contact	None, mucosa not inflamed
3	Fair	Superficial, thin white	5.1–5.5	Bleeds with scraping	Minimal
4	Good	Moderate, thin white	4.7–5.0	Not friable, thin mucosa	Moderate
5	Excellent	Normal (white flocculent)	4.6	Not friable, normal mucosa	Normal

*Lower score corresponds to greater urogenital atrophy.

Quality of life was evaluated at baseline and after 30 days of treatment by the short form-12 (SF-12) [24]. Finally, the overall effect of treatment on all individual symptoms was assessed by the Global Symptom Score (GSS) [25], a composite score calculated by adding the intensity score of each of the following symptoms: vaginal dryness, thinning rugae, mucosa pallor, mucosa fragility, and petechiae (range, 1–15: 1 = only mild vaginal dryness, 15 = all five symptoms severe in intensity). For these variables we evaluated the changes from baseline to day 30 (Final Visit) with comparisons within and between groups.

Safety was evaluated by collecting and analyzing adverse events during the study period. In addition, two global assessments of safety were used: Investigator's global assessment scale (IGAS) at the final visit, and patient's global assessment scale (PGAS) reported by the patient in the diary at each visit. A 4-point scale was applied for both parameters: 1 = very good safety, 2 = good safety, 3 = moderate safety and 4 = poor.

Sample size determination and statistical methods

The target sample size was based on VHI, the primary endpoint with expected values as reported from similar studies [26]. By using a Wilcoxon signed-rank test for matched pairs and pursuing an 80% power for the study with a 0.05 significance level, while considering a 10% non-inferiority margin defined as difference between mean VHI score at the Final Visit by the pooled standard deviations of the 2 study groups, PCV vs. HA, a sample size of 50 randomized participants was calculated (25 per each treatment arm). Estimating a 10% dropout rate, the total sample size used for the trial was 56 subjects.

The level of significance < 0.05 was considered statistically significant at a 95% confidence interval. Thus, if PCV was inferior to the comparative device HA, for the mean VHI scores at 30 days after treatment initiation by at least a 10% inferiority margin, the null hypothesis would be rejected when the difference between means was under the limit of 95 % confidence interval (CI) of 10% inferiority margin.

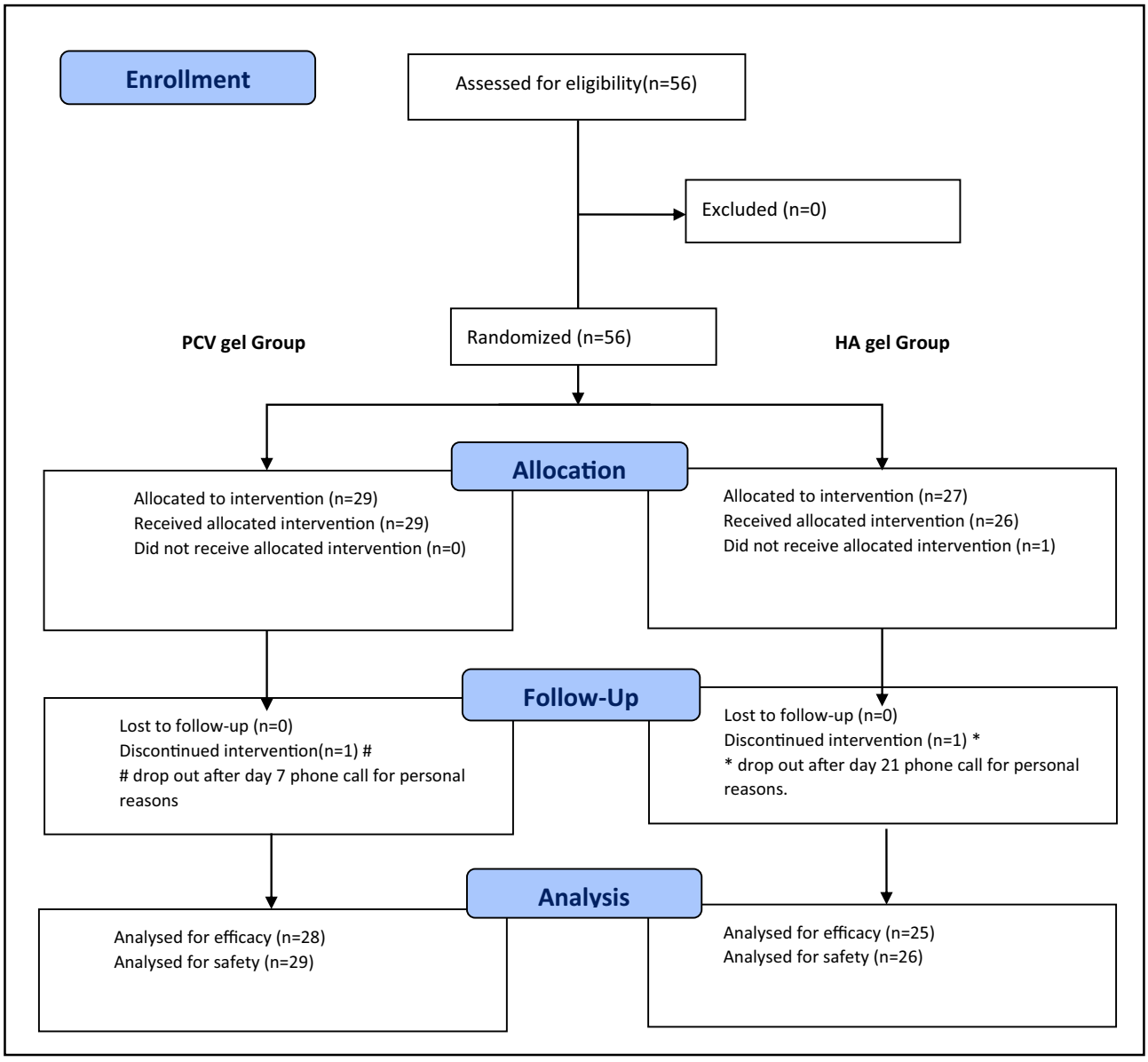

Fig. 1. Flow chart.

Table 2
Demography of all treated patients (Treated population).

	group A PCV gel			group B HA gel			All Patients		
Characteristic	N	Mean (SD)	Minimum/Maximum	N	Mean (SD)	Minimum/Maximum	N	Mean (SD)	Minimum/Maximum
Gender (female)	29			26			55		
Age (years)	29	48.76 (3.18)	45 55	26	50.23 (2.52)	45 55	55	49.45 (2.96)	45 55
Weight (kg)	29	66.28 (9.06)	45 84	26	69.0 (11.21)	55 98	55	67.56 (10.13)	45 98
Height (cm)	29	166.55 (7.19)	150 185	26	165.0 (5.23)	155 175	55	165.82 (6.33)	150 185
Body Mass Index (kg/m^2)	29	23.89 (3.05)	19.1 32.0	26	25.30 (3.67)	20.96 36.00	55	24.56 (3.40)	19.1 36.0

Statistical analyses included subjects successfully completing the study without a major protocol deviation. All participants who applied one of the study products at least once were included into the safety analysis. Statistical analysis was performed using the R statistical software v 3.5. The Student's *t*-test and the Mann-Whitney U were used to perform comparative analysis in accordance with the distribution of quantitative variables, while the chi^2 test was applied to perform comparative analysis of categorical variables. Data are expressed as mean + standard deviation.

Results

The trial was performed between April 2019 and September 2019. None of the women with VVA symptoms refused to be included (Fig. 1). A total number of 56 participants were enrolled and randomized to PCV or HA. Of these, 55 patients received at least one dose of the investigational products (IP) and were included in the safety analysis (PCV n = 29 and HA n = 26). On the contrary, one patient in the HA group did not receive the IP for personal reasons (Fig. 1). 53 participants who received the IP for the whole period without major protocol deviations were analyzed for efficacy (PCV n = 28 and HA n = 25). Two patients (1 in each arm) withdrew from the study prematurely for personal reasons, not related to the devices or to safety. General characteristics of enrolled women (all Caucasian) are reported in Table 2. No significant difference was observed between women of the two groups (Table 2). All subjects reported to have had regular sexual intercourses during the study period

Efficacy analysis

There was no significant difference between treatments for the primary efficacy outcome. VHI significantly increased from baseline to final visit in both groups ($p < 0.001$). The difference between mean final VHI in the PCV (16.36 ± 2.66) and HA group (16.60 ± 2.50) was 0.24 which is under the limit of 95% CI of 10% inferiority margin (−1.66 to 1.18) (Fig. 2).

No significant difference was found between PCV and HA for all secondary efficacy outcomes. VAS measured in both treatments showed a decrease of subjective vaginal dryness (from 48.14 ± 16.14 to 14.93 ± 16.72, $p < 0.001$ in PCV, from 45.92 ± 17.14 to 16.16 ± 13.27, $p < 0.0001$ in HA), local irritation (from 37.54 ± 20.03 to 8.86 ± 10.77, $p < 0.0001$ in PCV, from 36.68 ± 16.23 to 11.24 ± 10.00, $p < 0.0001$ in HA), and vaginal pain during sexual intercourse (from 35.50 ± 20.41 to 8.36 ± 10.03, $p < 0.0001$ in PCV, from 34.00 ± 18.25 to 9.68 ± 10.38, $p < 0.0001$ in HA). The decrease of vaginal dryness was already evident ($p < 0.001$) after 7 days, in both PCV or HA treated women, persisting at day 21 ($p < 0.001$) and at day 30 ($p < 0.001$) (Fig. 3).

No difference between the two groups was observed in the significant reduction at day 30 of subjective symptoms (itching, burning, dyspareunia, dysuria) (Table 3) and objective signs

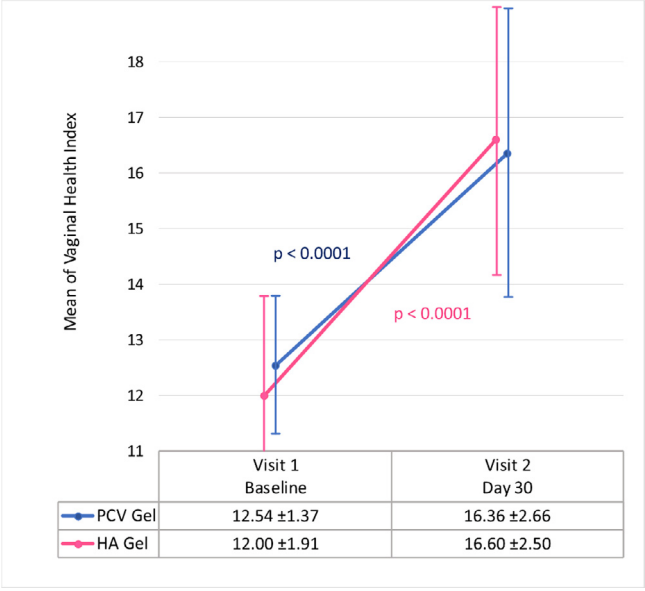

Fig. 2. Line chart of of vaginal health index (VHI) mean values observed at baseline and after 30 dys of PCV or HA. The difference between mean final VHI in PCV and in HA group (95%CI: −1.66 to 1.18) evidenced that PCV is non-inferior to HA.

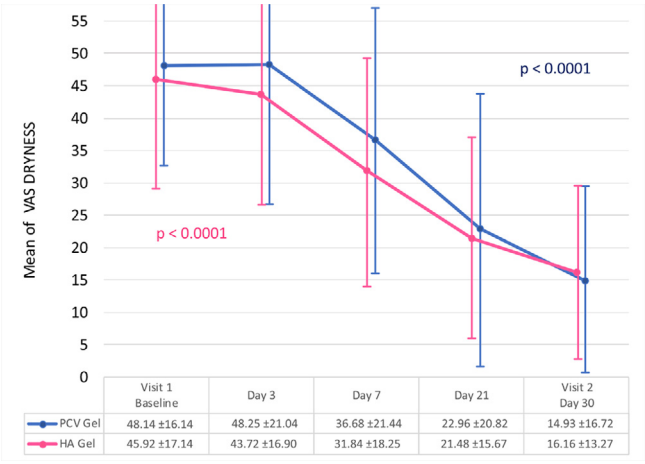

Fig. 3. Line chart of comparison of the overall mean of Visual Analogue Scale (VAS) for vaginal dryness in PCV and HA group at Baseline Visit V1, and Days 3, 7, 21, 30 of treatment. The difference between mean final VAS for vaginal dryness in PCV and in HA group (95%CI: −1.09 to 2.1) evidenced that PCV is non-inferior to HA.

Table 3
Subjective symptoms reported in patient diary: aggregate results for PCV group and HA group at Baseline Visit and day 30 Visit.

Groups					
Subjective Symptoms	*PCV gel (n = 28)*		*HA gel (n = 25)*		*P-value between visits*
Itching	*Baseline*	*Day 30*	*Baseline*	*Day 30*	
Severe	7.14%	0.00%	4.00%	0.00%	
Moderate	71.43%	3.57%	64.00%	4.00%	PCV p < 0.0001
Slight	17.86%	42.86%	24.00%	36.00%	HA p = 0.0006
Absence	3.57%	53.57%	8.00%	60.00%	
Burning	*Baseline*	*Day 30*	*Baseline*	*Day 30*	
Severe	10.71%	0.00%	4.00%	0.00%	
Moderate	42.86%	3.57%	52.00%	4.00%	PCV p < 0.0001
Slight	42.86%	28.57%	32.00%	24.00%	HA p = 0.0006
Absence	3.57%	67.86%	12.00%	72.00%	
Dyspareunia	*Baseline*	*Day 30*	*Baseline*	*Day 30*	
Severe	10.71%	0.00%	4.00%	0.00%	
Moderate	25.00%	3.57%	40.00%	8.00%	PCV p < 0.0001
Slight	60.71%	32.14%	44.00%	28.00%	HA p = 0.0014
Absence	3.57%	64.29%	12.00%	64.00%	
Dysuria	*Baseline*	*Day 30*	*Baseline*	*Day 30*	
Severe	3.57%	0.00%	0.00%	0.00%	
Moderate	7.14%	3.57%	16.00%	0.00%	PCV p = 0.00117
Slight	32.14%	10.71%	20.00%	12.00%	HA p = 0.027
Absence	57.14%	85.71%	64.00%	88.00%	

(thinning rugae, mucosa pallor, fragility, presence of petechiae) (Table 4).

Mean MV index values significantly increased during PCV from 55.18 ± 17.51 to 61.70 ± 14.21 (p = 0.005). The increase observed during HA (from 50.2 ± 21.24 to 56.10 ± 18.99), was not statistically significant (p = 0.235) (Fig. 4). pH decreased, from 5.81 ± 0.43 to 5.24 ± 0.34 during PCV (p < 0.001) and from 5.78 ± 0.37 to 5.21 ± 0.32 during HA (p < 0.001). No significant difference between treatments was found for pH.

Mean FSFI score increased similarly in the two groups, from 48.00 ± 15.43 to 63.14 ± 12.78 (p < 0.001) during PCV and from 47.52 ± 16.96 to 63.12 ± 14.52 during HA (p < 0.001) (Fig. 5).

SF-12 score similarly decreased in both groups from 61.36 ± 3.31 to 30.39 ± 1.15 during PCV (p < 0.001) and from 61.88 ± 4.75 to 30.80 ± 2.40 (p < 0.001) during HA.

GSS score assessing the overall effect of the medical devices on all symptoms, decreased similarly in the two groups, from 8.21 ± 1.79 to 4.39 ± 1.85 (p < 0.001) in the PCV and from 8.08 ± 2.29 to 4.56 ± 1.85 (p < 0.001) in the HA group.

Safety analyses

During the study, no adverse event was reported. Overall safety performed at the end of the study by patients was rated as: very good (89.29%) and good (10.71%) by patients treated with PCV; very good (84%) and good (16%) by patients treated with HA. At final visit most investigators rated PCV's safety as very good (88.9%) or good (10.71%), and HA safety as very good (88%) or good (12%).

Table 4
Objective signs evaluated by the Investigator: aggregate results for PCV group and HA group at Baseline Visit and Day 30 Visit.

Groups					
Objective Signs	PCV gel (n = 28)		HA gel (n = 25)		P value between visits
Mucosa Pallor	Baseline	Day 30	Baseline	Day 30	PCV p = 0.000034
HA p = 0.000214					
Severe	3.57%	0.00%	4.00%	0.00%	
Moderate	82.14%	7.14%	80.00%	12.00%	
Slight	14.29%	82.14%	16.00%	80.00%	
Absence	0.00%	10.71%	0.00%	8.00%	
Mucosa Fragility	Baseline	Day 30	Baseline	Day 30	PCV p = 0.000068
HA p = 0.00155					
Severe	10.71%	3.57%	4.00%	0.00%	
Moderate	78.57%	7.14%	60.00%	8.00%	
Slight	10.71%	85.71%	32.00%	84.00%	
Absence	0.00%	3.57%	4.00%	8.00%	
Thinning Rugae	Baseline	Day 30	Baseline	Day 30	PCV p = 0.0029
HA p = 0.0018					
Severe	3.57%	0.00%	4.00%	0.00%	
Moderate	39.29%	14.29%	56.00%	12.00%	
Slight	57.14%	67.86%	32.00%	72.00%	
Absence	0.00%	17.86%	8.00%	16.00%	
Presence of Petechiae	Baseline	Day 30	Baseline	Day 30	PCV p = 0.00058
HA p = 0.00044					
Severe	0.00%	0.00%	0.00%	0.00%	
Moderate	21.43%	3.57%	36.00%	4.00%	
Slight	53.57%	25.00%	40.00%	24.00%	
Absence	25.00%	71.43%	24.00%	72.00%	

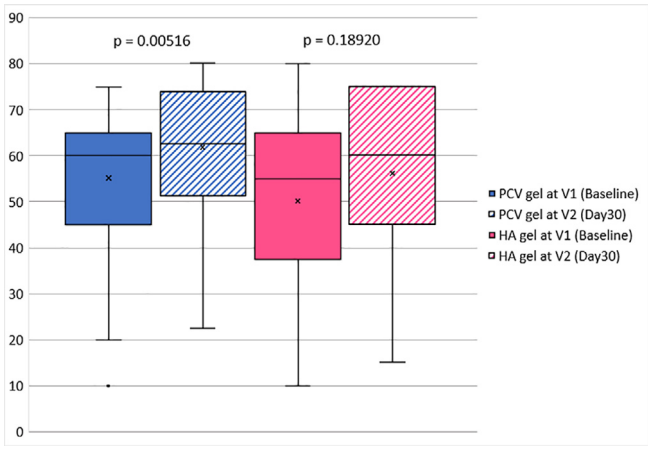

Fig. 4. Boxplots showing values of vaginal trophism maturation value (MV) in PCV and HA gel groups at baseline and after 30 days of treatment. No difference was observed in the response to the two treatments.

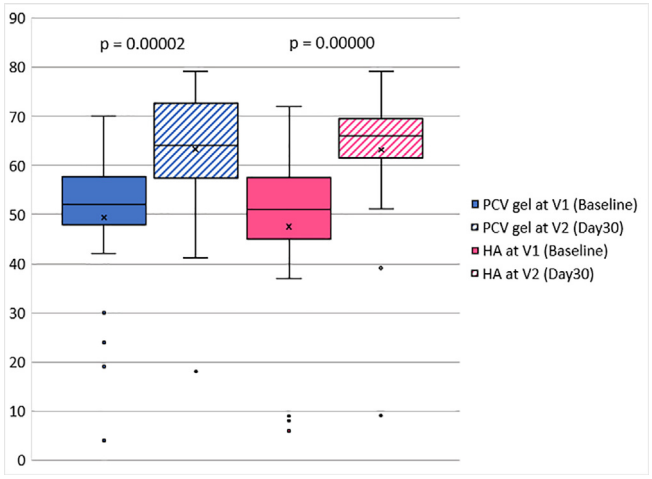

Fig. 5. Boxplots showing values of female sexual function index (FSFI) observed at baseline and after 30 days of treatment with PCV or HA. No difference was observed in the response to the two treatments.

Discussion

In women in the late menopausal transition the two products (HA and PCV) showed an optimal performance on VHI and on all symptoms evaluated during the study, HA gel does not offer additional improvement to PCV gel, when both are administered in accordance with the approved indication of a 30-days treatment. Vaginal dryness markedly decreased with both treatments. Similarly, severity and rate of dyspareunia markedly decreased in both groups. These symptoms affect sexuality (5), and their improvement was associated with better sexuality and quality of life. The effect of PCV or HA is mainly related to their capability to rehydrate mucosa and to mimick natural vaginal secretions thanks to their adhesion to vaginal lining [14]. A small but significant improvement of MV with a tendency to lower pH values was also observed. These possible improvements are going to be re-evaluated in a subsequent open label follow up study where PCV is administered for 180 days. Both PCV and HA showed an optimal safety.

Strengths and limitations of study

This is not a randomized clinical trial (RCT) with a double-blind design. It was unpractical to apply a double dummy design. The study is a study of non-inferiority. The second issue was the choice between a superiority and non-inferiority study design. We needed realistic data on the efficacy of HA in the late menopausal transition that were not available. The potential pitfall of applying a superiority trial in these conditions was to fail to demonstrate the superiority. The possible result of no statistical difference does not mean equivalence between the two treatmens. In addition, a significant superiority of one treatment may not be clinically relevant. For these reasons, we chose to perform a non-inferiority trial to verify if the medical device PCV moisturizer gel was not less effective than HA gel.

Conclusions

The results of this study demonstrate that the administration of PCV gel, for 30 days significantly alleviates symptoms of vaginal atrophy and dryness in women in the late menopausal transition. For all the parameters assessed, the performance of PCV was not inferior to that of HA.

These findings are of practical relevance for gynecologists that have the opportunity to choose among evidence-based therapeutic tool for treating vaginal dryness in women in the late menopausal transition.

Funding

A grant support was received from Italfarmaco SpA, Milano-Italy (https://www.italfarmaco.com). Italfarmaco SpA had no role in the study design, data collection and interpretation, or on the decision to submit the work for publication.

Ethics

The protocol was approved by the 3 local Independent Ethics Committees respectively on January 3, 2019 (#84), February 22, 2019, and April 19, 2019 (#265), and notified to the National Agency for Medicines and Medical Devices in Romania (Agentia Nationala a Medicamentului si a Dispozitivelor Medicale). Written informed consent was obtained from each participant. No financial incentive was offered to any of the participants. The study was conducted in accordance with good clinical practice (GCP) and the Declaration of Helsinki. The study was registered on clinicaltrials.gov as NCT04245293.

Data sharing and collaboration

Data will be made available on request.

Provenance and peer review

This article has undergone peer review

Supplementary data

Supplementary material related to this article can be found at online web: clinicaltrials.gov as NCT04245293.

CRediT authorship contribution statement

Angelo Cagnacci: Conceptualization, Validation, Writing – review & editing. **Dionisio Franco Barattini:** Methodology, Formal analysis, Supervision. **Elena Casolati:** Methodology, Writing – review & editing. **Alberto Pecoroni:** Methodology, Formal analysis, Visualization, Project administration. **Mario Mangrella:** Concep-

tualization, Methodology, Supervision. **Liviu Cristian Patrascu:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Declaration of Competing Interest

Angelo Cagnacci received fee as invited speaker for Italfarmaco, Shionogi, Bayer, Gedon-Richter, Theramex, MSD and Exeltis.

Dionisio Franco Barattini is employed at Opera CRO, the Contract Research Organization that managed the study.

Elena Casolati is a medical consultant for Italfarmaco SpA.

Alberto Pecoroni and Mario Mangrella are employed at Italfarmaco SpA.

Liviu Cristian Pătracu certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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