Hyaluronic acid sodium salt, Viscosuppletive joint device

-0.8% - 8 mg/ 1ml (MINI)
- 0.8% - 16 mg/ 2 ml
- 1,0% - 20 mg/ 2 ml
- 1.6% - 32 mg/ 2 ml (FORTE – HIGHVISC)
- 2.0% - 50 mg/ 2.5 ml (ONE - ONCE)

CLINICAL EVALUATION REPORT
Based on MEDDEV 2.7.1:2016
and
MEDDEV 2.12-2:2012
According to Directive 93/42/EEC
as amended by 2007/47/EC

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1 SUMMARY

Osteoarthritis (OA) is the most common form of arthritis and refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. The most commonly affected peripheral joints are the knees and the hips, but also small hand joints [16]. OA is characterised by localised loss of cartilage, remodelling of adjacent bone and associated inflammation. The main signs and symptoms are pain, stiffness and loss of movement and function [23]. OA includes a slow but efficient repair process that often compensates for the initial trauma, resulting in a structurally altered but symptom-free joint. However, because of either overwhelming trauma or compromised repair, in some people the process cannot compensate, resulting in eventual presentation with symptomatic osteoarthritis; this might be thought of as 'joint failure'.

Treatments available can only manage symptoms. Nonpharmacologic therapy is represented by strengthening exercises and aerobic exercise, in order to help improving stamina and energy levels and also help to reduce excess weight [63]. Also Ultrasounds and transcutaneous electrical nerve stimulation are often used as a physical therapy modality for OA [64].

The pharmacological approach consists of Acetaminophen, Nonsteroidal anti-inflammatory drugs (NSAIDs), Opioids and Topical analgesics, such as Diclofenac sodium gel and solution, Lidocaine patches, Methyl salicylate and menthol (Bengay) and Trolamine (Aspercreme), topical cream containing an aspirin-like drug that relieves inflammation and pain [66-68]. The main contraindications to the use of medicinal products are side effects of this type of treatment, such as slight or moderate liver, stomach and kidney problems [84-87].

Surgery should be reserved for patients whose symptoms have not responded to other treatments. If osteoarthritis has damaged one side of the knee more than the other, an osteotomy might be helpful, although this technique is not free from risks, such as infections and blood clots [89]. Also complementary and alternative medicine has been evidenced to be effective in reducing patients' pain [78-83].

Another non-surgical approach is the use of lubrication injections. Intra-articular hyaluronic acid injections, also known as viscosupplementation, are widely used by orthopedic surgeons to treat osteoarthritis of the knee and, according to several clinical studies, they are effective [76]. The two most common types of knee injection for OA are corticosteroids and hyaluronic acid [90].

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.
It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).
The medical device contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa).

HA is a naturally occurring glycosaminoglycan and a component of synovial fluid (SF) and cartilage matrix. The intra-articular injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: "viscosupplementation" [94]. It is also thought that HA temporarily restores the lubricating and shock-absorbing effects of SF.

Some clinical studies evaluating clinical outcomes of HA-based viscosupplementations have been commented in this Clinical Evaluation report.

The multicenter randomized controlled clinical study carried out by Jüni et al. (Citation 1) aimed to compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee. No evidence for a difference in efficacy between hylan and Has were found.

The observational clinical study performed by Gydek et al. (Citation 2) evaluated the clinical outcomes of the intra-articular administration of HA-based viscosupplementations. According to results, the product demonstrated high efficacy and good tolerance in the treatment of knee osteoarthritis.

The prospective, naturalistic, cohort clinical study carried out by Petrella (Citation 3) proved that Intraarticular hyaluronic acid injections were highly effective in improving resting and walking pain in patients with osteoarthritis of the knee on a first and a second treatment series. Duration of symptom control was about 6 months, and the therapy was highly satisfactory to patients.

Uebelhart *et al.* (Citation 4) indicated that the product containing a natural, non-chemically modified HA of fermentative origin, is a safe and effective therapy for knee OA, as much as the injection of chemically modified cross-linked HA derivative of avian origin.

Romàn *et al* (Citation 5) showed that the efficacy with a LMW-HA product at 3 months after treatment was greater than with the HMW-HA device (50% versus 21.1%). The maximum improvement with hyaluronic acid was seen at 5 weeks in 75.4%.

Van Den Bekerom *et al.* (Citation 6) carried out a prospective clinical study comparing three different hyaluronate formulations and evaluating functionality, time of satisfactory pain relief and also the delay in performing a total hip arthroplasty. Results reported that there was no significant difference in duration of the effect of the first infiltration between the three groups. The positive effect was still ongoing at the end point of the study in 46 hips: 51% of the patients did not undergo total hip arthroplasty, 3 years after viscosupplementation.

Mathies *et al.* (Citation 7) showed that the HA viscosupplementation evaluated was safe and effective, improving symptoms, quality of life and the viscous and elastic modulus of the synovial fluid of the knee. Similar results were obtained by Blanco *et al.* (Citation 8) who proved that the use of intra-articular HA to treat OA patients on the waiting list for KRS does not delay surgery. However, it could improve the physical condition of patients while they are waiting by surgery.

Monfort et al. (Citation 9) reported that both hyaluronic acid and betamethasone were effective for the management of rhizarthrosis. Hyaluronic acid was more effective over time and more efficiently improvedfunctionality and pain in patients with more severe symptoms.

Karatosun et al. (Citation 10) reported that both HA injections and exercise therapy provide functional improvement.

Tang et al. (Citation 11) revealed that IAHA injections can provide significant pain relief and improvement in activity of daily living function for patients with knee OA.

Eyigör et al. (Citation 12) proved thtat intraarticular HA injection through a lateral approach under

fluoroscopic control was shown to be a safe and effective method for patients with advanced hip OA. Finally, the prospective randomized clinical study of Petrella (Citation 13) showed that peri-articular HA treatment for tennis elbow was significantly better than control in improving pain at rest and after maximal grip testing.

The Clinical Evaluation of the medical device "*Hyaluronic acid sodium salt, viscosuppletive joint device*" resulted in a positive risk/benefit ratio for the application of the product after assessment of the risks/benefit with regard to the intended use. All risks addressed in the risk analysis are within an acceptable range or as far as possible.

Moreover, a critical assessment of data collected from the literature demonstrates that "*Hyaluronic acid sodium salt, viscosuppletive joint device*" achieves its intended purpose and claims made in relation to safety and performance, in compliance with Annex X of EC-Directive 93/42/EEC and the European guideline: MEDDEV 2.7.1 of June 2016.

2 SCOPE OF THE CLINICAL EVALUATION

Clinical evaluation is a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to analyse whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's instructions for use.

Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device. It is first performed during the conformity assessment process leading to the marketing of a medical device and then repeated periodically as new clinical safety and performance information about the device is obtained during its use. This information is fed into the ongoing risk analysis and may result in changes to the Instructions for Use.

Therefore, this Clinical evaluation is intended:

- To demonstrate that the medical device "Hyaluronic acid sodium salt, viscosuppletive joint device" reaches the prefixed scope regarding performance and safety during normal conditions of use, in accordance with Annex X of Medical Device Directive 93/42/EEC as amended by Directive 2007/47/EC, and that any claims made about the devices' performance and safety (e.g. product labelling and instructions for use) are supported by suitable evidence.
- To verify that the known and foreseeable risks, and any adverse events, are minimized and acceptable when weighed against the benefits of the intended performance.
- To review the state of the art of clinical data based on performance and safety criteria of "Hyaluronic acid sodium salt, viscosuppletive joint device".

3 CLINICAL BACKGROUND, CURRENT KNOWLEDGE, STATE OF THE ART

3.1 *IDENTIFICATION OF THE MEDICAL FIELD*

Viscosupplementation

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

3.2 *APPLICABLE STANDARDS AND GUIDANCE DOCUMENTS*

A list of applicable standards and guidance documents is reported below:

- MEDDEV 2.7.1:2016 rev. 4 - Clinical evaluation: a guide for Manufacturers and Notified Bodies under Directive 93/42/EEC and 90/385/EEC;
- EN ISO 14971:2012 - Medical devices – Application of Risk Management to medical devices;
- EN 1041:2008 - Information supplied by the manufacturer with medical devices;
- EN ISO 10993-1:2009 - Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process;
- EN ISO 10993-3:2014 - Biological evaluation of medical devices - Part 3: tests for genotoxicity, carcinogenicity and reproductive toxicity;
- EN ISO 10993-4: 2009- Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood;
- EN ISO 10993-5:2009 - Biological evaluation of medical devices - Part 5: Tests for *in vitro* cytotoxicity;
- EN ISO 10993-10:2010 - Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization;
- EN ISO 10993-11:2009 – Biological assessment of medical devices –Part 11: Systemic toxicity tests;
- EN ISO 10993-12:2012 - Biological evaluation of medical devices - Part 12: Sample preparation and reference materials;
- OECD Guideline for testing of chemicals 471 21st July 1997. Genetic Toxicology: *Salmonella Typhimurium*, Reversion Mutation Assay;
- EN 10993-6:2009 – Biological evaluation of medical devices - Part 6: Test for local effects after implantation;
- EN ISO 14155:2011 - Clinical investigation of medical devices for human subjects — Good Clinical Practice;
- IEC 62366-1:2015- Medical devices - Application of usability engineering to medical devices.

3.3 *ANATOMICAL BACKGROUND*

A joint, also known as an *articulation* or *articular surface*, is a connection that occurs between bones in the skeletal system. Joints can be structurally and functionally classified.

The structural classification divide joints into fibrous, cartilaginous, and synovial joints depending on the material composing the joint and the presence or absence of a cavity in the joint [1]:

- **Fibrous joints**: the bones of fibrous joints are held together by fibrous connective tissue. There is no cavity, or space, present between the bones, so most fibrous joints do not move at all. There are three types of fibrous joints: *sutures (skull)*, *syndesmoses (e.g. joint of the tibia and fibula in the ankle)*, and *gomphoses (e.g. joint between the teeh and their sockets)* (Figure 1).

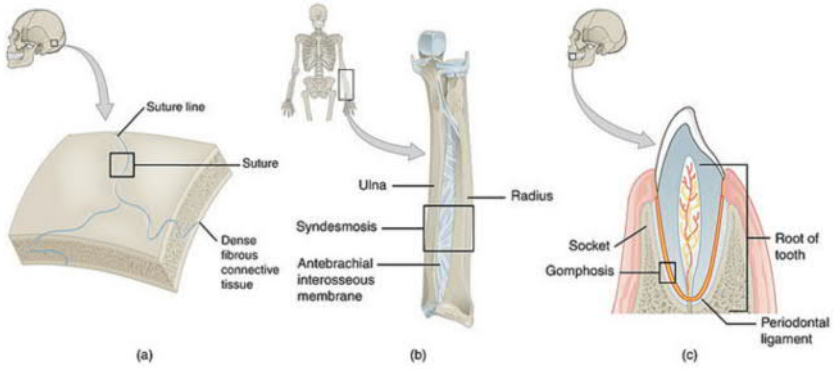


Figure 1. Three types of fibrous joints. a) Sutures b) Syndesmosis c) Gomphosis [1].

- **Cartilaginous joints**: cartilaginous joints are those in which the bones are connected by cartilage. There are two types of cartilaginous joints: *synchondroses* and *symphyses*. In a synchondrosis, the bones are joined by hyaline cartilage (e.*g. synchondroses are found in the epiphyseal plates of growing bones in children*). In symphyses, hyaline cartilage covers the end of the bone, but the connection between bones occurs through fibrocartilage (*e.g. joints between vertebrae and between the pubic bones*) (Figure 2).

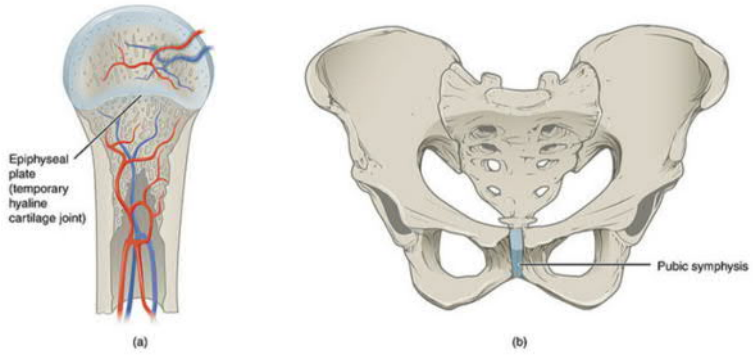


Figure 2. Synchondrosis joint with epiphyseal plate (temporary hyaline cartilage joint) indicated (a) and a symphysis (b) [1].

- **Synovial joints:** these joints not directly joined, and are the only joints that have a space between the adjoining bones**.** This space, referred to as the synovial (or joint) cavity, is filled with synovial fluid. Synovial fluid lubricates the joint, reducing friction between the bones and allowing for greater movement. The ends of the bones are covered with articular cartilage, a hyaline cartilage. The entire joint is surrounded by an articular capsule composed of connective tissue. This allows movement of the joint as well as resistance to dislocation. Articular capsules may also possess ligaments that hold the bones together. Synovial joints are capable of the greatest movement of the three structural joint types; however, the more mobile a joint, the weaker the joint. Knees, elbows, and shoulders are examples of synovial joints (Figure 3).

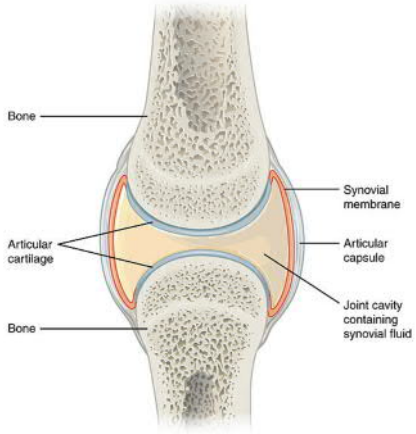


Figure 3. Synovial joint delineates the articular cartilage, articular capsule, bone, synovial membrane and joint cavity containing synovial fluid [1].

Joints can also be classified functionally according to the type and degree of movement they allow [2]:

- **Synarthroses (immovable articulations):** these include all those articulations in which the surfaces of the bones are in almost direct contact, fastened together by intervening connective tissue or hyaline cartilage, and in which there is no appreciable motion, as in the joints between the bones of the skull, excepting those of the mandible. There are four varieties of synarthrosis: sutura, schindylesis, gomphosis, and synchondrosis. A sutura is a form of articulation where the contiguous margins of the bones are united by a thin layer of fibrous tissue; it is met with only in the skull.
- **Amphiarthroses (slightly movable articulations):** in these articulations the contiguous bony surfaces are either connected by broad flattened disks of fibrocartilage, of a more or less complex structure, as in the articulations between the bodies of the vertebræ; or are united by an interosseous ligament, as in the inferior tibiofibular articulation. The first form is termed a symphysis, the second a syndesmosis.
- **Diarthroses (freely movable articulations):** this class includes the greater number of the joints in the body. In a diarthrodial joint, the contiguous bony surfaces are covered with articular cartilage, and connected by ligaments lined by synovial membrane. The joint may be divided, completely or incompletely, by an articular disk or meniscus, the periphery of which is continuous with the fibrous capsule while its free surfaces are covered by synovial membrane. Since they allow for free movement, synovial joints (e.g. knee or ankle joints) are classified as diarthroses.

<u>Knee joints</u>

The knee joint is one of the strongest and most important joint in the human body. It allows the lower leg to move relative to the thigh while supporting the body's weight. Movements at the knee joint are essential to many activities, including sitting, standing, walking and running [3].

The knee, also known as the tibiofemoral joint, is a synovial hinge joint formed between three bones: the femur, tibia, and patella (Figure 4). Two rounded, convex processes (known as condyles) on the distal end of the femur meet two rounded, concave condyles at the proximal end of the tibia. The patella lies in front of the femur on the anterior surface of the knee with its smooth joint-forming processes on its posterior surface facing the femur [3].

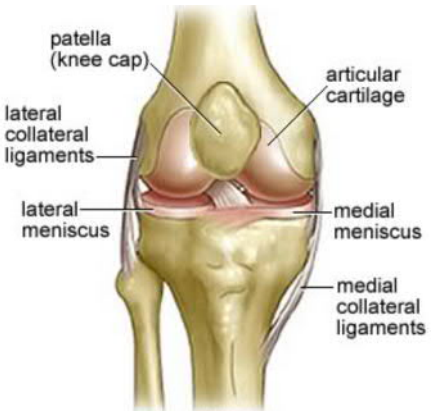


Figure 4. Right knee anatomy [3].

The joint-forming surfaces of each bone are covered in a thin layer of hyaline cartilage that gives them a smooth surface and protects the underlying bone from damages. Between the femur and tibia is a rubbery fibrocartilage known as the meniscus. The meniscus acts as a shock absorber inside the knee to prevent the collision of the leg bones during activities such as running and jumping [3].
Many strong ligaments surround the joint capsule of the knee to reinforce its structure and hold its bones in the proper alignment. In addition to the joint capsule and ligaments that support the knee, there are also several structures surrounding the knee that help and protect the joint from friction and outside forces. Small pockets of synovial fluid, known as bursae, surround the knee to reduce the friction from movement of tendons across the surface of the joint [3].

Hip Joint

The hip joint, or coxofemoral joint, is the articulation of the acetabulum of the pelvis and the head of the femur. These two segments form a diarthrodial ball-and-socket joint. The primary function of the hip joint is to support the weight of the head, arms, and trunk both in static posture and in dynamic postures such as ambulation, running, and stair climbing [4].
The acetabulum is formed by the merging of the ossification centers of ilium, ischium and pubis bones of pelvis. Hyaline cartilage lines both the acetabulum and the head of the femur, providing a smooth surface for the moving bones to glide past each other. Hyaline cartilage also acts as a flexible shock absorber to prevent the collision of the bones during movement. Between the layers of hyaline cartilage, synovial membranes secrete watery synovial fluid to lubricate the joint capsule. Surrounding the hip joint are many tough ligaments that prevent the dislocation of the joint. The strong muscles of the hip region also help to hold the hip joint together and prevent dislocation [5-7].

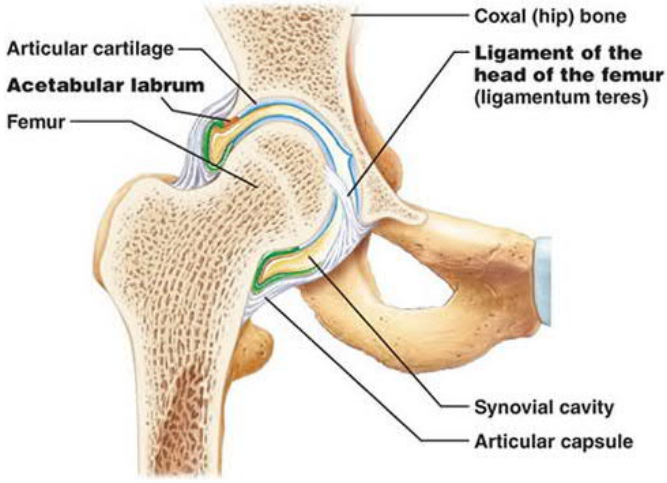


Figure 5. Frontal section of a hip joint [8].

3.3.1 *Histological characteristics of the sinovial cavity and its physiology*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations. *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is injected into the synovial cavity.

The sinovial cavity is the space found between bone segments and articular capsule; it is delimited by a fibrous wrap internally covered by a synovial membrane and contains a slight film of synovial fluid. The synovial cavity consists, depending on where it is found, of the **joint cavity**, the **bursae** and the **tendon sheaths** [9] (Figure 6).
The synovial fluid has a variable volume according to the dimension of the articular cavity and it represents, physiologically, a thin veil to protect the cartilage surface; it acts as a lubricant and it has nourishing functions for the cartilage itself. The synovial fluid is filtered from the blood plasma and it contains a maximum of 200 cell/cc. It also contains electrolytes, glucose, enzymes, immunoglobulins and proteins mainly originating from blood, with the addition of mucin - mostly hyaluronic acid - that makes the synovial fluid viscous, elastic and plastic [9].

The articular capsule consists of intertwisted bundles of connective fibrous tissue, whose insertion onto bone occurs as a continuous line. At some points the capsule is strengthened by the intrinsic capsular ligaments, represented by local thickenings (made of fibrous or fibro-elastic tissue) of the capsule itself, where the fiber bundles become parallel. The articular capsule is internally covered by the **synovial membrane**. The synovial membrane is a connective tissue of mesenchymal origin, covering any exposed osseous surface, the synovial bursae in communication with the joint cavity and the intracapsular ligament and tendons; it is not present on meniscal and discal surfaces and it stops right before the edge of joint cartilage,

the peripheral area of which, only a few millimeters thick, constitutes a zone of transition from synovial membrane to cartilage.
In the synovial cavities of some joints, adipose tissue is stored in specific regions, forming mobile and elastic pads that fill in the spaces of the articular cavity. Such adipose stores, when the joint moves, adapt to the changes of shape and volume of the synovial cavity, supporting the lubrication of the joint surfaces.
The synovial membrane is made of a cellular intima lying on a fibrovascular subintimal lamina consisting of abundant loose areolar tissue, collagen and elastic fibers. When the synovial membrane covers the intracapsular tendons or ligaments, the subintima is hardly identifiable as a separate layer, being fused together with the capsule, the ligament or the adjacent tendon [9].

The synovial intima is made of cells, called synoviocytes A and B, whose function is to remove the debris found in the joint cavity and to synthesize some molecules for the synovial fluid. The synoviocytes do not actively proliferate under basal conditions, while the speed of cellular division is considerably increased after trauma and acute hemarthrosis [9].

The bursae are virtual spaces localized in specific regions of the joint where high friction between closely opposing structures occurs. The bursae can be visualized almost solely in pathologic conditions, because they physiologically contain a slight film of synovial fluid. As above, the bursae are covered by the synovial membrane that continues from the synovial membrane of the articular cavity, so that it constitutes communicating bursae where the synovial fluid is freely circulating. The communicating bursae have a further biomechanical function: they decrease the endoarticular pressure when there is a fluid collection in the joint cavity [9].

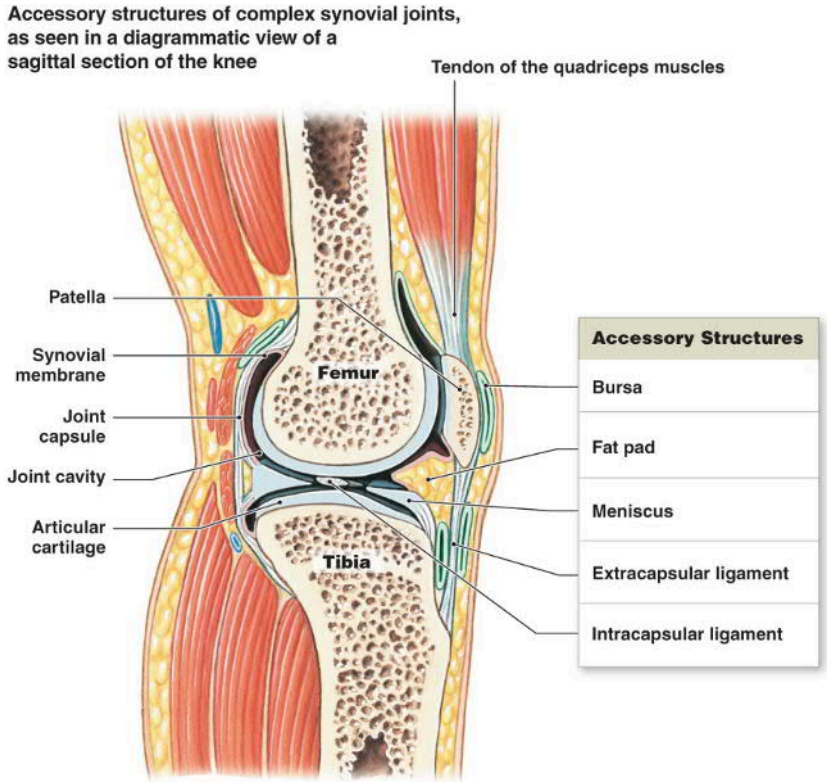


Figure 6. Structure of a synovial joint and joint cavity - the knee [14].

3.4 *GENERAL DESCRIPTION OF INTERESTED MEDICAL CONDITION*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.
It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).
Tendinopathy is a broad term encompassing painful conditions occurring in and around tendons in response to overuse [15].

Among degenerative/traumatic diseases, osteoarthritis (OA) is one of the most common conditions. OA refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. It is the most common form of arthritis, and one of the leading causes of pain and disability worldwide. The most commonly affected peripheral joints are the knees and the hips, but also small hand joints [16].

OA is characterized by multiple risk factors, which can be genetic factors (heritability estimates for hand, knee and hip osteoarthritis are high at 40–60%), constitutional factors (for example, ageing,

female sex, obesity, high bone density) and biomechanical risk factors (for example, joint injury, occupational/recreational usage, reduced muscle strength, joint laxity, joint malalignment*)* [17-20].

OA is characterised pathologically by localised loss of cartilage, remodelling of adjacent bone and associated inflammation. OA includes a slow but efficient repair process that often compensates for the initial trauma, resulting in a structurally altered but symptom-free joint. In some people, because of either overwhelming trauma or compromised repair, the process cannot compensate, resulting in eventual presentation with symptomatic osteoarthritis; this might be thought of as 'joint failure'. This in part explains the extreme variability in clinical presentation and outcome that can be observed between people, and also at different joints in the same person [21,22]. The main signs and symptoms of OA are pain, stiffness and loss of movement and function. As no cure exists for osteoarthritis, current treatments are mainly aimed at reducing pain and improving joint function [23].

3.5 *PREVALENCE OF OSTEOARTHRITIS*

The incidence and prevalence of OA are difficult to determine because clinical syndrome of osteoarthritis (joint pain and stiffness) does not always correspond with the structural changes of osteoarthritis (usually defined as abnormal changes in the appearance of joints identified by radiographs) [24].
This area is becoming more complex with sensitive imaging techniques such as magnetic resonance imaging, which demonstrate more frequent structural abnormalities than detected by radiographs [25].

OA at individual joint sites (notably knee, hip and hand) demonstrates consistent age-related increases in prevalence. However symptomatic osteoarthritis is not an inevitable consequence of ageing [25]. Although prevalence of osteoarthritis rises in frequency with age, it does affect substantial numbers of people of working age. The number of people with osteoarthritis in the UK is increasing as the population ages, and as the prevalence of risk factors such as obesity and poor levels of physical fitness also continues to rise [24].

3.6 *RISK FACTORS*

The main risk factors for OA are advancing age, genetic predisposition, mechanical stress and a sedentary lifestyle. However, there are factors that directly interfere in its prevalence, such as sex, trauma, ethnicity, inflammatory diseases, obesity (which accelerates the degradation process), primary changes in cartilage, heredity (woman), mechanical, hormonal and metabolic factors, and infections [26]. It is believed that the etiology of OA is related to a lack of adaptation to the functional demands of the body, i.e. surges, macro- or micro-traumas [27-32].

3.7 *PATOPHYSIOLOGY*

Osteoarthritis (OA) is a degenerative joint disease, chronic and progressive, affecting synovial joints [33-34].

These processes result in different interactions between the joint cartilage and adjacent tissues in response to injury or chondrocyte extracellular matrix [35,36].

From the lesion starts matrix degradation by proteolytic enzymes such as Matrix Metalloproteinase (MMPs). The specific collagenases include MMP-1 (collagenase up-1), MMP-8 (collagenase-2) and MMP-13 (collagenase-3). These enzymes are distinguished by the ability to degrade other regions of the triple helical helix of type I collagen, II and III. The gelatinases MMP-2 (gelatinase A) and MMP-9 (gelatinase B) is another group of enzymes that degrade collagen types IV, V, VII and XI. This group acts synergistically with collagenase in cleavage of collagen. In addition, degrade elastin, agrecans and cartilage link protein. Other enzymes are also able to degrade extracellular matrix, such as cathepsin D, degrade agrecans; cathepsins B and L cleave telopeptides regions of collagen types I and II resulting in depolymerized collagen fibrils, agrecans and helical regions of the collagen IX and XI. There are still serine proteases, such as plasmin, which directly degrade extracellular matrix, or by activating metalloproteinase precursors [37].

At the same time, the cartilage components are organized to control progression degeneration [38]. The decomposition of proteoglycan and collagen bundles triggers increased amount of water, the space between the fibrils followed by a superficial necrosis of chondrocytes and reduced density of these cells. Consequently, the joint surface will change affecting the joint capsule, subchondral bone, ligaments, muscles and tendons, including the synovial fluid. Increased hydration of cartilage and proteoglycans, promotes changes in mechanical properties of the tissue, triggering the loss of integrity of the articular surface and the presence of vertical cracks progressing to deep erosions with the consequent exposure of the subchondral bone [39-41]. These conditions cause pain, swelling and loss of joint mobility in osteoarthritis.

Acute pain of early osteoarthritis usually has a tendency to disappear within one year after having emerged, but may return and become chronic if no maintenance. Thus, immediate and proper treatment of osteoarthritic pain is crucial to maintain mobility and quality of life of the individual [42].

3.8 *CLINICAL PRESENTATION*

Osteoarthritis (OA) is as degenerative joint disease, a chronic condition characterized by the breakdown of joint cartilage, which becomes roguher and thinner. The bone underneath thickens and the joint becomes inflamed (Figure 7). The tissues around the joints, such as ligaments and the joint capsule, may thicken and become tighter, too.

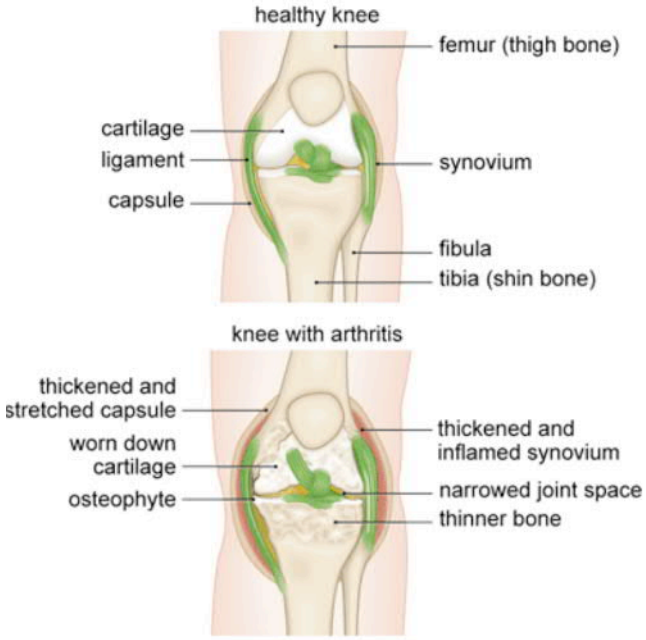


Figure 7. Normal knee compared with knee with osteoarthritis [43].

OA has many symptoms, which generally comprise those caused by mechanical or chemical stimulation. The main symptoms are pain and stiffness in the affected joint, but many other signs and symptoms may develop over time.

Pain is triggered by degenerative changes (bone remodeling, subchondral micro fractures, periostitis, nerve compression by osteophytes). In contrast to inflammatory arthritides - such as rheumatoid arthritis, with their prolonged morning stiffness and worsened pain in the morning - OA tends to worsen as the day progresses. The stiffness in OA is termed “inactivity stiffness” and contrasts with the prolonged “morning stiffness” of rheumatoid arthritis. Inactivity stiffness in osteoarthritic lower limb joints lasts about 5 to 10 minutes and occurs when the patient gets up and bears weight after prolonged immobility [44].

Pain may arise from the nociceptive fibers and mechanoreceptors in the synovium, subchondral bone, periosteum, capsule, tendons, or ligaments. Pain in large joint OA (such as knee or hip) is also thought to arise from bone marrow lesions, and synovitis/effusion by stimulation of nociceptive fibers and intra-articular hypertension, respectively, and a similar mechanism may also operate in the small joints. However, hyaline cartilage is aneural, and is not a source of pain in OA. Whatever its source, both central and peripheral sensitization perpetuate and amplify pain in OA [45,46].

Crepitus is a coarse crunching sensation or sound caused by friction between damaged articular cartilage and/or the bone. It may be more prominent during active movement than during passive movement during physical examination. It is often present throughout the range of movement. Crepitus may be exacerbated by stressing the joint surfaces. Transmitted

crepitus (felt on the adjacent periarticular bone) suggests a full-thickness cartilage defect on the affected side [47].

Tenderness in and around the joint is common in OA. Joint-line tenderness suggests an articular disorder, whereas tenderness away from the joint line suggests a periarticular soft tissue disorder [48].

Other common clinical manifestations of OA include [49,50]:

- Inelasticity;
- Paresthesia sensation of upper / lower limbs;
- Deformities. Malalignment with a bony enlargement may occur. Most cases of osteoarthritis do not involve erythema or warmth over the affected joint(s); however, a bland effusion may be present [51];
- Disease progression cause movement limitation associated with muscle spasm, contraction of the capsule and osteophytes or intra-articular bodies [52].

Other manifestations in patients with OA include sequelae such as muscle weakness, poor balance and comorbidities like fibromyalgia [53].

3.8.1 *Osteoarthritis classification*

OA can be classified as primary (idiopathic) when its etiology is not well defined and secondary when there is a specific disease-causing process. The primary is localized or widespread, more common in women, in middle age and progresses slowly as an accentuation of the normal aging process of the joint. The secondary OA is the result of genetic factors, trauma, more common in men at any age, inflammatory, neuropathic, metabolic or endocrine diseases result from congenital abnormality of the joint, joint infection, inflammatory disorders, metabolic arthritis, hemochromatosis repeated, traumatic injuries and deformities, acquired articular incongruity, joint misalignment or instability of the joint. Therefore, most of the cases are secondary to osteoarthritis another condition. The most commonly affected joints are the knees, hips, hands, neck, and lumbar spine [49,50].

One of the most accepted hypotheses would be a defect in the articular cartilage or collagen metabolism. Among the genes potentially involved in the disease are: Insulin-like Growth (IGF-I and IGF-II) factor of the Vitamin D Receptor (VDR), oligomer proteins of cartilage matrix and regions of the Human Leukocyte Antigen (HLA). There seem loci linked to osteoarthritis in areas of chromosomes 2q and 11q. Although the hypothesis of defects in structural proteins such as collagen type II and IX have been proposed, there is no concrete evidence of their involvement in disease occurrence. Osteoarthritis results from an imbalance in the metabolic processes mediated by chondrocytes and is characterized by a gradual degradation of extracellular matrix components of fibrocartilage, with or without secondary inflammatory factor [54-56].

3.9 *DIAGNOSTIC OPTIONS*

A diagnosis of osteoarthritis may be suspected after a medical history and physical examination is done. Blood tests are usually not helpful in making a diagnosis.

The current gold standard for morphological assessment of knee osteoarthritis is plain radiography [57], which can be used to establish the severity of joint damage and monitor disease progression [58]. However, there is a great deal of conflicting evidence about the relationship between radiographic findings and clinical symptoms [59,60].
Computed tomography (CT), ultrasound and magnetic resonance imaging (MRI) are used to assess the soft tissues and fluid-filled spaces or to exclude other diseases and conditions. Arthrocentesis should be performed to analyse synovial fluid for evidence of crystals or joint deterioration: joint aspiration may help rule out other medical conditions or other forms of arthritis [61].

3.9.1 *WOMAC score*

The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score in an index indicated to assess pain, stiffness, and physical function in patients with hip and/or knee osteoarthritis (OA). It is obtained through a questionnaire (Figure 8), consisting of 24 items divided into 3 subscales:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): stair use, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy household duties, light household duties [115].

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

Figure 8. WOMAC questionnaire [116].

3.10 *TREATMENT OPTIONS*

There is no cure for osteoarthritis, however treatments are available to manage symptoms. Treatment choices fall into four main categories: nonpharmacologic, pharmacologic, complementary and alternative, and surgical. Surgical management should be reserved for those who do not improve with behavioral and pharmacologic therapy, and who have intractable pain and loss of function [62].

Non-pharmacologic and physical therapy

Nonpharmacologic therapy often starts with exercise. While it may be hard to think of exercise when the joints hurt, moving is considered an important part of the treatment plan. Studies show that simple activities like walking around the neighborhood can reduce pain and help maintain (or attain) a healthy weight.

Strengthening exercises build muscles around OA-affected joints, easing the burden on those joints and reducing pain. Range-of-motion exercise helps maintain and improve joint flexibility and reduce stiffness. Aerobic exercise helps to improve stamina and energy levels and also help to reduce excess weight. A randomized clinical trial compared supervised home-based exercise with no exercise in 786 patients with osteoarthritis of the knee. The exercise program consisted of muscle strengthening and range-of-motion exercises. The researchers found statistically significant improvements in a validated arthritis symptom score at six, 12, 18, and 24 months [63].

The U.S. Department of Health and Human Services recommends that everyone, including those with arthritis, get 150 minutes of moderate exercise per week.

Therapeutic ultrasound is a physical therapy modality often used in OA treatment. A Cochrane review of this modality concluded that, although statistically significant improvements were noted in visual analog pain scales following therapeutic ultrasound for knee OA, the clinical significance of these changes is questionable. The authors found that the studies were underpowered to properly determine the effectiveness of therapeutic ultrasound for knee or hip osteoarthritis [64].

A Cochrane review on transcutaneous electrical nerve stimulation found no clinically significant improvement in knee osteoarthritis pain [64].

Pharmacological approach

OA symptoms, primarily pain, may be helped by certain medications, including [65]:

- Acetaminophen. Acetaminophen (Tylenol, others) is an OTC (over-the-counter) analgesic that has been shown to be effective for people with osteoarthritis who have mild to moderate pain. A 2006 Cochrane review concluded that acetaminophen is better than placebo for treating mild osteoarthritis, and equal to nonsteroidal anti-inflammatory drugs (NSAIDs), but with fewer gastrointestinal adverse effects [66].
- Nonsteroidal anti-inflammatory drugs (NSAIDs). When acetaminophen fails to control symptoms, or if symptoms are moderate to severe, NSAID therapy is recommended. Over-the-counter NSAIDs, including ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve, others), taken at the recommended doses, typically relieve osteoarthritis pain. Stronger NSAIDs, available by prescription, may also slightly reduce inflammation along with relieving pain.
- Opioids. These drugs are often used to treat pain and are an option for osteoarthritis pain. Because of the potential for abuse, opioids should be an option only if the

patient has not responded to acetaminophen or NSAID therapy, or cannot tolerate them because of adverse effects [67].

- Topical analgesics. These include Diclofenac sodium gel and solution, only available as a prescription, Lidocaine patches, Methyl salicylate and menthol (Bengay) and Trolamine (Aspercreme), topical cream containing an aspirin-like drug that relieves inflammation and pain [68].

Surgical approach

Surgery should be reserved for patients whose symptoms have not responded to other treatments. The well-accepted indication for surgery is continued pain and disability despite conservative treatment [69]:

- Cortisone injections. Injections of corticosteroid medications may relieve pain in the joint. During this procedure the physician numb the area around the joint, then places a needle into the space within the joint and injects medication. The use of intra-articular corticosteroids primarily provides short-term relief lasting four to eight weeks. It has proven effectiveness in osteoarthritis of the knee, but may not be as effective for osteoarthritis of the shoulder or hand [70,71]. Many physicians inject a corticosteroid and a local anesthetic, such as lidocaine (Xylocaine). The lidocaine can provide some immediate relief, which confirms that the medication was injected into the correct area. Patients should be warned of a potential flare-up of symptoms within the first 24 hours, followed by an improvement from baseline at 48 hours. Repeat injections are possible in the same joint, but usual practice is limited to four injections annually [72].
- Realigning bones**.** If osteoarthritis has damaged one side of the knee more than the other, an osteotomy might be helpful. In a knee osteotomy, a surgeon cuts across the bone either above or below the knee, and then removes or adds a wedge of bone. This shifts the body weight away from the worn-out part of the knee (Figure 9).

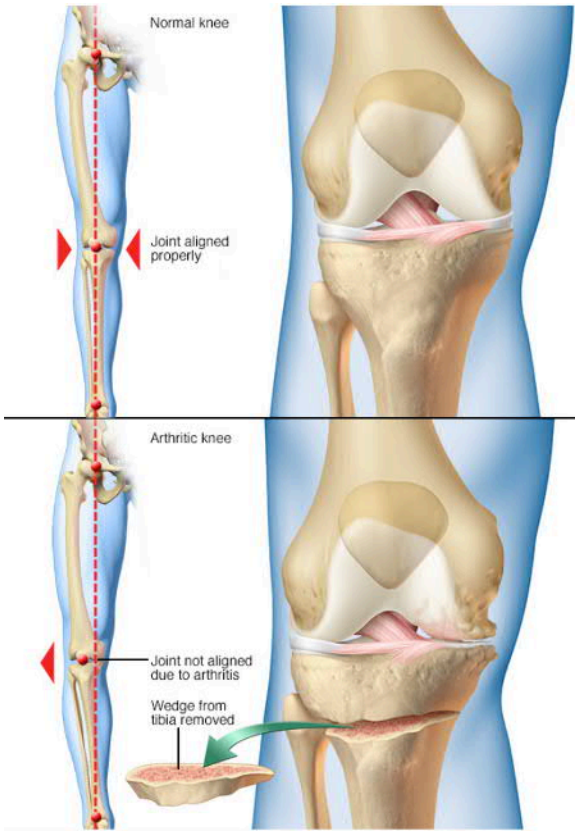


Figure 9. Knee osteotomy [73].

- Joint replacement. In joint replacement surgery (arthroplasty), the surgeon removes the damaged joint surfaces and replaces them with plastic and metal parts (Figure 10). Joint replacement is the most effective surgical intervention, with excellent patient outcomes following total joint replacement of the hip, knee, and shoulder [74].

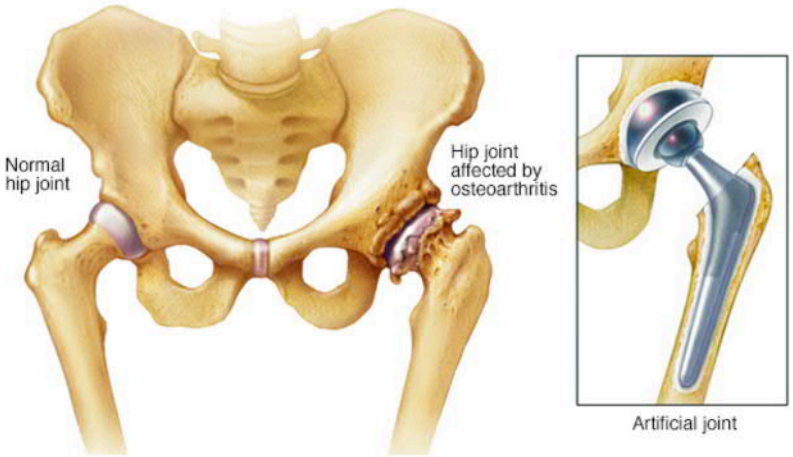


Figure 10. Hip prostheses are designed to mimic the ball-and-socket action of the hip joint. During hip replacement surgery, the surgeon removes the diseased or damaged parts of the hip joint and inserts the artificial joint [75].

- Lubrication injections. Intra-articular hyaluronic acid injections, also known as viscosupplementation, are widely used by orthopedic surgeons to treat osteoarthritis of the knee. A 2006 Cochrane review of 76 clinical trials concluded that viscosupplementation was effective for treating knee osteoarthritis. The treatment effect often lasted for up to 4 months and led to improvements in pain and function [76]. There have been trials comparing corticosteroid injections and hyaluronic acid injections. A meta-analysis of knee injections found that corticosteroids had a better short-term response rate and were equal to hyaluronic acid in the intermediate four- to eight-week range, but were inferior to hyaluronic acid after eight weeks from the time of injection [77]. Therefore, in stable patients with an acute flare-up of osteoarthritis symptoms, corticosteroids may be preferred. For patients experiencing chronic osteoarthritis pain, hyaluronic acid should be considered.

Complementary and alternative medicine

A meta-analysis on the effectiveness of acupuncture for osteoarthritis of the knee found only short-term benefit, which the authors described as clinically irrelevant [78].

The most widely used supplements for osteoarthritis are glucosamine and chondroitin. The literature consisted of small clinical trials until the release of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), which included more than 1,500 patients. The trial had five arms comparing glucosamine alone, chondroitin alone, a combination of glucosamine and chondroitin, celecoxib, and placebo. The results were favorable only for the combination of glucosamine and chondroitin, which appeared to be effective for moderate to severe osteoarthritis of the knee [79]. Chondroitin alone did not show benefit for osteoarthritis of the knee or hip in a meta-analysis [80].

There also is evidence supporting the use of the supplement S-adenosylmethionine (SAM-e) to reduce functional limitation, but not compared with placebo in patients with osteoarthritis pain. The effectiveness of SAM-e is comparable to that of NSAIDs in some studies but with fewer adverse effects [81].

Balneotherapy is a heterogeneous group of treatments also known as spa therapy or mineral baths. A Cochrane review concluded that mineral baths were of some benefit to patients with osteoarthritis, but the authors addressed methodologic flaws in the studies and urged caution in interpreting the findings [82].

Capsaicin cream is a topical analgesic derived from chili peppers, which has been found to be superior to placebo in treating osteoarthritis pain [83].

3.11 *IDENTIFIED DISADVANTAGES AND HAZARDS DUE TO SUBSTANCES/MATERIALS AND TECHNOLOGIES*

The main risk in OA treatment is related to the pharmacological approach (medications) and surgical approach.

Medications' side effects

Acetaminophen is an OTC analgesic used in suffering from OA who experience mild to moderate pain. The *Arthritis Foundation* recommends taking no more than 3,000 mg of acetaminophen per day, because taking higher doses for a long time can lead to liver damage or failure. This can also be fatal [84].

Systemic nonsteroidal anti-inflammatory drugs (NSAIDs) can cause stomach irritation that may result in bleeding, ulcers, or perforation of the stomach or intestines. NSAIDs can also cause cardiovascular problems, bleeding problems, liver and kidney damage, constipation, diarrhea, gas, heartburn, nausea, vomiting and dizziness. Topical NSAIDs have fewer side effects and may relieve pain just as well.

Corticosteroids have many risks if used for long-term treatment; like NSAIDs, they reduce inflammation but are hard on the stomach. Unlike NSAIDs, they do not cause kidney problems. Other side effects of steroids include stomach ulcers, high blood pressure, irritability, depression, osteoporosis and high blood sugar levels [85].

Opioids should be prescribed first at low dosages and carefully monitored to evaluate for potential dependence. Opioids also make the patient sleepy or impair balance, and cause chronic constipation and can place older patients at risk of falls [86,87].

Surgery side effects

As mentioned before, joint replacement is the most effective surgical intervention, with excellent patient outcomes following total joint replacement of the hip, knee, and shoulder [88]. This technique, however, is not free from risks: surgical risks include infections and blood clots. Moreover, artificial joints can wear out or come loose and may need to eventually be replaced [89].

The two most common types of knee injection for OA are corticosteroids and hyaluronic acid. Corticosteroid injections are useful for treating flare-ups of OA pain and swelling with fluid buildup in the knee. However, the number of injections each year is generally limited to 3 injections, because the medication can worsen joint damage over time. In some people who receive cortisone injections, the cartilage softens and the tendons weaken in the joint that is being treated. Infection at the site of your injection is a rare, but still serious potential side effect of cortisone shots [90].

Viscosupplementation with Hyaluronic acid (HA) injections works differently, by helping cushion and lubricate the moving parts within the joint area. However, generally HA require more than 1 (up to 5) injections, usually within a 5-week period. Viscosupplementation is considered a safe procedure, but like any medical procedure it does carry some risks and side effects. Patients who undergo viscosupplementation may have mild discomfort immediately after the procedure. Typical side effects at the injection site include: localized swelling, skin warmth and/or redness, soreness and joint stifness. It has been estimated that 1% to 3% of patients experience localized swelling and skin changes. However, side effects are usually mild and go away in 1 to 2 days [91].

4 MEDICAL DEVICE UNDER EVALUATION

4.1 *GENERAL DETAILS*

Table 1. Description of the medical device.

<table>
<tr><td>Device Name</td><td>"Hyaluronic acid sodium salt, viscosuppletive joint device"</td></tr>
<tr><td>Trade Name</td><td>
<table>
<tr><th>Brand names</th><th colspan="6">Percentage of hyaluronic acid</th></tr>
<tr><td></td><td colspan="2">0,8%</td><td>1,0%</td><td colspan="2">1,6%</td><td colspan="2">2,0%</td></tr>
<tr><td>Volume</td><td>1 ml</td><td>2 ml</td><td>2 ml</td><td colspan="2">2 ml</td><td colspan="2">2,5ml</td></tr>
<tr><td>Sinovial</td><td>X (Mini)</td><td>X</td><td>X</td><td>X (Forte)</td><td>X (Highvisc)</td><td>X (One)</td><td>X (Once)</td></tr>
<tr><td>Intragel</td><td>X (Mini)</td><td>X</td><td>X</td><td colspan="2">X (Forte)</td><td>X (One)</td><td>X (Once)</td></tr>
<tr><td>Yaral</td><td>X (Mini)</td><td>X</td><td>X</td><td colspan="2">X (Forte)</td><td>X (One)</td><td>X (Once)</td></tr>
<tr><td>Gony Alert MD</td><td>X (Mini)</td><td>X</td><td>X</td><td colspan="2">X (Forte)</td><td>X (One)</td><td>X (Once)</td></tr>
</table>
Note: for aspects referring to all product brand names, the general device name "Hyaluronic acid sodium salt, viscosuppletive joint device" will be used in this table.
</td></tr>
<tr><td>Manufacturer name and address</td><td>IBSA Farmaceutici Italia srl
Via Martiri di Cefalonia 2
26900 Lodi
Italy</td></tr>
<tr><td>Intended Purpose in accordance with device's IFU</td><td>"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.
It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).</td></tr>
</table>

Indications	Sinovial/Intragel/Yaral/Gony Alert MD 1,0% (2 ml): The product is indicated in the presence of pain or reduced mobility due to degenerative diseases and tendinopathy associated with joint disabilities. Sinovial Mini/Intragel Mini/Yaral Mini/Gony Alert MD Mini 0,8% (1 ml): The product is indicated for the treatment of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger). Sinovial/Intragel/Yaral/Gony Alert MD 0,8% (2 ml): The product is indicated in the presence of pain or reduced mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations. Sinovial Forte-Highvisc/Intragel Forte, Yaral Forte, Gony Alert MD Forte 1,6% (2 ml): The product is indicated in the presence of pain or reduced mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations. Sinovial One-Once/Intragel One-Once, Yaral One-Once, Gony Alert MD One-Once 2,0% (2,5 ml): The product is indicated in the presence of pain or reduced mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

Product Description (physico-chemical, mechanical and technical specifications)	"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is an intra-articular visco-supplementation product, which allows to restore the physiological and rheological properties of arthritic joints and tendon sheath. "*Hyaluronic acid sodium salt, viscosuppletive joint device*" contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid, to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in "*Hyaluronic acid sodium salt, viscosuppletive joint device*" is obtained by fermentation and has not undergone chemical change processes. It is a substitute for synovial fluid which allows the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, "*Hyaluronic acid sodium salt, viscosuppletive joint device*" reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action. The other components of "*Hyaluronic acid sodium salt, viscosuppletive joint device*" are: sodium chloride, sodium phosphate and water for injectable preparations.
Size(s)/Packaging	Sinovial/Intragel/Yaral/Gony Alert MD 1,0% (2 ml): packs of 1, 3 or 5 pre-filled syringes, provided with or without needles (2.25 ml glass syringes containing 2 ml of the solution). Sinovial Mini/Intragel Mini/Yaral Mini/Gony Alert MD Mini 0,8% (1 ml): pack with 1-3 pre-filled syringes (1,25 ml syringe containing 1 ml solution, i.e. 8 mg HA/ 1 ml in a buffered physiological solution of sodium chloride). Sinovial/Intragel/Yaral/Gony Alert MD 0,8% (2 ml): packs of 1, 3 or 5 pre-filled syringes, provided with or without needles (2.25 ml glass syringes containing 2 ml of the solution). Sinovial Forte-Highvisc/Intragel Forte, Yaral Forte, Gony Alert MD Forte 1,6% (2 ml): packs with 1, 3 or 5 pre-filled syringes provided with or without needles (2,25 ml syringe containing 2 ml solution, i.e. 32 mg HA/ 2 ml in a buffered physiological solution of sodium chloride). Sinovial One-Once/Intragel One-Once, Yaral One-Once, Gony Alert MD One-Once 2,0% (2,5 ml): pack with 1 pre-filled syringe (3 ml glass syringe containing 2.5 ml of solution, i.e. 50.0 mg hyaluronic acid sodium salt in 2.5 ml buffered physiological solution of sodium chloride)

Ingredients/materials in contact with the patient/user	"Hyaluronic acid sodium salt, viscosuppletive joint device" contains highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa) obtained by fermentation, sodium chloride, sodium phosphate and water for injectable preparations.
Directions of use	"Hyaluronic acid sodium salt, viscosuppletive joint device": • Aspirate any joint effusion before proceeding with the injection; • Pull out the cap of the syringe, being particularly careful to avoid contact with the opening; • Insert the needle, of 18-22 G diameter; • Screw the needle tightly to the Luer type closure neck of the syringe to ensure an airtight seal and prevent leakage of liquid during the medication; • Inject the product at ambient temperature and under strict asepsis conditions. Inject the product only into the synovial space.

Posology	It is specified that the intra-articular injections can only be administered by a doctor. "Hyaluronic acid sodium salt, viscosuppletive joint device" medical device is sold as prescription only. Sinovial/Intragel/Yaral/Gony Alert MD 1,0%: 3-5 injections, each administered one week apart, cause a reduction in pain and swelling in addition to an improvement in function, which can continue for up to 24 weeks. Sinovial Mini/Intragel Mini/Yaral Mini/Gony Alert MD Mini 0,8% (1 ml): 2-3 injections per year; there should be an interval of at least 4-6 months between injections according to physician's advise. Sinovial/Intragel/Yaral/Gony Alert MD 0,8% (2 ml): 3-5 injections, each administered one week apart, cause a reduction in pain and swelling in addition to an improvement in function, which can continue for up to 24 weeks. Sinovial Forte-Highvisc/Intragel Forte, Yaral Forte, Gony Alert MD Forte 1,6% (2 ml): Injections at weekly intervals for a total of 3 weeks. If necessary, further injections may be administered. It is the doctor’s responsibility to evaluate the appropriateness of repeating the cycle of treatment and its frequency for each patient, taking into consideration the risk/benefit ratio of the treatment in each case. Sinovial One-Once/Intragel One-Once, Yaral One-Once, Gony Alert MD One-Once 2,0% (2,5 ml): The medical device is a single-dose preparation and should be injected only once per cycle of treatment. If necessary, further injections may be administered. It is the doctor’s responsibility to evaluate the appropriateness of repeating the cycle of treatment and its frequency for each patient, taking into consideration the risk/benefit ratio of the treatment in each case.
Invasiveness (MD Directive)	The device is considered an invasive device, in accordance with Directive 93/42/EEC definition, "A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body". A body orifice is defined as "Any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening such as a stoma". It is applied in the joint cavity.

Parts of the body contacted by the device (ISO 10993-1)	The medical device is in contact with the joint cavity as substitute of the synovial fluid.
Duration of use or contact with the body (ISO 10993-1)	"Hyaluronic acid sodium salt, viscosuppletive joint device" medical device is categorized according to the duration of contact as "permanent" device, i.e. medical device whose cumulative single, multiple or repeated use or contact is > 30 days according to ISO 10993-1:2009 definition.
Primary Mechanism of Action, Principle of operation	"Hyaluronic acid sodium salt viscosuppletive joint device" is a substitute for synovial fluid, which allows the re-establishment of the physiological and rheological properties of joints affected by degenerative diseases, post-traumatic diseases or joint and tendons alterations (mechanical mode of action). The medical device acts only at the level of the joint into which it is injected, without exercising any systemic action.
Sterility (including sterilization method)	"Hyaluronic acid sodium salt viscosuppletive joint device" medical device is sterile. The content of the syringe is steam sterilized.
Single use/reusable device	The device is disposable.
Warnings	"Hyaluronic acid sodium salt viscosuppletive joint device": • The content of the pre-filled syringe is sterile. The syringe is packed in a sealed blister pack. The external surface of the syringe is not sterile; • Do not use the product after the expiry date shown on the pack. • Do not use the product if the packaging is open or damaged. • The injection site must be on healthy skin. • Do not inject intravenously. Do not inject outside the joint cavity, into the synovial tissue or into the articular capsule. • Do not administer the product in the presence of heavy intra-articular effusion. • Do not sterilise again. The device was foreseen as a throwaway device only. • Do not reuse to avoid any risk of contamination. • Store between 0-25°C away from heat sources. Do not freeze. • Once opened, the product must be used immediately and discarded after use. • Keep out of reach and sight of children. • After the intra-articular injection advise the patient to avoid any intense physical activity and to resume his or her normal activities only after several days; • The presence of an air bubble does not alter in any way the quality of the product.
Precautions	"Hyaluronic acid sodium salt viscosuppletive joint device": Do not concomitantly use disinfectants containing quaternary ammonium salts or chlorhexidine for skin preparation as hyaluronic acid can precipitate in their presence.

Contraindications	"Hyaluronic acid sodium salt viscosuppletive joint device": The product must not be injected in the presence of an infected or seriously inflamed joint or if the patient has a cutaneous disease or an infection in the area of the injection site.
Interactions	No interactions are currently known between "*Hyaluronic acid sodium salt viscosuppletive joint device*" and other medical products.
Identified side effects	"Hyaluronic acid sodium salt viscosuppletive joint device": • Extra-articular seepage of the device may cause undesired effects locally. • During the use of the device, symptoms such as pain, the sensation of heat, reddening or swelling may appear at the injection site. These secondary emergences can be relieved by applying ice to the treated joint. They generally disappear in a short space of time. • Doctors must ensure that patients notify them of any undesired effects which occur after the treatment.
Main claims	The therapeutic action of "Hyaluronic acid sodium salt viscosuppletive joint device" is carried out by the particular characteristics of the Hyaluronic Acid used in this medical device. The hyaluronic acid contained in this product is produced by fermentation and without any chemical modification, so that it can reach an excellent tolerability. After injection of "Hyaluronic acid sodium salt viscosuppletive joint device", the Improvement is instant: the WOMAC global index reduces and from the third injections onwards the reduction becomes statistically significant. The available studies confirm that 3-5 injections of "Hyaluronic acid sodium salt viscosuppletive joint device" (Sinovial/Intragel/Yaral/Gony Alert MD 1,0% 2ml, Sinovial/Intragel/Yaral/Gony Alert MD 0,8 % 2 ml), each administered one week apart, cause a reduction in pain and swelling in addition to an improvement in function, which can continue for up to 24 weeks.
Residual risk(s), relevant risks identified in the Risk Analysis	The Risk Management Team declares that no unacceptable risks related to the use of the medical device were detected, however the risk/benefit analysis has been carried out for each identified hazard. The risk/benefit ratio is in each case favourable. The Manufacturer establishes and maintains a post-marketing surveillance system for the medical devices marketed, in order to collect useful data pertaining to the product safety and start, when appropriate, further corrective and/or preventive actions for reducing risks related to the use of the device. In conclusion, The result of the risk analysis related to the medical device "Visco-suppletive joint device" leads to consider the overall risk as acceptable.

Regulatory status	Sinovial Mini/Intragel Mini/Yaral Mini/Gony Alert MD Mini 0,8% (1 ml): CE marked (certification year: 2010) Sinovial/Intragel/Yaral/Gony Alert MD 0,8% (2 ml): CE marked (certification year: 2010) Sinovial/Intragel/Yaral/Gony Alert MD 1,0 % (2 ml): CE marked (certification year: 2013) Sinovial Forte-Highvisc/Intragel Forte, Yaral Forte, Gony Alert MD Forte 1,6% (2 ml): CE marked (certification year: 2010) Sinovial One-Once/Intragel One-Once, Yaral One-Once, Gony Alert MD One-Once 2,0% (2,5 ml): CE marked (certification year: 2012)
Reference documentation	• Clinical Evaluation rev.0 dated February 25, 2016 (*HA sodium salt Viscosuppletive joint device_SP* and *HA sodium salt Viscosuppletive joint device_CLEV*) • Sinovial Mini 0,8% (1 ml) leaflet (Last revision: November 2014) • Sinovial 0,8% (2 ml) leaflet (Last revision: February 2015) • Sinovial/Intragel/Yaral/Gony Alert MD 1,0% leaflet (Last revision: February 2015) • Sinovial Forte 1,6% leaflet (Last revision: February 2015) • Sinovial One 2,0% leaflet (Last revision: February 2015) PRE-CLINICAL STUDIES: • CYTOTOXICITY - Cytotoxicity for elution test [Report Ref. 2011/2200.A1] and bacterial endotoxins test (LAL test) [Report Ref. 2011/2200.A2]; • DELAYED HYPERSENSITIVITY TEST [Report Ref. 2012/363.A3]; • SYSTEMIC TOXICITY - Systemic toxicity test [Report Ref. 2011/2199.A1] and Pyrogen test [Report Ref. 2011/2199.A2]; • INTRACUTANEOUS REACTIVITY TEST [Report Ref. 2012/363.A1]; • SUBCUTANEOUS IMPLANTATION TEST ON HYALURONIC SODIUM SALT 2% [Report Ref. 2012/364.AMi]; • OCULAR IRRITATION TEST [Report Ref. 2012/363.A1]; • DELAYED HYPERSENSITIVITY TEST (GMPT) ON SYNOVIAL ONE [Report Ref. 2011/1394 SAM]. RISK MANAGEMENT FILE - RMFI 22.04.03 current edition and RISK MANAGEMENT REPORT - RGR 22.04.03 current edition TECHNICAL FILE 22.04.03 - current edition

4.2 *DEVICE DESCRIPTION*

4.2.1 *The concept*

IBSA Farmaceutici developed *"Hyaluronic acid sodium salt, viscosuppletive joint device*", a medical device intended to be used on human beings for alleviation of a disease (degenerative diseases, post-traumatic diseases or joint and tendon alterations), whose main action is to substitute the synovial fluid and to allow the re-establishment of the physiological and rheological properties of joints affected by arthrosis.

4.2.2 *Description and composition*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

"Hyaluronic acid sodium salt, viscosuppletive joint device" is an intra-articular visco-supplementation product, which allows to restore the physiological and rheological properties of arthritic joints and tendon sheath.

"Hyaluronic acid sodium salt, viscosuppletive joint device" contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid, to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is obtained by fermentation and has not undergone chemical change processes.

It is a substitute for synovial fluid which allows the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, *"Hyaluronic acid sodium salt, viscosuppletive joint device"* reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action.

The other components of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* are: sodium chloride, sodium phosphate and water for injectable preparations.

"Hyaluronic acid sodium salt, viscosuppletive joint device" ingredients are shown in Table 2 below.

INCI UE
WATER
HYALURONIC ACID SODIUM SALT (0.8%, 1%, 1.6% and 2%)
SODIUM CHLORIDE
SODIUM PHOSPHATE

Table 2. *"Hyaluronic acid sodium salt, viscosuppletive joint device"* ingredients.

4.2.3 *Chemico-physical controls*

The analytical controls carried out during the manufacturing process on the bulk solution are: appearance, pH and dynamic viscosity; the analytical controls carried out on the finished product are appearance, extractable volume, pH, osmolality, dynamic viscosity, sodium hyaluronate identification and total sodium hyaluronate assay.

4.2.4 *Microbiological controls*

Both the sterility test and the determination of bacterial endotoxins are carried out on the finished product.

4.2.5 *Device specifications*

"Hyaluronic acid sodium salt, viscosuppletive joint device" finished product specifications are represented in the following table (Table 3):

Test	**Specification**
Appearance	Syringes containing a clear, colourless, homogeneous gel
Extractable Volume	≥ 1.0 ml (1 ml syringe) ≥ 2.0 ml (2 ml syringe) ≥ 2.5 ml (2.5 ml syringe)

pH	6.5 – 7.5
Dynamic Viscosity (25°C, 167.6 s^{-1})	! 50 mPa.s (0.8% concentration) ! 100 mPa.s (1.0% concentration) ! 500 mPa.s (1.6% concentration) ! 1000 mPa.s (1.0% concentration)
Osmolality	250 – 400 mOsm/Kg
Sodium Hyaluronate HMW – High Molecular Weight and LMW – Low Molecular Weight Identification (HPLC)	Positive
Total Sodium Hyaluronate assay (UV-vis method)	90.0 – 110.0% of the theoretical value
Sterility	Sterile
Bacterial Endotoxins	≤ 17,5 IU/ml (1 ml syringe) ≤ 8,75 IU/ml (2 ml syringe, 0.8% concentration) ≤ 5,62 IU/ml (2 ml syringe, 1% concentration) ≤ 8,75 IU/ml (2 ml syringe, 1.6% concentration) ≤ 4,5 IU/ml (2.5 ml syringe)

Table 3. *"Hyaluronic acid sodium salt, viscosuppletive joint device"* specifications.

4.2.6 *Packaging*

The medical device *"Hyaluronic acid sodium salt, viscosuppletive joint device"* in concentrations of 0.8% (16mg/2ml), 1.0% (20mg/2ml) and 1.6% (32mg/2ml) of hyaluronic acid sodium salt, is available in packages of 1, 3, and 5 pre-filled syringes.

The presentation 0.8 % MINI (8 mg/1ml) of hyaluronic acid sodium salt is available in packs of 1 and 3 pre-filled syringes.

The presentation 2.0% ONE/ONCE (50mg/2.5ml) of hyaluronic acid sodium salt is available in pack of 1 pre-filled syringe.

The product is steam sterilized and the syringes are disposable.

According to Manufacturer's declaration, primary packaging is phthalates-free.

In order to verify that the closure system of the pre-filled syringe (pre-filled syringe-cone cover-piston) is intact and does not allow the inward penetration of any external microbial agent, periodical tests for control are performed. The test provides that 500 pre-filled syringes are filled with a culture medium and then subjected to the normal sterilisation cycle foreseen for the manufacturing process.

At the end of the sterilization cycle in the autoclave, the syringes are placed in a sterile container and are submerged in culture medium inoculated with a suitable microbial agent with a concentration of 5 x 10^6 UFC/ml at minimum.

The pre-filled syringes are kept in contact with the culture medium for at least 24 hours at room temperature, then the culture medium is removed and the pre-filled syringes are put to incubate at room temperature for 14 days.

Lastly, no microbial growth must have occurred in any pre-filled syringe used for the execution of the negative control conducting using 500 syringes filled with cultural medium, sterilised and kept to incubate for 14 days at room temperature, without being placed in contact with the microbial agent.

4.3 *RATIONALE FOR THE USE OF "Hyaluronic acid sodium salt, viscosuppletive joint device" IN THE MANAGEMENT OF OSTEOARTHRITIS SYMPTOMS*

Osteoarthritis (OA) is the most common form of arthritis and refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. The most commonly affected peripheral joints are the knees and the hips, but also small hand joints [16]. OA is characterised by localised loss of cartilage, remodelling of adjacent bone and associated inflammation. The main signs and symptoms are pain, stiffness and loss of movement and function [23]. OA includes a slow but efficient repair process that often compensates for the initial trauma, resulting in a structurally altered but symptom-free joint. However, because of either overwhelming trauma or compromised repair, in some people the process cannot compensate, resulting in eventual presentation with symptomatic osteoarthritis; this might be thought of as 'joint failure'.

Pain may arise from the nociceptive fibers and mechanoreceptors in the synovium, subchondral bone, periosteum, capsule, tendons, or ligaments. Pain in large joint OA (such as knee or hip) is also thought to arise from bone marrow lesions, and synovitis/effusion by stimulation of nociceptive fibers and intra-articular hypertension, respectively, and a similar mechanism may also operate in the small joints [45,46]. Crepitus is a coarse crunching sensation or sound caused by friction between damaged articular cartilage and/or the bone [47]. Tenderness in and around the joint is common in OA. Joint-line tenderness suggests an articular disorder, whereas tenderness away from the joint line suggests a periarticular soft tissue disorder [48]. Other common clinical manifestations of OA include [49,50] inelasticity, paresthesia sensation of upper / lower limbs, deformities, malalignment with a bony enlargement [51] and movement limitation associated with muscle spasm [52].

OA can be classified as primary (idiopathic) when its etiology is not well defined and secondary

when there is a specific disease-causing process. The primary is localized or widespread, more common in women, in middle age and progresses slowly as an accentuation of the normal aging process of the joint. The secondary OA is the result of genetic factors, trauma, more common in men at any age, inflammatory, neuropathic, metabolic or endocrine diseases result from congenital abnormality of the joint, joint infection, inflammatory disorders, metabolic arthritis, hemochromatosis repeated, traumatic injuries and deformities, acquired articular incongruity, joint misalignment or instability of the joint [49,50].

Treatments available can only manage symptoms: they may be nonpharmacologic, pharmacologic, complementary and alternative, and surgical. Surgical management should be reserved for those who do not improve with behavioral and pharmacologic therapy, and who have intractable pain and loss of function [62].

Nonpharmacologic therapy often starts with exercise, since moving is considered an important part of the treatment plan. Strengthening exercises build muscles around OA-affected joints, easing the burden on those joints and reducing pain. Aerobic exercise helps to improve stamina and energy levels and also help to reduce excess weight [63]. Also Ultrasounds and transcutaneous electrical nerve stimulation are often used as a physical therapy modality for OA [64].

The pharmacological approach consists of some options [65]: Acetaminophen, Nonsteroidal anti-inflammatory drugs (NSAIDs), Opioids and Topical analgesics, such as Diclofenac sodium gel and solution, Lidocaine patches, Methyl salicylate and menthol (Bengay) and Trolamine (Aspercreme), topical cream containing an aspirin-like drug that relieves inflammation and pain [66-68]. The main contraindication to the use of medicinal products are side-effects of this type of treatment. In particular, Acetaminophen can lead to liver damage or failure [84]; Systemic nonsteroidal anti-inflammatory drugs (NSAIDs) can cause stomach irritation that may result in bleeding, ulcers, or perforation of the stomach or intestines; Corticosteroids may cause stomach ulcers, high blood pressure, irritability, depression, osteoporosis and high blood sugar levels, and have many risks if used for long-term treatment [85]. Opioids should be prescribed first at low dosages and carefully monitored to evaluate for potential dependence. Opioids may make the patient sleepy or impair balance, and cause chronic constipation and can place older patients at risk of falls [86,87].

Surgery should be reserved for patients whose symptoms have not responded to other treatments. The well-accepted indication for surgery is continued pain and disability despite conservative treatment [69], such as cortisone injections that may relieve pain in the joint [70,71], sometimes with lidocaine, which provides some immediate relief [72]. If osteoarthritis has damaged one side of the knee more than the other, an osteotomy might be helpful, while the most effective surgical intervention is joint replacement, with excellent patient outcomes [74]. This technique, however, is not free from risks: surgical risks include infections and blood clots. Moreover, artificial joints can wear out or come loose and may need to eventually be replaced [89].

Complementary and alternative medicine is performed with acupuncture, dietary supplements, such as glucosamine and chondroitin, balneotherapy and Capsaicin cream. All these methods have been evidenced to be effective in reducing patients' pain [78-83].

Another non-surgical approach is the use of lubrication injections. Intra-articular hyaluronic acid injections, also known as viscosupplementation, are widely used by orthopedic surgeons to treat osteoarthritis of the knee and, according to several clinical studies, they are effective [76].

The two most common types of knee injection for OA are corticosteroids and hyaluronic acid. Corticosteroid injections are useful for treating flare-ups of OA pain and swelling with fluid buildup in the knee. However, the number of injections each year is generally limited to 3or 3 injections, because the medication can worsen joint damage over time. In some people who receive cortisone injections, the cartilage softens and the tendons weaken in the joint that is being treated. Infection at the site of your injection is a rare, but still serious potential side effect of cortisone shots [90].

Viscosupplementation with Hyaluronic acid (HA) injections works by helping cushion and lubricate the moving parts within the joint area. However, generally HA require more than 1 (up to 5) injections, usually within a 5-week period. Viscosupplementation is considered a safe procedure, but like any medical procedure it does carry some risks and side effects. Patients who undergo viscosupplementation may have mild discomfort immediately after the procedure. Typical side effects at the injection site include: localized swelling, skin warmth and/or redness, soreness and joint stifness. It has been estimated that 1% to 3% of patients experience localized swelling and skin changes. However, side effects are usually mild and go away in 1 to 2 days [91].

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is a Hyaluronic acid-based viscosupplementation intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

The medical device contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid, to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in “Hyaluronic acid sodium salt, viscosuppletive joint device” is obtained by fermentation and has not undergone chemical change processes.
It is a substitute for synovial fluid, which allows the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, “*Hyaluronic acid sodium salt, viscosuppletive joint device*” reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action. Moreover, the hyaluronic acid contained in this product is produced by fermentation and without any chemical modification, so that it can reach an excellent tolerability.
The other components of “*Hyaluronic acid sodium salt, viscosuppletive joint device*” are: sodium chloride, sodium phosphate and water for injectable preparations.

HA is a naturally occurring glycosaminoglycan and a component of synovial fluid (SF) and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize HA and secrete into the joint. HA enhances viscosity and elastic nature of SF. SF with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements [92]. The adaptive ability reduces stress and friction on cartilage [93]. It also forms the backbone for the proteoglycans of the extracellular matrix. In the osteoarthritic joint, synovial inflammation leads to increased permeability of the synovial membrane for HA. Also, the elevated SF levels of free radicals, inflammatory cytokines, and proteolytic enzymes in osteoarthritic knees impair HA function and contribute to the progression of OA [94,95]. Therefore in OA, both the molecular weight and the concentration of HA are decreased [94-97].
The intra-articular injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: "viscosupplementation" [94]. It is thought that HA temporarily restores the lubricating and shock-absorbing effects of SF. Moreover, several studies suggest that viscosupplements also have effects, such as protection against cartilage erosion [98,99], and promotion of intra-articular HA production [97,99,100,102].

There are different commercially available products acting as viscosupplements for the relief from pain due to osteoarthritis. Most of them have Hyaluronic acid as the key ingredient, thanks to its high tolerability and efficacy.

Native HA of synovial fluid has a high molecular weight (4-10 $*10^6$ Da) and a concentration of about 0.35 g/100 ml. At present, preparations with different molecular weight are available (Low and High Molecular Weight). Some clinical study were carried out to compare clinical outcomes of low and high molecular weight; in some of them, high molecular weight hyaluronic acid (HMWHA) is considered more effective in relieving pain, compared to low molecular weight HA. This is due to the fact that HMWHA molecules are bigger than LMWHA: this property allows the compound to not penetrate the extracellular matrix and to concentrate in the joint cavity, leading to a higher lubrication and protection of the joint [103]. However, no conclusive theories have been confirmed regarding the correlation between molecular weight and efficacy [108-110].

Results from large animal models of OA shows that low weight HAs are more effective than high molecular weight HAs in restoring the rheological properties of synovial fluid [117]. Also, several preclinical studies evaluating joint-structure modification in animal models of OA have reported advantages of using HAs of molecular weight in the low- to mid-range, as they can access diseased tissue more easily, suggesting potential for disease modification [118]. Furthermore, some studies show no difference in efficacy but an overall risk: benefit profile favouring lower molecular weight HAs [118-120]. Moreover, a safety analysis demonstrated a two fold increased risk of local adverse events (pain, swelling or warming to severe inflammation) and flares with hylan.

Moreover, HA of "*Hyaluronic acid sodium salt, viscosuppletive joint device*" has a biofermentative origin. Industrial manufacturing of hyaluronan is based on two main processes, the extraction from animal tissues and microbial fermentation using bacterial strains. Both technologies produce polydisperse high molecular weight hyaluronan ($Mw \geq 1 \times 106$ Da, polydispersity ranging from 1.2

to 2.3) for biomedical and cosmetic applications [111-113]. The first process, to be applied at industrial scale, was the extraction of hyaluronan from animal waste which is still an important technology for commercial products, but is hampered by several technical limitations. One drawback in the extraction process is the inevitable degradation of hyaluronan, caused by (a) the endogenous hyaluronidase activity in animal tissues, breaking down the polymer chain through enzymatic hydrolysis, and (b) the harsh conditions of extraction. Extraction protocols have been improved over the years, but still suffer from low yields, due to the intrinsic low concentration of hyaluronan in the tissue, and from high polydispersity of polymer products due to both the natural polydispersity of hyaluronan and to the uncontrolled degradation during extraction. As in any process for the production of therapeutic compounds from animal sources, there is a potential risk of contamination with proteins and viruses, but this can be minimized by using tissues from healthy animals and extensive purification. Nevertheless, concerns on viral (particularly avian) and protein (particularly bovine) contamination increased the interest in the biotechnological production of hyaluronan [114].

Since the hyaluronan polymer produced in animals and bacteria is identical, bacterial hyaluronan is not immunogenic and therefore is an excellent source for medical grade hyaluronan. Extracting hyaluronan from microbial fermentation broth is a relatively simple process with high yields. An additional and important advantage of microbial hyaluronan production is that microbial cells can be physiologically and/or metabolically adapted to produce more hyaluronan of high molecular weight. Therefore, microbial hyaluronan production using either pathogenic streptococci or safe recombinant hosts, containing the necessary hyaluronan synthase, is nowadays more and more preferred [114]. In addition, in relation to hyaluronic acid synthesis, these substances can be classified into two types: hyaluronans, composed of long-chain molecules of avian or biofermentation origin, with a molecular weight of between 0.5 and 1.8 x 10^6 Da; hylan, i.e. hyaluronan molecule chemically modified by means of cross-links, with a liquid phase of higher molecular weight (around 6x10^6 Da), through crosslinking connections between long chains of hyaluronan, and a solid portion (of infinite molecular weight) formed by even greater presence of links [144].

In conclusion, efficacy and safety of Hyaluronic acid-based viscosupplementations are supported by some clinical trials [104-107].

4.4 *PRECLINICAL STUDIES CARRIED OUT ON "Hyaluronic acid sodium salt, viscosuppletive joint device"*

4.4.1 *Pre-clinical tests on "HYALURONIC ACID SODIUM SALT 2%"*

4.4.1.1 CYTOTOXICITY TESTS

On the test product *"HYALURONIC ACID SODIUM SALT 2%"* was carried out a toxicological study aimed to evaluate any cytotoxic effects.
The following test was performed:

- Cytotoxicity - elution test - according to ISO 10993-5:2009;
- Bacterial endotoxins test (LAL test).

4.4.1.1.1 *Cytotoxicity for elution test [Report Ref. 2011/2200.A1]*

The biocompatibility test was conducted to evaluate any cytotoxic effect of the test item "HYALURONIC ACID SODIUM SALT 2%" according to ISO 10993-5:2009 Standard.

To perform the cytotoxicity by direct contact test, a confluent BalbC 3T3 cell culture in exponential phase of growth was used.

The test product was directly applied on filter paper placed in the middle of each well contained BalbC 3T3 monolayer and was incubated at 37°C ± 1°C in CO_2 atmosphere for 24 hours. After 24 hours of incubation, the cells were observed to microscope (qualitative evaluation) to evaluate the biological reaction.

A qualitative evaluation was performed observing cell culture by an inverted microscope, while a quantitative evaluation was performed using the Neutral Red Uptake method

(NRU). The NRU is a method that allows to measure cell vitality using their capacity to incorporate and to bind a cellular vitality dye, the Neutral Red.

Qualitative evaluation

After incubation, the cells were observed to microscope (qualitative evaluation) to evaluate the biological reaction.

After 24 hours of contact, in the wells treated with test product, some malformed or degenerated cells under specimen were observed (reactivity grade 1, according to the grading scale showed in Table 4).

GRADE	REACTIVITY	CONDITIONS OF ALL CULTURES
0	None	Discrete intracytoplasmic granules; no cell lysis.
1	Slight	Not more than 20% of the cells are round, loosely attached, and without intracytoplasmic granules; occasional lysed cells are present.
2	Mild	Not more than 50% of the cells are round and devoid of intracytoplasmic granules; no extensive cell lysis and empty areas between cells.
3	Moderate	Not more than 70% of the cell layers contain rounded cells or are lysed.
4	Severe	Nearly complete destruction of the cell layers.

Table 4. Biological reactivity grading scale.

Quantitative evaluation

After the qualitative evaluation, cells were treated for 3 hours with the medium containing the cell vitality dye and then with a Desorb Solution that allows to obtain a cell lysate. the optic density was then calculated after a 540nm spectrophotometric reading.

Cells treated with test sample have not shown a cell vitality reuction.

On the basis of the results, interpreted according to ISO 10993-5:2009, the test product “HYALURONIC ACID SODIUM SALT 2%” must be considered NOT CYTOTOXIC

For further information, see report referenced as *2011/2200.A1*.

4.4.1.1.2 *Bacterial endotoxins test (LAL test) [Report Ref. 2011/2200.A2]*

To perform the Bacterial endotoxins test (LAL test), the test substance was diluted 1:50 (MVD) in LAL negative water.
The obtained solution was tested to evaluate a possible contamination by Gram negative bacterial endotoxins. For injection medical device, the endotoxin limits not more than 0.25 Endotoxin Units per ml.

The endotoxin concentration in the tested sample is < 0.25 EU/ml.

For further information, see report referenced as *2011/2200.A2*.

4.4.1.2 DELAYED HYPERSENSITIVITY TEST (GPMT) [Report Ref. 2012/363.A3]

The biocompatibility test was carried out to identify the potential sensitizing effects of the test item *"HYALURONIC ACID SODIUM SALT 2%"* according to ISO 10993-10:2010.

In the *Guinea Pig Maximisation test*, 15 guinea pigs were used, 10 of which were treated with the test item and 5 were used as a control group.

The maximization test consists of an induction phase and a challenge phase.

The grading scale use to evaluate the patch test reaction is showed in Table 5.

Patch test reaction	Grading scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intenses erythema and swelling	3

Table 5. Grading scale used for the evaluation of the sensistivity reaction during the patch test.

Induction phase

In the induction phase, guinea pigs were treated with 3 pairs of intradermal injections (each dose of 0.1 ml), thus subdivided:

1. Stable emulsion of Freud's complete adjuvant (FCA) in Sodium chloride injection 50:50 (v:v);
2. Test sample for treated animals, Sodium Chloride injection for control animals;

3. Test sample diluited 50:50 (v.v) with stable emulsion of FCA and Sodium Chloride injection (50%) for treated animals, sodium chloride injection diluted 50:50 (v:v) with stable emulsion of FCA and sodium chloride injection (50%) for treated animals.

Six days after performing the intradermal injections – treated and controls – a local application was performed on all animals by massaging 1 ml of Sodium Lauryl sulfate at 10%.
Seven days after performing the intradermal injections, a test sample in the volume of 1 ml/animal was applied to the skin in ten treated animals for 48 hours. The same treatment was performed on control group using Sodium Chloride injection.

Challenge phase

21 days after the beginning of the treatment, 1 ml of the test sample was applied on the right side and 1 ml of Sodium chloride injection/cottonseed oil on the left side of the back of all animals, both treated and control ones. Bandaging was left for 24 hours.

After 48 and 72 hours after starting the challenge phase, the reactions of both treated and control animals were evaluated: no abnormalities were observed neither in treated animals with the test sample nor in control animals.

Therefore, on the basis of the results, the test item "HYALURONIC ACID SODIUM SALT 2%" must be considered NOT SENSITIZING.

For further information, see report referenced as *2012/363.A3*.

4.4.1.3 SYSTEMIC TOXICITY TESTS

On the test product *"HYALURONIC ACID SODIUM SALT 2%"* was carried out a biological evaluation aimed to obtain the necessary data to evaluate its toxicity by means of the following tests:
The following test was performed:

- Systemic toxicity according to ISO 10993-11:2006;
- Pyrogen test according to USP 34 <151>

4.4.1.3.1 *Systemic toxicity test [Report Ref. 2011/2199.A1]*

The test product was intraperitoneally injected in ratio of 50 ml/kg of animal weight in one group of 5 mice.
Sodium chloride injection used as control was injected with the same modality in another group of 5 animals.
The animals were observed immediately after the injection and after 4, 24, 48 and 72 hours.
Each symptomatology was recorded.

During the study, no toxic symptoms were observed in treated and control animals.

On the basis of results, interpreted according to ISO 10993-11:2006, the test product "HYALURONIC ACID SODIUM SALT 2%" DOES NOT CAUSE toxic symptoms and SATISFIES the requirements of the test.

For further information, see report referenced as *2011/2199.A1.*

4.4.1.3.2 *Pyrogen test [Report Ref. 2011/2199.A2]*

The Pyrogen test is a test designed to limit to an acceptable level the risk of febrile reaction in the patient to the administration by intravenous injection of the test samples.

1 ml/kg of the test sample was injected into the ear vein of three albino rabbits and the temperature was recorded at intervals of 30 minutes in the three hours subsequent the injection with the purpose to individuate any temperature raising.

The individual rise in temperature are reported in the following table:

Rabbit N°	**Temperature rising**
1364	+ 0.10 °C
1233	+ 0.10 °C
1226	+ 0.00 °C

Table 6. Rabbit individual rise in temperature.

On the basis of results, interpreted according to USP 34 <151>, the test product *"HYALURONIC ACID SODIUM SALT 2%"* meets the requirements for the absence of pyrogens.

For further information, see report referenced as 2011/2199.A2.

4.4.1.4 INTRACUTANEOUS REACTIVITY TEST [Report Ref. 2012/363.A1]

The biocompatibility test was performed according to ISO 10993-10:2010.

0.2 ml of the test sample were intracutaneously injected in five sites of 3 albino rabbits.

Sodium Chloride injection, administrated with the same procedure, was used as control.

After 24, 48 and 72 hours were evaluated macroscopic signs of skin irritation as erythema, oedema or eschar, as shown in Table 7.

Reaction	Primary Irritation Score
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderte erythema	3
Severe erythema (beet redness to slight eschar formation; injuries in depth)	4
Oedema formation	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (edges raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extended beyond area of exposure)	4

Table 7. Tissue reactions grading scale.

All the sites treated with the test sample showed no sign of erythema nor sign of oedema.
All the control sites showed no sign of erythema nor sign of oedema.
Primary irritation index = 0.00

On the basis of the results, interpreted according to ISO 10993-10:2010, the test item "HYALURONIC ACID SODIUM SALT 2%" SATISFIES the requirements of the test.

For further information, see report referenced as *2012/363.A1*.

4.4.1.5 SUBCUTANEOUS IMPLANTATION TEST ON "HYALURONIC SODIUM SALT 2%" [Report Ref. 2012/364 AMi]

The biocompatibility test was performed according to ISO 10993-6:2007.

0.5 ml of test product was injected subcutaneous in four sites in the cranial and caudal dorsal region of albino rats divided in three groups (5 rats for each explanation time). In the cranial and caudal site of the dorsal region of the albino rabbits divided in three groups 85 rats for each explantations time) was subcutaneously injected 0.5 ml sodium chloride injection used as negative control.

In accordance to the Sponsors request, 3 explantations time are scheduled and performed at 4, 12 and 26 week from implantation procedure.

animals were daily submitted to general objective exam (EOG) with the purpose to detect possible local effects due to the sample.

After those animals were sacrified and a macroscopic evaluation of all implanted sites have been conducted.

All sites implanted with the test sample and with the negative control were subjected to histological exam. The Hostological evaluation scale is shown in Table 8 and Table 9.

Cell type/response	**Score**				
	0	1	2	3	4
Polymorphonuclear cells	0	Rare, 1-5/phf*	5-10/phf	Heavy infiltrate	Packed
Lymphocytes	0	Rare, 1-5/phf*	5-10/phf	Heavy infiltrate	Packed
Plasma cells	0	Rare, 1-5/phf*	5-10/phf	Heavy infiltrate	Packed
Macrophages	0	Rare, 1-5/phf*	5-10/phf	Heavy infiltrate	Packed
Giant cells	0	Rare, 1-2/phf*	3-5/phf	Heavy infiltrate	Sheets
Necrosis	0	Minimal	Mild	Moderate	Severe
*phf = per high powered (400x) field.					

Table 8. Example of a Histological evaluation system - cell type/response (according to Table E.1, ISO 10993-6,2007)

Reaction	**Score**

	0	1	2	3	4
Neovascularization	0	Minimal capillary proliferation, focal, 1-3 buds	Groups of 4-7 capillaries with supporting fibroblastic structures	Broad band of capillaries with supporting structures	Extensive band of capillaries with supporting fibroblastic structures
Fibrosis	0	Narrow band	Moderately thick band	Thick band	Extensive band
Fatty infiltrate	0	Minimal amount of fat associated with fibrosis	Several layers of fat and fibrosis	Elongated and broad accumulation of fat cells about the implant site	Extensive fat completely surrounding the implant

Table 9. Example of a histological evaluation system - Response (according to Table E.2, ISO 10993-6, 2007)

Results at 4 weeks can be summarized as follows:

GENERAL OBJECTIVE EXAM

Treated sites

During the observations conducted for the whole study, the treated sites with the test sample haven't shown any local effects.

Control sites

During the observations conducted for the whole study, the control sites with sodium chloride injection haven't shown any local effects.

MACROSCOPIC EVALUATION

Treated sites

No abnormalities were observed in all implantation sites.

Control sites

No abnormalities were observed in all implantation sites.

HISTOLOGICAL EVALUATION

Please reference to the test report *2012/364 AMi.*

Results at 12 weeks can be summarized as follows:

GENERAL OBJECTIVE EXAM

Treated sites

During the observations conducted for the whole study, the treated sites with the test sample haven't shown any local effects.

Control sites

During the observations conducted for the whole study, the control sites with sodium chloride injection haven't shown any local effects.

MACROSCOPIC EVALUATION

Treated sites

No abnormalities were observed in all implantation sites.

Control sites

No abnormalities were observed in all implantation sites.

HISTOLOGICAL EVALUATION

Please reference to the test report *2012/364 AMi.*

Results at 26 weeks can be summarized as follows:

GENERAL OBJECTIVE EXAM

Treated sites

During the observations conducted for the whole study, the treated sites with the test sample haven't shown any local effects.

Control sites

During the observations conducted for the whole study, the control sites with sodium chloride injection haven't shown any local effects.

MACROSCOPIC EVALUATION

Treated sites

No abnormalities were observed in all implantation sites.

Control sites

No abnormalities were observed in all implantation sites.

HISTOLOGICAL EVALUATION

Please reference to the test report *2012/364 AMi.*

On the basis of the results, interpreted according to ISO 10993-6:2007, the test product *"HYALURONIC ACID SODIUM SALT 2%"* after 4, 12 and 26 weeks of implantion in subcutaneous tissue, HAS NOT CAUSED local toxic effects significantly different respect to the control sample.

For further information, see report referenced as *2012/364 AMi*.

4.4.1.6 OCULAR IRRITATION TEST [Report Ref. 2012/363.A1]

The biocompatibility test was performed according to ISO 10993-10:2010.

0.1 of the test product *"HYALURONIC ACID SODIUM SALT 2%"* was instilled in the conjunctive sac of right eye of three albino male rabbits.
The left eye was not treated and was used as control.
Animals' eyes were examined after 1, 24, 48 and 72 hours from treatment by means of a binocular loupe.
The ocular areas examined were cornea, iris and conjunctivae.
During observation, the following abnormalities were observed:

- Cornea: No abnormalities were observed.
- Iris: No abnormalities were observed.
- Conjunctivae
- Redness: No abnormalities were observed.
- Chemosis: No abnormalities were observed.
- Discharge: No abnormalities were observed.

On the basis of the results, interpreted according to ISO 10993-10:2010, the test product "HYALURONIC ACID SODIUM SALT 2%" must be considered NOT IRRITANT at ocular level.

For further information, see report referenced as *2012/363.A1*.

4.4.2 *Preclinical tests on "SINOVIAL ONE"*

4.4.2.1 DELAYED HYPERSENSITIVITY TEST (GMPT) ON SYNOVIAL ONE [Report Ref. 2011/1394 SAM]

The biocompatibility test was carried out according to ISO 10993-10:2010.

In the *Guinea Pig Maximisation test*, 15 guinea pigs were used, 10 of which were treated with the test item and 5 were used as a control group.

The maximization test consists of an induction phase and a challenge phase.

The grading scale use to evaluate the patch test reaction is showed in Table 10.

Patch test reaction	Grading scale
No visible change	0

Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intenses erythema and swelling	3

Table 10. Grading scale used for the evaluation of the sensistivity reaction during the patch test.

Induction phase

In the induction phase, guinea pigs were treated with 3 pairs of intradermal injections (each dose of 0.1 ml), thus subdivided:

1. Stable emulsion of Freud's complete adjuvant (FCA) in Sodium chloride injection 50:50 (v:v);
2. Test sample for treated animals, Sodium Chloride injection for control animals;
3. Test sample diluited 50:50 (v.v) with stable emulsion of FCA and Sodium Chloride injection (50%) for treated animals, sodium chloride injection diluted 50:50 (v:v) with stable emulsion of FCA and sodium chloride injection (50%) for treated animals.

Six days after performing the intradermal injections – treated and controls – a local application was performed on all animals by massaging 1 ml of Sodium Lauryl sulfate at 10%.
Seven days after performing the intradermal injections, a test sample in the volume of 1 ml/animal was applied to the skin in ten treated animals for 48 hours. The same treatment was performed on control group using Sodium Chloride injection.

Challenge phase

21 days after the beginning of the treatment, 1 ml of the test sample was applied on the right side and 1 ml of Sodium chloride injection/cottonseed oil on the left side of the back of all animals, both treated and control ones. Bandaging was left for 24 hours.

After 48 and 72 hours after starting the challenge phase, the reactions of both treated and control animals were evaluated: no abnormalities were observed neither in treated animals with the test sample nor in control animals.

Therefore, on the basis of the results, the test item "SINOVIAL ONE" must be considered NOT SENSITIZING.

For further information, see report referenced as *2012/363.A3*.

5 METHOD

5.1 *LITERATURE REVIEW PROCESS*

According to MEDDEV 2.7.1:2016 Guidelines, the review process has been conducted on the basis of a customized Clinical Evaluation Plan in which is defined the search strategy and the method for conducting the Clinical Evaluation of "*Hyaluronic acid sodium salt, viscosuppletive joint device*".

5.2 *TYPES OF STUDIES*

Randomised controlled (RCT) and non-randomized controlled studies (non-RCTs) have been included, with a minimum follow-up of four weeks.

Randomized controlled trials (RCTs) have an advantage over non-randomized trials for the evaluation of therapeutic procedures, as randomization renders the groups of patients comparable not only in respect of known prognostic factors, but also with regard to unknown factors (e.g. genetic) that might affect the outcome. Theoretically, RCTs have a good internal validity but may have poor external validity whilst the converse may be true with non-randomized designs. A well-designed non-randomized controlled study may, in fact, be preferable to a small, poorly designed RCT. Although the inclusion of non-RCTs increases the susceptibility for bias, non-RCTs have been included because a variety of approaches and designs have been used for the management of pain and reduced mobility due to ostearthritis, and a limited number of RCTs have been conducted.

5.3 *TYPES OF INTERVENTIONS*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations. It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

Therefore, only data about Low Molecular Weight HA-based viscosupplementations for the management of pain and symptoms related to degenerative diseases and tendinopathy associated with small and large joint disabilities have been taken under consideration. The other therapeutic approach, such as non-pharmacological therapy (Ultrasound, Transcutaneous electrical nerve stimulation), pharmacological therapy (Acetaminophen, non-steroidal anti-inflammatory drugs, opioids, analgesics), Cortisone injections, surgical treatment like bones realignment and joint replacement, or alternative treatments such as acopunture, dietary supplements and balneotherapy have been excluded.

Therefore, only studies about Low Molecular Weight Hyaluronic acid-based viscosupplementation have been included, in order to support *"Hyaluronic acid sodium salt, viscosuppletive joint device"* effectiveness and safety, as they better reflect the mechanism of action of the medical device.

5.4 *TYPES OF OUTCOMES MEASURES*

The following outcomes have been defined for inclusion:

- Relief from pain/disability (WOMAC score);
- Improvement of joint mobility and walking ability;
- Quality of Life (QoL) improvement (Patients' evaluation - VAS, WOMAC scores);
- Positive physicians' global assessment.

Personal patients' performance and tolerability evaluation have been excluded if evaluated as the only outcome measure.

5.5 *SEARCH STRATEGY*

Search strategy has been developed using PubMed and key words selected in the Clinical Evaluation Plan for *"Hyaluronic acid sodium salt, viscosuppletive joint device"*, in order to identify the articles for grading. The search has been carried out also on the sites of manufacturers of equivalent devices for "Hyaluronic acid sodium salt, viscosuppletive joint device".

5.6 *ARTICLES' SELECTION*

Based on the pre-defined inclusion and exclusion selection criteria (see Clinical Evaluation Plan CEP_HA sodium salt Viscosuppletive joint device), relevant papers have been selected from the database search for the review. A preliminary selection of articles has been carried out accordingly with the inclusion/exclusion criteria defined in the Clinical Evaluation Plan. Grey literatures such as dissertation and non-peer review have been excluded. Full texts of the selected articles have been examined in order to avoid duplication of data.

5.7 *DATA EXTRACTION*

Data extracted has been compared in order to avoid consistency loss and, when possible, these inconsistencies have been corrected. Data extracted from pivotal articles has been discussed and inserted in comparison tables, including relevant information about study design, methods and results.

5.8 *STUDIES SUITABILITY*

Studies suitability has been evaluated through analysis of the characteristics of the trials and of the data contribution of the articles selected using the criteria defined in the Clinical Evaluation Plan for *"Hyaluronic acid sodium salt, viscosuppletive joint device"*.

6 DATA ANALYSIS

6.1 *LITERATURE SEARCH RESULTS*

As shown in Figure 11, the electronic searches yielded 58 hits. Following the removal of duplicates, 19 remained. Following the review of full text, 13 articles were identified as meeting the inclusion criteria. After the weighting for data contribution and the selection on the basis of a compounded weight, 9 pivotal articles have been retrieved, dealing with medical devices equivalent to *"Hyaluronic acid sodium salt, viscosuppletive joint device"*.

Other 4 clinical studies have been included as *Indirect supportive data*, since they deal with medical devices similar to *"Hyaluronic acid sodium salt, viscosuppletive joint device"*, suitable to support its performance and safety. In two cases (Citation 10 and 12), articles have been graded 0 because of the limited number of patients enrolled.

The full texts of all articles can be found in **Appendix 3**.

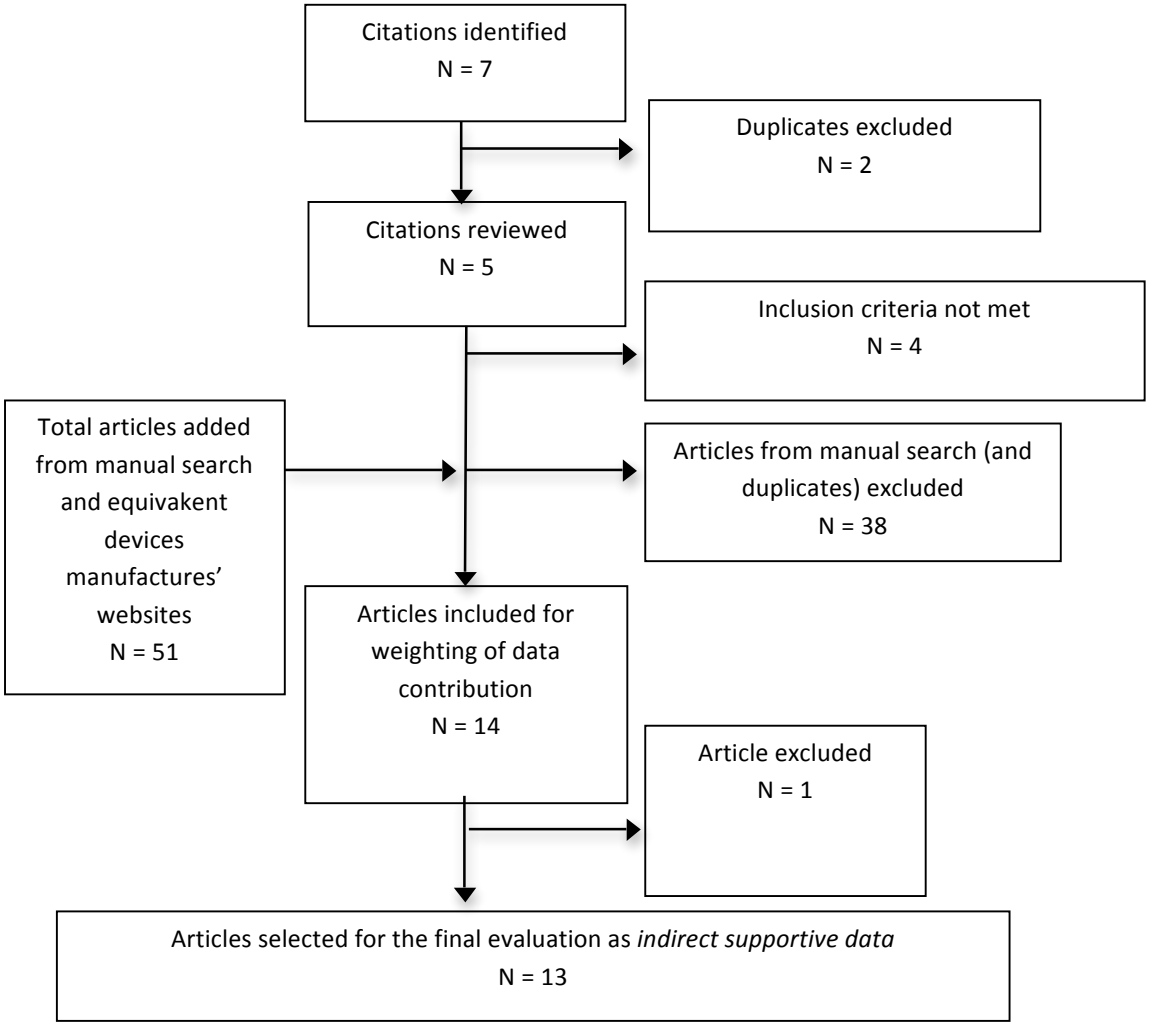


Figure 11. Flowchart: articles' selection.

7 SUMMARY AND APPRAISAL OF CLINICAL DATA

7.1 *SUITABILITY FOR APPRAISAL*

All the articles included as indirect supportive data are enclosed in Table 11 below.

Table 11. Evaluation of suitability for appraisal.

ID	Article	Brief description	Compounded Weight
PIVOTAL ARTICLES			
1.	Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, Jordi B, Züllig M, Guetg R, Häuselmann HJ, Schwarz H, Theiler R, Ziswiler HR, Dieppe PA, Villiger PM, Egger M; Swiss Viscosupplementation Trial Group. **Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial.**	This multicenter randomized controlled clinical study aimed to compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee. Patients were randomly assigned to receive 1 cycle of 3 intraarticular injections per knee of 1 of 3 preparations: a high molecular weight crosslinked hylan, a non–cross-linked medium molecular weight HA of avian origin, or a non–cross-linked low molecular weight HA of bacterial origin. No evidence for a difference in efficacy	**0.5**

	Arthritis Rheum. 2007;56(11):3610-9.	between hylan and Has were found. In view of its higher costs and potential for more local adverse events, authors see no rationale for the continued use of hylan in patients with knee OA.	
2.	Gydek A *et al.* **Efficacy and safety of intra-articular use of Hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis.** *Przegl Lek.* 2011;68(6) 307-10.	This observational clinical study was carried out to evaluate the clinical outcomes of the intra-articular administration of HA-based viscosupplementations (Suplasyn). According to results, Suplasyn demonstrated high efficacy and good tolerance in the treatment of knee osteoarthritis.	**0.5**
3.	Petrella R J. **Hyaluronic acid for the treatment of knee osteoarthritis: Long-term outcomes from a naturalistic primary care experience.** *Am J Phys Med Rehabil* 2005;84:287- 283.	This prospective, naturalistic, cohort clinical study aimed to evaluate long-term outcomes of intra-articular HA viscosupplementations, in case of repeated injections. Patients received a three–intraarticular injection series with Suplasyn (10 mg/ml, 2-ml injection) over 3 weeks. Patients were instructed to return for consideration of repeat injection series based on their perception of pain restricting daily activity and a resumption of severity similar to their initial presentation. Results proved that Intraarticular hyaluronic acid injections were highly effective in improving resting and walking pain in patients with osteoarthritis of the knee on a first and a second treatment series. Duration of symptom control was about 6 months, and the therapy was highly satisfactory to patients and was associated with very few local adverse events and limited use of concomitant therapeutic modalities.	**0.5**
4.	Uebelhart D, Berz S. **Safety and efficacy of fermentative hyaluronan in knee osteoarthritis: a retrospective study.** *Department of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Switzerland* 2003.	This retrospective study aimed to compare two HA viscosupplementations (Ostenil® and Synvisc®) for the treatment of osteoarthritis. Results indicated that Ostenil®, which contains a natural, non-chemically modified HA of fermentative origin, is a safe and effective therapy for knee OA, and supported previously published data indicating that i.a. injection of chemically modified cross-linked HA derivative of avian origin (Synvisc®) was associated with a higher incidence of adverse device	**0.5**

		reactions.	
5.	Román JA, Chismol J, Morales M, Donderis JL. **Intra-articular treatment with Hyaluronic Acid. Comparative study of Hyalgan and Adant.** *Clin Rheumatol* 2000;19: 204-6.	This blind randomized study aimed to compare two HA-based viscosupplementations (Adant and Hyalgan). According to results, the efficacy with Adant at 3 months after treatment was greater than with Hyalgan (50% versus 21.1%). The maximum improvement with hyaluronic acid was seen at 5 weeks in 75.4% and the adverse effects consisted of pain in the infiltration side, which was almost twice as great with Adant (16.3%).	**0.25**
6.	Van Den Bekerom MPJ, Rys B, Mulier M. **Viscosupplementation in the hip: evaluation of hyaluronic acid formulations.** *Arch Orthop Trauma Surg* 2008; 128(3): 275-80.	This prospective clinical study aimed to compare three different hyaluronate formulations and evaluates functionality, time of satisfactory pain relief and also the delay in performing a total hip arthroplasty. One hundred and twenty patients (126 hips) received viscosupplementation with one of the three hyaluronate formulations. All patients were candidate for surgical treatment with a total hip arthroplasty. Three different products were consecutively used: Adant® , Synocrom® or Synvisc®. Results reported that there was no significant difference in duration of the effect of the first infiltration between the three groups. The positive effect was still ongoing at the end point of the study in 46 hips: 51% of the patients did not undergo total hip arthroplasty, 3 years after viscosupplementation.	**0.25**
7.	Mathies B, Berger J, Siegfried C, Gurry R. **Effect of intra-articular sodium hyaluronate (Ostenil®) on improving the quality of life and delaying surgery in patients indicated for total knee replacement. An open, pilot, phase III study.** *5th Symposium of the International Cartilage Repair Society, Gent, Belgium.* May 26–29, 2004.	This open, pilot, phase III study aimed to evaluate efficacy of an intra-articular HA viscosupplementation (Ostenil®) for quality of life and delaying surgery in patients for total knee replacement. According to results, Ostenil® was safe and effective, improving symptoms, quality of life and the viscous and elastic modulus of the synovial fluid of the knee.	**0.25**
8.	Blanco FJ, Fernández-Sueiro JL, Pinto-Tasende JA, Fernández-	This prospective, single-center, double-blind, randomized, placebo-controlled,	**0.125**

	López JC, Ramallal M, Freire A *et al.* **Intra-articular hyaluronan treatment of patients with knee osteoarthritis waiting for replacement surgery.** *The Open Arthritis Journal* 2008; 1: 1-7.	pilot clinical trial aimed to determine whether hyaluronan (HA) delays and/or reduces the knee replacement surgery (KRS) in patients with osteoarthritis. The intra-articular treatments (HA or placebo) consisted of two cycles of five weekly injections with a 24-week interval between each cycle. According to results, the use of intra-articular HA to treat OA patients on the waiting list for KRS does not delay surgery. However, it could improve the physical condition of patients while they are waiting by surgery.	
9.	Monfort J, Rotés-Sala D, Segalésc N, Montanes FJ, Orellana C. **Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: Results of a6-month single-masked randomized study**. *Joint Bone Spine* 82 (2015) 116–121.	This single-center, randomized, controlled study was designed to determine the efficacy and safety of intra-articular injections of low molecular weight HA into the osteoarthritic thumb CMC joint in comparison with corticoid injections. Eighty-eight evaluable patients diagnosed with osteoarthritis of the thumb (Kellgren-Lawrencegrade II-III) received ultrasound-guided intra-articular treatment with hyaluronic acid (48) or betamethasone (40). Results reported that both hyaluronic acid and betamethasone were effective and well-tolerated for the management of rhizarthrosis. Hyaluronic acid was more effective over time and more efficiently improvedfunctionality and pain in patients with more severe symptoms.	**0.125**
INDIRECT SUPPORTIVE DATA			
10.	Karatosun V, Unver B, Ozden A, Ozay Z, Gunal I. **Intra-articular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up.** *Clin Exp Rheumatol* 2008; 26: 288-94.	This prospective clinical trial aimed to determine whether hyaluronic acid (HA) or exercise therapy could improve functional parameters in patients with osteoarthritis (OA) of the ankle. Patients receive three intra-articular HA injections, with one-week interval of or exercise therapy for six weeks. Results confirmed that, both HA injections and exercise therapy provide functional improvement. However, larger trials with longer follow-up are necessary for more definite conclusions.	-
11.	Tang AC, Tang SF, Hong WH, Chen HC.	This clinicaL trial was designed as a single-group repeated measures study to examine the kinetic features in patients	-

	Kinetics features changes before and after intra-articular hyaluronic acid injections in patients with knee osteoarthritis. Clin Neurol Neurosurg. 2015;129(1):21-6.	with knee osteoarthritis (OA) after intra-articular hyaluronic acid (IAHA) injections in different time periods. This study revealed that IAHA injections can provide significant pain relief and improvement in activity of daily living function for patients with knee OA. However, the reduction in pain and the increase in knee adduction moment may last up to 6 months. This may cause excessive loading on the knee joints, which may further accelerate the rate of knee degeneration.	
12.	Eyigör C, Pirim A, Eyigör S, Uyar M. **Efficacy of intraarticular hyaluronic acid injection through a lateral approach under fluoroscopic control for advanced hip osteoarthritis.** *Agri.* 2010;22(4):139-44.	This prospective clinical study aimed to determine the efficacy of intraarticular injection of HA through a lateral approach under fluoroscopic control for advanced hip OA. All patients received 2.5 ml HA injection once a week for 3 weeks by lateral approach under fluoroscopic control. This study proved that intraarticular HA injection through a lateral approach under fluoroscopic control is a safe and effective method for patients with advanced hip OA.	-
13.	Petrella RJ, Cogliano A, Decaria J, Mohamed N, Lee R. **Management of Tennis Elbow with sodium hyaluronate periarticular injections.** *Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology* 2010, 2: 4-9.	This prospective randomized clinical study aimed to determine the efficacy and safety of peri-articular hyaluronic acid injections in chronic lateral epicondylosis (tennis elbow). Three hundred and thirty one consecutive competitive racquette sport athletes with chronic (>3 months) lateral epicondylosis were administered 2 injections (first injection at baseline) into the subcutaneous tissue and muscle 1 cm. from the lateral epicondyle toward the primary point of pain using a two-dimensional fanning technique. A second injection was administered 1 week later. According to results, peri-articular HA treatment for tennis elbow was significantly better than control in improving pain at rest and after maximal grip testing. Further, HA treatment was highly satisfactory by patients and physicians and resulted in better return to pain free sport compared to control.	-

7.2 *CLINICAL DATA FROM LITERATURE*

7.2.1 *Pivotal data*

Citation 1

Title	Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, Jordi B, Züllig M, Guetg R, Häuselmann HJ, Schwarz H, Theiler R, Ziswiler HR, Dieppe PA, Villiger PM, Egger M; Swiss Viscosupplementation Trial Group. **Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial.** *Arthritis Rheum.* 2007;56(11):3610-9.
Aim of the study	This clinical trial aimed to determine the comparative efficacy and safety of a cross-linked high molecular weight hylan, a non–cross-linked medium molecular weight HA of avian origin, and a non–cross-linked low molecular weight HA of bacterial origin in patients with knee Osteoarthritis.
Relevance of the study	In patients with osteoarthritis (OA), synovial hyaluronic acid (HA) is depolymerized and cleared at higher rates than in normal individuals, resulting in a In patients with osteoarthritis (OA), synovial hyaluronic acid (HA). Meta-analyses found more pronounced pain reduction in sham-controlled trials of hylans than in trials of HAs. Conversely, case reports suggested that injection of hylans may lead to flares, typically defined as hot, painful, swollen knees occurring within 48 hours of injection. A nonrandomized study by Brown *et al* found hylans to be associated with a considerably higher rate of flares compared with conventional HAs.
Equivalent Device	**Test devices:** • Synvisc (high molecular weight cross-linked hylan derived from rooster combs); • Orthovisc (non-cross linked medium molecular weight HA derived from rooster combs (avian HA); • Ostenil (non cross-linked low molecular weight HA obtained through bacterial fermentation). *Ostenil® is a medical device fully equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device". It is a 1 % low hyaluronic acid viscosupplementation intended for pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.*
Study Design	This is a multicenter, patient-blind, randomized controlled trial.
Study period	The enrollment lasted from June 2003 and April 2004.
Sample size	660 patients were included in the trial. Two hundred twenty-two patients were allocated to receive hylan, 219 to receive avian HA, and 219 to receive bacterial HA. Figure 12 shows the enrollment flow-chart.

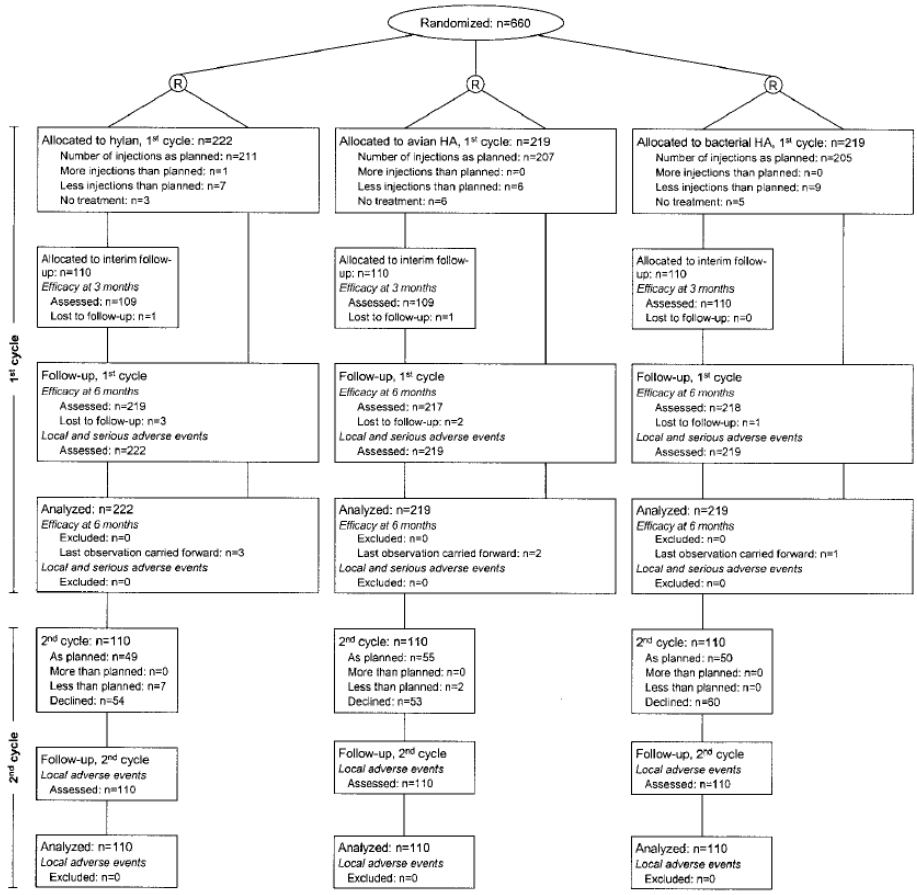
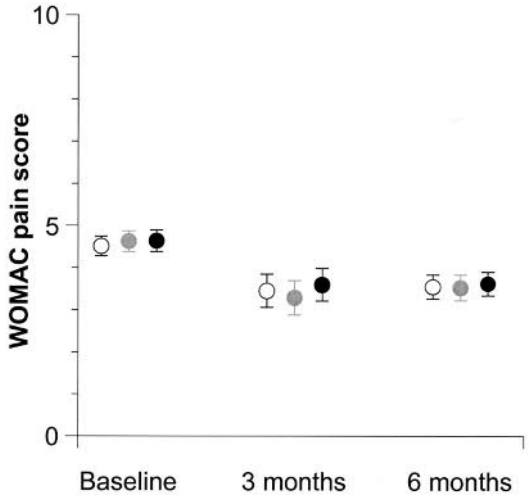


Figure 12. Flow of patients through the various stages of the trial. R = randomized; HA = hyaluronic acid.

Inclusion Criteria	Men and nonpregnant women with radiographically confirmed knee OA (Kellgren/Lawrence grade ≥ 2) who were symptomatic for at least 6 months and reported pain on most days for the previous 3 months were eligible. Patients had an American College of Rheumatology functional class rating of II to IV and had not responded sufficiently to, or could not tolerate, acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) taken regularly in adequate dosages.
Exclusion Criteria	Patients were excluded if they had inflammatory joint disease, chondrocalcinosis (evidence from radiographs or synovial fluid analysis), infection in or around the study knee, relevant skin disease in the area of the injection site, a history of allergy or intolerance to experimental preparations, or previous replacement surgery in the study knee, or if they were currently receiving anticoagulant therapy or had received previous viscosupplementation treatment within 6 months.
Intervention	Name and type of intervention Intra-articular HA viscosupplementation injections. Aim of intervention Comparison of the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee. Duration

	12-month follow-up. Description of intervention Patients were randomly allocated to receive 1 cycle of 3 intraarticular injections of 2 ml per treated knee of 1 of the following 3 preparations: 1) a high molecular weight cross-linked hylan derived from rooster combs (Synvisc; Genzyme, Cambridge, MA), 2) a non–cross-linked medium molecular weight HA derived from rooster combs (avian HA) (Orthovisc; Anika Therapeutics, Woburn, MA), or 3) a non–cross-linked low molecular weight HA obtained through bacterial fermentation (bacterial HA) (Ostenil; TRB Chemedica, Geneva, Switzerland). Injections were administered at weekly intervals. The decision about whether bilateral knee OA required injections in both knees and the designation of the study knee remained at the discretion of the treating physician. One cycle per knee was allowed during the first 6 months of the trial. Intraarticular corticosteroid injections concurrent with the injection of viscosupplementation preparations were not permitted. Injections were performed according to the guidelines of the Swiss Association of Rheumatologists. It was originally planned to offer patients a maximum of 2 additional treatment cycles during months 7–18. Due to resource limitations, patients were offered only 1 additional treatment cycle of 3 injections per knee during months 7–12. Since authors were unable to administer the expensive hylan and avian HA to all patients according to the original allocation, authors a priori selected a 50% random sample of patients, who were administered the originally allocated preparations, using a concealed randomization schedule stratified by allocated preparation. The schedule was computer generated before the beginning of the trial and held centrally at the trial coordination office. The remaining participants were offered the less expensive bacterial HA regardless of the previous treatment and were excluded from the analysis of the second cycle.
Outcomes	Primary outcomes The primary outcome measure was the change in the pain score of the WOMAC, version 3.1, between baseline and 6 months (21), with individual items graded on a 5-point Likert scale from 0 to 4. Secondary outcomes Secondary outcome measures were: • the WOMAC global score and subscores on stiffness and disability; • health-related quality of life based on the 5 dimensions and visual analog scale (VAS) of the European Quality of Life (EuroQol) questionnaire; • self-reported health care utilization for knee disease (23); • the frequency of local adverse events, defined as the occurrence of an effusion (evidence from clinical examination or arthrocentesis) or a flare (hot, painful, swollen knee occurring within 48 hours of injection of the study preparation); corticosteroid injections or treatment interruptions due to local adverse events; • the frequency of serious adverse events (adverse events leading to serious disability, hospital admission, or prolongation of hospitalization; life-threatening events; or death). • direct health care costs in each of the 3 groups. Measures and timepoints All efficacy outcomes were assessed at 6 months using patient-administered mailed questionnaires and, if necessary, telephone calls by blinded interviewers. For exploratory purposes authors performed an interim followup at 3 months, which was restricted to the prespecified 50% random sample described above. After completion of each treatment cycle, information on serious and local adverse events was actively gathered from patients and physicians using mailed questionnaires or telephone calls by blinded interviewers. All suspected events were adjudicated by 2 investigators who

	were blinded to the assigned treatment, based on medical records. Any disagreements were resolved by consensus. During the second cycle (months 7–12), only local adverse events were recorded, using the same procedures as described above.
Study Results **Performance**	WOMAC pain score Authors were unable to detect a difference in the WOMAC pain score between the hylan group and the HA groups at 3 and 6 months. In unadjusted analyses, the difference between hylan and HAs was 0.1 at 3 months and 0.1 at 6 months. Nearly identical results were seen in the analysis adjusted for concomitant treatments at 3 months and 6 months. No differences were observed in the number of patients receiving intraarticular steroid injections in the 4 weeks before the 6-month assessment; 27 (12%) in the hylan group received steroids, 22 (10%) in the avian HA group, and 26 (12%) in the bacterial HA group. Figure 13 presents the results of stratified analyses, again with no evidence of differential effects across various groups of patients. Other WOMAC scores and quality of life The difference in changes between baseline and 6 months between hylan and the HAs was 0.1. For the WOMAC overall score, 0.1 for the WOMAC stiffness score, and 0.1, 0.4) for the WOMAC disability score. There was little evidence for a difference between groups on the Euro-Qol VAS (0.1 [95% CI - 0.2, 0.4]) and health state index (0.2 [95% CI - 0.1, 0.4]).  **Figure 13.** Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (mean and 95% confidence interval) in groups receiving hylan (open circles), avian hyaluronic acid (HA) (shaded circles), or bacterial HA (solid circles) at baseline and at 3 months and 6 months. The analysis of baseline and 6-month scores was based on 660 patients, while the analysis of 3-month scores was based on a random sample of 330 patients. Health care utilization There was no statistical evidence for differences between groups in the use of pain medication or other disease-specific treatments, including surgical interventions (data not shown). Seventeen percent of all patients had undergone, or were on the waiting list for, knee replacement surgery at the end of the trial, again with no evidence for a difference between groups. Median direct costs were CHF 1,824 ($1,459) in the hylan group, CHF 1,548 ($1,238) in the avian HA group, and CHF 1,271 ($1,017) in the bacterial HA group. Corresponding mean costs were CHF 3,181 ($2,545), CHF 2,834 ($2,267), and CHF 2,640 ($2,112), respectively. Assuming identical costs of the 3 preparations in the sensitivity analysis, little differences were found between groups (median costs were CHF 1,684 for hylan, CHF 1,564 for avian HA, and CHF 1,533 for bacterial HA).

Study Results Safety

Serious adverse events during the first cycle, which occurred in 15 of 222 patients allocated to receive hylan and in 25 of 438 patients allocated to receive HAs are shown in Figure 14. There was little evidence for a difference between groups. Two serious adverse events were judged to be probably related to the evaluated intervention. These included 1 episode of septic arthritis, which occurred after injection of the avian HA, and 1 episode of anaphylactic shock, which occurred after injection of the hylan.

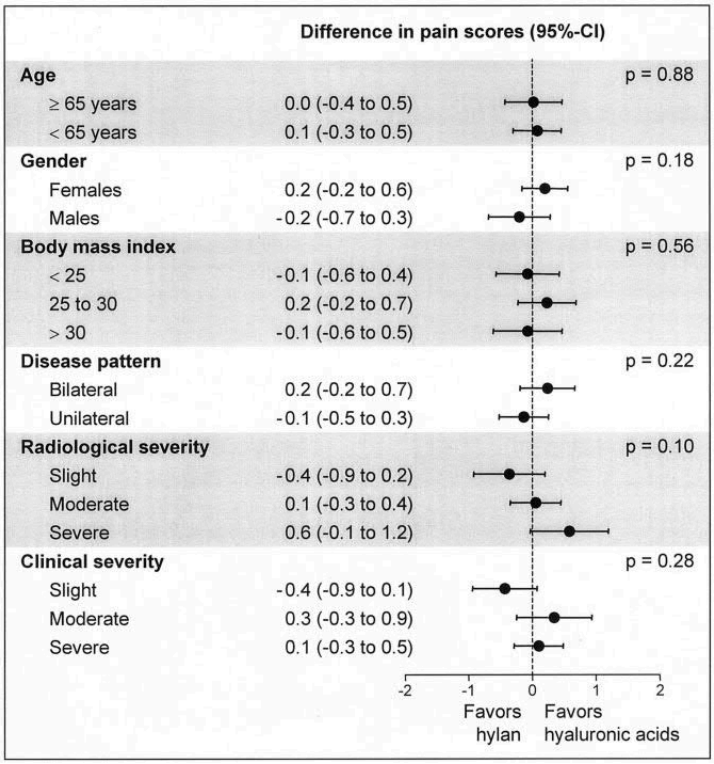


Figure 14. Results of the stratified analyses of the primary outcome according to the indicated characteristics. Values are differences in mean changes between hylan and the hyaluronic acids at 6 months, accompanied by 95% confidence intervals (95% CIs). P values are from tests of interaction between allocated treatment and stratum. Body mass index values are kg/m^2.

Figure 15 presents the number of patients experiencing local adverse events during the first and second cycles. During the first cycle, 9.5% of patients in the hylan group and 7.3% of patients in the HA groups experienced a local adverse event (difference 2.2% [95% CI -2.4, 6.7]). This trend was due to more flares in the hylan group (difference 3.3% [95% CI -0.9, 7.5]), while effusions appeared equally distributed between groups.

	Hylan (n = 222)	Avian HA (n = 219)	Bacterial HA (n = 219)
Serious adverse events	15 (6.8)	12 (5.5)	13 (5.9)
ICD class (code)			
Neoplasms (C or D)	1 (0.5)	0 (0.0)	2 (0.9)
Endocrine and metabolic disorders (E)	1 (0.5)	0 (0.0)	0 (0.0)
Mental and behavioral disorders (F)	1 (0.5)	1 (0.5)	0 (0.0)
Disorders of the nervous system (G)	1 (0.5)	0 (0.0)	0 (0.0)
Disorders of the circulatory system (I)	2 (0.9)	3 (1.4)	2 (0.9)
Disorders of the respiratory system (J)	0 (0.0)	0 (0.0)	2 (0.9)
Disorders of the digestive system (K)	0 (0.0)	2 (0.9)	1 (0.5)
Disorders of the musculoskeletal system and connective tissue (M)	3 (1.4)	1 (0.5)	2 (0.9)
Disorders of the genitourinary system (N)	1 (0.5)	0 (0.0)	2 (0.9)
Symptoms, signs, and other disorders, not classified elsewhere (R)	1 (0.5)	2 (0.9)	0 (0.0)
Injuries and complications of health care, not classified elsewhere (S or T)	4 (1.8)	3 (1.4)	2 (0.9)

* Values are the number (%) of patients. HA = hyaluronic acid; ICD = International Classification of Diseases.

Figure 15. Patients experiencing serious adverse events during the first cycle (months 0–6).

Three hundred thirty patients were randomly allocated to receive a second cycle of treatment with the originally assigned preparations, 110 in the hylan group and 220 in the HA groups. Figure 16 indicates that 50.9% of the patients randomly allocated to hylan and 48.6% of those randomly allocated to HAs received a second cycle of treatment. Local adverse events occurred more frequently in the hylan group than in the HA groups (difference 6.4% [95% CI 0.6, 12.2]). This difference was most pronounced for flares (difference 6.4% [95% CI 1.8, 10.9]), but was apparent for all outcome measures (Figure 16).

	First cycle			Second cycle		
	Hylan (n = 222)	HAs (n = 438)	Difference (95% CI)	Hylan (n = 110)	HAs (n = 220)	Difference (95% CI)
Local adverse event	21 (9.5)	32 (7.3)	2.2 (−2.4, 6.7)	10 (9.1)	6 (2.7)	6.4 (0.6, 12.2)
Type of local adverse event						
Effusion	7 (3.2)	14 (3.2)	0.0 (−2.9, 2.8)	8 (7.3)	6 (2.7)	4.6 (−0.8, 9.9)
Flare	19 (8.6)	23 (5.3)	3.3 (−0.9, 7.5)	7 (6.4)	0 (0.0)	6.4 (1.8, 10.9)
Corticosteroid injections because of local adverse event	5 (2.3)	5 (1.1)	1.2 (−1.1, 3.3)	4 (3.6)	0 (0.0)	3.6 (0.1, 7.1)
Treatment stopped because of local adverse event	2 (0.9)	6 (1.4)	−0.5 (−2.1, 1.2)	5 (4.5)	0 (0.0)	4.5 (0.7, 8.4)

* Values are the number (%) of patients. HAs = hyaluronic acids; 95% CI = 95% confidence interval.

Figure 16. Patients experiencing local adverse events during the first cycle (months 0–6) and the second cycle (months 7–12).

Limit/s of the study	The trial was covered by the basic health insurance in Switzerland. Therefore, resources were limited and only 50% of patients have been evaluated at 3 months.
Discussion	During the first treatment cycle, a clinically relevant risk of local adverse events in all treatment groups was found, but there was a trend toward more flares in patients allocated to receive hylan. During the second cycle, 7 of 57 patients allocated to receive hylan experienced flares, but this was true of none of the other patients. The incidence of effusions in the second cycle was also more pronounced in the hylan group. Only about half of the patients had opted for a second treatment cycle in this trial, and the ITT approach used as a measure against attrition bias may have resulted in too-conservative estimates of differences between groups. For example, the calculated difference in the rate of flares during the second cycle of 6.4% translates into a "number needed to harm" of 16 patients to be treated with a second cycle to cause 1 flare. If the analysis is based on treated patients only, the estimated difference between groups increases to 12.5%, and the number needed to harm decreases to 8.

Conclusions of the authors	Not reported.

Citation 2

Title	Gydek A *et al.* **Efficacy and safety of intra-articular use of Hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis.** *Przegl Lek.* 2011;68(6) 307-10.
Aim of the study	This clinical study aimed to evaluate efficacy and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis.
Relevance of the study	Osteoarthritis (OA) is one of the leading causes of disability in the elderly. Changes in the lubricating properties of synovial fluid lead to significant pain and functional disability. Viscosupplementation based on the injection of hyaluronic acid (HA) into the knee joint represents an important part of current therapeutic regimen of pain in knee OA. Intra-articular HA and hylan have proven to be an effective, safe, and tolerable treatment for symptomatic knee OA. In an effort to limit cardiovascular, gastrointestinal, and renal safety concerns related to COX-2 selective and non-selective Nonsteroidal antiinflammatory drugs (NSAIDs) and maximize HA efficacy, it is even proposed using HA earlier in the treatment paradigm for knee OA and also as part of a comprehensive treatment strategy.
Equivalent Device	**Test device:** Suplasyn 2 ml (viscosupplementation containing 20 mg of biofermentative low molecular weight Hyaluronic acid) **Control:** no control device *Suplasyn 2 ml is a medical device full equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device". It is designed for large joints, such as knees.*
Study Design	This was an observational clinical study.
Study period	This study was carried out from 30th January to 30th June 2008.
Sample size	Overall, 4519 patients (59% females, 41% males) with a mean age of 54.2 years (SD 13.2) were enrolled.
Inclusion Criteria	Patients were included if diagnosed with knee osteoarthritis.
Exclusion Criteria	Not reported.
Intervention	Name and type of intervention Intra-articular (knee joint) administration of a biofermentative low molecular weight HA-based viscosupplementation. Aim of the intervention Evaluation of the efficacy and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis.

	Duration Treatment mean duration was 3 months. Follow up lasted 30 days. Description of the intervention Affectation of the right knee was present in 39.4% of OA patients; the left knee affectation represented a 39.3%, and in 21.2% both knees were affected. Each patient received a mean of three intra-articular injections of Suplasyn (20 mg of sterile hyaluronic acid).
Outcomes	Primary outcomes Changes in pain intensity (basic scored characteristic for OA degree) and symptoms like morning stiffness, after rest stiffness, pain after ascending stairs and walking on the surface level were evaluated. Evaluation also included changes in the range of motion of the knee joint based on evaluation of extension and flexion restrictions. According to their disability degree, patients were classified into five groups: regular mobi-lity, slightly impaired mobility, moderately impaired mobility, severely impaired mobility and extremely impaired mobility. The study also evaluated the use of orthopaedic appliances (elbow crutches, orthoses). Secondary outcomes Besides all these parameters, doctors and patients opinions on efficacy and safety of Suplasyn were recorded. Each case of adverse reaction was registered. Measures and timepoints During the study, measures of intensity of symptoms were checked before and after treatment. The analysis involved all the patients enrolled to the study (n = 4519).
Study Results **Performance**	Patients scored the pain level at rest and during walking (Figure 17 and 18) before treatment as 3.4 (SD 2.2) and 5.0 (SD 2.1), respectively. After treatment the scores for pain level at rest and during walking decreased to 1.5 (SD 1.5) and to 2.2 (SD 1.7), respectively.

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4505	0	10	3	3.4	2.2
Follow-up visit	4505	0	9	1	1.5	1.5

No data: 14; p<0.001

Figure 17. Pain at rest (VAS).

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4505	0	10	5	5.0	2.1
Follow-up visit	4505	0	9	2	2.2	1.7

No data: 14; p<0.001

Figure 18. Pain during walking (VAS).

Mean scores of the morning stiffness intensity (Figure 19) before and after treatment were 3.5 (SD 2.2) and 1.8 (SD 1.6), respectively. Score of stiffness at rest (Figure 20) also decreased from 3.0 (SD

2.2) to 1.5 (SD 1.5). The treatment also showed some improvement in walking on surface level and walking up and down stairs; results are presented in Figure 21 and 22.

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4507	0	10	3	3.5	2.2
Follow-up visit	4507	0	9	2	1.8	1.6

No data: 12; p<0.001

Figure 19. Morning stiffness.

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4507	0	10	3	3.0	2.2
Follow-up visit	4507	0	9	1	1.5	1.5

No data: 16; p<0.001

Figure 20. Stiffness after rest.

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4487	0	10	3	3.6	2.1
Follow-up visit	4487	0	9	1	1.7	1.5

No data: 32; p<0.001

Figure 21. Walking on flat surface.

	Number of patients	Min	Max	Median	Mean	SD
Diagnostic visit	4494	0	10	5	5.1	2.1
Follow-up visit	4494	0	10	2	2.4	1.7

No data: 25; p<0.001

Figure 22. Walking up and down stairs.

Ability to extend and range of flexion after treatment changed significantly compared to the baseline. The total number of patients assigned to particular groups is presented in Figure 23 and Figure 24. After treatment, use of orthopaedic appliances decreased (Figure 25).

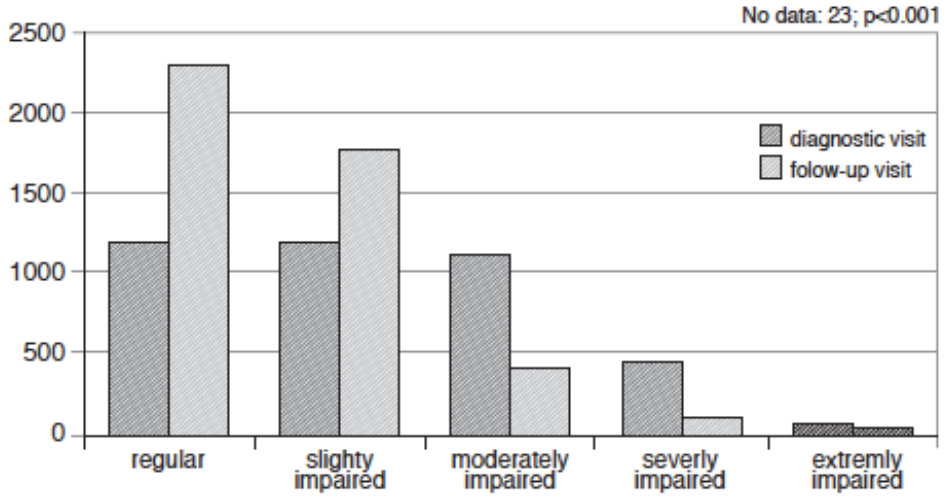


Figure 23. Ability of extent.

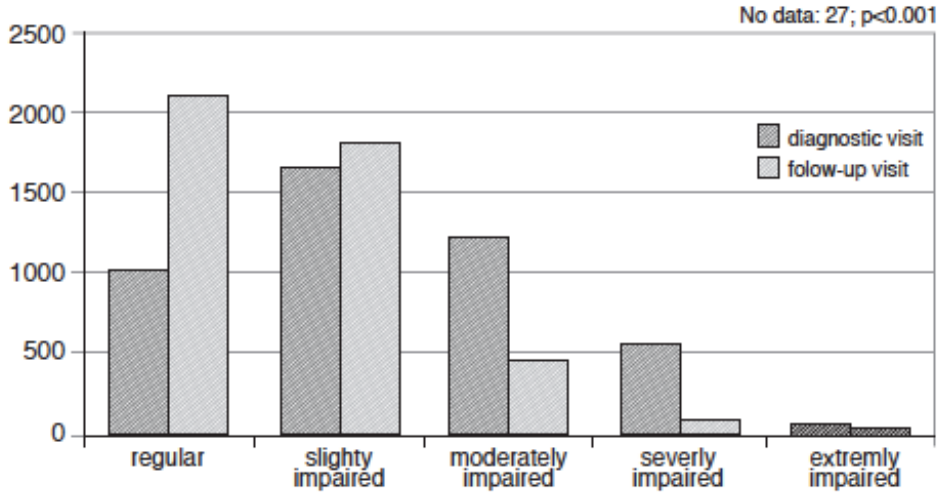
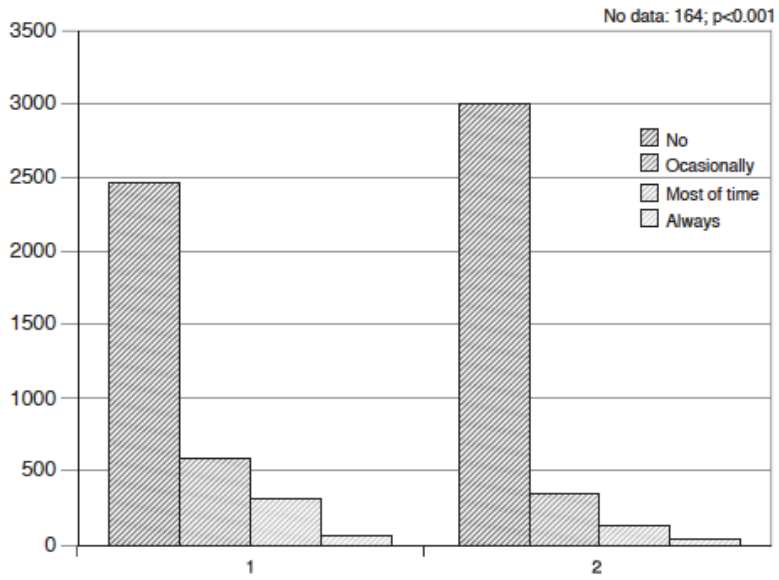


Figure 24. Range of flexion.

	 **Figure 25.** Use of orthopaedic appliances. According to the 59.1% of doctors, mean patient condition improved significantly, and 34.4% of them scored it as moderate. Patients scored improvement in a similar pattern, and the proportions were 59.9% and 32.6%, respectively.
Study Results **Safety**	Treatment tolerance was evaluated as very good and good in 68.8% and 29.6% of patients, respectively. Adverse effects, such as edema, exudate, pruritus, redness and pain occurred in 1.6% ofthe patients; association with some of these effects with the injection itself cannot be excluded. No serious adverse effects were reported.
Limit/s of the study	Not reported.
Discussion	This study results confirms the benefits from the administration of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis. Short and long term pain relief and mobility improvement are great important to patients because a significant improvement in quality of life. Despite short half-life of hyaluronic acid, its confirmed long-term action [6], produce some improvement on patient's quality of life for longer periods. The study confirms beneficial effect of HA. The functionality of the affected knee after treatment with Suplasyn improved, with the resolution of pain at rest and during walking. Extension ability and flexion range were improved. Patients reported less frequently complains on morning stiffness and stiffness after rest. Also, problems with daily activity, such as walking on flat surface and walking up and down stairs were reduced. A very important feature of the product is its extremely low rate of adverse effects. Good tolerance of HA also was confirmed in numerous studies [1,6]. Very good and good tolerance of the treatment was noted in 68.8% and 29.6% of the patients, respectively. Adverse effects, such as edema, exudate, pruritus, redness and pain occurred in 1.6% of the patients. However, association with some of these effects with the injection itself cannot be excluded. No severe adverse effects were reported.
Conclusions of the authors	The study confirmed high efficacy and good to-lerance of Suplasyn in the treatment of knee osteoarthritis. Due to adverse reactions related to the treatment with NSAIDs, treatment with hyaluronic acid is increasingly considered as the therapy of choice in patients suffering from osteoarthritis.

Citation 3

Title	Petrella R J. **Hyaluronic acid for the treatment of knee osteoarthritis: Long-term outcomes from a naturalistic primary care experience.** *Am J Phys Med Rehabil* 2005;84:287- 283.
Aim of the study	This clinical study aimed to evaluate long-term results of hyaluronic acid viscosupplementation for knee osteoarthritis.
Relevance of the study	Intraarticular HA is indicated currently for use in patients who may not have responded to a program of nonpharmacologic therapy and pain control with analgesics including acetaminophen. Clinical trials of intraarticular HA preparations have shown pain relief in HA-treated patients significantly greater than in those who were injected with placebo and comparable with or superior to intraarticular corticosteroids. Although pain relief is achieved more slowly with HA preparations than with intraarticular corticosteroid injections, the effect may last considerably longer. Similarly, intraarticular HA has shown comparable improvement in pain with oral anti-inflammatory preparations. This latter finding may be especially advantageous in patients in whom nonselective anti-inflammatories and cyclooxygenase-specific inhibitors are contraindicated or in those who have experienced either a lack of efficacy or other adverse events.
Equivalent Device	**Test device:** Suplasyn (biofermentative low molecular weight Hyaluronic acid viscosupplementation) **Control device:** No control devices. *Suplasyn is a medical device fully equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device". It is designed for large joints, such as knees.* *Actually, Suplasyn 2ml pre-filled syringe reaches full equivalence, because it has the same concentration of "Hyaluronic acid sodium salt, viscosuppletive joint device". The other Suplasyn devices share only partial equivalence with "Hyaluronic acid sodium salt, viscosuppletive joint device".*
Study Design	This was a prospective clinical study.
Study period	Not reported. Hiwever, recruitment lasted 6.7 years.
Sample size	The study population of 537 patients was extracted from a total referral group of 897 patients with unilateral knee osteoarthritis. The mean age of patients was 68 8 yrs, mean body mass index was 27.2 ± 2.1, and 65% of the patients were women.
Inclusion Criteria	At entry, all patients had, in the index knee, radiographic evidence of grade 1–3 medial compartment osteoarthritis, did not exhibit nonarthritis-related disease, had no regular (> 3 days/wk) concomitant nonsteroidal anti-inflammatory use, had no previous intraarticular HA or glucocorticoid injections, were not regularly using nutraceutical osteoarthritis products (including glucosamine sulfate or chondroitin sulfate), and all gave consent as approved by the University of Western Ontario ethics review board.
Exclusion Criteria	Not reported.
Intervention	<u>Name and type of intervention</u> Intra-articular (knee joint) administration of low molecular weight hyaluronic acid

	viscosupplementation. Aim of the intervention Evaluation of long-term results of hyaluronic acid viscosupplementation for knee osteoarthritis. Duration The mean time between the first and second series course of Suplasyn was 27 ± 7 wks (range, 12–84 wks) and 29 ± 15 wks (range 9–112 wks) between the second and third HA series. Follow-up lasted 6.7 years. Description of the intervention Suplasyn is a solution of HA of 500–730 kDa indicated for intraarticular injection for knee osteoarthritis. It is currently available and approved in 20 countries worldwide. Two milliliters of intraarticular HA at a concentration of 10 mg/ml was injected under sterile field using a medial approach. No anesthetics were used either topically or intra-articularly. Each injection (in the series of three injections) was performed 1 wk apart (±2 days) by an experienced clinician. All injections were initiated after baseline assessments of VAS and global satisfaction, which were performed by an independent technician. Return for consideration of a subsequent intraarticular HA series was based on patient request triggered by pain and disability interfering with activities of daily living and perception of similar symptoms to those experienced with their first presentation. This approach was aimed at replicating the usual clinical practice experience.
Outcomes	Primary outcomes The primary efficacy outcome was percentage of improvement from baseline in walking VAS pain. Secondary outcomes Secondary outcomes included improvement in VAS score of seated-rest pain, patient global satisfaction using a 5-point numerical scale weighted from completely satisfied5 to completely unsatisfied,1 presence of adverse events, and concomitant medications. Measures and timepoints All assessments were repeated by the same independent technician. This approach was repeated before a third HA series.
Study Results **Performance**	Primary outcomes The primary efficacy outcome was percentage of improvement from baseline in walking VAS pain. The significant improvements in walking VAS pain were seen at visit 2 (22.7%), visit 3 (36.1%), and visit 4 (81.3%) with the first HA series (Figure 26 and 27). No significant difference between baseline and visit 1 and visit 5 (return visit for second HA series) was observed.

First Series		Second Series	
Visit	Assessment[a]	Visit	Assessment[a]
1		5	10.3
2	22.7 ($P < 0.04$)	6	25.3 ($P < 0.01$)
3	36.1 ($P < 0.01$)	7	51.4 ($P < 0.001$)
4	81.3 ($P < 0.001$)	8	86.7 ($P < 0.001$)
		9	12.1

[a]Average percentage of improvement from baseline visual analog scale scores for walking pain.

Figure 26. Percentage improvement in visual analog scale scores for walking pain with first and second hyaluronic acid series.

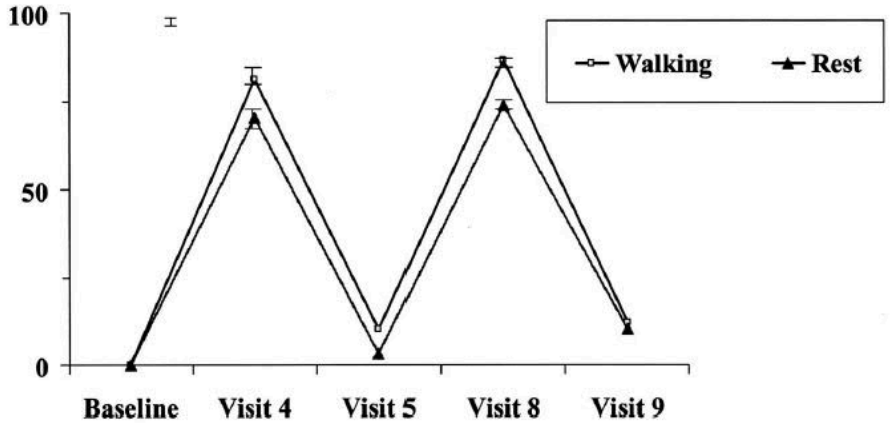


Figure 27. Changes in walking and rest visual analog scale pain for first and second hyaluronic acid series.

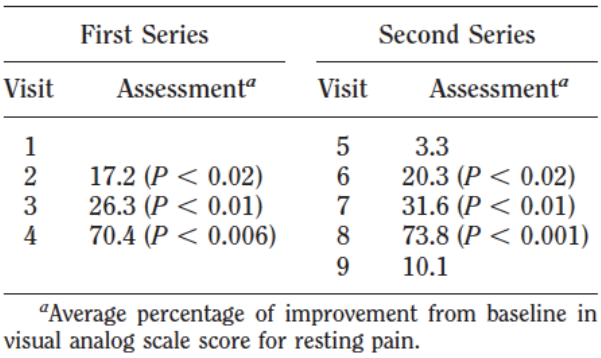
On presentation for a second HA series, a significant improvement in walking VAS pain at visit 6 (25.3%), visit 7 (51.4%), and visit 8 (86.7%) was observed from visit 5 (Figure 26 and 27). Furthermore, a significant improvement between visit 3 and visit 7 (36.1% vs. 51.4%) and visit 4 and visit 8 (81.3% vs. 86.7%) was observed with the second HA series (Figure 26). Visit 9 represented a return for a third HA series. There was a significantly greater improvement from visit 5 to visit 9 (10.3% vs. 12.1%) for these patients (Figure 27).

Secondary outcomes

Resting VAS pain was significantly improved from baseline to visit 2 (17.2%), visit 3 (26.3%), and visit 4 (70.4%).

There were similar improvements from visit 5 (return for second HA series) for visits 6, 7, and 8. No difference between visits 5 and 9 was observed.

Patient satisfaction with the first HA series (at visit 4) was 4.68 ± 0.6, and 4.83 ± 0.08 after the second series (at visit 8).

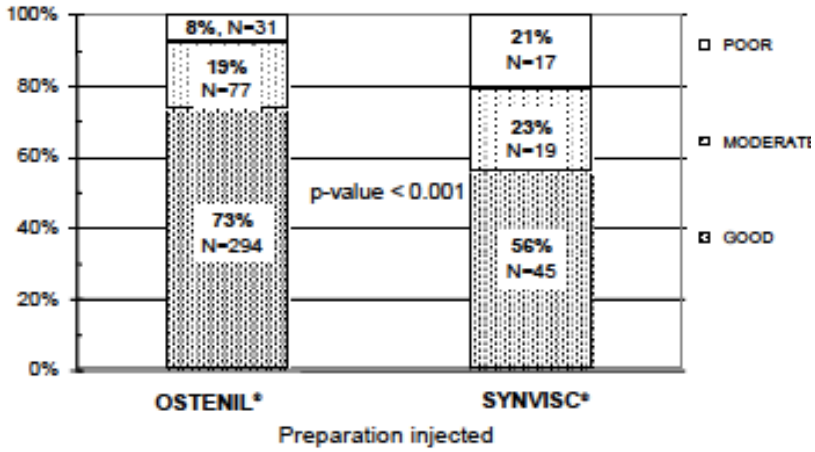
	 First Series / Second Series Visit / Assessment[a] / Visit / Assessment[a] 1 / 5 3.3 2 17.2 ($P < 0.02$) / 6 20.3 ($P < 0.02$) 3 26.3 ($P < 0.01$) / 7 31.6 ($P < 0.01$) 4 70.4 ($P < 0.006$) / 8 73.8 ($P < 0.001$) 9 10.1 [a]Average percentage of improvement from baseline in visual analog scale score for resting pain. **Figure 28.** Percentage improvement in visual analog scale score for resting pain with first and second hyaluronic acid series. Forty-one percent of patients returning for a second HA series reported regular (three or more times per week) concomitant use of alternate knee osteoarthritis therapeutic modalities. The most prevalent modalities included nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors (37%), acetaminophen (31%), nutraceuticals (12%), and physical therapy or bracing (12%). There was no significant difference between the use of concomitant therapeutic modalities for those at the second or third HA series. No other intraarticular injections were performed on any of the study patients observed at the second or third HA series.
Study Results **Safety**	There were no systemic adverse events reported. Local adverse events including pain and swelling at the injection site were observed in 1.48% and 1.32% of injections with the first and second HA series, respectively. Only three adverse events were reported among those who presented for a third HA series.
Limit/s of the study	A limitation of this study includes the absence of a control group. A control could have determined the size of a placebo effect, which has been described as high as 80%.10 Further, given that many patients purchased their own injections, this could have resulted in an even greater placebo effect than observed in clinical trials.
Discussion	This large cohort of 537 patients with knee osteoarthritis, who were naive to intraarticular injection with HA, received at least two successive series of intraarticular injections with 2.0 ml (10 mg/ml) of Suplasyn and demonstrated improved pain symptoms at rest and during walking with each treatment series. HA injections were highly satisfactory to patients with each HA series and included a very low rate of local adverse events and a very high retention rate. Patients returned for second and third HA series based on their own perception of restricted function and pain at a treatment interval of 27 wks, and they used relatively few alternate therapeutic modalities for osteoarthritis. Hence, this representative sample from a naturalistic, usual care clinical setting demonstrated that the use of HA in osteoarthritis of the knee was effective and acceptable in relieving symptoms and in improving function with few local adverse events and little use of concomitant therapeutic modalities. These findings suggest that intraarticular HA may be an important treatment option for patients with osteoarthritis of the knee.
Conclusions of the authors	Not reported.

Citation 4

Title	Uebelhart D, Berz S. **Safety and efficacy of fermentative hyaluronan in knee osteoarthritis: a retrospective study.** *Department of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Switzerland* 2003.
Aim of the study	This clinical study aimed to compare two HA viscosupplementations (Ostenil® and Synvisc®) for the treatment of knee osteoarthritis.
Relevance of the study	The use of intra-articular (i.a.) hyaluronan (HA) in the treatment of osteoarthritis (OA) is now well accepted and is based on the principle of viscosupplementation. Viscosupplementation restores the normal rheological properties of the synovial fluid and hence its protective, lubricating, shock absorbing and barrier functions resulting in improved joint homeostasis. Authors set up a retrospective survey to collect tolerability, safety and efficacy data following i.a. injections of Ostenil® (TRB Chemedica AG, Munich, Germany).
Equivalent Device	**Test devices:** – Ostenil® (viscosupplementation containing low molecular weight HA of biofermentative origin) – Synvisc® (viscosupplementation containing chemically-modified high molecular weight HA of animal origin - chicken combs) *Ostenil® is a medical device fully equivalent to to "Hyaluronic acid sodium salt, viscosuppletive joint device". It is an intra-articular low weight HA-based viscosupplementation intended for pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.*
Study Design	This was a retrospective clinical study.
Study period	Not reported.
Sample size	Data on 467 patients were obtained of which 436 had symptomatic OA and received one or more i.a. injections of HA into one or both knees. Demographic data are shown in Figure 29.
Inclusion Criteria	Subjects included were knee OA patients treated with i.a. HA within the previous 15-month period.
Exclusion	Not reported.

Parameter		Ostenil® group	Synvisc® group	P value
Age (years, mean)		60.8	64.1	p=0.04-0.06
Gender:	Female	221 (59.9%)	32 (47.8%)	p<0.09
	Male	145 (39.3%)	34 (50.8%)	
	Missing	3 (0.8%)	1 (1.5%)	
Knee OA severity:	Mild	17 (6.2%)	1 (1.5%)	p<0.06
	Moderate	129 (46.7%)	26 (40.0%)	
	Severe	130 (47.1%)	38 (58.5%)	

Figure 29. Patients group demographic data.

Criteria	
Intervention	Name and type of intervention Intra-articular administration of HA-based viscosupplementations. Aim of the intervention Comparison of two HA viscosupplementations (Ostenil® and Synvisc®) for the treatment of knee osteoarthritis. Duration The treatment with Ostenil lasted 5 weeks, while that of Synvisc lasted 3 weeks. Description of intervention A standard treatment cycle for Ostenil® was defined as 1 injection/week for 3 to 5 weeks, while the standard treatment cycle for Synvisc® was defined as 1 injection/week for 3 weeks. A total of 2022 i.a. injections were made: 1753 with Ostenil® (86.7%) and 264 with Synvisc® (13.1%).
Outcomes	Primary outcomes Effectiveness of the treatment judged as “good”, “moderate”, “poor” or “insufficient”. Safety was evaluated as the rate of adverse events and adverse device reactions for both treatments. Secondary outcomes Not reported. Measures and timepoints Outcomes were evaluated after each injection. Statistics are expressed per injection (first injection, subsequent injections).
Study Results **Performance**	Investigators judged global efficacy as “good” to “moderate” in 92.3% of the Ostenil® treated cases and 79.0% of the Synvisc® treated cases (p<0.001), and “poor” or “insufficient” in 7.7% and 21.0% of the cases, respectively, as shown in Figure 30.  **Figure 30.** Investigator’s judgement of efficacy in knee osteoarthritis. Efficacy was significantly better (p<0.001) in the Ostenil® group compared to the Synvisc® group.

	When the comparison is performed for patients having received 3 injections, the efficacy remains significantly better for the Ostenil® group (p=0.03). The investigator's judgement of tolerability was good to moderate in 98.7% of the patients treated with Ostenil® and in 92.6% of the patients treated with Synvisc® (Figure 31).

	Good		Moderate		Poor		Total	
	N	%	N	%	N	%	N	%
Ostenil® group	289	98.0	2	0.7	4	1.4	295	100.0
Synvisc® group	61	89.7	2	2.9	5	7.4	68	100.0

Figure 31. Assessment of tolerability in the treated OA knee by preparation.

Study Results Safety	The incidence of adverse device events (ADE's) in the Synvisc® treated cases was 7.7% compared to 2.1% in the Ostenil® group (p<0.0001) while the incidence of adverse device reactions (ADR's) was 5.1% in the Synvisc® group and 0.7% in the Ostenil® group (p<0.0001) - Figure 32. The overall incidence of ADR's with the HA products was 6.1%, with 3.9% in the Ostenil® group and 15.2% in the Synvisc® group. ADR's were significantly more frequent and more severe with Synvisc®.

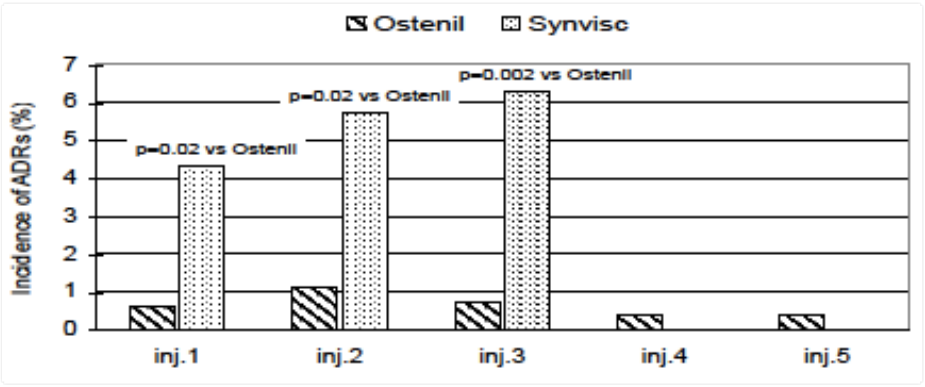


Figure 32. Adverse device reactions in OA. Incidence per injection. Survey made in 467 patients, 2141 injections.

Limit/s of the study	Not reported.
Discussion	No information available.
Conclusions of the authors	The results of this retrospective study indicate that Ostenil®, which contains a natural, non-chemically modified HA of fermentative origin, is a safe and effective therapy for knee OA, and support previously published data1 indicating that i.a. injection of chemically modified cross-linked HA derivative of avian origin (Synvisc®) is associated with a higher incidence of adverse device reactions.

Citation 5

Title	Román JA, Chismol J, Morales M, Donderis JL. **Intra-articular treatment with Hyaluronic Acid. Comparative study of Hyalgan and Adant.** *Clin Rheumatol* 2000;19: 204-6.

Aim of the study	The aim of this study was to assess the efficacy and safety of intra-articular therapy in patients suffering from gonarthrosis as a whole and to identify the variables resulting from the type of HA (Hyalgan versus Adant).
Relevance of the study	Different studies confirm that hyaluronic acid (HA) therapy relieves pain, reduces the consumption of non-steroidal anti-inflamatory drugs (NSAIDs) and delays surgery; however, results vary according to the product used, and to authors' knowledge no studies comparing the efficacy and safety of different HAs have been reported.
Equivalent Device	**Test devices:** – Adant - Low Molecular weight Hyaluronic acid viscosupplementation – Hyalgan - Low Molecular weight Hyaluronic acid viscosupplementation *Adant is one of the medical devices equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it reaches clinical, technical and biological equivalence. It is composed of Low Molecula Weight Hyaluronic acid of biofermentative origin.* *Hylagan has been excluded from the medical devices listed in the Clinical Evaluation Plan, since it contains Hyaluronic acid obtained from chicken combs.*
Study Design	This is a blind, randomized, comparative clinical study.
Study period	Not reported.
Sample size	49 patients were included, 8 were male and 41 were female; their ages ranged from 41 to 86 years (mean 65.14, SD 9.77 years).
Inclusion Criteria	Patients were included in the study if they had gonarthrosis following clinical and radiological criteria (states II and III according to Kellgren and Lawrence).
Exclusion Criteria	Not reported.
Intervention	Name and Type of intervention Intra-articular administration of a HA-based viscosupplementation. Aim of intervention Assessment of the efficacy and safety of intra-articular therapy in patients suffering from gonarthrosis as a whole and to identify the variables resulting from the type of HA (Hyalgan versus Adant). Duration 6 months follow-up. Description of intervention A total of 49 intra-articular treatments (245 infiltrations) were carried out on 49 patients, of whom 30 were given Adant and 19 Hyalgan. • Adant: 5 injections of 25 mg (2.5 ml). This is a 1% sodic hyaluronate solution with a mean molecular weight of 900 000 D biotechnically obtained. • Hyalgan: 5 injections of 20 mg (2 ml). This is a 1% sodic hyaluronate solution with a mean molecular weight of 800 000 D from an animal source (cock's crest).

Outcomes	Primary outcomes The clinical evaluation criteria were according to the subjective assessment of each patient. The results were divided into four groups according to clinical improvement criteria: excellent (>75%), good (50%–75%), fair (25%–50%) and no clinical response (<25%). Secondary outcomes All patients were also questioned on their consumption of analgesic and/or anti-inflammatory drugs at the beginning and end of treatment. Measures and timepoints The assessment took place the week following the fifth infiltration, at 3 months and at 6 months.
Study Results **Performance**	The results according to the efficacy assessment were good or excellent at 5 weeks in 40.8% of cases, in 38.8% at 3 months and in 26.5% at 6 months. The maximum improvement obtained in each patient was at 5 weeks in 75.4% (37 intra-articular treatments), at 3 months in 22.4% (11 intra-articular treatments) and at 6 months in only one case (2%); 73.5% of cases showed fair or no clinical response at 6 months. To summarise, when the result was excellent or good the improvement was immediate and maintained in time; however, when the result was fair or with no clinical response at 5 weeks no improvement could be expected. In the comparative study (Figure 33) excellent and good results were obtained at 3 months in 50% of cases with Adant and in 21.1% with Hyalgan.

		5 weeks	3 months	6 months	χ^2
Excellent	Adant	2 (6.7%)	1 (3.3%)	1 (3.3%)	n.s.
	Hyalgan	2 (10.5%)	1 (5.3%)	1 (5.3%)	n.s.
	χ^2	n.s.	n.s.	n.s.	
Good	Adant	11 (36.7%)	14 (46.7%)	9 (30%)	n.s.
	Hyalgan	5 (26.3%)	3 (15.8%)	2 (10.5%)	n.s.
	χ^2	n.s.	$p = 0.026$	n.s.	
Fair	Adant	8 (26.7%)	3 (10%)	3 (10%)	n.s.
	Hyalgan	9 (47.4%)	2 (10.5%)	1 (5.3%)	
	χ^2	$p = 0.13$	n.s.	n.s.	
No response	Adant	9 (30%)	12 (40%)	17 (56.7%)	$p<0.05$
	Hyalgan	3 (15.8%)	13 (68.4%)	15 (78.9%)	$p<0.0001$
	χ^2	n.s.	$p<0.05$	n.s.	
		49	49	49	

Figure 33. Results according to the assessment of the efficacy of Adant and Hyalgan.

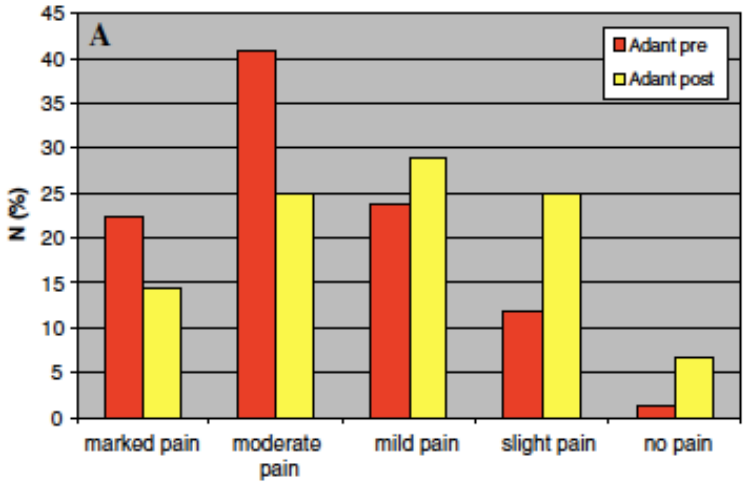
	Moreover, patients reported no changes in analgesic or anti-inflammatory drugs consumption.
Study Results **Safety**	Eight patients had some painful infiltrations (20%), six with Adant (16.3%) and two with Hyalgan (10.5%). The relative risk of suffering a painful injection was almost twice as great with Adant.
Limit/s of the study	Not reported.
Discussion	The overall results are consistent with literature, being good and excellent in 40.8% of cases. The efficacy of the viscosupplementation decreased according to the time elapsed since the end of the treatment. In this study 73.5% of cases were fair or with no clinical response at 6 months, and so authors recommend repeat treatment at 6 months if it has been effective. Most patients obtained maximum effect at 5 weeks and a few at 3 months: thus if no clinical improvement has occurred a different therapy should be suggested. In this study, the incidence of adverse effects with intra-articular injections of HA has been comparable to that described in the literature. Although it varies considerably between authors, probably because of the different subjective assessment of pain, it is usually located in the injection

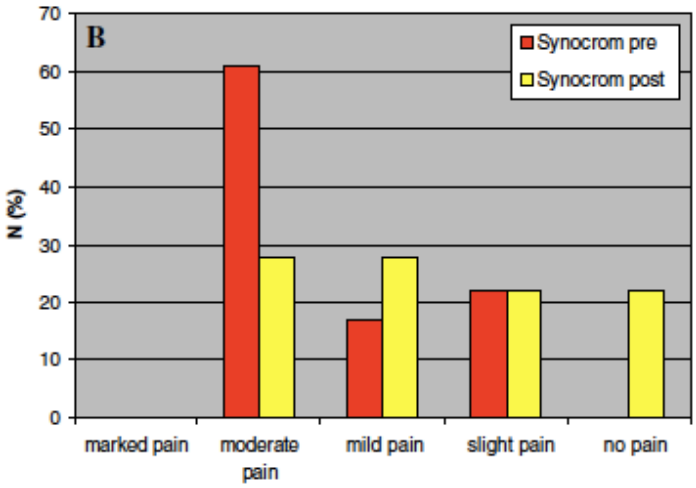
	site and consists of a painful transitory reaction, which at times is accompanied by a rise in temperature, which lasts 1 or 2 days and resolves spontaneously.
Conclusions of the authors	The efficacy with Adant at 3 months (50%) after treatment was greater than with Hyalgan (21.1%), probably because its greater viscosity increases its half-life in the joint.

Citation 6

Title	Van Den Bekerom MPJ, Rys B, Mulier M. **Viscosupplementation in the hip: evaluation of hyaluronic acid formulations.** *Arch Orthop Trauma Surg* 2008; 128(3): 275-80.
Aim of the study	This was a clinical trial comparing three formulations of HA.
Relevance of the study	Viscosupplementation (VS) is the administration of hyaluronan and/or hyaluronic acid preparations to joint synovial fluid for the treatment of OA in order to restore the biologic properties of normal hyaluronic acid (HA). The use of VS with HA was first described to provide pain relief and to increase mobility of the knee joint. The VS is an effective treatment for OA of the knee with beneficial effects on pain, function and patient global assessment. HA products have more prolonged effects than intraarticular corticosteroids. Since 1984, this technique is also used for the management of OA of the hip joint.
Equivalent Device	**Test devices:** • Adant (viscosupplementation containing biofermentative low molecular weight Hyaluronic acid); • Synocrom (viscosupplementation containing biofermentative high molecular weight Hyaluronic acid); • Synvisc (viscosupplementation containing high molecular weight Hyaluronic acid of animal origin - chicken combs) *Adant is a medical device equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it is a viscosupplementation of biofermentative and low molecular weight Hyaluronic acid. Moreover, it reaches also clinical and technical equivalence, as described in the Clinical Evaluation Plan.*
Study Design	This was a prospective clinical study.
Study period	Treatment was performed Between March 2001 and February 2005. Assessment was carried out in April 2005.
Sample size	120 patients (126 hips), 49 males and 71 females, with an age betwwen 30 and 70 years, received the treatment.
Inclusion Criteria	• Age between 30 and 70 years and suV ering idiopathic radiologically conW rmed hip OA. • Visual Analogue Scale (VAS) score for pain greater then 30 (on a 100-point scale; 0 no pain and 100 "the worst pain imaginable") • Have persistent pain for longer than 1 month despite use of analgesics or NSAID's. • Be candidate for surgical treatment with a THA, according to the following criteria: ○ continuous hip pain, also during the night, requiring daily intake of NSAID's or pain medication

	○ disabled gait pattern and need of walking aid • Be able to understand the information relative to viscosupplementation and to give informed consent.
Exclusion Criteria	• Pregnancy • Contraindications to intra-articular hyaluronic-acid preparations • Major hip dysplasia or congenital abnormality of the hip • Patients with systemic corticosteroids or intra-articular corticosteroid injections in the last 6 months • Contra-lateral THA or hip arthroscopy in the last 6 months • Oral or parenteral anticoagulant therapy • Previous hyaluronic acid hip inW ltrations • Skin diseases or infections • Signs of haemarthrosis • History of allergy or hypersensitivity to iodated contrast
Intervention	Name and type of intervention Intra-articular (hip joint) administration of HA-based viscosupplementations Aim of the intervention Comparison of three different hyaluronate formulations and evaluates functionality, time of satisfactory pain relief and also the delay in performing a total hip arthroplasty. Duration 3-year follow-up. Description of the intervention Patients received an intra articular infiltration with one of the three products. The manufacturer's treatment recommendations were followed. Patients having initially experienced a satisfactory pain relief are offered a second and third infiltration or THA when the condition deteriorates. Injection of the viscosupplementation was performed under sterile conditions by the same experienced orthopaedic surgeon (MM) in all patients. After skin cleaning a lumbar puncture needle was inserted in a lateral approach. Layer by layer local anaesthesia was performed using lidocaine 1%. Iodinated contrast agent was injected. The needle positioning into the joint cavity was fluoroscopically controlled. Arthrocentesis was carefully performed prior to each injection to remove any effusion. After resting for 2 h, the patient was allowed to walk and to return home. The patient was advised to rest at home until the next morning. Oral symptomatic slow acting drugs for osteoarthritis were authorized if they were taken at a stable dose for more than 3 months prior to inclusion in the study. These analgesics were continued at a stable dose during the VS treatment.
Outcomes	Primary outcomes Pain and functionality were evaluated using the VAS pain during walking score (100-point scale) and the Harris Hip Score (HHS). The latter is a clinical scoring system on a total of 100 points whereby the following subscales are rated: function (47 points), pain (44 points), range of motion of the hip (5 points) and absence of muscle contractures and length discrepancy (4 points). All side effects and complications of viscosupplementation were noted. In April 2005, all patients were contacted for follow-up assessment over the phone VAS and HHS.

	Secondary outcomes Not reported. Measures and timepoints All patients were assessed at baseline and 6 weeks after each infiltration.
Study Results Performance	The mean pre-infiltration HHS was comparable for the three groups and varied from 64.8 points in the Adant group to 66.8 points in the Synocrom-group. The post-infltration HHS increased with 6.3 points in the Adant group (P < 0.001), with 10.6 points in the Synocrom group (P < 0.05) and with 6.1 points in the Synvisc-group (P > 0.05; Figure 34). There was no statistical significant difference in the evolution of the HHS between the three groups (Figure 34). HHS pre / HHS post / Difference / *P* Adant: 64.8 ± 13.8 / 71.1 ± 15.7 / + 6.3 / < 0.001 Synocrom: 66.8 ± 13.8 / 77.4 ± 14.7 / + 10.6 / < 0.05 Synvisc: 66.3 ± 13.5 / 72.4 ± 14.5 / + 6.1 / > 0.05 **Figure 34.** Evolution in average HHS score. Viscosupplementation provided a highly significant pain reduction in the Adant-group (P < 0.0001), a significant pain reduction in the Synocrom-group (P < 0.05) and a pain reduction that did not reach significance in the Synvisc group (P > 0.05). There was no significant difference in pain relief between the three treatment products (Figure 35 and 36). 



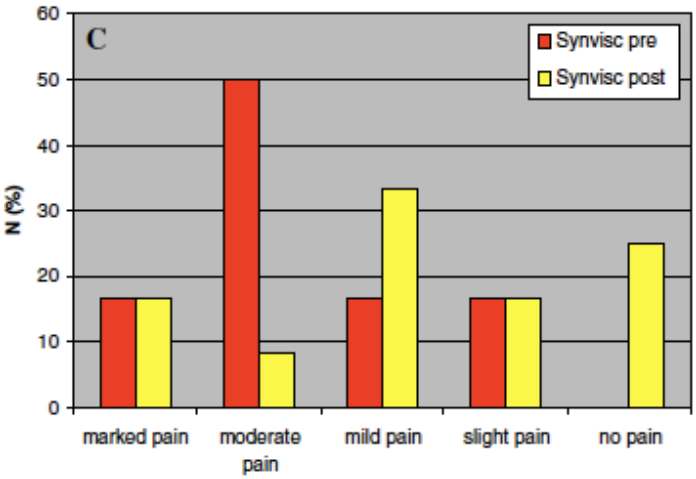


Figure 34. Pain relief in the three treatment groups a Adant, b Synocrom and c Synvisc.

	VAS pre	VAS post	Difference	*P*
Adant	51 ± 23	39 ± 27	− 12	< 0.0001
Synocrom	43 ± 22	29 ± 23	− 14	< 0.02
Synvisc	47 ± 26	30 ± 29	− 17	> 0.05

Pre: at first infiltration
Post: at follow-up

Figure 35. Duration of treatment effect after first infiltration.

The duration of the effect of the first infiltration in the three groups is shown in a Kaplan-Meier curve (Figure 36).

The first infiltration was the starting point. Endpoints were the second infiltration or operation of the afflicted hip, or when these were not applicable the latest patient contact, which can be considered as ongoing effect.

There is no significant difference between the three groups (P = 0.61).

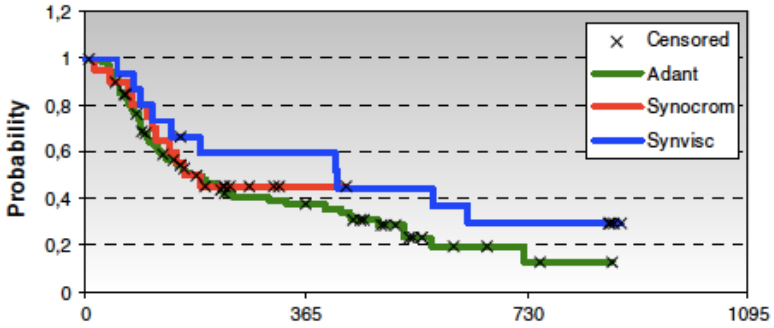


Figure 37. Kaplan-Meier survival curve of the duration of effect of the first infiltration in days for the three different treatment groups.

The positive effect was still ongoing in 46 hips, while in 80 hips patients had either received a second inW ltration or THA at, the end of the study.
The delay in performing a hip operation is analysed using a Kaplan-Meier survival curve (Figure 38). After 3 years, 51% of the patients have not undergone surgery.

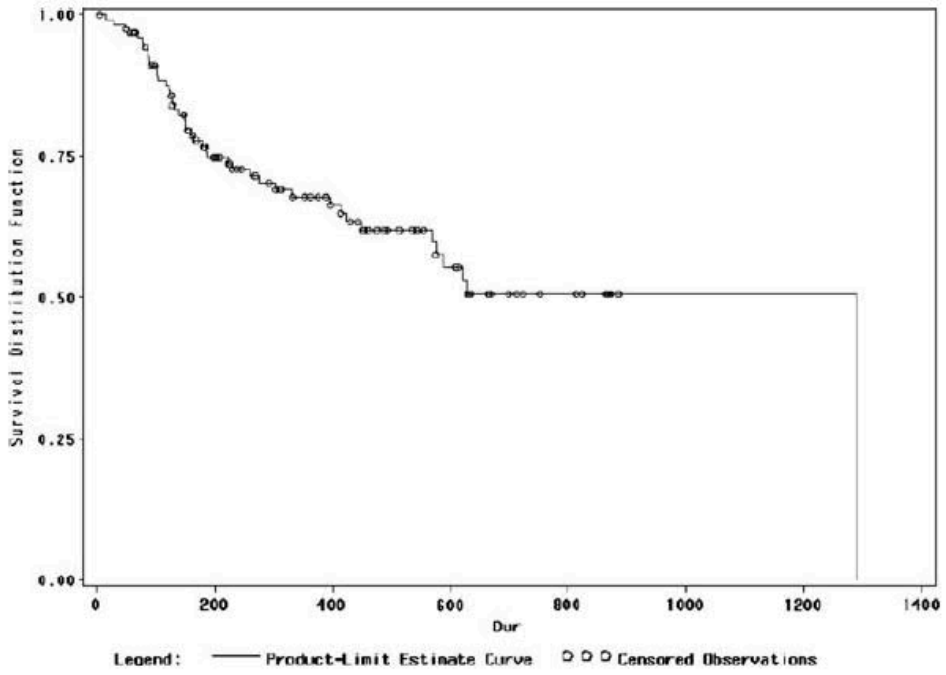


Figure 38. Kaplan-Meier survival curve for the delay to surgery in days for the three groups confounded.

Study Results Safety	Not reported.
Limit/s of the study	The results of this study should be considered in the light of the limitations of the design of this study. It is a nonplacebo controlled nonrandomised prospective study. It is known from experience with knee OA that the placebo effect of VS tends to be substantial. The dimension of the groups treated with the three different products differs from 15 to 91 patients.

Discussion	The VS method is widely used for OA of the knee joint, but there are only a few studies about its use in OA of the hip. Most authors agree that there should be a role for viscosupplementation in the treatment of hip OA. The findings of this study confirm the effect of VS in patients suffering OA of the hip. This is the largest series of patients with hip osteoarthritis treated with viscosupplementation. The three preparations provided a significant pain relief and improvement of the HHS. The isolated Synvisc group never reached statistical significance in HHS score evolution and VAS during walk test after VS treatment; possibly due to the small number of patients (N = 15) in this group. We saw no infectious adverse events and no serious systemic reactions, but all the interventions are performed in the operating theatre under strict aseptic conditions. The adverse events rates ranged from 10 to 30% that is slightly higher than the rates reported in VS treatment of knee OA. Repeated injections did not increase the risk of adverse events.
Conclusions of the authors	Not reported.

Citation 7

Title	Mathies B, Berger J, Siegfried C, Gurry R. **Effect of intra-articular sodium hyaluronate (Ostenil®) on improving the quality of life and delaying surgery in patients indicated for total knee replacement. An open, pilot, phase III study.** *5th Symposium of the International Cartilage Repair Society, Gent, Belgium.* May 26–29, 2004.
Aim of the study	This clinical study aimed to determine whether a treatment cycle with a sterile isotonic solution of hyaluronan (Ostenil®, TRB Chemedica, Munich, Germany) would delay the time to TKR and improve patients' quality of life.
Relevance of the study	Viscosupplementation1 using intra-articular (i.a.) hyaluronic acid (HA) is a recommended treatment option in the management of osteoarthritis (OA) of the knee. Moreover, the symptomatic benefits of i.a. treatment with HA have been demonstrated in several studies in patients with knee OA, with beneficial effects lasting between 6 months4,5 and 1 year after the administration of one i.a. injection of HA per week for five consecutive injections. The long-term benefits of HA have been attributed to an improvement in the viscoelastic properties of the synovial fluid.
Equivalent Device	**Test device:** Ostenil® (viscosupplementation containing biofermentative low molecular weight Hyaluronic acid) **Control:** No control devices. *Ostenil® is a medical device equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it is a viscosupplementation of biofermentative and low molecular weight Hyaluronic acid. Moreover, it reaches also clinical and technical equivalence, as described in the Clinical Evaluation Plan.*
Study Design	This was an open, pilot, phase III clinical study.
Study period	Not reported.
Sample size	A total of 24 patients (average age: 62.5 ± 10.6 years; average weight: 78.9 ± 12.1 kg; 50% female) with painful advanced knee OA [Kellgren–Lawrence grade II (33.3%), III (58.3%) and IV (8.3%)] requiring continuous NSAID treatment and who were candidates for TKR within 3 months were

	included in the study.
Inclusion Criteria	Male and female patients were included in the study if they showed evidence of painful advanced knee OA, were candidates to receive TKR within 3 months (based on Kellgren–Lawrence scale and severe clinical signs, i.e. WOMAC scores and pain on walking 20 m without support, assessed using the 100 mm Scott–Huskisson visual analogue scale, VAS) and required continuous treatment with non-steroidal anti-inflammatory drugs (NSAIDs). All patients were required to provide signed informed consent.
Exclusion Criteria	Factors leading to exclusion from the study included: • accompanying OA of the ipsilateral hip of sufficient severity to interfere with the functional assessment of the knee; • known or suspected infection of the affected joint painful knee conditions other than OA, such as Sudeck's atrophy, synovial pathologies, rheumatoid arthritis or other rheumatoid conditions severe obesity (BMI >40); • treatment with SYSADOAs (symptomatic slow-acting drugs in OA) or i.a. corticosteroid within the 3 months prior to the study start.
Intervention	Name and type of intervention Intra-articular (knee joint) administration of a Hyaluronic acid based viscosupplementation. Aim of the intervention Determination whether a treatment cycle with a sterile isotonic solution of hyaluronan (Ostenil®) would delay the time to TKR and improve patients' quality of life. Duration Treatment lasted 4 weeks (28 days). Follow up lasted from Day 28 to Month 12. Description of the intervention Injections were performed in the target knee under standardised conditions using the superolateral approach. When arthrocentesis was required, the amount of synovial fluid obtained was recorded. The treated knee was mobilised immediately after each injection and patients were advised to refrain from strenuous physical activities involving the knee.
Outcomes	Primary outcomes The primary efficacy criteria were pain on walking 20 m without support, assessed using the VAS, and pain using the WOMAC Index section A. Secondary outcomes The secondary efficacy criteria included joint stiffness and function (WOMAC Index sections B and C, respectively), physical examination of the knee, escape medication consumption, quality of life (SF-36 health survey), viscous/elastic moduli of the synovial fluid and efficacy judgements by the patients and the investigator. Measures and timepoints Efficacy parameters were assessed and synovial fluid collected prior to i.a. injection of Ostenil® on Days 0, 7, 14, 21 and 28 (i.e. Visit 1 to Visit 5). Follow-up visits were scheduled for Days 56 and 84 (Visits 6 and 7). An open visit (Visit 8), which took place during the period from Day 84 up to Month 12, was foreseen to determine the time at which the patient returned for re-treatment because of worsening symptoms (time to re-treatment) or when the patient had TKR (time to TKR).

Study Results

Performance

Three patients dropped out of the study for personal reasons and 21 patients were evaluated. Of these, three underwent TKR between 4.5 and 6 months after the start of treatment while the other 18 did not require TKR in the 12-month period after the start of treatment (end of study). TKR was delayed by a mean of 7.5 ± 2.3 months after a treatment cycle with Ostenil®.

The primary efficacy parameter of pain in the affected joint on walking 20 m without support decreased significantly (p = 0.0002) from 43.67 ± 14.65 mm (median: 44.0 mm) at baseline to 16.67 ± 16.61 mm (median: 9.0 mm) at Visit 5. This beneficial effect was maintained during the treatment-free follow-up period (Figure 39).

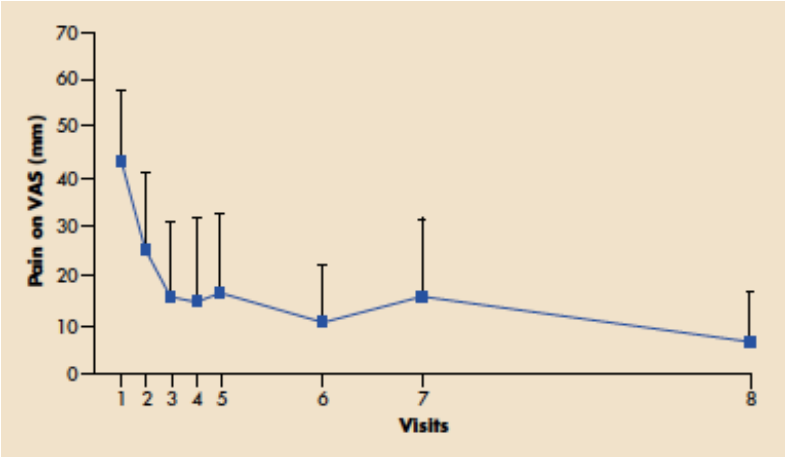


Figure 39. Pain on walking 20 m without support, measured on the visual analogue scale (VAS).

The same trend was observed for the other primary efficacy criterion, WOMAC A, which showed a significant (p = 0.002) decrease from 6.86 ± 3.02 (median: 7.0) at baseline to 2.43 ± 2.44 (median: 3.0) at Visit 8 (Figure 40).

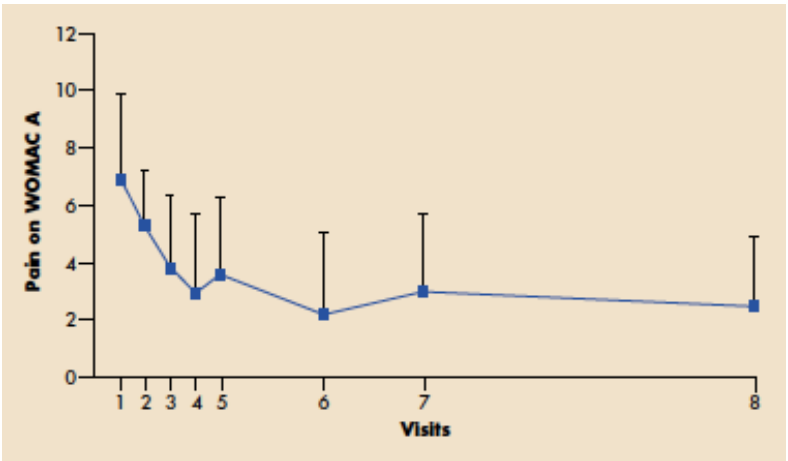


Figure 40. Pain assessment using WOMAC Index section A.

Joint stiffness (WOMAC B) (Figure 41) and impairment (WOMAC C) (Figure 42) improved significantly ($p<0.005$) from Visit 3 onwards compared with baseline values. WOMAC B showed a significant decrease from 3.24 ± 2.02 (median: 3.0) at baseline to 1.76 ± 1.64 (median: 2.0) at Visit 3. The same trend was observed for WOMAC C, which showed a significant decrease from 21.95 ± 9.55 (median: 21.0) at baseline to 14.29 ± 9.31 (median: 12.0) at Visit 3.

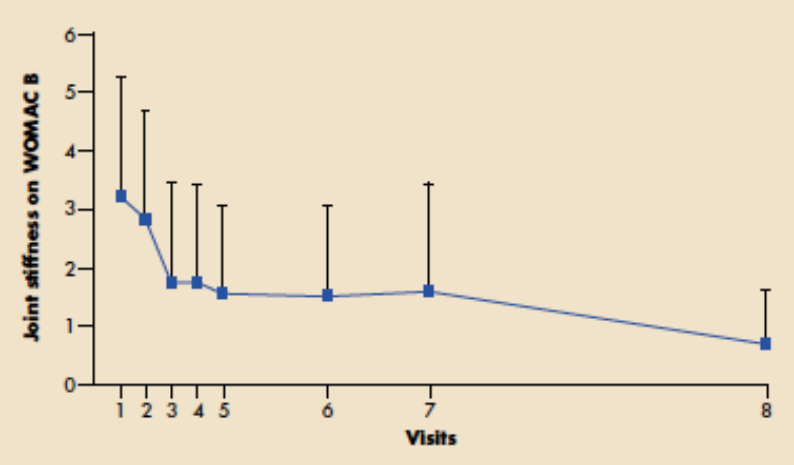


Figure 41. Joint stiffness assessed using WOMAC Index section B.

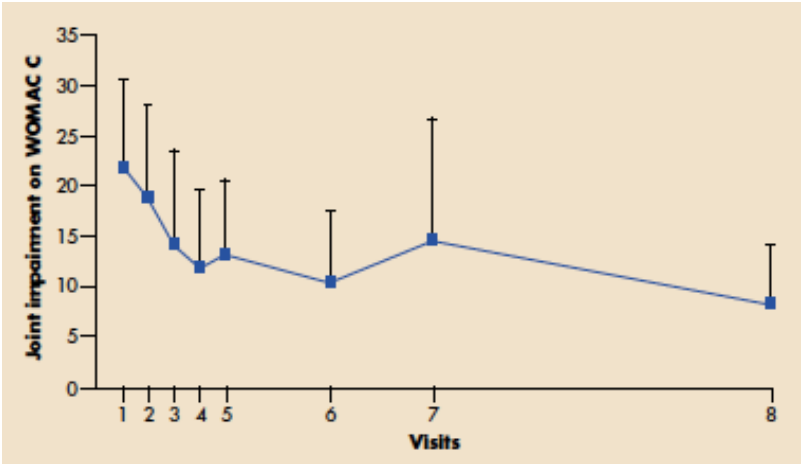


Figure 42. Joint impairment assessed using WOMAC Index section C.

SF-36 improved significantly (p = 0.02) up to Visit 7, with a 22% change in the median score (Figure 43).

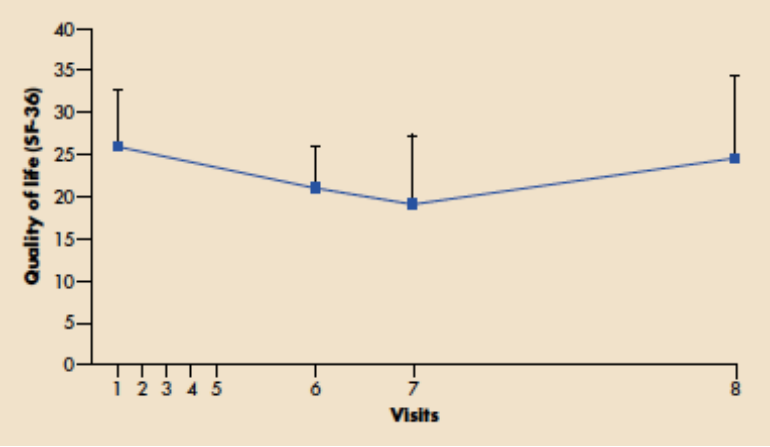


Figure 43. Quality of life as measured on the SF-36 health survey.

Knee effusion, which was present in 80% of the patients at Visit 1, was found in 57.1% of the patients at Visit 8.

Consumption of analgesics or NSAIDs did not change during the study period.

The dynamic elasticity (G') of the synovial fluid increased from 43.9 ± 8.6 mPa (median: 44.54 mPa) at baseline to 54.0 ± 25.4 mPa (median: 44.16 mPa) at Visit 7 (Figure 44), while dynamic viscosity (G'') increased from 112.1 ± 81.3 mPa (median: 89.83 mPa) at baseline to 171.9 ± 169.6 mPa (median: 104.5 mPa) at Visit 7 (Figure 45). Steady state viscosity (η) increased from 19.5 ± 12.5 mPa.s (median: 16.22 mPa.s) at baseline to 28.9 ± 27.0 mPa.s (median: 18.08 mPa.s) at Visit 7 (Figure 46).

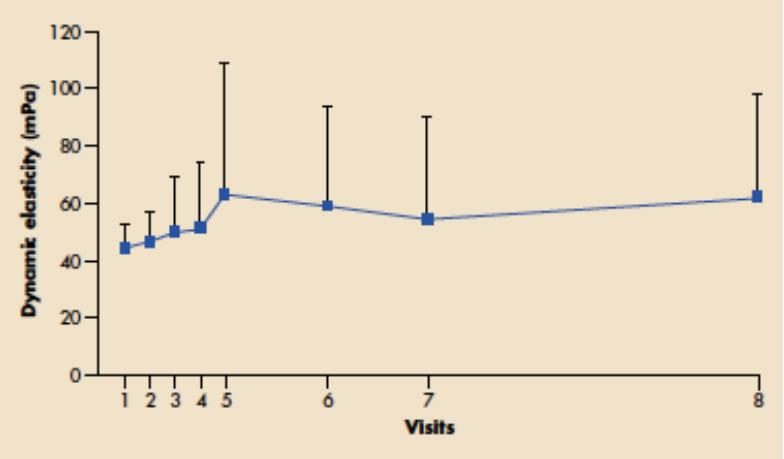


Figure 44. Dynamic elasticity of the synovial fluid.

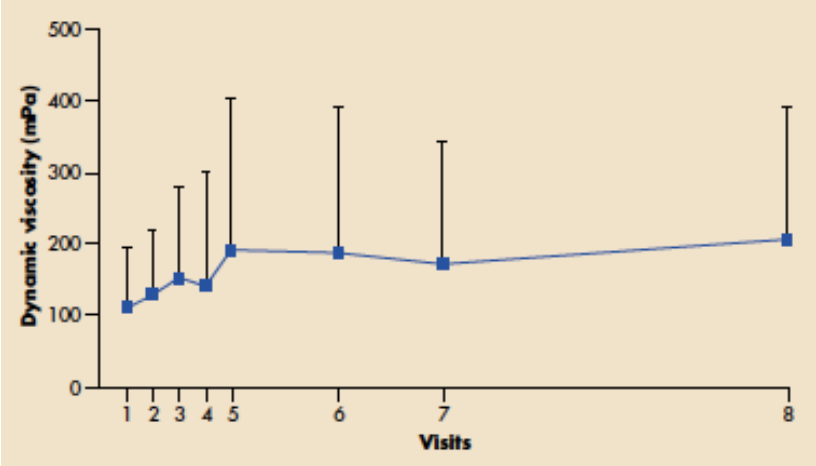
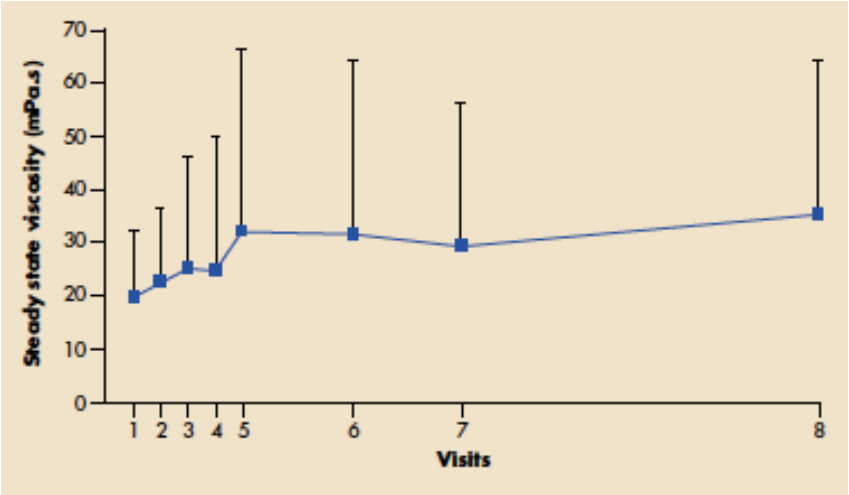


Figure 45. Dynamic viscosity of the synovial fluid.

	 **Figure 46.** Steady state viscosity of the synovial fluid. Patients judged treatment as 'good' or 'excellent' in 53% of the cases at Visit 6. At the end of the study, 43% of the patients judged the treatment as 'good' or 'excellent'. The efficacy judgements expressed by the investigator showed a similar trend.
Study Results **Safety**	One adverse event (impaired joint function, of moderate intensity, due to effusion occurring one day after the second injection and lasting more than 1 day but resolving spontaneously without sequelae and without the need for other interventions) was reported in one patient.
Limit/s of the study	Not reported.
Discussion	No information available.
Conclusions of the authors	This open, pilot, phase III study demonstrated that a treatment cycle with Ostenil®: • was safe and significantly improved symptoms in patients with painful advanced knee OA who were awaiting TKR; • delayed TKR by 4.5 to 6 months in 3 patients and up to 12 months in the other 18 patients improved the quality of life of these patients improved the viscous and elastic moduli of the synovial fluid, compared with baseline values, which seemed to correspond to the improvement in symptoms. The relationship between the improvement in clinical signs and the change in viscoelastic properties of the synovial fluid should be further investigated in a larger study.

Citation 8

Title	Blanco FJ, Fernández-Sueiro JL, Pinto-Tasende JA, Fernández-López JC, Ramallal M, Freire A *et al.* **Intra-articular hyaluronan treatment of patients with knee osteoarthritis waiting for replacement surgery.** *The Open Arthritis Journal* 2008; 1: 1-7.
Aim of the study	This clinical study aimed to determine whether hyaluronan (HA) delays and/or reduces the knee replacement surgery (KRS) in patients with osteoarthritis (OA).

Relevance of the study	The original rationale for the use of intra-articular HA to treat OA was to increase the viscosity of the synovial fluid. Hyaluronan is a heteropolysaccharide comprised of a variable number of repeating units of D-glucuronic acid and N- acetylglucosamine. Synoviocytes, fibroblasts and chondrocytes all synthesize HA, which is present in synovial fluid and the extracellular matrix of cartilage. Because HA is viscoelastic, it behaves as a viscous liquid at low shear rates and as an elastic solid at high shear rates. Intra-articular injections of HA are used to treat OA to reduce joint pain. For this reason, HA is indicated to treat knee OA grades II-III.
Equivalent Device	**Test device:** Adant (biofermentative low molecular weight Hyaluronic acid viscosupplementation) **Control device:** placebo - saline solution without HA. *Adant® is a medical device equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it is a viscosupplementation of biofermentative and low molecular weight Hyaluronic acid. Moreover, it reaches also clinical and technical equivalence, as described in the Clinical Evaluation Plan.*
Study Design	This was a prospective, double-blind, randomized, placebo-controlled, single-center, outpatient pilot clinical trial.
Study period	Not reported.
Sample size	52 patients (10M/42F) were enrolled in the study (HA group: 26; placebo group: 26). Four patients withdrawn their consent and were not administered treatment therefore, the safety population (SAF) consisted of 88.5% (n=23) of the placebo subjects and 96.2% (n=25) of the HA subjects. Furthermore, 76.9% from the placebo group (n = 20) and 84.6% (n = 22) from the HA group were included in the intention-to-treat population (ITT). The per-protocol population (patients whose completed 58 weeks of study) included 34.6% (n = 9) from the placebo subjects and 23.1% (n = 6) from the HA subjects.

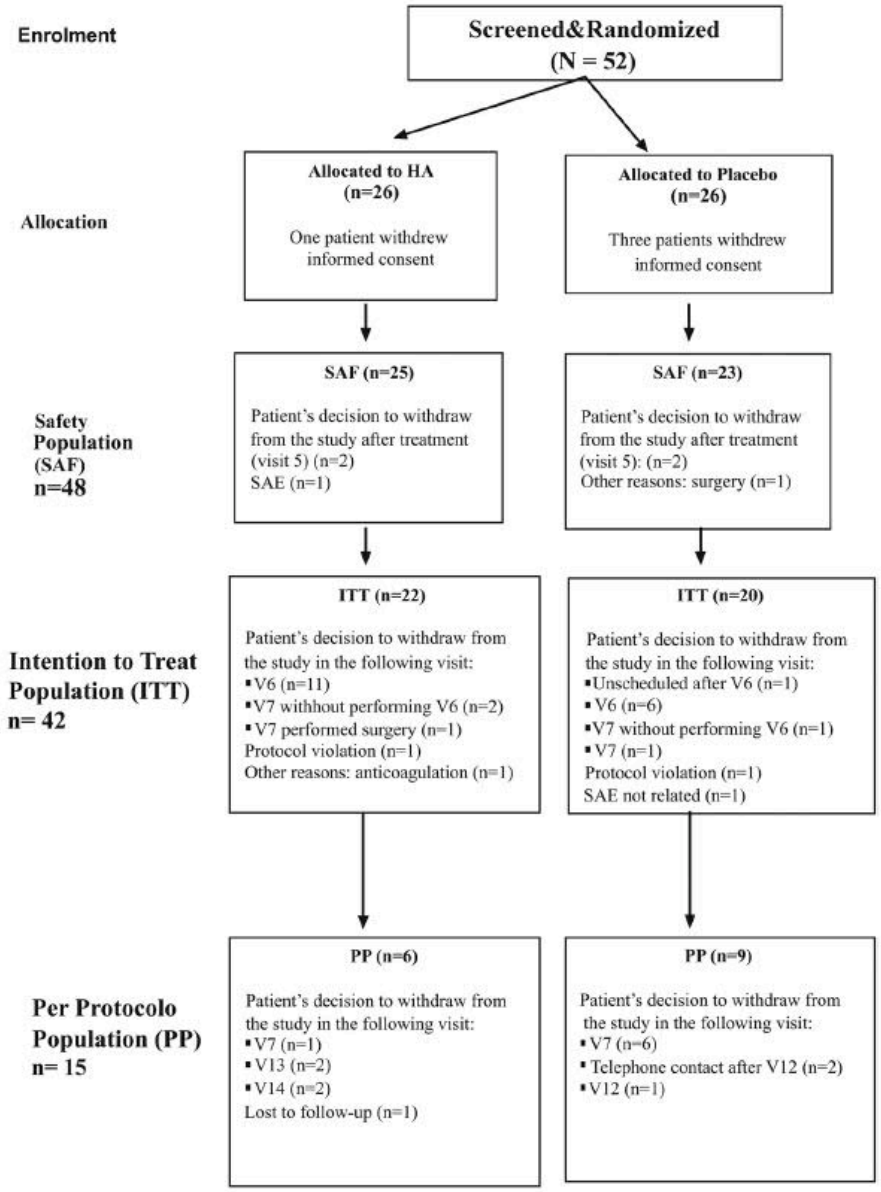


Figure 47. Subject disposition.

Inclusion Criteria	Subjects over 40 years of age without joint inflammation were selected for this study if symptomatic OA was evidenced by pain according to the American College of Rheumatology (ACR) criteria and if they were grade IV using the Kellgren-Lawrence (K-L) scoring.
Exclusion Criteria	Patients were excluded from this study if they had received intra-articular injections of corticosteroids in the target joints within three months of study entry or HA injections within one year of study entry. Patients who had received glucosamine sulphate during the three months prior to beginning the study or had used an investigational drug within 30 days of study entry or during the study schedule were excluded. Individuals with previous knee surgery that would interfere with the evaluation of the results of this study or who had a history of rheumatoid arthritis, ankylosing spondylitis, microcrystalline arthropathies, chondrocalcinosis, fibromyalgia or any other pathology of the knee that could interfere with the study and assessments were also excluded. Other exclusion criteria were patients with severely impaired central nervous systems, impaired coagulation, known sensitivity to

	HA, paracetamol or diclofenac, or were immuno-compromised, receiving systemic inmuno-suppressive therapy, or considered by the investigator to be unable to complete the treatment or follow-up.
Intervention	Name and type of intervention Intra-articular (knee joint) administration of a HA-based viscosupplementation. Aim of the intervention To determine whether hyaluronan (HA) delays and/or reduces the knee replacement surgery (KRS) in patients with osteoarthritis (OA). Duration Five-week treatment. 1-year follow-up. Description of the intervention Prior to each injection, synovial fluid, if present, was first aspirated and then 2.5 ml of HA (25 mg) in saline in the HA group or 2.5 ml of saline vehicle (without HA) in the placebo group was injected into the study knee at weekly intervals for five weeks (Cycle 1: V1-V5; Cycle 2: V8-V12).
Outcomes	Primary outcomes The primary objective was to analyze the efficacy of the treatment based on whether intra-articular HA treatment delayed the time of knee replacement surgery or reduced the number of knee replacement surgeries in OA patients on the waiting list for knee surgery at Hospital Universitario A Coruña. This delay would be the result of an improvement in the signs and symptoms of OA. This improvement was assessed by the WOMAC OA Index questionnaire scores, a multidimensional measure of pain, stiffness, and physical functional disability comprised of 24 questions and an overall score. Items are scored by a visual analogue scale (VAS) from 0 (no pain, symptoms, or physical disability) to 100 mm (extreme levels). Each subscale was transformed to a range from zero to 100 points, a score of 100 indicating best condition and 100 the worst condition. Efficacy analyses were performed on the intention-to treat (ITT) population, defined as all randomized subjects who took at least one dose of study medication and for whom a post-randomization efficacy measurement was available. Lack of efficacy was indicated by discontinuation due to insufficient pain relief. Secondary outcomes Safety was also monitored throughout the study. Assessments were performed on randomized subjects who were administered at least one dose of study medication and had at least one available post-baseline safety measurement. The number and percentage of subjects reporting adverse events and their severity were tabulated for both treatment groups, and subjects reporting serious adverse events or withdrawing due to an adverse event were recorded. An assessment of the relationship of adverse events to study medication was also conducted. Naranjo's algorithm was used to determine the degree of causality. Measures and timepoints Subjects were evaluated by telephone follow-up one week after each cycle and by visits 12 weeks (V6 and V13) and 24 weeks (V7 and V14) after each cycle.
Study Results **Perform**	For the ITT population, subjects in the HA group had a significantly improved, (lower) mean total WOMAC index score at 24 weeks compared to the placebo, with statistical significance (HA group = -23.9 vs placebo group = -5.6 p = 0.044) (Figure 48). In addition, subjects treated with HA also had an

ance

improved mean final WOMAC scale for physical function compared with the placebo group subjects (HA group = -24.7 vs placebo group = - 4.4 p= 0.019 (Figure 48).

Furthermore, although no statistical differences were found between the two treatment groups, it can be observed that the HA group subjects improved in the pain and stiffness subscale analyzed at 24 weeks post-first cycle of treatment by WOMAC (Figure 48).

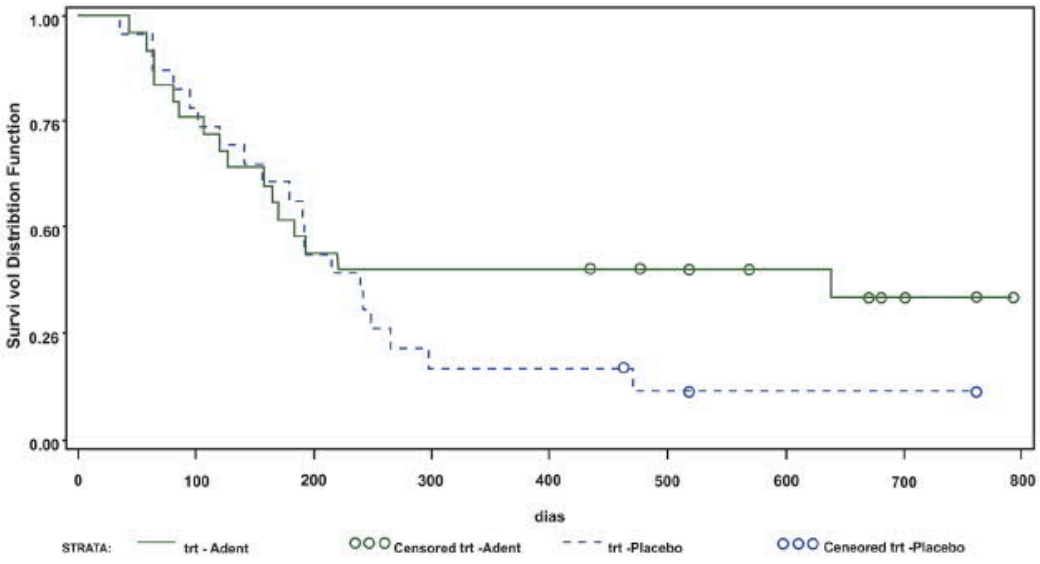
	Placebo n= 20 Mean (SD)	Hyaluronan n=22 Mean (SD)	p value
Total WOMAC index	-5.6 (21.2)	-23.9 (17.9)	0.044
Pain WOMAC subscale	-11.2 (21.0)	-21.7 (25.9)	0.307
Stiffness WOMAC subscale	-2.2 (40.3)	-22.4 (22.5)	0.081
Functional capacity WOMAC subscale	-4.4 (18.8)	-24.7 (18)	0.019

p value was calculated using Mann-Whitney Wilcoxon test.

Figure 48. Change at 6 Months in Total WOMAC Index and in WOMAC Subscale.

In the subjects treated with HA, the mean percentage of variation in WOMAC subscale of pain was -17.3%, with a 57.1% of patients experiencing reduction. In addition, in those patients treated with HA who rejected surgery, 75% showed decreases in the WOMAC pain subscale at 24 weeks. In these patients the mean percentage of decrease for the WOMAC pain subscale was -26.3%. Interestingly, the percentages of patients per group that use permitted rescue medication were only 47.8% and 56.0% for placebo and HA groups respectively (p = 0.571).

Prospective follow-up after 1 year was performed in all patients. Survival analysis showed that, although there was not statistical significance, survival functions differed. Survival time until knee replacement surgery in the HA group subjects (368.8 days) was higher than that in the placebo group subjects (253.9 days) (Figure 49). However, the Log-Rank test did not show statistical differences between the survival functions (p = 0.249). Furthermore, the proportion of subjects discontinuing treatment at 24 weeks due to lack of efficacy was higher in the placebo group (20/23, 87%) compared with the HA group (16/25, 64%) (p = 0.06) (Figure 49). Knee surgery was avoided in 9 and 3 patients from HA and placebo groups respectively (Figure 50).



Log-Rank test p=0.249

	Figure 49. Kaplan Maier curve showing evolution of patients treated with Hyaluronan and with placebo. **Figure 50.** Survival time to surgery.
Study Results **Safety**	A total of 48 patients (placebo group = 23 and HA group = 25) were evaluated for safety (SAF population). Only AE that occurred after the first injection of HA or placebo have been taken into account. Thus, 34.8% and 16.0% of patients in the placebo and HA groups respectively reported at least one AE (abdominal pain 8.7%, insomnia 8.7%). There were no significant differences between groups in the number of AEs. Related adverse events (AE) did not occur in either the placebo group or the HA group.
Limit/s of the study	Taking into account the limited number of patients included, this pilot study cannot provide robust evidence that HA injections are better than placebo injections for treating patients with K-G grade IV knee OA.
Discussion	This pilot study does have important data for the future treatment of patients prior to knee replacement surgery. The HA group subjects appear to have a good efficacy profile at six months. In some subjects receiving intra-articular injections surgery was avoided (3 patients in placebo group and 9 patients in HA group). Prospective follow-up of these patients showed that after 1 year, 2 patients from placebo group and none patients from HA group were submitted to surgery. In addition, the subjects receiving HA treatment improved their general condition while they were on the waiting list. These patients showed a numerical, although not statistically significant, improvement in knee pain on the scale used. Although the differences were not significant, about 57% of subjects from the HA group showed a reduction in knee pain. It has to keep in mind that analgesics and NSAIDs were permitted throughout the clinical trial and patients on a waiting list for knee surgery can overestimate the pain [24]. The clinical significance of these findings is supported by secondary outcomes that measured physical function, total WOMAC index score, WOMAC physical functional and WOMAC subscale for stiffness. Because patients on a waiting list for knee surgery have an important disability, minimal changes improving physical function may have a large effect on their activities of daily living. In addition to efficacy this clinical trial confirms that the intra-articular injection of HA is safe. Throughout the course of this study, 150 injections of HA were given and the safety evaluations of the subjects were excellent.
Conclusions of the authors	Not reported.

	Placebo n= 23	Hyaluronan n=25
Number of patients with surgery	20	16
Number of patients without surgery	3	9
Days to surgery (Mean-IC 95%)	253.8 (165-314)	368.7 (185-)

MannWithney Wilconxon test: p=0.186.

Citation 9

Title	Monfort J, Rotés-Sala D, Segalésc N, Montanes FJ, Orellana C. **Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: Results of a6-month single-masked randomized study.**

	Joint Bone Spine 82 (2015) 116–121.
Aim of the study	This clinical study was designed to determine the efficacy and safety of intra-articular injections of low molecular weight HA into the osteoarthritic thumb CMC joint in comparison with corticoid injections.
Relevance of the study	Hyaluronic acid (HA) is a macromolecular component of thenormal synovial fluid. In OA, there is a lower concentration ofthis compound. The effect of HA on joint lubrication and preven-tion of articular cartilage degradation has been extensively studied. Viscosupplementation with HA injections has been shownto relieve pain and improve function in the management of knee OA. The usefulness of intra-articular HA for treating symp-tomatic OA pain in other joints has also been reported, including the hip, ankle, temporomandibular joint, hand, spine, and foot. The experience with the use of intra-articular HA injectionsfor trapeziometacarpal OA is limited but has produced promising results. However, the superiority of HA injections as analternative to corticoid injections for the treatment of rhizarthrosisis unclear and the available evidence derived from small, random-ized, controlled studies is inconclusive.
Equivalent Device	**Test device:** Suplasyn (viscosupplementation containing biofermentative low molecular weight Hyaluronic acid) injection **Control:** 0.5 cm^3 of betamethasone disodium phosphate 1.5 mg andbetamethasone acetate 1.5 mg. *Suplasyn is a medical device equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it is a viscosupplementation of biofermentative and low molecular weight Hyaluronic acid. Moreover, it reaches also clinical and technical equivalence, as described in the Clinical Evaluation Plan.*
Study Design	This was a single-center, randomized, prospective, active-controlled and single-masked clinical study.
Study period	Not reported.
Sample size	One hundred patients were randomized to treatment withHA or betamethasone (1:1), although only 88 of them (HA = 48;betamethasone = 40) were finally evaluable: 5 of them did not carryout the washout period due to they were taking AINEs, 3 of themwere asymptomatic, and the remaining 4 did not fulfil radiological criteria. The final sample was composed of 11 men and 77 women, mean (SD) age 62.8 (8.7) years (range 45–92). No differences wereobserved between the study groups in sex and age distribution.
Inclusion Criteria	All male and female patients aged 18 years or older who receiveda diagnosis of thumb CMC joint OA between January 2005 andDecember 2009, as defined by criteria of the American College ofRheumatology [26], were eligible, provided that they had clinicalsymptoms in the affected thumb for at least the 90 days prior tothe start of the study, required treatment with analgesics or NSAIDson a routine basis, had an available confirmatory X-ray diagnosis (Kellgren–Lawrence grade I–III) [27] within the previous 6 months,gave written informed consent, and were able to understand andfollow the study procedures. Negative pregnancy test and appro-priate use of a safe contraceptive method were required for womenof childbearing age.
Exclusion Criteria	Exclusion criteria included the following: pregnant or lactatingwomen; liver dysfunction (serum aminotransferases > 3 timesthe upper limit of normal); hemodialysis or renal dysfunction (serum creatinine concentration > 1.5 mg/dL); physical therapyperformed by a physiotherapist at home or in a specialized center; history of any surgical procedure in the trapeziometacarpaljoint; diagnosis of OA of the trapezioscaphoid joint ormicrocrystalline arthritis; participation in a clinical trial inthe previous three months; and presence of any medical conditionjudged by the investigator to preclude the patient's inclusion inthe study. Patients were also excluded for a known allergy to cor-ticoids, paracetamol, or low-molecular-weight HA; concomitant treatment with antiepileptic drugs, oral

	anticoagulants, acetyl-salicylic acid > 325 mg/day, lithium, potassium-sparing diuretics, digoxin, minocycline, metalloprotease inhibitors, methotrex-ate, or regular use of analgesic and/or NSAIDs; treatment withchondroitin sulphate, glucosamine sulphate, diacerein, oral orparenteral corticosteroids, or corticosteroid injection in any otherjoint during the previous 3 months.
Intervention	Name and type of intervention Intra-articular administration of HA-based and corticoid-based injections for the treatment of thumb CMC joint osteoarthritis. Aim of the intervention To determine the efficacy and safety of intra-articular injections of low molecular weight HA into the osteoarthritic thumb CMC joint in comparison with corticoid injections. Duration 3-week treatment. Follow-up lasted 180 days from initiation of the treatment. Description of the intervention At baseline (visit 2, day 0), the following procedures were performed: physical examination, assessment of concomitantmedication, randomization, provision of rescue medication, intra-articular injection of the study medication under echographiccontrol, and VAS and FIHOA scores. Patients underwent one cycle of three injections (one per week, visits 2, 3 and 4) of 0.5 cm^3 of HA (5 mg) (Suplasyn®, Mylan Institutional, Galway, Ireland (between 500-1000 kDa, with a high degreeof purity, produced by fermentation of Streptoccus spp. Bacteria)) or 0.5 cm^3 of betamethasone disodium phosphate 1.5 mg and betamethasone acetate 1.5 mg. To receive the treatment, patientssat with the affected hand in a semi-prone position on a table. The intercarpometacarpal space was identified by palpation, the needle tip inserted lateral to the abductor pollicis longus tendon and the injection carried out under echographic control.
Outcomes	Primary outcomes The primary efficacy endpoint was the clinical improvementdetermined by the FIHOA score at the end of treatment as comparedwith baseline. Tolerability and safety parameters were the incidence and severityof adverse events reported throughout the study and changes inheart rate, blood pressure, and laboratory tests during the study. Secondary outcomes Secondary efficacy parameters included pain relief, changes in the physical component summary (PCS-36) and men-tal component summary (MCS-36) of the SF-36 questionnaire, andassessment of the overall condition by patients and investigators. Measures and timepoints Patients were instructed tocomplete the Short Form-36 (SF-36) quality of life questionnaire,using a Spanish validated version. SF-36 questionnaire hasmental and physical component summary (MCS-36, and PCS-36, respectively), and both scores range from 0 to 100, where 0 indi-cates the worst possible perceived mental and physical health, and100 the best. Patient's general condition was assessed by patients and investigators from 'very bad' to 'very good' on a 5-point Likert scale. The same procedures were repeated at visits 3 (day 7) and 4 (day 14), except for the administration of the SF-36 questionnaire. Moreover, assessments were performed at 30 days (visit 5), 90 days (visit6), and 180 days (visit 7, final visit) after initiation of the treatment,by an investigator who was blind to the treatment

	administered(patients were instructed not to disclose the treatment received). Atfollow-up visits, the same procedures as described for the baselinevisit were performed, except the SF-36 quality of life assessment, which was repeated only at visits 6 and 7. Adverse events wererecorded at each follow-up visit and a final laboratory test wasperformed as a safety index.
Study Results **Performance**	At baseline, scores on the study variables were similar in the HA and betamethasone groups (median FIHOA score 11.0 [IQR 7 − 14.7] vs 11.5 [8–14], P 0.814; mean VAS score 6.0 [1.8] vs 6.4 [1.3], P = 0.171; PCS-36 38.9 [8.1] vs 37.7 [10.3], P = 0.553; and MCS-36 45.4 [12.3] vs 48.9 [10.8], P = 0.178, respectively). The FIHOA and VAS scores decreased significantly for both groups after treatment. Values obtained for these two indexes at follow-up visits were all below baseline values; neither PCS-36 nor MCS-36 showed any statistically significant trend. Changes in these variables during the study period were not significantly different between the study groups; however, the median difference of FIHOA scores was greater in the HA arm than in the betamethasone arm.

	HA	Betamethasone
FIHOA[⊤]		
D7	0 (−3 and −1)	−1 (−2 and −1)
D14	−2 (−5 and −0)	−1 (−4 and −0)
D30	−3 (−6.7 and −0)	−3 (−7.5 and −0)
D90***	−4 (−8 and −1)	−1 (−3 and −1)
D180	−3 (−8.7 and −1)	−1 (−3 and −3)
VAS†		
D7	−0.71 (1.66)	−0.95 (1.60)
D14	−1.42 (2.23)	−2.01 (1.84)
D30	−1.97 (2.62)	−2.53 (2.26)
D90	−1.61 (2.53)	−1.55 (2.14)
D180	−1.97 (2.73)	−1.42 (2.35)
PCS-36†		
D90	0.51 (7.02)	1.70 (9.32)
D180	−1.66 (9.60)	1.31 (9.42)
MCS-36†		
D90	−0.46 (6.77)	1.73 (10.75)
D180	2.79 (11.78)	2.17 (9.64)

HA: hyaluronic acid; FIHOA: Functional Index for Hand Osteoarthritis score; D: day; VAS: Visual Analogue Scale score; PCS-36: physical component summary of the SF-36 questionnaire; MCS-36: mental component summary of the SF-36 questionnaire; [⊤] : median and interquartile range (25th and 75th percentiles); †: mean and standard deviation (SD).
*** $P = 0.071$.

Figure 51. Changes from the baseline in the study variables throughout the study period in both treatment groups.

Changes from baseline were −4.0 and −3.0 in the HA group in the assessments carried out at 90 and180 days, respectively, whereas the median difference was −1.0 at each of these visits in the betamethasone group (P = 0.071 at day 90). As shown in Figure 52, the percentage of patients rated by the investigator as being in 'good' or 'very good' general condition was higher for the HA group than for the betamethasone group, with differences especially remarkable at 90 days (61.6% vs 30.8%) and 180 days (53.4% vs 28.6%). Differences between the study groups in the categories of 'good' and 'very good' were also more favorable for the HA arm at follow-up when the patients themselves rated their general condition (Figure 52).

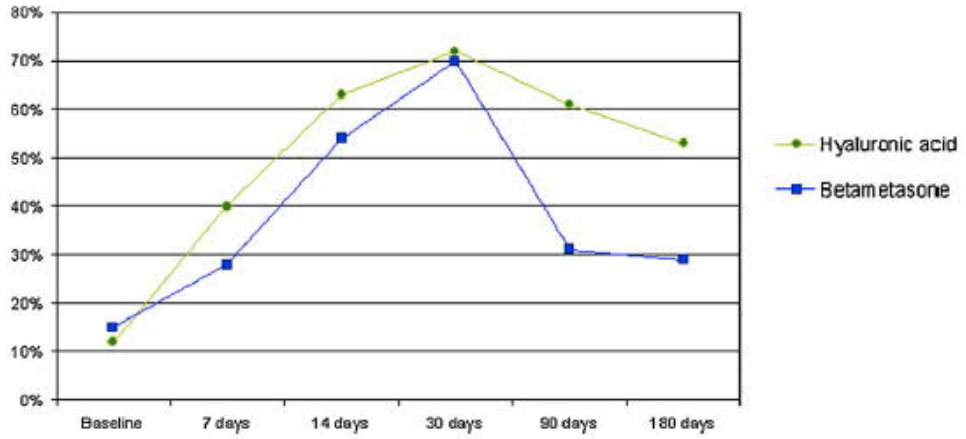


Figure 52. Percentage of patients whose general condition was rated as "good" or "very good" by the investigator throughout the study period.

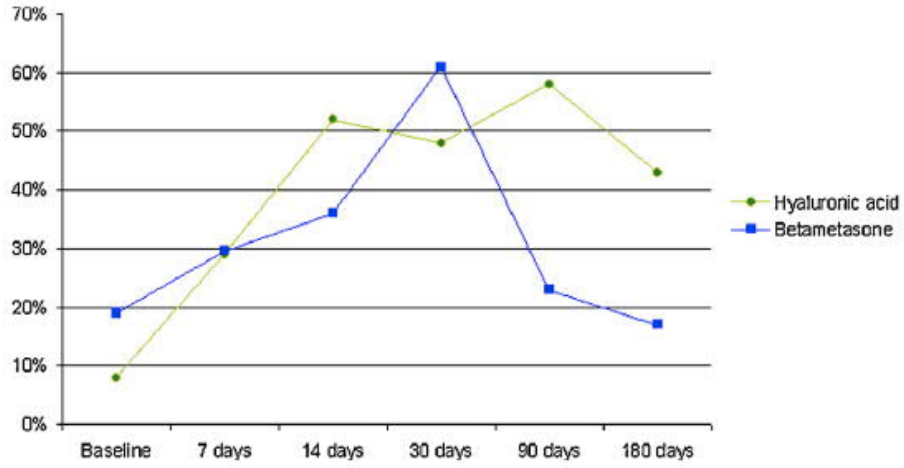


Figure 53. Percentage of patients who rated their own general condition as "good" or"very good" throughout the study period.

No significant differences in use of rescue medication were observed between study groups. The subset of patients with FIHOA score ≥ 5 and VAS score ≥ 3 at entry included 77 patients (9 men, 68 women; mean age of 62.7 years), 39 of whom were randomized to treatment with HA and 38 to treatment with betamethasone. At baseline, there were no significant differences in demographics or FIHOA, VAS, PCS-36, and MCS-36 scores between both treatment groups. However, patients treated with HA showed significantly higher differences between the median FIHOA scores at baseline and follow-up than the patients treated with betamethasone, both at 90 days (−5.0 [IQR −9 and −0.75] vs −1.0 [IQR−3.0 and 1.25]; P = 0.005) and 180 days (−5.0 [IQR −9 and 0] vs −2.0 [IQR −3.0 and 2.0]; P = 0.020) (Figure 54). Differences in the remaining study variables were not observed.

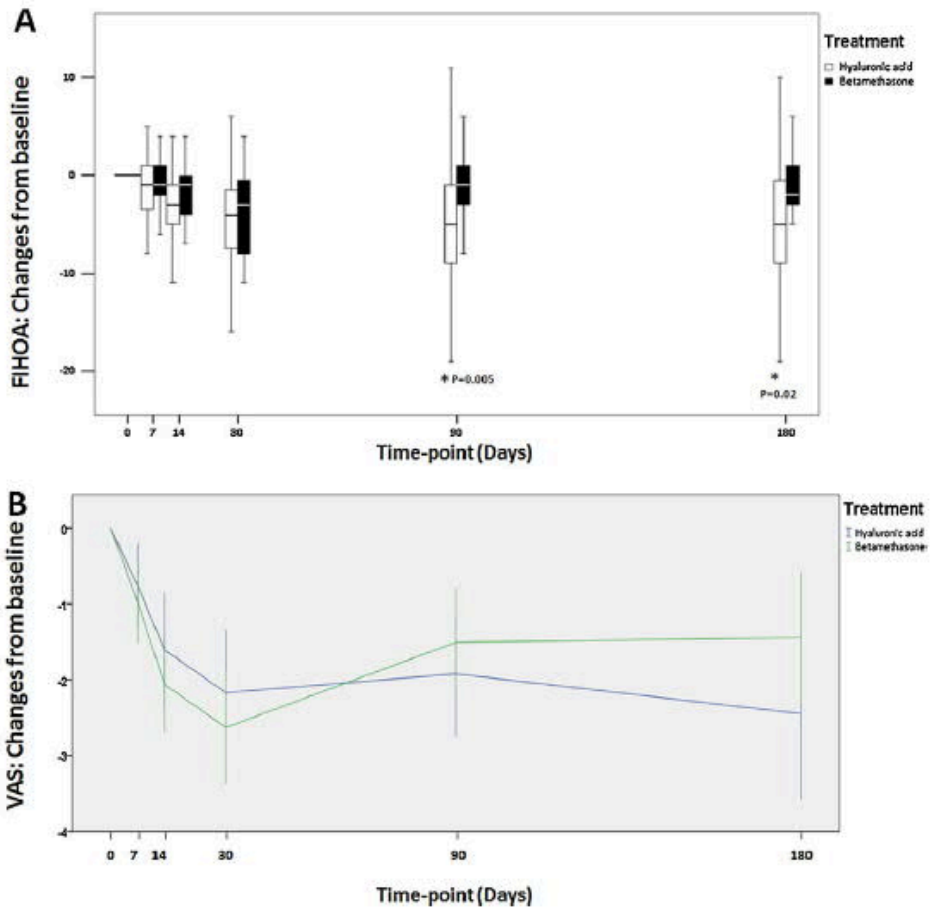


Figure 54. Changes from baseline in a subset of patients with FIHOA score ≥ 5 and VASscore ≥ 3 at entry.

A. Changes from baseline in Functional Index for Hand Osteoarthri-tis score. Median, interquartile range (25th and 75th percentiles) and maximum andminimum values are shown.

B. Changes from baseline in Visual Analogue Scale score. Mean and 95 percent confidence interval are shown.

The subgroup of patients with FIHOA score ≥ 5 and VAS score ≥ 5 at baseline included 65 patients (8 men, 57 women; mean age of 62.9 [9.2] years). Thirty-two patients were treated with HA and 33 with corticoid injection. Baseline characteristics of patients in both treatment arms were similar. Treatment with HA was superior to betamethasone, as shown by significantly greater differencesin FIHOA scores as compared with baseline, which were already apparent after the first intra-articular injection (Figure 55 and 56). Moreover, significant differences in mean changes of VAS score were also observed at the final assessment (P = 0.02). Changes in PMS-36 and MCS-36 during the study period were similar in both groups. The mean difference of Kellgren-Lawrence grade was not significant between study groups in either of three analyses.

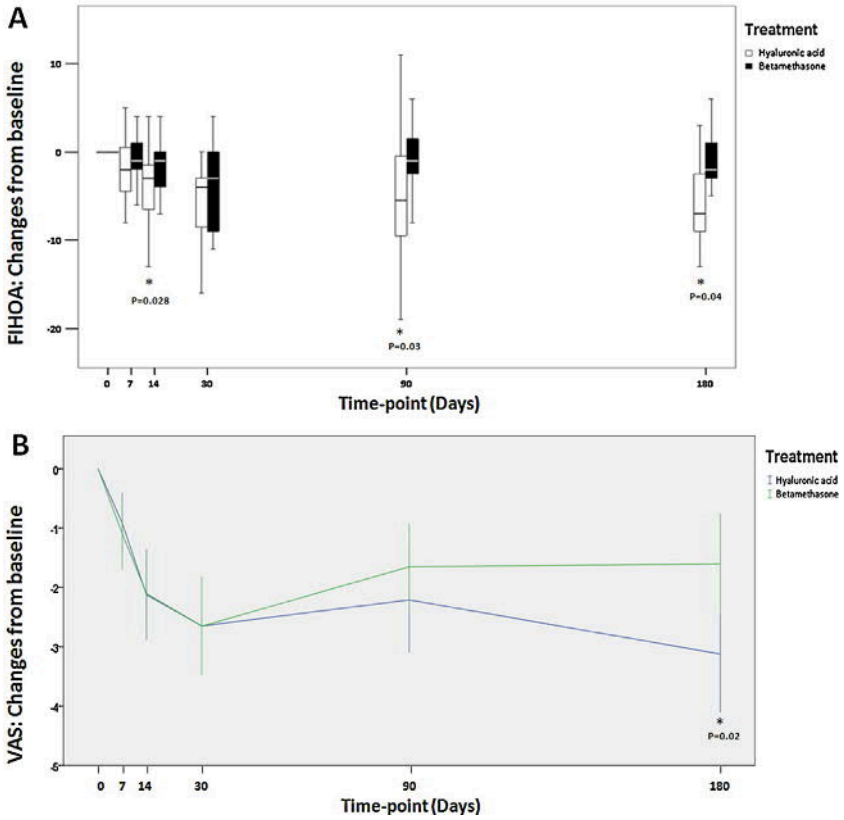


Figure 55. Changes from baseline in a subset of patients with FIHOA score ≥ 5 and VASscore ≥ 5 at entry.

A. Changes from baseline in Functional Index for Hand Osteoarthri-tis score. Median, interquartile range (25th and 75th percentiles) and maximum andminimum values are shown.

B. Changes from baseline in Visual Analogue Scale score.Mean and 95 percent confidence interval are shown.

	HA	Betamethasone
FIHOA[T]		
D7	−2 (−4.75 and 0.75)	−1 (−2 – 1)
D14**	−3 (−6.75 and −1.25)	−1 (−4 – 0)
D30	−4 (−8.75 and −3)	−3 (−9 – 0)
D90*	−5.5 (−9.75 and −0.25)	−1 (−3 – 2)
D180*	−7 (−9 and −2)	−2 (−3 – 1)
VAS[†]		
D7	−0.92 (1.44)	−1.10 (1.70)
D14	−2.12 (2.13)	−2.10 (1.81)
D30	−2.65 (2.29)	−2.65 (2.33)
D90	−2.21 (2.29)	−1.65 (1.98)
D180**	−3.12 (2.33)	−1.60 (2.29)

HA: hyaluronic acid; FIHOA: Functional Index for Hand Osteoarthritis score; D: day; VAS: Visual Analogue Scale score; [T]: median and interquartile range (25th and 75th percentiles); [†]: mean and standard deviation (SD).
*$P < 0.005$.
**$P < 0.05$.

Figure 56. Changes in the study variables throughout the study period as compared with baseline in patients with FIHOA score ≥ 5 and VAS score ≥ 5 at entry.

Study	Treatment was well-tolerated and no severe adverse events were reported during the study, only 10

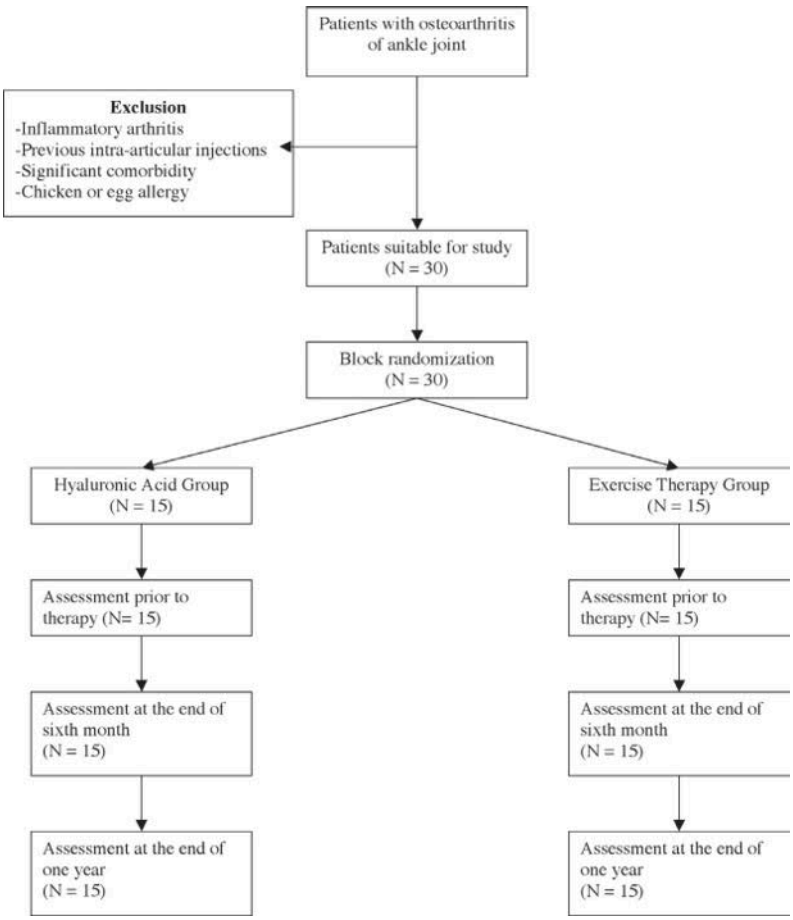
Results Safety	patients (5 of Bethametasone group and 5 of the HA group) shown minor or moderate local pain after intra-articular injection (5 of them including swelling (2 of the Bethametasone group and 3 of the HA)), which have disappeared at the following visit. No significant changes were observed in vital signs and laboratory test results.
Limit/s of the study	The most obvious limit of this study is the absence of a placebogroup. Some studies have confirmed a strong placebo effect linkedto the complexity of the treatment. Intra-articular injectionappears to be a technique that, due to its complexity, could increasepatient expectations of clinical improvement; therefore, it wouldhave been interesting to control for this effect. Moreover, it was not possible to assess patients for longer than 6 months, and others have suggested that a long-term follow-up would be of great interest in order to establish the duration of the treatment effect. Inthe case of knee OA, for instance, studies have demonstrated that the effect of HA infiltration may extend beyond 6 months.
Discussion	In this clinical study, although the analysis of the overall seriesof patients encountered no statistically significant differencesbetween the study groups, patients in the HA group experienced a functional improvement of greater magnitude than the patientstreated with betamethasone. Moreover, these findings were more evident, and reached statistical significance, when patients selectedfor analysis had a FIHOA score of at least 5 and a VAS score of 50 or more. According to these findings, HA injection seems to be anequivalent and possibly better alternative to corticoid injection inthe treatment of thumb CMC joint OA, particularly in patients withfunctional repercussions and moderate-severe pain level. Unlike steroids, shown to be effective for reducing acute pain, improvement due to injections of HA was more gradual but moreprolonged over time. These results are consistent with the widelyaccepted idea that corticosteroids could be more effective in reduc-ing inflammation and ameliorating pain in its earliest form, whilethe regeneration of the viscoelasticity of the sinovial fluid achieved by HA could improve the homeostasis of the joint, contributing tomore long-lasting improvement of both function and pain. The results of this study suggest that HA injections may be a bet-ter patient management option than betamethasone. In additionto the extended improvement observed in patient well-being, this therapy could decrease both the consumption of symptomatic analgesics or anti-inflammatory drugs and their potential secondary effects, as has been seen in knee OA. Moreover, it could alsoreduce the care burden on the health system by helping to decreaseoffice visits, pharmacology costs, and replacement surgeries.
Conclusions of the authors	Not reported.

7.2.2 *Indirect supportive data*

The articles described below have been selected as indirect supportive data.

Citation 10

Title	Karatosun V, Unver B, Ozden A, Ozay Z, Gunal I. **Intra-articular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up.** *Clin Exp Rheumatol* 2008; 26: 288-94.
Aim of the study	This clinical study aimed to determine whether hyaluronic acid (HA) or exercise therapy can improve functional parameters in patients with osteoarthritis (OA) of the ankle.

Relevance of the study	The ankle joint is subjected to more weight-bearing force per square centimeter and is more commonly injured than any other joint in the body, but the prevalence of symptomatic arthritis at the ankle is approximately nine times lower than that at the knee and hip. Hyaluronic acid (HA) injections have put in to OA knee with varying degrees of success. A review of the literature revealed only two studies on the use of HA in OA ankle, but neither has compared HA injections with other treatment options.
Equivalent Device	**Test device:** Adant - Low Molecular Weight Hyaluronic acid viscosupplementation **Compared treatment:** ankle joint exercise therapy *Adant is one of the medical devices equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it reaches clinical, technical and biological equivalence. It is composed of Low Molecular Weight Hyaluronic acid of biofermentative origin.*
Study Design	This was a prospective randomized clinical trial.
Study period	Not reported.
Sample size	The series consisted of 43 ankles. Seventeen patients (26 ankles) had primary ankle OA and 13 patients (17 ankles) had secondary ankle OA of the defined by the clinical and radiographic findings, and all of them were seeking treatment. Patients' progress flowchart is shown in Figure 57.  **Figure 57. Progress throughout the trial.**

Inclusion Criteria	Primary ankle OA or secondary ankle OA defined by the clinical and radiographic findings, and all of them were seeking treatment. All patients with secondary OA of the ankle had definite history of severe trauma. Additionally, all patients with primary OA had uni or bi-lateral involvement of the knees.
Exclusion Criteria	Exclusion criteria included, inflammatory arthritis, previous intra-articular injections or any other invasive procedures in the ankle, significant comorbidity (renal, hepatic or heart disease), and chicken or egg allergy.
Intervention	Name and type of intervention Intra-articular (ankle joint) administration of a low molecular weight HA-based Hyaluronic acid viscosupplementation. Aim of the intervention To determine whether hyaluronic acid (HA) or exercise therapy can improve functional parameters in patients with osteoarthritis (OA) of the ankle. Duration 3 weeks HA treatment; 6 weeks exercise therapy. Follow-up lasted 12 months. Description of the intervention The HA group received three injections of hyaluronic acid (Adant®, Na Hyaluronat, Erkim, Turkey) at 1-week intervals by the same physician. The dose of the HA was 2.5 mg in each injection. The injection was performed with the patient in half lying position with the knee fl exed and the foot flat on the plinth. Then the anterior ankle joint line was palpated and the needle was inserted slightly upward in order to run upper surface of the talus, which is slightly convex. When it was felt that the capsule was passed, then the joint fluid was aspirated if present, and then HA was injected. Patients were advised not to take part in strenuous activity for a few days. The exercise program included a series of progressive, simple, isometric, isotonic range of motion, resistance, closed kinetic chain and proprioceptive exercises for six weeks. The exercise program was taught to the participants by two physical therapists and performed in home-based regimen. This means, patients came to the hospital at 1, 2, 3 and 6 weeks for learning the exercises.
Outcomes	Primary outcomes Prior to the treatment, the ankle function of all patients was evaluated using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hind foot Score criteria that are based on a total of 100 points. A score of 100 points is possible in a patient with no pain, full range of sagittal and hind foot motion, no ankle or hind foot instability, good alignment, ability to walk more than six blocks, ability to ambulate on any walking surface, no discernible limp, no limitation of daily or recreational activities and no assistance devices needed for ambulation. Gait abnormality was categorized as none or slight, obvious or marked. Pain during activity and rest were evaluated with Visual Analog Scale (VAS). Secondary outcomes Not reported. Measures and timepoints All patients in both groups were evaluated at 1, 2, 3, weeks and 2, 3, 6, 12 months.
Study	Although demographic characteristics were similar, group 2 had significantly more total AOFAS Ankle-

Results

Performance

Hind foot Score, and sagittal motion (Figure 58). Additionally group 1 had more difficulty in walking on uneven surface (Figure 58).

Characteristics	Group 1 (HA, n=15)	Group 2 (PE, n=15)	*p* value
Age (years)	52.1 (11.3)	58.1 (12.1)	0.42
Height (cm)	165.2 (7.1)	165.0 (7.7)	0.53
Weight (kg)	78.9 (17.6)	75.5 (11.3)	0.33
Gender	9 ♀ / 6 ♂	12 ♀ / 3 ♂	0.01
Pain during activity (VAS)	5.4 (2.1)	4.7 (2.8)	0.16
Pain at rest (VAS)	2.4 (3.0)	2.1 (2.4)	0.90
Activity limitation[a]	6.6 (2.4)	7.2 (2.1)	0.41
Walking distance[a]	2.7 (1.3)	2.6 (1.6)	0.76
Walking surface[a]	2.1 (1.7)	3.2 (1.3)	0.02*
Gait abnormality[a]	5.6 (2.0)	5.8 (2.0)	0.80
Sagittal motion[a]	7.3 (1.4)	8.0 (0.0)	0.04*
Total AOFAS Ankle-Hindfoot Score	61.6 (16.8)	72.1 (16.6)	0.04*

SD: Standard Deviation; HA: Hyaluronic Acid; PE: Progressive Ankle Exercises; VAS: Visual Analog Scale; AOFAS: American Orthopaedic Foot and Ankle Society.
[a]Graded by the AOFAS Ankle-Hindfoot Score.

Figure 58. Baseline characteristics of the 30 patients with osteoarthritis studied. Mean (SD).

At the end of the study, all patients in both groups improved significantly as compared with the baseline values (Figure 59). This improvement was detected in all parameters, except for sagittal motion. On the other hand, there was no significant difference between the groups at the end of the study.

	Group	Baseline	12 months	*p* value
Pain during activity (VAS)	HA	5.4 (2.1)	1.4 (1.9)	0.01
	PE	4.7 (2.8)	2.4 (3.1)	0.04
Pain at rest (VAS)	HA	2.4 (3.0)	0.4 (1.5)	0.04
	PE	2.1 (2.4)	0.8 (1.6)	0.02
Activity limitation[a]	HA	6.6 (2.4)	8.5 (1.8)	0.01
	PE	7.2 (2.1)	8.8 (1.5)	0.02
Walking distance[a]	HA	2.7 (1.3)	4.1 (1.4)	0.08
	PE	2.6 (1.6)	4.3 (1.0)	0.01
Walking surface[a]	HA	2.1 (1.7)	4.1 (1.0)	0.03
	PE	3.2 (1.3)	3.8 (1.6)	0.04
Gait abnormality[a]	HA	5.6 (2.0)	7.7 (0.9)	0.05
	PE	5.8 (2.0)	7.2 (1.6)	0.08
Sagittal motion[a]	HA	7.3 (1.4)	7.5 (1.3)	0.31
	PE	8.0 (0.0)	8.0 (0.0)	1.00
Total AOFAS Ankle-Hind foot Score	HA	61.6 (16.8)	90.1 (9.7)	0.00
	PE	72.1 (16.6)	87.5 (17.5)	0.00

SD: Standard Deviation; HA: Hyaluronic Acid; PE: Progressive Ankle Exercises; VAS: Visual Analog Scale; AOFAS: American Orthopaedic Foot and Ankle Society.
[a]Graded by the AOFAS Ankle-Hindfoot Score.

Figure 59. Treatment outcomes. Mean (SD).

Group 2 showed statistically less pain at activity at three weeks and better gait at 12 weeks (Figure 59). When compared between primary and secondary OA cases with respect to HA treatment or in

	relation to the exercise therapy, no differences were found.
Study Results Safety	Throughout the study no complications due to HA injection, such as pain, effusion, synovitis, haemarthrosis or septic arthritis were recorded.
Limit/s of the study	Not reported.
Discussion	For symptomatic treatment of ankle OA, therapeutic options other than NSAIDs may benefit patients by decreasing the morbidity associated with the latter. Recently, it has been shown that OA of the knee can be effectively treated by the intra-articular injection of HA derivatives. The results of current study indicate that patients with moderate OA of the ankle (Kellgren Lawrence Grade III) benefi t either by three injections of HA or by 6 weeks of exercise therapy. In both groups the results after 12 months were statistically signifi cantly different from the baseline values. The advantage of exercise therapy may be its noninvasive nature to be preferred both by the patients and the physicians; however, while exercise therapy lasts 6 weeks, HA injections stop at three weeks. This point may be advantageous for the preference of HA injections.
Conclusions of the authors	As a result, authors conclude that both HA and exercise therapy are effective in alleviating the symptoms of OA and postponing definitive surgeries (total ankle replacement or arthrodesis) for 12 months, increasing the satisfaction levels of the patients. However, in authors' opinion, larger trials with longer follow-up and with cost effectiveness analyses are necessary for more definite conclusions.

Citation 11

Title	Tang AC, Tang SF, Hong WH, Chen HC. **Kinetics features changes before and after intra-articular hyaluronic acid injections in patients with knee osteoarthritis.** *Clin Neurol Neurosurg.* 2015;129(1):21-6.
Aim of the study	This clinical study aimed to examine the kinetic features in patients with knee osteoarthritis (OA) after intra-articular hyaluronic acid (IAHA) injections in different time periods.
Relevance of the study	Hyaluronic acid (HA), also known as hyaluronan, is a major component of synovial fluid (SF). It plays an important role in regulating the biochemical balance and matrix structure of the intra-articular (IA) environment. Both high and lower molecular weight (MW) hyaluronic acid are efficacious in treating patients with knee OA. The intraarticular hyaluronic acid (IAHA) treatment of knee OA has been investigated in randomized controlled clinical trials. In previous studies, primary outcome measures demonstrating the efficacy of IAHA injections are typically average self-reported scores of knee symptoms and functions. The long-term effect of IAHA injection on kinetic variables on the knee joints of the lower extremity is seldom thoroughly examined.
Equivalent Device	**Test device:** Low Molecular Weight hyaluronic acid viscosupplementation. **Control:** No control devices. *This article has been included since it deals with a Low Molecular Weight (860 kDA) hyaluronic acid-based viscosupplementation. HA origin is not specified. However, it may be support efficacy and safety of to "Hyaluronic acid sodium salt, viscosuppletive joint device".*
Study	This was a single group repeated measures study.

Design	
Study period	Not reported.
Sample size	Subjects were divided into 2 groups: the control group, and patients with knee OA. The OA group consisted of 25 patients with bilateral medial knee OA (9 male and 16 female subjects, mean age: 65.0±8.3 years; height: 156.5±7.3 cm; weight: 62.6±10.4 kg), with grade I or II based on Kellgren-Lawrence (K/L) grading system. Fifteen age-, height-, and weight matched healthy subjects were recruited as the control group (5 male and 10 female patients, mean age: 64.7±7.3 years; height: 158.3±7.1 cm; weight: 61.5±6.9 kg).
Inclusion Criteria	The inclusion criteria for the group with knee OA included bilateral knee pain for at least 6 months and showing no improvements after conservative non-steroid anti-inflammatory agents and physiotherapy treatments. Subjects in the control group had no history of lower limb arthritis, no knee pain for at least one year, and no neurological or vascular diseases involving the lower extremities.
Exclusion Criteria	Subjects with histories of other arthritis (non osteoarthritis), injuries to the lower limb joints, musculoskeletal diseases or a history of prolonged knee pain were excluded.
Intervention	Name and type of intervention Intra-articular (knee joint) administration of a low molecular weight HA-based Hyaluronic acid viscosupplementation. Aim of the intervention To examine the kinetic features in patients with knee osteoarthritis (OA) after intra-articular hyaluronic acid (IAHA) injections in different time periods. Duration 5 weeks HA treatment. Follow-up lasted 6 months. Description of the intervention In the knee OA group, IAHA injections were performed to bilateral knee joints. An amount of 2.5 mL of hyaluronate (molecular-weight (MW) of 860 kilodaltons (kd) was injected into each knee joint once a week, for a total of five consecutive weeks without the application of local anesthetics. The injection technique followed the standard lateral approach with the knee extended and patient in the supine position. Sterilized procedures were strictly followed to prevent any septic infection.
Outcomes	Primary outcomes The level of knee pain on walking was evaluated by the use of a 100 mm visual analog scale (VAS). Functional impairments in patients with knee OA was assessed by Lequesne's function index (LI). The LI questionnaire included knee discomfort, endurance of ambulation, and difficulties in daily life. A maximum score of 26 indicated the greatest degree of dysfunction. The degree of disability was graded by the scoring as follows: >14 points = extremely severe; 11-13 points = very severe; 8-10 points = severe; 4-7 points = moderate; 1-3 points = mild. For the analysis of spatiotemporal gait parameters, a 6-camera motion analysis system and two AMTI force plates were synchronized to collect the threedimensional (3D) marker trajectories at a sampling rate of 120 Hz and ground reaction force (GRF) at a frequency of 960 Hz. The reflective markers were placed on anatomic landmarks including bilateral anterior superior iliac spines, lateral thighs, medial/lateral epicondyles of femur, lateral shanks, medial/lateral malleoli, calcaneus, base of second metatarsal bones, and sacrum. Three successful gait cycles for comfortable

pace on a 10-m walkway in the gait laboratory.

Gait analyses were performed before the IAHA injections as baseline, and 1 week, 3 months, and 6 months after the completion of IAHA injections for the knee OA group. During the entire six-month post-IAHA period, patients in the knee OA group did not receive any additional nutritional supplements (e.g. glucosamine), non-steroidal anti-inflammatory agents or physiotherapy treatments.

Three-dimensional joint moments were calculated via the inverse dynamics approach. All joint moments in the frontal and sagittal planes were normalized according to the participant's body mass (Nm/kg). Gait velocity and step length were normalized according to the body height (%BH/sec and %BH).

Secondary outcomes

Not reported.

Measures and timepoints

An investigator made clinical assessment for each patient before IAHA injections (as baseline), and 1 week, 3 months and 6 months after the completion of the fifth injection.

Study Results

Performance

The average scores of VAS and LI were significant improved after IAHA injections (p<0.001) in patients with knee OA (Figure 60).

	Baseline		D30		D90		D356	
	HA	Control	HA	Control	HA	Control	HA	Control
Age (y)	49 ± 15	47 ± 11						
Male %	55	53						
Duration of symptoms (m)	18 ± 17	22 ± 18						
VAS-rest (cm)	8.5 ± 11.1	8.4 ± 1.6	2.2 ± 1.2*	7.1 ± 1.3*@	2.5 ± 1.4*	6.7 ± 1.5*@	2.4 ± 1.4*	7.7 ± 1.3*@
VAS-grip (cm)	9.8 ± 1.1	9.6 ± 0.4	2.0 ± 1.5*	9.9 ± 1.3*@	2.2 ± 1.8*	9.3 ± 1.4*@	2.9 ± 1.4*	9.1 ± 1.1*@
PGS	0.3 ± 1.1	0.4 ± 1.1	4.6 ± 1.4*	1.6 ± 2.2*@	4.8 ± 0.6*	1.9 ± 0.3*@	4.8 ± 0.9*	1.1 ± 1.8*@
Grip (PSI)	49.2 ± 1.1	47.9 ± 0.4	68.0 ± 2.1	45.5 ± 1.1*@	67.7 ± 3.0*	48.1 ± 2.3*@	65.7 ± 1.8*	45.6 ± 1.3*@
PANF	1.1 ± 2.1	1.7 ± 2.2	4.4 ± 0.2*	2.6 ± 0.4@	4.8 ± 0.1*	1.3 ± 0.7*@	4.6 ± 0.3*	0.9 ± 1.9*@
PGA	1.1 ± 1.0	0.9 ± 1.2	4.3 ± 1.1*	1.8 ± 2.2*@	4.6 ± 1.1*	2.0 ± 1.7*@	4.7 ± 0.5*	1.3 ± 0.7*@
AE (N)			3	5				

VAS-pain are scored as a 100 mm VAS (0 = no pain; 100 = worse pain ever); grip strength (conducted with the patient's elbow fully extended and the dynamometer's handle in the middle position. Patients will perform three grip tests on the affected arm with a mean score calculated and used for analysis–measure in kg); PGS is patient global satisfaction using a 5 point categorical scale (0 = not satisfied, 5 = fully satisfied); PANF is patient assessment of normal function using a 5 point categorical scale (0 = no return to normal function, 5 = full return to normal function); PGA is physician's global assessment of elbow injury using a 5 point categorical scale (0 = poor patient elbow function and poor pain management, 5 = normal patient elbow function and normal pain management); AE are adverse events reported.
* = p < 0.05 (within groups); @ = p < 0.05 (between groups)

Figure 60. Scores of visual analog scales (VAS) and Lequesne's functional index in patients with knee osteoarthritis before and after HA injections.

VAS score was reduced from 54.6±12.4 at baseline to 38.5±11.2 at 1 week and 42.4±10.0 at 6 months after IAHA injections. As indicated by LI, pain, maximum distance walked, and difficulties in daily life scores were all significantly improved after IAHA injections from 1 week to 6 months (p<0.001) when compared with the baseline.

Total scores of LI was significant improved from 14.8±3.6 at baseline, to 7.4±3.0 at 1 week and 8.7±3.0 at 6 months after IAHA injections. The OA knee group showed significantly slower walking speed (49.4%±11.7 % BH/s) (p<0.001) and shorter step length (30.8±5.2 %BH) (p=0.01) at baseline.

These parameters significantly increased after the completion of IAHA injections (Figure 61).

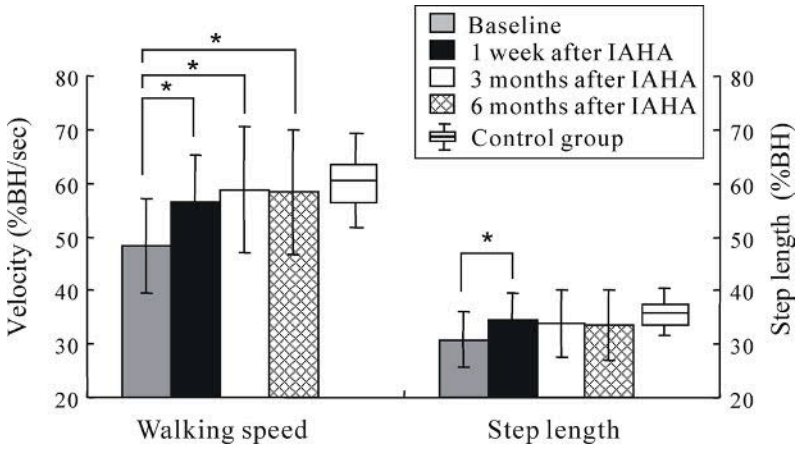


Figure 61. Comparisons of walking speed and step length for patients with knee OA at baseline and after IAHA injections.

Comparisons of the knee joint angles in the frontal plane between baseline, after IAHA injections in the knee OA and the control groups are shown in Figure 62. At 1 week and 3 months after IAHA injections, the knee adduction angles increased (more varus) during the initial and terminal phases of the gait cycle as compared with the knee adduction angles before IAHA injections and the control group.

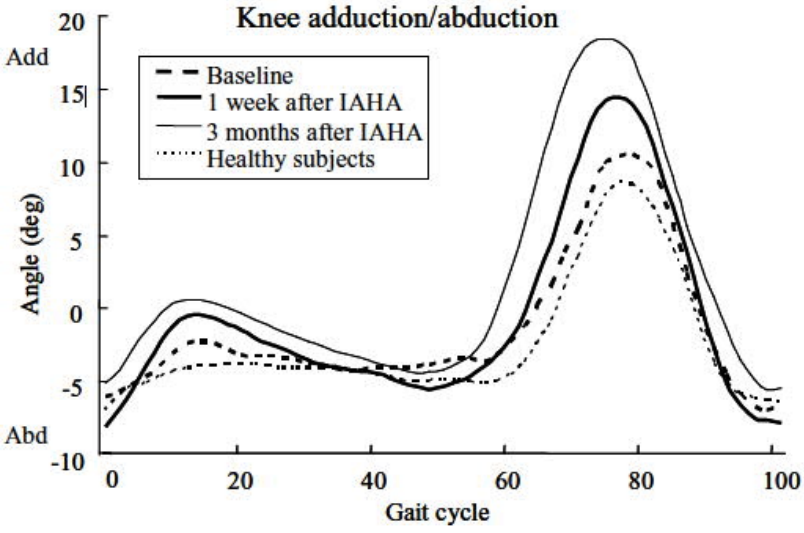


Figure 62. Angular motion of knee in frontal plane in both groups: +: adduction, -: abduction. Abbreviations: Add: adduction, Abd: abduction, deg: degree.

Figure 63a illustrated the average joint moment curves of the hip, knee and ankle in the frontal plane. ANOVA results showed that there were significant differences in adduction moments of hip and knee joints among baseline and after IAHA injections in knee OA group ($p<0.05$). At 1 week, 3 months and 6 months after IAHA injections, larger hip adduction moment at early stance was observed as compare with that at baseline. Larger knee adduction moments at 1 week, 3 months and 6 months

after IAHA injections at both early and terminal stance were found as compare with that before IAHA injections (Figure 63b).

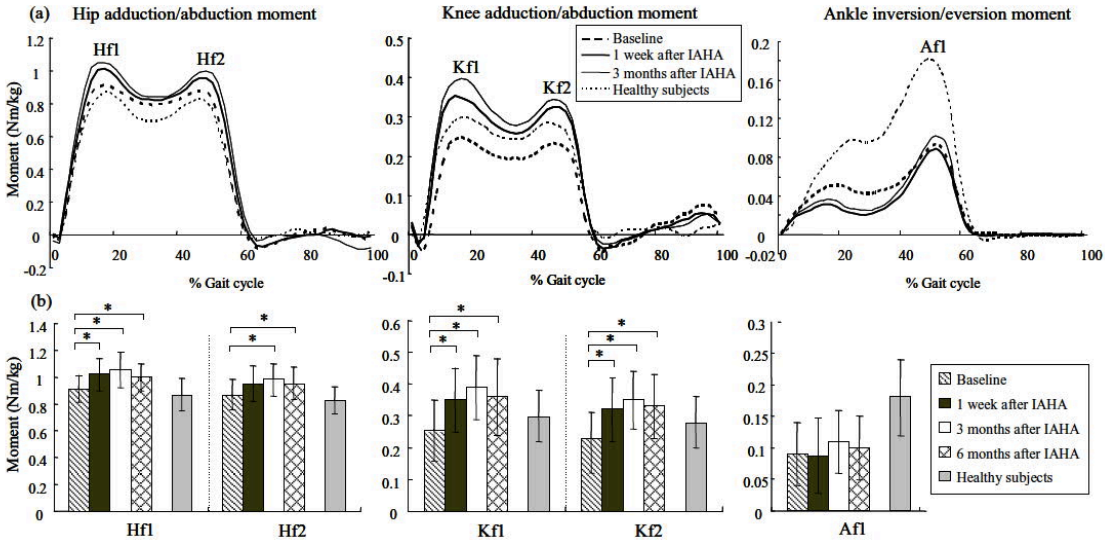


Figure 63. Comparisons of moments in frontal plane between baseline and after IAHA injections for patients with knee OA. (a) Mean moment waveforms in the frontal plane. Definition of parameters: Hf1, hip moment at early stance; Hf2, hip moment at terminal stance; Kf1, knee moment at early stance; Kf2, knee moment at terminal stance; Af1, ankle moment at terminal stance. (b) Comparisons of joint kinetics parameters. *p<0.05; Frontal plane: hip: +: adduction, -: abduction; knee: +: adduction, -: abduction; ankle: +: inversion, -: eversion.

No significant difference was found in moments at ankle before and after IAHA injections. Most importantly, authors found that the VAS pain scores were negatively correlated with knee adduction moments at early stance from baseline to post-IAHA injections (r=-0.656, p<0.001) (Figure 64).

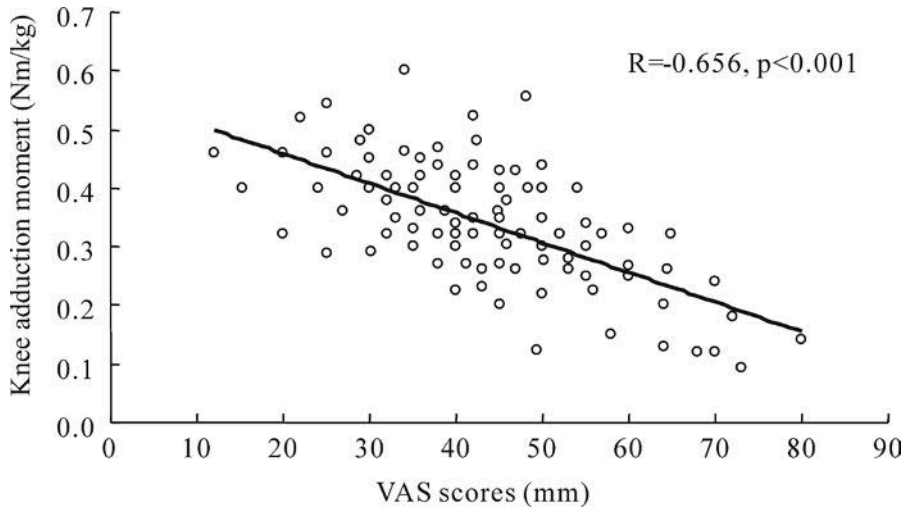
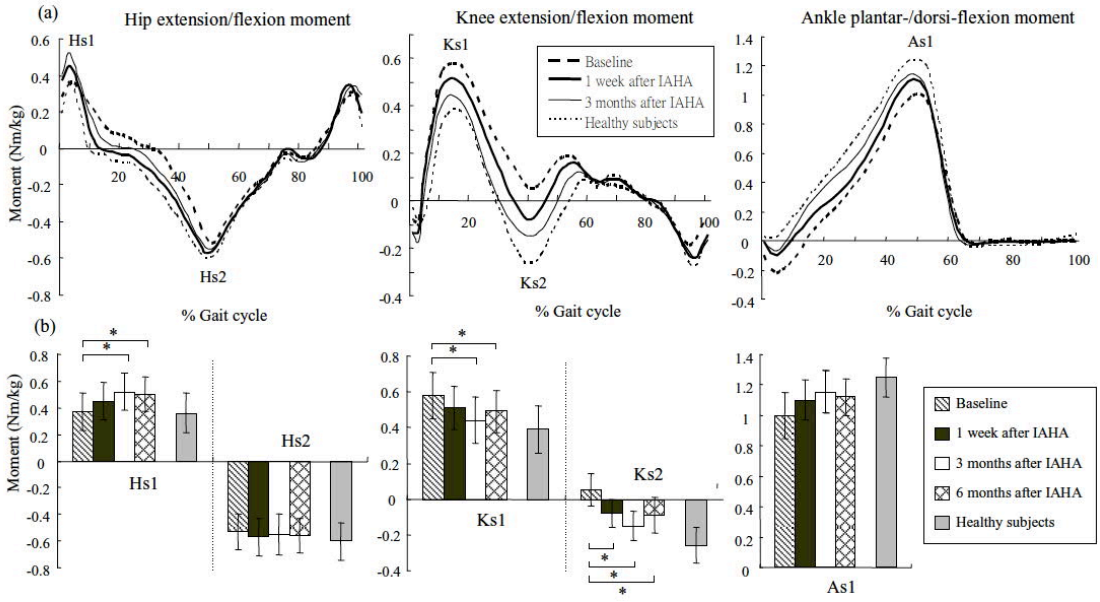


Figure 64. The correlation between VAS scores and knee adduction moments.

Figure 65a illustrated the average joint moment curves of the hip, knee and ankle in the sagittal plane. ANOVA results showed there were significant differences at hip extension moments and knee

	flexion moments at early stance (p<0.01) among baseline and after IAHA injections in OA group. After IAHA injections at 3 and 6 months, larger hip extension and lower knee extension moments were observed as compared to that at the baseline. At terminal stance, there were significantly larger knee flexion moments (p<0.01) at 1 weak, 3 and 6 months after IAHA injections as compared to those at baseline (Fig 65b). There were no significant differences in the ankle joint moments before and after IAHA injections.  **Figure 65.** Comparisons of moments in sagittal plane among baseline and after IAHA injections for patients with knee OA. (a) Mean moment curve in sagittal plane. Definition of parameters: Hs1, hip moment at early stance; Hs2, hip moment at terminal stance; Ks1, knee moment at early stance; Ks2, knee moment at terminal stance; As1, ankle moment at terminal stance. (b) Comparisons of joint kinetics parameters. *p<0.05; Sagittal plane: hip and knee: +: extension, -: flexion; ankle: +: plantar flexion, -: dorsiflexion.
Study Results **Safety**	Not reported.
Limit/s of the study	Not reported.
Discussion	In clinical assessment of this study, pain relief could be observed as soon as 1 week after IAHA injection by reducing VAS scores from 54.6±12.4 to 38.5±11.2, and the effect could be maintain up to 6 months (42.4±10.0). The ADL function in patients with knee OA improved from a degree of extremely severe to moderate severe disability as graded by Lequesne's function index (LI) after IAHA injections. Based on authors' results, the maximum effect seemed to have occurred at one week after the completion of IAHA injections. The effective of HA lasted up to a period of six months, which further supports the findings revealed by other literature about the efficacy of IAHA injections. Moreover, this study did not compare the effect of IAHA injection treatment with a placebo group or groups of knee OA patients receiving other injection methods such as steroid. The treatment effects between hyaluronate and steroid on OA knees have already been well documented and compared. However, literature on the kinetic changes of the knee joints after knee IAHA injections are limited.

	As a result, a placebo group or the comparison of treatment effect between hyalurate and other medications such as steroid was not included in this study. Evidences from this study have shown that increased knee adduction angles and moments after IAHA injections may cause medial tibial cartilage volume loss and accelerate knee joint degeneration process. Whether shoe inserts or other treatment strategies that should be applied to reduce knee adduction moments after IAHA injections need further thorough investigations.
Conclusions of the authors	IAHA injections can provide pain relief and improved ADL function in patients with knee OA. Increased knee adduction moment after IAHA injections may last up a period of 6 months. This may be detrimental to the knee joints in patients with knee OA as it may accelerate the process of knee degeneration. Further studies are needed to determine whether the observed kinetic findings in this study are harmful to the knee joints and whether treatment strategies to reduce knee adduction moments are needed to prevent the possible accelerated degeneration process after knee IAHA injections.

Citation 12

Title	Eyigör C, Pirim A, Eyigör S, Uyar M. **Efficacy of intraarticular hyaluronic acid injection through a lateral approach under fluoroscopic control for advanced hip osteoarthritis.** Agri. 2010;22(4):139-44.
Aim of the study	This clinical study aimed to determine the efficacy of intraarticular injection of HA through a lateral approach under fluoroscopic control for advanced hip OA.
Relevance of the study	Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage erosion, changes in subchondral bone, osteophyte formation and synovial inflammation. Hyaluronic acid (HA) used intraarticularly in the treatment of OA is a major constituent of the synovial fluid and cartilage. HA is known to increase viscosity of the synovial fluid; facilitate gliding via layer formation on the cartilage and protect soft tissue from trauma by acting as a shock absorbant. Although commonly used in clinical practice, there are no strict rules concerning the injection technique, age, radiographic staging of osteoarthritis, severity of symptoms, physical activity level, previous trauma or deformity; therefore patient selection has not been clearly delineated.
Equivalent Device	**Test devices:** Adant - Low Molecular weight Hyaluronic acid viscosupplementation **Control:** No control devices. *Adant is one of the medical devices equivalent to "Hyaluronic acid sodium salt, viscosuppletive joint device", since it reaches clinical, technical and biological equivalence. It is composed of Low Molecular Weight Hyaluronic acid of biofermentative origin. Therefore, it may support efficacy and safety of "Hyaluronic acid sodium salt, viscosuppletive joint device".*
Study Design	This was a prospective clinical study.
Study period	Not reported.
Sample size	Study included 21 patients, 5 men and 16 women, with a mean age of 61.3 years.
Inclusion Criteria	Patients that were diagnosed as primary hip OA by physical, laboratory and radiologic examinations according to American College of Rheumatology (ACR) criteria; rated as grade 3 or 4 according to

	Kellgreen-Lawrence criteria; and had symptoms for 2 years or more, with no intraarticular injection within the last 6 months, and suffered from severe pain despite WHO second line medical treatment were enrolled into the study.
Exclusion Criteria	Patients that had inflammatory joint disease (rheumatoid arthritis, ankylosing spondylitis etc), active synovitis of the joint, a history of hip surgery or replacement, intraarticular injection within the last 6 months, a history of trauma within the last 6 months or use of an oral or muscular steroid, or had any disease that precludes exercising or that caused loss of muscle power, advanced cardiovascular disease, pregnancy, malignancy, bleeding diathesis, mental disease were excluded from the study.
Intervention	Name and type of intervention Intra-articular (hip joint) administration of a low molecular weight HA-based Hyaluronic acid viscosupplementation. Aim of the intervention To determine the efficacy of intraarticular injection of HA through a lateral approach under fluoroscopic control for advanced hip OA. Duration Three-weeks treatment. Follow-up lasted 6 months. Description of the intervention All patients received three injections of 2.5 ml HA (Adant®) once a week. Patients were laid supine on the application table. C-arm fluoroscopy was set in the anterolateral position to view the hip joint. Intersection of the imaginary line at the level of trochanter major on lateral of femur with the line corresponding to the superior of the hip joint in the anterolateral view was determined as the injection point and local anesthesia was achieved by %2 prilocaine. Injection was performed by 15 cm long 22 G needle. Access to hip joint was confirmed by 0.5 ml of contrast material. Patients were monitored for side effects throughout the study.
Outcomes	Primary outcomes • Visual analog scale (VAS) 100 mm (scale 0 = no pain, 100 = worst pain possible) was used. • Severity of pain, walking capacity and disability in daily activities were assessed by Lequesne index; • Analgesic use was determined according to WHO analgesic ladder (1st step paracetamol ≤2 g/day, if this did not provide sufficient analgesia, tramodol PO ≤200 mg/day was used as 2nd step medicine). Secondary outcomes Not reported. Measures and timepoints All patients were assessed before the injections and 1, 3 and 6 months after the injections.
Study Results Performance	VAS Pain Scores VAS pain scores of the patients 1, 3 and 6 months after treatment showed statistically significant reduction compared to that of before treatment ($p<0.001$). Reductions in the pain scores 1, 3 and 6 months after treatment were 62.6%, 61.3% and 39.9% respectively (Fig. 66). Lequesne index Lequesne indexes of the patients 1, 3 and 6 months after treatment showed statistically significant reduction compared to that of before treatment ($p<0.001$). Reductions in the Lequesne indexes 1, 3

and 6 months after treatment were 25.6%, 22.8% and 17.4% respectively (Fig. 67).

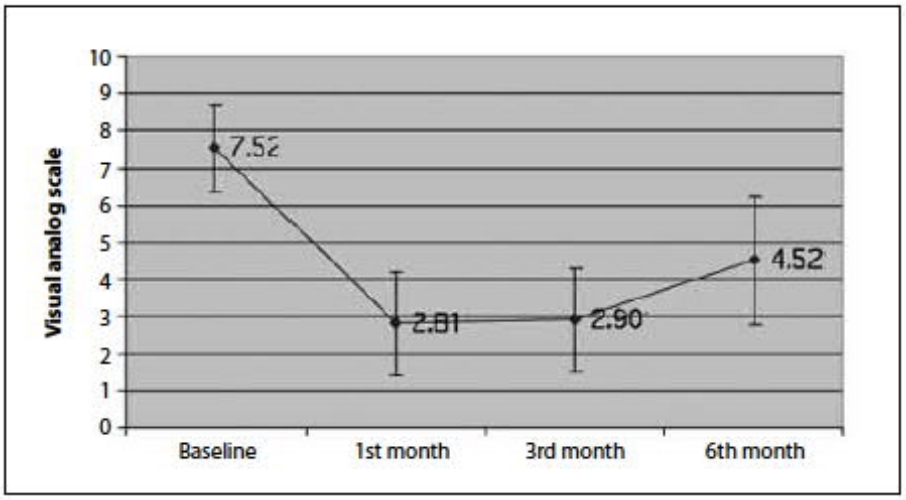


Figure 66. Pain (VAS) changes in 1st, 3rd and 6th months. *p<0.001

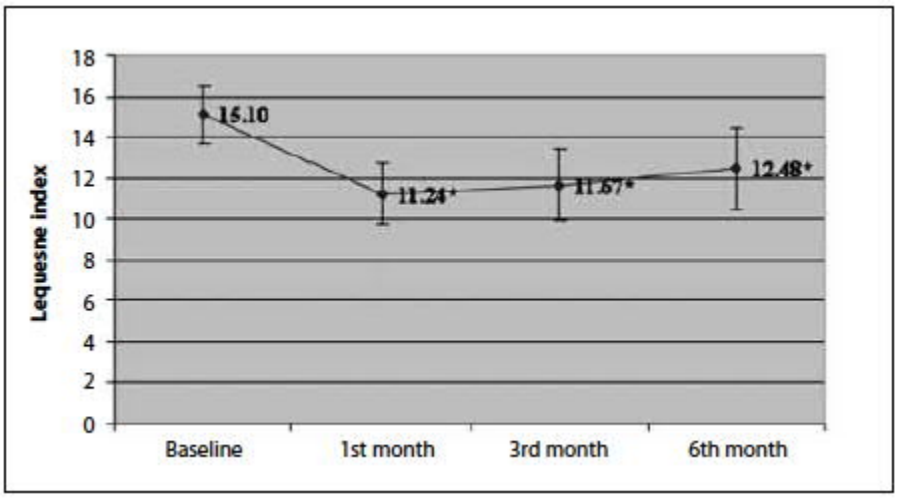
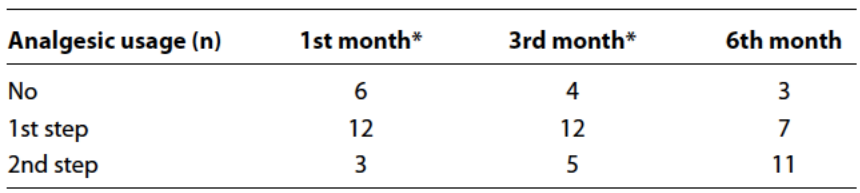


Figure 67. The Lequesne index changes in over time. *p<0.001

Analgesic use

One month after the treatment 6 patients (28.6%) need no analgesics. Twelve patients (57.1%) used 1st step analgesics, whereas 3 patients (14.3%) required 2nd step analgesics.

Three months after the treatment 4 patients (19%) required no analgesic. Twelve patients (57.1%) used 1st step analgesics, whereas 5 patients (23.8%) used 2nd step analgesics. Reduction in analgesic use 1 and 3 months after treatment were statistically significant (p<0.05). Six months after the treatment, 3 patients (14.3%) need no analgesics. Seven patients (33.3%) used 1st step analgesics, whereas 11 patients (52.4%) used 2nd step analgesics. Analgesic use 6 months after the treatment did not show significant difference compared to baseline (p>0.05) (Figure 68).

	 **Figure 68.** Analgesic consumption of the patients.
Study Results **Safety**	None of the patients developed a systemic side effect during the study period. Three of the 21 patients (14.29%) reported a moderate pain around the needle insertion site on the lateral side of the hip that lasted 3-5 days. No complication was observed in other patients during injection and within the follow-up period.
Limit/s of the study	This study has several limitations. Authors have not considered forming a placebo group as patients enrolled for the study had advanced stage OA with higher pain and disability scores. Additionally, lack of assessment of quality of life and the psychological status of the patients and relatively insufficient follow-up period may be considered as other limitations of this study.
Discussion	This study showed that intraarticular HA injection through lateral approach under fluoroscopic control provided significant reduction in pain scores, disability scores and analgesic use in advanced hip OA. In this study, VAS pain scores showed significant reduction consistent with the studies in the literature. VAS pain scores at the 6th month were higher compared to 1st and 3rd months, yet still lower than the baseline VAS scores. Lequesne index scores were also reduced significantly similar to the VAS pain scores during and at the end of the treatment period. Lack of corresponding improvement in disability scores despite a significant decrease in the pain scores was attributed to selection of patients with advanced OA for the study. It should also be remembered that pain is only a symptom, whereas improvement of disability depends on several factors.
Conclusions of the authors	In conclusion, intraarticular HA injection through lateral approach under fluoroscopic control has proved to be a safe and effective method for patients with advanced hip OA. Results of authors' study obtained by 6 months of follow-up are encouraging. But authors' results have to be supported by studies that have higher number of patients with control group and a long-term follow-up.

Analgesic usage (n)	1st month*	3rd month*	6th month
No	6	4	3
1st step	12	12	7
2nd step	3	5	11

*$p<0.05$

Citation 13

Title	Petrella RJ, Cogliano A, Decaria J, Mohamed N, Lee R. **Management of Tennis Elbow with sodium hyaluronate periarticular injections.** *Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology* 2010, 2: 4-9.
Aim of the study	This clinical study aimed to determine the efficacy and safety of peri-articular hyaluronic acid injections in chronic lateral epicondylosis (tennis elbow).
Relevance of the study	Chronic tennis elbow or lateral epicondylosis produces symptoms of pain and functional disability. There is no consensus on treatment while efficacy of existing treatments is poor. Intra-articular hyaluronic acid (HA) has shown efficacy equivalent to NSAID in the treatment of osteoarthritis while its periarticular efficacy and safety have recently been reported for soft tissue use in acute ankle sprain. Previous studies regarding treatment of chronic tennis elbow have shown lack of consensus as well as variable efficacy and high incidence of adverse effects. Hyaluronic acid has been used in soft tissue application for acute ankle sprain with high degree of efficacy and very limited side effect. Hence,

	given the biocompatibility of HA in treatment of acute ankle sprain authorsmay show efficacy in terms of pain and function with low incidence of side effect and treatment of chronic tennis elbow.
Equivalent Device	**Test device:** a clear solution of sterile 1% sodium hyaluronate in a phosphate buffered saline contained in a prefilled syringe - brand name is not specified. **Control:** placebo - saline solution without HA. *This article has been included since the tested device is a pre-filled syringe mainly composed of low molecular weight Hyaluronic acid indicated for intra-articular administration, such as "Hyaluronic acid sodium salt, viscosuppletive joint device". Therefore, it may support efficacy and safety of "Hyaluronic acid sodium salt, viscosuppletive joint device".*
Study Design	This was a Prospective randomized clinical trial in primary care sport medicine.
Study period	Not reported.
Sample size	A total of 497 patients were enrolled. 331 consecutive patients administered HA versus 166 patients administered 1.2 cc saline placebo. Both groups (HA = 165 vs placebo = 166) were similar for age (49 ± 15 vs 47 ± 11) and gender (55 vs 53% male).
Inclusion Criteria	Patients eligible for the study were 18 or older, with clinically or radiographic diagnosis of tennis elbow, and who were newly referred to the medical outpatient clinics at the author's institution which are primary sport medicine referral centers serving a population of 1.5 million patients. Inclusion criteria were pain at the lateral side of the elbow that had persisted more than 3 months and pain at the lateral epicondyle during resisted dorsiflexion of the wrist with the elbow in full extension.
Exclusion Criteria	Exclusion criteria were previous local injection treatments (ie. corticosteroid injections or acupuncture), nerve entrapment or systemic neuromuscular disorders.
Intervention	Name and type of intervention Intra-articular (elbow joint) administration of a HA-based viscosupplementation. Aim of the intervention To determine the efficacy and safety of peri-articular hyaluronic acid injections in chronic lateral epicondylosis (tennis elbow). Duration 1-year follow-up. Description of the intervention Treatment course was randomized and consisted of 2 injections (1 at baseline and a second at 7 days). Injections were administered using blinded syringes affixed to a 27-gauge, 1-inch needle. Skin was prepped using betadine 1%. Injections were delivered by the study physician using a standard approach along the lateral epicondyle with the affected arm flexed and resting on a firm surface. Injections were be administered into the soft tissue 1 cm from the lateral epicondyle at the point of greatest pain in two planes using a fanning technique whereby contents were injected on withdrawl of the needle from the point of maximal tenderness in a single puncture.
Outcomes	Primary outcomes The primary outcome measures were an improvement on the VAS-pain at rest in the affected elbow

	and VASpain immediately following grip strength testing. Secondary outcomes Secondary outcome measures included patients' global assessment of elbow injury (5 point categorical scale), patients' assessment of normal function/activity (5 point categorical scale), physician's global assessment of elbow injury (5 point categorical scale), patients/physician satisfaction assessment (10 point categorical scale), time to return to pain and disability-free sport, concomitant medication use and adverse events. Measures and timepoints Assessments included general demographics, comorbidities and previous treatments. Patients rated pain on a 10 cm VAS, with 0 representing no pain and 10 representing maximal pain. Patients' global assessment of elbow injury (5 point categorical scale; 1 = no disability, 5 = maximal disability), patients' assessment of normal function/activity (5 point categorical scale; 1 = no change in function/activity, 5 = maximal change in normal function/activity) and physician's global assessment of elbow injury (5 point categorical scale; 1 = no impact of injury on function, 5 = maximal impact of injury on function) were also collected. Global assessments have not been validated but have been used previously by authors' and other groups to link the findings to implementation into routine practice. Time to return to pain and disability-free sport and adverse events were determined from review of a patient diary. After enrollment, patients were randomized (1:1) to one of two treatments using a computer-generated randomization schedule: HA or placebo. Follow-up examinations were completed at Day 14 (± 2 days), Day 30 (± 2 days), Day 90 (± 2 days) and at Day 356 (± 7 days). Patients will assess pain on a VAS at rest and after assessment of grip strength. Assessment will be conducted with the patient's elbow fully extended, shoulder in neutral position and the dynamometer's handle in the middle position. Patients will perform three grip tests on the affected arm with a mean score calculated and used for analysis. During the study, including the follow-up period, the patients received usual care including RICE (rest, ice, compression and elevation). Use of any analgesics was prohibited and all concomitant medication use was recorded in the patient's diary. Specifically, no NSAID, corticosteroid or topical analgesics were allowed during the study. ASA at the dose of 325 mg and less for cardiovascular prophylaxis was allowed. Patients were assessed for pain on a VAS at rest and after assessment of grip strength. Patients' global assessment of elbow injury (5 point categorical scale), patients' assessment of normal function/activity (5 point categorical scale), and physician's global assessment of elbow injury (5 point categorical scale) was performed. Also, patients/physician satisfaction assessment (10 point categorical scale; 1 = no satisfaction with the procedure, 10 = very high satisfaction with the procedure) and review of a patient diary for adverse events and return to pain and disability-free sport was performed.
Study Results Performance	There was no difference among groups in the duration of their symptoms (26 vs 33 months).
Study Results Safety	There were no serious adverse events reported throughout the study. Three patients (1.8%) in the HA and 5 patients (4%) in the control reported pain during injection. No other adverse events were reported. Mean baseline rest VAS was similar (8.5 ± 1.1 cm and 8.4 ± 1.6 cm) for HA and control respectively. VAS pain at rest and after grip testing was significantly better in the HA vs control (Figure 69) at D 30. This was associated with significantly greater grip strength, patient global satisfaction and assessment of normal elbow function in the HA group vs control (Figure 69). Physician global assessment of elbow

	injury was significantly better for the HA vs the control (Figure 69). These differences persisted at each follow up assessment (90 and 356 days). Time to return to pain-free and disability-free sport was 18 (± 11) days in the HA group (in 147 patients; 89% response rate) but was not achieved in any of the control group patients.

	Baseline		D30		D90		D356	
	HA	Control	HA	Control	HA	Control	HA	Control
Age (y)	49 ± 15	47 ± 11						
Male %	55	53						
Duration of symptoms (m)	18 ± 17	22 ± 18						
VAS-rest (cm)	8.5 ± 11.1	8.4 ± 1.6	2.2 ± 1.2*	7.1 ± 1.3*@	2.5 ± 1.4*	6.7 ± 1.5*@	2.4 ± 1.4*	7.7 ± 1.3*@
VAS-grip (cm)	9.8 ± 1.1	9.6 ± 0.4	2.0 ± 1.5*	9.9 ± 1.3*@	2.2 ± 1.8*	9.3 ± 1.4*@	2.9 ± 1.4*	9.1 ± 1.1*@
PGS	0.3 ± 1.1	0.4 ± 1.1	4.6 ± 1.4*	1.6 ± 2.2*@	4.8 ± 0.6*	1.9 ± 0.3*@	4.8 ± 0.9*	1.1 ± 1.8*@
Grip (PSI)	49.2 ± 1.1	47.9 ± 0.4	68.0 ± 2.1	45.5 ± 1.1*@	67.7 ± 3.0*	48.1 ± 2.3*@	65.7 ± 1.8*	45.6 ± 1.3*@
PANF	1.1 ± 2.1	1.7 ± 2.2	4.4 ± 0.2*	2.6 ± 0.4@	4.8 ± 0.1*	1.3 ± 0.7*@	4.6 ± 0.3*	0.9 ± 1.9*@
PGA	1.1 ± 1.0	0.9 ± 1.2	4.3 ± 1.1*	1.8 ± 2.2*@	4.6 ± 1.1*	2.0 ± 1.7*@	4.7 ± 0.5*	1.3 ± 0.7*@
AE (N)			3	5				

VAS-pain are scored as a 100 mm VAS (0 = no pain; 100 = worse pain ever); grip strength (conducted with the patient's elbow fully extended and the dynamometer's handle in the middle position. Patients will perform three grip tests on the affected arm with a mean score calculated and used for analysis–measure in kg); PGS is patient global satisfaction using a 5 point categorical scale (0 = not satisfied, 5 = fully satisfied); PANF is patient assessment of normal function using a 5 point categorical scale (0 = no return to normal function, 5 = full return to normal function); PGA is physician's global assessment of elbow injury using a 5 point categorical scale (0 = poor patient elbow function and poor pain management, 5 = normal patient elbow function and normal pain management); AE are adverse events reported.
* = $p < 0.05$ (within groups); @ = $p < 0.05$ (between groups)

Figure 69. Comparison of HA and control baseline, 30, 90 and 356 days followup.

Limit/s of the study	Not reported.
Discussion	There is currently no consensus in the management of chronic tennis elbow. Several, reviews have included various therapies targeting local or systemic interventions. In this study, patients who received HA for lateral epicondylosis (tennis elbow) had significantly greater improvement in VAS pain at rest and after grip testing than control that persisted to 356 days follow-up. The treatment was highly satisfactory to patients and physicians and was associated with very few minor and transient adverse effects. Given the less than optimal treatment options for tennis elbow and given the associated chronic morbidity associated with this condition, peri-articular injection with HA may provide an alternative for clinicians and their patients.
Conclusions of the authors	Not reported.

8 ANALYSIS OF THE CLINICAL DATA

8.1 *INTENDED USE*

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

8.2 *CRITICAL ANALYSIS AND COMPARISON WITH THE "STANDARD OF CARE"*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is an intra-articular visco-supplementation product, which allows restoring the physiological and rheological properties of arthritic joints and tendon sheath.

"Hyaluronic acid sodium salt, viscosuppletive joint device" contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid, to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in "Hyaluronic acid sodium salt, viscosuppletive joint device" is obtained by fermentation and has not undergone chemical change processes.

It is a substitute for synovial fluid, which allows the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, *"Hyaluronic acid sodium salt, viscosuppletive joint device"* reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action.

The other components of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* are: sodium chloride, sodium phosphate and water for injectable preparations.

8.2.1 *Standard of care for osteoarthritis*

Osteoarthritis (OA) is the most common form of arthritis and refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. The most commonly affected peripheral joints are the knees and the hips, but also small hand joints [16]. OA is characterised by localised loss of cartilage, remodelling of adjacent bone and associated inflammation. The main signs and symptoms are pain, stiffness and loss of movement and function [23]. OA includes a slow but efficient repair process that often compensates for the initial trauma, resulting in a structurally altered but symptom-free joint. However, because of either

overwhelming trauma or compromised repair, in some people the process cannot compensate, resulting in eventual presentation with symptomatic osteoarthritis; this might be thought of as 'joint failure'.

There is no cure for osteoarthritis; treatments available may only manage symptoms. there are four mainly therapeutic approaches: nonpharmacologic, pharmacologic, complementary and alternative, and surgical. Surgical management should be reserved for those who do not improve with behavioral and pharmacologic therapy, and who have intractable pain and loss of function [62].

The pharmacologic treatment consists mainly of Acetaminophen, antibiotics, non-steroidal anti-inflammatory drugs, opioids and topical analgesics. Their proven efficacy is counteracted by side effects: Acetaminophen is an OTC analgesic used in suffering from OA who experience mild to moderate pain. The Arthritis Foundation recommends taking no more than 3,000 mg of acetaminophen per day, because taking higher doses for a long time can lead to liver damage or failure. This can also be fatal [84]. Systemic nonsteroidal anti-inflammatory drugs (NSAIDs) can cause stomach irritation that may result in bleeding, ulcers, or perforation of the stomach or intestines. NSAIDs can also cause cardiovascular problems, bleeding problems, liver and kidney damage, constipation, diarrhea, gas, heartburn, nausea, vomiting and dizziness. Topical NSAIDs have fewer side effects and may relieve pain just as well. Corticosteroids have many risks if used for long-term treatment; like NSAIDs, they reduce inflammation but are hard on the stomach. Unlike NSAIDs, they do not cause kidney problems. Other side effects of steroids include stomach ulcers, high blood pressure, irritability, depression, osteoporosis and high blood sugar levels [85]. Opioids should be prescribed first at low dosages and carefully monitored to evaluate for potential dependence. Opioids also make the patient sleepy or impair balance, and cause chronic constipation and can place older patients at risk of falls [86,87].

Non-pharmacological therapy is often represented by physical exercises. Studies show that simple activities like walking around the neighborhood can reduce pain and help maintain (or attain) a healthy weight. Strengthening exercises build muscles around OA-affected joints, easing the burden on those joints and reducing pain. Range-of-motion exercise helps maintain and improve joint flexibility and reduce stiffness. Aerobic exercise helps to improve stamina and energy levels and also help to reduce excess weight, as proven by a randomized clinical trial compared supervised home-based exercise with no exercise in 786 patients with osteoarthritis of the knee, which found statistically significant improvements in a validated arthritis symptom score at six, 12, 18, and 24 months in the exercise group [63].

Also Ultrasound and transcutaneous electrical nerve stimulation are available as physical therapies, even if their efficacy is questionable [64].

No particular side effects have been reported regarding the non-pharmacological therapeutic approach.

The surgical option is commonly taken into consideration for patients whose symptoms have not responded to other treatments. The two main procedures performed in patients with osteoarthritis are bones realignment and joint replacement. The former is the most effective surgical intervention, with excellent patient outcomes following total joint replacement of the hip,

knee, and shoulder [74]. However, its risks include infections and blood clots. Moreover, artificial joints can wear out or come loose and may need to eventually be replaced [89].

Finally, complementary and alternative medicine is another therapeutic approach widely spread: in particular, the most used supplements for osteoarthritis are glucosamine and chondroitin, which efficacy has been investigated by some small clinical trials. Results were favorable only for a combination of glucosamine and chondroitin, which appeared to be effective for moderate to severe osteoarthritis of the knee [79]. Chondroitin alone did not show benefit for osteoarthritis of the knee or hip in a meta-analysis [80].

There also is evidence supporting the use of the supplement S-adenosylmethionine (SAM-e) to reduce functional limitation, but not compared with placebo in patients with osteoarthritis pain. The effectiveness of SAM-e is comparable to that of NSAIDs in some studies but with fewer adverse effects [81].

Capsaicin cream is a topical analgesic derived from chili peppers, which has been found to be superior to placebo in treating osteoarthritis pain [83].

Also balneotherapy has been introduced as a therapeutic option for OA patients, consisting of spa therapy or mineral baths. A Cochrane review concluded that mineral baths were of some benefit to patients with osteoarthritis, but the authors addressed methodologic flaws in the studies and urged caution in interpreting the findings [82].

8.2.1.1 Intra-articular injections

Osteoarthritis is characterized by the breakdown of joint cartilage, which becomes rougher and thinner. The bone underneath thickens and the joint becomes inflamed. Moreover, the tissues around the joints, such as ligaments and the joint capsule, may thicken and become tighter, too. This anatomical modifications cause pain, disability and limited joint mobility, which increase with time [44].

In order to obtain relief from pain and to directly act on joint cavity, intra-articular injections have been introduced as a promising approach for the management of OA symptoms, together with their advantage of not being systemically absorbed.

In particular, injections of corticosteroid medications may relieve pain in the joint. During this procedure, the physician numbs the area around the joint, then places a needle into the space within the joint and injects medication. The use of intra-articular corticosteroids primarily provides short-term relief lasting four to eight weeks. It has proven effectiveness in osteoarthritis of the knee, but may not be as effective for osteoarthritis of the shoulder or hand [70,71]. Many physicians inject a corticosteroid and a local anesthetic, such as lidocaine. The lidocaine can provide some immediate relief, which confirms that the medication was injected into the correct area. Patients should be warned of a potential flare-up of symptoms within the first 24 hours, followed by an improvement from baseline at 48 hours. Repeat injections are possible in the same joint, but usual practice is limited to four injections annually [72]. Corticosteroid injections are useful for treating flare-ups of OA pain and swelling with fluid buildup in the knee. However, the number of injections each year is generally limited to

3or 3 injections, because the medication can worsen joint damage over time. In some people who receive cortisone injections, the cartilage softens and the tendons weaken in the joint that is being treated. Infection at the site of your injection is a rare, but still serious potential side effect of cortisone shots [90].

A more safe approach is the intra-articular administration of exogenous lubricating agents, also defined as “viscosupplementation”.

Synovial fluid is composed of polysaccharides, among other elements. These contain glucosamine, glucuronic acidand hyaluronic acid, and this last substance is considered to be a key molecule in joint biomechanics. Hyaluronic acid is a biopolymer formed by glucuronic acid and N-acetylglucosamine. It has a viscous texture and is found in the synovial fluid, vitreous humour and collagenous connective tissue of numerous organisms and is an important glycosaminoglycan (GAG) in constituting the joint. This molecule is the only non-sulfated GAG. It has the capacity to become associated with proteins in order to form molecular aggregates, but it does not form proteoglycans. In joints affected by osteoarthrosis, the concentration and molecular weight of hyaluronic acid in the synovial fluid become reduced, which alters its properties through diminishing its viscosity and reducing its capacity to absorb shock and provide lubrication, and leads to damage to cartilage and increased symptoms. HA injections have also been introduced for OA patients in whom the other therapeutic approaches have failed and for whom surgical procedure is contraindicated.

The intra-articular injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: “viscosupplementation” [94]. It is thought that HA temporarily restores the lubricating and shock-absorbing effects of SF. Moreover, several studies suggest that viscosupplements also have effects, such as protection against cartilage erosion [98,99], and promotion of intra-articular HA production.

In a multicenter randomized controlled clinical trial with 40 months of follow-up, named the Amelia Project, Navarro-Sarabia *et al.* [122] evaluated 306 patients over the age of 45 years who presented knee osteoarthrosis (Kellgren–Lawrence grades II and III, with a minimum joint space of 2 mm). Four cycles of intra-articular injection of hyaluronic acid or placebo were performed. The patients were evaluated with regard to clinical and functional improvement and side effects. These authors concluded that the treatment was safe and that there were significant improvements in functional capacity and symptoms, in relation to the control group, with an effect thatwas maintained even 1 year after the last application.

Efficacy and safety of Hyaluronic acid viscosupplementations seem to depend also on molecular weigth and origin of the compound. In particular, Hyaluronic acid molecular weight may be classified as Low or High, with 1.5 mDa as the quantitative threshold.

Several clinical trials compared HA-based viscosupplementations with a different molecular weight. High molecular weight hyaluronic acid (HMWHA) is considered more effective in relieving pain, compared to low molecular weight HA. This is due to the fact that HMWHA

molecules are bigger than LMWHA: this property allows the compound to not penetrate the extracellular matrix and to concentrate in the joint cavity, leading to a higher lubrication and protection of the joint [103]. However, no conclusive theories have been confirmed regarding the correlation between molecular weight and efficacy [108-110].

However, results from large animal models of OA shows that low weight HAs are more effective than high molecular weight HAs in restoring the rheological properties of synovial fluid [117]. Also, several preclinical studies evaluating joint-structure modification in animal models of OA have reported advantages of using HAs of molecular weight in the low- to mid-range, as they can access diseased tissue more easily, suggesting potential for disease modification [118]. Furthermore, some studies show no difference in efficacy but an overall risk/benefit profile favouring lower molecular weight HAs [118-120]. Moreover, a safety analysis demonstrated a two fold increased risk of local adverse events (pain, swelling or warming to severe inflammation) and flares with hylan.

Two studies compared the use of high and lowmolecular weight hyaluronic acid for treating osteoarthrosis. According to Raman *et al*. [123] use of high-weight hyaluronicacid (Hylan G-F 20) has the advantage of a more long-lastingeffect, but with clinical efficacy and tolerability similar to otherpresentations. In a clinical trial that compared three presenta-tions of hyaluronic acid for treating osteoarthrosis of the knee, Jüni et al. (Citation 1) concluded that the different molecular weights of weights of hyaluronic acid did not give rise to any significant differ-ences. In a systematic review of 76 studies of medium quality, Bellamy *et al.* [121] came to the conclusion that viscosupplementation was safe and led to significant clinical and functional improvements, in comparison with placebo. They also reported that the effect of this treatment was longer lasting than that of intra-articular corticosteroids. Many of thestudies included in their review presented design inadequacies.

Another important feature is the origin of hyaluronic acid, since it may be biofermentative or animal. The latter is obtained by microbial fermentation using bacterial strains, while the former is mainly extracted from chicken combs. The second process is hampered by several technical limitations. One drawback in the extraction process is the inevitable degradation of hyaluronan, caused by (a) the endogenous hyaluronidase activity in animal tissues, breaking down the polymer chain through enzymatic hydrolysis, and (b) the harsh conditions of extraction. Extraction protocols have been improved over the years, but still suffer from low yields, due to the intrinsic low concentration of hyaluronan in the tissue, and from high polydispersity of polymer products due to both the natural polydispersity of hyaluronan and to the uncontrolled degradation during extraction. Moreover, as in any process for the production of therapeutic compounds from animal sources, there is a potential risk of contamination with proteins and viruses, but this can be minimized by using tissues from healthy animals and extensive purification [114].

In contrast, bacterial hyaluronan is not immunogenic and is an excellent source for medical grade hyaluronan. An additional and important advantage of microbial hyaluronan production

is that microbial cells can be physiologically and/or metabolically adapted to produce more HA [114].

Generally, HA viscosupplementations require more than 1 (up to 5) injections, usually within a 5-week period. Viscosupplementation is considered a safe procedure, although it may carry some risks and side effects. Patients who undergo viscosupplementation may have mild discomfort immediately after the procedure. Typical side effects at the injection site include: localized swelling, skin warmth and/or redness, soreness and joint stifness. It has been estimated that 1% to 3% of patients experience localized swelling and skin changes. However, side effects are usually mild and go away in 1 to 2 days [91].

Finally, HA viscosupplementations are designed also for more than one course of treatment, thanks to their tolerability and safety. In a prospective open-label study, Waddell *et al* [131] evaluated the efficacy and tolerability of a second course of HA for the treatment of osteoarthritic knee pain over a 12-month period in patients who previously experienced a beneficial initial course of therapy. Most patients experienced continued pain relief as all efficacy parameters significantly improved ($p< 0.001$) from baseline at weeks 1, 2, 4, 8, 12, 26, and 52. Furthermore, Raynauld and colleagues, in a randomized controlled trial also demonstrated the safety of repeat treatment with no evidence of higher incidence of local mild adverse events than with a first course of therapy. This safety profile of viscosupplementation is also supported in a recent meta-analysis by Pagnano *et al* [132].

8.2.1.2 Hyaluronic acid viscosupplementations versus standard of care

Viscosupplementations have been widely compared with the other therapeutic approaches for osteoarthritis.

Filardo *et al.* [124] evaluated the benefit provided by platelet-rich plasma (PRP) injections to treat knee joint degeneration in comparison with hyaluronic acid (HA). Platelet-rich plasma (PRP) is created from a blood sample obtained from a patient. Then, platelets are separated from other blood cells and their concentration is increased during a process called centrifugation. Finally, the increased concentration of platelets is combined with the remaining blood. PRP is often injected into an injured joint. For example, in Achilles tendonitis, a condition commonly seen in runners and tennis players, the heel cord can become swollen, inflamed, and painful. A mixture of PRP and local anesthetic can be injected directly into this inflamed tissue. Afterwards, the pain at the area of injection may actually increase for the first week or two, and it may be several weeks before the patient feels a beneficial effect [125]. However, this randomized controlled trial showed thta PRP does not provide a superior clinical improvement with respect to HA, and therefore it should not be preferred to viscosupplementation as injective treatment of patients affected by knee cartilage degeneration and OA.

In addition, Increasing attention has shifted toward comparing HA with other nonoperative knee osteoarthritis treatment strategies. These include NSAIDs and intra-articular steroid injections. Several randomized controlled trials comparing HA viscosupplementation with NSAIDs have reported that the benefit obtained with intra-articular HA was similar to or greater than that observed with NSAIDs, with fewer gastrointestinal side effects [126, 127]. In a multicenter Canadian trial, Adams *et al.* [128] compared three treatment groups: oral NSAIDs alone, HA treatment (3 weekly injections), and a combination of oral NSAIDs and HA treatment. At 6 months, both the HA only and the combined NSAID and HA groups were statistically superior to the NSAID only group. These findings are further supported by a Cochrane review, which reported that when HA was added to pre-existing NSAID therapy, combination therapy was associated with greater improvement in pain and joint function than use of NSAIDs alone [121].

A number of trials have compared IA HA to IA corticosteroids.

In a systematic review of 76 studies of medium quality, Bellamy *et al.* [121] came to the conclusion that viscosupplementation was safe and led to significant clinical and functional improvements, in comparison with placebo. They also reported that the effect of this treatment was longer lasting than that of intra-articular corticosteroids.

Other data [121, 129] indicate that IA corticosteroids significantly improved pain during the first 4 weeks after injection but that IA HA were shown to be more effective from 5 to 14 weeks post-injection. Pain relief was greatest following IA corticosteroids at 2 weeks, but not at 4 weeks after injection. By contrast IA HA demonstrated superior reduction in pain at 8 weeks and continued to be significant until 14 weeks after the injections. Two recent prospective trials have compared intra-articular HA to intra-articular corticosteroids.

Leopold *et al.* [130] prospectively compared 2 treatment arms. The first groups received 3-weekly injections of HA, and the second group received 1 injection of intra-articular betamethasone. At the 6-month follow-up, both groups improved and there was no statistically significant difference between the two groups for VAS and WOMAC scores, or the Knee Society Scoring System. Caborn and associates also studied similar cohorts. In their comparison of intra-articular HA (3 weekly injections) and intra-articular triamcinolone (1 isolated injection) they found that although the maximal benefit of corticosteroids appeared more rapidly (week 2), pain reduction and functional improvement were significantly superior ($p<0.01$ and $p<0.001$, respectively) with HA viscosupplementation at the 3- to 6-month follow up periods.

8.3 *SUMMARY OF CONFORMITY ASSESSMENT WITH REQUIREMENT ON SAFETY (MED ER1)*

According to Directive 93/42/EEC Essential requirements (Annex I), 1:

"The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

This shall include:

- *Reduce as far as possible the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and*
- *Consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users)".*

The medical device *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is an intra-articular viscosupplementation product, which allows restoring the physiological and rheological properties of arthritic joints and tendon sheath.

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid, to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in "*Hyaluronic acid sodium salt, viscosuppletive joint device*" is obtained by fermentation and has not undergone chemical change processes.

It is a substitute for synovial fluid, which allows the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, "*Hyaluronic acid sodium salt, viscosuppletive joint device*" reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action.

The other components of "*Hyaluronic acid sodium salt, viscosuppletive joint device*" are: sodium chloride, sodium phosphate and water for injectable preparations.

8.3.1 *Safety features related to "Hyaluronic acid sodium salt, viscosuppletive joint device" ingredients*

No special formulation features of the device have been identified that could pose particular safety concerns. In particular, "*Hyaluronic acid sodium salt, viscosuppletive joint device*" mechanism of action is based only on Hyaluronic acid, the key ingredient, while the other compounds, sodium chloride and sodium phosphate, are excipients. Excipients are more or less inert substances added to a compound to give suitable consistency or form to the compound; they are also named vehicles.

As excipients of intra-articular viscosupplementations, Sodium chloride and Sodium phosphate irrigate the joint and are both proven to be nontoxic and nonirritant. Sodium phosphate is often in the form of Sodium phosphate dibasic anhydrous & sodium phosphate monobasic monohydrate.

Hyaluronic acid is a viscous ingredient widely use in cosmetic products and medical devices, thanks to its safety and tolerability. Regarding interactions with other drugs or products, no one is known between HA viscosupplementations and products commonly used for osteoarthritis, such as oral drugs, supplements or corticosteroid/PRP injections.

Furthermore, HA-based intra-articular viscosupplementations are safe and highly tolerable, as proved by clinical data commented below and in Section 7.2.1 and 7.2.2 of this Clinical Evaluation report.

"Hyaluronic acid sodium salt, viscosuppletive joint device" is indicated to restore the physiological and rheological properties of arthritic joints and tendon sheath in case of pain or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations. It is to be used in small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint), large joints and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

It acts as a substitute for synovial fluid, allowing the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, "Hyaluronic acid sodium salt, viscosuppletive joint device" reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action.

In 2008, the Osteoarthritis Research Society International (OARSI) cited intra-articular hyaluronic acid as a useful therapeutic modality, which has delayed onset, but prolonged duration of symptomatic benefit, in treating patients with osteoarthritis of

the knee or hip [133]. In addition, although marketed as analgesics, viscosupplements have been postulated to have potential chondroprotective effects as well [134].

Hyaluronic acid, also known as hyaluronan or hyaluronate, is a high-molecular-weight glycosaminoglycan made up of repeating disaccharide units of N-acetylglucosamine and glucoronic acid [135]. The average molecular weight of synovial fluid HA is 5 to 7 × 10^6 Da. It is widely present in mammalian tissues and has the highest concentration in synovial fluid. Type B synoviocytes and fibroblasts synthesize HA and secrete it into the joint space. HA molecules occupy a large spheroidal space while in their fully hydrated state. Therefore, the viscoelasticity and flow characteristics of synovial fluid are intimately tied to its HA content [136,137].

HA provides important viscoelasticity and lubricating properties to synovial fluid, thereby reducing articular cartilage wear and acting as a lubricant during slow movements and as a shock absorber during rapid movements [135,136,137,138]. Furthermore, HA molecules restrict large plasma protein from entering into the synovial fluid while facilitating the passage of small molecules into the joint for maintenance of nutrition.

The normal adult knee contains approximately 2 mL of synovial fluid, with a HA concentration of 2.5 to 4.0 mg/mL. In the arthritic joint, the concentration and molecular weight of HA are decreased by 33% to 50% because the synthesis of HA in OA is disrupted by increased levels of pro-inflammatory cytokines, free radicals and proteinases [137,139]. These alterations lead to dramatically poorer viscous and elastic properties and, thus, distorted joint mechanics. Decreased lubrication leads to increased stress on the already diseased cartilage, which further disrupts the collagen network and the integrity of the chondral surface. The loss of barrier integrity also adversely affects cartilage nutrition and waste removal.

The goal of IA HA injections is to replenish the pathologically altered SF and to restore its normal viscoelastic properties, creating a sort of pad into the synovial cavity thanks to the viscosity of Hyaluronic acid [94]. HA temporarily restores the lubricating and shock-absorbing effects of SF. Moreover, several studies suggest that viscosupplements also have effects, such as protection against cartilage erosion [98,99], and promotion of intra-articular HA production.

The safety profile of HA viscosupplementation has been well established over its 20 years of clinical use. In fact, no viscosupplement product has been withdrawn because of safety concerns. Intra-articular HA is generally well tolerated with low incidence of local adverse events [140]. The overall incidence of adverse events has been reported to be approximately 1% to 4% per injection [145,146]. The most common adverse event is local reaction at the injection site, consisting of mild pain, swelling, or effusion, and warmth or redness, or both. Such injection site reactions are usually mild and self-limited, resolving with 1 to 3 days and generally respond to NSAIDs and local modalities. Other mild adverse effects that have been reported include post-injection itching, headaches, and calf pain [147]. Furthermore, the incidence of adverse events with

viscosupplementation is similar to that observed with other intra-articular procedures. The incidence of adverse events has been proved to being significantly related to the injection technique used: a medial approach to a partially bent knee was associated with 5.2% adverse events by injection, compared with 1.5% with straight lateral injections. Interestingly, injection laterally has also been shown to have a higher incidence of intra-articular injection accuracy when compared with injection into the flexed knee using conventional arthroscopic portal approaches [148]. Brockmeir and Schaffer [149] postulated that adverse reactions are related more closely to the accuracy of intra-articular injection than to the substance itself.

Although the cause of local adverse events associated with HA injection is not clear, these events are typically mild-to-moderate in nature, resolve spontaneously or after treatment of symptoms, and do not result in any longterm sequelae. Therefore, it is often difficult to clinically distinguish the symptoms of a reaction from the symptoms of osteoarthritis. Additionally, the types of usual local adverse events observed after viscosupplementation are not as potentially serious as the systemic adverse effects that may occur with NSAIDs or COX-2 inhibitors [150].

An important property of hyaluronic acid influencing its efficacy and safety is the molecular weight (MW). HA contained in the synovial fluid has a MW of 5 to 7 × 10^6 Da, classified as high molecular weight (HMW). High molecular weight hyaluronic acid (HMWHA) is considered more effective in relieving pain, compared to low molecular weight HA. This is due to the fact that HMWHA molecules are bigger than LMWHA: this property allows the compound to not penetrate the extracellular matrix and to concentrate in the joint cavity, leading to a higher lubrication and protection of the joint [103]. However, no conclusive theories have been confirmed regarding the correlation between molecular weight and efficacy [108-110].

"Hyaluronic acid sodium salt, viscosuppletive joint device" contains low molecular weight (LMW) Hyaluronic acid - 800-1200 kDa. However, results from large animal models of OA shows that low weight HAs are more effective than high molecular weight HAs in reducing synovial inflammation and for restoring the rheological properties of synovial fluid [117]. Also, several preclinical studies evaluating joint-structure modification in animal models of OA have reported advantages of using HAs of molecular weight in the low- to mid-range, as they can access diseased tissue more easily, suggesting potential for disease modification [118]. Furthermore, some studies show no difference in efficacy but an overall risk/benefit profile favouring lower molecular weight HAs [118-120].

Generally, both LMW and HMW HA are very well tolerated treatments. The most common adverse effect is mild, short-lived pain and inflammation at the injection site. Two meta-analyses assessed the frequency of adverse events vs. placebo and noted only a slight increase in the risk of mild adverse events (RR 1.19, 95% CI 1.01-1.41 and RR 1.08, 95% CI 1.01-1.15). However, there is some evidence to suggest a unique safety

concern for rare localized inflammatory reactions, pseudosepsis, granulomatous inflammation and severe acute inflammatory reactions (SAIR) with the cross-linked hyaluronic acid. Some clinical studies report pseudosepsis or severe acute inflammatory reactions (SAIR) and at least a few reporting granulomatous inflammation after the use of High Molecular weight HA [141].

In addition, Jüni *et al* (Citation 1) carried out a multicenter randomized controlled trial aimed to compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee. Patients were randomly assigned to receive 1 cycle of 3 intraarticular injections per knee of 1 of 3 preparations: a high molecular weight crosslinked hylan, a non–cross-linked medium molecular weight HA of avian origin, or a non–cross-linked low molecular weight HA of bacterial origin. No evidence for a difference in efficacy between hylan and HAs were found. In view of its higher costs and potential for more local adverse events, no rationale for the continued use of hylan in patients with knee OA has been found.

Another safety concern regarding Hyaluronic acid is its derivation. *"Hyaluronic acid sodium salt, viscosuppletive joint device"* contains biofermentative Hyaluronic acid, i.e. obtained from bacterial chains. The alternative is HA derived from animal tissues, especially chicken combs.

The former process, to be applied at industrial scale, was the extraction of hyaluronan from animal waste which is still an important technology for commercial products, but is hampered by several technical limitations. One drawback in the extraction process is the inevitable degradation of hyaluronan, caused by (a) the endogenous hyaluronidase activity in animal tissues, breaking down the polymer chain through enzymatic hydrolysis, and (b) the harsh conditions of extraction. Extraction protocols have been improved over the years, but still suffer from low yields, due to the intrinsic low concentration of hyaluronan in the tissue, and from high polydispersity of polymer products due to both the natural polydispersity of hyaluronan and to the uncontrolled degradation during extraction. As in any process for the production of therapeutic compounds from animal sources, there is a potential risk of contamination with proteins and viruses, but using tissues from healthy animals and extensive purification can minimize this. Nevertheless, concerns on viral (particularly avian) and protein (particularly bovine) contamination increased the interest in the biotechnological production of hyaluronan [114].

Since the hyaluronan polymer produced in animals and bacteria is identical, bacterial hyaluronan is not immunogenic and therefore is an excellent source for medical grade hyaluronan. Extracting hyaluronan from microbial fermentation broth is a relatively simple process with high yields. An additional and important advantage of microbial hyaluronan production is that microbial cells can be physiologically and/or metabolically adapted to produce more hyaluronan of high molecular weight. Therefore, microbial hyaluronan production using either pathogenic streptococci or safe recombinant hosts,

containing the necessary hyaluronan synthase, is nowadays more and more preferred [114].

Uebelhart *et al.* (Citation 4) reported that intra-articular injections of chemically modified cross-linked HA derivative of avian origin was associated with a higher incidence of adverse device reactions. Similar results were obtained from Romàn *et al* (Citation 5), who compared two HA-based viscosupplementations, one with HA obtained from bacterial fermentation and the other with avian HA. They reported that the former led to side effects almost twice as great than the latter.

The therapy with Hyaluronic acid-based viscosupplementation is likely to be prescribed more times, in order to enhance its effectiveness and to late surgical procedures such as total knee replacement. In a prospective open-label study, Waddell *et al.* [151] evaluated the efficacy and tolerability of a second course of HA for the treatment of osteoarthritic knee pain over a 12-month period in patients who previously experienced a beneficial initial course of therapy, reporting no adverse effects. Moreover, Raynauld *et al.* [152], in a randomized controlled trial also demonstrated the safety of repeat treatment with no evidence of higher incidence of local mild adverse events than with a first course of therapy. This safety profile of viscosupplementation is also supported in a recent meta-analysis by Pagnano *et al* [153].

8.3.2 *Safety results of clinical supportive data analysed*

Gydek *et al.* (Citation 2) evaluated the clinical outcomes of the intra-articular administration of HA-based viscosupplementations. According to results, the product demonstrated to be highly tolerable in the treatment of knee osteoarthritis.

Petrella *et al.* (Citation 3) reported results of a prospective, naturalistic, cohort clinical study aimed to evaluate long-term outcomes of intra-articular HA viscosupplementations, in case of repeated injections. Patients received a three–intraarticular injection series (10 mg/ml, 2-ml injection) over 3 weeks. Patients were instructed to return for consideration of repeat injection series based on their perception of pain restricting daily activity and a resumption of severity similar to their initial presentation. Results proved that therapy was highly satisfactory to patients and was associated with very few local adverse events and limited use of concomitant therapeutic modalities.

Mathies *et al.* (Citation 7) carried out an open, pilot, phase III study aimed to evaluate efficacy of an intra-articular HA viscosupplementation for quality of life and delaying surgery in patients for total knee replacement. According to results, the product was safe and effective, improving symptoms, quality of life and the viscous and elastic modulus of the synovial fluid of the knee.

Hyaluronic acid viscosupplementations are nowadays widely used and preferred to systemic therapies and medicinal intra-articular injections, as proven by several clinical trials [124-130].

In addition, Monfort *et al. (*Citation 9) carried out a single-center, randomized controlled study aimed to determine the efficacy and safety of intra-articular injections of low molecular weight HA into the osteoarthritic thumb CMC joint in comparison with corticoid injections. Eighty-eight evaluable patients diagnosed with osteoarthritis of the thumb (Kellgren-Lawrencegrade II-III) received ultrasound-guided intra-articular treatment with hyaluronic acid (48) or betamethasone (40). Results reported that both hyaluronic acid and betamethasone were effective and well-tolerated for the management of rhizarthrosis. Hyaluronic acid was more effective over time and more efficiently improved functionality and pain in patients with more severe symptoms.

Hyaluronic acid was also compared to exercise therapy, which could improve joint mobility despite of pain due to reduced lubrication of ostaoparthritic joints. Karatosun *et al.* (Citation 10) determined whether hyaluronic acid (HA) or exercise therapy could improve functional parameters in patients with osteoarthritis (OA) of the ankle. Patients receive three intra-articular HA injections, with one-week interval of or exercise therapy for six weeks. Results confirmed that, both HA injections and exercise therapy provide functional improvement.

As previously explained, an important property of hyaluronic acid influencing its efficacy and safety is the molecular weight (MW). HA contained in the synovial fluid has a MW of 5 to 7 × 10^6 Da, classified as high molecular weight (HMW). High molecular weight hyaluronic acid (HMWHA) is considered more effective in relieving pain, compared to low molecular weight HA. This is due to the fact that HMWHA molecules are bigger than LMWHA: this property allows the compound to not penetrate the extracellular matrix and to concentrate in the joint cavity, leading to a higher lubrication and protection of the joint [103].

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In addition, Jüni *et al* (Citation 1) carried out a multicenter randomized controlled trial aimed to compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee. Patients were randomly assigned to receive 1 cycle of 3 intraarticular injections per knee of 1 of 3 preparations: a high molecular weight crosslinked hylan, a non–cross-linked medium molecular weight HA of avian origin, or a non–cross-linked low molecular weight HA of bacterial origin. No evidence for a difference in efficacy between hylan and HAs were found. In view of its higher costs and potential for more local adverse events, no rationale for the continued use of hylan in patients with knee OA has been found.

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Uebelhart *et al.* (Citation 4) reported that intra-articular injections of chemically modified cross-linked HA derivative of avian origin was associated with a higher incidence of adverse device reactions. Similar results were obtained from Romàn *et al* (Citation 5), who compared two HA-based viscosupplementations, one with HA obtained from bacterial fermentation and the other with avian HA. They reported that the former led to side effects almost twice as great than the latter.

Other clinical studies commented in this Clinical Evaluation report supported the safety of *"Hyaluronic acid sodium salt, viscosuppletive joint device".*

Van Den Bekerom *et al.* (Citation 6) carried out a prospective clinical study comparing three different hyaluronate formulations and evaluating functionality, time of satisfactory pain relief and also the delay in performing a total hip arthroplasty. Results reported that there was no significant difference in duration of the effect of the first infiltration between the three groups. The positive effect was still ongoing at the end point of the study in 46 hips: 51% of the patients did not undergo total hip arthroplasty, 3 years after viscosupplementation.

Blanco *et al*. (Citation 8) reported results of a prospective, single-center, double-blind, randomized, placebo-controlled, pilot clinical trial aimed to determine whether hyaluronan (HA) delays and/or reduces the knee replacement surgery (KRS) in patients with osteoarthritis. Results proved that the use of intra-articular HA to treat OA patients on the waiting list for KRS does not delay surgery. However, it could improve the physical condition of patients while they are waiting by surgery.

Karatosun *et al.* (Citation 10) carried out a prospective clinical study comparing hyaluronic acid (HA) and exercise therapy for the improvement of functional parameters in patients with osteoarthritis (OA) of the ankle. 77 patients were randomized into two groups. The HA group received three injections of hyaluronic at 1-week intervals by the same physician. The dose of the HA was 2.5 mg in each injection. Throughout the study

no complications due to HA injection, such as pain, effusion, synovitis, haemarthrosis or septic arthritis were recorded.

Tang *et al.* (Citation 11) reported results of a single-group repeated measures study aimed to examine the kinetic features in patients with knee osteoarthritis (OA) after intra-articular hyaluronic acid (IAHA) injections in different time periods. This study revealed that IAHA injections could provide significant pain relief and improvement in activity of daily living function for patients with knee OA. However, the reduction in pain and the increase in knee adduction moment may last up to 6 months. This may cause excessive loading on the knee joints, which may further accelerate the rate of knee degeneration.

Eyigör *et al.* (Citation 12) evaluated intraarticular injection of HA through a lateral approach under fluoroscopic control for advanced hip OA. Patients enrolled received 2.5 ml HA injection once a week for 3 weeks by lateral approach under fluoroscopic control. This study proved thtat intraarticular HA injection through a lateral approach under fluoroscopic control was shown to be a safe and effective method for patients with advanced hip OA.

Finally, the prospective randomized clinical study of Petrella (Citation 13) aimed to determine the efficacy and safety of peri-articular hyaluronic acid injections in chronic lateral epicondylosis (tennis elbow). Three hundred and thirty one consecutive competitive racquette sport athletes with chronic (>3 months) lateral epicondylosis were administered 2 injections (first injection at baseline) into the subcutaneous tissue and muscle 1 cm from the lateral epicondyle toward the primary point of pain using a two-dimensional fanning technique. A second injection was administered 1 week later. According to results, peri-articular HA treatment for tennis elbow was significantly better than control in improving pain at rest and after maximal grip testing. Further, HA treatment was highly satisfactory by patients and physicians and resulted in better return to pain free sport compared to control.

8.3.3 *Summary of "Hyaluronic acid sodium salt, viscosuppletive joint device" preclinical studies' results*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended to be injected into the joint cavity and to get in contact with the intra-articular synovial fluid, cartilage and tendons. Therefore, this interaction is required to be safe. The pre-clinical studies have been carried-out on 2% Hyaluronic acid, which is the highest HA concentration contained in "*Hyaluronic acid sodium salt, viscosuppletive joint device"* products. The other two ingredients, sodium chloride and calcium phosphate, are used as excipients and have a favourable safety profile.

Pre-clinical studies carried out aimed to prove the product cytotoxicity, systemic toxicity, hypersensitivity, intracutaneous reactivity and subcutaneous implantation toxicity. Biocompatibility tests concluded that the medical device is noncytotoxic, non sensitizing,

non-irritant, without systemic toxicity and with no adverse effects due to the intra-articular injection ("implantation") of HA.

The non-sensitizing power of the product is due also to the absence of preservatives, which represents one of the main causes of allergic reaction after the use of cosmetic products or medical devices in contact with human skin and mucosas.

For further details, please refer to paragraph 4.4 ("Preclinical studies carried out on "*Hyaluronic acid sodium salt, viscosuppletive joint device*") and paragraph 8.7 ("Adequacy of preclinical testing").

8.3.4 *Medical device interactions with other substances/treatments*

Another critical point is the use of "*Hyaluronic acid sodium salt, viscosuppletive joint device*" with other concomitant therapies.

Hyaluronic acid is a compound commonly combined with other ingredients, thanks to its water binding and moisturizing properties; moreover, it is used as a vehicle for the local delivery of compounds, allowing avoiding systemic therapies. No particular side effects deriving from the combined use of HA with active ingredients have been identified in literature during this clinical evaluation, due to the established safety and biocompatibilty of Hyaluronic acid. This compound is a key ingredient of ophthalmic, nasal, pulmonary, parenteral and topical products, and no safety concern has commonly been highlighted.

However, the Manufacturer has identified a harmful interaction between Hyaluronic acid and quaternary ammonium salts or chlorhexidine, commonly contained into disinfectants used for skin preparation before injections. The product leaflet states *"Do not concomitantly use disinfectants containing quaternary ammonium salts or chlorhexidine for skin preparation as hyaluronic acid can precipitate in their presence".*

No sufficient data have been found in literature with regard to the use of HA-based viscosupplementations during pregnancy or breastfeeding. Commonly, HA is not recommended to pregnant women, lactating women, and children under 18, because the safety and effectiveness have not been established.
However, no contraindications regarding pregnant or breastfeeding women have been specified on the product leaflet. This is due to the fact that "*Hyaluronic acid sodium salt, viscosuppletive joint device*" is indicated to be sold by medical prescription only and to be administered only by a healthcare professional, who may exclude these classes of patients from the target population of the device.

8.3.5 *Medical device posology justification*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is packaged in a pre-filled syringe of different sizes and HA concentrations: 8 mg/1ml (0.8% HA), 16 mg/2 ml (0.8% HA), 20 mg/2 ml (1% HA), 32 mg/2 ml (1.6% HA) and 50 mg/2.5 ml (2% HA). It is designed as a single-use sterile medical device.

No particual safety concern regarding accidental wrong use of the product are expected, since "*Hyaluronic acid sodium salt, viscosuppletive joint device*" is intended to be sold only by medical prescription and to be administered only by a doctor, as written in the product leaflet:

"To be sold on medical prescription only. The intra-articular injection may only be administered by a doctor".

This may limit situations in which the device would be used wrongly or out of its intended use.

"Hyaluronic acid sodium salt, viscosuppletive joint device" is contained in a pre-filled syringe indicated to be completely emptied into the joint cavity. Posology changes according to the concentration of HA contained:

- 1,0%: 3-5 injections, each administered one week apart, cause a reduction in pain and swelling in addition to an improvement in function, which can continue for up to 24 weeks.
- 0,8% (1 ml solution): 2-3 injections per year; there should be an interval of at least 4-6 months between injections according to physician's advise.
- 0,8% (2 ml): 3-5 injections, each administered one week apart, cause a reduction in pain and swelling in addition to an improvement in function, which can continue for up to 24 weeks.
- 1,6%: Injections at weekly intervals for a total of 3 weeks. If necessary, further injections may be administered. It is the doctor's responsibility to evaluate the appropriateness of repeating the cycle of treatment and its frequency for each patient, taking into consideration the risk/benefit ratio of the treatment in each case.
- 2,0%: The medical device should be injected only once per cycle of treatment. If necessary, further injections may be administered. It is the doctor's responsibility to evaluate the appropriateness of repeating the cycle of treatment and its frequency for each patient, taking into consideration the risk/benefit ratio of the treatment in each case.

The posology is the same of some of the medical devices identified in the Clinical Evaluation Plan. In particular, the standard treatment protocol consists of at least three injections, commonly one week apart.

The recommended posology of the three medical devices equivalent to *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is the following:

Adant®: *"As a general rule, an intra-articular injection once a week for 3 to 5 consecutive weeks is recommended."*

Ostenil®: *"Depending on the size of the joint inject 2ml or less of Ostenil® into the joint cavity once a week for 3 to 5 injections. Several joints may be treated at the same time. Repeated treatment cycles may be administered as required."*

Suplasyn®: *"The recommended schedule for Suplasyn® supplied in a 2ml syringe is 1 injection per week for 3 weeks, but up to 6 may be given depending on patient's condition."*

In addition, all the other medical devices described in the Clinical Evaluation Plan and considered nonequivalent to *"Hyaluronic acid sodium salt, viscosuppletive joint device*" have a similar posology, i.e. from 3 to 5 injections to be administered once a week.

The precise posology is to be decided by the clinician, depending on the type of joint and the severity of osteoarthritis/tendinopathy. However, this dosage may be justified also by the mechanism of action of Hyaluronic acid into the joint cavity. In particular, higher the HA concentration, higher the product viscosity, more consistent the replenishment of the intra-articular synovial fluid and the duration of HA shock-absorbing and lubricant effects. This leads to the need of a lower dosage, since the efficacy of Hyaluronic acid is more durable. This is the reason why, for some high-concentration HA viscosupplementations, one injection is sufficient to reach the expected efficacy. In contrast, the molecular weight of hyaluronic acid seems to not be significant for the posology of intra-articular viscosupplementations [142,143].

Furthermore, in all clinical studies found in literature dealing with HA-based viscosupplementations, effective and safe intra-articular injections are performed weekly within 3 to 5-week treatment courses (Citation 1 to 13, 104-107).

8.3.6 *Relevant safety features*

Absence of preservatives substances

"Hyaluronic acid sodium salt, viscosuppletive joint device" does not contain preservatives, i.e. compounds intended to prevent decomposition by microbial growth or by undesirable chemical changes. These substances may cause sensitizing or irritation reactions to some people.

The absence of preservatives in *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is justified since the device is sterilized and contained in a sterile syringe.

However, the damaged packaging or the reuse of the product may lead to a risk of contamination of the device. The leaflet states: "

- *Do not use the device if the packaging is open or damaged.*
- *Do not reuse to avoid any risk of contamination."*

Absence of perfumes

"Hyaluronic acid sodium salt, viscosuppletive joint device" does not contain fragrances, i.e. compounds that, such as preservatives, may cause sensitizing or irritation in some people.

HA molecular weight

"Hyaluronic acid sodium salt, viscosuppletive joint device" contains low molecular weight (LMW) Hyaluronic acid - 800-1200 kDa. However, results from large animal models of OA shows that low weight HAs are more effective than high molecular weight HAs in reducing synovial inflammation and for restoring the rheological properties of synovial fluid [117]. Also, several preclinical studies evaluating joint-structure modification in animal models of OA have reported advantages of using HAs of molecular weight in the low- to mid-range, as they can access diseased tissue more easily, suggesting potential for disease modification [118]. Furthermore, some studies show no difference in efficacy but an overall risk/benefit profile favouring lower molecular weight HAs [118-120].

Generally, both LMW and HMW HA are very well tolerated treatments. The most common adverse effect is mild, short-lived pain and inflammation at the injection site. Two meta-analyses assessed the frequency of adverse events vs. placebo and noted only a slight increase in the risk of mild adverse events (RR 1.19, 95% CI 1.01-1.41 and RR 1.08, 95% CI 1.01-1.15). However, there is some evidence to suggest a unique safety concern for rare localized inflammatory reactions, pseudosepsis, granulomatous inflammation and severe acute inflammatory reactions (SAIR) with the cross-linked hyaluronic acid. Some clinical studies report pseudosepsis or severe acute inflammatory reactions (SAIR) and at least a few reporting granulomatous inflammation after the use of High Molecular weight HA [141].

Exogenous HA derivation

Another safety concern regarding Hyaluronic acid is its derivation. *"Hyaluronic acid sodium salt, viscosuppletive joint device"* contains biofermentative Hyaluronic acid, i.e. obtained from bacterial chains. The alternative is HA derived from animal tissues, especially chicken combs.

In the first case, Hyaluronan is exctracted from animal waste. It is still an important technology for commercial products, but is hampered by several technical limitations. However, one drawback in the extraction process is the inevitable degradation of hyaluronan, caused by (a) the endogenous hyaluronidase activity in animal tissues,

breaking down the polymer chain through enzymatic hydrolysis, and (b) the harsh conditions of extraction. [114].

Bacterial hyaluronan is not immunogenic and therefore is considered an excellent source for medical grade hyaluronan. Extracting hyaluronan from microbial fermentation broth is a relatively simple process with high yields. An additional and important advantage of microbial hyaluronan production is that microbial cells can be physiologically and/or metabolically adapted to produce more hyaluronan of high molecular weight. Therefore, microbial hyaluronan production using either pathogenic streptococci or safe recombinant hosts is nowadays more preferred [114].

8.3.7 *Risk analysis outcomes*

The results of the risk analysis of "*Hyaluronic acid sodium salt, viscosuppletive joint device*" lead to consider the residual risk acceptable for each hazard identified. The overall residual risk has been judged as acceptable by the Risk Management Team, as reported in the risk management report for "*Hyaluronic acid sodium salt, viscosuppletive joint device*". More precisely, no unacceptable risks related to the use of the medical device were detected.

8.3.8 *Post-market information about similar/predicate devices*

No recall of fully equivalent or partially equivalent medical devices has been retrieved on MoH; FDA and MHRA medical devices recall databases.

Information regarding Post-Market Surveillance of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* and equivalent devices can be found in **Appendix 9**.

8.4 *SUMMARY OF CONFORMITY ASSESSMENT WITH REQUIREMENT ON PERFORMANCE (MDD ER3)*

According to Directive 93/42/EEC Essential requirements (Annex I), 3:

The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a), as specified by the manufacturer.

8.4.1 *Medical device overview and general features*

The medical device *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" is an intra-articular visco-supplementation product, which allows restoring the physiological and rheological properties of arthritic joints and tendon sheath.

"*Hyaluronic acid sodium salt, viscosuppletive joint device*" contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid, to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in "*Hyaluronic acid sodium salt, viscosuppletive joint device*" is obtained by fermentation and has not undergone chemical change processes.

It is a substitute for synovial fluid that allows the re-establishment of the physiological and rheological properties of joints affected by arthrosis. By naturally re-establishing the viscoelastic properties of the synovial fluid, "*Hyaluronic acid sodium salt, viscosuppletive joint device*" reduces the pain quickly and re-establishes joint and tendinous mobility acting only at the level of the joint into which it is injected, without exercising any systemic action.

The other components of "*Hyaluronic acid sodium salt, viscosuppletive joint device*" are: sodium chloride, sodium phosphate and water for injectable preparations. Sodium chloride and sodium phosphate are used as excipients, i.e. vehicles that irrigate the joint cavity.

8.4.2 *Specific physico-chemical requirements for HA-based intra-articular viscosupplementations*

Intra-articular viscosupplementations are a non-pharmacological approach for the management of osteoarthritis symptoms. They consist of injection of exogenous hyaluronic acid into diarthrodial joints, with the aim of restoring the rheological properties of the synovial fluid, thereby producing mechanical and chondroprotective effects.

The structural benefit of viscosupplementation has been seen through second-look arthroscopy, performed one year after treatment started, in which the joint surface was seen to have a better visual appearance, compared with a placebo group [154].

Increased cartilage volume was observed by means of imaging examinations; and biopsies performed before and after viscosupplementation showed that, six months later, the surface layer had been reconstituted, with better matrix quality, higher chondrocyte density and greater numbers of organelles inside [155]. Diminished loss of joint space was observed one year after the procedure, also in comparison with the placebo group [156].

Hyaluronic acid is a high-viscosity polysaccharide that is produced naturally by the B-cells of the synovial membrane. From a biochemical point of view, it is classified in the glycosaminoglycan (GAG) group. It is a component of the synovial fluid, enhancing viscosity and elastic nature of SF. SF with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements [92]. Moreover, several studies suggest that viscosupplements also have effects, such as protection against cartilage erosion [98,99], and promotion of intra-articular HA production [97,99,100,102].

The mechanism of action of Hyaluronic acid contained in "*Hyaluronic acid sodium salt, viscosuppletive joint device*" is mechanical: it promotes better force distribution, diminishes the pressure due to weight and recovers the rheological properties of the synovial fluid. In particular, it creates a sort of pad improving the shock-absorbing and lubricating properties of the synovial fluid, which are decreased due to osteoarthritis, and enhancing joint and limb mobility.

Physico-chemical properties of Hyaluronic acid are mainly determined by its molecular weight.

Native HA of synovial fluid has a high molecular weight ($4*10^6$ Da) and a concentration of about 0.35 g/100 ml. At present, preparations with different molecular weight are available (Low and High Molecular Weight). Some clinical study were carried out to compare clinical outcomes of low and high molecular weight; in some of them, high molecular weight hyaluronic acid (HMWHA) is considered more effective in relieving pain, compared to low molecular weight HA, since it is composed of bigger mulecules. Therefore, it does not penetrate the extracellular matrix, but it concentrate in the joint cavity, leading to a higher lubrication and protection of the joint [103]. However, no conclusive theories have been confirmed regarding the correlation between molecular weight and efficacy [108-110]. Some studies shows that low weight HAs are more effective than high molecular weight HAs in restoring the rheological properties of synovial fluid [117]. Also, several preclinical studies evaluating joint-structure modification in animal models of OA have reported advantages of using HAs of molecular weight in the low- to mid-range, as they can access diseased tissue more easily, suggesting potential for disease modification [118].

A large number of different studies explored the effect of the high versus low molecular weight preparations of HA. In a randomized, controlled, blinded study, Karlsson *et al.*

[157] evaluated 3 parallel cohorts of patients with knee osteoarthritis. The patients in each group received 1 of 3 treatments: 3-weekly injections of low molecular weight HA, 3-weekly injections of high molecular weight HA, or placebo. No significant differences were noted between those treated with low or high molecular weight preparations. Kotevoglu *et al* also examined the efficacy of different molecular weight preparations. Their 6-month follow-up data revealed no statistically significant difference in clinical efficacy between the preparations.

Finally, in a 2005 review, Goldberg and Buckwalter [10] stated that, to date, no substantive clinical evidence has been put forth to suggest that differences in the molecular weight of currently available viscosupplements have any impact on clinical efficacy.

Through the years there has been considerable diversity in the outcomes between many of these trials. Previous data had suggested that the higher-molecular-weight products had a greater efficiency, especially in pain relief, but recent studies indicated that the pool ed effect size of higher molecular weights were not more effective in relieving pain. Furthermore, the data suggested that pain reduction diminished with time and was no longer significant after 14 weeks [11-13].

Molecular weight of Hyaluronic acid is related also to its derivation. Exogenous hyaluronic acid is produced from two sources: avian origin, i.e. from poultry material (cock crest). This presents allergenic potential due to avian antigens; non-avian origin, i.e. bio-fermentation obtained from fermentation of bacteria (*Streptococcus zooepidermicus*). These have lower allergenic potential [144].

In addition, in relation to hyaluronic acid synthesis, these substances can be classified into two types: hyaluronans, composed of long-chain molecules of avian or biofermentation origin, with a molecular weight of between 0.5 and 1.8 x 10^6 Da; hylan, i.e. hyaluronan molecule chemically modified by means of cross-links, with a liquid phase of higher molecular weight (around 6x10^6 Da), through crosslinking connections between long chains of hyaluronan, and a solid portion (of infinite molecular weight) formed by even greater presence of links [144].

8.4.3 *Performance data from pivotal studies*

The multicenter randomized controlled clinical study carried out by Jüni *et al.* (Citation 1) aimed to compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee. Patients were randomly assigned to receive 1 cycle of 3 intraarticular injections per knee of 1 of 3 preparations: a high molecular weight crosslinked hylan, a non–cross-linked medium molecular weight HA of avian origin, or a non–cross-linked low molecular weight HA of bacterial origin. No evidence for a difference in efficacy between hylan and HAs were found. In view of its higher costs and potential for more local adverse events, no rationale for the continued use of hylan in patients with knee OA was seen.

The observational clinical study performed by Gydek *et al.* (Citation 2) evaluated the clinical outcomes of the intra-articular administration of HA-based viscosupplementations. Each patient received a mean of three intra-articular injections of 20 mg of sterile hyaluronic acid and followed for a 30-day period. During the study, measures of intensity of symptoms were checked before and after treatment, including pain at rest and pain during walking (using VAS score). Changes in pain intensity (basic scored characteristic for OA degree) and symptoms like morning stiffness, after rest stiffness, pain after ascending stairs and walking on the surface level were evaluated. According to results, the product demonstrated high efficacy and good to-lerance in the treatment of knee osteoarthritis.

The prospective, naturalistic, cohort clinical study carried out by Petrella (Citation 3) aimed to evaluate long-term outcomes of intra-articular HA viscosupplementations, in case of repeated injections. Patients received a three intra-articular injection series with 10 mg/ml, 2-ml HA solution over 3 weeks. Patients were instructed to return for consideration of repeat injection series based on their perception of pain restricting daily activity and a resumption of severity similar to their initial presentation. Results proved that Intraarticular hyaluronic acid injections were highly effective in improving resting and walking pain in patients with osteoarthritis of the knee on a first and a second treatment series. Duration of symptom control was about 6 months, and the therapy was highly satisfactory to patients.

Uebelhart *et al.* (Citation 4) carried out a retrospective study aimed to compare two HA viscosupplementations of low and high molecular weight for the treatment of osteoarthritis. Results indicated that the product containing a natural, non-chemically modified HA of fermentative origin, is a safe and effective therapy for knee OA, as much as the injection of chemically modified cross-linked HA derivative of avian origin.

Romàn *et al* (Citation 5) compared two low- and high- molecular weight HA-based viscosupplementations in a blind randomized clinical study. Results showed that the efficacy with the LMWHA product at 3 months after treatment was greater than with the HMWHA device (50% versus 21.1%). The maximum improvement with hyaluronic acid was seen at 5 weeks in 75.4%.

Van Den Bekerom *et al.* (Citation 6) carried out a prospective clinical study comparing three different hyaluronate formulations and evaluating functionality, time of satisfactory pain relief and also the delay in performing a total hip arthroplasty. One hundred and twenty patients (126 hips) received viscosupplementation with one of the three hyaluronate formulations. All patients were candidate for surgical treatment with a total hip arthroplasty. Results reported that there was no significant difference in duration of the effect of the first infiltration between the three groups. The positive effect was still ongoing at the end point of the study in 46 hips: 51% of the patients did not undergo total hip arthroplasty, 3 years after viscosupplementation.

Mathies *et al.* (Citation 7) evaluated the efficacy of an intra-articular HA viscosupplementation for quality of life and delaying surgery in patients for total knee replacement in an open, pilot, phase III clinical study. According to results, the HA

viscosupplementation evaluated was safe and effective, improving symptoms, quality of life and the viscous and elastic modulus of the synovial fluid of the knee.

Similar results were obtained by Blanco et al. (Citation 8) with a prospective, single-center, double-blind, randomized, placebo-controlled, pilot clinical trial aimed to determine whether hyaluronan (HA) delays and/or reduces the knee replacement surgery (KRS) in patients with osteoarthritis. The intra-articular treatments (HA or placebo) consisted of two cycles of five weekly injections with a 24-week interval between each cycle. Results proved that the use of intra-articular HA to treat OA patients on the waiting list for KRS does not delay surgery. However, it could improve the physical condition of patients while they are waiting by surgery.

Monfort *et al.* (Citation), instead, compared HA-based viscosupplementations and corticoid injections in a single-center, randomized, controlled study. Eighty-eight evaluable patients diagnosed with osteoarthritis of the thumb (Kellgren-Lawrencegrade II-III) received ultrasound-guided intra-articular treatment with hyaluronic acid (48) or betametha-sone (40). Results reported that both hyaluronic acid and betamethasone were effective for the management of rhizarthrosis. Hyaluronic acid was more effective over time and more efficiently improvedfunctionality and pain in patients with more severe symptoms.

8.4.4 *Performance data from indirect supportive articles*

Karatosun *et al.* (Citation 10) carried out a prospective clinical study comparing hyaluronic acid (HA) and exercise therapy for the improvement of functional parameters in patients with osteoarthritis (OA) of the ankle. 77 patients were randomized into two groups. The HA group received three injections of hyaluronic at 1-week intervals by the same physician. The dose of the HA was 2.5 mg in each injection. Results confirmed that both HA injections and exercise therapy provide functional improvement.

Tang *et al.* (Citation 11) reported results of a single-group repeated measures study aimed to examine the kinetic features in patients with knee osteoarthritis (OA) after intra-articular hyaluronic acid (IAHA) injections in different time periods. This study revealed that IAHA injections could provide significant pain relief and improvement in activity of daily living function for patients with knee OA. However, the reduction in pain and the increase in knee adduction moment may last up to 6 months. This may cause excessive loading on the knee joints, which may further accelerate the rate of knee degeneration.

Eyigör *et al.* (Citation 12) evaluated intraarticular injection of HA through a lateral approach under fluoroscopic control for advanced hip OA. Patients enrolled received 2.5 ml HA injection once a week for 3 weeks by lateral approach under fluoroscopic control. This study proved thtat intraarticular HA injection through a lateral approach under fluoroscopic control was shown to be a safe and effective method for patients with advanced hip OA.

Finally, the prospective randomized clinical study carried out by Petrella (Citation 13) aimed to determine the efficacy and safety of peri-articular hyaluronic acid injections in chronic lateral epicondylosis (tennis elbow). Three hundred and thirty one consecutive competitive racquette sport athletes with chronic (>3 months) lateral epicondylosis were administered 2 injections (first injection at baseline) into the subcutaneous tissue and muscle 1 cm from the lateral epicondyle toward the primary point of pain using a two-dimensional fanning technique. A second injection was administered 1 week later. According to results, peri-articular HA treatment for tennis elbow was significantly better than control in improving pain at rest and after maximal grip testing. Further, HA treatment was highly satisfactory by patients and physicians and resulted in better return to pain free sport compared to control.

8.5 *SUMMARY OF CONFORMITY ASSESSMENT WITH REQUIREMENT ON ACCEPTABILITY OF UNDESIRABLE SIDE-EFFECTS (MDD ER6)*

According to Directive 93/42/EEC Essential requirements (Annex I), 6:

Any undesirable side effect must constitute an acceptable risk when weighed against the performances intended.

There are no undesirable side effects expected deriving from the instillation of "*Hyaluronic acid sodium salt, viscosuppletive joint device"*, according to its indications, target population and mode of use as described on product's leaflet. Hazards leading to harm to the user/patients due to various causes will be covered by the risk analysis, for example use in case of known or suspected hypersensitivity, use of the product after the expiry date, etc.

There are no particular concerns about the use of the device, since *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is intended to be administered by a doctor and to be sold by medical prescription only. In addition, no training is necessary due to the easiness of use of the device. Therefore, risks related to the improper use of "*Hyaluronic acid sodium salt, viscosuppletive joint device"* may be reasonably considered negligible.

However, the product leaflet specifies: *"*

- *The injection site must be on healthy skin.*
- *Do not inject intravenously. Do not inject outside the joint cavity, into the synovial tissue or into the articular capsule.*
- *Do not administer the device in the presence of heavy intra-articular effusion."*

Some adverse events (no SAEs) occurred during the studies described. In the majority of the cases, these events were not related to the test product. No clinical data from literature describe particular side effects or severe adverse events that may derive from a Hyaluronic acid-based intra-articular viscosupplementation for the relief from pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations.

8.6 *SUMMARY OF CONFORMITY ASSESSMENT WITH REQUIREMENT ON ACCEPTABLE BENEFIT/RISK PROFILE (MDD ER1)*

The information material supplied by the manufacturer has been reviewed. The description provided by the manufacturer correctly and precisely identifies the medical conditions for which *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is intended to be used.

To date no clinical investigation has been performed with *"Hyaluronic acid sodium salt, viscosuppletive joint device"*, according with EN ISO 14155:2011 (Clinical investigation of medical devices for human subjects – Good clinical practice). So, the clinical evaluation of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is based exclusively on literature route.

All risks addressed in the risk analysis are within an acceptable range or as far as possible. It is believed that the benefits deriving from the use of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* outweigh the risks.

Altogether, the clinical evaluation of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* results in a positive risk/benefit ratio for the application of the product after assessment of the risks and benefits with regard to its specific intended use, as discussed in the previous paragraphs (Section 8.3, 8.4, 8.5).

8.7 *ADEQUACY OF PRECLINICAL TESTING*

"Hyaluronic acid sodium salt, viscosuppletive joint device" is an invasive medical device according to Directive 93/42/EEC definition, since it is intended to be injected into the joint cavity through the joint skin. For permanent contact (> 24 h to 30 days) devices, ISO 10993-1 suggests the following tests: cytotoxicity, sensitization, irritation, systemic toxicity, subchronic toxicity and implantation.

The following biocompatibility studies have been conducted on *"Hyaluronic acid sodium salt, viscosuppletive joint device"*:

- *CYTOTOXICITY - Cytotoxicity for elution test [Report Ref. 2011/2200.A1] and bacterial endotoxins test (LAL test) [Report Ref. 2011/2200.A2];*
- *DELAYED HYPERSENSITIVITY TEST [Report Ref. 2012/363.A3];*
- *SYSTEMIC TOXICITY - Systemic toxicity test [Report Ref. 2011/2199.A1] and Pyrogen test [Report Ref. 2011/2199.A2];*
- *INTRACUTANEOUS REACTIVITY TEST [Report Ref. 2012/363.A1];*
- *SUBCUTANEOUS IMPLANTATION TEST ON HYALURONIC SODIUM SALT 2% [Report Ref. 2012/364.AMi];*
- *OCULAR IRRITATION TEST [Report Ref. 2012/363.A1];*
- *DELAYED HYPERSENSITIVITY TEST (GMPT) ON SYNOVIAL ONE [Report Ref. 2011/1394 SAM].*

Based on the results of biocompatibility studies, the product was judged as not cytotoxic, not sensitizing, not irritant, without systemic and implant toxicity.

8.8 *USABILITY*

The Risk Management Team did not prepare a specific Usability Report for *"Hyaluronic acid sodium salt, viscosuppletive joint device"* due to the fact that no critical usability-related risks were identified. Possible risks and related hazards resulting from non-correct use (improper or wrong use) of the medical device shall be taken into account in the Risk Management for "Hyaluronic acid sodium salt, viscosuppletive joint device". However, the device is intended to be administered only by a doctor; in addition, the use of the product dose not need training, according to the safety characteristics and the intended use of the medical device.

8.9 *CLAIMS CONFIRMATION*

A resuming table for claims confirmation is reported here below. Once the device leaflet and labeling will be finalized, the table below would be updated according to the claims highlighted by the manufacturer.

Claim	Evidence	Reference
"Hyaluronic acid sodium salt, viscosuppletive joint device" is intended for pains or reduced joints mobility due to degenerative diseases, post-traumatic diseases or joint and tendons alterations. It can also be used for visco-supplementation of small joints (all the joints of the wrist and hand, including the interphalangeal, intercarpal, metacarpal-phalangeal, carpo-metacarpal, distal radio-ulnar and the radio carpal joint, all the joints in the foot and the temporo-mandibular joint) and tendon sheath (e.g. in case of stenosing tenosynovitis/trigger finger).	Clinical evaluation based on literature route.	*Clinical Evaluation:* *CEP_ HA sodium salt Viscosuppletive joint device, Date: 03/03/2017; rev.01* *CER_HA sodium salt Viscosuppletive joint device, Date: 03/03/2017; rev.01*
"Hyaluronic acid sodium salt, viscosuppletive joint device" contains 0,8% or 1% or 1,6% or 2% of highly purified hyaluronic acid sodium salt with a molecular weight (800 – 1200 kDa). Hyaluronic acid sodium salt (hyaluronan) is formed by repetitive chains of disaccharide units of N-acetylglucosamine and sodium glucuronate. It is a fundamental component of synovial fluid,	Clinical evaluation based on literature route.	*Clinical Evaluation:* *CEP_ HA sodium salt Viscosuppletive joint device, Date: 03/03/2017; rev.01* *CER_HA sodium salt Viscosuppletive joint device, Date: 03/03/2017; rev.01*

to which it confers special viscoelastic properties. The hyaluronic acid sodium salt in "Hyaluronic acid sodium salt, viscosuppletive joint device" is obtained by fermentation and has not undergone chemical change processes. The other components of "Hyaluronic acid sodium salt, viscosuppletive joint device" are: sodium chloride, sodium phosphate and water for injectable preparations.		
"Hyaluronic acid sodium salt viscosuppletive joint device" is a substitute for synovial fluid, which allows the re-establishment of the physiological and rheological properties of joints affected by degenerative diseases, post-traumatic diseases or joint and tendons alterations (mechanical mode of action). The medical device acts only at the level of the joint into which it is injected, without exercising any systemic action.	Clinical evaluation based on literature route.	*Clinical Evaluation:* *CEP_ HA sodium salt Viscosuppletive joint device,* *Date: 03/03/2017; rev.01* *CER_HA sodium salt Viscosuppletive joint device,* *Date: 03/03/2017; rev.01*

Table 12. Confirmation of "Hyaluronic acid sodium salt, viscosuppletive joint device" claims.

9 CONCLUSIONS IN COMPLIANCE WITH THE ESSENTIAL REQUIREMENTS OF EC-DIRECTIVE

The information presented in this clinical evaluation indicates that *"Hyaluronic acid sodium salt, viscosuppletive joint device"* is equivalent to few products available on the market and partially equivalent to some products available on the market.

The Clinical Evaluation of *"Hyaluronic acid sodium salt, viscosuppletive joint device"* resulted in a positive benefit/risk ratio for the application of the product after assessment of the risks/benefit with regard to the intended use. In conclusion, a critical assessment of clinical experience and data collected from the literature supports that *"Hyaluronic acid sodium salt, viscosuppletive joint device"* safety and performance, in compliance with Essential Requirements and Annex X of EC-Directive 93/42/EEC as amended by 2007/47/EC and with the European guideline MEDDEV 2.7.1 of June 2016.

10 BIBLIOGRAPHY

[1]https://www.boundless.com/biology/textbooks/boundless-biology-textbook/the-Musculoskeletal-system-38/joints-and-skeletal-movement-217/classification-of-joints-on-the-basis-of-structure-and-function-820-12063/

[2] http://www.theodora.com/anatomy/classification_of_joints.html

[3] http://www.innerbody.com/image/skel16.html

[4] Levangie, Pamela K., and Cynthia C. Norkin. *Joint Structure and Function: A Comprehensive Analysis.* Philadelphia, PA: F.A. Davis Co, 2005.

[5] Moore K, Dalley AI: Clinically Oriented Anatomy, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 1999.

[6] Brinckmann P, Frobin W, Hierholzer E. Stress on the articular surface of the hip joint in healthy adults and persons with idiopathic osteoarthrosis of the hip joint. *Biomechanics* 1981; 14:149–156.

[7]Bullough P, Goodfellow J, O'Connor J. The relationship between degenerative changes and loadbearing in the human hip. *J Bone Joint Surg Br* 1973; 55:746–758.

[8] Marieb E, Hoehn K. Human Anatomy and Physiology, 7ed. 2007 Pearson Education, Inc.

[9] http://www.alpfmedical.info/power-doppler/synovial-cavity-and-articular-capsule.html

[10] Goldberg VM, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. *Osteoarthritis Cartilage.* 2005;13(3):215–224.

[11] Ghosh P. The role of hyaluronic acid (hyaluronan) in health and disease: interactions with cells, cartilage and components of synovial fluid. Clin Exper Rheumatol 1994;12(1):75–82.

[12] Bellamy N, Campbell J, Robinson V, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.2-CD005321,* 2006.

[13] Dougados M, Nguyen M, Listrat V, et al. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis Cartilage* 1993;l:97–103.

[14]http://www2.highlands.edu/academics/divisions/scipe/biology/faculty/harnden/2121/notes/art.htm

[15] Andres BM, Murrell GAC. Treatment of tendinopathy: what works, what does not and waht is on the horizon. *Clin Orthop Relat Res.* 2008 Jul; 466(7): 1539–1554

[16] https://www.ncbi.nlm.nih.gov/books/NBK333078/

[17] Arden N, Nevitt M. *Osteoarthritis: Epidemiology. Best Pract Res Clin Rheumatol.* 2006;20:3-25.

[19] Kellgren J, Moore R. *Generalized osteoarthritis and Heberden's nodes*. *Br Med J.* 1952;1:181-187.

[18] Cooper C, Snow S, McAlindon T, et al. Risk factors for the incidence and progression of radiographicknee osteoarthritis. *Arthritis Rheum.* 2000;43:995-1000.

[20] Lanyon P, Muir K, Doherty S, Doherty M. Assessment of a genetic contribution to osteoarthritis of the hip: sibling study. *BMJ.* 2000;321:1179-1183.

[21] Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, Zheng MH. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. *Arthritis Res Ther.* 2013; 15(6): 223.

[22] https://www.ncbi.nlm.nih.gov/books/NBK333078/

[23] http://austinpublishinggroup.com/physical-medicine/fulltext/pmr-v1-id1021.php

[24] https://www.ncbi.nlm.nih.gov/books/NBK333078/

[25]*Arthritis and Musculoskeletal Alliance. Standards of care for people with osteoarthritis.* London: ARMA; 2004. Available from: www.arma.uk.net

[26]https://www.esciencecentral.org/ebooks/osteoarthritis_therapeutics/pathophysiology-and-etiology-of-osteoarthritis.php

[27] *Osteoarthritis: Care and management in adults* (2014) National Clinical Guideline Centre - Clinical guideline Methods Commissioned by the National Institute for Health and Care Excellence-London.

[28] Maldonado M1, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. 2013.

[29] Evans CH. Advances in regenerative orthopedics. *Mayo Clin Proc* 2013;88:1323-1339.

[30] Chang H, Docheva D, Knothe UR, Melissa L, Knothe T. Arthritic Periosteal Tissue From Joint Replacement Surgery: A Novel, Autologous Source of Stem Cells. *Stem Cells Translational Medicine,* 2014;3: 308-317.

[31] Martin JA Buckwalter JA. Roles Of Articular Cartilage Aging And Chondrocyte Senescence In The Pathogenesis Of Osteoarthritis. *The Iowa Orthopaedic Journal* 2001;21:1-7.

[32] Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, *et al.* Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum* 2004;50: 1501-1510.

[33] Cross M, Smith E, Hoy D, Nolte S, Ackerman I *et al*. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323-1330.

[34] Sangha O. Epidemiology of rheumatic diseases. *Rheumatology* 2000;39(2):3-12.

[35] Huang K, Wu LD. Aggrecanase and aggrecan degradation in osteoarthritis: a review. *J Int Med Res* 2008;36: 1149-1160.

[36] Roelofs AJ, Rocke JP, De Bari C. Cell-based approaches to joint surface repair: a research perspective. *Osteoarthritis Cartilage* 2013;21: 892-900.

[37] Ruettger A, Schueler S, Mollenhauer JA, Wiederanders B. Cathepsins B, K, and L are regulated by a defined collagen type II peptide via activation of classical protein kinase C and p38 MAP kinase in articular chondrocytes. *J Biol Chem* 2008; 283: 1043-1051.

[38] Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. *Biomed Res Int* 2013: 284873.

[39] Osteoarthritis: Care and management in adults. National Clinical Guideline Centre - Clinical guideline Methods Commissioned by the National Institute for Health and Care Excellence-London 2014.

[40] Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. See comment in PubMed Commons below Biomed Res Int 2013: 284873.

[41] Huang K, Wu LD. Aggrecanase and aggrecan degradation in osteoarthritis: a review. See comment in PubMed Commons below J Int Med Res 2008;36: 1149-1160.

[42] Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. *Semin Arthritis Rheum* 2014;44: 145-154

[43] http://www.bupa.co.uk/health-information/directory/o/osteoarthritis

[44]http://www.bcmj.org/article/clinical-features-and-pathogenetic-mechanisms-osteo%C2%ADarthritis-hip-and-knee

[45] E. Yusuf, M.C. Kortekaas, I. Watt, et al. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70(1):60–67.

[46] N.J. Goddard, P.T. Gosling. Intra-articular fluid pressure and pain in osteoarthritis of the hip. *J Bone Joint Surg Br* 1988;70(1):52–55.

[47] R. Ike, K.S. O'Rourke. Compartment-directed physical examination of the knee can predict articular cartilage abnormalities disclosed by needle arthroscopy. Arthritis Rheum 1995;38(7):917–925.

[48] http://www.sciencedirect.com/science/article/pii/S0889857X12001196

[49] Evans CH. Advances in regenerative orthopedics. *Mayo Clin Proc* 2013;88:1323-1339.

[50] Mobasheri A, Kalamegam G, Musumeci G, Batt ME. Chondrocyte and mesenchymal stem cell-based therapies for cartilage repair in osteoarthritis and related orthopaedic conditions. *Maturitas* 2014;78: 188-198.

[51] http://emedicine.medscape.com/article/330487-clinical#b3

[52] http://www.sciencedirect.com/science/article/pii/S0889857X12001196

[53] http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-osteoarthritis

[54]Spector TD, MacGregor AJ .Risk factors for osteoarthritis: genetics. *Osteoarthritis Cartilage* 2004;12(A):39-44;

[55] Jones G. Sources of pain in osteoarthritis: implications for therapy. *Int J Clin Rheumatol*, 2013;8:335-45.

[56] Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. *Biomed Res Int* 2013: 284873.

[57] Zhang W, Doherty M, Peat G, *et al*. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Ann Rheum Dis*. 2010;69:483-489.

[58] Michael JW-P, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int. 2010;107:152-162; Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115-2126

[59] Cho HJ, Chang CB, Yoo JH, Kim SJ, Kim TK. Gender differences in the correlation between symptom and radiographic severity in patients with knee osteoarthritis. *Clin Orthop Relat Res.* 2010;468:1749-1758.

[60] Dieppe PA, Cushnaghan J, Shepstone L. The Bristol 'OA500' study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. *Osteoarthritis Cartilage.* 1997;5:87-97.

[61] http://www.arthritis.org/about-arthritis/types/osteoarthritis/diagnosing.php

[62] http://www.aafp.org/afp/2012/0101/p49.html

[63] Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. *BMJ.* 2002;325(7367):752.

[64] Rutjes AW, Nüesch E, Sterchi R, Jüni P. Therapeutic ultrasound for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2010(1):CD003132.

[65]http://www.mayoclinic.org/diseases-conditions/osteoarthritis/diagnosis-treatment/treatment/txc-20198275

[66] Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev.* 2006;(1):CD004257.

[67] http://www.aafp.org/afp/2012/0101/p49.html#afp20120101p49-b20

[68] http://www.healthline.com/health/osteoarthritis/medications-list#Topicalanalgesics6

[69]http://www.aafp.org/afp/2012/0101/p49.html#afp20120101p49-b34; http://www.mayoclinic.org/diseases-conditions/osteoarthritis/diagnosis-treatment/treatment/txc-20198275

[70] American Academy of Orthopaedic Surgeons. The treatment of glenohumeral joint osteoarthritis: guideline and evidence report. Rosemont, Ill.: *American Academy of Orthopaedic Surgeons;* 2009.

[71] Stephens MB, Beutler AI, O'Connor FG. Musculoskeletal injections: a review of the evidence. *Am Fam Physician.* 2008;78(8):971–976.

[72] Bettencourt RB, Linder MM. Arthrocentesis and therapeutic joint injection: an overview for the primary care physician. *Prim Care.* 2010;37(4):691–702.

[73]http://www.mayoclinic.org/diseases-conditions/osteoarthritis/diagnosis-treatment/treatment/txc-20198275

[74] St Clair SF, Higuera C, Krebs V, Tadross NA, Dumpe J, Barsoum WK. Hip and knee arthroplasty in the geriatric population. *Clin Geriatr Med.* 2006;22(3):515–533.

[75]http://www.mayoclinic.org/diseases-conditions/osteoarthritis/diagnosis-treatment/treatment/txc-20198275

[76] Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2006;(2):CD005321.

[77] Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum. 2009;61(12):1704–1711.

[78] Manheimer E, Linde K, Lao L, Bouter LM, Berman BM. Meta-analysis: acupuncture for osteoarthritis of the knee. *Ann Intern Med.* 2007;146(12):868–877.

[79] Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med.* 2006;354(8):795–808.

[80] Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med.* 2007;146(8):580–590.

[81] Soeken KL, Lee WL, Bausell RB, Agelli M, Berman BM. Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. *J Fam Pract.* 2002;51(5):425–430.

[82] Verhagen AP, Bierma-Zeinstra SM, Boers M, et al. Balneotherapy for osteoarthritis. *Cochrane Database Syst Rev.* 2007;(4):CD006864.

[83] Ernst E. Complementary treatments in rheumatic diseases. *Rheum Dis Clin North Am.* 2008;34(2):455–467.

[84] http://www.healthline.com/health/osteoarthritis/medications-list#Analgesics2

[85] http://www.healthline.com/health/osteoarthritis/medications-list#Corticosteroids4

[86] Hunter DJ, Lo GH. The management of osteoarthritis: an overview and call to appropriate conservative treatment. Rheum Dis Clin North Am. 2008;34(3):689–712;

[87] Manek NJ, Lane NE. Osteoarthritis: current concepts in diagnosis and management. Am Fam Physician. 2000;61(6):1795–1804.

[88] St Clair SF, Higuera C, Krebs V, Tadross NA, Dumpe J, Barsoum WK. Hip and knee arthroplasty in the geriatric population. *Clin Geriatr Med.* 2006;22(3):515–533.

[89] http://www.ortho-surgery.com/orthopedic-information/total_hip_replacement.pdf

[90]http://www.everydayhealth.com/osteoarthritis/the-pros-and-cons-of-cortisone-for-osteoarthritis.aspx

[91] http://www.arthritis-health.com/treatment/injections/viscosupplementation-risks-and-side-effects

[92] Brockmeier SF, Shaffer BS. Viscosupplementation therapy for osteoarthritis. *Sports Med Arthrosc.* 2006;14:155–162.

[93] Goa KL, Benfield P. Hyaluronic acid. A review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs.* 1994;47:536–566.

[94] Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol Suppl.* 1993;39:3–9.

[95] Greenwald RA. Oxygen radicals, inflammation, and arthritis: pathophysiological considerations and implications for treatment. *Semin Arthritis Rheum.* 1991;20:219–240.

[96] Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg.* 2000;8:277–284.

[97] Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther.* 2003;5:54–67.

[98] Amiel D, Toyoguchi T, Kobayashi K, Bowden K, Amiel ME, Healey RM. Long-term effect of sodium hyaluronate (Hyalgan) on osteoarthritis progression in a rabbit model. *Osteoarthritis Cartilage.* 2003;11:636–643.

[99] Wenz W, Breusch SJ, Graf J, Stratmann U. Ultrastructural findings after intraarticular application of hyaluronan in a canine model of arthropathy. *J Orthop Res.* 2000;18:604–612.

[100] Pozo MA, Balazs EA, Belmonte C. Reduction of sensory responses to passive movements of inflamed knee joints by hylan, a hyaluronan derivative. *Exp Brain Res.* 1997;116:3–9.

[101] Ghosh P. The role of hyaluronic acid (hyaluronan) in health and disease: interactions with cells, cartilage and components of synovial fluid. *Clin Exp Rheumatol.* 1994;12:75–82.

[102] Goldberg VM, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. *Osteoarthritis Cartilage.* 2005;13:216–224.

[103] Abate M, Salini V. Hyaluronic Acid in the Treatment of Osteoarthritis: What is New. Osteoarthritis - Diagnosis, Treatment and Surgery, Prof. Qian Chen (Ed.), ISBN: 978-953-51-0168-0, *InTech.*

[104] Peyron JG, Balazs EA. Preliminary clinical assessment of Na-hyaluronate injection into human arthritic joints. Pathol Bio 1974;122:731-736.

[105] Weiss C, Balazs EA, St Onge R, Denlinger JL (1980) Clinical studies of the intraarticular injection of Healon (sodium hyaluronate) in the treatment of osteoarthritis of human knees. *Semin Arthritis Rheum* 1980;11(1): 143-144 45.

[106] Namiki O, Toyoshima H, Morisaki N. Therapeutic effect of intra-articular injection of high molecular weight hyaluronic acid on osteoarthritis of the knee. *Int J Clin Pharmacol Ther Toxicol* 1982;20:501-507.

[107] Kopp S, Wenneberg B, Haraldson T, Carlsson GE. The short-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint pain and dysfunction. *J Oral Maxillofac Surg* 1985;43:429-435.

[108] Aviad AD, Houpt JB. The molecular weight of therapeutic hyaluronan (sodium hyaluronate): how significant is it? *J Rheumatol.* 1994;21(2):297–301.

[109] Maneiro E, de Andres MC, Fernández-Sueiro JL, Galdo F, Blanco FJ. The biological action of hyaluronan on human osteoartritic articular chondrocytes: the importance of molecular weight. *Clin Exp Rheumatol.* 2004;22(3):307–312.

[110] Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through Jan 2009. *Osteoarthritis Cartilage.* 2010;18(4):476–499.

[111] Shiedlin A, Bigelow R, Christopher W. *et al.,* Evaluation of hyaluronan from different sources: streptococcus zooepidemicus, rooster comb, bovine vitreous, and human umbilical cord. *Biomacromolecules* 2004, 5(6):2122–2127.

[112] Soltes L, Mendichi R, Lath D, Mach M, Bakos D, Molecular characteristics of some commercial high-molecular-weight hyaluronans. *Biomedical Chromatography* 2022;16(7):459–462, 2002.

[113] Harmon PS, Maziarz EP, and Liu XM. Detailed characterization of hyaluronan using aqueous size exclusion chromatography with triple detection and multiangle light scattering detection. *Journal of Biomedical Materials Research B*, 100(7):1955–1960, 2012.

[114] Springer J, Kooy F, Van Den Broek LAM, Eggink G. Production Methods for Hyaluronan. *International Journal of Carbohydrate Chemistry* 2013.

[115]http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Western-Ontario-McMaster-Universities-Osteoarthritis-Index-WOMAC

[116] http://www.performanceptpc.com/paperwork/womac.pdf

[117] Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? *Semin Arthr Rheum* 2001;32(1):10–37.

[118] Vitanzo PC Jr, Sennett BJ. Hyaluronans: is clinical effectiveness dependent on molecular weight? *Am J Orthop* 2006;35(9):421–428.

[119] Onel E, Kolsun K, Kauffman JI. Post-Hoc analysis of a head-to-head hyaluronic acid comparison in knee osteoarthritis using the 2004 OMERACT-OARSI responder criteria. *Clin Drug Investig* 2008;28(1):37–45.

[120] Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. *Rheumatol Int* 2006;26(4):325–330.

[121] Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis ofthe knee. *Cochrane Database Syst Rev.* 2006;(2).

[122] Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, De laSerna AR, Naranjo A, et al. A 40-month multicentre,randomised placebo-controlled study to assess the efficacyand carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: *the Amelia project.Ann Rheum Dis.* 2011;70(11):1957–62.18.

[123] Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV.Efficacy of hylan G-F 20 and sodium hyaluronate in thetreatment of osteoarthritis of the knee – a prospective randomized clinical trial. *Knee.* 2008;15(4):318–24.

[124] Roffi A, Di Matteo B, Krishnakumar GS, Kon E, Filardo G. Platelet-rich plasma for the treatment of bone defects: from pre-clinical rational to evidence in the clinical practice. A systematic review. *Int Orthop.* 2017;41(2):221-237.

[125] http://orthoinfo.aaos.org/topic.cfm?topic=A00648

[126] Brzusek D, Petron D. Treating knee osteoarthritis with intra-articular hyaluronans. *Curr Med Res Opin* 2008;24(12):3307–3322.

[127] Waddell DD. Viscosupplementation with hyaluronans for osteoarthritis of the knee. *Drugs Aging* 2007;24(8):629–642.

[128] Adams ME, Atkinson MH, Lussier AJ, *et al.* The role of viscosupplementation with hylan G-F 20 in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDS) and NSAIDS alone. *Osteoarthritis Cartilage* 1995;3(4):213–225.

[129] Bannuru RR, Natov NS, Obadan IE, *et al*: Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Arthritis and Rheum* 2009; 61:1704–1711.

[130] Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee: a prospective, randomized trial. *J Bone Joint Surg Am* 2003;85(7):1197–1203.

[131] Waddell DD, Cefalu CA, Bricker DC. A second course of hylan G-F 20 for the treatment of osteoarthritic knee pain: 12-month patient follow-up. *J Knee Surg* 2005;18(1)7–15.

[132] Pagnano M, Westrich G. Successful nonoperative treatment of chronic osteoarthritis pain of the knee: safety and efficacy of retreatment with intra-articular hyaluronans. *Osteoarthritis Cartilage* 2005;13(9):751–761.

[133] Zhang W, Moskowitz RW, Nuki G, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16(2):137–162.

[134] Kawasaki K, Ochi M, Uchio Y, Adachi N, Matsusaki M. Hyaluronic acid enhances proliferation and chondroitin sulfate synthesis in cultured chondrocytes embedded in collagen gels. *J Cell Physiol* 1999;17(2):142–148.

[135] Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheum* 1993;39(Aug):3–9.

[136] Goldberg VM, Goldberg L. Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis. Journal of Pain Research 2010;3 51–56.

[137] Conduah AH, Baker CL, Baker Jr CL. Managing joint pain in osteoarthritis: safety and efficacy of hylan G-F 20. Journal of Pain Research. 2009:2 87–98.

[138] Goldberg VM, Buckwalter JA: Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. *Osteoarthritis and Cartilage* 2005;31:216–224.

[139] Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther* 2003;5(2):54–67.

[140] Hammesfahr JFR, Knopf AB, Stitik T. Safety of intra-articular hyaluronates for pain associated with osteoarthritis of the knee. *Am J Orthop* 2003;32(6):277–283.

[141]https://www.google.ch/url?sa=t&rct=j&q=&esrc=s&source=web&cd=26&cad=rja&uact=8&ved=0ahUKEwiQ0ZzEiLXSAhWFtBoKHYqJCd84FBAWCDEwBQ&url=http%3A%2F%2Fcrespinegel.no%2Fpdf%2Fha_5.pdf&usg=AFQjCNFzdavU5FUJjbXw2xDA256VPPiEHA

[142]https://www.google.ch/url?sa=t&rct=j&q=&esrc=s&source=web&cd=11&ved=0ahUKEwi9xZ2Zm7XSAhVDiRoKHdaEBL44ChAWCBswAA&url=http%3A%2F%2Farthritis.arizona.edu%2Fsites%2Fdefault%2Ffiles%2Ftesser_viscosupplementation_deck_v1_may_12_2014_tesser.pdf&usg=AFQjCNE5GROOM4ZaWlU91IC2qsRtlsGOnw

[143]https://www.google.ch/url?sa=t&rct=j&q=&esrc=s&source=web&cd=14&cad=rja&uact=8&ved=0ahUKEwi9xZ2Zm7XSAhVDiRoKHdaEBL44ChAWCC4wAw&url=http%3A%2F%2Fwww.ubortho.com%2Fwp-content%2Fuploads%2F2015%2F07%2FUBOSM_Medicare_Recommendations_for_Knee_Injection.pdf&usg=AFQjCNGF2BzctpgVL9VSkkzmB20hiKmTwA

[144] De Rezende MU, De Campos GC. Viscosupplementation. *Rev Bras Ortop.* 2012;47(2):160-4.

[145] Waddell DD. Viscosupplementation with hyaluronans for osteoarthritis of the knee. *Drugs Aging* 2007;24(8):629–642.

[146] Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg* 2000;8(5):277–284.

[147] Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementaion: diagnosis and treatment. *Clin Orthop Relat Res* 2004;419:130–137.

[148] Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. *J Bone Joint Surg Am* 2002;84(9):1522–1527.

[149] Brockmeier SF, Shaffer BS. Viscosupplementation therapy for osteoarthritis. *Sports Med Arthrosc Rev* 2006;14(3):155–162.

[150] Waddell DD, Cefalu CA, Bricker DC. An open-label study of a second course of hylan G-F 20 for the treatment of pain associated with knee osteoarthritis. *Curr Med Res Opin* 2003;19(6):499–507.

[151] Waddell DD, Cefalu CA, Bricker DC. A second course of hylan G-F 20 for the treatment of osteoarthritic knee pain: 12-month patient follow-up. *J Knee Surg* 2005;18(1)7–15.

[152] Raynauld JP, Goldsmith CH, Bellamy N, et al. Effectiveness and safety of repeat courses of hylan G-F 20 in patients with knee osteoarthritis. *Osteoarthritis Cartilage* 2005;13(2):111–119.

[153] Pagnano M, Westrich G. Successful nonoperative treatment of chronic osteoarthritis pain of the knee: safety and efficacy of retreatment with intra-articular hyaluronans. *Osteoarthritis Cartilage* 2005;13(9):751–761.

[154] Listrat V, Ayral X, Patarnello F, Bonvarlet JP, Simonnet J, Amor B, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis Cartilage.* 1997;5(3):153-60.

[155] Guidolin DD, Ronchetti IP, Lini E, Guerra D, Frizziero L. Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500-730 kDa

sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2001;9(4):371-81.

[156] Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. *Int J Clin Pract.* 2003;57(6):467-74.

[157] Karlsson J, Sjogren S, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis: a controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford)* 2002;41(11):1240–1248.

11 DECLARATIONS OF INTERESTS

Declarations of interests of all the authors of the Clinical Evaluation are enclosed in **Appendix 7**.

12 DOCUMENT APPROVAL / 1MED CERTIFICATIONS

The present Clinical Evaluation has been draw up and internally approved by 1MED sa. 1MED is a consulting Company based in Switzerland, ISO 9001 and ISO 13485 certified by TÜV Rheinland Notified Body. The scope of the certifications (**Appendix 8**) covers the activities conducted (bibliographic clinical evaluation for the medical device *"Hyaluronic acid sodium salt, viscosuppletive joint device"*):

"Design and provision of consultancy services and management of clinical trials in the field of medical devices and in vitro diagnostics medical devices"

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Enrico Perfler
Chief Executive Officer 1MED sa

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13 APPENDICES

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