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A randomized, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis

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AIMS: Intravesical instillation of hyaluronic acid (HA) plus chondroitin sulfate (CS) in women with bladder pain syndrome/interstitial cystitis (BPS/IC) has shown promising results. This study compared the efficacy, safety, and costs of intravesical HA/CS (Ialuril®, IBSA) to dimethyl sulfoxide (DMSO).

METHODS: Randomized, open-label, multicenter study involving 110 women with BPS/IC. The allocation ratio (HA/CS:DMSO) was 2:1. Thirteen weekly instillations of HA (1.6%)/CS (2.0%) or 50% DMSO were given. Patients were evaluated at 3 (end-of-treatment) and 6 months. Primary endpoint was reduction in pain intensity at 6 months by visual analogue scale (VAS) versus baseline. Secondary efficacy measurements were quality of life and economic analyses.

RESULTS: A significant reduction in pain intensity was observed at 6 months in both treatment groups versus baseline ($P < 0.0001$) in the intention-to-treat population. Treatment with HA/CS resulted in a greater reduction in pain intensity at 6 months compared with DMSO for the per-protocol population (mean VAS reduction 44.77 ± 25.07 vs. 28.89 ± 31.14, respectively; $P = 0.0186$). There were no significant differences between treatment groups in secondary outcomes. At least one adverse event was reported in 14.86% and 30.56% of patients in the HA/CS and DMSO groups, respectively. There were significantly fewer treatment-related adverse events for HA/CS versus DMSO (1.35% vs. 22.22%; $P = 0.001$). Considering direct healthcare costs, the incremental cost-effectiveness ratio of HA/CS versus DMSO fell between 3735€/quality-adjusted life years (QALY) and 8003€/QALY.

CONCLUSIONS: Treatment with HA/CS appears to be as effective as DMSO with a potentially more favorable safety profile. Both treatments increased health-related quality of life, while HA/CS showed a more acceptable cost-effectiveness profile.

KEYWORDS
bladder pain syndrome, chondroitin sulfate, DMSO, hyaluronic acid, interstitial cystitis, Ialuril

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1 | INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic bladder condition[1,2] characterized by pelvic pain, increased urinary frequency and urgency, in addition to high levels of sexual dysfunction, sleep disturbance, and impairment in quality of life.[3,4] Debilitating pelvic pain associated with BPS/IC is challenging to treat,[2] and both physicians and patients may be unsatisfied with the quality of care.[5]

Although the precise etiology of BPS/IC remains unknown,[6,7] bladder urothelial dysfunction, bladder inflammation, neuropathic pain, and infection have been proposed as the main etiologies.[8] Strong evidence suggests that pathophysiological disruption of the bladder mucosa surface leads to loss of glycosaminoglycans (GAGs)[9] exposing the urothelium to toxic agents or bacteria in urine causing alterations in the bladder wall.[9,10] This damage can trigger a cascade of inflammatory and neurogenic responses resulting in pain, problems in voiding, and chronic changes to the bladder.[10–12]

Accordingly, restoration of the urothelial barrier with exogenous GAG administration can help to re-establish its integrity in patients with BPS/IC.[9,13–16] In this regard, the combination of hyaluronic acid (HA) and chondroitin sulfate (CS) has shown promising results in small patient cohorts,[17,18] and has been confirmed for up to 3 years.[11]

Dimethyl sulfoxide (DMSO) is the only intravesical treatment for BPS/IC approved by the FDA and grade A recommended by the European Association of Urology (EAU). This study compared intravesical treatment of HA/CS with DMSO in female patients with BPS/IC to better understand its efficacy, safety, and direct/indirect healthcare costs.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

This was a phase III, randomized, controlled study (EudraCT 2010-021556-25). An open-label design was adopted due to the garlic-like taste of DMSO after intravesical administration, which would have been impossible to mask.

A total of 110 women were randomized to receive 13 weekly instillations (3 months) of HA (1.6%) and CS (2.0%) (Ialuril®; IBSA) or 50% DMSO solution (RIMSO®; Bioniche), with a 2:1 allocation ratio (HA/CS:DMSO). A randomization scheme for the preparation of a centralized randomization procedure was generated by the Moses-Oakford algorithm, using the procedure Etcetera of the software WinPEPI v.10. The study was conducted in accordance with the Declaration of Helsinki. All patients signed a written consent for participation in the study. The trial was performed at six centers in Italy and approved by the respective Ethics Committees.

The study enrolled female patients aged 18 years or more with a diagnosis of BPS/IC, according to the European Society for the Study of IC/PBS (ESSIC) Criteria,[19] unresponsive to first line non-invasive treatments (e.g., oral drugs considered to be a standard treatment for BPS/IC, such as antidepressants, antiepileptics, antihistaminics, cyclosporine-A, pentosan polysulfate) or at first observation. Relevant inclusion criteria included the presence of pain (pelvic, pressure, or discomfort) with at least one other urinary symptom such as urgency, increased urination frequency for at least 6 months, discomfort, or pain during sexual intercourse. Pregnant or breastfeeding women, presence of other confusable diseases as the main cause of urinary symptoms, or those who had undergone previous intravesical treatments were excluded. A minimum time of 3 months from last treatment to start of therapy was required for all patients. A randomization visit, during which treatment was started, was carried out 15–20 days following the screening visit. The first patient was enrolled on 30 Jun 2011, and the last patient completed the study on 30 Sep 2013.

2.2 | Clinical assessments

An initial screening visit was performed to determine patient eligibility and obtain informed consent. In addition to clinical examination and history, renal and vesical ultrasound scan was carried out in all patients; urodynamic test, cystourethroscopy, and vulvoscopy were performed at the discretion of the clinician. The primary endpoint was reduction in pelvic pain intensity, evaluated by a 0–100 visual analog scale (VAS), at 6 months (i.e., after a treatment-free period of 3 months) compared with baseline. Pain perceived by the patients as "my pain today" on the occasion of the control visits was indicated by drawing a line on a 0–100 mm VAS, where 0 = no pain and 100 = worst possible pain. Responders were defined as those with at least 50% VAS reduction in pain from baseline. Secondary endpoints were reduction in pain intensity after the 3-month treatment period and changes from baseline in other urinary symptoms recorded using the O'Leary-Sant Interstitial Cystitis Symptom and Problem Index (ICSI/ICPI),[20] the Pelvic Pain and Urgency/Frequency Symptom Scale (PUF),[21] and a 3-day voiding diary. The EuroQol five dimensions questionnaire (EQ-5D), a standardized instrument for measuring generic health status, and consisting of a health state index (EQ Index) and VAS for the patient's self-rated health status (EQ VAS), was used to evaluate quality of life. The assessment of safety included the registration of all investigator-assessed adverse events (AEs). All study visits were carried out by a clinician.

2.3 | Statistical analysis

Sample size was calculated in terms of difference between treatments on VAS pain level from baseline to 6 months considering a medium-large effect size of 0.6 with power ≥80% and $\alpha = 0.05$. Analysis of covariance (ANCOVA), with baseline as covariate, a modified baseline observation carried forward (mBOCF) approach to impute missing data in case of dropouts for lack of efficacy or adverse event, and a last observation carried forward (LOCF) strategy in case of dropouts for other reasons, were used to compare HA/CS and DMSO. The VAS score changes from baseline after 6 months (primary endpoint) were analyzed in the intention to treat (ITT) population, including all randomized patients, and in the per protocol (PP) population, including patients completing the study without any major protocol violation and without receiving any grade A/B recommended treatment for BPS/IC, according to EAU Criteria,[22] within 3 months from inclusion or during the study. The secondary endpoints were analyzed in the ITT population, and safety endpoints in the safety population, including all patients who received at least one dose of treatment. SAS Software (release 9.4) was used for statistical analyses. A *P*-value <0.05 was considered statistically significant.

2.4 | Economic evaluation

The primary objective of the economic analysis was to evaluate the incremental cost-effectiveness ratio (ICER) of HA/CS versus DMSO over a period of 12 months after the start of therapy in the ITT population. No discounting was performed. The ICER was calculated by dividing the incremental costs by the incremental quality-adjusted life years (QALY). Specific forms were designed to record data about direct healthcare resource consumption, productivity losses, and informal care. Direct medical costs were estimated from the Italian National Healthcare Service perspective, including drugs, hospitalization, exams, and additional pharmacological therapies necessitated by concomitant adverse events. Unitary costs, expressed as euro (€) 2010, were derived from a previous publication.[23] Indirect costs included productivity loss (i.e., days absent from work due to the disease), informal care, domestic assistance, travel, and accommodation expenses to receive inpatient or outpatient assistance. For productivity losses and informal care, gross hourly wages were derived from Italian National Institute of Statistics (ISTAT) tables.[24] The utility scores, providing a single index value for health status ranging from 0 (death) to 1 (perfect health), were derived from the EQ Index, using a utility scoring function.[25] QALY were calculated as the area under the utility profile over time with relevant time-points set at baseline, 3 months and 6 months. Since data were only collected up to 6 months, two different scenarios were considered in order to provide a 1-year time span for the ICER calculation: an optimistic one, assumed the utility measured at 6 months would hold until 12 months, and a pessimistic one, assumed the utility values return to levels observed at baseline. No additional cost was imputed. Given the generalized small sample size in the dataset, statistical hypothesis testing was not attempted.

3 | RESULTS

Figure 1 shows the CONSORT diagram of the study. A total of 110 women were screened, 74 for HA/CS and 36 for DMSO, with a mean age of 50.2 years (range 18–88 years). All patients were of Caucasian origin, with exception of one Asian patient in the DMSO group. All patients were randomized and included in the safety and ITT analysis. Overall, 22 patients, 15 (20.3%) in the HA/CS group and 7 (19.4%) in the DMSO group, withdrew before the end of the study. The two groups were well represented and well balanced in terms of first observation (68.9% vs. 66.7% of patients in the HA/CS vs DMSO groups) and those previously treated and unresponsive to first-line non-invasive treatments (31.1% vs. 33.3%, respectively).

A total of 88 patients, 61 for HA/CS and 27 for DMSO, were included in the PP population, mainly excluding patients who received grade A/B recommended treatments for BPS/IC within 3 months from inclusion or during the study.

Demographic and baseline clinical characteristics were comparable in the two treatment groups at baseline (Table 1). Urinary frequency and bladder capacity appeared more severe in the DMSO group compared with the HA/CS group, but neither reached statistical significance.

A significant reduction in pain intensity was observed at 6 months in both treatment groups versus baseline ($P < 0.0001$) in the ITT population (Fig. 2A). Patients treated with HA/CS reported a greater mean VAS reduction compared with those treated with DMSO at 6 months (-39.15 ± 29.14 vs. -30.36 ± 30.53, respectively), however, the between treatment group difference was not statistically significant (−8.03; 95%CI −17.95, 1.88; $P = 0.1110$) (Fig. 2A). The percentage of responders at 3 and 6 months was also numerically higher for HA/CS compared with DMSO (70.27% vs. 55.56% and 63.51% vs. 55.56%, respectively) (Supporting Information Table S1).

Reduction in pain intensity at 6 months was significantly different between treatment groups in the PP population, with a mean VAS reduction of 44.77 ± 25.07 versus 28.89 ± 31.14 for HA/CS versus DMSO, respectively (−13.34; 95%CI −24.399, −2.283; $P = 0.0186$) (Fig. 2B). There was also a higher percentage of responders for HA/CS compared with DMSO at both 3 and 6 months (77.05% vs. 51.85% [$P = 0.025$] and 72.13% vs. 55.56% [$P =$ not significant], respectively) (Supporting Information Table S1).

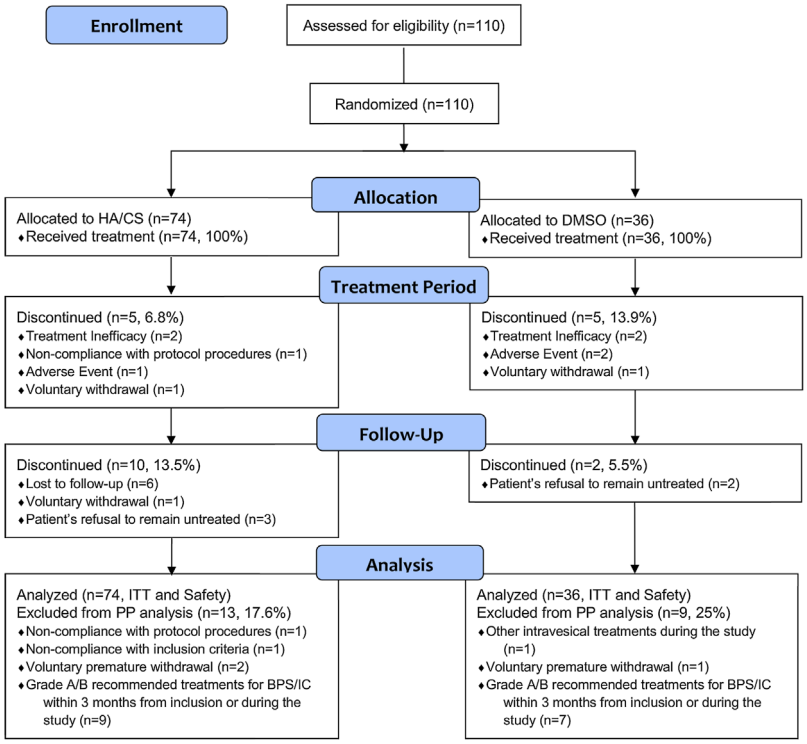

FIGURE 1 CONSORT diagram of study

For secondary endpoints, both treatment groups showed significant improvements in pain reduction (Fig. 2A) and urination frequency at 3 months, and in ICSI/ICPI, PUF, and EQ-5D at 3 and 6 months (all $P < 0.0001$ vs. baseline) (Table 2). Bladder capacity also improved significantly at 3 months compared with baseline ($P = 0.0004$) (Table 2). There were no significant differences between treatment groups at 3 or 6 months for any of these parameters (Table 2). However, 6-month urinary frequency/bladder capacity data are not shown as data were available for only a limited number of patients (<50%).

TABLE 1 Demographic and baseline clinical characteristics of patients (ITT population)

Parameter	HA/CS mean (SD)	DMSO mean (SD)	*P*-value*
Age, years	50.95 (14.97)	48.78 (17.70)	0.503
BMI, kg/m^2	23.26 (3.26)	23.27 (5.00)	0.988
Years from diagnosis	2.97 (4.10)	3.96 (8.54)	0.654
Pain VAS, mm	65.53 (21.00)	64.58 (20.53)	0.824
Pain VAS, mm (PP population)	*69.13 (17.11)*	*65.56 (20.05)*	*0.394*
ICSI score	12.47 (3.66)	12.72 (3.74)	0.733
ICPI score	12.92 (2.76)	12.42 (3.02)	0.389
PUF score	22.53 (5.25)	22.64 (5.38)	0.923
EQ Index	0.25 (0.47)	0.26 (0.41)	0.921
EQ VAS	54.36 (21.09)	59.09 (18.61)	0.262
Urinary frequency	10.31 (4.12)	12.15 (5.55)	0.080
Bladder capacity, mL	172.24 (96.54)	133.99 (65.46)	0.083

BMI, body mass index; CS, chondroitin sulfate; DMSO, dimethyl sulfoxide; EQ, EuorQol; HA, hyaluronic acid; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; ITT, intent to treat; PP, per protocol; PUF, Pelvic Pain and Urgency/Frequency Symptom Scale; SD, standard deviation; VAS, visual analog scale.
*P values obtained using ANOVA.

AEs are summarized in Table 3. A total of 52 and 39 AEs were reported in the HA/CS and DMSO groups, respectively, with 14.86% (11/74) and 30.56% (11/39) of patients reporting at least one AE, respectively ($P = 0.075$). There were no differences in serious AEs or in the severity of AEs between groups. In the HA/CS group, treatment-related adverse events were seen in 1 of 74 patients (1.35%) with 1 event, compared with 8 of 36 patients (22.22%) with 12 events in the DMSO group ($P = 0.001$). The most common treatment-related AEs were related to renal and urinary disorders, in particular bladder irritation or pain, cystitis, dysuria, and strangury (Table 3). Lastly, it is important to note that 5.56% (2/36) of patients in the DMSO group discontinued treatment due to inefficacy compared with 2.70% (2/74) in the HA/CS group ($P = 0.596$).

Economic analyses (Table 4) showed that when direct healthcare costs are considered, the ICER of HA/CS versus DMSO falls between 3735€/QALY (optimistic assumption) and 8003€/QALY (pessimistic assumption). Moreover, DMSO is dominated by HA/CS when both direct and indirect costs are considered (overall costs are 18996.75€ in DMSO vs. 17865.38€ in the HA/CS group), meaning that it appears

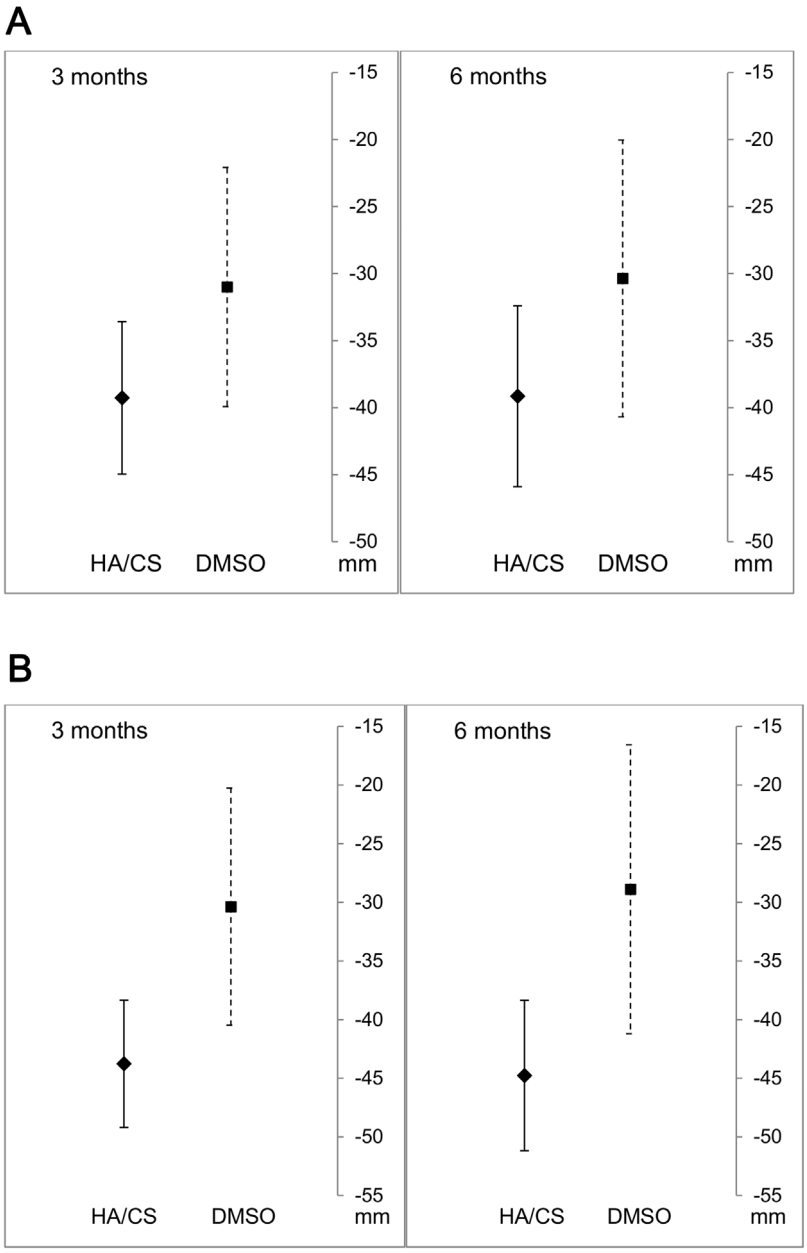

FIGURE 2 (A) Mean change (95%CI) in pain VAS scores (0–100 mm) from baseline to 3 and 6 months (ITT population, $n = 110$). (B) Mean change (95%CI) in pain VAS scores (0–100 mm) from baseline to 3 and 6 months (PP population, $n = 88$). CI, confidence interval; ITT, intent to treat; PP, per protocol; VAS, visual analog scale

to be both less effective and more expensive than the innovative treatment.

4 | DISCUSSION

Improving the integrity of the urothelium through GAG substitution therapy is a valid approach for treatment of BPS/IC. Therapy with HA/CS has shown encouraging response rates[11,12,18,26] as highlighted in a recent meta-analysis,[27] and has received a high recommendation rating, according to the Centre for Evidence-Based Medicine[28] and EAU guidelines.[29] The aim of this study was to compare the efficacy and safety of HA/CS with DMSO.

In the ITT population, VAS pain reduction was significant in both groups. While numerically greater with HA/CS at both the end of treatment (59.93% vs. 48.00%, respectively) or after 3 months without any treatment (59.74% vs. 47.01%, respectively), the differences between groups in VAS pain reduction did not reach statistical significance. Of note, however, the efficacy results in the PP population, eliminating a possible confounding effect of any grade A/B recommended treatment for BPS/IC, showed a statistically

TABLE 2 Mean change from baseline after 3 and 6 months and mean difference between treatment groups in secondary endpoints (ITT population) in female patients with bladder pain syndrome/interstitial cystitis

Mean ± SD (95%CI)		HA/CS	DMSO	HA/CS–DMSO
ICSI	*N*	73	36	
	3 m	−6.33 ± 5.55*	−5.61 ± 5.95*	−0.91
		(−7.62; −5.03)	(−7.63; −3.60)	(−2.92; 1.09)
				$P = 0.3666$
	6 m	−6.14 ± 5.67*	−5.42 ± 6.11*	−0.92
		(−7.46; −4.81)	(−7.49; −3.35)	(−2.98; 1.15)
				$P = 0.3807$
ICPI	*N*	73	36	
	3 m	−6.68 ± 5.45*	−5.64 ± 5.96*	−0.66
		(−7.96; −5.41)	(−7.65; −3.62)	(−2.76; 1.45)
				$P = 0.5373$
	6 m	−6.47 ± 5.46*	−5.86 ± 6.06*	−0.19
		(−7.74; −5.19)	(−7.91; −3.81)	(−2.30; 1.91)
				$P = 0.8555$
PUF	*N*	73	36	
	3 m	−10.18 ± 9.23*	−8.94 ± 9.42*	−1.31
		(−12.33; −8.02)	(−12.13; −5.76)	(−4.77; 2.16)
				$P = 0.4562$
	6 m	−10.01 ± 9.25*	−9.75 ± 9.55*	−0.33
		(−12.17; −7.85)	(−12.98; −6.52)	(−3.85; 3.18)
				$P = 0.8515$
EQ index	*N*	73	35	
	3 m	+0.39 ± 0.48*	+0.39 ± 0.43*	−0.005
		(0.28; 0.50)	(0.24; 0.53)	(−0.15; 0.14)
				$P = 0.9443$
	6 m	+0.39 ± 0.49*	+0.31 ± 0.64*	0.08
		(0.28; 0.51)	(0.09; 0.52)	(−0.10; 0.26)
				$P = 0.3753$
EQ VAS	*N*	72	35	
	3 m	+9.79 ± 33.47*	+3.54 ± 31.43*	+2.17
		(−70.00; 18.00)	(−80.00; 0.00)	(−9.29; 13.63)
				$P = 0.7082$
	6 m	+13.56 ± 32.79*	+5.74 ± 35.21*	+3.12
		(−76.00; 19.50)	(−80.00; 5.00)	(−7.97; 14.20)
				$P = 0.5785$
Urinary frequency	*N*	59	31	
	3 m	−1.99 ± 3.77*	−2.38 ± 3.99*	−0.49
		(−2.97; −1.01)	(−3.85; −0.92)	(−1.90; 0.92)
				$P = 0.4927$
Bladder capacity (mL)	*N*	44	25	
	3 m	+38.07 ± 71.53**	+20.60 ± 61.62**	+30.04
		(16.33; 59.82)	(−4.84; 46.03)	(−1.88; 61.94)
				$P = 0.0647$

CI, confidence interval; CS, chondroitin sulfate; DMSO, dimethyl sulfoxide; EQ Index, EuroQol Index; EQ VAS, EuroQol Visual Analog Scale; HA, hyaluronic acid; ICPI, O'Leary-Sant Interstitial Cystitis Problem Index; ICSI, O'Leary-Sant Interstitial Cystitis Symptom Index; ITT, intent to treat; m, months; N, number; PP, per protocol; PUF, Pelvic Pain and Urgency/Frequency Symptom Scale; SD, standard deviation.
P values obtained using ANCOVA, $*P < 0.0001$ and $**P = 0.0004$ versus baseline.

TABLE 3 Summary of adverse events in the ITT population

	HA/CS ($N = 74$)		DMSO ($N = 36$)		
	Events	***n*[a] (%)**	**Events**	***n*[a] (%)**	***P*-value[b]**
AEs	52	11 (14.86)	39	11 (30.56)	0.075
Treatment-related AEs	1	1 (1.35)	12	8 (22.22)	0.001
Instillation site odor	0	0 (0.0)	1	1 (2.78)	0.327
Renal and urinary disorders	1	1 (1.35)	11	8 (22.22)	0.001
Bladder irritation	0	0 (0.0)	1	1 (2.78)	0.327
Bladder pain	1	1 (1.35)	1	1 (2.78)	0.550
Cystitis	0	0 (0.0)	4	2 (5.56)	0.105
Dysuria	0	0 (0.0)	4	4 (11.11)	0.010
Strangury	0	0 (0.0)	1	1 (2.78)	0.327
AEs leading to withdrawal	1	1 (1.35)	2	2 (5.56)	0.249
Serious AEs	0	0 (0.0)	0	0 (0.0)	–

AEs, adverse events; CS, chondroitin sulfate; DMSO, dimethyl sulfoxide; HA, hyaluronic acid; ITT, intent to treat.
[a]Number of patients experiencing at least one AE during the study period. One patient could experience more than one adverse event.
[b]Fisher's exact test.

significant difference in VAS pain reduction in favor of HA/CS ($P = 0.0186$).

The proportion of responders (50% VAS reduction from baseline) was 26.48% after 3 months and 14.31% after 6 months higher with HA/CS in the ITT population. In the PP population, this result was statistically significant at 3 months ($P = 0.025$), with a 48.60% higher proportion of responders with HA/CS, which became 29.82% after 6 months.

The efficacy of both HA/CS and DMSO is suggested based on the CSI/ICPI, PUF, and EQ-5D questionnaires alongside improvements in urination frequency and bladder capacity, although no significant differences between treatments were seen.

The percentage of AEs was roughly twice that with DMSO and there were significantly fewer treatment-related AEs and fewer discontinuations for lack of efficacy with HA/CS. These results suggest that HA/CS has a more favorable safety profile than DMSO, although further studies are needed.

The results of the present study support the reduction in pain scores and urination frequency, as well as improvements in bladder capacity and quality of life, observed in previous smaller studies.[11,12,18,26] In addition, this study showed sustained pain reductions and improvement in all secondary endpoints at 3 months after treatment ended, suggesting that improvements are maintained over the long-term. It would thus be of interest to further increase the follow-up time.

Finally, economic evaluation showed an ICER (i.e., the cost of an additional life year in perfect health gained by HA/CS over DMSO) between 3735 and 8003€/QALY, which is well below commonly used thresholds indicating societies' willingness to pay per QALY gained. Moreover, when a

TABLE 4 Cost-effectiveness analyses results (ITT population)

						ICER* = €/*QALY	
			DMSO	**HA/CS**	**Δ**	***Optimistic*[a]**	***Pessimistic*[b]**
Costs	Direct		398.37€	538.43€	+140.06€	*3735.04€/QALY*	*8003.67€/QALY*
	Direct and indirect		18996.75€	17865.38€	−1131.37€	DMSO dominated[c]	DMSO dominated[c]
Utility	Baseline		0.26	0.25			
	3 months		0.66	0.64			
	6 months		0.58	0.65			
QALY		*Optimistic*[a]	0.5600	0.5975	0.0375		
		Pessimistic[b]	0.4800	0.4975	0.0175		

Direct costs include the cost of the visits (GP and specialists), instrumental and laboratory tests and additional pharmacological therapies assumed because of concomitant adverse events. Indirect costs include the cost of the productivity loss, informal care, domestic assistance, travels and accommodation.
Δ, HA/CS-DMSO; QALY, Quality-Adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio (ΔCosts/ ΔQALY); ITT, intent to treat.
[a]Scenario assuming the utility values measured at 6 months to hold until 12 months.
[b]Scenario assuming the utility values to go back at the level observed at baseline from month 6–12 months.
[c]DMSO is both less effective and more expensive than HA/CS when indirect costs are included in the analysis.

broader societal perspective is taken into account instead of the NHS one, DMSO is dominated by HA/CS. The limited amount of data available at the end of the study period reduces the validity of this analysis; however, the attempt to collect resource consumption and costs alongside clinical trials should be encouraged in the future in order to provide additional information that allows the identification of the cost-effectiveness profile of health technologies.

One possible limitation of the present study is that it was not placebo-controlled. However, the main objective was to compare the efficacy of HA/CS to currently approved therapy, namely DMSO, and it was, nonetheless, randomized.

5 | CONCLUSIONS

In conclusion, the present trial provides further support to previous data showing sustained improvement in symptoms following treatment of BPS/IC with HA/CS, in addition to subjective improvement in the quality of life and a more favorable safety profile compared with DMSO.

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POTENTIAL CONFLICTS OF INTEREST

Silvia Trevisan and Valeria Frangione are employees of IBSA Institut Biochimique SA. All other authors have no conflicts of interest that are directly relevant to the content of this article.

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SUPPORTING INFORMATION

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