Clinical Evaluation Report

FOCUSIAL

Change Index

Rev.	Date	Changes
1	14/11/2016	First edition
2	28/04/2017	Upgrade according to MEDDEV 2.7/1 rev.4
3	03/09/2017	FDA MAUDE database source added

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1 Summary

The medical device **FOCUSIAL** is an injectable gel based on the salt of the hyaluronic acid intended to be used for human adults to compensate the deficiency of the synovial fluid of patients suffering of the osteoarthritis in the knee. Thanks to its viscoelastic and lubricant properties, **FOCUSIAL** promotes the restoration of the rheological conditions of the knee. **FOCUSIAL** improves the characteristics of the synovial fluid, exerts a protective action of the knees and helps the improvement of joint function and the reduction of pain symptoms.

The present clinical evaluation report has been issued as part of the technical documentation necessary for the CE certification of the device in accordance with MEDDEV 2.7/1 rev.4 (June 2016).

FOCUSIAL is indicated for patients suffering of osteoarthritis in the knee (thus specifically elderly patients). It must be used by medical professionals only, with proven expertise in the treatment of degenerative conditions of the joints in the context of normal clinical practices.

The determination of the acceptability of the benefit/risk profile has been developed on the basis of the clinical data available in the medical scientific literature related to equivalent medical devices. Specifically, fundamental performances of **FOCUSIAL** are based on relief from joint pain and improvement of sinovial fluid properties that determine the joint functionality. At the same time the risks associated with the use of **FOCUSIAL** are based on the expected unwilling side effects already known for equivalent hyaluronic acid based medical devices used for the same indications.

At last, acceptability of the benefit/risk profile of FOCUSIAL is based on the current state of the art in the medical management of knee osteoarthritis. In fact, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends intra-articular hyaluronic acid (IA HA) for management of knee osteoarthritis as second-line treatment in patients who remain symptomatic despite use of non-steroidal anti-inflammatory drugs (NSAIDs). This recommendation is based upon accumulating evidence that IA HA provides a significant benefit in knee osteoarthritis. There is good evidence that IA HA injections reduce pain and increase function in knee osteoarthritis, and the benefits are long-lasting as compared with IA corticosteroids. Evidence from real-life studies of repeat courses of IA HA demonstrates an improvement in pain or function lasting up to 40 months (12 months after the last injection cycle), a reduction in use of concomitant analgesia by up to 50%, and suggests that there may be a delay in the need for total knee replacement of around 2 years. The clinical benefit of IA HA on knee osteoarthritis may be 2-fold: (i) mechanical viscosupplementation of the joint (allowing lubrication

and shock absorption) and (ii) the re-establishment of joint homeostasis through induction of endogenous HA production, which continues long after the exogenous injection has left the joint. The magnitude of the clinical effect may be different for different HA products, but this has not been proven so far and requires further investigation. IA HA injections are generally considered to be safe, although a slightly higher number of cases of local reactions and post-injection non-septic arthritis has been reported with high molecular weight cross-linked HAs. The use of IA HA in knee osteoarthritis patients with mild–moderate disease, and for more severe patients wishing to delay total knee replacement surgery, is recommended by the ESCEO task force. Further investigation into the knee osteoarthritis patient types most likely to benefit from IA HA is warranted. Viscosupplementation with IA HA is a safe and effective component of the multi-modal management of knee osteoarthritis (**Maheu 2013**). While there is increasing evidence that HA injections provide a significant benefit in knee osteoarthritis, the level of recommendation afforded to HA by international and national societies varies. The European League Against Rheumatism (EULAR) guidelines recommend IA HA based upon level 1B evidence for both pain reduction and joint functional improvement. Both the American College of Rheumatology (ACR) guidelines and ESCEO algorithm recommend IA HA in patients whose symptoms persist despite prior treatments. The 2014 Osteoarthritis Research Society International (OARSI) guidelines give an “uncertain” recommendation to IA HA. This “uncertain” classification “is not intended to be a negative recommendation or preclude use of that therapy. Rather it indicates a role for physician–patient interaction in determining whether this treatment may have merit in the context of its risk/benefit profile and the individual characteristics, co-morbidities, and preferences of the patient”, leading to the prescription of IA HA for specific clinical phenotypes and not for all individuals with knee osteoarthritis. In conclusion, the use of hyaluronic acid for the treatment of knee osteoarthritis is recognized as an established therapeutic option with a widespread consensus and it appears in protocols algorithms (see figure below) where the medical decision tree, based on the specific case analysis, is paramount in the success of the treatment, as pointed out by the ORASI group.

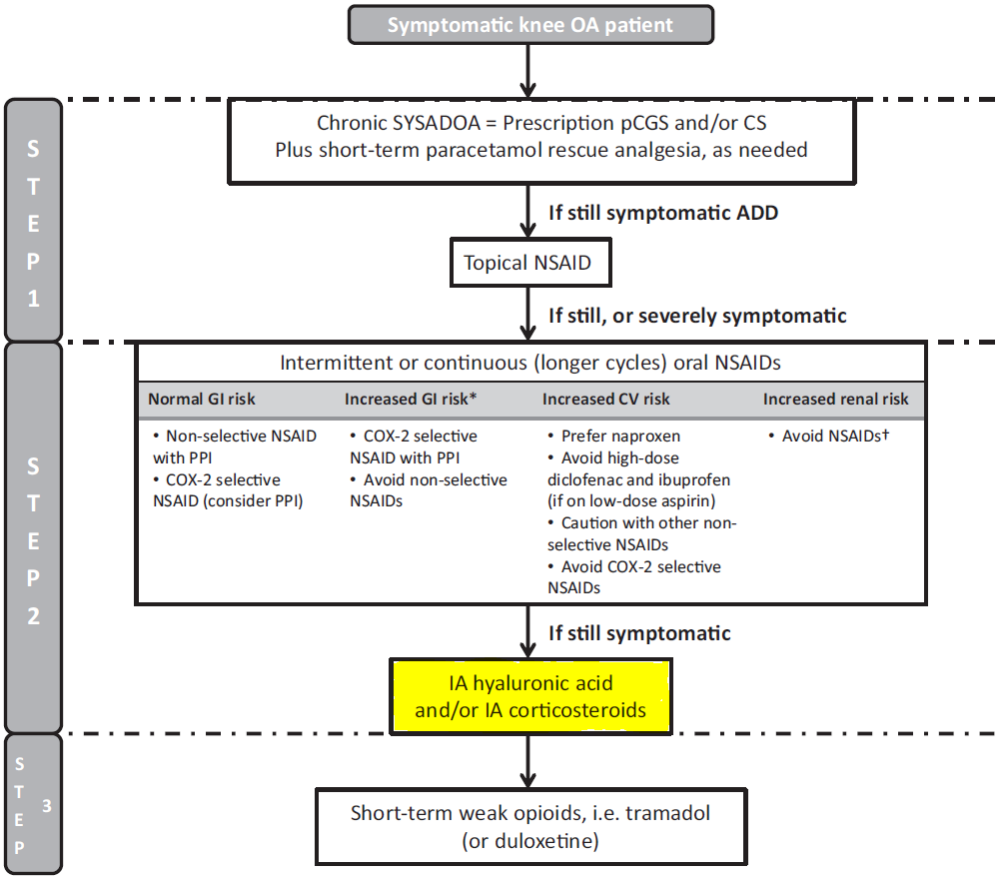


Figure: Simplified stepwise algorithm for the management of knee osteoarthritis by the ESCEO group (Bruyère 2016). Highlighted in yellow the step option for the use of hyaluronic acid intraarticular injections.

2 General details

This clinical evaluation report (CER) is based on the guidelines on medical devices given in MEDDEV 2.7.1 rev.4 (Jun. 2016) to the European Directive 93/42/EEC and following amendment directive. It is focused on the medical device:

FOCUSIAL

The manufacturer, hereinafter referred to as MAN, of **FOCUSIAL** is:

The Wave Innovation Group S.r.l.s

Via Giacomo Barucchi 47/A

37139 Verona

Italy

3 Scope of the clinical evaluation

3.1 Description of the device

FOCUSIAL is a sterile, biodegradable, non-pyrogenic, clear, transparent, isotonic injectable gel. The device contains sodium hyaluronate obtained by the biofermentation from Streptococcus equi bacteria. The device is provided sterile and is intended for single use only. The sterilisation is made by moist heat.

No medicinal substances, human tissues, blood products or material from animal origin are integrated into the device.

The device is provided in a vial syringe. One syringe contains 2 ml or 4 ml of the device.

3.2 Composition and characteristics

2.0 ml (4 ml) of the device contains:

- 40.0 mg (80.0 mg) of sodium hyaluronate with molecular weight in range 1.5-2.0 MDa or 2.5-3.5 MDa;
- 16.0 mg (32.0 mg) of non-pyrogenic sodium chloride;
- 0.6 mg (1.2 mg) of sodium phosphate monobasic x 2 H2O;
- 3.0 mg (6.0 mg) of sodium phosphate dibasic x 12 H2O;
- Water for injection q.s. for 2 ml (4 ml).

The device has the following components apart from the sodium hyaluronate solution:

- 1 Vial syringe;
- needles of diameter size range 18 - 22 G (not supplied).

The following analytical controls of the finished product are performed to measure the relevant characteristics:

- Appearance: clear and colourless gel
- pH: 6.50 - 7.50
- Extractable volume: 2.0 - 2.2 ml (4.0 - 4.4 ml)
- Osmolality: 250 - 350 mOsm/Kg
- Sodium hyaluronate identification (HPLC): Positive
- Sodium hyaluronate assay (HPLC): 18 - 22 mg/ml
- Sterility test (according to Ph.Eur.): pass the test, sterile
- Bacterial endotoxins (LAL test): < 8.75 EU/ml

3.3 Intended application

FOCUSIAL is an absorbable implant intended to be used for human adults to compensate the deficiency of the synovial fluid of patients suffering of the osteoarthritis in the knee (KOA).
Thanks to its viscoelastic and lubricant properties, **FOCUSIAL** promotes the restoration of the rheological conditions of the joints, altered following degenerative or posttraumatic conditions that are typical of patients in geriatric age. **FOCUSIAL** improves the characteristics of the synovial fluid, exerts a protective action of the joints and helps the improvement of joint function and the reduction of pain symptoms. **FOCUSIAL** action is local, it does not exert any systemic action as its primary function is merely mechanical.

The device is designed to be injected in the knee joint and it is not reusable.

The content of the syringe is provided sterile.

The device is not active and without measuring function.

3.4 Mechanism of action

Hyaluronan or hyaluronic acid (HA) is a glycosaminoglycan (GAG) composed of repeating polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronidic β (1→3) bond (Fig.1), with a unique capacity to bind and retain water molecules, to provide a mechanical matrix that attenuate the collisions of the cellular and tissue structures during motion, and lastly to absorb mechanical shocks from hits due to external factors.

HA is an essential component of the extracellular matrix (ECM). HA exists naturally in various animal tissues, including rooster combs, shark skin, bovine eyeballs, bovine nasal cartilage, rabbit brain and heart and in various human tissues, including the umbilical cord, serum, vitreous body, dermis, epidermis, thoracic lymph, urine and synovial fluid (SF).

However, the highest amounts of HA in the human body are found in the ECM of soft connective tissues. In OA joints, synovial fluid contains a lower concentration of HA than in healthy joints, so intra-articular therapy with exogenous HA can restore its viscoelastic properties.

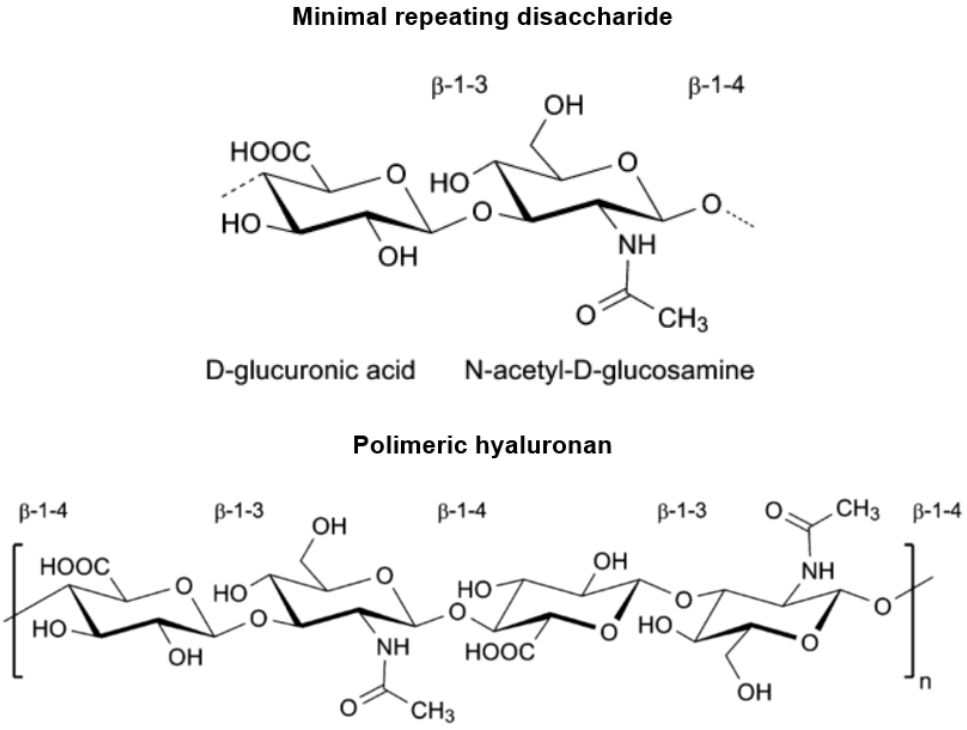


Figura 1 structure of hyaluronan.

Other processes can be activated as a consequence of HA viscosupplementation, in fact various intracellular signal events such as cytokine release and stimulation of cell cycle proteins can be promoted. The consequences of these interactions is to stimulate cell functional activities such as cell migration and proliferation. Various physiological effects of exogenous HA may contrast the mechanisms involved in OA pathogenesis. Indeed, exogenous HA can enhance chondrocyte synthesis of endogenous HA and proteoglycans, prevent the degradation of cartilage and promote its regeneration. Moreover it can reduce the production of proinflammatory mediators and matrix metalloproteinases, and reduce nerve impulses and nerve sensitivity associated with OA pain.

3.5 Classification

FOCUSIAL is a sterile device to be implanted and resorbed in the body knee joint to compensate the loss of natural HA in the KOA, decreasing pain and increasing normal functionality until endogenous degradation occurs.

According to Rule 8 of Annex IX of the European Directive 93/42/EEC and following amendments directive, that reads:

"All implantable devices and long-term surgically invasive devices are in Class IIb unless they are intended:

— to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class III."

FOCUSIAL is thus a class III medical device.

The medical device generic group according to the GMDN classification is:

CODE 44757: A viscous/elastic solution or gel (e.g. comprised of hyaluronic acids and ther polymeric derivatives) that can be injected into joints (particularly large, load-bearing joints such as the hip or knee) to help cushion the joint, especially in cases of endogenous synovial fluid reduced viscosity from degenerative disease.

3.6 Dosage and lifetime of the device

The maximal recommended dosage is 4 mL per treatment session and 20 mL per patient per year. The device must be stored at 2–25 °C (36–77 °F) in a dry place in the original box and it must be protected from light, heat and frost.

Hyaluronic acid is a natural component of human synovial fluid and implanted linear HA usually lasts about 3 weeks to 6 months. As time passes by, the practical possibility to distinguish the implanted HA from the endogenous HA decreases as they are essentially identical. For this reason, the presence of the implanted HA can be inferred only by subjective assessment.

As summarized in (Guidolin 2014), the pharmacokinetics of 14C-glucose-labelled HA was measured after intra-articular injection into the knee joint cavity of rabbits. After a single administration the measured half-life was of 24 hours. However, 10% of the high MW material was still present in the joint cavity after 72 hours and the radioactivity disappeared in about 120 hours. The observed half-life and residence time following a single intra-articular injection were significantly higher than the ones exhibited by HA with MW < 1000 KDa (which are of about 16 hours and 60 hours respectively).

3.7 Conditions and restriction of use and special precautions

FOCUSIAL is a synovial fluid substitute which, thanks to its viscoelastic and lubricant properties, promotes the restoration of rheological conditions of the joints, altered in degenerative or posttraumatic conditions. The device, improving the characteristics of the synovial fluid, exerts a protective action of the joints and helps the improvement of joint function and the reduction of pain symptoms. **FOCUSIAL** acts only at the knee joint where it is injected, without exerting any systemic action.

The device is a solution intended to compensate the loss of hyaluronic acid in the synovial fluid of patients with degenerative osteoarthritis of the knee.

It is indicated to be injected into the knee joint cavity.

The device must not be used:

- In the presence of an infected or severely inflamed joint;
- In presence of skin diseases in the area of the injection site;
- In patients with ascertained individual hypersensitivity to the components present in the device;
- In pregnant or breastfeeding women, as FOCUSIAL has not been tested in such cases;
- In patients under 18 years of age;

After the intra-articular injection it is advisable to recommend to the patient to avoid physical activities demanding stress for the articulation and resume normal activities after a few days.

FOCUSIAL is a disposable product, the quality and sterility are guaranteed only if the syringe is sealed. Any residue must be discarded and not reused even after new sterilisation.

FOCUSIAL must not be used if the package is already opened or damaged.

There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds, such as solutions of benzalkonium chloride. Contact between **FOCUSIAL** and these substances must be therefore avoided.

3.8 Known and commonly reported adverse events

The following events and inflammatory reactions have been observed with equivalent devices: pain, stiffness, warmth, redness or swelling. These secondary manifestations may be relieved by applying ice on the treated articulation. Usually these effects disappear after a short time. If symptoms persist, a physician must be consulted.

As for any intra-articular treatment, septic arthritis may rarely occur when general precautions for injections are not observed or the site of injection is not aseptic.

4 State of the art, medical background and clinical data

4.1 Device development in the medical context up to date

The present CER deals with the medical device **FOCUSIAL** that is a medical device based on a well established technology, already in use on human patients since the 90s. In fact, **FOCUSIAL** is made of not chemically modified linear HA as functional component with the purpose to supplement the loss of endogenous HA that is typical of knee osteoarthritis. First devices of this class commercially available were Hyalgan (Fidia Farmaceutici SpA) and Hylan G-F 20 (Biomatrix Inc).

Viscosupplementation is an intra-articular (IA) therapeutic modality for the treatment of knee OA based on the physiologic importance of hyaluronan in synovial joints. Its therapeutic goal is to restore the viscoelasticity of synovial hyaluronan, decrease pain, improve mobility and restore the natural protective functions of hyaluronan in the joint. The short-term mode of action of viscosupplementation is believed to be based on the pain-relieving effect of the elastoviscous fluid in the affected joint. In the long term, the restoration of joint mobility due to relief of pain is thought to trigger a sequence of events which restores the trans-synovial flow and subsequently the metabolic and rheological homeostases of the joint (Bellamy 2006).

Among specific joint diseases, osteoarthritis (OA) is the most frequent cause of rheumatic complaints. OA of the knee (KOA) is a major cause of pain and disability. Guidelines and recommendations for the management of KOA that also include discussion on the use of intra-articular injections of hyaluronic acid have been reported in at least four publications of medical organizations (latest updated version: Jordan 2003 from the EULAR group, Hochberg 2012 from the American College of Rheumatology, AAOS 2013 from the American Academy of Orthopaedic Surgeons, McAlindon 2014 from the OARSI group).

Consensus statements on the same topic have been published in at least four publications (Punzi 2004, from the Italian Society of Rheumatology and the Italian League against Rheumatism, Henrotin 2015 from a group of eight experts, Bruyere 2016 from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis - ESCEO, Paoloni 2016 from a group of 52 Italian experts).

It has been reported that 40% of people over the age of 80 will have at least one joint involved and 27 million people in the United States have clinical OA (Goldberg 2010). It has been shown that HA is a highly biocompatible polymer (naturally occurring in the human extracellular matrix through

endogenous production), used for a pletora of medical applications thanks to its properties and safety profile (Necas 2008).

The safety profile of intra-articular injections of HA has been recently assessed by a meta-analysis of the clinical data available in the scientific-medical literature with results indicating that the safety risk is acceptable (Miller 2013). This finding is in contrast with a previous meta-analysis where higher risks of withdrawals were pointed out in trials of KOA treatment with HA (Rutjes 2012). However, there were several important subtleties associated with the latter analysis: the association between serious adverse events and treatment was not considered, in fact Miller analysis showed that 100% of reported SAEs were unrelated to treatment. Second, the safety analysis of Rutjes was heavily influenced by inclusion of unpublished, unverifiable data. In contrast, Miller included only included data from full-text manuscripts published in peer-reviewed journals. Lastly, Rutjes analyzed all safety data using an odds ratio, a statistic that excludes zero total event trials.

Overall pain is a central symptom of OA and requires an integrated approach to it's treatment. Both nonpharmacological and pharmacological treatments offer the best chance for pain relief. Pharmacological treatments include NSAIDs, cox-2 inhibitors, opioids, anti-inflammatory creams and IA corticosteroids. IA corticosteroids have been shown to be effective in relieving pain during the first 2 weeks after treatment. Intra-articular HA injections have a longer onset of action and longer duration of effect. The exact mechanism of action on pain is still to be delineated, although it is clear that IA HA reduces pain through its effect on peripheral pain receptors as well as an impact on the synovial tissue and its role in enhancing the viscoelastic properties of synovial fluid. HA has an excellent safety profile with few serious side-effects (Bellamy 2006, Miller 2013, Maheu 2016, Paoloni 2016).

The present CER is based on the demonstration of compliance with the essential requirements through equivalency of **FOCUSIAL** to other devices for which clinical data are critically evaluated (according to point 1.1.1 of Annex X 93/42/EEC and following amendment directive). This is justified by the following reason: a broad literature analysis including all intra-articular hyaluronan products demonstrates that (1) hyaluronate is a natural constituent of the synovial fluid present in the knee joint, so that reactions against hyaluronate are not to be expected with proper use. (2) The favourable safety profile of hyaluronate is supported by numerous clinical investigations and

consolidated practice. (3) The risk/benefit ratio of the device is supported by clinical data from several equivalent products (documented in this report, below).

Data used in this CER are based on the research protocol reported in Sec.9 and selection criteria defined in Sec.5 The following data have been appraised to assess the performance, safety and the benefit/risk ratio of the device:
data generated through literature search. This search was performed in order to identify published clinical data that is not in the possession of the MAN. Literature published until June-November 2016 was considered, without past date restriction. Among the many brands currently in commerce in EU, US, and other markets, in this CER are reported only those equivalent devices for which direct clinical data are retrievable: Hyalubrix, Orthovisc, Artz/Supartz, GenVisc 850/Adant, Euflexxa, Sinovial, Fermathron, Suvenyl, Ostenil, Go-On, Hyalgan, and Suplasyn which are all linear HA and are considered equivalent devices because the critical performance is based on the native HA whereas Synvisc/Hylan G-F 20, Hymovis, Gel-One/Gel-200, Durolane contain a fraction of cross-linked/stabilized HA and can be considered as equivalent devices because no efficacy differences are attributed to the native or cross-linked property of the devices (for example, they are deemed equivalent by FDA in the US market). Literature searches have also been extended with the aim of retrieving a wider collection of literature to cover safety and address possible risks.

4.2 Demonstration of device equivalence

In this paragraph a justification for equivalence of **FOCUSIAL** with the other devices assessed in this CER is given through comparsion of the requirements to meet the equivalence definition given in Appendix A1 of MEDDEV. 2.7/1 rev.4:
Twelve totally equivalent medical devices have been considered for which direct clinical data are available and have been discussed in this CER.
In commerce, there are other devices claimed to be equivalent by respective manufacturers to the listed ones but no clinical data are available and thus excluded from equivalence in this CER.
Availability of clinical data from recognized scientific journals hase been chosen as a sufficient requirement to be fulfilled for compliance to the requirements in Appendixes A1 and A12.2.3, because usage of HA as therapeutic option for the treatment of pain and functionality in knee OA is worldwide considered as normal practice, so that scientific medical data are avilable and do

represent the fundamental background for the assessment of this therapeutic option by the scientific method. Restricted, confidential, or private data from corresponding manufacturers is deemed unnecessary given that all the data collected and assessed in this CER are publicly available.

Equivalence is shown for each single device with respect to **FOCUSIAL**. All mentioned devices are marketed in Europe and/or USA. In addition, as proof of equivalence, according to FDA all devices belonging to this therapeutic group must have the same claims in the information material.

Abbreviations: IA= intra-articular, MW= molecular weight, HA= hyaluronic acid, KOA= knee osteoarthritis, VS= viscosupplementation, MDa= million Dalton unit.

Device	**Hyalubrix** **Fidia Farmaceutici Spa** **variants:Hyalubrix 60/HyalOne**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in joints OA/ Hyal.60/Hyalone for KOA and hip	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the OA joints through IA injections to	VS of HA in the KOA joints through IA injections to reduce	yes

	supplement natural degraded HA	pain and increase joint functionality	
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution. highly pure grade HA produced by biofermentation.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	yes
Be of similar design	HA of MW 1.5-2.0 Mda Concentration of 15mg/ml. Syringe of 2 ml. Hyalone/Hyal.60 4ml	HA of medium MW 1.5-2.0 Mda or high MW 2.5-3.5 Mda. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint	VS of degraded native HA in the joint	yes

	reproducing normal function and reducing pain.	reproducing normal function and reducing pain.	
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1.5% HA or 30 mg HA in 2ml of buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes
Device	**Orthovisc** **Anika Therapeutics Inc.** **variants:Orthovisc Mini**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b Orthovisc-P030019B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in joints OA/ Orth. Mini for hand, wrist, foot, ankle, shoulder and temporomandibular joint.	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to	VS of HA in the OA joints through IA	VS of HA in the KOA joints through IA	yes

expected clinical effect for specific intended use	injections to supplement natural degraded HA	injections to reduce pain and increase joint functionality	
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic, clear sodium hyaluronate in physiologic saline solution. Highly pure grade HA produced by biofermentation. 2ml sterilized in vial syringe.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	yes
Be of similar design	HA of MW 1.1-2.9 Mda Concentration of 15mg/ml. Syringe of 2 ml. Ortho.Mini 1ml	HA of medium MW 1.5-2.0 Mda or high MW 2.5-3.5 Mda. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal	VS of degraded native HA in the joint reproducing normal	yes

	function and reducing pain.	function and reducing pain.	
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1.5% HA or 30 mg HA in 2ml of buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**Artz/Supartz** **Seikagaku Corp.** **variants:artzal**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b Supartz P98004B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**

Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate having pH of 6.8-7.8. Highly pure grade HA produced by chicken combs. 2.5ml syringe.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	yes
Be of similar design	HA of MW 0.6-1.2 Mda Concentration of 10mg/ml. Syringe of 2.5 ml.	HA of medium MW 1.5-2.0 Mda or high MW 2.5-3.5 Mda. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**

Use same materials in contact with the same human tissue or body fluids	1% HA or 25 mg HA in 2ml of physiologic buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**GenVisc 850** **OrthogenRx Inc.** **or** **Adant** **Meiji Seika Pharma Co.** **equivalent to Artz**	**Focusial**	
Information source	GenVisc 850 P140005B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA Adant Treatment of pain and function in KOA/Shoulder/trapezoid-metacarpal joint	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee Adant IA injection also in shoulder and trapezoid-metacarpal joint	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain Adant	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes

	increase joint functionality in knee, shoulder, trapezoid-metacarpal joint		
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate having pH of 6.8-7.8. Highly pure grade HA produced by bacterial fermentation 2.5ml glass syringe.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	yes
Be of similar design	HA of MW 0.6-1.2 MDa average 0.85 MDa Concentration of 10mg/ml. Syringe of 2.5 ml.	HA of medium MW 1.5-2.0 Mda or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes

have similar principles of operation	VS of degraded native HA in the joints reducing pain. Adant also increases functionality of knee, shoulder, trapezoid-metacarpal joint	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 25 mg HA in 2.5ml of physiologic buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**Euflexxa** **Ferring Pharmaceuticals Inc** **variants: nuflexxa**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b Euflexxa P010029S008B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water)	yes

	Highly pure grade HA produced by bacterial cells. 2ml glass syringe.	Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW 2.4-3.6 MDa Concentration of 10mg/ml. Syringe of 2 ml.	HA of medium MW 1.5-2.0 Mda or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joints reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 20 mg HA in 2ml of physiologic buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**Sinovial** **IBSA Institute Biochimique SA** **equivalent brand: Yaral/ Intragel/ GelSyn 3** **variants: Jointex/ Sinovial Forte/ Sinovial Mini/ Sinovial One/ Sinovial HighVisc 1.6%/ Intragel 0.8%/ Intragel 1.6%/ Intragel Mini/ Jointex Starter/ Jointex Mini**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b Gel-Syn P110005B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA (US only) Pain and functionality of different joints in (other countries and variants)	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee and other joints	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes

Technical Equivalence			Equiv.
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate. Highly pure grade HA produced through fermentation and without chemical modification. 1 to 2.5 ml syringe depending on variant.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	yes
Be of similar design	HA of MW 0.8-1.2 MDa Concentration of 8 to 32 mg/ml depending on variant. Syringe from 1 to 2.5 ml depending on variant.	HA of medium MW 1.5-2.9 Mda or high MW 2.5-3.5 Mda. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joints	VS of degraded native HA in the joint	yes

	reducing pain and restoring normal function of the joint	reproducing normal function and reducing pain.	
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	0.8 to 3.2% HA or 8 to 32 mg HA in syringe from 1 to 2.5 ml of physiologic buffer solution, depending on variant. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	Fermathron Hyaltech ltd UK variants: Fermathron Plus/ Fermathron S	Focusial	
Information source	Migliore 2016 Migliore 2016b	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in KOA Fermathron Plus for all joints Fermathron S for hip and shoulder too	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee other joints for variants	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear,	yes

	purified sodium hyaluronate. Highly pure grade HA produced by fermentation/ Fermathron S cross-linked. 2ml syringe/ Fermathron S 3ml syringe	colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW average 1.0 MDa/ Fermathron Plus 2 MDa/ Fermathron S cross-linked. Concentration of 10 to 23 mg/ml depending on variant. Syringe from 2 to 3 ml depending on variant.	HA of medium MW 1.5-2.0 Mda or high MW 2.5-3.5 Mda. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal	VS of degraded native HA in the joint reproducing normal	yes

	function and reducing pain.	function and reducing pain.	
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1 to 2.3% HA or 10 to 23 mg HA in syringe from 2 to 3 ml of physiologic buffer solution, depending on variant. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**Suvenyl** **Chugai Pharmaceutical Co.** **other brand name: NRD101**	**Focusial**	
Information source	Pham 2004 Ishijima 2014	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate. Purified HA produced by fermentation (streptococcus equus)	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained	yes

	2.5ml syringe	from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW average 1.9 MDa/ NRD101 average 2.7MDa. Concentration of 10mg/ml. Syringe of 2.5 ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal function and reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 25mg/2.5ml sodium hyaluronate in buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**Ostenil** **TRB Chemedica** **variants: Ostenil Mini/ Ostenil Plus**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in KOA, hip, shoulder,ankle other joints for variants	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the joint	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the OA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate/ Ostenil Plus with Mannitol Purified HA produced by biofermentation	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained	yes

	2ml syringe/ Ostenil Mini 1ml.	from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW 1.0-2.0MDa, average 1.9MDa. Concentration of 10mg/ml./ Ostenil Plus 20mg/ml. Syringe of 2 ml./ Ostenil Mini 1 ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal function and reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 20mg/2ml sodium hyaluronate in buffer solution./ Ostenil Plus 2% HA 40mg/2ml In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	Go-On Rottapharm Madaus variants: Go-On Mini/ Go-On matrix	Focusial	
Information source	Migliore 2016 Migliore 2016b	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in KOA and shoulder/ Go-On Mini other joints	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee and shoulder	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, viscoelastic, apyrogenic solution of purified sodium hyaluronate/ Go-On matrix with sorbitol	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water)	yes

	Purified HA produced by biofermentation 2.5ml syringe/ Go-On Mini 1ml/ Go-On matrix 2ml.	Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW 0.8-1.5MDa. Concentration of 10mg/ml Go-On matrix 20mg/ml Syringe of 2.5 ml./ Go-On Mini 1ml./ Go-On matrix 2ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal function and reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 25mg/2.5ml sodium hyaluronate in buffer solution./	2% HA or 40mg/2ml (80mg/4ml) sodium	yes

	Go-On matrix 2% or 40mg/20ml. In contact with joints internal tissues.	hyaluronate in buffer solution. In contact with joints internal tissues.	

Device	**Hyalgan** **Fidia Farmaceutici S.p.a.** **other brand name: Hyalart**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, apyrogenic, viscous solution consisting of fraction of purified sodium hyaluronate in phoshate buffered physiological sodium chloride, having a pH of 6.8-7.5.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water)	yes

	HA is extracted from rooster combs. 2ml syringe.	Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW 0.5-0.7MDa. Concentration of 10mg/ml Syringe of 2 ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal function and reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 20mg/2ml sodium hyaluronate in buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

Device	**Suplasyn** **Mylan N.V.** **variants: Suplasyn 1-Shot/ Suplasyn m.d.**	**Focusial**	
Information source	Suplasyn Patient Leaflets	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in OA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the joints	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the OA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	sterile, apyrogenic, solution. HA obtained from fermentation.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained	yes

	2ml syringe./ Suplasyn 1-Shot 6ml.	from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW 0.5-0.7 MDa. Concentration of 10mg/ml Syringe of 2 ml./ Suplasyn 1-Shot 6ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	yes
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint reproducing normal function and reducing pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 20mg/2ml sodium hyaluronate in buffer solution. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	yes

In addition to the products compared above, there are other products that are based on the cross-linking technology, where chemical agents are introduced to produce bonds between the hyaluronic acid chains in order to produce an overall HA more resistant to natural biodegradation in the joints. Such devices can be considered a worst case scenario in terms of safety profile with respect to native linear HA, given that the addition of these agents can induce adverse reactions while in contact with body tissues. Furthermore, cross-linked HA can be chemically modified up to 50% because HA is a natural polymer and a high level of cross-linkage will render the polymer from being natural to being foreign. Hence a foreign body reaction can take place. It results that also cross-linking technologies do not produce a gel of HA completely linked.

In conclusion, available clinical data and regulatory governmental agencies resolutions, such as FDA, consider both native linear and cross-linked HA-based medical devices as equivalent in terms of efficacy in the treatment of pain in the knee of OA patients.

On the basis of this current view, four more medical devices with cross-linked/stabilized HA have been added as equivalent devices and compared in the following, although design and biological characteristics are partially equivalent:

Device	**Synvisc-One or Hylan G-F 20** **Genzime – Sanofi** **other band name: Synvisc**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b Synvisc P940015S012B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the OA joints through IA injections to reduce pain in the knee	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	Elastoviscous high molecular weight fluid containing hylan A and hylan B polymers. Hylans are derivatives of sodium hyaluronate.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water)	partial

	The hyaluronan is chemically crossliked. HA obtained from chicken combs. 6ml syringe./ Synvisc 2ml syringe.	 Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	HA of MW average 6MDa crosslinked Concentration of 8mg/ml Syringe of 6 ml./ Synvisc 2ml	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	partial
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint to reduce pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes

Biological Equivalence			Equiv.
Use same materials in contact with the same human tissue or body fluids	0.8% HA or 48mg/6ml sodium hyaluronate as 80% HMW crosslinked and 20% gel. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	partial

Device	**Hymovis** **Fidia Farmaceutici S.p.a**	**Focusial**	
Information source	Migliore 2016 Migliore 2016b Hymovis P150010B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the OA joints through IA injections to reduce pain in the knee	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	Sterile, apyrogenic, highly viscous hydrogel dissolved in physiologic saline. Prepared by modification of HA with proprietary process.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water)	partial

	HA obtained from bacterial fermentation (streptococcus equi) 3ml syringe.	Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	Crosslinked HA of high MW (not specified) Concentration of 8mg/ml. Syringe of 3 ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	partial
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint to reduce pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	0.8% HA or 24mg/3ml crosslinked HA. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	partial

Device	**Gel.One or Gel-200** **Seikagaku Corp.**	**Focusial**	
Information source	Hymovis P150010B	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Treatment of pain in KOA	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the OA joints through IA injections to reduce pain in the knee	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	Sterile, transparent, viscoelastic hydrogel composed of cross-linked hyaluronate. HA obtained from chicken combs.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water) Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi)	partial

	3ml syringe.	2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	Crosslinked HA of high MW (not specified) Concentration of 8mg/ml. Syringe of 3 ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	partial
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint to reduce pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	1% HA or 30mg/3ml crosslinked HA. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	partial

Device	Durolane Q-Med AB variant: Durolane SJ	Focusial	
Information source	Migliore 2016 Migliore 2016b	MAN present Technical Documentation	
Clinical Equivalence			**Equiv.**
Used for the same clinical condition or purpose	Reduce pain and increase function in KOA/ Durolane SJ for other joints.	Reduce pain and increase function in KOA	yes
At the same site in the body	Intra-articular injections in the knee	Intra-articular injections in the knee	yes
In similar population *(restrictions not considered)*	Adults with OA	Adults with OA	yes
Have similar relevant critical performance according to expected clinical effect for specific intended use	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	VS of HA in the KOA joints through IA injections to reduce pain and increase joint functionality	yes
Technical Equivalence			**Equiv.**
Used under similar condition of use	IA injections	IA injections	yes
have similar specifications and properties	Sterile, transparent, viscoelastic gel of non-animal stabilized hyaluronic acid (NASHA) in buffered physiological sodium chloride solution.	sterile, biodegradable, isotonic, viscoelastic, apyrogenic, clear, colourless gel (solution in water)	partial

	Biosynthetically produced HA, purified and stabilized. 3ml syringe. Durolane SJ 1ml syringe.	Non animal sodium hyaluronate obtained from biofermentation (streptococcus equi) 2ml or 4ml vial syringe sterilized by moist heat.	
Be of similar design	Biosynthetical crosslinked HA of high MW (not specified) Concentration of 20mg/ml. Syringe of 3 ml.	HA of medium MW 1.5-2.0 MDa or high MW 2.5-3.5 MDa. Concentration of 20mg/ml. Syringe of 2 or 4 ml.	partial
use similar deployment methods	IA injections	IA injections	yes
have similar principles of operation	VS of degraded native HA in the joint to reduce pain.	VS of degraded native HA in the joint reproducing normal function and reducing pain.	yes
Biological Equivalence			**Equiv.**
Use same materials in contact with the same human tissue or body fluids	2% HA or 60mg/3ml stabilized HA. In contact with joints internal tissues.	2% HA or 40mg/2ml (80mg/4ml) sodium hyaluronate in buffer solution. In contact with joints internal tissues.	partial

4.3 Essential requirements relevant to the device from a clinical perspective

The following essential requirements have been addressed on the basis of the clinical data as relevant from a clinical perspective: (1) performance of the device; (2) safety of the device; (3) risks and favourable benefit/risk ratio related to the intended use; (4) target group and indications to be met.

The device is intended for a well established use. No special design features have been developed and implemented that pose special performance or safety concerns. The information supplied by the MAN through the instructions for use are assessed in Sec.6.3.

4.4 Brief outline of the search-retrieval process of published scientific literature

Literature searches were performed in the timeframe June-November 2016, using the databases from PubMed, Cochrane library, and ClinicalTrial.gov without time restrictions.

The search protocol reported in Sec.9, for retrieval of clinical data on equivalent devices, has been based on the following key terms in all fields, without any other filter, in the PubMed database (total unedited hits in parentheses):

Adant *[AND]* hyaluron* (10)	Intragel *[AND]* hyaluron* (1)
Arthrease *[AND]* hyaluron* (2)	Jointex *[AND]* hyaluron* (1)
Arthrum *[AND]* hyaluron* (3)	Monovisc *[AND]* hyaluron* (2)
Artz *[AND]* hyaluron* (22)	Neovisc *[AND]* hyaluron* (0)
Artzal *[AND]* hyaluron* (6)	NRD101 *[AND]* hyaluron* (2)
Athenavis *[AND]* hyaluron* (0)	NRD-101 *[AND]* hyaluron* (2)
BioHy *[AND]* hyaluron* (5)	Orthovisc *[AND]* hyaluron* (25)
Coxarthrum *[AND]* hyaluron* (1)	Ostenil *[AND]* hyaluron* (12)
Durolane *[AND]* hyaluron* (12)	Proial *[AND]* hyaluron* (0)
Euflexxa *[AND]* hyaluron* (12)	Promovia *[AND]* hyaluron* (0)

Fermathron *[AND]* hyaluron* (4)	Renehavis *[AND]* hyaluron* (0)
Gel-200 *[AND]* hyaluron* (4)	Replasyn *[AND]* hyaluron* (2)
Gel-one *[AND]* hyaluron* (1)	Sinovial *[AND]* hyaluron* (7)
Genvisc *[AND]* hyaluron* (1)	SLM-10 *[AND]* hyaluron* (2)
Go-on *[AND]* hyaluron* (7)	Sportvis *[AND]* hyaluron* (1)
HYADD4 *[AND]* hyaluron* (6)	Supartz *[AND]* hyaluron* (14)
Hyalart *[AND]* hyaluron* (3)	Suplasyn *[AND]* hyaluron* (9)
Hyalgan *[AND]* hyaluron* (82)	Suvenyl *[AND]* hyaluron* (4)
Hyalone *[AND]* hyaluron* (2)	Syaloset *[AND]* hyaluron* (0)
Hyalubrix *[AND]* hyaluron* (7)	Synocrom *[AND]* hyaluron* (2)
Hylan G-F 20 *[AND]* hyaluron* (82) - trials	Synolis *[AND]* hyaluron* (1)
Hylan G-F20 *[AND]* hyaluron* (10)	Synvisc *[AND]* hyaluron* (83) - trials
Hymovis *[AND]* hyaluron* (3)	Viscoplus *[AND]* hyaluron* (4)
Inartral *[AND]* hyaluron* (0)	Yaral *[AND]* hyaluron* (1)
	(Zeel compositum) *[AND]* hyaluron* (2)

The results have been assessed first for their title and abstract to discard all non relevant documents and then screened for substantial information about the safety and performance of the equivalent and partially equivalent devices. The check has been based on the following inclusion/exclusion criteria:

Inclusion criteria

- Works including clinical data about the performance of the device
- Works including clinical data about the safety of the device
- Works reflecting current state-of-the-art

- Works published in recognized scientific journals or trials databases
- Works reporting the outcome of a study according to scientific principles

Exclusion criteria

- Non-clinical works (no data, in vitro or animal, no new information, no humans)
- Works based on applications and clinical purposes not relevant to this evaluation (e.g. dermal filler among others)
- Works not on equivalent devices

These criteria can be justified by considering that the goal of the literature search is to retrieve substantial new clinical data about the performance and safety of equivalent devices. Thus, works not reporting clinical data or applied for not relevant clinical purposes can be excluded.

5 Device under evaluation

5.1 Scope

The scope of the present CER is to demonstrate that all the relevant information about safety and performance of **FOCUSIAL** are sufficiently addressed for in the scientific literature on equivalent devices, so that an acceptable benefit/risk ratio is achieved in light of the acceptability of the expected side effects.

As prescribed by the essential requirements in Annex I to the Medical Device Directive 93/42/EEC and following amendment directive:

- Requirement on safety and on the acceptability of the benefit/risk profile is given in MDD ER1 as:

  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: — reducing, 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).

- Requirement on performance is given in MDD ER3 as:

  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.

- Requirement on acceptability of side-effects is given in MDD ER6 as:

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

6a. Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.

The present CER will show that on the basis of collected clinical data and of the assessment made herein, **FOCUSIAL** can be considered to satisfy the essential requirements and thus to be lawfully designated for placing into the market.

5.2 Background

All the documents retrieved from the literature search have been included in this CER according to the method defined in the following section. Given that HA and its applications are extensively known in several medical fields and for a timeframe spanning the last three decades, the literature search procedure led to hundreds of documents.

Selection and appraisal has been focused to the relevance of the documents with respect to the purpose of this CER, thus absolute completeness of documents listing has been deemed beyond the scope of this CER. In this section the importance of the data relevant from a clinical perspective are categorized by taking into account first the equivalent devices, i.e. devices based on the same critical performance given by HA, sharing the same field of application and deployment methods. At last a summary of appraisals on meta-analyses performed in the same field of application of **FOCUSIAL**, which represent high value analyses due to the more systematic and rigorous assessment of the clinical data extractable from published trials.

All the referenced documents are stored (in pdf format) in the Bibliography folder of the clinical evaluation annex to the technical documentation of **FOCUSIAL**.

5.3 Methods and validity of data

The criteria to select the documents to evaluate in this CER have been defined in accordance to MEDDEV 2.7/1 rev.4 and tailored with respect to the specific field of HA and the MAN needs to comply with the requirements of Annexes I and X (MDD 93/42/EEC and following amendments directive).

Appraisal of documents has been based on the grading system defined in Appendix D of the Clinical Evaluation document SG5/N2R8:2007 by the GHTF in order to provide a quantitative weighting order of importance for each selected document. Consequently, with the aim of addressing the

safety and performance properties of **FOCUSIAL**, suitability and data contribution have been chosen as main areas of interest.

All safety related information was not subject to screening or exclusion criteria, although the widespread use of HA in medical fields led, until present date, to a well known and documented set of safety issues that specialized practitioners/scientists are aware of, as it is shown in this CER.

Each document is identified by the first author and the year of publication. Full bibliographic reference is written in the summary of appraisals and all references are reported.

Some documents referenced in this CER are not directly related to the safety or performance of **FOCUSIAL** but to better and comprehensively understand the background of the device and its field of medical application (i.e., reviews and guidelines). For this reason they are not included in the grading system of appraisal.

5.4 Summary of the clinical data and pivotal results from equivalent devices

Table 1 lists an overview and key results (pivotal data according to Sec.9.3.2 of MEDDEV 2.7/1 rev.4) of clinical studies performed with equivalent medical devices and studies where the safety profile was assessed through events reporting. Given that several meta-analyses have been published in the last ten years, it is deemed unnecessary to report the published studies that have already been assessed at least once in the same meta-analyses also assessed in this CER.

Tab. 1: Summary of clinical data from studies on equivalent devices.

Abbreviations: IA= intra-articular, HA= hyaluronic acid, KOA= knee osteoarthritis, SAE= serious adverse event, RCT= randomized clinical trial, MA= meta-analysis, VAS= visual analogue scale, WOMAC= Western Ontario McMaster universities Arthritis, KOOS= knee injury and OA outcome score, NSAID= non-steroidal anti-inflammatory drugs, PRP= platelet rich plasma, QoL= quality of life, PhGA= patient physician global assessment, ITT= intent to treat.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Totally equivalent linear HA						
Hyalubrix / Hyalone						
Vetro 2014	Hyalone	168	To evaluate the effects of a single IA injection in patients suffering from mild to moderate KOA.	Single-site, investigator-initiated, open, cohort study. 1 ultra-sound guided IA injection of 4ml HA and followed up for 24 weeks. Primary efficacy outcome was change from baseline in pain perception using VAS. Additional outcome WOMAC and KOOS assessed at 4,12, and 24 weeks.	Mild transient AE in 5 patients. Mostly post injection pain and swelling which resolved spontaneously after few days. Daily activities unaffected. No SAE.	Single IA injection well tolerated and provides relief from pain. Benefit to knee function confirmed with WOMAC and KOOS. Patients overall health improved with QoL

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
						and sport and recreation subscales.
Giarratana 2014	Hyalubrix	36	randomized, double-blind, parallel-group clinical trial aims to assess the equivalence of intraarticular polynucleotides compared to standard HA VS in the treatment of KOA.	All patients underwent three intra-articular injections of Condrotide or Hyalubrixwith an interval of 1 week. Participants, care givers, and investigators responsible for outcome assessment were all blinded to group assignment. Primary outcome measurements (KOOS and pain level (1)at rest, (2)at weight-bearing and (3) during physical activity) were evaluated at baseline and after 1,2,6,10, and 26 weeks. Secondary measurements COMP serum levels.	one drop-out was lost at follow-up. No significant adverse events were reported.	Condrotide is as effective as Hyalubrix in reducing knee OA symptoms but showed an earlier response on pain reduction and can therefore be considered a valid alternative to the use of HA in the treatment of OA, avoiding the adverse events of NSAIDs and of intra-articular corticosteroids.
Filardo 2012	Hyalubrix	55	To show, through a randomized double blind prospective trial, the efficacy of this	Patients were treated and evaluated at 12 months of follow-up. A cycle of 3 weekly injections was administered blindly. All patients were prospectively	Only minor adverse events were detected in some patients, such as	Results suggest that PRP injections offer a significant clinical

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			procedure, by comparing PRP to HA injections for the treatment of knee chondropathy or OA.	evaluated before and at 2, 6, and 12 months after the treatment by: IKDC, EQ-VAS, TEGNER, and KOOS scores. Range of motion and knee circumference changes were measured over time.	mild pain and effusion after the injections.	improvement up to one year of follow-up. However, conversely to what was shown by the current literature, for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections.
Foti 2011	Hyalubrix	1266	To investigated the safety and efficacy of IA HA (Hyalubrix) in the treatment of synovial joint OA.	Participants received IA injections of the study treatment (2 mL) once per week for 3 weeks. The primary endpoints were tolerability and details of usage of the IA HA syringe device. Efficacy parameters included assessment of self-reported pain via the VAS, and evaluation of motor function via the HAQ. QoL was	AE rate was 0.8% (95% CI, 0.4 to 1.5). 13 AEs were reported, 12 of which were mild or moderate in severity. Only one participant discontinued study	The study treatment was safe and well tolerated. The study treatment reduced pain, improved mobility, and increased QoL in participants with OA.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
				assessed using the Euro QoL questionnaire.	treatment following an AE. No SAE.	
Orthovisc						
Juni 2007	Synvisc Orthovisc Ostenil	222 219 219	To compare the efficacy and safety of IA hylan and 2 HAs in KOA.	Patients were randomly assigned to receive 1 cycle of 3 IA injections per knee of 1 of 3 HA preparations. The primary outcome measure was the change in the WOMAC pain score at 6 months. Secondary outcome measures included local adverse events (effusions or flares) in injected knees. During months 7–12, patients were offered a second cycle of VS.	There was a trend toward more local AE in the hylan group than in the HA groups during the first cycle (difference 2.2% [95% CI 2.4, 6.7]), and this trend became more pronounced during the second cycle (difference 6.4% [95% CI 0.6, 12.2]). SAE during the first cycle, which	No evidence found for a difference in efficacy between hylan (Synvisc) and HAs. In view of its higher costs and potential for more local AEs, we see no rationale for the continued use of hylan in patients with KOA.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
					occurred in 15 of 222 patients allocated to receive hylan and in 25 of 438 patients allocated to receive HAs.	
Kotevoglu 2005	Orthovisc Synvisc	26 26	To compare the elastoviscous properties of a HMW viscosupplement, hylan GF 20, with that of the lower MW Orthovisc in order to determine the relationship of elastoviscosity to efficacy, alongside placebo, in the treatment of patients with KOA.	Prospective, randomized clinical trial. Three weekly injections versus placebo. Primary outcome measures included WOMAC for pain, stiffness and function scores, and PGA/PhGA. Follow-up assessments were made at intervals of 1, 3 and 6 months after the first injection.	Local adverse events, such as transient pain at the injection site or warm knee lasting for one night, were recorded in two patients (3%).	Treatment with both HAs showed clinical improvement for pain, though no different from the placebo. WOMAC stiffness scores were better than placebo in the HAs, whereas PGA scores showed improvement in all but HAs were better than placebo. PhGA scores were worse in the

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
						placebo, but not to a statistically significant extent. The HAs did not differ in terms of clinical efficacy.
Atamaz 2006 assessed in MAs of Bellamy 2006, Reichenbach 2007, Monticone 2015 Neustadt 2005 assessed in MAs of Bellamy 2006, Trigkilidas 2013 Karatosum 2005 assessed in MAs of Bellamy 2006, Reichenbach 2007 Tascioglu 2003 assessed in MAs of Bellamy 2006, Bannuru 2009 Brandt 2001 assessed in MAs of Lo 2003, Aggarwal 2004, Wang 2004, Bellamy 2006, Bannuru 2011, Miller 2013, Strand 2015						
Artz / Supartz / Artzal						
Zhang 2015	Artz vs Durolane	174 175	We tested whether single and multiple injectionVS with HA is associated with clinically meaningful pain relief in a new RCT. Our objective was to compare safety and efficacy of IA HA	The Durolane group received a 3.0 ml injection at week 0 (baseline), with sham skin punctures at weeks 1, 2, 3, and 4. The Artz group received one 2.5 ml injection at each of the same time points. The primary assessment tool was the Likert-type WOMAC pain scale at weeks 0, 6, 10, 14, 18, and 26.	Artz vs Durolane 1)Patients with at least one treatment emergent AE: 74 (42.5%) vs 83 (47.4%) 2)Treatment-related AE:	Overall study retention was excellent; 332 patients (95.1%) completed 18 weeks and 319 (91.4%) completed 26 weeks, with no significant retention difference between treatment

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			in two formulations: one 3.0 ml injection of Durolane versus five 2.5 ml injections of Artz for the treatment of KOA pain.	Secondary assessments were WOMAC physical function, knee stiffness, and global self-assessment, at identical time points. Statistically-controlled analyses were non-inferiority of Durolane over 18, then over 26 weeks.	17 (9.8%) vs 23 (13.1%) 3)Musculoskeletal and connective tissue disorders: 16 (9.2%) vs 18 (10.3%) 4) Arthralgia: 13 (7.5%) vs 15 (8.6%) 5) Joint swelling: 3 (1.7%) vs 3 (1.7%) All others only 1 case (0.6%).	arms. All variables met non-inferiority criteria over 18 and 26 weeks. Efficacy response in both arms was >90%. Treatment-related AEs were 9.8% (17/174) for Artz and 13.1% (23/175) for Durolane. A single injection of Durolane is non-inferior to 5 injections of Artz over 18 and 26 weeks for pain, physical function, global self-assessment, and knee stiffness. Both treatments were

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
						efficacious, safe, and well tolerated.
Sun 2006	Artzal	68	To investigate the effects of IA HA (Artzal) in geriatric participants with unilateral KOA.	prospective, observer-blind study with 6 months follow-up. 68 patients, aged 65 years or above, with symptoms and radiographic Patients received 5 weekly IA injections of Artzal into symptomatic knees. VAS, Lequesne index and 4 balance tests including single-leg stance test, function reach test, timed ‘‘Up and-Go’’ test and Berg balance scale were assessed before injection and at each follow-up visit in the OA group.	Local AEs with transient pain at injection site and local warmth and swelling with varying intensities were reported in 4 patients (7.1%). No SAE or systemic AE were observed in the participants during the study.	Significant improvement in pain, physical function and balance tests was demonstrated after 5 weekly Artzal injections in geriatric patients with KOA. The effect had rapid onset at 1 week and may last for 6 months.
Day 2004 assessed in MAs of Arrich 2005, Medina 2006, Bellamy 2006, Bannuru 2011, Miller 2013, Trigkilidas 2013, Strand 2015 Karlsson 2002 assessed in MAs of Lo 2003, Arrich 2005, Medina 2006, Bellamy 2006, Reichenbach 2007, Bannuru 2011, Strand 2015 Wu 1997 assessed in MAs of Aggarwal 2004, Wang 2004, Arrich 2005, Bellamy 2006, Bannuru 2011, Miller 2013, Trigkilidas 2013, Strand 2015 Lohmander 1996 assessed in MAs of Lo 2003, Aggarwal 2004, Wang 2004, Arrich 2005, Bellamy 2006, Miller 2013, Trigkilidas 2013, Strand 2015 Puhl 1993 assessed in MAs of Lo 2003, Wang 2004, Arrich 2005, Bellamy 2006, Miller 2013, Richette 2015, Strand 2015						
Adant / GenVisc 850						

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Blanco 2008	Adant	26 (52 tot)	To determine whether HA delays and/or reduces the knee replacement surgery (KRS) in patients with KOA.	Prospective, single-center, double-blind, randomized, placebo-controlled, pilot clinical trial with two treatment groups (HA Adant treatment group and placebo). IA treatments (HA or placebo) of 2 cycles of 5 weekly injections with a 24-week interval between each cycle. Efficacy variables determined by change in pain, articular mobility and functional capacity as measured by WOMAC. All efficacy variables analyzed for the ITT population.	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 AE did not occur in either the placebo group or the HA group.	The use of IA HA to treat OA patients on the waiting list for KRS does not delay surgery. However, treatment with HA could significantly improve the physical condition of the patients because it reduces significantly the WOMAC total score and the physical function WOMAC subscale.
Navarro 2011 assessed in MA of Richette 2015 Roman 2000 assessed in MA of Bellamy 2006						
Euflexxa / Nuflexxa / BioHy						

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Lana 2016	Euflexxa PRP HA+PRP	36 36 33	To evaluate the clinical effects of PRP and HA as individual treatments for mild to moderate OA and it also examines the potential synergistic effects of PRP in combination with HA.	Multi-center, randomized, controlled, double blind, prospective trial. Mild to moderate KOA allocated to one of three interventions. 3 IA injections in knee with 2 week intervals between each injection. Clinical outcomes were evaluated using WOMAC Arthritis Index and VAS questionnaire at baseline and after 1,3,6 and 12months.	In all of the 105 patients, a mild adverse reaction in the form of a knee swelling was reported 3-5 days after the application. It was not a reported as a major complication by any patient.	PRP have significant reduction in VAS scores at 1 (p= 0.003), 3 (p= 0.0001), 6 (p= 0.0001) and 12 (p= 0.000) months when compared to HA. PRP illustrated greater improvement in WOMAC physical activity scale at 12 months (p= 0.008) when compared to the HA. HA+PRP resulted in a significant decreases in pain (p=0.0001) and functional limitation (p=0.0001) when compared to HA alone at 1 year post

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
						treatment; and significantly increased physical function at 1 (p=0.0004) and 3 (p=.011) months when compared to PRP alone.
Altman 2009 assessed in MAs of Bannuru 2011, Miller 2013, Richette 2015, Strand 2015 Kirchner 2006 assessed in MAs of Bellamy 2006, Reichenbach 2007 Tamir 2001 assessed in MAs of Lo 2003, Wang 2004, Arrich 2005, Bellamy 2006						
Sinovial / Yaral / Intragel / Jointex						
Pavelka 2011	Sinovial Synvisc	183 171	To demonstrate the non-inferiority of the highly purified IA injection of HA Sinovial in comparison to Hylan G-F20 (Synvisc) in the treatment of KOA.	Phase III, double-blind, multicenter, randomized, non-inferiority study. Patients were randomly assigned to receive either the test drug (Sinovial), or the comparative drug (Synvisc). The duration of the treatment was 2 weeks (three injections at 1-week interval), followed by an observation period of 6 months.	Effusion >15 ml in the target knee, lost to follow-up (2 each). Of the AEs, 6 were considered treatment-related, with 5 events in 4 patients in the	Sinovial and Synvisc treatments were found to be equivalent, both in terms of efficacy and safety.There were no statistically significant differences between groups at 26 weeks,

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
				The primary efficacy variable was the improvement in mean WOMAC pain subscore from baseline to the final visit (week 26), compared between the two treatment groups.	Synvisc [injection site hematoma, injection site pain, arthralgia and joint swelling (2 episodes in 1 patient)] and 1 case of injection site pain in Sinovial. There were 7 SAE: 6 in Synvisc and 1 in Sinovial. None of the SAE were thought to be treatment-related.	although Sinovial-treated patients tended to have a slightly better outcome for select variables. Both HA were well-tolerated, with no statistically significant differences in tolerability profile.
Fermathron						
Van der Weegen 2015	Fermathron Plus	99	To examine the effectiveness and safety of Fermathron plus in patients with	Randomized, controlled, double-blind trial. Patients were given either 3 weekly IA injections of HA or saline (placebo). Efficacy variables the range	There were no SAE in either group.	Although pain and functional scores (WOMAC scale) improved significantly

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			mild to moderate KOA vs placebo.	of motion, WOMAC scores for pain, stiffness and function, VAS fo pain at rest and in motion, knee flexion and recording of limitations in sports and work activities. Assessments at 1, 3, and 6 months.		from baseline up to 6 months, HA was not superior to placebo at any follow-up (VAS pain 50 m walking from 56.4 to 38.1, P b .001, and 58.2 to 39.6, P b .001, respectively). No subgroup analysis resulted in superior outcomes. HA treatment is generally well-tolerated with little to no AE.
Suvenyl / NRD101						
Ishijima 2014	Suvenyl	99	To clarify the efficacy and safety of early-phase IA-HA in comparison to those of	Multicenter, randomized, open-label, parallel-group, non-inferiority comparison study. NSAIDs three times per day for five weeks (n = 100) or IA-	The frequency of both withdrawal and AE in the IA-	The early efficacy of IA-HA is suggested to be not inferior to that of NSAIDs, and that

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			NSAIDs for patients with KOA.	HA once a week for five weeks (n = 100). The primary endpoint was the percentage change in the patient-oriented outcome measure for knee OA, the Japanese Knee Osteoarthritis Measure (JKOM) score. All patients were questioned regarding any adverse events during treatment. The full analysis set was used for analysis. The margin of non-inferiority was 10%.	HA were significantly lower than those in the NSAID (P = 0.026 vs 0.004, respectively). As one patient complained of stiffness in the affected knee after injection, the frequency of AE in patients treated with the IA-HA was 1.0%. 10 (symptom related to GI disorder, 7; drug allergy, 3) of 93 patients (10.8%) exhibited AE in NSAID.	the safety of the early phase of IA-HA is superior to that of NSAIDs for patients with KOA.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Pham 2004 assessed in MAs of Lo 2003, Medina 2006, Bellamy 2006, Bannuru 2011						
Ostenil						
Juni 2007	Synvisc Orthovisc Ostenil	222 219 219	Already discussed. See Orthovisc section above.			
Skwara 2009	Ostenil	20	Evaluation of gait performance and muscle activity patterns as well as clinical efficacy and safety after IA injections with Ostenil compared with triamcinolone (Volon A10) injections in patients with KOA.	Prospective, randomised, double-blind clinical trial. The study period was 16 to 18 weeks for each patient. This period included the screening visit (visit 1) and the wash-out period of previous medication for two weeks if necessary, five injections of HA/TA and 2 follow up visits, 1 week (visit 7) and 12 weeks (visist 8) after the last injection. For the clinical evaluation VAS for pain, Lequesne index, and Knee Society Score were used. Quality of life was estimated with the SF-36. Instrumented gait analysis was performed with reflective markers	No AE in both groups.	HA was not superior to triamcinolone. The results suggest that treatment with HA can reduce pain and improve knee function. A significant short term improvement in gait and muscle activity patterns, however, was not observed, in either HA or triamcinolone.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
				applied according to the Helen–Hayes marker set.		
Go-On						
Berenbaum 2012	Go-On Hyalgan	171 172	To compare the effects of an intermediate MW IA HA with a low MW product on KOA symptoms.	Randomised, double-blind, controlled , parallel- group, non-inferiority trial. Single injections at 3-weekly intervals. The primary outcome was 6-month change in the WOMAC pain subscale. Secondary endpoints included OARSI-OMERACT responder rates.	Joint effusion/swelling 1 (0.4%) vs 4 (1.9%) between Go-On and Hyalgan respectively. Joint pain 3 (1.4%) vs 2 (0.9%). Injection site haematoma 0 vs 2 (0.9%). Injection site warmth 0 vs 1 (0.5%). Total number of patients with any of the above local AE	ITT WOMAC pain decreased by 22.9±1.4 mm with Go-On and 18.4±1.5 mm with Hyalgan after 6 months. Mean (95% CI) differences in WOMAC pain change favouring Go-On, satisfying the claim for non-inferiority and for statistical superiority (95% CI all>0, p=0.021). Both preparations well tolerated.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
					4 (1.8%) vs 8 (3.8%).	
Kausch 2009	Go-On	1533	To examine the efficacy, the treatment effect persisting beyond therapy, and the safety of injections of Go-On under practical conditions in a non-selected patient population.	Non-interventional study. Efficacy was examined two weeks after the conclusion of the injection series and twelve weeks after the start of the injection series. Injections up to 5 times into the joint space of the diseased joint, with a 1 week interval between injections. Efficacy after 3 or 5 injections is examined comparatively. Parameters pain, functional impairment, overall assessment by patient and physician.	1 female patient withdrew from the study after the second injection because of pain which occurred on the day of the injection. 1 other female patient experienced a pulmonary embolism which occurred more than one month after the third injection, however.	Relative to the total number of joints treated the treatment resulted in statistically significant pain relief and functional improvement. AE that could be associated with the trial preparation were reported extremely rarely. The IA therapy with the trial preparation can be considered effective beyond treatment and very safe in therapeutic routine.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Arensi 2006	Go-On Hyalgan	20 20	To compare the efficacy and therapeutic safety of two formulations of HA, in patients with KOA.	Controlled, randomized, parallel-group study, treatment with 2 intra-articular injections every week for 5 weeks with 3 months of follow-up. Symptoms and function parameters were assessed weekly until week 5 and at 3 months of follow-up. Primary parameters were pain, articular stiffness and joint function, as WOMAC index subscales, Lequesne index and movement restriction and ability of walking, and general health state evaluated with the VAS scale.	No AE reported.	the two formulations of HA employed in the treatment of KOA exhibit a totally overlapping efficacy and therapeutic safety.
Hyalgan / Hyalart						
Askari 2016	Hyalgan CS	71 69	To evaluate the therapeutic effect of Iia HA in comparison to	Randomized, controlled trial. By receiving one injection of drug during the enrollment in the study, the patients were treated. With the	No AE reported.	WOMAC score represented that pain and stiffness did not

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			corticosteroids (CS) for KOA.	WOMAC index, Knee injury and OA Outcome Score (KOOS), and the VAS pain scale, an independent, blinded evaluator assessed the patients three times.		improve in neither groups at any time points after intervention (P > 0.05). KOOS score suggested that symptoms improved after 3 months in both CS and HA groups. Besides, daily activity improved in both groups (P < 0.05). HA is suggested to be superior in the duration of pain relief when compared to CS.
Berenbaum 2012	Go-On Hyalgan	171 172	Already discussed. See Go-On section above.			
Arensi 2006	Go-On	20	Already discussed.			

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
	Hyalgan	20	See Go-On section above.			
Kolarz 2003	Hyalgan	108	To assess the long-term efficacy and tolerability of Hyalgan after 1 cycle of 5 IA injections in patients with KOA. Benefits of a second treatment cycle also assessed.	IA injections of Hyalgan administered at baseline and then once weekly for 4 consecutive weeks for a total of 5 injections. Efficacy and safety recorded at the time of each injection, 1 week after the last injection and then monthly for up to 12 months after the end of therapy. The primary efficacy parameter was pain on movement with VAS. Secondary parameters included pain on movement and at rest assessed on a 5-point Likert ordinal pain scale and pain at rest (VAS) as well as knee joint function was assessed according to the Larson Total Score. Other clinical parameters, including onset of effect, maximum walking time, and global assessment of efficacy scored by the	Of 4 patients who withdrew because of adverse events, only 1 event (knee joint effusion) was judged as possibly drug related. Two other adverse events judged to be drug related (generalized skin eruption; pruritus and knee joint effusion) resolved and did not lead to study withdrawal.	Significant improvements in all efficacy parameters compared with the baseline values starting from 1 week after the last injection until month 12 for the 59 completed patients and also for all 108 enrolled patients. Safety and tolerability of Hyalgan were good or very good in more than 90% of patients.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
				investigator and the patient, consumption of acetaminophen, and signs of inflammation also evaluated.		
Huang 2011 assessed in MAs of Miller 2013, Strand 2015 Jorgensen 2010 assessed in MAs of Miller 2013, Strand 2015 Lundsgaard 2008 assessed in MAs of Bannuru 2011, Miller 2013, Richette 2015, Strand 2015 Jubb 2003 assessed in MAs of Lo 2003, Arrich 2005, Bellamy 2006, Bannuru 2011, Miller 2013, Richette 2015, Strand 2015 Forster 2003 assessed in MAs of Bellamy 2006 Miltner 2002 assessed in MAs of Aggarwal 2004, Bellamy 2006 Roman 2000 assessed in MAs of Bellamy 2006 Huskisson 1999 assessed in MAs of Lo 2003, Aggarwal 2004, Wang 2004, Medina 2006, Bellamy 2006, Bannuru 2011, Miller 2013, Trigkilidas 2013, Strand 2015 Jones 1995 assessed in MAs of Bellamy 2006, Bannuru 2009, Trigkilidas 2013 Henderson 1994 assessed in MAs of Lo 2003, Wang 2004, Bellamy 2006, Bannuru 2011, Miller 2013, Trigkilidas 2013, Strand 2015						
Suplasyn						
Blanch 2012	Suplasyn 1-Shot	411	Evaluation of the effectiveness and safety in real-life conditions of a	International multicentre, non-interventional, observational study. Pain at rest and pain at walking was evaluated based on VAS in each visit,	9 patients (2.2%) had at least 1 AE. 7 AE related or possibly related to	After injection, mean VAS pain at rest was significantly lower 3

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			viscoelastic solution of HA for IA one-shot injection in OA.	as well as the Lequesne functional index for QoL impact of OA. AE were registered during the follow up. Efficacy of the injection was evaluated in terms of the functional impact on KOA, using patient self-evaluation.	the injection, which 3 of them were related to local AE: post injection pain (n = 1), local swelling (n = 1) and sensation of hot knee (n = 1) (Table 3). All AEs related to product resolved within 0-5 days.	and 6 months after treatment wrt baseline VAS score. IA 1-shot injection of viscoelastic solution of HA is effective in providing clinically relevant pain relief over a period of at least 6 months in KOA.
Gydek 2011	Suplasyn	4505	To reconfirm efficacy and safety of IA use of Suplasyn in the treatment of KOA.	Observational study. Each patient received a mean of 3 IA injections of Suplasyn and followed for 1 month. Measures included pain at rest and pain during walking (VAS score). Changes in pain intensity (basic scored characteristic for OA degree) and symptoms like morning stiffness, after rest stiffness, pain after	AE, such as edema, exudate, pruritus, redness and pain occurred in 1.6% of the patients. However, association with some of these effects with the	The study confirmed high efficacy and good to-lerance of Suplasyn in the treatment of KOA. Due to adverse reactions related to the treatment with NSAIDs, treatment with HA is increasingly

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
				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.	injection itself cannot be excluded. No SAE reported.	considered as the therapy of choice in patients suffering from OA.
Mazieres 2007	Suplasyn	296	To evaluate treatment benefits in terms of pain, function, and QoL.	Observational, multicenter, longitudinal, before-after study of the medical benefits and costs of VS with Suplasyn in symptomatic KOA. 3 injections at intervals of 1 week. Evaluated 3 months and 6 months after last injection.	Skin allergy at the injection site (n=1)	The cost of the medication was more than offset by the decreased need for other treatments. Clinical benefits were obtained. In daily practice, HA may provide medical benefits at an acceptable cost.
Petrella 2006 assessed in MAs of Bannuru 2011, Trigkilidas 2013, Richette 2015 Petrella 2002 assessed in MAs of Aggarwal 2004, Arrich 2005, Medina 2006, Bellamy 2006, Bannuru 2014						
Cross-Linked / stabilized HA						

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Sinvisc / Hylan G-F 20						
Pavelka 2014	Sinovial Synvisc	183 171	Already discussed. See Sinovial section above.			
Juni 2007	Synvisc Orthovisc Ostenil	222 219 219	Already discussed. See Orthovisc section above.			
Kotevoglu 2005	Orthovisc Synvisc	26 26	Already discussed. See Orthovisc section above.			
Chevalier 2010 assessed in MAs of Bannuru 2011, Trigkilidas 2013, Richette 2015 Kirchner 2006 assessed in MAs of Bellamy 2006, Reichenbach 2007 Atamaz 2006 assessed in MAs of Bellamy 2006, Reichenbach 2007, Monticone 2015 Karatosum 2005 assessed in MAs of Bellamy 2006, Reichenbach 2007 Carbon 2004 assessed in MAs of Bellamy 2006, Bannuru 2009 Leopold 2003 assessed in MAs of Bellamy 2006, Trigkilidas 2013 Kahan 2003 assessed in MAs of Bellamy 2006 Raynauld 2002 assessed in MAs of Aggarwal 2004, Bellamy 2006 Karlsson 2002 assessed in MAs of Lo 2003, Arrich 2005, Medina 2006, Bellamy 2006, Reichenbach 2007, Bannuru 2011, Strand 2015 Wobig 1999 assessed in MAs of Bellamy 2006, Reichenbach 2007						

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Wobig 1998 assessed in MAs of Lo 2003, Aggarwal 2004, Wang 2004, Arrich 2005, Bellamy 2006, Bannuru 2011, Miller 2013, Trigkilidas 2013, Strand 2015 Adams 1995 assessed in MAs of Aggarwal 2004, Bellamy 2006, Bannuru 2014						
Hymovis						
Zorzi 2015	Hymovis	25	To investigate the efficacy of IA injections of Hymovis in the management of meniscal tears and in meniscal tear repair vs conservative treatment.	Single-site, observer-blind, parallel-group study. Clinical evaluations were performed at baseline and after 14, 30 and 60 days. Clinical outcomes included: pain reduction (VAS), improvement of knee functionality (WoMAC questionnaire), reduction in length and depth of the meniscal lesion (MRi-confirmed) and SF-36 questionnaire scores.	10 AE (2 in HA and 8 in the control group): worsening of the disease or the occurrence of a new lesion detected by MRI: 1 (4%) in HA developed a new lesion versus 3 (12%) in the control group.	this study may indicate a new treatment option in the conservative management of patients complaining of pain due to meniscal tears. the MRI data suggest that the HA used in this study may also play a role in the healing process of the lesion.
Gel One / Gel-200						
Strand 2016	Gel-200	251	To analyses the safety of retreatment with	379 patients were enrolled in the RCT (Gel-200 vs PBS). Safety of retreatment with Gel-200 was	In the OLE, the safety of Gel-200, including	In the OLE, the safety of a second injection of Gel-200 was

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
			Gel-200 from the 13-week, pivotal, multicenter, RCT followed by an open-label extension trial (OLE).	assessed by comparing AE and device-related AEs reported through Week 4 following retreatment with Gel-200 to those reported in patients receiving their first injection in the OLE.	percentages of patients who experienced any AEs (p = 0.547) and device-related AEs (p = 0.521), did not significantly differ between those receiving a second versus a first injection of Gel-200 following PBS in the RCT.	comparable to that of a first injection and effectiveness was similar, as previously reported.
Strand 2012 assessed in MAs of Miller 2013, Strand 2015						
Durolane						
Zhang 2015	Artz vs Durolane	174 175	Already discussed. See Artz section above.			

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
Leighton 2014	Durolane	221	To compare HA gel as single-injection IA treatment for KOA against methylprednisolone acetate (MPA).	Prospective, multi-centre, randomized, active-controlled, double-blind, non-inferiority clinical trial. A unique, open-label extension phase (OLE) was undertaken to answer further clinical questions. Subjects with painful unilateral KOA were treated and followed for 26 weeks (blinded phase). At 26 weeks patients were offered HA treatment, with a subsequent 26-week follow-up period (extension phase). The primary objective was to show non-inferiority of HA vs MPA in WOMAC pain responder rate at 12 weeks.	No SAE device-related were reported. Arthralgia 38 (17.2%) Injection site pain 3 (1.4%) Joint stiffness 4 (1.8%) Joint swelling 5 (2.3%) Open label extension: Arthralgia 30 (18.4%) Joint stiffness 1 (0.6%) Joint swelling 2 (1.2%)	Effect size for WOMAC pain, physical function and stiffness scores favoured HA over MPA from 12 to 26 weeks. In response to HA treatment at 26 weeks, sustained improvements were seen in WOMAC outcomes irrespective of initial treatment.

Study	Device	#Patients	Study Aim	Treatment and Assessment	Adverse reactions	Conclusion performance
					Musculoskeletal discomfort 3 (1.8%).	
Altman 2004 assessed in MAs of Medina 2006, Bellamy 2006, Bannuru 2011, Trigkilidas 2013, Richette 2015						

5.5 Summaries of studies and appraisal

Vetro 2014 A.**,** et al.: **Pain relief and functional recovery over a six-month period after intra-articular injection with sodium hyaluronate (MW 1500-2000 Kda) in osteoarthritis of the knee** European Journal of Musculoskeletal Diseases vol. 3, no.1, 25-33 (2014).
Objective: The present study aimed to evaluate the effects of a single intra-articular injection of a high molecular weight (MW) (1500-2000 KDa) naturally linear hyaluronic acid (HA) in patients suffering from knee osteoarthritis (OA). Method: One hundred and sixty-eight patients with mild to moderate OA of the knee were enrolled to receive one ultrasound-guided intra-articular (IA) injection of 4 ml Sodium Hyaluronate (HyalOne) and were followed up for 24 weeks. The primary efficacy outcome was the change from baseline to week 24 in patients' pain perception using a 100 mm visual score scale (VAS). Additional outcomes included the Western Ontario McMaster Universtities Arthritis score (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS) assessed at 4, 12 and 24 weeks. Results: The patients enrolled showed a significant improvement from baseline in all symptomatic outcome measures. Pain significantly decreased after treatment. VAS pain decreased from the baseline mean value of 77.7 mm (SD 8.8 range: 60-90) to the mean value of 13.8 mm (SD 4.9, range: 10-20) at week 24. The analysis of variance for repeated measures conducted on VAS, on each WOMAC subscale, on the total WOMAC score and on each KOOS subscale score showed a significant reduction in all scores at each study point (week 4, 12 and 24) ($p<0.001$). Comparisons between

week 4 and week 12 scores and week 12 and week 24 scores showed a significant and progressive improvement ($p<0.05$, Wilcoxon test) during the study.

Conclusions: The present study suggests that a single IA injection of linear high MW HA in patients suffering from knee OA is well tolerated and provides relief from pain. Benefit to the knee function was confirmed by both the WOMAC and the KOOS scores. The patients' overall health status also improved as demonstrated by the high scores registered at the post-treatment KOOS Function in daily Living, Quality of Life and Function in Sport and Recreation subscales.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use
Appropriate patients	Patient group (168) discussed was representative of the intended treatment population.
Acceptable reporting/data	Assessments at 4, 12 and 24 weeks. Trends of parameters analysed.
Appropriate study design	Single-site, investigator-initiated, open, cohort study. Limitation due to no control group and no blinding.
Outcome measures	Variation wrt baseline of: pain, stiffness, functional impairment, function in daily living, function in sport and recreation, quality of life. Acknowledged methodology but limitation due to subjective nature of the parameters values.
Follow up period	24 weeks, enough for pain and function assessment on short-medium time range but not long range.
Statistical significance	Number of patients sufficient but only descriptive analysis used. Parameters gave statistically significant results.
Clinical significance	Injection of HA increases the pain, functionality and quality of life in the short-medium time range for patients suffering from KOA with more than acceptable AE and no SAE reported.

Giarratana 2014 L.S., et al.:

A randomized double-blind clinical trial on the treatment of knee osteoarthritis: The efficacy of polynucleotides compared to standard hyaluronian viscosupplementation.

The Knee 21 (2014) 661–668.

Background: This randomized, double-blind, parallel-group clinical trial aims to assess the equivalence of intraarticular polynucleotides compared to standard hyaluronic acid (HA) viscosupplementation in the treatment of knee osteoarthritis (OA).

Methods: 75 patients affected by knee OA were assessed for eligibility and 72 were enrolled and randomized to receive either intra-articular polynucleotides (Condrotide-36 patients) or hyaluronic acid (Hyalubrix-36 patients) at the Orthopedic Institute “Gaetano Pini” (Milan). All patients underwent three intra-articular injections of Condrotide or Hyalubrixwith an interval of 1 week. Participants, care givers, and investigators responsible for outcome assessment were all blinded to group assignment. Primary outcome measurements (KOOS and pain level (1)at rest, (2)at weight-bearing and (3)

during physical activity) were evaluated at baseline (T0) and after one (T1), two (T2), six (T6), ten (T10), and 26 (T26) weeks.
Secondary measurements included the determination of COMP serum levels at T0, T6 and T26.

Results: The reduction of pain and the increase of KOOS values frombaselinewere statistically significant for both treatments; nevertheless, for parameter KOOS “symptoms” the treatment with Condrotide showed significant results already after two weeks (at T2 p= 0.003) while the results obtained with Hyalubrix became significantonly after 18 weeks (at T18 p = 0.01). No significant adverse events were reported.

Conclusions: Condrotide is as effective as Hyalubrix in reducing knee OA symptoms but showed an earlier response on pain reduction and can therefore be considered a valid alternative to the use of HA in the treatment of OA, avoiding the adverse events of NSAIDs and of intra-articular corticosteroids.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. HA as control group vs polynucleotides.
Appropriate patients	Patient group (36) discussed was representative of the intended treatment population.
Acceptable reporting/data	Assessments at 6 time points up to 26 weeks. Trends of parameters analysed. Extensive methodology and data reporting.
Appropriate study design	Randomized, double-blind, parallel-group clinical trial Limitation due to number of total patients enrolled and AE not accurately described.
Outcome measures	Variation wrt baseline of key parameters as pain and functionality in daily living, function in sports and recreation and QoL, also COMP serum level and adverse events. Acknowledged methodology but limitation due to subjective nature of the parameters values.
Follow up period	26 weeks, enough for pain and function assessment on short-medium time range but not long range.
Statistical significance	Limited number of total patients but extensive statistical analysis. Parameters gave statistically significant results but trends at the end of follow up point to HA rise over polynucleotides.
Clinical significance	HA performance on pain and functionality increasing over time until follow up end whereas polynucleotides was picked

	in between the timeframe considered. Good safety profile but limited by the population number.

Filardo 2012 et al.: **Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial.** BMC Musculoskeletal Disorders 2012 13:229.
Background: Platelet Rich Plasma (PRP), a blood-derived product rich in growth factors, is a promising treatment for cartilage defects but there is still a lack of clinical evidence. The aim of this study is to show, through a randomized double blind prospective trial, the efficacy of this procedure, by comparing PRP to Hyaluronic Acid (HA) injections for the treatment of knee chondropathy or osteoarthritis (OA). Methods: 109 patients (55 treated with HA and 54 with PRP) were treated and evaluated at 12 months of follow-up. The patients were enrolled according to the following inclusion criteria: age> 18 years, history of chronic (at least 4 months) pain or swelling of the knee and imaging findings of degenerative changes of the joint (Kellgren-Lawrence Score up to 3). A cycle of 3 weekly injections was administered blindly. All patients were prospectively evaluated before and at 2, 6, and 12 months after the treatment by: IKDC, EQ-VAS, TEGNER, and KOOS scores. Range of motion and knee circumference changes were measured over time. Adverse events and patient satisfaction were also recorded. Results: Only minor adverse events were detected in some patients, such as mild pain and effusion after the injections, in particular in the PRP group, where a significantly higher post-injective pain reaction was observed (p=0.039). At the follow-up evaluations,

both groups presented a clinical improvement but the comparison between the two groups showed a not statistically significant difference in all scores evaluated. A trend favorable for the PRP group was only found in patients with low grade articular degeneration (Kellgren-Lawrence score up to 2).

Conclusions: Results suggest that PRP injections offer a significant clinical improvement up to one year of follow-up. However, conversely to what was shown by the current literature, for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections, and thus it should not be considered as first line treatment. More promising results are shown for its use in low grade degeneration, but they still have to be confirmed.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. HA compared to platelet-rich plasma.
Appropriate patients	Patient group (55) discussed was representative of the intended treatment population.
Acceptable reporting/data	Assessments at 6 time points up to 26 weeks. Trends of parameters analysed. Extensive methodology and data reporting.
Appropriate study design	Randomized, double-blind, prospective study. Good population size, follow-up time and objective parameters.
Outcome measures	Widely used methodology to assess the key parameters. Beyond typical outcome measures, relevant choice of objective parameters as ROM and transpatellar circumferences.
Follow up period	12 months, enough for pain and function assessment on medium-long time range.
Statistical significance	Extensive statistical analysis. Parameters gave statistically significant results.

Clinical significance	Superiority of HA in a wider population class of KOA grades. High safety profile but not extensively reported.

Foti 2011 C., et al.:

A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis.

EUR J PHYS REHABIL MED 2011;47:407-15.

Background. Clinical trials have demonstrated the safety and efficacy of hyaluronic acid-based products for the treatment of synovial joints affected by osteoarthritis (OA), but data from observational studies of normal medical practice are sparse.

Aim. This study investigated the safety and efficacy of intra-articular (IA) sodium hyaluronate (MW 1500-2000 KDa; Hyalubrix®) in the treatment of synovial joint OA. Design. This is prospective, and observational study. Setting. This study was carried out at 47 specialist centers for physiatrists, orthopedics and rheumatology in Italy; the enrolled population, 1266 outpatient, was predominantly female (66%, 840/1266), with a mean age of 66 years, and a mean weight of 74 kg. Population. The Participants with OA received IA injections of the study treatment (2 mL) once per week for 3 weeks. The knee was the joint most commonly affected by OA (right knee 802/1266 [63%]; left knee 598/1266 [47%]), and the longest median duration of disease occurred in the carpal joint (right carpal joint 40 months; left carpal joint 60 months).

Methods. The primary endpoints were tolerability and details of usage of the IA sodium hyaluronate syringe device. Efficacy parameters included assessment of self-reported pain via the Visual Analogue Scale (VAS), and evaluation of motor function via the

Health Assessment Questionnaire (HAQ). Quality of life (QoL) was assessed using the Euro QoL questionnaire (Clinical Trial Registration Number: ISRCTN 42690497).

Results. Data from 1266 participants were collected. The adverse event (AE) rate was 0.8% (95% CI, 0.4 to 1.5). Thirteen AEs were reported, 12 of which were mild or moderate in severity. Only one participant discontinued study treatment following an AE. No serious adverse events occurred. Coadministration of local anesthetic was required by up to 10% of patients. Statistically significant improvements in VAS, HAQ and EuroQoL were recorded in multiple joints (P<0.0001 for each).

Conclusion. The study treatment was safe and well tolerated. Clinical rehabilitation impact. The study treatment reduced pain, improved mobility, and increased QoL in participants with OA.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use only for knee.
Appropriate patients	Patient population (1266) discussed was representative of the intended treatment population for the knee application only.
Acceptable reporting/data	Assessments at 1 time points after 3 weeks from last application. Extensive data reporting and parameters analysis on the tolerability profile.
Appropriate study design	Prospective, observational study. Good population size, although different conditions were assessed on assumption of equivalence.
Outcome measures	Widely used methodology to assess the key parameters. Beyond typical outcome measures, relevant choice of specifically assessing the tolerability and safety profiles.
Follow up period	Very short, 3 weeks but a longer follow-up beyond the scope of the study.

Statistical significance	Extensive statistical analysis. Parameters gave statistically significant results. Primary endpoints related to the tolerability profile of the treatment itself.
Clinical significance	Effective tolerability of HA treatment of joints OA and acceptable safety profile versus risks.

Jüni 2007 P., et al.:

Efficacy and Safety of Intraarticular Hylan or Hyaluronic Acids for Osteoarthritis of the Knee A Randomized Controlled Trial.

ARTHRITIS & RHEUMATISM Vol. 56, No. 11, November 2007, pp 3610–3619 DOI 10.1002/art.23026.

Objective. To compare the efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) in osteoarthritis (OA) of the knee.

Methods. This was a multicenter, patient-blind, randomized controlled trial in 660 patients with symptomatic knee OA. 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. The primary outcome measure was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score at 6 months. Secondary outcome measures included local adverse events (effusions or flares) in injected knees. During months 7–12, patients were offered a second cycle of viscosupplementation.

Results. Pain relief was similar in all 3 groups. The difference in changes between baseline and 6 months between hylan and the combined HAs was 0.1 on the WOMAC pain score (95% confidence interval [95% CI] 0.2, 0.3). No relevant differences were observed in any of the secondary efficacy outcomes, and stratified analyses provided

no evidence for differences in effects across different patient groups. There was a trend toward more local adverse events in the hylan group than in the HA groups during the first cycle (difference 2.2% [95% CI 2.4, 6.7]), and this trend became more pronounced during the second cycle (difference 6.4% [95% CI 0.6, 12.2]).

Conclusion. We found no evidence for a difference in efficacy between hylan and HAs. In view of its higher costs and potential for more local adverse events, we see no rationale for the continued use of hylan in patients with knee OA.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use for all 3 HAs
Appropriate patients	Patient population (660) discussed was representative of the intended treatment population
Acceptable reporting/data	Comprehensive analysis on multiple data shown in the article. Extensive explanation of methodology, assessment, and results selection.
Appropriate study design	Multicenter, single-blind, randomized, controlled trial. Large population size, detailed statistical analysis.
Outcome measures	Change in pain score of WOMAC. Secondary WOMAC global score and subscores on stiffness and disability,health related quality of life and visual analog score.
Follow up period	6 months. In line to gather information on safety and performance of the 3 different HAs used.
Statistical significance	Extensive statistical analysis. Parameters gave statistically significant results. High power due to large population size.
Clinical significance	The different types of HA gave no difference in efficacy but cross-linked HA associated with higher risks.

Kotevoglu 2005 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 Feb;26(4):32530. Epub 2005 Jun 15., DOI: 10.1007/s0029600506110.

This prospective, controlled, doubleblind, randomised clinical trial was aimed at comparing the elastoviscous properties of a high molecular weight viscosupplement, hylan GF 20, with that of a lower molecular weight hyaluronan product in order to determine the relationship of elastoviscosity to efficacy, alongside placebo, in the treatment of patients with knee OA.

The results were analysed as a "completers" analysis with 59 patients. Primary outcome measures included the Western Ontario and Mc Master Universities' Osteoarthritis Index (WOMAC) for pain, stiffness and function scores, and patient and physician global assessments (0100 scale). For patient (PGA) and physician global assessments (PhGA), the 0100 scale was used, with 100 being the worst. Follow up assessments were made at intervals of 1, 3 and 6 months after the first injection. Local adverse events, such as transient pain at the injection site or warm knee lasting for one night, were recorded in two patients (3%). In all groups, the WOMAC pain score exhibited a significant difference from the baseline value; neither treatment group was significantly different from the placebo group, but total pain score was significantly better than baseline for both of the HA groups at the end of 6 months ($p < 0.05$). Improvement in WOMAC physical function score favoured both sodium hyaluronate and hylan GF 20 after the first month, and remained significant until the end of 6 months ($p < 0.01$). In the placebo group, the physical function scores became worse after the end of the 1st month; the scores at the end of 6 months were no different from those at the beginning. The WOMAC stiffness scores of both of the hyaluronic acid groups improved with the

first injection, and remained significantly better than the placebo group until the end of the survey ($p < 0.001$). All groups expressed improvement with PGA scores after the first injection. At the end of 6 months all three groups were similar, but the treatment groups were significantly better than the placebo group ($p < 0.05$), and all were significantly better than at the beginning ($p < 0.05$). The PhGA scores were similar in all groups until after the third injection. The second group was slightly better in the controls at 1 and 3 months, but all the groups were similar at the end of 6 months. Although the placebo group seemed worse, it was not statistically significant.

Compared with lower molecular weight HA, the higher molecular weight HA might be more efficacious in treating knee OA, but heterogeneity of previous studies limited definitive conclusions. Patients treated by injection of either of two hyaluronan preparations showed clinical improvement for pain, though no different from the placebo group; WOMAC stiffness scores were better than placebo in the HA groups, whereas PGA scores showed improvement in all groups but HA groups were better than placebo. PhGA scores were worse in the placebo group, but not to a statistically significant extent. The HA groups did not differ in terms of clinical efficacy.

Appraisal	
Appropriate device	Equivalent HA.
Appropriate application	Same intended use for both HAs.
Appropriate patients	Patient population (52) discussed was representative of the intended treatment population.
Acceptable reporting/data	Comprehensive analysis on multiple data shown in the article. Extensive explanation of methodology, assessment, and results selection.
Appropriate study design	Prospective, randomized clinical trial. Three weekly injections versus placebo. In line with other trials on the same application. Limitation due to no blinding.
Outcome measures	Change in score of WOMAC for pain, stiffness and function.

	Assessments made by patients and physicians. Limitation due to other typical parameters not included.
Follow up period	6 months. In line to gather information on safety and performance of the 2 HAs versus placebo.
Statistical significance	Extensive analysis on data but limitation due to total patients per group.
Clinical significance	The clinical efficacy of both types of HAs was the same but the superiority wrt placebo was not statistically significant.

Zhang 2015 H, et al.:

Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz.

Arthritis Research & Therapy (2015) 17:51. DOI 10.1186/s13075-015-0557-x.

Introduction: Intra-articular injection of hyaluronic acid (HA) is often used as therapy for knee osteoarthritis because it is less expensive and less aggressive than total knee replacement. Therefore, it is important to document whether HA is safe and efficacious. We tested whether single and multiple injection viscosupplementation with HA is associated with clinically meaningful pain relief in a new randomized clinical trial (RCT). Our objective was to compare safety and efficacy of intra-articular HA in two formulations: one 3.0 ml injection of Durolane versus five 2.5 ml injections of Artz for the treatment of knee osteoarthritis pain.

Methods: Patients (N = 349) from the People's Republic of China were randomized to treatment (Durolane = 175, Artz = 174). The Durolane group received a 3.0 ml injection at week 0 (baseline), with sham skin punctures at weeks 1, 2, 3, and 4. The Artz group received one 2.5 ml injection at each of the same time points. The primary assessment

tool was the Likert-type Western Ontario and McMaster University (WOMAC) pain scale at weeks 0, 6, 10, 14, 18, and 26. Secondary assessments were WOMAC physical function, knee stiffness, and global self-assessment, at identical time points. Statistically-controlled analyses were non-inferiority of Durolane over 18, then over 26 weeks, with a priori non-inferiority defined as 8% of the relevant scale. Acetaminophen was permitted as rescue analgesia and all adverse events (AEs) were recorded.

Results: Overall study retention was excellent; 332 patients (95.1%) completed 18 weeks and 319 (91.4%) completed 26 weeks, with no significant retention difference between treatment arms. All variables met non-inferiority criteria over 18 and 26 weeks. Efficacy response in both arms was >90%. Treatment-related AEs were 9.8% (17/174) for Artz and 13.1% (23/175) for Durolane.

Conclusions: A single injection of Durolane is non-inferior to 5 injections of Artz over 18 and 26 weeks for pain,physical function, global self-assessment, and knee stiffness. Both treatments were efficacious, safe, and well tolerated.

Trial registration: ClinicalTrials.gov NCT01295580. Registered 11 February 2011.

Appraisal	
Appropriate device	Equivalent HA.
Appropriate application	Same intended use for both HAs.
Appropriate patients	Patient population (349) discussed was representative of the intended treatment population.
Acceptable reporting/data	Comprehensive analysis on multiple data shown in the article. Extensive explanation of methodology, assessment, and results processing and selection.
Appropriate study design	Multicenter, randomized, double-blind, non-inferiotiry trial. Comparison of safety and efficacy profile of 2 different HAs at several time points and wrt several parameters.

Outcome measures	Beyond usual outcomes used, WOMAC on walking on flat surface, OMERCAT-OARSI values, All measures extensively analysed and discussed.
Follow up period	26 weeks. In line to gather information on safety and performance of the 2 HAs up to medium time range.
Statistical significance	Total number of patients quite high and statistical extensively reported and applied.
Clinical significance	The clinical efficacy, safety and tolerance of both types of HAs is deemed equivalent although the different treatment protocol of application.

Sun 2006 S-F, et al.:

Hyaluronate improves pain, physical function and balance in the geriatric osteoarthritic knee: a 6-month follow-up study using clinical tests.

OsteoArthritis and Cartilage (2006) 14, 696e701. doi:10.1016/j.joca.2006.01.010.

Objective: To investigate the effects of intraarticular hyaluronic acid (HA) (Artzal, Seikagaku Corp., Japan) in geriatric participants with unilateral knee osteoarthritis (OA).

Method: This was a prospective, observer-blind study with 6 months follow-up done in the setting of an outpatient rehabilitation department in a university-affiliated tertiary care medical center. Sixty-eight patients, aged 65 years or above, with symptoms and radiographic evidence of unilateral knee OA for at least 6 months were recruited. Patients received five weekly intraarticular injections of Artzal into symptomatic knees. Fifty-six participants completed the study. Fifty age-, body mass- and gender-matched healthy individuals were selected as control. Visual analog scale (VAS), Lequesne index and four balance tests including single-leg stance test (SLS), function reach test (FRT), timed ‘‘Upand-Go’’ test (TUG) and Berg balance scale (BBS) were assessed before

injection and at each follow-up visit in the OA group. Four balance tests were obtained on healthy participants for data comparison.

Results: Before Artzal injections, the OA group showed significantly worse VAS, Lequesne index and four balance tests scores than did the control group ($P < 0.001$). Significant improvement in all outcome measures were noted at 1 week, 1, 3 and 6 months post the fifth injection compared with baseline before injection. Local adverse events were reported in four patients (7.1%).

Conclusion: Significant improvement in pain, physical function and balance tests was demonstrated after five weekly Artzal injections in geriatric patients with knee OA. The effect had rapid onset at 1 week and may last for 6 months.

Appraisal	
Appropriate device	Equivalent HA.
Appropriate application	Same intended use.
Appropriate patients	Patient population (68) discussed was representative of the intended treatment population.
Acceptable reporting/data	Comprehensive analysis on multiple data shown in the article. Extensive explanation of methodology, assessment, and results processing and selection, and also limitations of the same study.
Appropriate study design	Prospective, single-blind, controlled study. No treatment on control group (healthy individuals). Several parameters evaluated at different time points.
Outcome measures	Beyond usual outcomes used, single-leg test, functional reach test, timed up-and-go test, Berg balance scale
Follow up period	6 months. In line to gather information on safety and performance up to medium time range.
Statistical significance	Total number of patients sufficient, several parameters used and analysis reported for each outcome.

Clinical significance	The clinical efficacy of the HA treatment was significant up to 6 months. AE acceptable with no serious events.

Blanco 2008 F.J., et al.:

Intra-Articular Hyaluronan Treatment of Patients with Knee Osteoarthritis Waiting for Replacement Surgery.

The Open Arthritis Journal, 2008, 1, 1-7.

Abstract: Aim: To determine whether hyaluronan (HA) delays and/or reduces the knee replacement surgery (KRS) in patients with osteoarthritis (OA).

Material and Methods: A prospective, single-center, double-blind, randomized, placebo-controlled, pilot clinical trial with two treatment groups [HA (Adant®) treatment group and placebo treatment group] was conducted. The intra-articular treatments (HA or placebo) consisted of two cycles of five weekly injections with a 24-week interval between each cycle. The efficacy variable was determined by change in pain, articular mobility and functional capacity as measured by WOMAC. All efficacy variables have been analyzed for the intention-to-treat population.

Results: 52 patients (10M/42F) were enrolled in the study (HA group: 26; placebo group: 26). Time until KRS in the HA group subjects (368.8 days) was longer than that in the placebo group (253.9 days). The change in the WOMAC stiffness subscale at 24 weeks, compared to the baseline score, was –22.4 in the HA group and -2.2 in the placebo group (p = 0.081). The change in the physical function WOMAC subscale, compared to the baseline score, was statistically significant at 24 weeks (HA group = -24.7 placebo group = -4.4 p = 0.019). Similar results were found in the change in the total WOMAC index score (HA group = -23.9 vs placebo group = -5.6 p = 0.044).

Conclusion: 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.	
Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. HA compared to placebo.
Appropriate patients	Patient group (26) discussed was not representative of the intended treatment population. Patients awaiting knee replacement surgery can be considered a worst case group of patients.
Acceptable reporting/data	Study extensively discussed and data shown. Relations among parameters values and results well reported.
Appropriate study design	Prospective, randomized, double-blind, placebo controlled trial. Population size lower and for target HA population but it is a subgroup given that patients were in waiting list for knee replacement.
Outcome measures	Widely used methodology to assess the key parameters. Beyond typical outcome measures, the survival time to surgery was considered.
Follow up period	Not needed. Study aimed at measuring delay in knee replacement surgery time.
Statistical significance	Extensive analysis but limited by total population considered.
Clinical significance	HA did not show a statistically significant delay of knee replacement surgery for K-L grade IV patients, although the sample size was limited.

Lana 2016 JFSD, et al.:

Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and

the combination of both in the treatment of mild and moderate osteoarthritis of the knee.

Journal of Stem Cells and Regenerative Medicine. Vol.12 No.2, 2016; P1. JSRM Code: 012030200002EPA050716.

Objective: This study aims at evaluating the clinical effects of Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) as individual treatments for mild to moderate Osteoarthritis (OA) and it also examines the potential synergistic effects of PRP in combination with HA. Research continues to emerge examining the potential therapeutic efficacy of HA and PRP as autologous injectable treatments for joint arthritis. However, there is a paucity of research investigating the effects of combining HA and PRP on pain and functional status in patients with OA.

Design: In this multi-center, randomized, controlled, double blind, prospective trial, 105 patients with mild to moderate knee osteoarthritis, who met the study criteria, were randomly allocated to one of three interventions: HA (n=36), PRP (n=36), or HA+PRP (n=33). Each patient received 3 intra-articular knee injections of their assigned substance, with 2 week intervals between each injection. Clinical outcomes were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale (VAS) questionnaire at baseline and after 1,3,6 and 12 months.

Results: The study showed that the PRP group have significant reduction in VAS scores at 1 (p= 0.003), 3 (p= 0.0001), 6 (p= 0.0001) and 12 (p= 0.000) months when compared to HA. In addition, the PRP group illustrated greater improvement in WOMAC physical activity scale at 12 months (p= 0.008) when compared to the HA group. Combining HA and PRP resulted in a significant decreases in pain (p=0.0001) and functional limitation (p=0.0001) when compared to HA alone at 1 year post treatment; and significantly increased physical function at 1 (p=0.0004) and 3 (p=.011) months when compared to PRP alone.

Conclusion: The findings of the study support the use of autologous PRP as an effective treatment of mild to moderate knee osteoarthritis. It also shows that the combination of HA and PRP resulted to better outcomes than HA alone up to 1 year and PRP alone up to 3 months. Furthermore, the results suggest that combination of PRP and HA could potentially provide better functional outcomes in the first 30 days after treatment with both PRP and HA alone.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. HA compared to PRP.
Appropriate patients	Patient group (36) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Randomized, multicenter, double-blind, controlled trial assessed to medium-long time range. High quality.
Outcome measures	Widely used methodology to assess the key parameters. Beyond typical outcome measures, the survival time to surgery was considered.
Follow up period	Up to 12 months. Above average time, useful to assess medium-long time range.
Statistical significance	Extensive analysis but limited by total population considered.
Clinical significance	Combination of HA+PRP shown to be superior to HA alone but on a limited population size. Wider trials needed.

Pavelka 2011 K., Uebelhart D.:

Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial) vs hylan G-F20 (Synvisc) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study.

Osteoarthritis and Cartilage 19 (2011) 1294-1300

Objective: Knee osteoarthritis is a major cause of disability and pain. This phase III, double-blind (patient and observer blinded,) multicenter, randomized, non-inferiority study was conducted to demonstrate the non-inferiority of the highly purified intra-articular injection of hyaluronic acid (Sinovial) in comparison to Hylan G-F20 (Synvisc) in the treatment of knee osteoarthritis.

Methods: A total of 381 patients were randomly assigned to receive either the test drug, 16 mg/2 ml (0.8%) highly purified ia hyaluronic acid of biofermentative origin (Sinovial), or the comparative drug, 16 mg/2 ml of 0.8% hylan G-F20 (Synvisc). The duration of the treatment was 2 weeks (three injections at 1-week interval), followed by an observation period of 6 months. The primary efficacy variable was the improvement in mean Western Ontario and McMaster Universities (WOMAC) pain subscore from baseline to the final visit (week 26), compared between the two treatment groups. The acceptable margin for non-inferiority was chosen to be 8 mm.

Results: At week 26,WOMAC pain subscores decreased by a mean of 32.5 for both Sinovial and Synvisc. These results met prespecified criteria for non-inferiority for both the Intent-to-Treat and Per-Protocol populations. There were no statistically significant differences between groups at 26 weeks, although Sinovial-treated patients tended to have a slightly better outcome for select variables, as they did at earlier time-points, some of which reached statistical significance. Both hyaluronic acid preparations were well-tolerated, with no statistically significant differences in tolerability profile between groups.

Conclusion: Sinovial and Synvisc treatments were found to be equivalent, both in terms of efficacy and safety.

Clinical Trial Number: NCT00556608

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison of 2 HAs.
Appropriate patients	Patient group (354) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Randomized, multicenter, double-blind, controlled,parallel-group, non-inferiority trial on large sample size. High quality.
Outcome measures	Primary and secondary parameters typical of the investigated treatment. Extensively analysed and discussed on ITT population, groups and subgroups.
Follow up period	26 weeks. Typical for the kind of treatment to assess short-medium time range.
Statistical significance	Extensive description with strength on population size, analysis used and power.
Clinical significance	Equivalence of both HAs proved in terms of statistically significant efficacy and tolerability but trend on safety apparently better for linear HA wrt cross-linked HA.

Van der Weegen 2015 W, et al.:

No Difference Between Intra-Articular Injection of Hyaluronic Acid and Placebo for Mild to Moderate Knee Osteoarthritis: A Randomized, Controlled, Double-Blind Trial.

The Journal of Arthroplasty 30 (2015) 754–757. dx.doi.org/10.1016/j.arth.2014.12.012.

The main goal of our study was to examine the effectiveness and safety of Fermathron plus, a specific brand of hyaluronic acid (HA), in patients with mild to moderate knee osteoarthritis.

In a randomized, controlled, double-blind trial, 196 patients with symptomatic knee osteoarthritis (mean age ± SD, 59.4 ± 9.9 years, Kellgren–Lawrence grade 1–3) were given either 3 weekly intra-articular injections of HA or saline (placebo).

Although pain and functional scores (WOMAC scale) improved significantly from baseline up to 6 months, HA was not superior to placebo at any follow-up (VAS pain 50 m walking from 56.4 to 38.1, P b .001, and 58.2 to 39.6, P b .001, respectively). No subgroup analysis resulted in superior outcomes. No serious adverse events were noticed.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison to placebo.
Appropriate patients	Patient group (99) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Randomized, double-blind, controlled trial on large sample size. Good quality but limitations given by no ultra-sound guidance and no exclusion of patients with bilateral kne OA.
Outcome measures	Parameters typical of the investigated treatment. Beyond usual outcomes, knee flexion and limitation in work activities.
Follow up period	6 months. Typical for the kind of treatment to assess short-medium time range.
Statistical significance	Good description of analysis performed but too high P values can indicate undetected bias.

Clinical significance	Equivalence of statistically significant results between treated and control groups. HA well tolerated and safe but not superior to placebo.

Ishijima 2014 et al.:

Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial.

Arthritis Research & Therapy 2014 16:R18.

Introduction: While many of the commonly used conservative treatments for knee osteoarthritis (OA) have been recognized to be effective, there is still insufficient evidence available. Among the pharmacological treatments for knee OA, oral non-steroidal anti-inflammatory drugs (NSAIDs) act rapidly and are recommended for the management of OA. However, frequent and serious adverse effects of NSAIDs have been recognized. Intra-articular injections of hyaluronic acid (IA-HA) for the treatment of knee OA have been shown to reduce pain and improve joint function. However, there has been no qualified direct comparison study of the efficacy and safety between IA-HA and NSAIDs for patients with knee OA. The aim of this study was to clarify the efficacy and safety of early-phase IA-HA in comparison to those of NSAIDs for patients with knee OA.

Methods: This multicenter, randomized, open-label, parallel-group, non-inferiority comparison study with an oral NSAID involved a total of 200 patients with knee OA. An independent, computer-generated randomization sequence was used to randomly assign patients in a 1:1 ratio to NSAIDs three times per day for five weeks (n = 100) or IA-HA once a week for five weeks (n = 100). The primary endpoint was the percentage change in the patient-oriented outcome measure for knee OA, the Japanese Knee Osteoarthritis Measure (JKOM) score. All patients were questioned regarding any

adverse events during treatment. The full analysis set (FAS) was used for analysis. The margin of non-inferiority was 10%.

Results: The analyses of primary endpoint included 98 patients in the IA-HA group and 86 patients in the NSAID group. The difference in the percentage changes of the JKOM score between the two intervention arms (IA-HA; -34.7% (P<0.001), NSAID; -32.2% (P<0.001)) was −2.5% (95% confidence interval (CI): -14.0 to 9.1), indicating IA-HA was not inferior to NSAID. The frequency of both withdrawal and adverse events in the IA-HA group were significantly lower than those in the NSAID group (P = 0.026 and 0.004, respectively).

Conclusions: The early efficacy of IA-HA is suggested to be not inferior to that of NSAIDs, and that the safety of the early phase of IA-HA is superior to that of NSAIDs for patients with knee OA.

Trial registration: UMIN Clinical Trials Registry (UMIN-CTR), UMIN000001026.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison to NSAID treatment.
Appropriate patients	Patient group (99) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported. High quality reporting.
Appropriate study design	Multi-center, randomized, open-label, parallel-group, non-inferiority study on large sample size. Limitation due to no blinding and time range (5 weeks)
Outcome measures	Japanese knee OA measure used as primary outcome measure but other parameters typical of the treatment.
Follow up period	5 weeks Too short for medium terms efficacy evaluation but enough for safety vs NSAID.

Statistical significance	Sample size and analysis extensively described and assessed with high power. Small subgroups for conclusive assessment.
Clinical significance	HA can perform as well as NSAID on efficacy but it is better on the safety profile in the short time range.

Skwara 2009 A., et al.:

Changes of gait patterns and muscle activity after intra-articular treatment of patients with osteoarthritis of the knee A prospective, randomised, double-blind study.

The Knee 16 (2009) 466–472. doi:10.1016/j.knee.2009.03.003.

Evaluation of gait performance and muscle activity patterns as well as clinical efficacy and safety after intraarticular injections with hyaluronan (Ostenil) compared with triamcinolone (Volon A10) injections in patients with knee osteoarthritis.

This was a prospective, randomised, double-blind clinical trial evaluating the influence of five injections of hyaluronan or triamcinolone on gait pattern and muscle activity. For the clinical evaluation visual analogue scale, Lequesne index, and Knee Society Score were used. Quality of life was estimated with the SF-36. The definitive analysis was performed on the population who received all five injections and were examined in the two follow-up visits. Fifteen patients were treated with triamcinolone and 20 with hyaluronan.

Significant improvement could be demonstrated for pain scale and clinical scores in both groups. Gait patterns showed significant differences only for Knee Abduction Moment (p=0.007) in the hyaluronan group and for Maximum Vertical Force 1 and 2 between the both groups in the follow up visit (p=0.018) (p=0.019). In both groups there was no

significant difference regarding to muscle activity. Quality of life showed no changes in all visits between the groups.

Hyaluronan was not superior to triamcinolone. The results suggest that treatment with hyaluronan can reduce pain and improve knee function. A significant short term improvement in gait and muscle activity patterns, however, was not observed, in either hyaluronan or triamcinolone.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison to triamcinolone.
Appropriate patients	Patient group (20) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported. High quality reporting.
Appropriate study design	Prospective, randomized, double-blind trial on small sample size. Limitation due to time range (12 weeks).
Outcome measures	Beyond usual parameters, gait and muscle activity were assessed. Vertical force and SF-36.
Follow up period	12 weeks, too short for medium-long time range assessment.
Statistical significance	Small sample size but description and analytical evaluation well documented and extensive. Low power due to small population size.
Clinical significance	HA not superior to triamcinolone but pain and function improved in both treatments. No gait and muscle improvement in short term but limited overall population.

Berenbaum 2012 F., et al.:

A randomised, double-blind, controlled trial comparing two intra-articular

hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis.

Ann Rheum Dis 2012;71:1454–1460. doi:10.1136/annrheumdis-2011-200972.

Objectives To compare the effects of an intermediate molecular weight (MW) intra-articular hyaluronic acid (HA) with a low MW product on knee osteoarthritis (OA) symptoms.

Methods Patients with symptomatic knee OA were enrolled inarandomised, controlled, double-blind, parallelgroup, non-inferiority trial with the possibility to shift to superiority. Patients were randomised to GO-ON(MW 800–1500 kD, 25 mg/2.5 ml) or Hyalgan(MW 500–730 kD, 20 mg/2 ml) injected at 3-weekly intervals. The primary outcome was 6-month change in the WOMAC pain subscale (0–100 mm). Sample size was calculated on a non-inferiority margin of 9 mm, lower than the minimum perceptible clinical improvement. Secondary endpoints included OARSI-OMERACT responder rates.

Results The intention-to-treat (ITT) and per-protocol (PP) populations consisted of 217 and 209 patients and 171 and 172 patients in the GO-ON and Hyalgan groups, respectively. ITT WOMAC pain of 47.5±1.0(SE) and 48.8±1.0 mm decreased by 22.9±1.4 mm with GO-ON and 18.4±1.5 mm with Hyalgan after 6 months. The primary analysis was conducted in the PP population followed by the ITT population.Mean (95% CI) differences in WOMAC pain change were 5.2 (0.9 to 9.6)mm and 4.5 (0.5 to 8.5)mm, respectively,favouring GO-ON, satisfying the claim for non-inferiority (lower limit>−9 mm) and for statistical superiority (95% CI all>0, p=0.021). A higher proportion of OARSI/OMERACT responders was observed with GO-ONthan with Hyalgan (73.3% vs58.4%, p=0.001). Both preparations were well tolerated.

Conclusions Treatment with 3-weekly injections of intermediate MW HA may be superior to low MW HA on knee OA symptoms over 6 months, with similar safety.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison of 2 HAs.
Appropriate patients	Patient group (343) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Randomized, multicenter, double-blind, controlled, parallel-group, non-inferiority trial on large sample size. High quality.
Outcome measures	Primary and secondary parameters typical of the investigated treatment. Extensively analysed and discussed on ITT population also.
Follow up period	6 months. Typical for the kind of treatment to assess medium time range.
Statistical significance	Extensive description with strength on population size, analysis used and power.
Clinical significance	Efficacy and safety of both HAs formulations equivalent with trend for superiority of Go-On over Hyalgan.

Kausch 2009 R, et al.:

Intraarticular Hyaluronic Acid in the Treatment of Arthroses.

Orthopädische Praxis 45, 5, 2009.

This observational study (OS) examined the efficacy, the treatment effect persisting beyond therapy, and the safety of injections of an intraarticular sodium hyaluronate solution (GO-ON) under practical conditions in a non-selected patient population.

1743 patients (88 % with gonarthrosis (osteoarthritis of the knee), 4.4 % with coxarthroses (osteoarthritis of the hip), 2.9 % with omarthrosis (osteoarthritis of the shoulder) were treated. Efficacy was examined two weeks after the conclusion of the injection series and twelve weeks after the start of the injection series.

Relative to the total number of joints treated the treatment resulted in statistically significant pain relief and functional improvement. Adverse effects that could be associated with the trial preparation were reported extremely rarely.

The i.a. therapy with the trial preparation can, therefore, be considered effective beyond treatment and very safe in therapeutic routine.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use for knee only.
Appropriate patients	Patient group (1533) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Non interventional study. Prospective analysis on multiple applications of the HA. Only strength in sample size for short-term efficacy and safety.
Outcome measures	Basic parameters on pain and functionality, typical for the treatment under consideration. Limitation on few parameters.
Follow up period	12 weeks. Only good for short term time range.
Statistical significance	Extensive description with strength on population size.
Clinical significance	Efficacy on pain and functionality of the KOA statistically significant with high safety profile.

Arensi 2006 F:

Comparison of efficacy and therapeutic safety of two treatments based on hyaluronic acid (Go-On and Hyalgan) in knee osteoarthritis.

Minerva Ortop Traumatol 2006;57:105-11.

Aim. To compare the efficacy and therapeutic safety of two formulations of hyaluronic acid, in patients with knee osteoarthritis.

Methods. In this controlled, randomized, parallel-group study, 40 patients (30 females, 10 males, mean age 64 years), with diagnosis of knee osteoarthritis (OA) and pain severity over 20 mm on the Visual Analogue Scale (VAS), were assigned by randomization to one of the two study formulations of hyaluronic acid, Go-On (Go) and Hyalgan (Hy). The patients were treated with two intra-articular injections every week for 5 weeks with 3 months of follow-up. Symptoms and function parameters were assessed weekly until the fifth week and at 3 months of follow-up. At the end of the treatment, the physician's and the patient's overall evaluations were recorded.

Results. Pain, articular stiffness and joint function, as WOMAC index subscales, Lequesne index and general health state improved with both treatments and showed no statistically significant difference between formulations. Treatment tolerability was excellent. The physician's evaluation on treatment efficacy was good in 55% of patients with both treatments as well as patient's evaluation on acceptability was good in 55% of patients treated with Go and in 50% of patients treated with Hy.

Conclusion. It may be stated that the two formulations of hyaluronic acid employed in the treatment of knee OA exhibit a totally overlapping efficacy and therapeutic safety.

Appraisal	
Appropriate device	Equivalent HA

Appropriate application	Same intended use. Comparison of 2 HAs.
Appropriate patients	Patient group (40) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study reported and discussed with no deep details. All parameters and outcomes reported without details on background analysis of methodology.
Appropriate study design	Randomized, controlled, parallel-group study. Unclear blinding.
Outcome measures	Basic parameters, typical of the investigated treatment.
Follow up period	3 months. Typical for the kind of treatment to assess short time range.
Statistical significance	Small population size with unclear methodological analysis.
Clinical significance	Efficacy and safety of both HAs formulations equivalent with no statistically relevant differences.

Askari 2016 A., et al.:

Hyaluronic acid compared with corticosteroid injections for the treatment of osteoarthritis of the knee: a randomized control trail.

SpringerPlus (2016) 5:442 DOI 10.1186/s40064-016-2020-0.

Background: Osteoarthritis (OA) is the most common chronic condition of the joints that takes place when the cartilage or a low friction surface between joints breaks down which leads to pain, stiffness and swelling. The purpose of the present study was to evaluate the therapeutic effect of intra-articular hyaluronic acid (HA) in comparison to corticosteroids (CS) for knee osteoarthritis.

Methods: 140 patients with knee osteoarthritis, who were followed for 3 months, were randomized to receive intraarticular injection of either hyaluronic acid or corticosteroid. By receiving one injection of drug during the enrollment in the study, the patients were

treated. With the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), Knee injury and Osteoarthritis Outcome Score (KOOS), and the visual analog pain scale, an independent, blinded evaluator assessed the patients three times.

Results: The mean age of the patients in the corticosteroid group were 57 Â± 1.9 years and in Hyaluronic acid group were 58.5 Â± 8.3 years. WOMAC score represented that pain and stiffness did not improve in neither groups at any time points after intervention (P > 0.05). KOOS score suggested that symptoms improved after 3 months in both CS and HA groups. Besides, daily activity improved in both groups (P < 0.05).

Conclusions: As a conclusion, it is argued that the most important difference between the two intervention groups is the duration of effectiveness. HA is suggested to be superior in the duration of pain relief when compared to CS. We can propose that HA can be administered every 3 months intra-articular for knee joint OA. Therefore, when CS has to be injected every 2 months, it will be more convenient to use HA.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison wrt corticosteroid.
Appropriate patients	Patient group (71) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Randomized, controlled, parallel-group study.
Outcome measures	Basic parameters, typical of the investigated treatment.
Follow up period	3 months. Typical for the kind of treatment to assess short time range.
Statistical significance	Proper analysis with sufficient population size but few details on background methodology.
Clinical significance	Meaningful difference given by pain reduction of HA wrt to corticosteroid in the short time range considered.

Kolarz 2003 G, Kotz R, Hochmayer I:

Long-Term Benefits and Repeated Treatment Cycles of Intra-Articular Sodium Hyaluronate (Hyalgan) in Patients With Osteoarthritis of the Knee.

Seminars in Arthritis and Rheumatism, Vol 32, No 5 (April), 2003: pp 310-319.

Objectives: To assess the long-term efficacy and tolerability of sodium hyaluronate (Hyalgan) after 1 cycle of 5 intra-articular (IA) injections in patients with osteoarthritis (OA) of the knee. The benefits of a second treatment cycle in patients with renewed need for therapy also were examined.

Methods: One hundred eight patients with knee pain (Kellgren-Lawrence grade 1, 2, or 3) for at least 20 days per month, and a score for pain on movement of at least 3.3 cm on a 10-cm Visual Analogue Scale (VAS) were treated with Hyalgan once weekly for 5 weeks in a multicenter, observational study. A repeat course was administered if patients continued to fulfill the inclusion criteria but not earlier than month 4. The primary efficacy parameter was pain on movement measured by VAS. Secondary parameters were pain on movement and pain at rest (5-point Likert ordinal rating scale), pain at rest (VAS), knee joint function (Larson scale), walking time, and global assessment of efficacy.

Results: The 59 patients completed the first 12-month follow-up period without the necessity for a second treatment cycle; 14 of the remaining 49 patients received a second treatment cycle. There were significant improvements in all efficacy parameters compared with the baseline values starting from 1 week after the last injection until month 12 for the 59 completed patients and also for all 108 enrolled patients (last observation carried forward). Safety and tolerability of Hyalgan were good or very good in more than 90% of patients. Of 4 patients who withdrew because of adverse events, only 1 event (knee joint effusion) was judged as possibly drug related. Two other adverse

events judged to be drug related (generalized skin eruption; pruritus and knee joint effusion) resolved and did not lead to study withdrawal.

Conclusion: The results of this observational study suggest that Hyalgan, administered either as a single or repeat course, is an effective and well tolerated therapy for the long-term treatment of the pain of OA.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use.
Appropriate patients	Patient group (108) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Open-label, observational, uncontrolled study. Not high quality due to in-process defections but ITT analysis performed.
Outcome measures	Basic parameters, typical of the investigated treatment.
Follow up period	12 months. Good to assess medium-long time range.
Statistical significance	Proper analysis with good sample size but methodological description not extensive.
Clinical significance	Efficacy of HA to reduce pain in KOA on medium-long time range with high tolerability of the treatment.

Blanch 2012 Rubio J, et al.:

ASKOT STUDY: Effectiveness and safety of a 1-shot injection of sodium Hyaluronate for knee osteoarthritis treatment.

Springer Experience & Drug Evidence. 2012 Springer Healthcare Iberica SL.

BON2ES5311.

Purpose: Evaluation of the effectiveness and safety in real-life conditions of a viscoelastic solution of hyaluronic acid for intra-articular one-shot injection in Osteoarthritis.

Patients and methods: An international multicentre, non-interventional, observational study with 411 patients who were attending rheumatology/ orthopaedics units for pain due to knee osteoarthritis. Three visits were performed to register general data and specific information for OA history and current treatment. Pain at rest and pain at walking was evaluated based on a Analogic Visual Scale in each visit, as well as the Lequesne functional index for quality of life impact of OA. Adverse events were registered during the follow up. Efficacy of the injection was evaluated in terms of the functional impact on knee osteoarthritis, using patient self-evaluation.

Results: Population average age and time since OA diagnosis were 62 and 3.64 years, respectively. Both knees affectation were found in 23% of patients and pharmacological treatment was indicated in the last year for 73% overall studied population. Pain was the most relevant symptom. After injection, mean VAS pain at rest was significantly lower 3 and 6 months after treatment in comparison to baseline VAS score (mean [SD]: 18.97 [19.37] vs. 30.79 [22.93]; $p < 0.001$ and 18.50 [19.46] vs. 30.79 [22.93]; $p < 0.001$). Significantly lower Lequesne mean overall score at 3 and 6 months compared to baseline (7.25 [4.37] vs. 10.60 [4.07]; $p < 0.001$ and 6.85 [4.45] vs. 10.60 [4.07]; $p < 0.001$) was also found. Overall, 86.7% of patients declared an improvement in their health at 3-months post-injection and a lower number and intensity of pain exacerbations between baselines (65.2% at 3 months) of patients and (48.8% between 3 and 6 months).

Conclusion: Treatment with an intra-articular 1-shot injection of viscoelastic solution of hyaluronic acid is effective in providing clinically relevant pain relief over a period of at least 6 months in patients suffering from knee osteoarthritis.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use.
Appropriate patients	Patient group (411) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	International multicentre, non-interventional, observational study on large sample size.
Outcome measures	Basic parameters, typical of the investigated treatment.
Follow up period	6 months. Typical to assess medium time range.
Statistical significance	Proper analysis with good sample size but methodological description not extensive. Safety related information extensively treated.
Clinical significance	HA effective in the treatment of KOA through medium time range with benefits from economic and safety topics wrt alternative treatments.

Gydek 2011 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.
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.

Our study reconfirmed efficacy and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use.
Appropriate patients	Patient group (4505) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study basically reported and discussed. All parameters and outcomes sufficiently reported.
Appropriate study design	Observational study. Good for trend assessments over intervention data.
Outcome measures	Beyond typical parameters, morning stifness and walking up- and down-stairs.
Follow up period	30 days. Too short for extension to longer time range.
Statistical significance	Very large sample size for trend assessment.
Clinical significance	The trend on efficacy and safety profile of considered HA confirmed through large sample size.

Mazieres 2007 B, et al.:

Medicoeconomic evaluation of hyaluronic acid for knee osteoarthritis in everyday practice: The MESSAGE study.

Joint Bone Spine 74 (2007) 453-460. doi:10.1016/j.jbspin.2007.01.037.

Introduction: Medicoeconomic data on treatments for osteoarthritis are scant. We investigated the impact of hyaluronic acid therapy on the cost of management of knee osteoarthritis. Our primary objective was to compare medical costs (admissions, outpatient visits, investigations, and treatments) and non-medical costs (sick leaves and transportation) from the perspective of the national health insurance system during the 3 months before and the 6 months after three intraarticular injections of hyaluronic acid. Our secondary objective was to evaluate treatment benefits in terms of pain, function, and quality of life.

Methods: Observational, multicenter, longitudinal, before-after study of the medical and economic effects of hyaluronic acid therapy for symptomatic knee osteoarthritis.

Results: Of the 296 assessable patients (mean age, 69 years; 30% with obesity; 65% women), only 5% of patients were withdrawn prematurely from the study. Significant improvements in the Lequesne index were found 3 and 6 months after treatment; the improvement was greater than 50% in over half the patients. Pain and quality-of-life scores improved significantly. Total cost of the disease decreased from V334 for the 3 pretreatment months to V295 and V233 for post treatment months 1e3 and 4e6, respectively.

Conclusion: The costs of knee osteoarthritis decreased during the 6 months after Suplasyn therapy, indicating that the cost of the medication was more than offset by the decreased need for other treatments. Concomitantly, clinical benefits were obtained. Under the conditions of everyday practice, hyaluronic acid may provide medical benefits at an acceptable cost.

Appraisal	
Appropriate device	Equivalent HA

Appropriate application	Same intended use.
Appropriate patients	Patient group (296) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively reported.
Appropriate study design	Observational, multicenter, longitudinal, before-after study. Good design for evaluation of economic implications of the KOA treatment options.
Outcome measures	Basic parameters for the type of treatment.
Follow up period	6 months. Typical length for medium time range treatment assessment.
Statistical significance	Extensive analysis of main parameters based on large size population.
Clinical significance	Cost-benefit of HA treatment outweighed overall costs for alternative/concomitant costs and risks.

Zorzi 2015 C, et al.:

A new hydrogel for the conservative treatment of meniscal lesions: a randomized controlled study.

Joints 2015;3(3):136-145.

Purpose: this study aimed to investigate the efficacy of intra-articular (iA) administration of a hydrogel formulation obtained from a hyaluronic acid (HA) derivative (HYADD4Â®) in the management of meniscal tears and in meniscal tear repair.

Methods: fifty subjects with degenerative meniscal tears were enrolled into this single-site, observer-blind, parallel-group study. Clinical evaluations were performed at baseline and after 14, 30 and 60 days. Clinical outcomes included: pain reduction (Visual Analog scale), improvement of knee functionality (WoMAC questionnaire), reduction in

length and depth of the meniscal lesion (MRi-confirmed) and sF-36 questionnaire scores. Local tolerability and safety were also investigated.

Results: a significant reduction in VAs pain (p<0.001) in favor of HYADD4Â® was recorded at day 14 and maintained at all the follow-up assessments. Data on knee functionality were in line with the VAs pain assessment results. A significant reduction in length and depth of the meniscal lesion, assessed using Mri, was found in the HYADD4Â® group compared to the control group (p<0.001).

Conclusions: the results of this study may indicate a new treatment option in the conservative management of patients complaining of pain due to meniscal tears. the MRi data suggest that the hydrogel formulation of HA used in this study may also play a role in the healing process of the lesion.

Level of evidence: Level I, prospective randomized clinical trial.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same body site but not intended use – meniscal tear
Appropriate patients	Patient group (25) discussed was not representative of the intended treatment population. Extrapolation only comparison.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively analysed and reported.
Appropriate study design	Single-site, observer-blind, parallel-group, prospective study.
Outcome measures	Several parameters included that are also typical of KOA treatment.
Follow up period	30 days. Short time range, useful for the assessment of the treatment itself.

Statistical significance	Extensive analysis of main parameters but based on small size population.
Clinical significance	Proof that HA may be considered as alternative treatment in conservative management of pain in meniscal tear patients.

Strand 2016 V, Lim S, Takamura J:

Evidence for safety of retreatment with a single intra-articular injection of Gel-200 for treatment of osteoarthritis of the knee from the double-blind pivotal and open-label retreatment clinical trials.

BMC Musculoskeletal Disorders (2016) 17:240 DOI 10.1186/s12891-016-1101-0.

Background: Gel-200 is a cross-linked hyaluronate single-injection device for treatment of osteoarthritis pain in the knee. This report summarizes new analyses of the safety of retreatment with Gel-200 from the 13-week, pivotal, multicenter, randomized controlled trial (RCT) followed by an open-label extension trial (OLE).

Methods: 379 patients were enrolled in the RCT [Gel-200; phosphate-buffered saline (PBS)]. Safety of retreatment with Gel-200 was assessed by comparing adverse events (AEs) and device-related AEs reported through Week 4 following retreatment with Gel-200 to those reported in patients receiving their first injection in the OLE.

Results: 350 patients completed the initial RCT (231 Gel-200; 119 PBS); 258 patients enrolled in the OLE (162 Gel-200; 96 PBS). In total, 202 patients (125 Gel-200; 77 PBS) qualified for retreatment, while 56 (37 Gel-200; 19 PBS) did not. There were no significant demographic or disease characteristic differences between Gel-200 patients who were and were not retreated; those who were not eligible for retreatment experienced greater pain relief from Gel-200 in the RCT by all effectiveness endpoints (all $p < 0.001$), without differences in their safety profile. In the OLE, the safety of Gel-200, including percentages of patients who experienced any AEs ($p = 0.547$) and device-

related AEs (p = 0.521), did not significantly differ between those receiving a second versus a first injection of Gel-200 following PBS in the RCT.

Conclusion: In the OLE, the safety of a second injection of Gel-200 was comparable to that of a first injection and effectiveness was similar, as previously reported.

Trial registration: ClinicalTrials.gov identification numbers NTC 00449696 and NTC 00450112

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use
Appropriate patients	Patient group (251) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively analysed and reported.
Appropriate study design	Randomized, double-blind plus open-label trials
Outcome measures	Basic parameters included typical of KOA treatment.
Follow up period	13 weeks, typical of short time range assessment of the KOA treatment.
Statistical significance	Extensive analysis of main parameters based on large size population. Extensive safety profile assessment.
Clinical significance	Effectiveness of second treatment with HA similar to first course of treatment.

Leighton 2014 R, et al.:

NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial.

Osteoarthritis and Cartilage 22 (2014) 17-25.

Objective: To compare NASHA hyaluronic acid gel as single-injection intra-articular (IA) treatment for knee osteoarthritis (OA) against methylprednisolone acetate (MPA).

Design: This was a prospective, multi-centre, randomized, active-controlled, double-blind, noninferiority clinical trial. A unique, open-label extension phase (OLE) was undertaken to answer further important clinical questions. Subjects with painful unilateral knee OA were treated and followed for 26 weeks (blinded phase). All patients attending the clinic at 26 weeks were offered NASHA treatment, with a subsequent 26-week follow-up period (extension phase). The primary objective was to show noninferiority of NASHA vs MPA in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain responder rate (percentage of patients with 40% improvement from baseline in WOMAC pain score and an absolute improvement of 5 points) at 12 weeks.

Results: In total, 442 participants were enrolled. The primary objective was met, with NASHA producing a non-inferior response rate vs MPA at 12 weeks (NASHA: 44.6%; MPA: 46.2%; difference [95% CI]: 1.6% [11.2%; Ã¾7.9%]). Effect size for WOMAC pain, physical function and stiffness scores favoured NASHA over MPA from 12 to 26 weeks. In response to NASHA treatment at 26 weeks, sustained improvements were seen in WOMAC outcomes irrespective of initial treatment. No serious device-related adverse events (AEs) were reported.

Conclusions: This study shows that single-injection NASHAwas well tolerated and non-inferior to MPA at 12 weeks. The benefit of NASHA was maintained to 26 weeks while that of MPA declined. An injection of NASHA at 26 weeks conferred long-term improvements without increased sensitivity or risk of complications.

Study identifier: NCT01209364.

Appraisal	
Appropriate device	Equivalent HA
Appropriate application	Same intended use. Comparison with methylprednisolone acetate.
Appropriate patients	Patient group (221) discussed was representative of the intended treatment population.
Acceptable reporting/data	Study extensively reported and discussed. All parameters and outcomes extensively analysed and reported.
Appropriate study design	Prospective, randomized, multicenter, double-blind, active-controlled, non-inferiority trial plus open-label extension. High quality.
Outcome measures	All typical parameters of KOA treatment and extensive reporting of safety issues.
Follow up period	26 weeks + 26 weeks. Effective for long time range assessment of treatment effects.
Statistical significance	Extensive analysis of parameters based on large size population. Extensive safety profile assessment.
Clinical significance	HA showed better performance on long time range wrt MPA and without safety issues complication over time.

5.6 Summaries of meta-analyses and appraisal

Strand 2015 V., et al.:

Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials.

Journal of Pain Research 2015:8 217–228.

Background: Intra-articular injection of hyaluronic acid is a common, yet controversial, therapeutic option for patients with knee osteoarthritis (OA). The purpose of this research was to determine the safety and efficacy of US-approved viscosupplements for symptomatic knee OA.

Methods: We searched MedLine and EMBase for randomized, sham-controlled trials evaluating safety and/or clinical efficacy of US-approved viscosupplements in patients with symptomatic knee OA. Knee pain severity and knee joint function were assessed at 4 to 13 weeks and 14 to 26 weeks. Safety outcomes included serious adverse events, treatment-related serious adverse events, patient withdrawal, and adverse event-related patient withdrawal occurring at any time during follow-up.

Results: A total of 29 studies representing 4,866 unique patients (active: 2,673, control: 2,193) were included. All sham-controlled trials used saline injections as a control. Viscosupplementation resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to preinjection values, with standardized mean difference values ranging from 1.07 to 1.37 (all P,0.001). Compared to controls, standardized mean difference with viscosupplementation ranged from 0.38 to 0.43 for knee pain and 0.32 to 0.34 for knee function (all P,0.001). There were no statistically significant differences between viscosupplementation and controls for any safety outcome, with absolute risk differences of 0.7% (95% confidence interval [CI]: -0.2 to 1.5%) for serious adverse events, 0% (95% CI: -0.4 to 0.4%) for treatment-related serious adverse events, 0% (95% CI: -1.6 to 1.6%) for patient withdrawal, and 0.2% (95% CI: -0.4 to 0.8%) for adverse event-related patient withdrawal.

Conclusion: Intra-articular injection of US-approved viscosupplements is safe and efficacious through 26 weeks in patients with symptomatic knee OA.

Appraisal

No date restrictions were applied to the searches. Main inclusion criteria were injection of a US-approved HA product; randomized, sham-control study design; primary

diagnosis of knee OA; identical treatment and follow-up conditions between IAHA and sham-control groups; and at least one extractable efficacy or safety outcome. Trials were excluded if concomitant interventional therapies were uniformly administered; were published in non-English language journals;

Methodologic quality of studies was assessed using the Jadad score, rated from 0 to 5 according to the presence of three key methodological features: randomization, blinding, and patient accountability. We defined a higher-quality trial as Jadad score from 3. Main outcomes included pain severity, joint function, and safety variables.

The meta-analysis is associated with several issues that may influence interpretation. Most, but not all, studies excluded patients with end-stage (Kellgren–Lawrence grade IV or equivalent) knee OA and, therefore, the efficacy of viscosupplements in these patients cannot be determined. Due to sample size considerations, it was not attempted to analyze treatment effects by viscosupplement type or molecular weight. Lastly, efficacy outcomes were inconsistent across studies and influenced by study design factors and publication bias.

Strengths of this meta-analysis are inclusion of only randomized, saline-controlled trials, structured data extraction methodology, inclusion of all zero total event trials in safety analyses, and sensitivity analyses that accounted for choice of statistical test and potentially influential studies.

Monticone 2015 M, et al.:

Hyaluronic Acid Intra-articular Injection and Exercise Therapy: Effects on Pain and Disability in Subjects Affected by Lower Limb Joints Osteoarthritis. The Italian Society of Physical and Rehabilitation Medicine (SIMFER) systematic review.

Eur J Phys Rehabil Med 2015 Sep 10, pISSN 1973-9087 - eISSN 1973-9095.

Background. It is debated whether intra-articular viscosupplementation with hyaluronic acid (HA) can lead to improvements in subjects with osteoarthritis (OA) undergoing physical and rehabilitative interventions.

Aim. To assess the effects of intra-articular viscosupplementation on disability in subjects with OA undergoing physical and rehabilitative interventions. Information on pain and quality of life were also collected.

Methods. The databases of PubMed, Medline, EMbase and CINAHL were searched for English language full-text randomized controlled trials comparing intra-articular viscosupplementation alone or associated with physical and rehabilitative interventions to viscosupplementation alone, shame treatment, waiting lists, and any type of rehabilitative interventions. Methodological quality of each study was assessed by using the Physiotherapy Evidence Database scale (PEDro).

Results. A total of 115 references were retrieved, and 8 studies were selected. Three trials compared HA injection and physical therapy in knee OA, with disability and pain improvements in all studies, and between-group differences in favor of physical therapy in two studies; two trials compared HA injection and home exercises in knee OA, with improvements in pain, disability and quality of life in all studies, without between-group differences; two trials compared HA injection plus physical therapy agents and exercises to exercises plus physical therapy agents in knee OA, with improvements in disability and pain in both studies, and between-group differences in favor of the inclusion HA in one study; one trial compared HA injection and home exercises in ankle OA, with improvements in disability and pain in both arms without between-group differences.

Conclusion. Physical therapy agents seemed have greater effects than intra-articular viscosupplementation on disability and pain. In the other cases both intra-articular viscosupplementation and physical and rehabilitative interventions seemed to be equally

effective in improving disability, pain, and quality of life in subjects with knee and ankle OA.

Appraisal

This systematic review has some limitations. The exclusion of studies written in languages other than English may have introduced a selection bias. Meta-analysis was not performed owing to the small number of trials available (7 dealing with knee OA, 1 concerning ankle OA). Finally, the limited number of subjects enrolled (less than 600), most of them females, might represent a limitation in the generalisability of results. OA affected 33.6% of adults aged 65 years and older, so the sample size of this systematic review might not be faithfully representative of the real OA population.

The inclusion of only RCTs and their high quality as demonstrated by the PEDro score scale varying from 5 to 7 can be considered two strengths of this work. The PEDro scale had been widely used as a tool to rate methodological quality of RCTs, as its 10 criteria assessed internal validity of a clinical trial. Even though validated cutoff scores for the PEDro scale had not been published yet, it can be considered that shown results are as satisfactory as the most relevant criteria for a rehabilitative RCT were fulfilled.

Bannuru 2014 RR, et al.:

Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis.

Seminars in Arthritis and Rheumatism 43 (2014) 593–599.

Objective: To assess the relative efficacy of intra-articular hyaluronic acid (IAHA) in comparison with non-steroidal anti-inflammatory drugs (NSAIDs) for knee osteoarthritis (OA).

Methods: We searched Medline, EMBASE, Google Scholar, ISI Web of Science, and Cochrane Database from inception until February 2013. Randomized controlled trials comparing HA with NSAIDs for knee OA were included if they reported at least one pain outcome. Two reviewers abstracted data and determined quality. Outcomes included pain, function, and stiffness. Random-effects meta-analyses were performed.

Results: Five trials (712 participants) contributed to the pain analysis. Both groups showed improvement from baseline. The analysis found an effect size (ES) of 0.07 (95% CI: 0.24 to 0.10) at trial end, favoring neither treatment. There were no statistically significant differences between the groups at 4 and 12 weeks in function [ES -0.08 (95% CI: -0.39 to 0.23)] or stiffness [ES -0.03 (95% CI: 0.27 to 0.34)] analyses based on two trials. Injections site pain was the most common adverse event reported in the HA group, and gastrointestinal adverse events were more common in the NSAIDs group.

Conclusion: This meta-analysis suggests that IAHA is not significantly different from continuous oral NSAIDs at 4 and 12 weeks. Our study detected no safety concerns; however, the included trials had only a short follow-up duration. Given the favorable safety profile of IAHA over NSAIDs, this result suggests that IAHA might be a viable alternative to NSAIDs for knee OA, especially for older patients at greater risk for systemic adverse events.

Appraisal

This study is unique because no similar comparisons have been published in the scientific literature.

This meta-analysis had several limitations and strengths. Only a few RCTs were eligible for inclusion, and some of them were unable to contribute to certain time points or outcome measures analyses. Because direct evidence comparing IAHA to NSAIDs is limited, a better option would have been to conduct an indirect comparison using placebo-controlled trials of both NSAIDs and IAHA; however, previous research has

established that IA placebo possesses a significant benefit over oral placebo. Assuming these placebos are equal would violate a key assumption of transitivity in mixed treatment comparisons, thus making the alternative of indirect comparison by way of placebo inappropriate.

All of the included studies were randomized and active-controlled by design, though only three were double-blinded, and the quality of the studies varied. However, the level of clinical heterogeneity among the contributing RCTs appeared low with close range of baseline characteristics such as mean age and BMI, which was supported by the low level of heterogeneity I2 score (16%). Another strength of this analysis was that all but one of the studies employed some kind of a placebo injection in the form of arthrocentesis, IA saline injection, or a combination of the above measures.

Trigkilidas 2013 D, Anand A:

The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain.

Ann R Coll Surg Engl 2013; 95: 545–551. doi 10.1308/003588413X13629960049432.

Introduction: Knee osteoarthritis (OA) is a common and progressive joint disease. Treatment options for knee OA vary from simple analgesia in mild cases to knee replacement for advanced disease. Knee pain due to moderate OA can be targeted with intra-articular injections. Steroid injections have been used widely in managing acute flare-ups of the disease. In recent years, viscosupplementation has been used as a therapeutic modality for the management of knee OA. The principle of viscosupplementation is based on the physiological properties of the hyaluronic acid (HA) in the synovial joint. Despite a sound principle and promising in vitro studies, clinical studies have been less conclusive on the effectiveness of HA in managing osteoarthritic

knee pain. The aim of this systematic review was to assess the effectiveness of HA intra-articular injections in the management of osteoarthritic knee pain.

Methods: A systematic review of the literature was performed using MEDLINE, Embase and CINAHL (Cumulative Index to Nursing and Allied Health Literature). The databases were searched for randomised controlled trials available on the effectiveness of HA intra-articular injections in managing osteoarthritic knee pain.

Results: The search yielded 188 studies. Of these, 14 met the eligibility criteria and were reviewed in chronological order.

Conclusions: HA intra-articular injections have a modest effect on early to moderate knee OA. The effect peaks at around 6–8 weeks following administration, with a doubtful effect at 6 months.

Appraisal

There were some limitations with this review. The search was limited to the English language, human studies and RCTs. Another major limitation was that only papers with full text available from the Warwick university library or Google Scholar were analysed. Despite this, a relatively large number of RCTs were identified and studied. Consequently, reasonable conclusions on the efficacy of HA on knee OA could be made.

An important observation that appears to be consistent among many RCTs is that there is a high placebo effect with knee arthrocentesis. In most trials, the placebo group had a significant reduction in pain scores and improvement of function from the baseline.

Miller 2013 LE, Block JE:

US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials.

Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2013:6 57–63. doi: 10.4137/CMAMD.S12743

We conducted a systematic review and meta-analysis of randomized saline-controlled trials to determine the safety and efficacy of US-approved intra-articular hyaluronic acid (IAHA) injections for symptomatic knee osteoarthritis. A total of 29 studies representing 4,866 unique subjects (IAHA: 2,673, saline: 2,193) were included. IAHA injection resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to pre-injection values, with standardized mean difference (SMD) values ranging from 1.07–1.37 (all P , 0.001). Compared to saline controls, SMDs with IAHA ranged from 0.38–0.43 for knee pain and 0.32–0.34 for knee function (all P , 0.001). There were no statistically significant differences between IAHA and saline controls for any safety outcome, including serious adverse events (SAEs) (P = 0.12), treatment-related SAEs (P = 1.0), study withdrawal (P = 1.0), and AE-related study withdrawal (P = 0.46). We conclude that intra-articular injection of US-approved HA products is safe and efficacious in patients with symptomatic knee osteoarthritis.

Appraisal

This was the first systematic review and meta-analysis of US-approved HA products on knee OA symptoms. The most notable finding from this meta-analysis is that US-approved HA products are not associated with increased safety risks.

This meta-analysis has some limitations that may influence interpretation. Most, but not all, studies excluded subjects with end-stage (Kellgren-Lawrence grade IV or equivalent) knee OA and, therefore, the efficacy of IAHA in these patients cannot be determined. Next, it was not consider the HA products without US approval and, therefore, implied comparisons of safety and efficacy between US approved vs. non-US approved

products should be performed with caution. Due to sample size considerations, they did not attempt to analyze treatment effects by HA brand. Lastly, efficacy outcomes were inconsistent across studies and publication bias was evident for knee pain outcomes.
Strengths of this meta-analysis are inclusion of only randomized, saline-controlled trials, structured data extraction methodology, inclusion of all zero total event trials in safety analyses, and sensitivity analyses that accounted for choice of statistical test and potentially influential studies.

Rutjes 2012 AW, et al.:

Viscosupplementation for osteoarthritis of the knee.

Annals of Internal Medicine 2012; 157(30): 180-191.

Background: Viscosupplementation, the intra-articular injection of hyaluronic acid, is widely used for symptomatic knee osteoarthritis. Purpose: To assess the benefits and risks of viscosupplementation for adults with symptomatic knee osteoarthritis.
Data Sources: MEDLINE (1966 to January 2012), EMBASE (1980 to January 2012), the Cochrane Central Register of Controlled Trials (1970 to January 2012), and other sources. Study Selection: Randomized trials in any language that compared viscosupplementation with sham or non intervention control in adults with knee osteoarthritis.
Data Extraction: Primary outcomes were pain intensity and flare-ups. Secondary outcomes included function and serious adverse events. Reviewers used duplicate abstractions, assessed study quality, pooled data by using a random-effects model, examined funnel plots, and explored heterogeneity by using meta-regression.
Data Synthesis: Eighty-nine trials involving 12 667 adults met inclusion criteria. Sixty-eight had a sham control, 40 had a follow-up duration greater than 3 months, and 22 used cross-linked forms of hyaluronic acid. Overall, 71 trials (9617 patients) showed that viscosupplementation moderately reduced pain (effect size, −0.37 [95% CI, −0.46

to −0.28]). There was important between-trial heterogeneity and an asymmetrical funnel plot: Trial size, blinded outcome assessment, and publication status were associated with effect size. Five unpublished trials (1149 patients) showed an effect size of −0.03 (CI, −0.14 to 0.09). Eighteen large trials with blinded outcome assessment (5094 patients) showed a clinically irrelevant effect size of −0.11 (CI, −0.18 to −0.04). Six trials (811 patients) showed that viscosupplementation increased, although not statistically significantly, the risk for flare-ups (relative risk, 1.51 [CI, 0.84 to 2.72]). Fourteen trials (3667 patients) showed that viscosupplementation increased the risk for serious adverse events (relative risk, 1.41 [CI, 1.02 to 1.97]).

Limitations: Trial quality was generally low. Safety data were often not reported.

Conclusion: In patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.

Appraisal

This MA was heavily influenced by inclusion of unpublished, unverifiable data.

It is found that HA can increase the risk of serious adverse events. However, these findings, never reported in an MA, have raised severe criticism in terms of the methodology used to assess HA safety.

They analysed all safety data using an odds ratio, a statistic that excludes zero total event trials.

Bannuru 2011 RR, et al.:

Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis e meta-analysis.

Osteoarthritis and Cartilage 19 (2011) 611-619.

Objective: To evaluate the therapeutic trajectory of intra-articular hyaluronic acid (IAHA) vs placebo for knee osteoarthritis (OA).

Design: Our data sources include Medline, EMBASE, CINAHL, BIOSIS, Web of Science, Google Scholar, Cochrane database; hand searched reviews, manuscripts, and, supplements; author contacts for unpublished data. Randomized trials that reported effects of IAHA vs placebo on knee OA were selected based on inclusion criteria. We computed effect sizes for change from baseline at 4, 8, 12, 16, 20 and 24 weeks, using Bayesian random effects model. We performed multivariate analyses adjusting for correlation between time points. Meta-regressions were performed adjusting for potential confounders.

Results: The 54 eligible trials included 7545 participants. The conduct and quality of these trials varied in number of aspects. The effect size (ES) favored IAHA by week 4 (0.31; 95% CI 0.17, 0.45), reaching peak at week 8 (0.46; 0.28, 0.65), and then trending downwards, with a residual detectable effect at week 24 (0.21; 0.10, 0.31). This therapeutic trajectory was consistent among the subset of high quality trials and on multivariate analysis adjusting for correlation between time points.

Conclusions: Our meta-analysis highlights a therapeutic trajectory of IAHA for knee OA pain over 6 months post-intervention. With this additional perspective, we are able to infer that IAHA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable at 24 weeks. On the other hand, the peak effect size (0.46; 0.28, 0.65), is greater than published effects from other OA analgesics [acetaminophen (ES 0.13; 0.04, 0.22); NSAIDs (ES 0.29; 0.22, 0.35); COX-2 inhibitors (ES 0.44; 0.33, 0.55)]. An effect size above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. Thus, its properties could have utility for certain clinical situations, or in combination with other therapies.

Appraisal
One unique aspect of this meta-analysis is that it was examined the therapeutic response over time by pooling the data for each time point separately. The product of this analysis was informative in laying out the pattern of therapeutic response attributable to the intervention. However, two limitations to this approach are that not all trials provided data for each of the time points, and the possibility of correlations among outcomes between time points. These issues were addressed by running a multivariate longitudinal regression model that adjusted for time. A strength of the MA was in the assessments and techniques to minimize data biases. Another strength was in the management of pooling several hyaluronic acid agents which differ in many characteristics including molecular weights, origin, viscosity, cross-linking etc. This issue was addressed by performing several sensitivity analyses wherever possible.

Bannuru 2009 RR, et al.: **Therapeutic Trajectory of Hyaluronic Acid Versus Corticosteroids in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis.** Arthritis & Rheumatism (Arthritis Care & Research) Vol. 61, No. 12, December 15, 2009, pp 1704–1711. DOI 10.1002/art.24925.
Objective. To compare the efficacy of intraarticular hyaluronic acid with corticosteroids for knee osteoarthritis (OA). Methods. Our data sources were Medline, EMBASE, CINAHL, BIOSIS, and the Cochrane database, as well as handsearched reviews, manuscripts, and supplements. For unpublished data we used author contacts. Randomized trials that reported effects of intraarticular hyaluronic acid versus corticosteroids on knee OA were selected based

on inclusion criteria. Two reviewers extracted data independently. Using a random-effects model, we computed effect sizes for pain change from baseline at 2, 4, 8, 12, and 26 weeks. We also performed multivariate analyses accounting for within and between-study covariance. We performed sensitivity analyses for trials that reported intent-to-treat (ITT) analysis and blinding, and directly compared Hyalgan with methylprednisolone.

Results. The 7 eligible trials included 606 participants. Five reported ITT analyses. At week 2 the effect size was -0.39 (95% confidence interval [95% CI], -0.65, -0.12) favoring corticosteroids; at week 4 it was -0.01 (95% CI -0.23, -0.21) suggesting equal efficacy. At week 8 the effect size was 0.22 (95% CI -0.05, 0.49) favoring hyaluronic acid, and at week 12 it was 0.35 (95% CI 0.03, 0.66) favoring hyaluronic acid. At week 26 the effect size was 0.39 (95% CI 0.18, 0.59), favoring hyaluronic acid. The multivariate analyses and sensitivity analyses generated consistent results.

Conclusion. From baseline to week 4, intraarticular corticosteroids appear to be relatively more effective for pain than intraarticular hyaluronic acid. By week 4, the 2 approaches have equal efficacy, but beyond week 8, hyaluronic acid has greater efficacy. Understanding this trend is useful to clinicians when treating knee OA.

Appraisal

One unique aspect of this meta-analysis is that they examined the therapeutic response over time by separately pooling the data for each time point. The product of this analysis was highly informative in contrasting the pattern of therapeutic response attributable to each intervention. However, there are some limitations to this approach, including that not all of the clinical trials provided data relating to each of the time points and the possibility of correlations among outcomes between the time points. These issues were addressed by performing multivariate analyses accounting for within- and between-study variance. The multivariate results were consistent with the primary analysis and, in fact, demonstrated an additional significant difference at the 12-week time point.

Reichenbach 2007 S, et al.:

Hylan Versus Hyaluronic Acid for Osteoarthritis of the Knee: A Systematic Review and Meta-Analysis.

Arthritis & Rheumatism (Arthritis Care & Research) Vol. 57, No. 8, December 15, 2007, pp 1410–1418. DOI 10.1002/art.23103.

Objective. To compare the effectiveness and safety of intraarticular high-molecular hylan with standard preparations of hyaluronic acids in osteoarthritis of the knee.

Methods. We performed a systematic review and meta-analysis of randomized controlled trials comparing hylan with a hyaluronic acid in patients with knee osteoarthritis. Trials were identified by systematic searches of Central, Medline, EMBase, Cinahl, the Food and Drug Administration, and Science Citation Index supplemented by hand searches of conference proceedings and reference lists (last update November 2006). Literature screening and data extraction were performed in duplicate. Effect sizes were calculated from differences in means of pain-related outcomes between treatment and control groups at the end of the trial, divided by the pooled standard deviation. Trials were combined using random-effects meta-analysis.

Results. Thirteen trials with a pooled total of 2,085 patients contributed to the meta-analysis. The pooled effect size was -0.27 (95% confidence interval [95% CI] -0.55, 0.01), favoring hylan, but between-trial heterogeneity was high (I2 88%). Trials with blinded patients, adequate concealment of allocation, and an intent-to-treat analysis had pooled effect sizes near null. The meta-analyses on safety revealed an increased risk associated with hylan for any local adverse events (relative risk [RR] 1.91; 95% CI 1.04, 3.49; I2 28%) and for flares (RR 2.04; 95% CI 1.18, 3.53; I2 0%).

Conclusion. Given the likely lack of a superior effectiveness of hylan over hyaluronic acids and the increased risk of local adverse events associated with hylan, we

discourage the use of intraarticular hylan in patients with knee osteoarthritis in clinical research or practice.
Appraisal
A major limitation relates to the inability to fully explain heterogeneity between trials: the decrease in heterogeneity was only modest in stratified analyses and P values for interaction between effect size and trial characteristics did not reach conventional levels of statistical significance. It should be noted that the relatively low number of trials included in this meta-analysis means that interaction tests only had limited power to detect relevant differences. Another problem relates to insufficient standardization of safety outcomes: definitions and reporting of local adverse events differed considerably among the trials and the validity of this meta-analysis of local adverse events with variable definitions might therefore be low. In this MA they did not use a scale to assess the methodologic quality of trials because they did not want to affect the methodologic judgments. At last, they combined data where different hyaluronic acids were used as control interventions and where pain was measured with different scales. To achieve it they used effect sizes to standardize data from different pain scales.

Medina 2006 JM, Thomas A, Denegar CR: **Knee osteoarthritis: Should your patient opt for hyaluronic acid injection? A meta-analysis of hyaluronic acid's effects on pain, stiffness, and disability.** The Journal of Family Practice, vol 55, no 8, August 2006.
Practice recommendations - Hyaluronic acid (HA) injection may provide short-term relief of pain and improved functionality for patients with osteoarthritis of the knee, but benefits do not last beyond 6 months.

- Examine the HA option from a cost-benefit perspective on a case-by-case basis. Based on our meta-analysis, there is no sufficient reason to recommend or not recommend HA injection for treatment of osteoarthritis of the knee.
- You may want to help select patients weigh the possible benefit of HA therapy against its cost.

Appraisal

This study examined only the pooled effects of hyaluronic acid carried out to at least 24 weeks and up to 52 weeks.
Only studies that used an identical method for reporting outcome scores were included in this MA.
As a result, to few studies considered.

Bellamy 2006 N, et al.:

Viscosupplementation for the treatment of osteoarthritis of the knee.

Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005321. DOI: 10.1002/14651858.CD005321.pub2.

Objectives
To assess the effects of viscosupplementation in the treatment of OA of the knee. The products were hyaluronan and hylan derivatives (Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease, Euflexxa, Nuflexxa), Durolane, Fermathron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), Hyruan, NRD-101 (Suvenyl), Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject and Zeel compositum).

Search methods
MEDLINE (up to January (week 1) 2006 for update), EMBASE, PREMEDLINE,CurrentContents up to July 2003, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Specialised journals and reference lists of

identified randomised controlled trials (RCTs) and pertinent review articles up to December 2005 were hand-searched.

Selection criteria

RCTs of viscosupplementation for the treatment of people with a diagnosis of OA of the knee were eligible. Single and double-blinded studies, placebo-based and comparative studies were eligible. At least one of the four OMERACT III core set outcome measures had to be reported (Bellamy 1997).

Data collection and analysis

Each trial was assessed independently by two reviewers for its methodological quality using a validated tool. All data were extracted by one reviewer and verified by a second reviewer. Continuous outcome measures were analysed as weighted mean differences (WMD) with 95% confidence intervals (CI). However, where different scales were used to measure the same outcome, standardized mean differences (SMD) were used. Dichotomous outcomes were analysed by relative risk (RR).

Main results

Seventy-six trials with a median quality score of 3 (range 1 to 5) were identified. Follow-up periods varied between day of last injection and eighteen months. Forty trials included comparisons of hyaluronan/hylan and placebo (saline or arthrocentesis), ten trials included comparisons of intra-articular (IA) corticosteroids, six trials included comparisons of nonsteroidal anti-inflammatory drugs (NSAIDs), three trials included comparisons of physical therapy, two trials included comparisons of exercise, two trials included comparisons of arthroscopy, two trials included comparisons of conventional treatment, and fifteen trials included comparisons of other hyaluronans/hylan. The pooled analyses of the effects of viscosupplements against 'placebo' controls generally supported the efficacy of this class of intervention. In these same analyses, differential efficacy effects were observed for different products on different variables and at different timepoints. Of note is the 5 to 13 week post injection period which showed a percent improvement from baseline of 28 to 54% for pain and 9 to 32% for function. In general, comparable efficacy was noted against NSAIDs and longer-term benefits were

noted in comparisons against IA corticosteroids. In general, few adverse events were reported in the hyaluronan/hylan trials included in these analyses.

Authors' conclusions

Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment; and at different post injection periods but especially at the 5 to 13 week post injection period. It is of note that the magnitude of the clinical effect, as expressed by the WMD and standardised mean difference (SMD) from the RevMan 4.2 output, is different for different products, comparisons, timepoints, variables and trial designs. However, there are few randomised head-to-head comparisons of different viscosupplements and readers should be cautious, therefore, in drawing conclusions regarding the relative value of different products. The clinical effect for some products, against placebo, on some variables at some timepoints is in the moderate to large effect-size range. Readers should refer to relevant tables to review specific detail given the heterogeneity in effects across the product class and some discrepancies observed between the RevMan 4.2 analyses and the original publications. Overall, the analyses performed are positive for the HA class and particularly positive for some products with respect to certain variables and timepoints, such as pain on weight bearing at 5 to 13 weeks postinjection.

In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events. In other analyses HA products had more prolonged effects than IA corticosteroids.

Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

Appraisal
Overall the most comprehensive and detailed MA published on HA treatment in KOA.

Limitations of this review are the omission of open trials and case series, the omission of studies that failed to meet inclusion criteria, the lack of standard outcome measures restricting pooling opportunities, and restricted access to source data.

Strengths of the review are the inclusion of only randomised controlled trials, the focus on four core OARSI and OMERACT outcome measures, and adherence to the principles of Cochrane systematic reviews.

Last five meta-analyses, the oldest in chronological order, have not been appraised in this CER as developments, new results, and a wider understanding of the state-of-the-art limits have evolved over time and because they can be considered as consolidated knowledge from the past, in fact they are all already evaluated in the above mentioned meta-analyses. In synthesis, in (Modawal 2005) the authors found that HA has a modest effect on pain from osteoarthritis of the knee at 5 to 7 weeks and at 8 to 10 weeks after the last injection, but not at 15 to 22 weeks. The authors stated that the decision to give three to five injections of hyaluronic acid should only be made after patients have had a trial of conservative treatment for at least 3 months, or if patients cannot tolerate NSAIDs. Patients receiving hyaluronic acid injections should be advised that benefits may not be felt until 5 to 10 weeks after the last injection. The cost-benefit of using hyaluronic acid injections must be compared with alternative treatments.

In (Arrich 2005) the authors concluded that according to the evidence available at the time (and according to their inclusion-exclusion criteria) intra-articular HA injections was not proven to be clinically effective and that could be associated with an increased risk of adverse events. So the need for more and larger trials was expressed. They also found no difference in effects of the products with different molecuar weights of the HA.

In (Wang 2004) the authors found the HA injections to be effective and safe in the treatment of KOA. The need for larger RCT trials with high metodological quality was expressed, in particular to accertain the potential difference in products performances and population to be treated. In fact, they found patients over 65 years of age or with the most advanced stage of KOA to be less likely to benefit from the treatment.

In another meta-analysis of the same year (Aggarwal 2004), the authors found that viscosupplementation with high molecular weight HA (> 500KDa) to be effective in patients with KOA who have ongoing pain or are unable to tolerate conservative treatment or joint replacement. Viscosupplementation appeared to have a slower onset of action than intra-articular steroids but the effect seemed to last longer.

At last, in a previous meta-analysis (Lo 2003), the authors found that HA injections to have a small effect with respect to placebo. They also pointed out that higher molecular weight HA could have a better efficacy in treating KOA but that heterogeneity of available tudies hindered definitive conclusions.

6 Analysis of data

6.1 Overall performances with equivalent devices (MDD ER3)

Many of the clinical data dealing with direct application of equivalent devices in real practice conditions have already been assessed through the several meta-analyses published on the topic of intra-articular injection of HA in the treatment of knee osteoarthritis (KOA). These meta-analyses have been used through the years to make up a series of guidelines, recommendations and expert opinions that have highlighted both strenghts and weaknesses of HA in KOA (see Table 1 for comparisons of essential information).

Table 1: results from meta-analyses of last 10 years.

Meta-Analysis	No. articles	Main outcome	Results/Effect (95% CI) or assessment	Conclusion
Strand 2015 (US approved HA) vs placebo	29	Pain/function	SMD: 0.38 to 0.42 for pain; 0.32 to 0.34 for function	Positive
Richette 2015 vs placebo	8	Pain/function	SMD: -0.21 (-0.32 to -0.10) for pain; -0.12 (-0.22 to -0.02) for function	Positive
Monticone 2015 vs various physical therapies	8	disability/pain	Physical therapy better at short term	Case to case choice
Bannuru 2014 vs NSAIDs	5	Pain at endpoint	Hedges's g: -0.07 (-0.24 to 0.10)	No difference
Trigkilidas 2013 vs placebo or corticosteroids	14	Pain	Small effect vs placebo Effect superior vs steroid after week 4	Modest positive
Miller 2013 (US approve HA) vs placebo	29	Pain/function at endpoint	SMD: 0.38-0.43 for pain; 0.82-0.34 for function	Positive
Rutjes 2012 vs sham or no intervention	89	Pain/function	SMD: -0.37 (-0.46 to -0.28) for pain; -0.33 (-0.43 to -0.22)	Modest positive weigh vs risks

Meta-Analysis	No. articles	Main outcome	Results/Effect (95% CI) or assessment	Conclusion
Bannuru 2011 terapeutic trajectory	54	Pain change from baseline	ES: 0.46 (0.28-0.64) at week 8; 0.21 (0.10-0.31) at week 24	Positive
Bannuru 2009 vs corticosteroids	7	Pain change from baseline	ES: 0.22 (-0.05 to 0.49) at week 8 in favour of HA	Positive from week 8
Reichenbach 2007 vs Hylan G-F 20	13	Pain at endpoint	ES: on between group difference -0.27 in favor of Hyaln but more post--injection flares	discourage Hylan use
Medina 2006 vs placebo	7	Pain	Differnce: 95% CI: -0.6043-5.4755	No difference
Bellamy 2006 vs placebo	40	Pain/function (WMD or SMD)	-28% to 54% reduction in pain at weeks 5-13	Positive

The meta-analysis from the Cochrane review of 2006 (Bellamy 2006) included 76 trials of a number of different HA products mostly administered at weekly intervals for 3–5 weeks, in comparison with placebo, intra-articular corticosteroids, NSAIDs, andother therapies. The analysis found that viscosupplementation is an effective treatment for OA of the knee. Beneficial effects on pain, function, and patient global assessment at different post-injection time periods were noted, but especially at 5–13 weeks post-injection which showed a percent improvement from baseline of 28–54% for pain and 9–32% for function.

A recent network meta-analysis was performed on 137 studies comprising 33.243 participants using a Bayesian random-effects model to determine the comparative effectiveness of pharmacological interventions for knee OA (Maheu 2016). For pain, all interventions significantly outperformed oral placebo, with the exception of paracetamol; the most efficacious treatment was found to be intra-articular HA with an effect size (ES) of 0.63 (95% central credible interval [CrI]: 0.39–0.88). The least effective treatment was paracetamol (ES: 0.18, 95% CrI: 0.04–0.33). For function, all interventions with the exception of intra-articular corticosteroids and paracetamol were significantly superior to oral placebo,and for stiffness most of the treatments did not differ significantly from one another. It was notable that the use of the intra-articular deliver ymethod itsel fwas found to have a significant effect, with an ES of 0.29 (95% CrI: 0.04–0.54) for IA placebo compared with oral placebo. Nonetheless, when compared with intra-articular placebo, a statistically significant ES of 0.34 (CrI:

0.26–0.42) was observed for intra-articular HA on pain at 3 months, which is of the magnitude observed in conventional meta-analyses, e.g., ES on pain of 0.46 (95% confidence interval [CI] 0.28–0.65) at week 8 in the Bannuru meta-analysis, and ES of 0.37 (95%CI:0.46–0.28) in the Rutjes meta-analysis (Bannuru 2011, Rutjes 2012). A further analysis of trials directly comparing intra-articular HA and NSAIDs suggests that the effect of IA HA is not significantly different from continuous oral NSAIDs in the short term, at 4 and 12 weeks for pain, function, and stiffness in knee OA (Bannuru 2014). Injection site pain was the most common adverse event (AE) reported in the HA group, and gastrointestinal (GI) AEs were more common in the NSAIDs group. Given the favorable safety profile of intra-articular HA over NSAIDs, this result suggests that intra-articular HA might be a good alternative to NSAIDs for knee OA, especially for older patients or in those at greater risk for NSAID-induced AEs (Bruyere 2014).

Intra-articular HA has a long lasting effect on pain in OA (Bannuru 2009, Bannuru 2011, Miller 2013). The recent analysis of 29 studies of US-approved HA injections versus placebo found a large treatment effect from 4 weeks up to 26 weeks for knee pain and function compared to pre-injection values (Miller 2013). Compared to saline controls, standardized mean difference (SMD) with HA was maintained at 0.38 for knee pain and 0.32 for kne efunction at weeks 14–26 ($p < 0.001$), which equates to a moderate but true effect [10]. A therapeutic trajectory of HA versus placebo found that HA is efficacious by4 weeks (ES: 0.31; 95% CI:0.17–0.45), reaching a peak in effectiveness at 8 weeks (ES: 0.46, 95% CI:0.28–0.65), and with a residual detectable effect for knee OA pain at 6 months post-intervention (ES: 0.21, 95% CI:0.10–0.31) (Bannuru 2011). In addition, HA induces longer-lasting pain control compared with intra-articular corticosteroids (Bannuru 2009). The analysis of 7 head-to-head randomized clinical trials (RCTs) of 606 participants, found that the pattern of relative efficacy varied over time following injection. From baseline to week 4, intra-articular corticosteroids were relatively more effective for pain than HA, but by week 4 the two approaches had equal efficacy, and beyond week 8 up to 26 weeks HA had greater efficacy (Bannuru 2009).

At last, a summary of recommendations, guidelines and consencus statements expressed from several organizations or groups of experts in the field pointed out some aspects to take into account in the management of the degenerative osteoarthritis of the knee: just recently an Italian panel of 10 experts reporting the results of a Delphi consensus survey (Paoloni 2016) indicated that for knee OA, high- and medium-molecular weight HA (above 500 KDa), and mobile reticulum and cross-

linked HA are the most appropriate products according to the experts, whereas homotoxicological products and collagen medical devices are considered as inappropriate. In particular, both corticosteroids and HA intra-articular injections are considered to relieve the patients symptoms. Furthermore, intra-articular injections of HA are considered to be valid as a means of controlling the objective manifestations of OA. In another recent consensus statement from eight experts (Henrotin 2015), HA was considered as en effective and safe therapeutic modality to treat mild to moderate knee OA. HA injections should be performed after a careful clinical and imaging analysis, to improve the chances of a successful treatment. In knee OA, viscosupplementation could also be helpful in advanced stages of the disease in patients who cannot be or do not want to be operated. The European society for clinical and economic aspects of osteoporosis and osteoarthritis (EULAR, Bruyere 2014) recommends, as second step of the treatment protocol, an advanced pharmacological management in the persistent symptomatic patient and that is centered on the use of oral COX-2 selective or non-selective NSAIDs, chosen based on concomitant risk factors, with intra-articular corticosteroids or HA for further symptom relief, if insufficient. A similar stance was taken by the osteoarthritis research society international (OARSI) to the uncertain use of HA, in their last updated guidelines (McAlindon 2014). The American association of orthopoedic surgeons (AAOS 2013) did not recommend HA in patients with symptomatic OA of the knee because there are evidences that all the scores have statstically significant effects but the mimimum clinically important improvement thresholds could not be reached. The American college rheumatology (Hochberg 2012) found that if the patient does not have a satisfactory clinical response to full-dose acetaminophen, then strong recommendation is to use of oral or topical NSAIDs or intra-articular corticosteroid injections. Nonetheless, health care providers should not use oral NSAIDs in patients with contraindications to these agents and should be aware of the warnings and precautions associated with the use of these agents. Furthermore, for persons older than 75 years of age, they strongly recommends the use of topical rather than oral NSAIDs. In this scenario, they conditionally recommends the use intra-articular injections of HA.

6.2 Safety (MDD ER1)

6.2.1 Adverse events from equivalent devices (MDD ER6)

In this paragraph an adverse event is reported if present at least as single entry in each of the clinical data publications considered in this CER, without restriction on severity, treatment relationship, duration, or any other analysis or conclusion by the authors.

Injection pain	Vetro 2014, Filardo 2012, Foti 2011, Sun 2006, Pavelka 2011, Berenbaum 2012, Kaush 2009, Kolarz 2003, Blanch 2012, Gydek 2011, Leighton 2014
Site swelling	Vetro 2014, Foti 2011, Zhang 2015, Sun 2006, Lana 2016, Pavelka 2011, Blanch 2012, Strand 2016, Leighton 2014
Effusion	Filardo 2012, Juni 2007, Zhang 2015, Pavelka 2011, Berenbaum 2012, Kolarz 2003, Gydek 2011, Strand 2016
Local warmth	Sun 2006, Berenbaum 2012, Blanch 2012
Arthralgia	Zhang 2015, Pavelka 2011, Strand 2016, Leighton 2014
Injection site hematoma	Pavelka 2011, Berenbaum 2012
Musculoskeletal and connective tissue disorder	Juni 2007, Zhang 2015
Pruritus	Kolarz 2003, Gydek 2011
Redness	Gydek 2011
Edema	Gydek 2011
Erythema	Zhang 2015
Skin allergy at injection site	Mazieres 2007
Septic arthritis (avian HA)	Juni 2007

anaphylactic shock	Juni 2007
Myalgia	Zhang 2015

6.2.2 Risk Analysis from a clinical perspective (MDD ER6)

Infected or severely inflamed joint

- Exclusion criteria in clinical trials

Risk Control Measure: Include in the insructions for use

- section “WARNING - PRECAUTIONS FOR USE”:

“The product must not be injected in presence of an infected or severely inflamed joint. The infiltration must be avoided in the case of infections in place or inflammatory conditions of the skin in proximity of the injection.”

Skin disease in the area of the injection site

- Exclusion criterion in clinical trials

Risk Conrol Measure: Include in the Instructions for Use

- section “WARNING - PRECAUTIONS FOR USE”:

“**FOCUSIAL** must not be used in presence of skin disease in the area of the injection site.”

Hypersensitivity

- Exclusion criterion in clinical trials

Risk Conrol Measure: Include in the Instructions for Use

- section “WARNING - PRECAUTIONS FOR USE”:

“**FOCUSIAL** must not be used in patients who are known to be hypersensitive to hyaluronic acid or any of the product components.”

Pregnant or breastfeeding women

- Exclusion criteria in clinical trials

Risk Conrol Measure: Include in the Instructions for Use

- section “WARNING - PRECAUTIONS FOR USE”:

"**FOCUSIAL** must not be used in pregnant of breastfeeding women as it has not been tested in such cases."

Under 18 years of age

- Exclusion criteria in clinical data

Risk Conrol Measure: Include in the Instructions for Use

- section "WARNING - PRECAUTIONS FOR USE":

"**FOCUSIAL** must not be used in patients under 18 years of age as it has not been tested in such population."

Incompatibilities

- Interaction between hyaluronic acid and quaternary ammonium compounds is known to give rise to incompatibility of concomitant application.

Risk Conrol Measure: Include in the Instructions for Use

- section "INCOMPATIBILITIES":

"There are incompatibilities between sodium hyaluronate and quaternary ammonium compounds, such as solutions of benzalkonium chloride. Contact between **FOCUSIAL** and these substances must be therefore avoided."

Adverse events from previous section

Risk Conrol Measure: Include in the Instructions for Use

- section "Undesired Side Effects":

"There may be some temporary side reactions following injection of **FOCUSIAL**, such as local pain, stiffness, warmth, redness, swelling, effusion, prutirus, edema, erythema, hematoma, myalgia or arthralgia. These secondary manifestations may be relieved by applying ice on the treated articulation. Usually these effects disappear after a short time.

If symptoms persist, consult a physician. A for any intra-articular treatment, septic arthritis may rarely occur when general precautions for injections are not observed or the site of injection is not aseptic. Any other unwanted side effects associated with the injection of **FOCUSIAL** must be reported to a doctor."

- section “WARNINGS - PRECAUTIONS FOR USE”:

“FOCUSIAL is suitable only for intra-articular injections and must only be dispensed by a doctor.
Before use, check the integrity of the syringe and the expiration date.
Do not use needles other than those listed.
After the intra-articular injection it is advisable to recommend to the patient to avoid physical activities demanding stress for the articulation and resume normal activities after a few days.
FOCUSIAL is a disposable product, the quality and sterility are guaranteed only if the syringe is sealed. Any residue must be discarded and not reused even after new sterilisation.
Do not use the product if the package is already opened or damaged.
After use, dispose of the needle into a suitable container.”

The proposed product literature and Instructions for Use are consistent with the clinical data available on equivalent devices and cover all the identified hazards and other clinically relevant information that may impact on the use of **FOCUSIAL**.
The end user must be an experienced physician in the field of application of **FOCUSIAL** as specified in the Instructions for Use:
- section “Methods of Use”:
“FOCUSIAL must be used only by doctors who have received specific training on the injection technique in the treatment of knee osteoarthritis.”

6.2.3 General assessment and conclusion (benefit/risk profile MDD ER1)

In Vetro et al (Vetro 2014) the treatment is described as well tolerated with mild transient adverse events (AE) reported in 5 patients. These AE are considered device-related local, post injection pain and swelling which resolved spontaneously after a few days. Patients daily activities were unaffected by these events and no SAEs was reported.

Filardo et al (Filardo 2012) compared the intra-articular injections of HA to platelet-rich plasma (PRP) and found that only minor AEs were detected in some patients, such as mild pain and effusion after the injections, in particular in the PRP group, where a significantly higher post-injective pain reaction was observed.

In the prospective observational study by Fot et al (Foti 2011) data from 1266 participants were collected. The AE rate was 0.8% (95% CI, 0.4 to 1.5). Thirteen AEs were reported, 12 of which were mild or moderate in severity (6 injection site pain, 1 swelling and other unclassified). Only one participant discontinued study treatment following an AE and no SAEs occurred.

In Sun et al (Sun 2006) local AEs with transient pain at injection site and local warmth and swelling with varying intensities were reported in four patients (7.1%) and no SAEs or systemic AEs were observed in the participants during the study.

In the clinical trial by Pavelka et al (Pavelka 2011) six AEs were considered treatment-related, with five events in four patients in the Synvisc group [injection site hematoma, injection site pain, arthralgia and joint swelling (two episodes in one patient)] and one case of injection site pain in a patient who received Sinovial. Overall both HA products were found well tolerated and equally effective.

In the trial by Berenbaum et al (Berenbaum 2012) on a total of 436 patients treated with HA, local AEs were 5 cases of effusion or swelling, 5 joint pain, 2 injection site hematomas for a total of 12 local AEs (2.7%) so that the treatments were considered were well tolerated locally and with no case of acute pseudoseptic arthritis.

In the observational study by Kaush et al (Kaush 2009) on 1743 patients, only one treatment-related case resulted in withdrawal due to pain.

In the observational study from Kolarz et al (Kolarz 2003) of 4 patients who withdrew because of AEs, only 1 event (knee joint effusion) was judged as possibly drug related. Two other AEs judged to be drug related (generalized skin eruption; pruritus and knee joint effusion) resolved and did not lead to study withdrawal, so that the overall treatment was considered well tolerated.

In the ASKOT study by Blanch et al (Blanch 2012) 9 patients (2.2% of the treated population) reported having at least one AE. AEs of 7 patients were related or possibly related to the injection, which 3 of them were related to local AEs: post injection pain (1), local swelling (1) and sensation of hot knee (1). All the events related to product administration resolved within a few days (0-5 days) so that the AEs were restricted to minor and transient local events.

In the observational study on 4519 patients by Gydek et al (Gydek 2011) AEs such as edema, exudate, pruritus, redness and pain occurred in 1.6% of the patients but the association of some of these effects with the injection procedure itself could not be excluded. No SAEs were reported so that considering the low rate of AEs it was concluded that HA seems to be particularly indicated in the osteoarthritis treatment in individuals with bad tolerance to NSAIDs (such as elderly patients) or for whom NSAIDs are contraindicated (e.g. patients with peptic ulcer).

In the non inferiority trial between HA and methylprednisolone by Leighton et al (Leighton 2014), arthralgia was the most common treatment-related AE in both study groups, with injection site pain, joint stiffness and joint swelling also occurring in more than 1% of patients. Most treatment-related AEs were reported within 3 days of injection and resolved within 2-3 weeks. The reported AEs were largely anticipated in nature, with a lack of differences between the two treatments regarding the type, onset and duration of AEs, so that the overall treatment was deemed well tolerated.

In the non inferiority trial by Zhang et al (Zhang 2015) arthralgia was the common treatment related AE but arthralgia was expected among patients who receive HA injections. On 348 total treated patients there were only single cases of joint effusion, myalgia and erythema.

In the clinical trial by Strand et al (Strand 2016) the most common AEs were joint swelling, joint effusion, arthralgia. Overall, the profile of the safety data collected in the RCT was similar between patients who did and did not receive retreatment with HA. A mild AE in the form of a knee swelling was reported 3-5 days after the application by Lama et al (Lama 2016). It was not reported as a major complication by any patient. Skin allergy was also reported as AE in the observational study by Mazières et al (Mazieres 2007). At the end, in the trial by Juni et al (Juni 2007) it was pointed out that the use of HA of avian origin can be associated to a higher risk of AEs.

In conclusion, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events (Bellamy 2006). In the meta-analysis comparing HA to NSAIDs (Bannuru 2014), injection site pain was the most common adverse event reported in the HA group, and gastrointestinal adverse events were more common in the NSAIDs group. Given the favorable safety profile of intra-articular HA over NSAIDs, this result suggests that HA might be a viable alternative to NSAIDs for knee OA, especially for older patients at greater risk for systemic adverse events. HA preparations are generally considered safe

with infrequent local reactions and paucity of systemic adverse events. In the meta-analysis of Medina et al (Medina 2006) side effects were uncommon and complications with HA injections were relatively mild. A few cases of HA allergy have been reported, including sweating, paleness, feelings of pressure in the chest and stomach, skin turning blue, or a decrease in blood pressure. In two meta-analyses on only FDA approved HA (Miller 2013, Strand 2015) the conclusion on the safety profile was that HA products are safe and efficacious in patients with symptomatic knee osteoarthritis. However, it must be noted that according to the meta-analysis of Reichenbach et al (Reichenbach 2007) the patients treated with cross-linked HA are approximately twice as likely to experience local adverse events.

7 Conclusions

This clinical evaluation report aimed at providing sufficient evidence that the essential requirements of **FOCUSIAL**, from a clinical viewpoint, in terms of performance and safety do justify a favourable benefit/risk profile with respect to the intended use of the device.

It is based on the critical evaluation of relevant clinical data available in the specific medical field, on the state-of-the-art knowledge and understanding of the interactions and effects of hyaluronic acid and knee joint in the scientific community, and on the clinical data available in studies performed with equivalent devices. Given that HA is a well known constituent itself of the extracellular matrix in human body, the scientific literature reviewed in this CER summarized the extensive knowledge about the properties, actions, and effects that HA can play specifically in the context of intra-articular injection in the knee joint.

It has been shown that adverse events with HA products are extremely rare, mostly confined to local reactions and manageable with standard therapy. HA is one of the major components of the extracellular matrix in human body, so that adverse reactions are not to be expected with proper use. Treatment with native HA may improve parameters such as pain and functionality in patients suffering from knee osteoarthritis. Intra-articular injections of HA can thus be considered as an effective treatment to counteract pain and functionality in the treated joint. The viscoelastic properties of linear HA can thus supplement the natural and degenerative loss in osteoarthritic knee thus providing an on-site substitute to reduce unwilling factors.

Clinical data have been included from clinical studies with native hyaluronic acid, which demonstrate statistically significant improvement in pain and functionality of the knee joint.

All studies confirmed the safety and efficacy profile of the HA treatment. As shown in the data appraisal section, the data can be regarded as suitable for a demonstration of conformity with the essential requirements covering safety and performance of the device in terms of clinical outcomes. All reported adverse events were transient and mostly related to treatment itself. No serious adverse event were reported.

The risks associated with the use of the device, if used as claimed, are acceptable when weighed against the benefits to the patient. The clinical evidence demonstrates conformity with the relevant essential requirements.

8 Date of the next clinical evaluation update

The present CER is an upgrade of the previous revision according to the requirements of MEDDEV 2.7/1 rev.4.

FOCUSIAL is a medical device in class III. For this reason the MAN considers as responsible conduct to perform a revision of the clinical evaluation conclusions with a frequency not longer than 1 year.

Given that the MAN is provided of a quality management system, the results of the clinical evaluation will be assessed in the framework of the periodic managament review. However, if new information on the safety and performance of **FOCUSIAL** that pose risks to the patients will be collected before by any member of the MAN organization, the update to the conclusions will be assessed before the end of the said one year period.

9 Date and signature

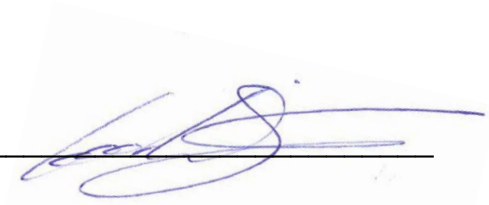
The issue date of the present CER is: 03/09/2017

The team of evaluators who produced this CER do agree with its contents.

Author:
Andrea Simonatti
External expert, Surgeon, Implantologist

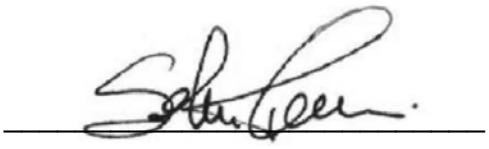
Revised and approved by:
Massimo Unali
Design Manager, Head of M.D. Vigilance

Evaluator:
Corrado Bait
External expert in Orthopedics and Traumatology



The MAN approves the final version of the present report of the clinical evaluation in date: 03/09/2017

Approval:
Salvatore Terrani
General Manager



10 Qualification of the responsible evaluators

The team who prepared the present CER is made of experts operating in the medical field of production and marketing of the medical device concerned, of the clinical application and use of the medical device concerned as required by MEDDEV 2.7/1 rev.4.

The MAN has deemed this expertise to be appropriate and sufficient to fulfill the task.

The internal side of the team is made of professional with knowledge of:
Massimo Unali, industrial chemical expert with biomedical laboratory degree, is a Quality Assurance and Design Manager, Responsible of supervision and control of the manufacture, post-market surveillance and vigilance activities of medical devices.
Salvatore Terrani, doctor in neurobiology, researcher and developer of innovative medical devices for Aesthetic Medicine, Urology, Gynecology, Traumatology, Dermatology.

The external side of the team directly related to the medical use of the device has the following expertise:
Andrea Ero Simonatti, surgeon specialized in implants, both intraosseous with titanium-based, that intradermal with hyaluronic acid-based gel. He worked in departments of Implantology, Orthodontics, Oral Surgery, and Maxillofacial Surgery.

The evaluators CVs are attached as annex to this CER.

Declaration of interests from team members are available upon request by the Notified Body.

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12 Literature search report

12.1 Introduction

The search, selection and evaluation of the data from available literature has been performed according to the requirements of Annex X, point 1.1.1 of the European Medical Directive 93/42/EEC and following amendments directive.

The format and content of this report is based on Appendix A to the Clinical Evaluation SG5/N2R8:2007 by the GHTF, adapted to requirements of Appendix A5 of MEDDEV 2.7/1 rev.4.

12.2 Scope

Given that **FOCUSIAL** is equivalent to many other HA products already CE-marked, the clinical evaluation has been based on the data coming from clinica data publicly available on all possible equivalent devices (already marketed in Europe as well as in other markets).

The search has been focued on the retrieval of all relevant information related to the performance and safety profile of the hyaluronic acid in the intra-articular injections of knee osteoarthritis, through the role and action of endogenous HA to the use and outcomes of native and cross-linked HA in the devices.

12.3 Methods

i. **Date of research:** June-November 2016 the process time frame has spanned few months during which the clinical evaluation has evolved to the final form.

ii. **Name of persons undertaking the literature search:** Andrea Simonatti and Corrado Bait (see CV in attachment 1).

iii. **Period covered by search:** No time restrictions have been applied from scratch in order to gather as much information as possible and avoid the time bias in the retrieval process. During the retrieval process, as evidence emerged on the widespread use of hyaluronic acid in several medical fields (hits above 50), the filter on the time span (5 years: 2011-2016) became necessary to restrict to more recent data and state-of-the-art knowledge in the specific field of interest. Retrieval of safety realted information became unnecessary as more

and more clinical trials, meta-analyses were found to provide all the necessary information and redundant results.

iv. **Literature sources used to identify data:** The following databases have an extensive archive of published articles and documents. They represent a transveral reference globally recognized in the medical, scientific, and regulatory fields. The archive management is publicly identified and the searches are reproducible. All the relevant publications of medical-scientific level are retrievable and their state-of-the-art advancements can be drawn.

iv.1. Scientific bibliographic database: Medline

iv.2. Clinical trials database: Medline, clinicaltrials.gov

iv.3. Systematic reviews database: Medline, Cochrane Collaboration

v. **Database search details:** The search in the Medline database has been performed with the following key terms (hits in parentheses) and filtered to show data related to clinical trials and iterature reviews in order to have a first comprehensive overview of the data available on hyaluronic acid:

(osteoarthritis) *AND* hyaluron* (257) Filter: Title/Abstract

In the Cochrane database the search has been focused on reviews on the hyaluronic acid (as keyword in the title, abstract):

“hyaluron*” filter Cochrane Reviews (26)

“hyaluron*” filter Technology Assessments (26)

“hyaluron*” filter Other Reviews (40)

In the Clinical Trials database:

hyaluronic acid, condition: osteoarthritis, has results (15)

No editing of results have been made. All the results obtained have been stored in the Bibliography folder and are available for checking.

Following paper assessment, other results have been generated through internal citations and references to more studies to be checked for inclusion.

In addition to the above mentioned searches, data related to equivalent devices in terms of materials used, bioequivalence, mechanism of action and functioning, technology, intended use and deployment methods, medical device category and clinical equivalence have been retrieved in the Medline database. This additional searching protocol has been based on the key terms expressing the commercial name of the device wherever in the text and without imposing any filter, time restriction, document type restriction.

The search results are reported in the following (total hits in parentheses):

Adant [AND] hyaluron* (10)

Arthrease [AND] hyaluron* (2)

Arthrum [AND] hyaluron* (3)

Artz [AND] hyaluron* (22)

Artzal [AND] hyaluron* (6)

Athenavis [AND] hyaluron* (0)

BioHy [AND] hyaluron* (5)

Coxarthrum [AND] hyaluron* (1)

Durolane [AND] hyaluron* (12)

Euflexxa [AND] hyaluron* (12)

Fermathron [AND] hyaluron* (4)

Gel-200 [AND] hyaluron* (4)

Gel-one [AND] hyaluron* (1)

Genvisc [AND] hyaluron* (1)

Go-on [AND] hyaluron* (7)

HYADD4 [AND] hyaluron* (6)

Hyalart [AND] hyaluron* (3)

Hyalgan [AND] hyaluron* (82)

Hyalone [AND] hyaluron* (2)

Hyalubrix [AND] hyaluron* (7)

Hylan G-F 20 [AND] hyaluron* (82) - trials

Hylan G-F20 [AND] hyaluron* (10)

Hymovis [AND] hyaluron* (3)

Inartral [AND] hyaluron* (0)

Intragel [AND] hyaluron* (1)
Jointex [AND] hyaluron* (1)
Monovisc [AND] hyaluron* (2)
Neovisc [AND] hyaluron* (0)
NRD101 [AND] hyaluron* (2)
NRD-101 [AND] hyaluron* (2)
Orthovisc [AND] hyaluron* (25)
Ostenil [AND] hyaluron* (12)
Proial [AND] hyaluron* (0)
Promovia [AND] hyaluron* (0)
Renehavis [AND] hyaluron* (0)
Replasyn [AND] hyaluron* (2)
Sinovial [AND] hyaluron* (7)
SLM-10 [AND] hyaluron* (2)
Sportvis [AND] hyaluron* (1)
Supartz [AND] hyaluron* (14)
Suplasyn [AND] hyaluron* (9)
Suvenyl [AND] hyaluron* (4)
Syaloset [AND] hyaluron* (0)
Synocrom [AND] hyaluron* (2)
Synolis [AND] hyaluron* (1)
Synvisc [AND] hyaluron* (83) - trials
Viscoplus [AND] hyaluron* (4)
Yaral [AND] hyaluron* (1)
(Zeel compositum) [AND] hyaluron* (2)

In the FDA MAUDE database the search has been focused on adverse events related to similar intra-articular medical devices containing hyaluronic acid:
Product class: Acid, Hyaluronic, Intrarticular; Event type: all; Product Code: MOZ; Device Class: 3; has results (399).

For Euflexxa 1% there was 37 recent reports of adverse events, a lot of them not stricktly connected to the use of device (other important condition of the patients like brain tumor ecc…). The other events were about swelling, redness, irritation of the treated zone.
For Orthovisc 1,5% there was 6 tecent report of adverse events, 4 of them was undefined, 1 is about swelling and irritation, the other is about increase of pain, and short breath.
Number of recalls: No recalls have been reported.
Number of new unknown events: 0

vi. **Selection criteria:** Given that HA and its applications are extensively known in several medical fields and for a timeframe spanning the last three decades, the literature search procedure led to hundreds of documents. Selection has been focused to the relevance of the documents with respect to the purpose of the search, thus absolute completeness of documents retrieved has been deemed beyond the scope of the clinical evaluation.
The first selection criterion is the relevance with respect to the condition of the knee in osteoarthritis, the technique of intra-articular injection, the aim of pain reduction, functionality improvement and synovial fluid supplementaiotn of hyaluronic acid. Excessive search refinement has been ruled out for the risk of missing relevant information, whereas selection of retrieved data has been subjected to relevance, completeness of information, and repetition avoiding criterion by selecting in order of importance:

- Government information: not only for its laws setting level but also for the recognized validity of the medical, scientific, and technical background upon which the document is based;
- Clinical trials: the only source of direct clinical data;
- Meta-analysis of clinical data: the best source of systematic and comprehensive analysis on more than one trial;
- Medical association guidelines: as expression of the topmost knowledge and decision making authority in the medical field in question;
- Recommendations, opinions and the like made by appointed entities: as expression of a shared solution to a known problem/issue of common interest or of development of a shared strategy in the field in question made by nominated experts;

- Review documents: as expression of a comprehensive overview on many studies, by themselves and in relation to one another, in the wider context of the clinical/scientific state of the art, and of concise appraisal by studies grouping;
- Citation rank: as expression of the impact, spread, influence, and popularity of the information enclosed in the document within the scientific-medical community.

The selection process discussed, put in place during the evolution of the appraisal process, allowed the collection of increasingly repeating information about performance and safety of the devices and technique in question to deem as useless further appraisal on the same topics. The appraisal process on the scientific literature was based on the chronological order, from the newest to the older publications, so that the evolution and line up of knowledge and information could be followed coherently.

12.4 Outputs

i. Apart from the results hits reported in previous section, all the un-edited search results are stored in pdf format in the Bibliography folder to the clinical evaluation report, under folder "Search Results".

ii. Flow chart of the data selection process: