MEDDOCS Open Access Publisher

ISSN: 2640-4389

Journal of Orthopedics and Muscular System

Open Access | Research Article

Evaluation of Safety and Performance of Hyaluronic Acid Combined with Niacinamide Versus Standard Infiltrative Therapy in the Treatment of Joint Degenerative and Post-Traumatic Diseases

Alberto Gobbi; Katarzyna Herman; Leandra Bizzoco*; Giulia Avio

OASI Bioresearch Foundation Gobbi N.P.O., Milan, Italy.

***Corresponding Author(s): Leandra Bizzoco**

OASI Bioresearch Foundation Gobbi N.P.O., Milan, Italy.

Email: fellow@oasiortopedia.it

Received: Sep 07, 2023

Accepted: Sep 27, 2023

Published Online: Sep 30, 2023

Journal: Journal of Orthopedics and Muscular System

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Bio-orthopedics; Cartilage; Hyaluronic acid; Osteoarthritis; Visco-supplementation; Intra-articular injections; Regenerative medicine.

Abstract

Background: This study aims to evaluate the safety and efficacy of high molecular weight hyaluronic acid with addition of niacinamide (N-HA) versus standard medium molecular weight HA in patients with joint degenerative and post-traumatic diseases.

Methods: Sixty patients with persistent symptomatic knee pain resulting from early Osteoarthritis (OA) were randomized into two groups: Hyaluronic acid with niacinamide (N-HA) or standard hyaluronic acid (HA). Each patient received 3 doses of the selected product in 15 days intervals, with follow-up at 3 (T1) and 6 (T2) months. Outcomes were measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS) and compared with basal scores and between groups.

Results: Each group consisted of 30 patients, none was lost at final follow up. N-HA group showed a statistically significant improvement at 3 and 6 months when compared to basal score with KOOS Final Score ($P < 0.05$). HA group revealed an improvement at 3 months ($P < 0.01$) but at 6 months there was a deterioration of the results and KOOS score was similar to pre- treatment ($P > 0.05$). At 3 months a statistically significant improvement was seen in SPORT, ADL, PAIN and SYMPTOMS scores for N-HA group ($P < 0.05$) furthermore SPORT scores maintained the improvement from month 3 to 6 ($P < 0.05$). Finally, at 6 months N-HA had significantly better results.

Conclusions: Both HA and N-HA are safe and effective for the treatment of joints degenerative and post-traumatic diseases. N-HA showed superiority in terms of efficacy and longer-lasting effects when compared to hyaluronic acid alone. Further studies are needed to determine the exact duration of symptom relief of niacinamide-hyaluronic acid.

Cite this article: Gobbi A, Herman K, Bizzoco L, Avio G. Evaluation of Safety And Performance of Hyaluronic Acid Combined with Niacin-amide Versus Standard Infiltrative Therapy in the Treatment of Joint Degenerative and Post-Traumatic Diseases. J Orthop Muscular Syst. 2023; 6(2): 1024.

Introduction

OA is a common chronic musculoskeletal disease that causes structural alterations in the cartilage, the subchondral bone, the ligaments, the capsule, the synovium and the periarticular muscles destroying the entire joint structure [1]. OA causes pain, inflammation and finally results in significant disability [2]. Thus it is crucial to understand which treatment can offer the best improvement in quality of life. A variety of conservative therapies has been proposed to provide viable long-term results. Hyaluronic acid, also referred to as "visco-supplementation", is one of the most used infiltrative therapies to relieve pain in knee osteoarthritis.

Role of Hyaluronic Acid in OA

Hyaluronic acid is a glycosaminoglycan (GAG) with negatively-charged polysaccharide compound. It consists of sequentially repeated glucuronic acid and N-acetyl glucosamine unit. It is also the major component of synovial fluid. Because of its negative charge, it is highly hydrophilic and therefore highly soluble. These properties ensure the hydration of the tissue maintaining the articular matrix viscosity, joint lubrication and shock absorption [3].

During OA, the dynamic mechanisms involve the release of inflammatory cytokines, such as interleukin 1 beta (IL-1β), which leads to the mitochondrial dysfunction. The consequence is the increase of the Reactive Oxygen Species (ROS) production and the triggering of an apoptosis cascade causing a persistent oxidative stress environment. One of the properties of HA is anti-inflammatory effect by the capacity of decreasing in ROS synthesis and the prevention of IL-1β-induced oxidative stress. In this mechanism, cytokines cause the deregulation and loss of crucial macromolecules from the extracellular matrix (ECM) such as type II collagen and proteoglycan biosynthesis. HA has an anabolic effect, so it stimulates glycosaminoglycans and type II collagen formation.[3] In addition, HA reduces the formation of peroxide hydrogen (H_2O_2) and oxygen species in the synovial fluid causing the suppression of the cell death induced by H_2O_2 [4].

Niacinamide

Nicotinamide (NAM) and nicotinic acid (NA), known as vitamin B3 (or niacin), is water-soluble vitamin of the B complex vitamins. NAM and NA are components of the enzyme cofactors nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which play important physiological roles, e.g. in various redox processes [5,6]. Niacin is classified as a semi-essential vitamin due to the endogenous formation from the amino acid tryptophan, with approximately 60 mg of tryptophan being equivalent to 1 mg NA [7]. The structure of NAM consists of a pyridine ring to which a primary amide group is attached in the meta position (Figure 1). It is an amide of nicotinic acid [8]. As an aromatic compound, it undergoes electrophilic substitution reactions and transformations of its two functional groups.

A product based on high molecular weight hyaluronic acid and niacinamide (pre-filled syringe with 2 ml of product with 40 mg of high molecular weight hyaluronic acid) has been tested for safety in pre-clinical studies [9-11]. High molecular weight combined with high concentration of HA (2%) creates a product with high viscosity that makes it suitable for visco-supplementation. The most important thing is that niacinamide provides protection from hyaluronidaseactivity. Giardina in his in vitro study showed that HA combined with niacinamide had improved resistance to hyaluronidase enzyme degradation when compared to standard HA and showed a longer activity. Thus the sample containing niacinamide showed a 22% amount of hydrolyzed hyaluronic acid in the reaction mix after 60 minutes, while the control 65,6% ($P<0.05$) [12].

Material and Methods

Patients with persistent symptomatic OA of the knee received N-HA or standard HA. The Consolidated Standards of Reporting Trials (CONSORT) Statement was followed [13]. The study was performed according to the ethical standards outlined in the 2013 revision of the 1975 Declaration of Helsinki, approved, and monitored by our institutional review board. Additionally, niacinamide hyaluronate is marketed under Directive 93/42/EEC; it is compliant with medical device documents (MEDDEV 2.7/1 Rev. 4 Clinical evaluation: guide for manufacturers and notified bodies.)

Participants

The patients were recruited at a single clinical institution by the chairman of the orthopedic department. Patients aged 18 to 80 years, with symptomatic knee OA, grade II to III according to Kellgren-Lawrence classification were included in the study groups. Every patient had to sign the informed consent before enrollment; the potential benefits and risks of hyaluronic acid injections were explained and understood by all. The main exclusion criteria were any recent intra-articular injection therapy, knee instability, significant axial deviation, systemic disorders such as rheumatoid arthritis, coagulopathies, or infections. All inclusion and exclusion criteria have been listed in Table 1.

Inclusion Criteria:

- Patients between 18 and 80 years of age.
- Patients who have volunteered after signing the informed consent.
- Osteoarthritis grade 2-3 according to the Kellgren & Lawrence grading scale, as defined on knee radiographs.
- The patient is able to read and understand the language of the content of the study.
- Patients who are willing to provide questionnaires at the first infiltration and at 3- 6 months.
- Bilateral osteoarthritis was accepted and both knees were treated.

Exclusion Criteria:

- Refusal to sign or inability to give Informed Consent.
- Immunosuppressive state (AIDS) or immunocompromised patients caused by therapies with corticosteroids, chemotherapy and immunosuppressant.
- Paediatric patients.

- History of allergy to hyaluronic acid or to any components of the device.
- Inability to understand or comply with the requirements of the study.
- Pregnancy or breastfeeding or planning pregnancy during the study.
- Grade < 2 or > 3 OA according to the Kellgren and Lawrence grading scale.
- Malignant diseases.
- Rheumatological disorders.
- Clinical evidence of local inflammation such as redness or warmth of the joint.
- Surgery or arthroscopy surgery in the affected knee in the past 3 months.
- Local infection in the affected knee.
- Hematologic or clotting disorders (thrombocytopenia) or blood coagulation (deficit-blood dyscrasia).
- Viral disorders (hepatitis, herpes, varicella, zona, etc.).
- Anticoagulant treatment.
- Renal failure or haemodialysis.
- Recent fever (within previous 2 weeks) or serious disorders (liver disease, active gastroduodenal ulcer, digestive haemorrhage etc.).
- Uncontrolled diabetes.
- Participation in another clinical study in the past 3 months or ongoing participation in another OA clinical study.
- Fracture, skeletal dysplasia, congenital or acquired deformity that affects the knee.
- Being diagnosed for fibromyalgia, neuropathic pain syndrome or depression in the past.
- Bilateral osteoarthritis provided that the contralateral knee has a pain more than 3 on the 0-10 point scale and requires systemic analgesic treatment or paracetamol more than 4g per day.
- Untreated instability of the knee (i.e. anterolateral rotatory with grade 3 pivot shift with daily incidents of instability, multidirectional instability, MCL or PLC insufficiency).

Sixty patients who met our inclusion criteria were enrolled and divided into two groups of 30 patients each.

Statistical methods

Normal distribution was determined by the Shapiro-Wilk test for all pre-injections scores in every category between patients treated with N-HA and those treated with NN-HA. Wilcoxon-Mann was used for variables non-normally distributed while one sample t test was chosen for variables normally distributed.

Treatment

The manufacturer provided the products with the same syringe, color (transparent), texture, and quantity (2 mL). One of the two infiltration products used was HA composed of medium-weight sodium hyaluronate (1.0-1.5 x 10^6 Da) that is a non–animal source, obtained by bacterial fermentation (Streptococcus Equi). The other one was HA composed of high-weight sodium hyaluronate (1800-2600 kDa) plus the addition of 0,8% niacinamide. Both came in the dosage presentation of 2 mL, 40 mg/2 mL hyaluronate.

After basal clinical scores were recorded, an intra articular injection with either of the products was performed always by the same orthopedic physician in a sterile environment. The knee was held in extension, and a suprapatellar approach was used. Precisely, 2 mL of hyaluronate were injected with a 20 gauge after which ice was applied for 5 minutes. Then patients were instructed to avoid intense exercise for 48 hours and to apply ice for 15 minutes 3 times a day. Each patient received 3 doses of the same product in 15 days intervals. Afterward, they were invited for follow-up at 3 and 6 months. Follow up for clinical evaluation was by the same senior author. None was lost at final follow up. The use of medication by the patients was not recorded.

Results

To obtain the primary endpoint, patients were clinically evaluated using KOOS [14] (percentage score obtained from the evaluation of 5 separately scored subscales: pain, other symptoms, functions of daily living, function in sport and recreation, and knee-related quality of life. Scoring systems were recorded through questionnaires filled by the same patients before the first injection (T0), at 3 months (T1) and 6 months (T2). Patients were also assessed for any adverse reaction such as effusion, flare or pain during the clinical evaluation. After clinical evaluation and score recording, an independent researcher archived the data into a database.

The mean age of the 30 study patients treated with N-HA was 58.8 ± 16.1 years (BMI: mean 24.5 ± 4.5). Patients treated with HA had a mean age of 56.4 ± 15.6.

N-HA group showed a statistically significant improvement at 3 and 6 months when compared to basal score with KOOS Final Score ($P < 0.05$) (Figure 1).

HA group revealed an improvement at 3 months ($P < 0.01$) but at 6 months there was a deterioration of the results and KOOS score was similar to pre-treatment ($P > 0.05$) (Figure 2).

At 3 months a statistically significant improvement was seen in KOOS SPORT, ADL, PAIN and SYMPTOMS scores for N-HA group ($P < 0.05$), furthermore SPORT scores maintained the improvement from month 3 to 6 ($P < 0.05$) (Figure 3,4,5,6).

When comparing both groups at 6 months, N-HA reported significant clinical outcomes for QOL (P value = 0.0081), ADL (P value = 0.0091), SYMPTOMS (P value = 0.0081) when compared to HA (Figure 7,8,9).

Finally, at 6 months N-HA resulted to have significant better results ($P < 0.01$) (Figure 10).

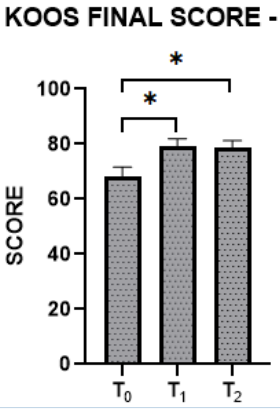

Figure 1: Deviation of different spine parameters.

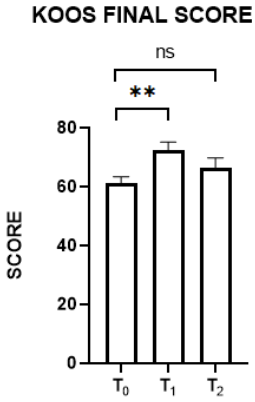

Figure 2: Koos Final Score - HA

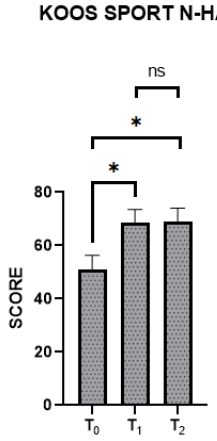

Figure 3: Koos Sport N-HA.

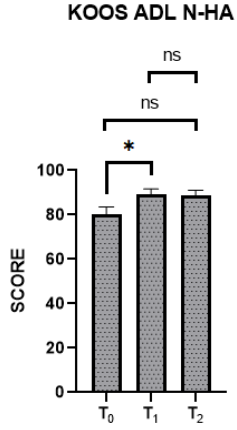

Figure 4: Koos ADL N-HA.

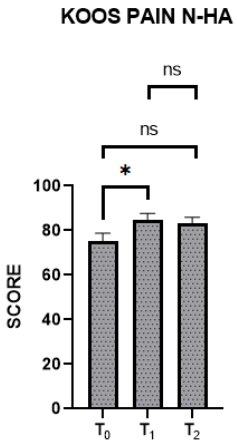

Figure 5: Koos Pain N-HA.

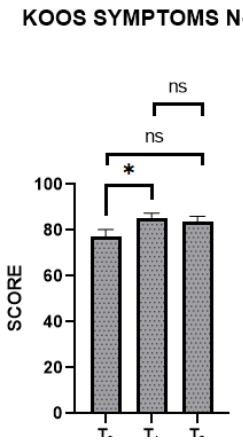

Figure 6: Koos Symptoms N-HA.

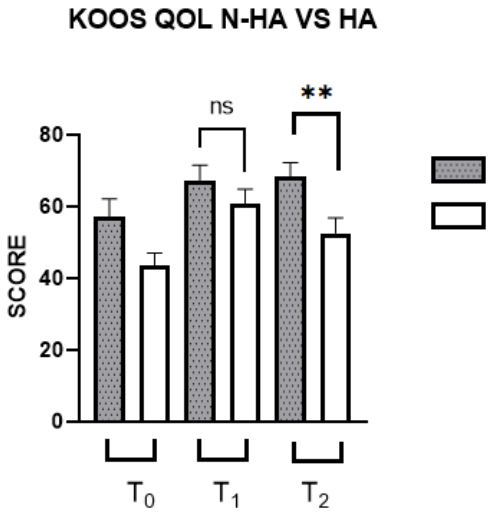

Figure 7: Koos QOL N-HA vs HA.

Discussion

To our knowledge, this is the first prospective randomized controlled trial comparing the effects of a niacinamide hyaluronate formulation used as an infiltrative therapy for knee OA.

Our results are in line with other studies in the literature regarding the effectiveness of hyaluronic acid as a treatment for symptomatic OA of the knee, as both compounds of hyaluronic acid demonstrated a statistically significant improvement in pain and function from the basal time point [15,16].

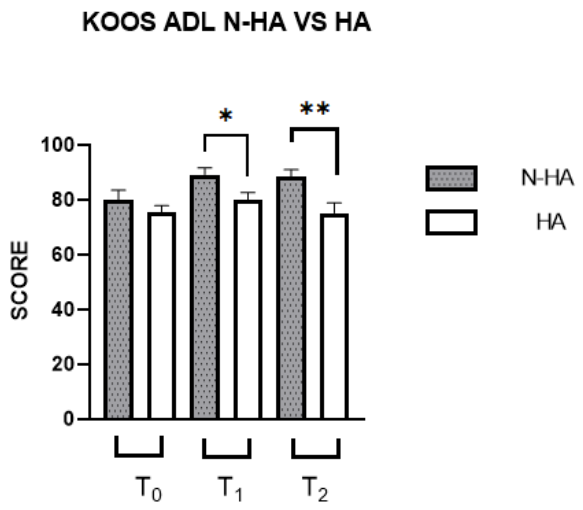

Figure 8: Koos ADL N-HA vs HA.

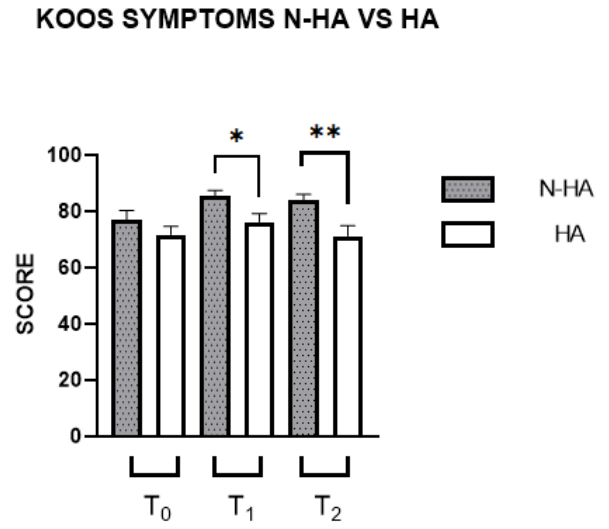

Figure 9: Koos Symptoms N-HA vs HA.

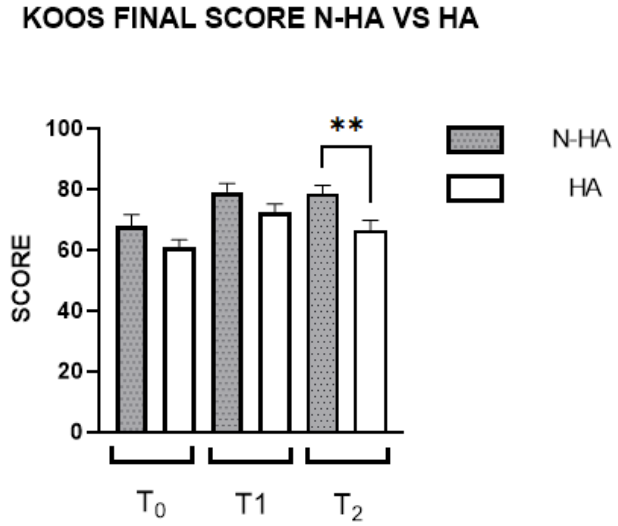

Figure 10: Koos Final Score N-HA vs HA.

The background of niacinamide is not new; some studies indicate that niacinamide reduces inflammation and some OA symptoms [17,18].

Another study by Hadjab et al. has shown that niacinamide has a dual positive effect: a major resistance to oxidative degradation and greater protection from the hyaluronidase. Furthermore, niacinamide provides more stability of HA against thermal degradation preserving its viscosity [19].

Protein-based compounds such as hyaluronic acid are easily degraded by strong acids, bases, inorganic salts and organic solvents. The active end groups of these proteins, generally associated with hydrogen-bonded water, can bind to other molecules, leading to its denaturation and loss of function. Niacinamide helps preserving the structure and function of proteins giving more stability.

In this setting, the new product does not react with the hyaluronidase enzyme and thus extends its effects, as previously demonstrated *in vitro*.

This fact is highly relevant in orthopaedics because further inflammatory damage could be prevented by stabilizing chemical reactions in the knee joint. Due to the niacinamide, hyaluronic acid resulted to have more resistance to hyaluronidase

Our therapy was performed with high-weight hyaluronic acid using sodium hyaluronate HW (1800-2600 KDa). The high concentration of HA (2,0 %) maintains an high viscosity suitable enough for supplementation.

Some studies show that high-weight hyaluronic acid has a positive effect for the treatment of knee OA improving pain and function [20]. However, the disadvantage of high viscosity hyaluronate is that the product is more difficult to administrate.

Overall, there isn't an evidence that supports the superiority of one kind of HA preparation over another [21]. In a randomised double-blind controlled trial, a slightly lower efficacy for low weight HA preparations versus intermediate and high weight hyaluronic acid was demonstrated [22]. This fact also correlates with our findings as with our control, we did not find significant adverse reactions proving it to be safe to administer.

The new niacinamide hyaluronic acid resulted a viable treatment improving the clinical outcomes at 3 and 6 months when compared to standard HA products.

Our study demonstrated that the difference of clinical outcomes was statistically significant at 6 months when the standard products markedly returned to basal scores at the same time.

Comparing both hyaluronic acids at 3 months, niacinamide-HA resulted to have a statistically significant advantage in KOOS symptoms; furthermore, the difference was statistically significant with KOOS activity daily life and patients treated with niacinamide-HA nearly returned back to their normal life ($P<0.05$).

At 6 months niacinamide-HA resulted to be more effective with KOOS quality of life when compared with standard infiltrative therapy, however, similar effects were shown in terms of pain and sport.

Limitations

Our study is not exempt from limitations. The small number of patients should be taken into consideration. Furthermore,

the short clinical follow-up doesn't allow determining the total lasting effects of N-HA. Another limitation is the lack of recording of the rescue medicine by the patients during the follow-up period. Additionally compared hyaluronates were different, used with niacinamide was a high molecular weight HA compared to sole medium-weight sodium hyaluronate.

Conclusions

Hyaluronic acid therapy with or without niacinamide is a safe and effective treatment of early arthritis; however, our study demonstrated that a particular hyaluronic acid at high molecular weight with niacinamide offers long lasting effects.

Further studies with longer follow up are needed to determine the complete duration of symptom relief of niacinamide-hyaluronic acid.

Funding: This research received no external funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: Not applicable.

Conflicts of interest: The authors declare that they have no conflict of interest.

References

1. Herman, Katarzyna, and Alberto Gobbi. "Evidence-Based Approach to Orthobiologics for Osteoarthri-tis and Other Joint Disorders." Physical Medicine and Rehabilitation Clinics. 2023; 34: 71-81.

2. Dallo, Ignacio, et al. A prospective study comparing leukocyte-poor platelet-rich plasma combined with hyaluronic acid and autologous microfragmented adipose tissue in patients with early knee osteoarthritis. Stem cells and development. 2021; 30: 651-659.

3. Gobbi, Alberto, Ignacio Dallo, and Riccardo D'Ambrosi. Autologous microfragmented adipose tissue and leukocyte-poor platelet-rich plasma combined with hyaluronic acid show comparable clinical outcomes for symptomatic early knee osteoarthritis over a two-year follow-up period: A prospective randomized clini-cal trial. European Journal of Orthopaedic Surgery & Traumatology. 2022: 1-10.

4. Yu, Chia-Jung, et al. "Proteomic analysis of osteoarthritic chondrocyte reveals the hyaluronic ac-id-regulated proteins involved in chondroprotective effect under oxidative stress." Journal of Proteomics. 2014; 99: 40-53.

5. Bogan, Katrina L, Charles Brenner. "Nicotinic acid, nicotinamide, and nicotinamide riboside: a molec-ular evaluation of NAD+ precursor vitamins in human nutrition." Annu. Rev. Nutr. 2008; 28: 115-130.

6. Sauve, Anthony A. "NAD+ and vitamin B3: from metabolism to therapies." Journal of Pharmacology and Experimental Therapeutics. 2008; 324: 883-893.

7. Horwitt, MK, AE Harper; Henderson LM. Niacin-tryptophan relationships for evaluating niacin equiv-alents. The American journal of clinical nutrition. 1981; 34: 423-427.

8. Knip M, et al. Safety of high-dose nicotinamide: A review." Diabetologia. 2000; 43: 1337-1345.

9. Subcutaneus implantation test on intra-articular/intra-dermal gel based on hyaluronic acid sodium salt (high molecular weight) and niacinammide-local and systemic effects-2 weeks. Report number STULV19AA0017-1 GLP performed by Eurofins Biolab srl.

10. Subcutaneus implantation test on intra-articular/intra-dermal gel based on hyaluronic acid sodium salt (high molecular weight) and niacinammide- local and systemic effects-4 weeks. Report number STULV19AA0018-1 GLP performed by Eurofins Biolab srl.

11. Subcutaneus implantation test on intra-articular/intra-dermal gel based on hyaluronic acid sodium salt (high molecular weight) and niacinammide-local and systemic effects-4 weeks. Report number STULV19AA0019-1 GLP performed by Eurofins Biolab srl.

12. Giardina S. In vitro efficacy study: Evaluation of susceptibility of a hyaluronate- based product to the activity of the hyaluronidase. Report number E.IT.076_2018/2116 B. performed by Complife group. 2018.

13. Cuschieri, Sarah. The CONSORT statement. Saudi journal of anaesthesia. 2019; 13: 27.

14. Monticone M, Ferrante S, Salvaderi S, et al. "Development of the Italian version of the knee injury and osteoarthritis outcome score for patients with knee injuries: Cross-cultural adaptation, dimensionality, relia-bility, and validity." Osteoarthritis Cartilage. 2012; 20: 330–335.

15. Migliore, Alberto, et al. Systematic literature review and expert opinion for the use of viscosupplemen-tation with hyaluronic acid in different localizations of osteoarthritis." Orthopedic Research and Reviews. 2021: 255-273.

16. Wang, Chen-Ti, et al. "Therapeutic effects of hyaluronic acid on osteoarthritis of the knee: a me-ta-analysis of randomized controlled trials. JBJS. 2004; 86: 538-545.

17. Jonas WB, Rapoza CP, Blair WF. The effect of niacinamide on osteoarthritis: A pilot study. Inflammation Research. 1996; 45: 330-334.

18. Bellamine, Aouatef. "Nicotinate supplements slow onset and severity of symptoms in the monosodium iodoacetate (MIA) rat model for osteoarthritis (OA)." The FASEB Journal. 2019; 33: lb552-lb552.

19. Hadjab, F. AB0046 RESISTANCE TO OXIDATIVE DEGRADATION OF A FORMULATION COMBINING HYALURONIC ACID AND NIACINAMIDE. 2022: 1158-1158.

20. Hermans, Job, et al. "The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial." BMC Musculoskeletal Disorders. 2019; 20: 1-10.

21. Gigis I, et al. Comparison of two different molecular weight intra-articular injections of hyaluronic acid for the treatment of knee osteoarthritis." Hippokratia. 2016; 20: 26.

22. Berenbaum, Francis et al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis." Annals of the rheumatic diseases. 2012; 71: 1454-1460.