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## The Knee



## Safety and efficacy of intra-articular injections of a combination of hyaluronic acid and mannitol (HAnOX-M) in patients with symptomatic knee osteoarthritis

### Results of a double-blind, controlled, multicenter, randomized trial

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## ABSTRACT

**Background:** To compare both safety and efficacy of a novel intra-articular viscosupplement made of intermediate molecular weight (MW) hyaluronic acid (HA) mixed with high concentration of mannitol with a marketed high MW HA, in patients with knee osteoarthritis (OA).

**Methods:** Patients with symptomatic knee OA, with radiological OARSI grades 1 to 3, were enrolled in a controlled, double-blind, parallel-group, non-inferiority trial. They were randomized to receive three intra-articular injections, at weekly intervals, of either HAnOX-M made of a combination of HA (MW one to 1.5 MDa, 31 mg/2 ml) and mannitol (70 mg/2 ml) or Bio-HA (MW 2.3 to 3.6 MDa, 20 mg/2 ml). The primary outcome was six-month change in the WOMAC pain subscale (0 to 20). Sample size was calculated according to a non-inferiority margin of 1.35. Secondary endpoints included six-month change in function and walking pain, analgesic consumption and safety.

**Results:** The intention-to-treat (ITT) and per-protocol (PP) populations consisted of 205 and 171 patients. HAnOX-M and Bio-HA groups did not differ statistically at baseline. The primary analysis was conducted in the PP population, then in the ITT population. The average WOMAC pain score at baseline was 9.5 in both groups. Mean (SD) variations in WOMAC pain score were  $-4.4$  (3.8) and  $-4.5$  (4.3) mm, for HAnOX and Bio-HA respectively, satisfying the claim for non-inferiority. Similar results were obtained for all other secondary endpoints.

**Conclusion:** Treatment with of HAnOX-M is effective to alleviate knee OA symptoms and to improve joint function over six months, with similar safety than conventional HA viscosupplement.

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## 1. Introduction

Current recommendations for the treatment of knee osteoarthritis (OA) include a combination of non-pharmacological and pharmacological modalities [1–4]. Among them, viscosupplementation is a therapeutic modality consisting in intra-articular (IA) injection(s) of hyaluronic acid (HA) or its derivatives [5]. The aim of viscosupplementation is to reduce joint pain and improve function, likely by restoring the physiological joint homeostasis [5,6]. In vitro and in vivo studies have also

suggested that HA could have protective effects on cartilage [7–12]. Viscosupplementation is a widely used therapy in knee OA patients not adequately relieved with conventional therapy and a recent meta-analysis has ranked it as one of the most effective treatments for this condition [13]. However clinical trials showed controversial results regarding the effectiveness of viscosupplementation [14–17]. There are several possible explanations for these conflicting results. Discrepancies may originate from differences in study design, outcome measures, but also differences of efficacy between the studied products, that widely vary in concentration, molecular weight and molecular cross-linkage [18]. Recommended dosing regimens are ranging from one to five injections, at weekly intervals, according to the assumed time of intra-articular residence of the device into the joint. Indeed, when injected into the joint, HA is rapidly degraded, limiting the time of intra-

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articular residence to, at best a few weeks [19,20] for the solutions of cross-linked HA and at worst a few days for linear molecules [21]. Among the multiple mechanisms contributing to HA degradation, reactive oxygen free radicals play a key role [22,23]. Then OA is a degenerative joint disease of multifactorial origin in the pathogenesis of which reactive oxygen species (ROS) play a deleterious effect [24,25]. Furthermore ROS are directly involved in the mechanisms of HA degradation in addition to their role on the extracellular matrix breakdown. Optimizing clinical efficacy of viscosupplementation by decreasing the in situ HA degradation, is a challenging research approach.

HAnOX-M is a new viscosupplement, that combines sodium hyaluronate with a high concentration (3.5%) of mannitol, a polyol known for its anti-oxidant properties by scavenging radical oxygen species (ROS). The in vitro effectiveness of mannitol to protect HA against ROS-mediated depolymerization has been widely demonstrated [23, 26,27] suggesting that addition of mannitol to HA might slightly increase the intra-articular residence time of the latter and consequently might allow a more rapid onset of action than HA alone. Nevertheless the IA half-life of mannitol, is probably much too short (<4 h after intravenous or after administration by inhalation) to protect HA from degradation for several weeks and consequently to increase its duration of efficacy. Hastening the onset of action of hyaluronic acid would be a therapeutic advance, since the delayed action (up to eight weeks) of IA HA, compared to IA steroids, is one of the main concerns about viscosupplementation [28].

The aim of the survey was to assess the efficacy of three weekly injection of HAnOX-M in patients with symptomatic knee OA, by comparing both its efficacy and safety to that of a proved effective and well-tolerated HA viscosupplement [29,30].

## 2. Patients and methods

### 2.1. Regulatory

The study was carried out in compliance with the principles of Good Clinical Practice (GCP), and the Declaration of Helsinki concerning medical research in humans and the country-specific regulations. Before enrolment, patients were required to sign an informed consent form and were free to withdraw at any time for any reason. The patient informed consent form and the protocol, that complied with the requirements of the International Conference on Harmonization (ICH), were reviewed and approved by the Ethics Committee of Lyon Sud-Est IV.

### 2.2. Study design

This study was a prospective, double-blind, randomized, multicenter, parallel-group, trial, conducted in 26 centers in France, between October 2012 and April 2014 (study number EudraCT 2012-A00570-43). It aimed to compare the efficacy and safety of HAnOX-M with that of Bio-HA, according to a non-inferiority design. The choice of a non-inferiority trial has been imposed by the French Health Authority (HAS) in order to request the reimbursement on the basis of same prices as the currently marketed viscosupplements (price maintenance for reimbursement in France: 100 to 120€).

Males and females, aged 40 to 85 years, fulfilling the American College of Rheumatology criteria for knee osteoarthritis [31] could be enrolled if they had failed to respond or were intolerant to analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs), or weak opioids. To fulfill the inclusion criteria patients had also to self-assess their walking pain from three to eight on an 11 point Likert scale (11 pt.-LS: 0 to 10) at the screening visit "Day(D)0". Tibio-femoral OA must be evidenced by bilateral knee radiographs, performed within the three previous months and including the following incidences: standing postero-anterior view, Lyon-Schuss view, lateral view and skyline incidence of the patella. To be eligible, the OARSI radiological score

[32] for tibio-femoral joint space narrowing must range from one to three. Patients with tibial or femoral bone attrition were not eligible. Only the most painful joint (target knee) was treated and assessed, but patients with bilateral knee OA could be included, only if walking pain of the contra lateral knee was <3. The main exclusion criteria were: OA flare with KOFUS score >7 [33], lack of tibio-femoral joint space narrowing, tibial plateau or femoral condyle bony attrition, isolated patella-femoral OA, symptomatic hip OA or any other active inflammatory or microcrystal rheumatic disease, excessive ( $\geq 8^\circ$ ) varus or valgus knee malalignment, viscosupplementation in the target knee within the prior nine months, systemic/IA corticosteroids within the prior three months. If female and of child-bearing potential, a negative serum pregnancy test at screening and the use of contraception throughout the study were needed.

At the screening visit, after written informed consent was signed, demographic data, patient characteristics, medical history, prior treatments for knee OA and all other medications were collected. Randomization was carried out at the screening visit (Day 0) using a computer-generated randomization scheme. Patients were randomized to one of the following treatment groups: HAnOX-M or Bio-HA in a 1:1 ratio by blocks of four treatments, balanced 2:2.

During all the study duration, the physicians who performed evaluations and the patients remained blinded to the treatment. Unblinded physicians achieved intra-articular injections of HAnOX-M or Bio-HA, in order to maintain double-blinding. Both treatments were supplied in two milliliter syringes and both volume and viscosity of the two treatments were indistinguishable.

### 2.3. Treatments under study

The treatment to be studied was HAnOX-M (HAPpyVisc®, LABRHA SAS, Lyon, France), a solution made of an intermediate MW (one to 1.5 MDa) HA of non-animal origin, in a concentration of 1.55 mg/ml, combined with mannitol, concentrated at 35 mg/ml. The comparator was Bio-HA (Euflexxa®, Ferring Pharmaceuticals, Inc., Parsippany, USA), solution of a high MW (2.4 to 3.6 MDa) of non-animal origin, in a 10 mg/ml concentration. Both viscosupplements were supplied in two milliliter syringes containing two milliliters of HA solution and were administered, one week apart, three consecutive weeks, into the target knee through a 18- to 21-gauge needle, after careful removal of synovial fluid effusion if present, by an experienced physician (orthopedic surgeon or rheumatologist), who was unblinded to treatment and different from the clinical evaluator. The patient and the clinical evaluator were both blinded to treatment throughout the follow-up.

### 2.4. Concomitant treatments

The following concomitant medications for knee OA were allowed: paracetamol (up to 4 g/day), weak opioids (tramadol, codein), analgesic doses of ibuprofen (daily dose  $\leq$  800 mg) and naproxen (daily dose < 500 mg), topical NSAIDs, symptomatic slow acting drugs for OA (glucosamine, chondroitin sulfate, diacerhein, or avocado/soya unsaponifiables) if started at least two months before screening and not substantially altered during the study. Intra-articular corticosteroids were permitted only for other joints than the target knee. NSAIDs at anti-inflammatory doses, strong opioids, systemic corticosteroids, IA corticosteroids and viscosupplements into the target knee were prohibited throughout the follow-up. Patients were asked to discontinue analgesic therapy 48 h before each evaluation visit.

### 2.5. Efficacy outcome measures

Patients were assessed by the clinical evaluator, blinded to treatment, at D0, at the time of each injection on Weeks (W) one, two and three, then at the follow-up visits at W12 and W26. The screening visit and the first injection (W1) could be carried out the same day if

NSAIDs wash-out was not necessary and if the patient and the two physicians were all available. The primary efficacy outcome was the change, between W1 and the last follow-up visit W26, in the WOMAC A pain sub-score [34], patients scoring their pain using a five point Likert scale (five pt.-LS: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme) for each of the five items (total score ranging 0 to 20). Secondary efficacy outcomes were the change throughout the follow-up of the following criteria: walking pain on a 11 pt.-LS (0 to 10), patient global assessment on a 11 pt.-LS (PGA:0 to 10), WOMAC function sub-score (0 to 68) and WOMAC total score (0 to 96) on five pt.-LS for each item. WOMAC A, walking pain, PGA were assessed at weeks one, two, three, 12 and 26. WOMAC C and WOMAC total scores were obtained only at weeks one, 12 and 26.

Analgesic consumption was assessed at each visit by recording any change since the previous visit. The variation in analgesic consumption was also self-assessed by the patient using a four point scale ( $\leq 25\%$ ; 26–50%, 51–75%;  $> 75\%$ ). All concomitant medications were also recorded at each visit.

## 2.6. Safety evaluation

Adverse events (AEs) were recorded at each visit and categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Safety was assessed by physical examination with particular attention on the target knee, by searching knee injection-site reactions, swelling and joint effusion. Definition of adverse events (AEs) and serious adverse events (SAEs) were in accordance with the European standard EN ISO 14155: 2011. Throughout the follow-up, investigators had to note all AEs, on the report form. Any AE had to be assessed by the investigator regarding severity, intensity into “mild, moderate or severe”. In case of SAE, the investigator was required to declare it immediately to the sponsor on a specific form to be sent by fax within 24 h after becoming aware of the event. The investigator also assessed the causal relationship as “excluded” or “not excluded” with the treatment and/or the procedure of IA injection. All AEs whose occurrence could not reasonably be attributed to causes other than the injected treatment were to be considered potential reactions to it and the relationship was assessed “not excluded”.

## 2.7. Study population

All randomized subjects were included in the “Safety” population.

The intent-to-treat (ITT) population included all subjects who were randomized, fulfilled the inclusion/exclusion criteria, received at least one injection of HAnOX-M or Bio-HA and had at least one post baseline evaluation. The per-protocol (PP) population was made of the patients from the ITT population who completed the study without major deviation to the protocol.

In accordance with the EMA guidelines, the non-inferiority analysis was performed on the PP population. A robustness analysis was performed on the ITT population in order to confirm the results. All other analyses were done on the ITT population except for the safety analysis which was performed on the “Safety” population.

## 2.8. Statistics

The SAS version 9.2 software was used for carrying out the statistical analyses. The primary objective of this trial was to demonstrate that HAnOX-M was non-inferior to Bio-HA with respect to the mean change in WOMAC pain sub-score from baseline to the final visit in the PP population. The sample size was calculated from a non-inferiority margin (NIM) of 1.35 (six percent) for the primary criteria, whose value was calculated from data of literature [35]. NIM was 4.68 for WOMAC function, and 6.01 for total WOMAC score. Requiring 80% power to detect such differences between HAnOX-M and Bio-HA, at the two-sided five percent significance level and a 15% dropout rate by week 26, resulted

in a sample size of 208, so that the PP population was made of 176 subjects.

Descriptive statistical analyses (means, standard deviations, medians, percentages, confidence intervals) were used to describe the demographics, history of the disease and treatments, the clinical and radiological examinations, treatment effectiveness and adverse effects (AEs). All variables collected at baseline (prior to any treatment administration) were described in the two treatment groups. A descriptive statistical analysis of the two groups was performed on both PP and ITT populations to ensure their comparability.

The following methods were used to assess the efficacy and tolerability of treatments: the normality of variables was previously evaluated using Shapiro–Wilk test. If normality, they were evaluated by analysis of variance on repeated measures if relevant. If matched data, this analysis was complemented by an appropriate *t*-test. In case of non-normality, a generalized non-linear model was performed in addition to or replacement of non-parametric tests. For quantitative data analysis, a model of logistic regression was performed and was supplemented if necessary by the McNemar test or by Fisher's exact test for confirmation of the effect significance. The homogeneity of the two treatment groups was assessed using non-parametric statistical tests. Descriptive analyses of outcome measures were performed at all follow-up times. The demonstration of non-inferiority of HAnOX-M versus Bio-HA was obtained by calculating 95% confidence interval (CI) of the differences between groups.

## 3. Results

Two-hundred-twenty-six patients were randomized. Four withdrew their consent before the start of the study. The “Safety” population included 222 subjects. Among them 109 were randomized to receive HAnOX-M and 113 to receive Bio-HA. Two-hundred-five patients met the inclusion criteria and had no exclusion criteria. They constituted the ITT population including 103 patients in the HAnOX-M group and 102 in the Bio-HA group. A patient from Bio-HA group received only two injections instead of three. Eighteen patients from HAnOX-M group and 16 from Bio-HA group did not complete the follow-up, so that PP population consisted of 171 patients (Figure 1).

Characteristics of the patients at entry in the study were consistent with those expected, namely an average age of 65, a slight female predominance, an overweight attested by an average BMI of 27.5. The PP and ITT populations did not significantly differ on any criteria. Demographic data, clinical and radiological characteristics of the patients at baseline are summarized in Table 1.

Similarly the two treatment groups were statistically comparable for all the studied parameters, despite the proportion of men, bilateral knee OA and grade 1 OARSI score were slightly more frequent in the Bio-HA group, without it reaching the level of significance.

### 3.1. Primary endpoint

The study was designed to demonstrate the non-inferiority of HAnOX-M compared to Bio-HA in terms of pain reduction on the WOMAC index (WOMAC A). In the PP population, the mean WOMAC A (SD) was 9.5 (3.4) and 9.5 (3.2) at W1 and 5.4 (4.0) and 5.3 (4.4) at W26 for HAnOX-M and Bio-HA respectively. The mean difference was respectively  $-4.4$  (4.6) and  $-4.5$ , leading to a between-treatment difference of 0.03 ( $-\infty$ ; 1.34) (Table 2). The non-inferiority of HAnOX-M versus Bio-HA was demonstrated. Similar results were obtained in the ITT population (between-treatment difference of 0.04) (Figure 2).

### 3.2. Efficacy secondary endpoints

In the PP population the average WOMAC sub-score (SD) at baseline was 25.9 (11.4) and 26.6 (12.5) for HAnOX-M and Bio-HA respectively. The average change between W1 and W26 was  $-12.7$  (12.5) for HAnOX-M and  $-12.3$  (13.8) for Bio-HA giving a between-group difference of  $-0.41$  ( $-\infty$ ; 3.59). The non-inferiority of HAnOX-M versus Bio-HA was also demonstrated. The results of the PP population were confirmed in the ITT population (between-group difference of 0.22).

The average change in the walking pain between W1 and W26 was  $-2.9$  (2.8) for HAnOX-M and  $-2.6$  (2.4) for Bio-HA ( $p = 0.49$ ). Regarding PGA, it was  $-2.4$  (2.6) for HAnOX-M and  $-2.2$  (2.5) for Bio-HA ( $p = 0.74$ ). The magnitude of effect was greater than Minimal Clinically Important Difference for pain, function and patients' global assessment [35,36].

In the ITT population, 82.6% of patients considered that they were improved by treatment at W12, this number rising to 85.5% at W26 without any difference between-treatment groups. Among them, 67% reported an improvement  $> 50\%$  compared to pre-treatment status and 30.1% considered that it was  $> 75\%$ , again without significant

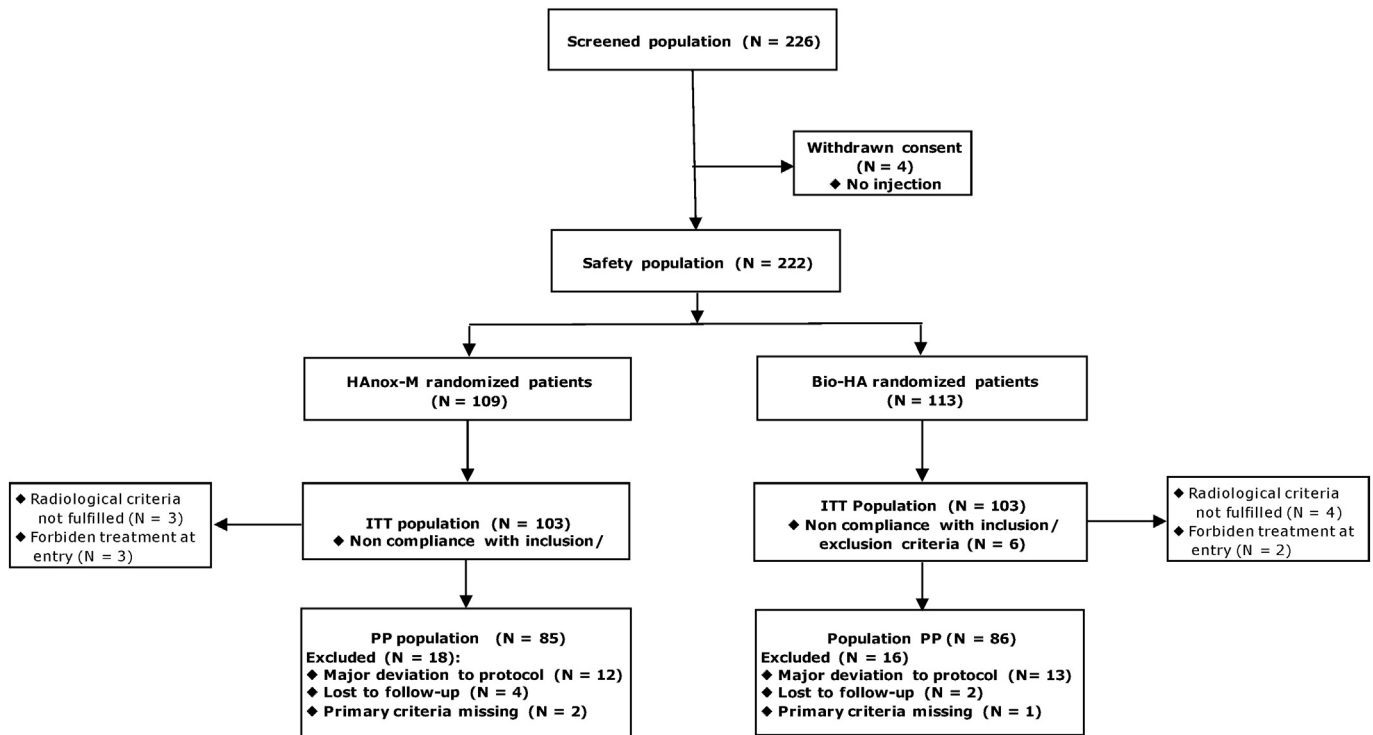


Figure 1. Distribution of patients in the trial.

between-group difference. Changes in pain score throughout the follow-up (repeated measures) are given in Figure 2.

3.3. Analgesic consumption

In the ITT population, 129 patients were taking analgesics at D1, 63 in the HAnOX-M group and 66 in the Bio-HA group (p = 0.96). Among them 58.2% reduced their analgesic consumption between W1 and W26: 49.2% in the HAnOX-M group and 56.3% the Bio-HA group (p = 0.73). The reduction was over 50% in most cases. Fifteen patients (23.8%) treated with HAnOX-M and 19 (28.8%) belonging to the Bio-HA group completely stopped analgesics intake (p = 0.72).

3.4. Safety evaluation

The 222 subjects of the “SAFETY” group were analyzed. Sixty-nine AEs were reported in 52 patients. Thirty-six AEs occurred in the HAnOX-M group (25 patients). In 24 cases

the viscosupplement responsibility was excluded. Among the 12 cases in which it was suspected, nine involved the target knee (8.25% of the HAnOX-M patients). Adverse reactions were a transient enhancement of pain in the target knee few days following an injection in six patients and, in the three other cases, the occurrence of an effusion (all occurred in the same patient). The three other reported AEs were transient headache, insomnia, and skin petechial rash. All three resolved without further sequelae, without the responsibility of HAnOX-M could be asserted or excluded (Table 3).

Thirty-three AEs occurred in the Bio-HA group (27 patients). In 21 cases the responsibility of treatment was excluded. Of the remaining 12 cases, 10 involved the target knee (8.85%). Five AEs were transient enhancement of the target knee pain, four (three of which occurred in the same patient) the occurrence of a knee effusion in the days following an injection. One patient experienced acute knee pain during injection. The two other adverse reactions were skin rashes, among which only one persisted at the end of follow-up.

Nine SAEs were reported during follow-up (two in HAnOX-M group, seven in Bio-HA group). All required hospitalization. None of them was related to viscosupplements or injection procedure. No death occurred during the study.

Table 1 Patients' characteristics at baseline – ITT population.

		Population ITT (N = 205)	HAnOX-M (N = 103)	Bio-HA (N = 102)	p-Value
Age (years)	Mean (SD)	65.3 (10.5)	65.2 (10.1)	65.3 (10.9)	0.96
	Median (range)	65.0 (41;85)	65.0 (46;85)	65.0 (41;84)	
Height (cm)	Mean (SD)	165.9 (9.3)	165.5 (8.9)	166.4 (9.8)	0.51
	Median (range)	165.0 (130;188)	165.0 (147;188)	167.5 (130;188)	
Weight (kg)	Mean (SD)	76.1 (15.4)	76.0 (15.3)	76.2 (15.6)	0.93
	Median (range)	75.0 (36;128)	75.0 (49;128)	75.0 (36;117)	
BMI (kg/m <sup>2</sup> )	Mean (SD)	27.59 (4.92)	27.72 (5.00)	27.47 (4.86)	0.72
	Median (range)	26.75 (19.6;46.5)	26.64 (19.6;46.5)	27.00 (19.7;44.4)	
Sex	Females	117 (57.1%)	63 (61.2%)	54 (52.9%)	0.23
	Males	88 (42.9%)	40 (38.8%)	48 (47.1%)	
Contralateral knee OA	No	97 (47.3%)	55 (53.4%)	42 (41.2%)	0.08
	Yes	108 (52.7%)	48 (46.6%)	60 (58.8%)	
Location	Medial TF	181 (88.3%)	92 (89.3%)	89 (87.3%)	0.65
	Lateral TF	34 (16.6%)	14 (13.6%)	20 (19.6%)	
	PF	41 (20.0%)	16 (15.5%)	25 (24.5%)	
Disease duration (months)	Mean (SD)	49.2 (66.7)	47.0 (64.6)	51.3 (69.0)	0.11
	Median (range)	24.5 (0;468)	24.0 (0;432)	25.5 (1;468)	
Target knee OARSIS grade	1	46 (22.4%)	21 (20.4%)	25 (24.5%)	0.68
	2	73 (35.6%)	36 (35.0%)	37 (36.3%)	
	3	86 (42.0%)	46 (44.7%)	40 (39.2%)	

ITT: intent-to-treat; BMI: body mass index; TF: tibio-femoral; PF: patello-femoral; OARSIS: Osteoarthritis Research Society.

**Table 2**  
WOMAC pain sub-score over the 6 month follow-up. Per-protocol (PP) population.

		PP population	HAnOX-M	Bio-HA	HAnOX-M-Bio-HA mean [CI 97.5%]
WOMAC A W1	N	171	85	86	
	Mean (SD)	9.5 (3.3)	9.5 (3.2)	9.5 (3.4)	
WOMAC A W12	N	168	83	85	
	Mean (SD)	5.2 (3.9)	5.1 (4.1)	5.3 (3.7)	
WOMAC A W26	N	171	85	86	
	Mean (SD)	5.1 (4.1)	5.1 (3.8)	5.0 (4.3)	
WOMAC A: variation W1–W26	Mean (SD)	−4.4 (4.3)	−4.4 (4.6)	−4.5 (4.0)	0.03 [−∞; 1.34]

The non-inferiority margin (NIM = 1.35) is not included in the confidence interval. Non-inferiority is established.

#### 4. Discussion

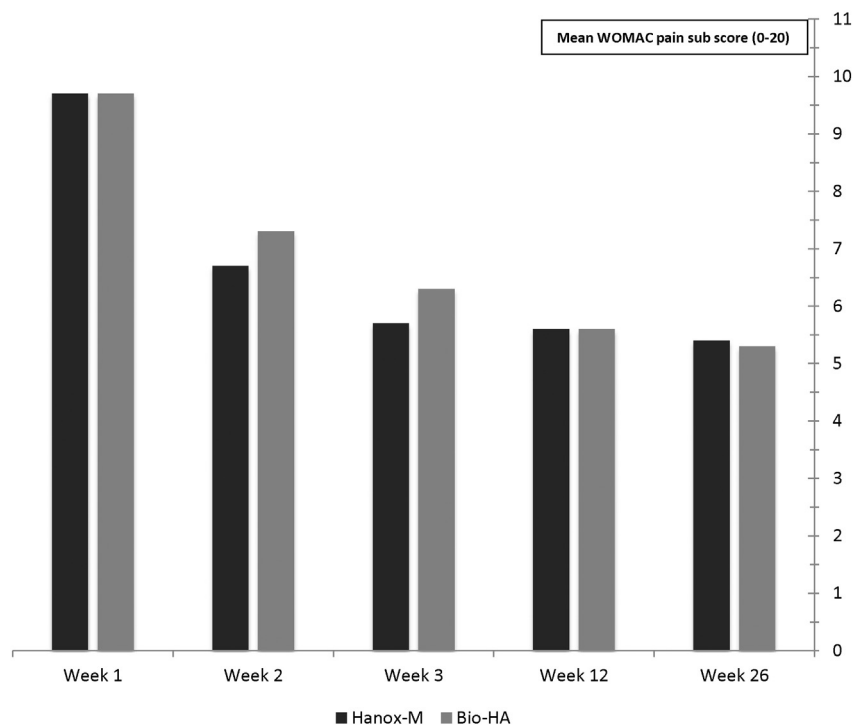
This study, conducted according to the strict rules of randomized controlled trials (RCTs), clearly demonstrates that HAnOX-M is an effective and a well-tolerated treatment for mild and moderate knee OA. Performed under a non-inferiority design, it shows that HAnOX-M is not less effective than its comparator Bio-HA, in terms of pain relief and function improvement over six months, without inducing more side effects. Bio-HA is a robust comparator that has demonstrated both superiority versus placebo [30] and non-inferiority versus Hylan GF-20 [29], compared with which it was shown to be better tolerated, even after repeated cycles of injections [37]. Furthermore a recent study showed that Bio-HA is also a cost-effective treatment of knee OA [38].

Safety was one interesting point to study regarding HAnOX-M. Indeed, this trial was the first one that investigated a treatment containing such a high concentration of mannitol. In our study tolerability of HAnOX-M was very good and similar to that of Bio-HA, showing that the addition of mannitol to HA does not modify the local or general

tolerability of the latter. No treatment-related SAE has been reported during follow-up. The most frequent AEs were, not surprisingly, transient increase of pain in the target knee, occurring a few hours after injection(s), whose evolution has been consistently favorable in less than seven days. The frequency was similar in both groups and consistent with what was expected. The number of post-injection effusion was also very low, since only three patients were concerned. They occurred in one patient of HAnOX-M group (0.9%) and two of Bio-HA group (1.7%), which is consistent with the literature data [29,30]. Among the five AEs possibly related to treatment (three HAnOX-M and two Bio-HA) that have not affected the target knee, three were rashes (one petechial, one urticarial, one eczematous). The first two disappeared before the end of follow-up. In the two other systemic AEs, which both resolved spontaneously (transient insomnia and headache), accountability of the treatment was much more debatable. In summary, the present study failed to demonstrate an increasing risk of adverse events due to the combination of mannitol to HA. These results are comparable with those of previous open-label studies that suggested the good tolerability of viscosupplements containing mannitol [39,40] and sorbitol [41]. We cannot exclude the possibility of adverse effect with low incidence in such a sample size. However, based on the very short half-life of mannitol (four hours) it is unlikely that significant adverse reactions occur more than two days after injection.

Regarding the efficiency, both medical devices enabled a rapid decrease in pain and functional impairment, evidenced by a significant reduction in the pain and function indices at all assessment visits. The reduction of the score of WOMAC A at W26, selected as primary endpoint, was similar in the two treatment groups, fulfilling the conditions for non-inferiority of HAnOX-M compared to Bio-HA. This non-inferiority was reinforced by the fact that effectiveness of both treatments was strictly similar for all secondary endpoints.

Our study also highlights the fact that viscosupplementation with HAnOX-M allows us to significantly reduce the use of analgesics in about half of the patients. So, if about 68% of patients consumed painkillers at least once during the follow-up period, 52.8% of those taking analgesics were able to reduce them by more than half and nearly one



**Figure 2.** Changes in the WOMAC pain sub-score throughout the 26 week follow-up, in patients with knee osteoarthritis treated with HAnOX-M or Bio-HA (intent-to-treat population).

**Table 3**  
Number, relationship to treatment, and location of adverse events that occurred throughout the 26 week follow-up, in patients treated with intra-articular injections of HAnOX-M or Bio-HA for knee osteoarthritis (safety population; n = 222).

Relationship to treatment Location	HAnox-M				Bio-HA			
	Excluded	Possible	Probable	Proven	Excluded	Possible	Probable	Proven
Target knee	9	5	4	0	5	6	3	1
Musculo-skeletal system	12	0	0	0	9	0	0	0
Cardio-Vascular system	1	0	0	0	1	0	0	0
Skin	1	1	0	0	0	2	0	0
Infection	1	0	0	0	4	0	0	0
Others	0	2	0	0	2	0	0	0
Total	24	8	4	0	21	8	3	1

out of four patients could stop completely their analgesic consumption, whatever the treatment group was. If at the individual level, this might seem marginal, from an economic point of view, this is a substantial element when taking into account the direct cost of painkillers, as well as their indirect costs related to the potential problems of intolerance, common in an elderly population [42,43]. Our population was indeed highly representative of the daily practice knee OA population, as attested by an average age of 65.3, ranging from 41 to 86 years, a slight female predominance (57% women and 43% men) a moderate overweight (mean BMI 27.6), and proportion of about 60% of patients with co-morbidities requiring one or more concomitant medications.

However the study suffers some limitations we must not omit to mention. The number of post-randomization exclusion (n = 17, 7.5%) was not negligible but has been made necessary by several radiographic misinterpretations that have been corrected after a centralized review of the radiographs. The second limitation was the number of patient withdrawals related to the intake of prohibited treatment (i.e. corticosteroid injections, prolonged and continuous NSAID prescription). This was likely due to the choice of the radiological inclusion criteria (OARS stages one to three) allowing the inclusion of patients with severe joint space narrowing, greater than 2/3 of the original joint space width. This choice, validated by the French Health Authorities, was designed to ensure that the studied population was as close as possible to the conditions of real life, where most of the subjects treated with viscosupplementation have relatively advanced OA.

Overall, despite some limitations argued above, this study, designed and rigorously conducted according to validated recommendations, demonstrates that HAnOX-M is an effective and well-tolerated treatment for knee OA, which allows long lasting pain relief, decrease of analgesic consumption and functional improvement comparable to those obtained with Bio-HA. Furthermore both viscosupplements showed similar safety profiles, indicating that addition of mannitol to HA does not modify the tolerability of HA.

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### Competing interest

Thierry Conrozier: received fees from LABRHA SAS for scientific consultant services and study coordination.

Jean-Charles Balblanc: received honoraria from LABRHA SAS as a principal investigator of the study.

Naji Afif: received honoraria from LABRHA SAS as a principal investigator of the study.

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Virginie Legré-Boyer: None.

Xavier Chevalier: None.

### Authors' contribution

TC: participated in the design of the study, was the national coordinator of the trial and wrote the manuscript.

FE: participated in the manuscript redaction and the statistical data interpretation.

NA and JCB: participated in the study and collected data as principal investigators of the trial.

VLB participated in the design of the study as a member of the scientific committee.

XC participated in the design of the study and validated the final results as the president of the scientific committee.

All authors read, commented, made changes and then approved the final manuscript.

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