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Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee

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Summary

Objective: Non-animal stabilized hyaluronic acid (NASHA) is a novel hyaluronan (HA) preparation with a 4-week intra-articular half-life. This study compared the efficacy of a single injection of NASHA with placebo in patients with osteoarthritis (OA) of the knee.

Design: This was a 26-week randomized, double-blind, multicenter study of a single intra-articular knee injection with either NASHA or placebo (saline). Assessments included the Western Ontario McMasters Universities osteoarthritis index (WOMAC, Likert Scale) and patients' overall global disease status. A positive response was defined as a reduction in WOMAC pain score for the study knee of 40% from baseline with a minimum improvement of ≥ 5 points.

Results: A total of 346 (NASHA 172; placebo 174) patients were treated. WOMAC scores and quality of life were improved in both the NASHA and placebo groups. For the overall population, there were no statistically significant between-group differences in response rates for any efficacy parameters. In patients with OA confined to the knee ($N = 216$), a greater response to NASHA than placebo was observed at week 6 ($P = 0.025$). There were few treatment-related events.

Conclusions: NASHA was not superior to placebo for the primary efficacy analysis. However, these data may be confounded by the inclusion of patients with OA at other sites, as significant benefits over placebo were found among patients with OA confined to the knee. Future trials of OA that examine a local therapy might need to consider restricting the study population to those patients having OA of only the signal joint.

Key words: Hyaluronic acid, Osteoarthritis, Knee, Intra-articular, Randomized controlled trial.

Introduction

Osteoarthritis (OA) is the most common form of arthritis[1,2], and is often debilitating[3,4]. OA has become the most costly form of arthritis[5], collectively accounting for up to 1–2.5% of the gross national product of Western nations[2]. The prevalence of OA increases with age, with more than 60% of those over 60 years old likely to have some cartilage abnormality in a major joint[6].

To date, management strategies for OA have been directed at symptoms, primarily pain. The focus has been on non-pharmacologic measures with analgesics and anti-inflammatory drugs[7,8]. Intra-articular corticosteroids and hyaluronic acid (hyaluronan; HA) therapy have supplemented this approach.

HA is a widely distributed, linear glycosaminoglycan constituent of cartilage, synovial fluid, skin and aqueous humor, identical in all forms of biological life. HA lubricates synovial joints, assists with shock-absorption and structure-stabilization and has direct effects on synovial cell function. Furthermore, *in vitro* data indicate that HA may slow chondrocyte apoptosis in OA by binding CD44 and ICAM-1 receptors, thereby regulating the processes of cartilage matrix degradation[9]. Synovial fluid from arthritic joints contains lower concentrations of HA than that from normal joints[10]. As the elasticity and viscosity of synovial fluid are

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directly proportional to HA content and integrity, intra-articular injection of HA is a rational approach to the treatment of OA. Use of HA in human arthritic knees was first investigated in the 1970s[10] with efficacy and safety subsequently demonstrated in knees and other joints in several studies[11–15]. Multiple injections of most HA preparations are required to achieve efficacy; perhaps due to a short residence time in the joint[12]. Most currently used HA preparations are derived from rooster-comb tissue and, although purification processes have improved in recent years, there remains at least a theoretical risk of impurities such as proteins, viruses or other materials of animal origin.

Some adverse effects of injected HA may be attributable to impurities of biological origin. Non-animal stabilized hyaluronic acid (NASHA) is synthesized by Streptococci and is readily purified further—thus the risk of contamination with materials of animal origin is minimal. The stabilization process (carefully controlled cross-linking of HA) creates a somewhat viscous gel with increased density of HA, without changing the polyanionic character of the polysaccharide chain thus retaining its biocompatibility[16]. The resulting prolonged residence time in the joint may allow reduced number of injections to achieve long-term efficacy in the treatment of OA.

This study was performed to investigate the safety and efficacy of single-injection NASHA compared with placebo in patients with OA of the knee.

Methods

This randomized, double-blind, multicenter study was conducted in accordance with the Declaration of Helsinki and the World Medical Assembly and its amendments. The study protocol and subsequent protocol amendments were reviewed and approved by local Ethics Committees at the investigative sites. Written informed consent was obtained and the study performed in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice.

STUDY POPULATION

Patients were recruited from 18 centers across the USA ($N = 7$), Canada ($N = 6$) and Sweden ($N = 5$). Inclusion criteria were: OA of the knee as defined by the American College of Rheumatology criteria[17] that was refractory to non-pharmacologic therapies; a Western Ontario McMasters Universities osteoarthritis index (WOMAC; Likert scale) pain subscale score (range 0–20) of at least 7 in one knee and no greater than 15 in either knee; and significant knee pain in the signal knee for the majority of the preceding 3 months (patients had to be normally active and able to walk 50 m, unaided). Exclusion criteria included: isolated patellofemoral OA; use of systemic steroids, glucosamine or chondroitin within the past 3 months; intra-articular injection into the knee of corticosteroids in the past 3 months or intra-articular HA within the last 9 months; treatment with oral or topical NSAIDs during the previous week; use of topical non-NSAIDs within the previous 3 days; arthroscopy or other surgical procedure within the last 12 months and anticoagulant treatment (except acetylsalicylic acid, $\leq$325 mg/day). Patients were also excluded if they presented with a systemic active inflammatory condition or infection, septic knee arthritis within the previous 3 months, significant venous or lymphatic stasis of the legs, active skin disease or infection at the injection site, or any other medical condition rendering the patient unsuitable for inclusion according to the investigator. Pregnant or breast-feeding women and those of childbearing potential not practicing adequate contraception were ineligible.

STUDY DESIGN

Patients fulfilling the inclusion and exclusion criteria were randomized (1:1) to either NASHA (Durolane®, Q-Med AB, Uppsala, Sweden) or saline administered intra-articularly into the study knee. The randomization list was prepared by Q-Med. Patients who had passed the eligibility check and who had completed the baseline efficacy assessments were allocated patient numbers in consecutive order. The packaging for each syringe was labeled with the appropriate patient number (according to the randomization list) prior to shipment to the study center. The treating investigator documented the IA injection in the CRF. The performance of all patient assessments by an evaluating investigator, blinded to the randomization code, ensured that the study was blinded. Additionally, patients were not informed of which treatment they received. For patients with bilateral OA, the study knee was designated the knee with the higher WOMAC pain score, or the clinically worse-affected knee (clinically, radiographically) if there was no difference in WOMAC score. The study consisted of a screening visit, a baseline visit—during which intra-articular injection was made—and follow-up visits at 2, 6, 13, and 26 weeks.

Patients randomized to NASHA received a single 3 ml injection. The study product contained HA 60 mg in buffered sodium chloride, 0.9% (pH 7). The placebo contained the identical buffered sodium chloride vehicle used in the study product. Both NASHA and placebo were supplied in identical 3 ml syringes. The recommended needle size for injection was 18–22 G.

Acetaminophen (paracetamol; maximum daily dose, 4 g) was permitted as rescue medication except during the 48-h period prior to each study visit. Use of rescue medication was recorded in a patient diary.

Blinding of the evaluating investigator was achieved by ensuring that the treating clinician who administered the injection was not involved in conducting the clinical evaluations. As an assessment of masking, both the evaluating investigator and patient were asked to hypothesize at baseline (immediately after treatment) and at the 26-week visit whether NASHA or saline had been injected.

CLINICAL ASSESSMENTS

The WOMAC pain subscale was assessed at the screening visit. The screening visit included collection of demographic information (Table I). Information on OA of other joints was historical and confirmed by physical examination. Clinical assessments were subsequently performed at baseline and at follow-up at each regularly scheduled visit.

A responder (positive response to treatment)—the primary endpoint—was defined as a reduction in the WOMAC pain score of at least 40% with an absolute improvement of at least 5 points compared with baseline for the study knee at the final visit[18]. Secondary outcome measures included the WOMAC stiffness score, WOMAC physical function score, and patient assessment of global disease status on a 5-point scale. The 36-item short form health survey (SF-36) was completed as a quality-of-life

Table I
Baseline characteristics of the study population

Variable	NASHA ($N = 172$)	Saline ($N = 174$)
Age in years [mean (range)]	62.9 (41–85)	63.3 (35–85)
Women:Men [*n* (%)]	79/93 (46:54)	111/63 (64:36)
BMI women [mean (range)]	31.3 (21.4–61.1)	29.8 (18.4–54.6)
BMI men [mean (range)]	29.5 (21.7–44.4)	29.0 (22.2–41.4)
Duration of OA in years [mean (range)]	5.0 (0.0–45.5)	6.5 (0.0–50.5)
Kellgren Lawrence grade [*n* (%)]		
Grade 2	40 (23)	39 (22)
Grade 3	92 (53)	90 (52)
Grade 4	40 (23)	45 (26)
Previous treatment [*n* (%)]		
NSAIDs or analgesics	146 (85)	142 (82)
Glucosamine	50 (29)	51 (29)
Intra-articular depocorticosteroids	62 (36)	56 (32)
Intra-articular hyaluronate	37 (22)	34 (20)
Previous knee surgery [*n* (%)]†	63 (37)	57 (33)
Joint effusion [*n* (%)]†	46 (27)	74 (43)
Tenderness on palpation [*n* (%)]†	110 (64)	102 (59)
WOMAC pain [mean (range)]†	9.90 (6–15)	10.42 (7–15)
WOMAC pain of non-study knee [mean (range)]	4.84 (0–14)	4.63 (0–15)
WOMAC stiffness [mean (range)]	3.91 (0–8)	4.30 (0–7)
WOMAC physical function [mean (range)]	30.70 (5–61)	32.16 (2–59)
Patient's assessment, global status [mean (range)]	3.23 (1–5)	3.17 (1–5)
SF-36, physical component summary [mean (range)]	33.54 (15.1–54.5)	32.91 (14.1–53.2)
SF-36, mental component summary [mean (range)]	55.55 (25.8–72.8)	55.92 (27.2–70.9)

NASHA = non-animal stabilized hyaluronate; BMI = body mass index; OA = osteoarthritis; NSAIDs = non-steroidal antiinflammatory drugs; WOMAC = Western Ontario McMasters University Osteoarthritis Index; SF-36 = short form 36.

†Of study (signal) knee.

instrument by the patient at baseline and at 13 and 26 weeks.

Adverse events were both reported by the patient and observed by the investigator. The occurrence of all adverse events (AEs) was recorded, including a description of the event, duration, causality, grading (serious/non-serious), intensity, action taken and outcome.

STATISTICAL METHODS

The sample size was based on testing for a difference between the two treatment groups at the 5% significance level (80% power), assuming response rates of 35% to Durolane and 20% to placebo. This resulted in a sample size of 138 patients in each group, 276 in total.

Statistical analyses were based on an intention-to-treat (ITT) principle. The null hypothesis of no difference in responder rate between the two treatments at 26 weeks was analyzed using logistic regression approach with treatment as the main effect. The impact of relevant covariates was explored by their inclusion in the main effect model. The ITT analysis was performed using the last observed data. For patients who were prematurely withdrawn from the study the missing data after dropout were replaced with the last observed value according to the principle of last observation carried forward (LOCF). There were no baseline differences between those completing the study and those not completing the study in demographic or clinical characteristics.

The Wilcoxon rank sum test was used to compare the treatment groups with respect to change from baseline in WOMAC pain, WOMAC stiffness and WOMAC physical function scores. Comparison of the groups with respect to change in patient assessment of global status from baseline was made after adjustment for the WOMAC pain score in the untreated knee. This was made by performing ordinal logistic regression, using the proportional odds model. Analysis of the SF-36 involved calculating the Physical Component Summary (PCS) and Mental Component Summary (MCS) for each patient. Wilcoxon rank sum test was used to test the change from baseline between the treatment groups. There was no adjustment for multiple comparisons in the secondary analyses.

Results

PATIENT CHARACTERISTICS

A total of 454 patients were screened, of whom 347 (76%) were randomized to treatment and hence included in the safety analysis (Fig. 1). The ITT population comprised 346 patients (172 NASHA and 174 saline recipients) and were included in the efficacy analysis. The remaining randomized patients did not receive treatment due to pain on the initial attempted needle insertion; the injection was aborted. Seventy-four patients did not complete the study (39 NASHA and 35 saline recipients), and the per protocol population comprised 232 patients (113 NASHA and 119 saline).

The demographics and baseline characteristics of the study population are recorded in Table I. Although statistical comparison was not performed, the two treatment groups appeared comparable with the following exceptions: there was a trend towards higher WOMAC pain, stiffness and physical function scores in the saline group. Also, there were more women in the saline group than the NASHA group and the incidence of joint effusion in the signal knee at screening was greater in the saline group.

EFFICACY EVALUATIONS

Overall response

The response rate with NASHA reached 29.1% by week 2, and remained at or above this level out to 26 weeks, with a maximum response rate of 36.6% occurring at 6 weeks post-treatment (Table II). However, by ITT or per protocol analysis, there was no significant difference between the number of responders between placebo and NASHA groups at 26 weeks (the primary efficacy variable). The number of responders changed little between 2 and 26 weeks for both groups, while there were no between-group

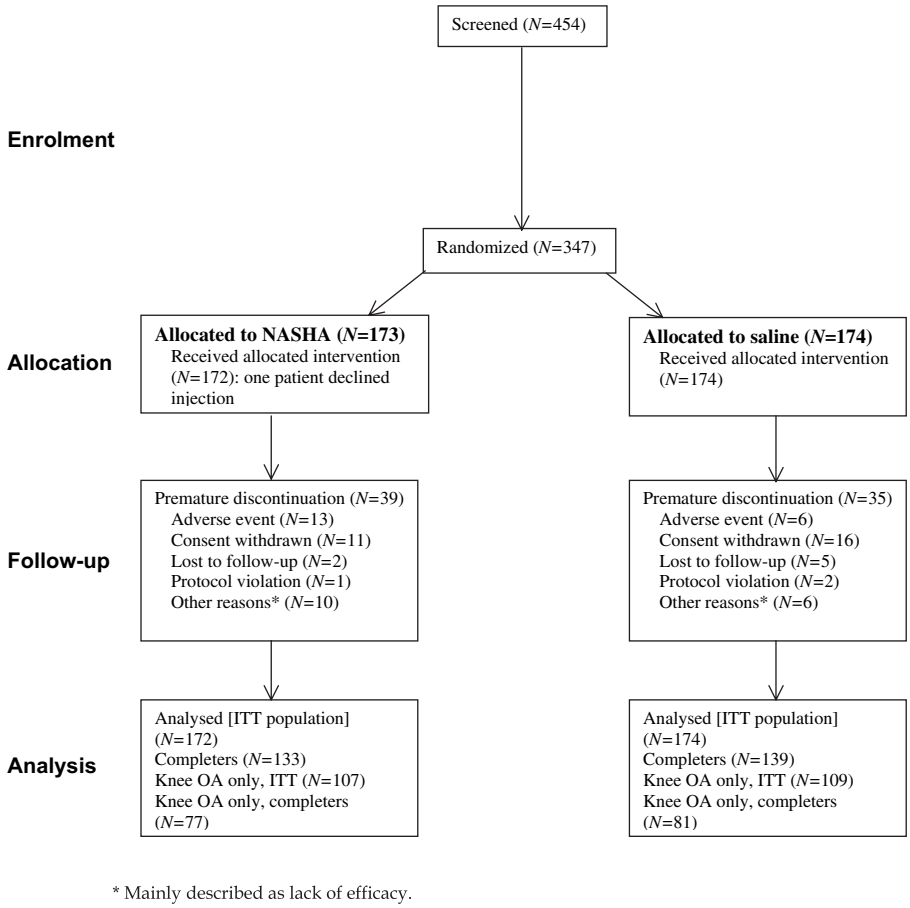

Fig. 1. Study population.

differences in response rate at any of the time-points evaluated in this study, for either the ITT or per protocol population.

Among patients who were classified as responders at 6 weeks, 59% in the NASHA group remained as responders at 26 weeks; however, this compared with 56% in the saline group. Conversely, 87% of patients in the NASHA group who were non-responders at 6 weeks remained as non-responders at the subsequent two follow-up visits; the corresponding proportion was 72% in the saline group, perhaps indicating a lower degree of fluctuation between response and non-response in the active treatment group.

Table II
Response rates in all patients and in those with OA confined to the knee

	Weeks			
	2	6	13	26
ITT				
NASHA ($N = 172$)	29.1	36.6	32.0	29.1
Placebo ($N = 174$)	36.2	29.9	35.1	32.2
Per protocol				
NASHA ($N = 113$)	32.7	42.5	38.1	36.3
Placebo ($N = 119$)	41.2	34.5	40.3	37.8
Knee only, ITT				
NASHA ($N = 107$)	33.6	42.1*	35.5	30.8
Placebo ($N = 109$)	34.9	27.5*	33.0	32.1
Knee only, per protocol				
NASHA ($N = 77$)	33.8	46.8*	39.0	36.4
Placebo ($N = 81$)	37.0	29.6*	37.0	35.6

*Statistically significant difference, NASHA vs placebo.

The WOMAC pain, stiffness and physical function scores in both groups decreased over the study period (Table III). There was no significant between-group difference in WOMAC pain score in the study knee at any follow-up time-point; small but significant differences in favor of saline were observed in WOMAC stiffness score (2 weeks and 6 months) and physical function score (2 weeks). The change from baseline in patient assessment of global status and SF-36 did not differ significantly between treatment groups at any time-point assessments.

At baseline, the majority of all patients guessed that NASHA had been administered—80% in the NASHA group compared with 71% in the placebo group. The corresponding proportions for investigators were 68% and 66%, respectively. At 26 weeks, the proportion of patients guessing NASHA was 55% in the NASHA group, compared with 44% in the saline group; for investigators, these proportions were 46% and 38%, respectively.

SUBGROUP ANALYSIS

Within the overall ITT population, 216 patients had OA confined to the knee (Fig. 1). Among this patient subgroup,

Table III

ITT analyses of WOMAC pain in the study knee, stiffness and physical function scores at each follow-up visit. Values at baseline are absolute; those at other time-points are changes from baseline. N, NASHA treatment group (N = 172); S, saline treatment group (N = 174); P-values were derived from Wilcoxon rank sum test on change in score from baseline

	Baseline			2 weeks			6 weeks			13 weeks			26 weeks		
	N	S	P	N	S	P	N	S	P	N	S	P	N	S	P
WOMAC pain															
Mean score ± SD	9.90 ± 2.2710	10.42 ± 2.28	–	−2.75 ± 3.27	−3.49 ± 3.59	0.091	−3.15 ± 3.90	−3.39 ± 3.81	0.85	−2.87 ± 3.97	−3.42 ± 4.10	0.34	−2.50 ± 4.00	−2.89 ± 4.17	0.40
Median score	0.00	10.00		−3.00	−3.00		−3.00	−3.00		−3.00	−3.00		−2.00	−2.50	
WOMAC stiffness															
Mean score ± SD	3.91 ± 1.654	4.30 ± 1.50	–	−0.48 ± 1.63	−0.99 ± 1.73	0.003	−0.87 ± 1.96	−1.03 ± 1.39	0.44	−0.71 ± 1.87	−1.05 ± 1.96	0.11	−0.47 ± 1.77	−0.82 ± 1.96	0.048
Median score	0.00	4.00		0.00	−1.00		−1.00	−1.00		−1.00	−1.00		0.00	−1.00	
WOMAC physical function															
Mean score ± SD	30.70 ± 11.00	32.16 ± 11.06	–	−6.35 ± 10.48	−8.50 ± 11.22	0.042	−7.52 ± 12.12	−8.52 ± 12.41	0.60	−6.98 ± 12.27	−8.72 ± 13.39	0.36	−5.82 ± 12.16	−7.42 ± 13.52	0.32
Median score	32.00	33.50		−5.00	−7.00		−7.00	−6.50		−6.00	−7.00		−5.00	−5.00	

21.3% recorded use of NSAIDs or analgesics until baseline compared with 38.5% in patients with OA at other sites. Mean WOMAC pain scores (study knee) for the two subgroups were 10.0 and 10.4, respectively. Mean intake of rescue medication during the first 6 weeks of the study was 7 g in patients with OA confined to the knee, compared with 24 g in those with OA at other sites.

Patients with OA confined to the knee demonstrated a greater response following NASHA treatment compared with the overall study population (Fig. 2; Table II). Accordingly, those on NASHA had a significantly greater response rate compared with saline at 6 weeks ($P < 0.025$). Eighty-two patients within this subgroup (38%) had OA localized only to the study knee with no other joints affected by OA. The response rate associated with NASHA treatment was more pronounced in these patients ($N = 38$) compared with saline recipients ($N = 44$) at 6 weeks (47.4% vs 20.1%; $P < 0.0097$).

SAFETY EVALUATION

The safety evaluation included all recruited patients ($N = 347$) (Table IV). A total of 513 AEs were reported by 227 patients (65.4%) over the study period. The majority of AEs (79.3%) were classified as mild/moderate. The number of patients reporting treatment-related AEs was 22 (12.8%) in the NASHA group, and 14 (8.0%) in the saline group. The most common treatment-related AE was arthralgia, reported by 11 patients (6.4%) and 5 patients (2.9%) in the NASHA and saline groups, respectively. The majority of treatment-related AEs (>70%) were reported within 2 days of injection in both treatment groups.

Treatment withdrawal attributable to AEs occurred in 13 and 6 patients in the two groups, respectively; 5 and 4 of these events were considered related to treatment. Of the nine treatment-related AEs leading to withdrawal, seven were knee pains, one was worsening OA pain in the knee (NASHA group), and one was knee synovitis (placebo group). Ten patients (seven in the NASHA and three in the saline group) reported serious adverse events (SAEs), all of which were assessed by the investigator as being unrelated to the study treatment.

Fig. 2. Comparison of the response rates associated with NASHA in three subgroups of the ITT population: patients with generalized OA, bilateral OA of the knee, and unilateral OA of the knee.

Table IV
Breakdown of AE occurrence and relationship to treatment over the study period

Adverse events	NASHA ($N = 173$)	Saline ($N = 174$)
	No. of patients affected (%)	No. of patients affected (%)
Non-serious	112 (64.7%)	114 (65.5%)
Treatment-related	22 (12.7%)	15 (8.0%)
Related to device only	3 (1.7%)	2 (1.1%)
Related to injection only	1 (0.6%)	2 (1.1%)
Treatment-unrelated	101 (58.3%)	109 (63.0%)
Serious	7 (4.0%)	3 (1.7%)
Treatment-related	0 (0.0%)	0 (0.0%)
Treatment-unrelated	7 (4.0%)	3 (1.7%)

The safety outcomes in the subgroup of patients with OA confined to the knee (216 patients) were similar to those for the overall population. In the subgroup, a total of 290 AEs were reported among 62.6% of the patients. Treatment-related AEs were reported by 12 patients (11.2%) in the NASHA group, compared with 6 (5.5%) in the saline group. As in the overall population, arthralgia was the most common AE.

Discussion

This trial is the first placebo-controlled investigation of a single injection of NASHA for OA of the knee. There was a favorable reduction in pain with NASHA that began by 2 weeks and persisted throughout the 26-week protocol. However, for the overall population there was no between-group difference in the response rate at any time-point.

Despite the failure to achieve a between-group difference in the primary efficacy variable, there are important messages within our data. In the subset analysis, it appears that there is potential interference in the evaluation from symptomatic OA at other sites. If one examines those with OA confined to one or both knees, there was a difference between the NASHA and placebo study groups at 6 weeks (42.1% vs 27.5%; $P = 0.025$). In addition, a higher NASHA-associated response rate was obtained in patients with OA confined to the knee compared with the overall ITT population at all time-points (Fig. 2). The subgroup with OA restricted to the signal knee differed in that there were fewer NSAID/analgesic users at screening—correspondingly, the use of rescue medication was considerably lower in this group than in patients with generalized OA. It is possible that the ability to measure the efficacy of a local intra-articular agent was hindered by the lack of a generalized effect (e.g., as might be expected with an oral medication).

Although the subgroup of patients with OA confined to the knee is likely to reflect more closely the true treatment effect with NASHA, it must be borne in mind that within that group there was a potential confounding factor. One hundred and thirty-four patients (62%) presented with bilateral knee OA, which, owing to the difficulty of identifying the exact source of pain, could have masked the treatment effect of NASHA. This notion is supported by the observation that the greatest NASHA-associated response rate was observed in the subgroup of 82 patients who presented with unilateral OA (Fig. 2). In this comparatively homogeneous patient population, the difference in responder rate between NASHA and saline was even more pronounced at 6 weeks, although results for this group need to be interpreted with caution owing to the small number of patients (less than one-third of the sample size calculated for the original comparison). In addition, there was no adjustment for multiple comparisons in this analysis.

The present study tested a single injection. The logic for the single injection was based on the proposed benefit of a long intra-articular half-life of NASHA (4 weeks) in knee joints of healthy volunteers[19]. The long residence half-life is attributable to the stabilized network of HA molecules within NASHA[16]. HA molecules within this network (gel) are unable to move freely and therefore not readily available to be degraded by the synovial cells that degrade unmodified HA; i.e., these cells are only able to engulf free HA molecules.

Several intra-articular HAs have been shown to be beneficial for OA of the knee[14,20,21]. However, unlike NASHA these HAs have required 3–5 weekly injections, which may be due to more rapid degradation following injection into the joint[12]. Animal studies have demonstrated that unmodified HA has a half-life of 24 h or less[22–26]. One HA (Hylan G-F 20) has two HA components, one with a half-life of 1.5 days and the other is extensively cross-linked with a half-life of 8.8 days (present in a 4:1 ratio). The half-life of Hylan G-F 20 is shorter and the total dose of HA is less than with NASHA[27].

The next important finding is related to the timing of clinical effect. The duration of response in the present study is consistent with the half-life of NASHA. Peak efficacy with NASHA occurred at 6 weeks, by which time approximately one-third of the injected material may be expected to remain in the joint in accordance with its 4-week half-life[19]. Assuming that NASHA is effective in the majority of patients for between 6 and 13 weeks post-treatment, re-injection around this time could and probably should be considered. Such an injection schedule would be a significant advance compared with previously available hyaluronic acid preparations, which require weekly injections for a period of 3–5 weeks. It should also be borne in mind that in the present study a prolonged response to 26 weeks was apparent in the majority of patients who were responders at 6 weeks, raising the possibility that re-injection could be delayed to 26 weeks in some patients. Although a prolonged response was also evident in the placebo group, it is our opinion that this finding is consistent with the notion that the study was confounded, possibly by the inclusion of subjects with generalized OA.

Blinding was carefully monitored. The results of examining the patient's awareness of receiving the NASHA or the placebo were consistent with effective blinding of evaluating investigators and patients, as well as the broadly similar efficacy in the two groups.

Treatment-related AEs (mainly arthralgia) occurred with similar frequency in the NASHA and saline groups. The favorable AE profile for NASHA demonstrated in this study is consistent with previously reported safety and tolerability for NASHA from its alternative applications (cosmetic surgery as well as treatment of vesicoureteral reflux and stress urinary incontinence)[11,28]. Presently available HA preparations are derived from rooster combs. Although the HA is highly purified, there remain some potential concerns regarding allergy to chicken products and, possibly, presence of viruses or other animal-derived infectious agents. Since NASHA is produced entirely in a laboratory environment using non-animal sources, the risk of contamination with allergens or infectious agents of animal origin is minimal (theoretically zero). No immune reactions have

been reported with the NASHA, whereas there have been reported reactions to the animal derived HAs including local inflammation at the injection site, anaphylactoid reactions, pseudoseptic reactions and granuloma formation[29–31].

In conclusion, although NASHA failed to demonstrate statistical benefit over placebo, NASHA was found to be superior to placebo in the subset of patients with OA isolated to the signal knee; this superiority was present at 6 weeks, consistent with the half-life of the agent. Thus, treatment with NASHA may require injections at intervals of 6–13 weeks, compared with 1 week for previously available HA preparations. Additional studies are needed to establish whether a defined population with OA of the knee will demonstrate a benefit in response to intra-articular NASHA and to establish the optimal approach to re-injection of this agent and other HA preparations.

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