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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Background

Hasten the onset of action of hyaluronic acid (HA) would be a therapeutic advance, since the delayed action (up to 8 weeks) of intraarticular (IA) HA, compared to IA steroids, is one of the main concern about viscosupplementation

HAnox-M is a new viscosupplement, that combines sodium hyaluronate with a high concentration (3.5%) of **mannitol**, a polyol known for its antioxidant properties by scavenging radical oxygen species (ROS). The *in vitro* effectiveness of mannitol to protect HA against ROS-mediated depolymerization has been widely demonstrated suggesting that addition of mannitol to HA might increase the intra-articular residence time of the latter and consequently might allow a more rapid onset of action than HA alone.

Objective

To compare both safety and efficacy of a novel intra-articular viscosupplement made of intermediate molecular weight (MW) HA combined with high concentration of mannitol, **Hanox-M**, with a marketed high MW HA, **Bio-HA** in patients with knee osteoarthritis (OA).

Methods

226 patients **Aged 40-85, with symptomatic knee OA, radiological OARSI grade 1 to 3, were enrolled in a controlled, double-blind, parallel group, non-inferiority trial.**

Patients were randomized to receive 3 weekly IA injections of either Hanox-M or Bio-HA.

Primary criteria: WOMAC A (0-20) changes between baseline and week 26.

Non inferiority Margin = 1.35

Follow-up: 6 months

- **Data at baseline:**
  - **Demographics**
  - **History of knee OA**
  - **WOMAC index A (0-20), B (0-8), C (0-68), Total (0-96)**
  - **Analgesic or NSAIDs consumption**
  - **Pain on a 10 point Likert scale (LS)**
- **Data at week 1, 2 and 3 (dates of injection):**
  - **WOMAC Pain subscore A**
  - **Analgesic or NSAIDs consumption**
  - **Pain on a 10 point Likert scale (LS)**
  - **Patient's self-evaluation of efficacy using a 4 point LS**
  - **Tolerability (4 pt LS)**
  - **Safety (Adverse events AEs report)**
- **Data at week 12 and 26 (Follow-up)**
  - **WOMAC index A, B, C, Total**
  - **Analgesic or NSAIDs consumption**
  - **Pain on a 10 point Likert scale (LS)**
  - **Patient's self-evaluation of efficacy using a 4 point LS**
  - **Tolerability (4 pt LS)**
  - **Safety (AEs report)**
- **AEs: Recorded at each visit and categorized using MedDRA.**

. EudraCT study N°2012-A00570-43

Treatments

HANOX-M-XL (HappyVisc®, Laboratoire LABRHA, Lyon, France) is a novel viscosupplement, that combines:

- ► **high concentration** (15.5 g/L) of **1-1.5 MDa MW sodium hyaluronate** of non-animal origin
- ► **high concentration** (35 g/L) **of mannitol**, a polyol known for its antioxidant properties by scavenging radical oxygen species (ROS)

Bio-HA (Euflexxa®, Ferring Pharmaceuticals, Inc., Parsippany,USA) was used as a comparator

- ► **2.3-3.6 MDa MW sodium hyaluronate** of non-animal origin, at a concentration of 10 g/L

Results 1

HAnox-M and BioHA groups did not differed statistically at baseline.

The primary analysis was conducted in PP population, then confirmed in 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 BioHA respectively, satisfying the claim for non-inferiority.

Similar results were obtained for all other secondary endpoints.

Conclusion 1

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

Results 2

Table I: Patients characteristics at baseline– ITT population
ITT: intent-to-treat; BMI: body mass index; TF: tibio-femoral; PF: patello-femoral; OARSI: Osteoarthritis research Society

		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/m²)	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%)	
Contra-lateral 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%)	0.25
	PF	41 (20.0%)	16 (15.5%)	25 (24.5%)	0.11
Disease duration (months)	Mean (SD)	49.2 (66.7)	47.0 (64.6)	51.3 (69.0)	
	Median (range)	24.5 (0;468)	24.0 (0;432)	25.5 (1;468)	0.65
Target knee OARSI 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%)	

No safety concern:

Number, relationship to treatment, and location of adverse events that occurred throughout the 26 week follow-up, in patients treated with intraarticular 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

Results 3

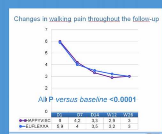
Table II: WOMAC pain subscore over the 6 month follow-up. Per-protocol (PP) population

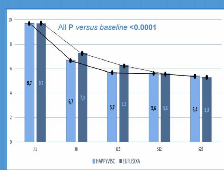
		PP population	HAnox-M	Bio-HA	HAnox-M – Bio-HA Mean [CI 97.5%]
WOMAC A W1	N	171	85	86	
	Mean (SD)	9.5 (3.3)	9.5 (3.2)	9.5 (3.4)	
WOMAC A W12	N	168	83	85	
	Mean (SD)	5.2 (3.9)	5.1 (4.1)	5.3 (3.7)	
WOMAC A W26	N	171	85	86	
	Mean (SD)	5.1 (4.1)	5.1 (3.8)	5.0 (4.3)	
WOMAC A : variation W1-W26	Mean (SD)	-4.4 (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

In the ITT population, 82.6% of patients considered they were improved 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 between-group difference.





Although the difference did not reach statistical significance we observed that **HAnox-M might act more quickly than Bio-HA** .

This was particularly marked **in subjects with severe joint space narrowing** (n=84). In this subgroup the decrease of pain (SD) was greater in patients treated with HAnox-M than in those treated with Bio-HA at both W2 and W3 (p= 0.05)

Conclusion 2

►Both viscosupplements showed **similar safety profiles**, indicating that addition of mannitol to HA does not modify the tolerability of HA.

►A trend to an **earlier reduction of pain with HAnox-M**, suggests that mannitol might have an own analgesic effect due to anti-inflammatory properties and/or through its ability in reducing the *in situ* HA degradation