RESEARCH | Article in Press

Oral full-spectrum sodium hyaluronate for vulvovaginal atrophy in postmenopausal women: a randomized, parallel-group clinical trial

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Received: 4 May 2026 / Accepted: 27 September 2026
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Abstract

Background Vulvovaginal atrophy (VVA), a major component of the genitourinary syndrome of menopause (GSM), is highly prevalent and often undertreated. Given the chronic nature of symptoms, safe and effective non-hormonal strategies suitable for long-term use are needed. Hyaluronic acid (HA) is effective when administered locally and emerging evidence suggests potential benefits of oral full-spectrum HA formulations.

Purpose To explore the efficacy and tolerability of an oral full-spectrum sodium hyaluronate formulation (ExceptionHYAL® Blossom) in postmenopausal women with VVA, and to assess its potential adjuvant effect when combined with a vaginal HA ovule.

Patients and methods In this 60-day exploratory open-label randomized clinical trial, 60 postmenopausal women with VVA were allocated (1:1:1) to oral sodium hyaluronate, vaginal HA ovule, or combined oral plus vaginal treatment. Assessments at baseline, day 30, and day 60 included the Vaginal Health Index (VHI), Visual Analog Scales (VAS) for symptom severity, Vulvovaginal Symptom Questionnaire (VSQ), gynaecological examination, and global patient evaluations.

Results VHI scores increased significantly in all groups at day 30 and day 60. At day 60, the combination group showed significantly higher VHI values than both monotherapy groups, and oral treatment alone was superior to vaginal treatment alone. All VVA-related symptoms significantly decreased across all groups, with greater improvements in the oral and combination groups.

Conclusions Oral full-spectrum sodium hyaluronate significantly improves objective vaginal health and patient-reported symptoms in postmenopausal women with VVA. The greatest benefit was observed when oral supplementation was combined with vaginal HA, supporting its role as an effective non-hormonal strategy for GSM management.

Keywords Genitourinary syndrome of menopause · Hyaluronic acid · Sodium hyaluronate · Non-hormonal therapy · Post-menopause

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https://doi.org/10.1186/s12937-026-01404-9

Published online: 03 October 2026

Introduction

Menopause is a physiological phase characterized by the progressive decline of ovarian function and circulating estrogen levels, leading to endocrine, somatic, and urogenital changes [1]. Among the tissues, the most affected by estrogen deficiency are the genital and lower urinary tract structures, where hormonal decline leads to progressive structural and functional alterations [2]. Within this context, vulvovaginal atrophy (VVA), now included in the broader definition of genitourinary syndrome of menopause (GSM), represents one of the most prevalent and clinically relevant menopausal conditions [3].

VVA is characterized by thinning of the vaginal epithelium, reduced vascularization, loss of elasticity, increased vaginal pH, and decreased lubrication, changes that progressively compromise mucosal integrity and contribute to chronic inflammation and tissue fragility [4]. Epidemiological data indicate that approximately 50% of postmenopausal women experience symptoms attributable to VVA, with prevalence increasing with age and time since menopause [5]. The clinical manifestations typically include vaginal dryness, burning, irritation, itching, dyspareunia, dysuria, and urinary symptoms, which often persist over time and may significantly impair sexual health, emotional well-being, and overall quality of life [3, 6].

Despite its high prevalence, VVA frequently remains underdiagnosed and undertreated, as many women perceive symptoms as an inevitable consequence of aging or hesitate to report intimate discomfort [7]. Current therapeutic strategies include non-hormonal vaginal moisturizers and lubricants, low-dose local estrogen therapy, intravaginal dehydroepiandrosterone, selective estrogen receptor modulators, and systemic hormone replacement therapy [8, 9]. However, growing attention has been directed toward non-hormonal therapeutic approaches that are effective, well tolerated, and suitable for long-term use, particularly in women with contraindications to hormonal treatments [10].

Among these options, hyaluronic acid (HA), a naturally occurring glycosaminoglycan, has attracted increasing interest due to its biological role in maintaining tissue hydration, supporting extracellular matrix organization, modulating inflammation, and promoting epithelial repair and regeneration [11–12]. Several clinical studies have demonstrated that topical HA-based vaginal formulations significantly improve both objective parameters of vaginal health and patient-reported symptoms of VVA, showing favourable tolerability and, in some settings, clinical efficacy comparable to low-dose local estrogen therapy [13–15].

Beyond topical application, recent research has suggested that orally administered HA may exert systemic biological effects, including enhancement of tissue hydration and stimulation of endogenous HA synthesis [16]. The bioavailability and biological activity of oral HA largely depend on its molecular weight distribution [17]. To address this aspect, full-spectrum hyaluronan formulations containing a balanced mixture of different molecular weight fractions have been developed, allowing both rapid absorption of lower molecular weight components and sustained biological activity of higher molecular weight fractions [18–19].

ExceptionHYAL® Blossom is a full-spectrum sodium hyaluronate obtained through controlled biofermentation and designed to mimic the physiological heterogeneity of endogenous hyaluronan [20]. Preclinical and clinical studies indicate that such formulations may enhance tissue hydration, elasticity, and extracellular matrix remodeling, while increasing circulating HA levels following oral administration [16, 21]. Preliminary clinical observations further suggest that oral HA supplementation may support the management of vulvovaginal atrophy, particularly when used in combination with local treatments, potentially enhancing and prolonging symptom improvement [11, 22, 23].

Based on this rationale, the present randomized clinical trial was designed to evaluate the efficacy and tolerability of an oral formulation containing 200 mg of full-spectrum sodium hyaluronate (ExceptionHYAL® Blossom) in postmenopausal women with vulvovaginal atrophy. A secondary objective was to investigate the potential adjuvant effect of oral supplementation when combined with a low-molecular-weight HA–based vaginal ovule [9].

Materials and methods

Study design and population

This was a 60-day exploratory open-label randomized clinical trial conducted in postmenopausal women aged 45–70 years presenting with signs and symptoms of VVA. Of 80 women assessed for eligibility, 20 were excluded because they did not meet the study inclusion criteria; the remaining 60 eligible participants were randomized (1:1:1) to the three treatment groups ($n=20$ per group): an oral HA–based supplement, a vaginal HA ovule, or the combination of both treatments (Fig. 1). Participants were eligible if they were postmenopausal and reported clinically relevant symptoms consistent with VVA, including vaginal dryness, itching, and dyspareunia. Women experiencing menopause-related VVA following oncological treatments were also considered eligible. Exclusion criteria included uncontrolled systemic diseases, use of systemic corticosteroids, known hypersensitivity to HA, and ongoing treatments specifically targeting vulvovaginal atrophy.

The randomization sequence was generated using a computerized procedure based on a random allocation list with a 1:1:1 allocation ratio. The randomization schedule was prepared by an independent individual who was not involved in the clinical assessments, thereby minimizing the risk of selection bias, and the allocation sequence was implemented according to the predefined randomization list only after verification of the eligibility criteria and acquisition of written informed consent, ensuring adequate allocation concealment. Participant recruitment and enrollment were carried out by the investigator gynecologist at the outpatient clinic, who assessed eligibility, provided study information, obtained informed consent, and enrolled eligible participants according to the

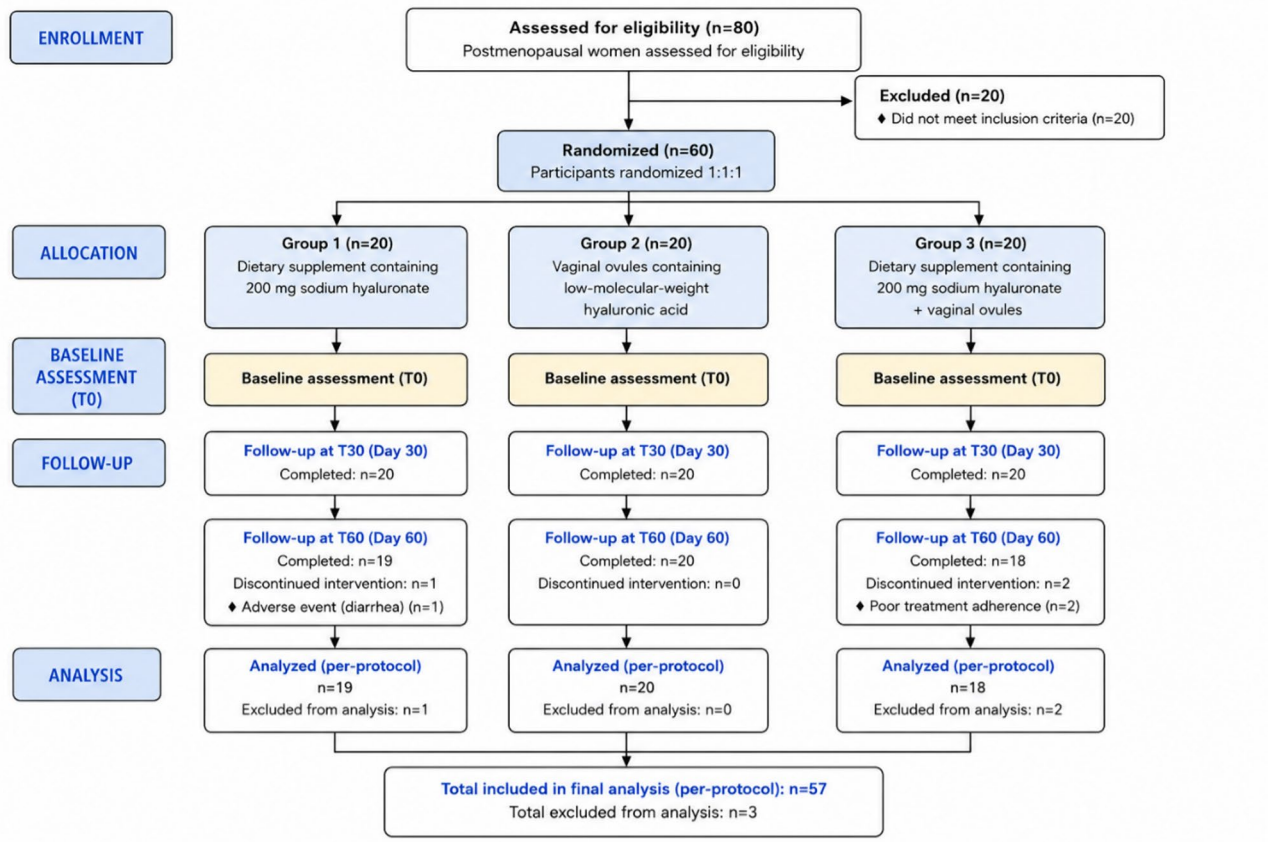


Fig. 1 CONSORT participant flow diagram

randomization list. The study protocol was approved by an independent ethics committee and conducted in accordance with the principles of the Declaration of Helsinki.

Interventions

Participants received the assigned treatment for 60 consecutive days. Group 1 received an oral food supplement containing 200 mg of full-spectrum sodium hyaluronate (ExceptionHYAL® Blossom), administered once daily. Group 2 was treated with a low-molecular-weight HA–based vaginal ovule administered according to a cyclic regimen during the study period. Group 3 received the combination of oral supplementation and vaginal ovule, following the same schedules as the respective monotherapy groups. Specifically, vaginal ovules were administered at bedtime for 10 consecutive days followed by 10 treatment-free days, repeated for three cycles (60 days total).

No additional local or systemic therapies for vulvovaginal atrophy were permitted during the study period in order to avoid potential confounding effects on the evaluated outcomes. Treatment adherence and tolerability were monitored throughout the trial. Participants were instructed to maintain their usual lifestyle habits and to avoid initiating any new treatments that could influence vulvovaginal symptoms during the study period.

Outcome measures

Efficacy and safety evaluations were performed at baseline (T0), day 30 (T30), and day 60 (T60). Baseline and final visits included an in-clinic gynecological examination, while the intermediate assessment was conducted via structured interview. To ensure a comprehensive evaluation of vulvovaginal health, both objective clinical assessments and patient-reported outcome measures were collected. The integration of clinician-rated and patient-reported tools allows the study to capture structural changes of the vaginal mucosa, symptom intensity, and the broader impact of symptoms on daily functioning and quality of life. Vulvovaginal health and symptom severity were therefore assessed using a combination of validated instruments (Table 1), including the Vaginal Health Index (VHI), Visual Analog Scales (VAS), the Vulvovaginal Symptom Questionnaire (VSQ), and gynecological examination. At the end of the study, both investigators and participants provided a global assessment of treatment efficacy. All clinical evaluations were performed by the same investigator to ensure consistency across assessments. This approach was adopted to minimize potential inter-observer variability in the evaluation of clinical parameters. The study endpoints were:

- Primary endpoint - the improvement in VHI total score from baseline to day 60, serving as the core objective measure of vulvovaginal health improvement.
- Secondary endpoints included patient-reported symptom severity assessed by VAS, functional impact evaluated via the VSQ, and gynecological examination findings.

Table 1 Outcome measures used to assess vulvovaginal health and symptom severity

Assessment tool	Main domains assessed	Time points
Vaginal Health Index (VHI)	Elasticity, vaginal secretions, pH, epithelial integrity, lubrication	T0, T30, T60
Visual Analog Scale (VAS)	Severity of vulvovaginal and urinary symptoms	T0, T30, T60
Vulvovaginal Symptom Questionnaire (VSQ)	Vulvovaginal symptoms, sexual discomfort, impact on quality of life	T0, T30, T60
Gynecological examination	Vaginal dryness, erythema, edema, dyspareunia	T0, T30, T60
Global assessment	Overall treatment efficacy and satisfaction	T60

Vaginal health index (VHI)

The Vaginal Health Index (VHI) is a clinician-rated composite scale widely used in clinical studies investigating vulvovaginal atrophy to objectively assess the structural and functional condition of the vaginal mucosa. The index evaluates five parameters: vaginal elasticity, vaginal secretions, pH, epithelial integrity, and mucosal lubrication. Each parameter is scored on a 5-point ordinal scale, with lower scores reflecting more pronounced atrophic changes and higher scores indicating improved vaginal tissue condition. The sum of these parameters provides a global measure of vaginal mucosal health.

Visual analog scale (VAS)

The severity of vulvovaginal and urinary symptoms was assessed using Visual Analog Scales (VAS), a widely adopted patient-reported instrument for quantifying subjective symptom intensity. Participants rated the severity of specific symptoms on a scale ranging from 0 (no symptom) to 10 (maximum perceived severity). VAS measurements allow a sensitive evaluation of changes in symptom perception over time and are commonly used in clinical research to monitor treatment-related symptom improvement. For each treatment group, the total VAS score at each timepoint was calculated as the sum of the mean scores of all individual VAS items; assessed items included both vulvovaginal symptoms (e.g., vaginal dryness, dyspareunia) and urinary symptoms (e.g., urinary incontinence), each rated on the same 0–10 scale, so that higher total scores indicate greater overall symptom burden.

Vulvovaginal symptom questionnaire (VSQ)

The Vulvovaginal Symptom Questionnaire (VSQ) was used to assess the presence and impact of vulvovaginal symptoms on daily functioning and sexual well-being. This patient-reported questionnaire explores multiple domains, including vulvovaginal discomfort, sexual symptoms, and the impact of symptoms on quality of life. The use of the VSQ complements symptom intensity measures by capturing the functional and psychosocial consequences associated with vulvovaginal atrophy. Participants who were not currently sexually active remained in the study population; unanswered sexual-function items were excluded from item-level analyses, without data imputation. The VSQ total score was calculated as the percentage of affirmative ("yes") responses relative to the total number of items answered at each timepoint, expressed on a range from 0% to 100%, with lower percentages reflecting fewer reported symptoms. For unanswered sexual-function items, responses were not counted in the calculation, and the 100% denominator was recalculated based on the actual number of items answered by each participant, without further imputation.

Gynecological examination

In addition to questionnaire-based assessments, a gynecological examination was performed to document objective clinical signs of vulvovaginal atrophy, including vaginal dryness, erythema, edema, and dyspareunia. These parameters allow direct clinical observation of mucosal atrophy and inflammatory changes and support the interpretation of patient-reported symptoms in relation to observable tissue conditions.

Global assessment

At the end of the study (T60), both physicians and participants provided an overall evaluation of treatment efficacy. This global assessment integrates clinical findings and patient perception of benefit, providing an overall measure of treatment effectiveness in a real-world clinical context.

Safety assessment

Safety and tolerability were evaluated through continuous monitoring of adverse events throughout the study period. All reported adverse events were recorded and assessed for severity and potential relationship with the study treatments. Participants were also asked at each visit to report any new symptoms or discomfort potentially related to the study interventions.

Statistical analysis

Statistical analyses were conducted using NCSS 10 software. Efficacy analyses were performed on the per-protocol population. Changes over time within each treatment group were analyzed using repeated-measures analysis of variance (ANOVA), followed by appropriate post hoc testing when required. Between-group comparisons were performed using two-tailed Student's t tests. A p value < 0.05 was considered statistically significant. The sample size was established during the study planning phase based on the expected recruitment capacity of the participating investigator within the predefined enrolment period, without a formal statistical power calculation, consistent with the exploratory nature of the study. Accordingly, 60 participants were considered a feasible sample for the study.

Results

Participant characteristics, tolerability, and compliance with treatment

A total of 60 postmenopausal women were randomized (20 per group), and 57 completed the study and were included in the per-protocol efficacy analyses. Three participants discontinued the study (one in the oral supplementation group and two in the combination group): the participant in the oral supplementation group (Group 1) discontinued due to an adverse event (i.e. diarrhea), while the two participants in the combination group (Group 3) discontinued because of poor treatment adherence. Baseline demographic and clinical characteristics, including Vaginal Health Index (VHI) and symptom severity scores, were comparable across the three treatment groups, with no statistically significant differences observed. All study treatments were generally well tolerated, and no serious adverse events were reported during the study period. One treatment-related adverse event, leading to study discontinuation, was reported in the oral supplementation group (Group 1); no other treatment discontinuations due to adverse events occurred in the vaginal ovule (Group 2) or combined treatment (Group 3) groups (supplementary Table 1). Overall treatment tolerability was good and comparable across all three groups.

Baseline demographic and clinical characteristics of the study population are summarized in Table 2.

Table 2 Baseline demographic and clinical characteristics of the study population (mean ± SD unless otherwise indicated)

Variable	Group 1 ($n=20$)	Group 2 ($n=20$)	Group 3 ($n=20$)	Total ($n=60$)
Age (years)	60.6 ± 3.5	59.1 ± 5.3	59.4 ± 3.1	59.7 ± 4.1
Years since menopause	9.9 ± 2.8	9.2 ± 3.1	9.1 ± 2.2	9.4 ± 2.7
BMI (kg/m²)	n.d.*	n.d.*	n.d.*	24.2 ± 4.5
Vaginal pH	n.d.*	n.d.*	n.d.*	6.0 ± 0.8
VHI at baseline (T0)	7.8 ± 1.6	7.6 ± 1.8	7.4 ± 1.6	7.6 ± 1.7
VAS for vaginal dryness (T0)	7.8 ± 1.6	7.9 ± 1.3	8.4 ± 1.0	8.0 ± 1.3
VAS for dyspareunia (T0)	8.8 ± 1.6	9.1 ± 1.3	8.8 ± 1.1	8.9 ± 1.3
VSQ, % symptomatic responses (T0)	80.5%	84.6%	80.1%	81.8%

*BMI and baseline vaginal pH were not broken down by group in the source data provided; only the overall ($n=60$) values supplied by the sponsor could be reported. Per-group values should be added if/when available. Age, years since menopause, *VHI*, VAS (dryness and dyspareunia) and VSQ (% symptomatic responses) were calculated directly from the individual patient-level data provided

Vaginal health index (VHI)

At baseline, mean VHI values were comparable across the three groups and consistent with severe vulvovaginal atrophy (approximately 7–8 points), with no statistically significant intergroup differences. Across the study period, VHI scores increased progressively in all treatment groups, with improvements already evident at the intermediate evaluation (T30) and further increases at the final assessment (T60). As reported in Table 3, mean VHI values increased from baseline to T60 in all treatment arms, indicating an overall improvement in objective vaginal health parameters. The magnitude of change differed among groups, with larger increases observed in participants receiving oral supplementation either alone or in combination with the vaginal ovule. In the oral supplementation group (ExceptionHYAL® Blossom), VHI values increased steadily throughout the study, rising from baseline levels consistent with severe atrophy to values approaching those associated with improved vaginal mucosal condition at T60. The combined treatment group showed the greatest overall increase in VHI score, reaching the highest mean value at the final timepoint, whereas the vaginal ovule group also demonstrated improvement but with a comparatively smaller magnitude of change. The improvement in VHI total score (Table 2) reflected the changes across the individual components of the index (elasticity, vaginal secretions, mucosal integrity, lubrication, and pH).

Total VHI scores increased significantly from baseline at both T30 and T60 in all treatment groups. The magnitude of change from baseline is illustrated in Fig. 2. Dispersion measures performed on the per-protocol population comprising 57 participants who completed the 60-day protocol were as follows for total VHI scores (mean ± SD): oral supplementation group ($N=19$), 7.8 ± 1.6 (T0), 12.5 ± 1.8 (T30), and 15.2 ± 1.5 (T60); vaginal ovule group ($N=20$), 7.6 ± 1.8 (T0), 11.3 ± 1.8 (T30), and 12.6 ± 2.5 (T60); combined treatment group ($N=18$), 7.4 ± 1.6 (T0), 13.3 ± 1.5 (T30), and 16.7 ± 2.1 (T60). The mean change from baseline in total VHI score was +4.74 ± 1.53 ($p=0.000081$) at T30 and +7.47 ± 2.22 ($p=0.000120$) at T60 in the oral supplementation group; +3.65 ± 1.04 ($p=0.000063$) at T30 and +5.05 ± 1.86 ($p=0.000083$) at T60 in the vaginal ovule group; and +5.85 ± 2.37 at T30 and +9.25 ± 2.84 (both $p=0.000086$) in the combined treatment group (Fig. 2).

The between-group mean difference in total VHI score change from baseline at T30 was +1.09 (95%CI: 0.38–1.80, $p=0.037592$) favoring oral HA over vaginal ovules, +1.11 (95%CI: −0.10–2.33, n.s.) between combined treatment and oral HA, and +2.20 (95%CI: 1.03–3.37, $p=0.000659$) between combined treatment and vaginal ovules (Fig. 2). Consistent mean differences were registered also at T60: +2.42 (95%CI: 1.37–3.57, $p=0.000755$) favoring oral HA over vaginal ovules, +1.78 (95%CI: 0.29–3.26, $p=0.001229$) between combined treatment and oral HA, and +4.20 (95%CI: 2.71–5.79, $p=0.000027$) between combined treatment and vaginal ovules (Fig. 2).

Table 3 Mean parameters of Vaginal Health Index Scores (VHI) in the three groups at the three timepoints considered

Mean VHI Score	Group 1 (Blossom) $N=19$			Group 2 (Ovule) $N=20$			Group 3 (Combined treatment) $N=18$		
	T0	**T30**	**T60**	**T0**	**T30**	**T60**	**T0**	**T30**	**T60**
Elasticity	1.7	2.6	3.1	1.6	2.2	2.4	1.7	2.8	3.5
Vaginal secretion	1.6	2.5	3.0	1.5	2.2	2.5	1.6	2.8	3.5
pH	1.2	2.3	2.7	1.3	2.1	2.3	1.3	2.3	3.0
Mucosal integrity	1.8	2.6	3.2	1.7	2.4	2.6	1.5	2.8	3.3
Lubrication	1.4	2.2	3.0	1.3	2.2	2.8	1.3	2.5	3.3
Total Score	**7.8**	**12.5**	**15.2**	**7.6**	**11.3**	**12.6**	**7.4**	**13.3**	**16.7**

Each of the five VHI parameters (elasticity, vaginal secretion, pH, mucosal integrity, and lubrication) is scored on a 5-point ordinal scale (1 = worst, 5 = best); the Total Score is the sum of the five parameters (range 5–25), with higher scores indicating better vaginal mucosal health

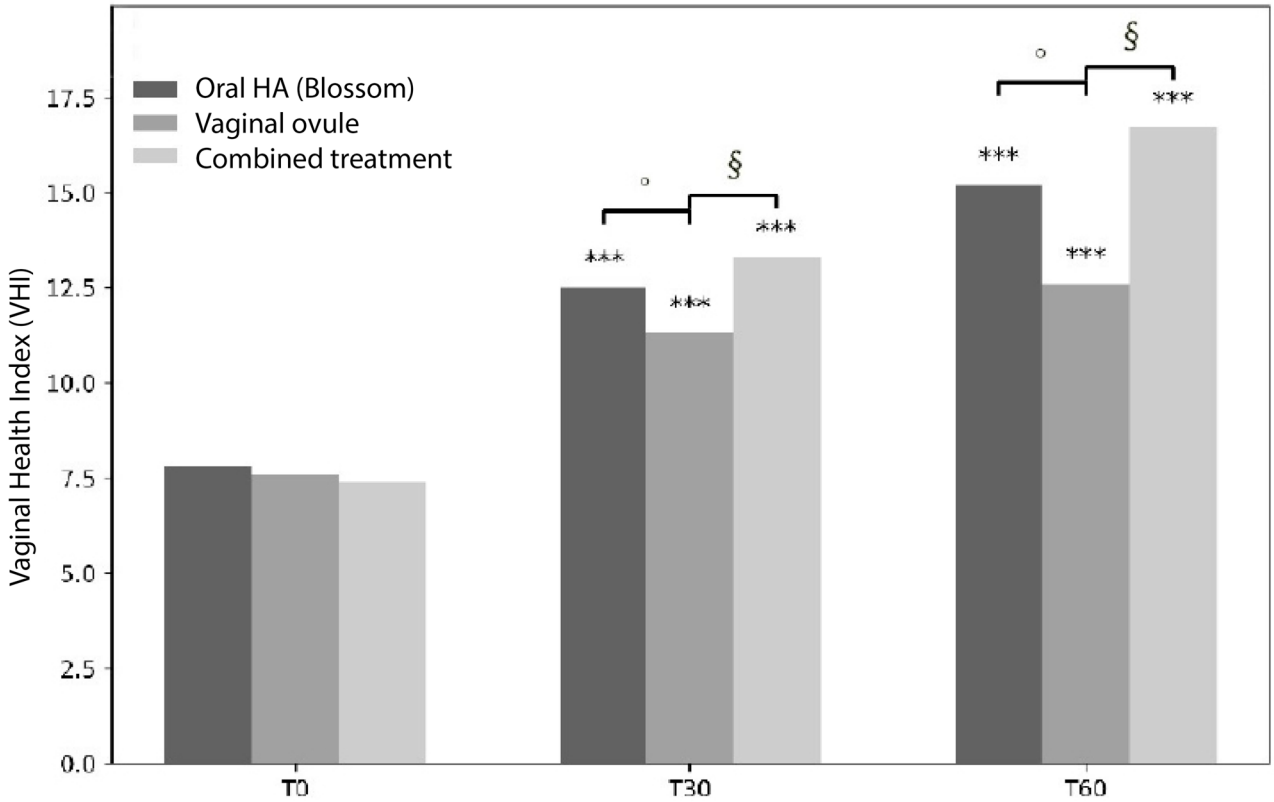


Fig. 2 Changes in Vaginal Health Index (VHI) scores during the study period. Mean VHI scores at baseline (T0), day 30 (T30), and day 60 (T60) in postmenopausal women receiving oral hyaluronic acid supplementation (ExceptionHYAL® Blossom), vaginal hyaluronic acid ovules, or combined treatment. Significant improvements from baseline were observed in all treatment groups at both follow-up timepoints. At T60, higher VHI values were observed in the oral supplementation and combined treatment groups compared with the vaginal ovule group. *$p<0.001$ vs. baseline (T0) in all groups. At T30: °$p=0.038$ Oral HA (Blossom) vs. Vaginal ovule; §$p=0.001$ Combined treatment vs. Vaginal ovule; Combined treatment vs. Oral HA was not statistically significant ($p=0.116$). At T60: $p<0.001$ for all between-group comparisons (°Oral HA vs. Vaginal ovule and §Vaginal ovule vs. Combined treatment). Values represent mean scores

Symptom severity (VAS)

Consistent with the improvements observed in objective vaginal health parameters measured by the Vaginal Health Index (VHI), patient-reported symptoms assessed by the Visual Analog Scale (VAS) also showed a progressive reduction over the study period. This parallel trend indicates that the improvements documented in vaginal tissue condition were accompanied by a measurable decrease in symptom burden. Baseline VAS scores for vaginal dryness and other vulvovaginal symptoms were comparable among the three groups, with mean values indicating moderate-to-severe symptom severity and no relevant intergroup differences at study entry. Across the study period, VAS scores decreased progressively in all treatment arms, with reductions already evident at the intermediate evaluation (T30) and further decreases at the final assessment (T60).

Considering the overall VAS symptom burden, mean total scores decreased substantially from baseline to T60 in all groups (Fig. 3). In the oral supplementation group ($N=19$), the mean total VAS score decreased from 36.20 at baseline to 20.37 at T30 and 8.74 at T60, corresponding to an overall reduction of approximately 76% from baseline. In the vaginal ovule group ($N=20$), mean VAS scores decreased from 38.60 at baseline to 26.40 at T30 and 21.30 at T60, corresponding to an overall reduction of approximately 45% over the study period. The combined treatment group ($N=18$) showed the largest reduction in overall symptom burden, with mean VAS scores decreasing from 41.35 at baseline to 22.51 at T30 and 8.09 at T60, corresponding to an overall reduction

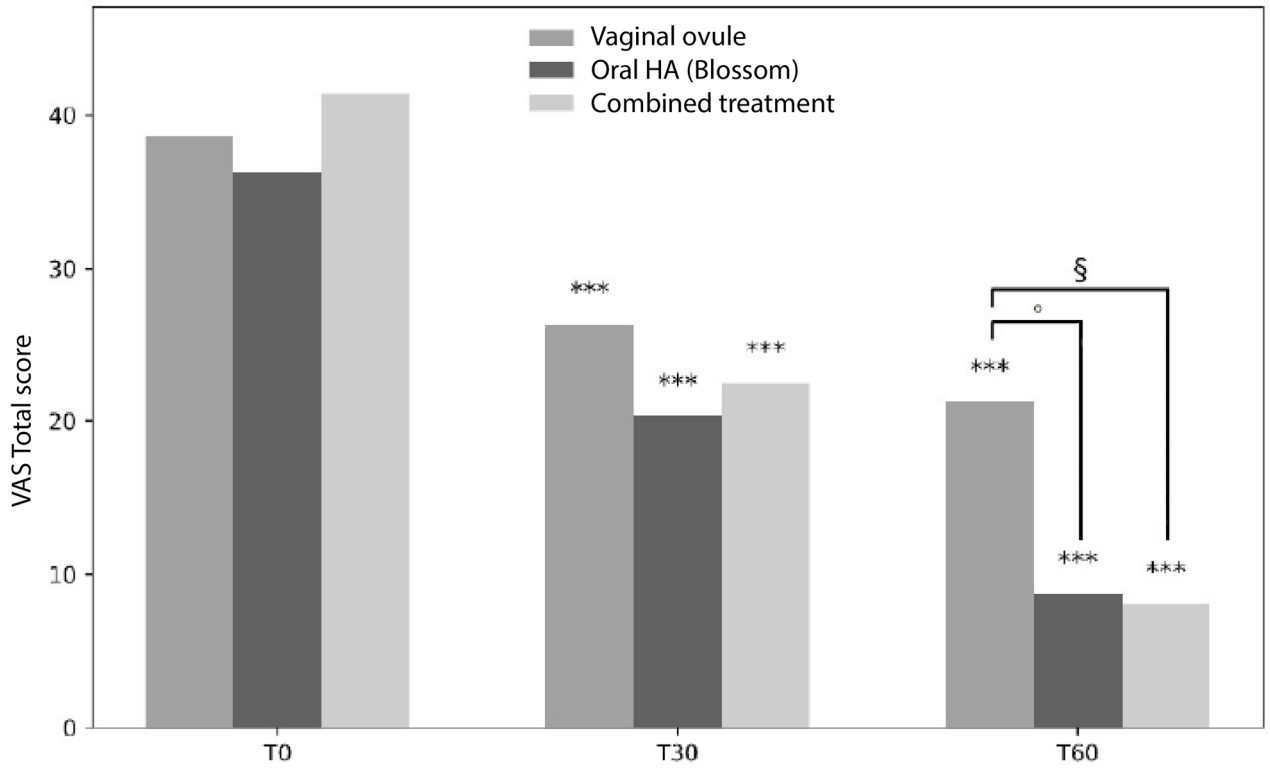


Fig. 3 Changes in total VAS symptom score during the study period. Mean total Visual Analog Scale (VAS) scores for vulvovaginal and urinary symptoms measured at baseline (T0), day 30 (T30), and day 60 (T60) in postmenopausal women receiving oral hyaluronic acid supplementation (ExceptionHYAL® Blossom), vaginal hyaluronic acid ovules, or the combination of both treatments. A progressive reduction in symptom severity was observed across all treatment groups over time. *$p<0.001$ vs. baseline (T0) within the same treatment group. At T60, lower VAS scores were observed in the oral supplementation and combined treatment groups compared with the vaginal ovule group. °$p<0.05$ Oral HA (Blossom) vs. Vaginal; §$p<0.05$ Combined vs. Vaginal

of approximately 80% from baseline. At the final evaluation (T60), total VAS scores were markedly lower in the oral supplementation and combination groups compared with the vaginal ovule group, reflecting a greater reduction in overall symptom severity in participants receiving systemic HA supplementation. Similar temporal trends were observed across all individual vulvovaginal and urinary symptoms assessed by VAS, with statistically significant reductions from baseline at T60 in all treatment groups (Fig. 2). Dispersion measures for total VAS scores (mean ± SD) showed a reduction from 36.00 ± 9.83 (T0) to 20.37 ± 7.62 (T30), and to 8.74 ± 5.84 (T60) in the oral supplementation group ($N=19$); from 38.60 ± 7.93 (T0) to 26.40 ± 7.37 (T30), and to 21.30 ± 9.20 (T60) in the vaginal ovule group ($N=20$); from 41.35 ± 8.94 (T0) to 22.51 ± 6.27 (T30), and to 8.09 ± 7.40 (T60) in the combined treatment group ($N=18$). The changes of individual VAS parameters and total VAS scores were statistically significant in all three groups at both T30 and T60 compared to baseline ($p<0.05$), with the T30 comparison in the combined treatment group reaching the stricter threshold ($p<0.01$) (Fig. 3).

The between-group mean difference in total VAS score change from baseline was mostly evident at T60 reaching −9.96 (95%CI: -14.92 - −5.00, $p<0.05$) for oral supplementation vs. vaginal ovule, and −15.95 (95%CI: −21.36 - −10.54, $p<0.05$) for combined treatment vs. vaginal ovule (Fig. 3).

Vulvovaginal symptom questionnaire (VSQ)

At baseline, VSQ responses indicated a comparable symptom burden across the three treatment groups, with a high proportion of participants reporting multiple vulvovaginal symptoms affecting daily comfort and sexual

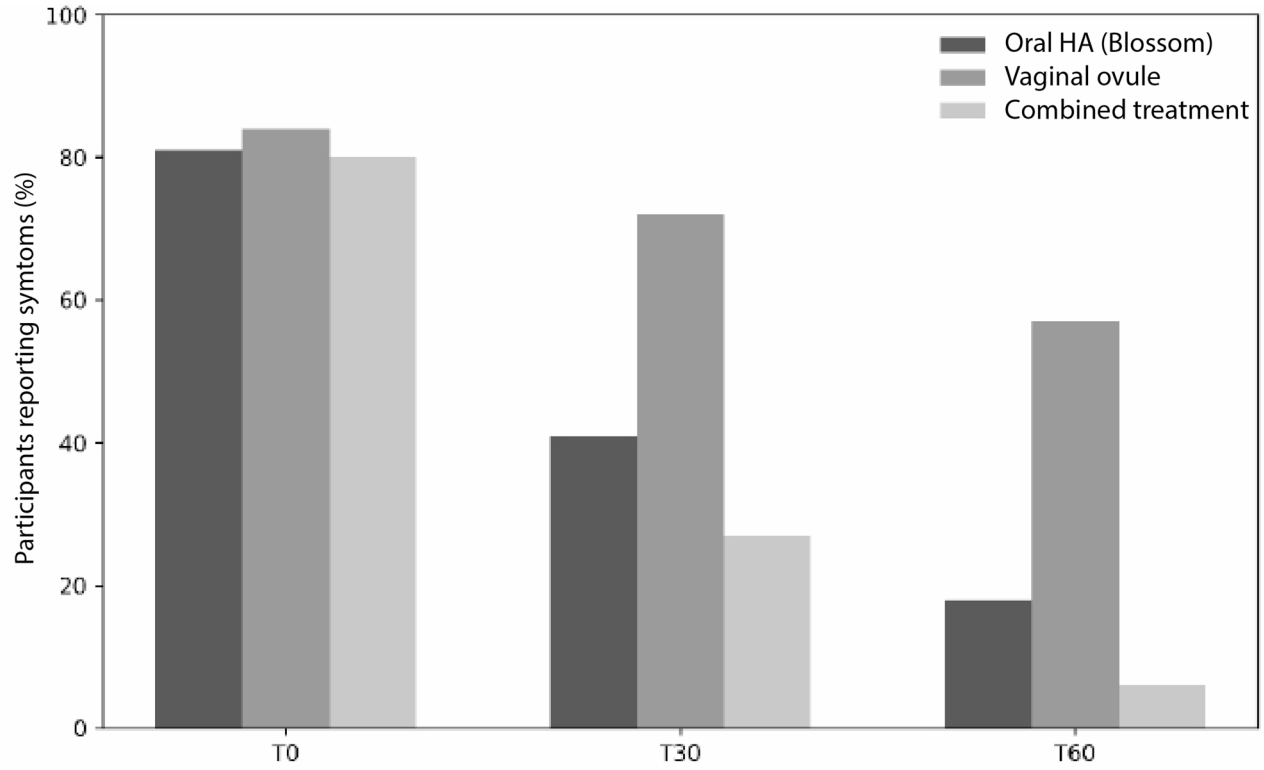


Fig. 4 VSQ Score over time in the three treatment groups. The bar chart shows the percentage of participants reporting symptoms (VSQ Score) at baseline (T0), day 30 (T30), and day 60 (T60) in the three study arms: Oral HA (ExceptionHYAL® Blossom), Vaginal ovule, and Combined treatment. Values are reported as percentages at each time point

well-being. Over the course of the study, a progressive reduction in VSQ-reported symptoms was observed across all treatment arms, with improvements already evident at the intermediate evaluation (T30) and further reductions at the final assessment (T60) (Fig. 4). The reduction in VSQ score reflects a decrease in the proportion of participants reporting clinically relevant symptoms across the different questionnaire domains, including vulvovaginal discomfort, sexual-related symptoms, and impact on quality of life. The most pronounced reductions in symptom reporting were observed in the oral supplementation and combination groups, in which the proportion of symptomatic responses progressively declined from baseline to T60. By the end of the study, the lowest proportion of residual symptoms was observed in participants receiving oral supplementation either alone or in combination with vaginal treatment, whereas a higher proportion of symptoms remained reported in the vaginal ovule group.

Gynecological examination

Baseline gynecological examination findings were consistent with vulvovaginal atrophy in all groups, including clinical signs such as vaginal dryness, erythema, reduced mucosal elasticity, and tenderness, with comparable findings across treatment arms. During follow-up evaluations, a progressive improvement in gynecological parameters was observed in all groups. At both T30 and T60, clinical examination showed reductions in the frequency and severity of atrophic signs, including vaginal dryness, mucosal erythema, edema, and tenderness. The improvement in objective gynecological findings paralleled the trends observed in both VHI scores and patient-reported symptom measures, indicating a consistent pattern of clinical improvement across different assessment methods. At the final evaluation (T60), fewer signs of vulvovaginal atrophy were observed overall, with a greater reduction in atrophic findings in the oral supplementation and combination groups.

Global assessments

At the end of the study (T60), both physician and patient global assessments indicated an overall improvement in vulvovaginal condition across all treatment groups. The distribution of global assessment ratings differed among treatment arms, with a higher proportion of favorable evaluations reported in the oral supplementation and combination groups. In these groups, a greater number of participants were classified as having achieved good or excellent overall improvement, whereas global assessments in the vaginal ovule group more frequently indicated partial or moderate improvement. These findings are consistent with the trends observed across objective clinical measures and patient-reported outcomes, supporting a coherent pattern of improvement across the different evaluation tools used in the study.

Discussion

The present exploratory open-label randomized study shows that treatment with HA–based formulations is associated with clinically relevant improvements in both objective vaginal health parameters and patient-reported symptoms in postmenopausal women with vulvovaginal atrophy over a 60-day period. Across all treatment arms, VHI total score – which reflected the changes across individual components of the index – increased, and symptom severity decreased, indicating a measurable improvement of multiple aspects of vaginal tissue condition and clinical symptom burden. Importantly, these improvements were more pronounced in participants receiving oral HA supplementation, either as monotherapy or in combination with vaginal treatment. These findings support a potential role for systemic HA administration in the management of vulvovaginal atrophy. While HA has traditionally been used in topical vaginal formulations, the present results suggest that oral supplementation may contribute substantially to the restoration of vulvovaginal health, with outcomes that appear more favorable than those observed with local treatment alone.

Previous clinical studies have demonstrated that topical HA preparations improve vaginal lubrication, epithelial integrity, and vaginal pH, leading to relief of symptoms such as dryness and dyspareunia, with a favorable safety profile and efficacy comparable to low-dose local estrogen therapy in selected populations [13–15]. Consequently, vaginal HA formulations are currently recognized as an effective non-hormonal option for women with vulvovaginal atrophy, particularly for those who prefer to avoid hormonal treatments or have contraindications to estrogen therapy [10]. Building on this established evidence, the present study highlights the potential contribution of systemic HA supplementation. The improvements observed in the oral supplementation group, together with the greater responses documented in the combined treatment group, suggest that systemic administration may enhance the therapeutic effects of local HA by supporting tissue hydration and extracellular matrix homeostasis.

Experimental and clinical data indicate that orally administered HA may exert systemic biological effects, possibly through stimulation of endogenous HA synthesis and modulation of extracellular matrix turnover [11, 16, 17]. In line with these observations, improvements were observed across both clinician-rated and patient-reported outcomes following oral full-spectrum sodium hyaluronate supplementation, suggesting a beneficial effect on vaginal tissue hydration and mucosal function. The combined administration of oral and vaginal HA resulted in the highest VHI values at the end of the study period, supporting the hypothesis that systemic and local administration may provide complementary therapeutic effects. Previous studies have similarly suggested that oral HA may enhance or prolong the benefits of local vulvovaginal treatments [20, 22, 23]. A combined systemic–local strategy may therefore represent a rational approach to target multiple aspects of vaginal tissue physiology and maximize clinical benefit.

From a clinical perspective, the consistent improvements observed across objective clinical indices, symptom scales, and global assessments are particularly relevant, considering the well-documented impact of vulvovaginal atrophy on sexual health and quality of life in postmenopausal women [3, 5, 6]. In addition, oral administration

may offer practical advantages in terms of ease of use and treatment acceptability, factors that may positively influence adherence in the long-term management of genitourinary syndrome of menopause [7, 10].

While the present study provides encouraging evidence, the findings should be interpreted in light of some methodological considerations. The relatively small sample size and the open-label design may restrict the generalizability of the results. Moreover, the absence of a placebo control group should also be acknowledged. This decision was primarily guided by ethical considerations, as the study population consisted of postmenopausal women experiencing clinically relevant and symptomatic vulvovaginal atrophy. In this context, withholding any active intervention for the entire study period was considered inappropriate, given the potential impact of untreated symptoms on quality of life and daily functioning. Consequently, the study design focused on comparing different therapeutic strategies rather than evaluating treatment against placebo, a limitation that has also been described in previous exploratory studies investigating HA–based interventions [20]. Furthermore, the internal registration under the protocol name 'Atrofia 2024' without a public clinical trial registration number represents a methodological limitation of the present study. Despite these limitations, several strengths of the study should be highlighted. These include the randomized parallel-group design, the use of validated clinician-rated and patient-reported outcome measures, and the direct comparison between oral supplementation, vaginal treatment, and their combination within the same study population. Furthermore, the convergence of findings across multiple assessment tools strengthens the internal consistency of the results and supports the robustness of the observed clinical trends.

In conclusion, the present findings suggest that oral full-spectrum sodium hyaluronate may represent a promising non-hormonal option for the management of vulvovaginal atrophy in postmenopausal women, either as a standalone intervention or as an adjunct to local therapy. Further large-scale and longer-term controlled studies are warranted to confirm these observations and to better define the role of oral HA supplementation within the therapeutic landscape of genitourinary syndrome of menopause [11, 20, 22, 23].

Abbreviations

GSM	Genitourinary Syndrome of Menopause
HA	Hyaluronic Acid
NCSS	Number Cruncher Statistical System
VAS	Visual Analog Scale
VHI	Vaginal Health Index
VSQ	Vulvovaginal Symptom Questionnaire
VVA	Vulvovaginal Atrophy

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1186/s12937-026-01404-9.

Acknowledgements The authors wish to acknowledge MediAbout Srl, Milan, Italy, for editorial assistance.

Author contributions Conceptualization: L. G., F. V., V. L., V.N.; methodology: L. G., F. V., V. L., V. N.; data curation: L. G., F. V., V. L., V. N.; writing: L. G., F. V., V. L., V. N.; supervision: L. G.

Funding The study was funded by ROELMI HPC, Origgio, VA (Italy), which had no role in the study design, data collection, or interpretation.

Data availability All data supporting the findings of this study are available within the paper and its Supplementary Data.

Declarations

Ethics approval and informed consent The study protocol was approved by the *"Comitato Etico Indipendente"*. The protocol was registered under the code name of "*Atrofia 2024*". Registration date: 17 July 2024. Clinical trial number: not ap-

plicable. The lack of a public clinical trial registry identifier is acknowledged as a study limitation. All participants provided written informed consent to participate before enrollment. Human Ethics and Consent to Participate declarations: not applicable. The full study protocol was not submitted to a public registry and is not publicly available; it is held internally by the sponsor as reference [24] and can be made available by the corresponding author upon reasonable request.

Disclosure The authors report no conflicts of interest in this work.

Competing interests The authors declare no competing interests.

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