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	TITLE: Suplasyn®, Suplasyn® *m.d.*, Suplasyn® 1-Shot & GO-ON® ONE Clinical Evaluation Report			

CLINICAL EVALUATORS

Function	Name	Signature and Date
COMPILER		
Senior Regulatory Consultant EMERGO	Karen Hill	see attached BG 25/03/19 Signature / Date
Senior Specialist, Regulatory Affairs Mylan Institutional	Bernadette Griffin	Bernadette Griffin 28 Mar 19 Signature / Date
REPORT APPROVAL The evaluators listed below agree and verify that the Suplasyn®, Suplasyn® *m.d.*, Suplasyn® 1-Shot & GO-ON® ONE Clinical Evaluation Report contains an accurate statement of the analyses.		
APPROVED BY		
Regulatory Affairs Director Mylan Institutional	Suzanne Spence	SSpence 28Mar19 Signature / Date
Clinical Expert	Dr. Alex Aguilera	see attached BG 25/03/19 Signature / Date

MASTER

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Regulatory Affairs Director Mylan Institutional	Suzanne Spence	..... Signature / Date
Clinical Expert	Dr. Alex Aguilera	..... 28/03/2019 Signature / Date

Foreword

This Clinical Evaluation Report has been generated in compliance with MEDDEV 2.7/1 Revision 4: Clinical Evaluation: A guide for manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC. The subject of this Clinical Evaluation are the Suplasyn® range of medical devices (Suplasyn®, Suplasyn® *m.d.*, Suplasyn® 1-Shot & GO-ON® ONE) intended for symptomatic treatment of osteoarthritis. The devices are CE marked as detailed below;

Device Name	First CE Marked	Marketing Status - Europe
Suplasyn	October 1998	Marketed
Suplasyn *m.d.*	November 2003	Marketed
Suplasyn 1- Shot	February 2010	Marketed
GO-ON ONE (brand extension Suplasyn 1-Shot)*	January 2019	Not Marketed

**GO-ON ONE was approved in January 2019, as a labelling brand extension only of Suplasyn 1-Shot. References to Suplasyn 1-Shot through out this report support the use of GO-ON ONE.*

There is ample clinical evidence both in the literature and obtained through post market experience to support the safety and performance of the devices. Literature searches were performed and documented in accordance with the requirements of MEDDEV 2.7/1 Rev 4: Clinical Evaluation: A guide for manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC, IRLGWY-SOP-RA-GEN-0004: Procedure for Conducting Clinical Evaluation for New and Existing Medical Devices and Protocol 09-RAP-002 – Clinical Evaluation Plan for Suplasyn, Suplasyn *m.d.* & Suplasyn 1-Shot.

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List of Acronyms

AC: acromio-clavicular

AE: adverse event

AMSSM: American Medical Society for Sport Medicine

CER: clinical evaluation report

CMC: carpometacarpal

COX-2: Cyclooxygenase-2

DIP: distal interphalangeal

ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

ER: essential requirements

ESR: erythrocyte sedimentation rate

EU: European Union

EULAR: European League Against Rheumatism

FAOS: foot and ankle outcome scores

FIHOA: functional index for hand osteoarthritis

FSCA: Field Safety Corrective Action

HA: hyaluronic acid, also known as sodium hyaluronate

HHS: Harris Hip Score

IACI: Intra-articular corticosteroid injection

IAI: Intra-articular injection

IFU: instructions for use

kDa: Kilodaltons

KOA: knee osteoarthritis

KL: Kellgren-Lawrence

KSS: Knee Society Score

MCP: metacarpophalangeal

MDD: Medical Devices Directive

MHRA: Medicines and Healthcare Products Regulatory Agency

MRI: magnetic resonance imaging

MTP: metatarsal phalangeal

MVMO: Maximum voluntary mouth opening

MW: molecular weight

N/A: not applicable

NSAID: non-steroidal anti-inflammatory drugs

OA: osteoarthritis

OARSI: Osteoarthritis Research Society International

ODQ: Oswestry Disability Questionnaire

PMS: post market surveillance

PMCF: post market clinical follow-up

PRP: platelet-rich plasma

ROM: range of motion

SAE: serious adverse event

SAI: secondary adrenal insufficiency

SF-12: 12-item Short Form questionnaire

SYSADOA: symptomatic slow acting drugs for OA

TMJ: temporomandibular joint

U.S.: United States

VAS: visual analogue scale

WOMAC: Western Ontario and McMaster Universities

1 SUMMARY

1.1 Introduction

Conformity assessment with the Medical Devices Directive (MDD) 93/42/EEC amended by Directive 2007/47/EC requires a medical device manufacturer to demonstrate that the claims made in relation to the device's safety and performance, under the normal conditions of its use, are achieved. Generally, this requires clinical data (Annex X, §1.1, MDD). Annex X of the MDD allows that evidence of the satisfactory clinical safety and performance of a device may be provided in the form of a critical evaluation of published and/or unpublished data on clinical experience with the device, or on a similar device to which equivalence can be demonstrated. This report provides a documented critical evaluation of published clinical data as it relates to Suplasyn, Suplasyn *m.d.*, Suplasyn 1-Shot and GO-ON ONE for the purpose of demonstrating conformity of Suplasyn, Suplasyn *m.d.*, Suplasyn 1-Shot and GO-ON ONE devices with Annex X, MDD. GO-ON ONE was approved as a brand extension of Suplasyn 1-Shot in January 2019. Since the GO-ON ONE device is identical to Suplasyn 1-Shot with the exception of the brand name the clinical data for Suplasyn 1-Shot supports the safety and performance of GO-ON ONE.

Evaluation of the clinical performance and safety of the devices was performed through a systematic search and critical review of published and unpublished clinical data demonstrating use of the devices for symptomatic treatment of osteoarthritis (OA) of the knee, hip, shoulder and smaller synovial joints including the temporomandibular joint (TMJ), thumb, ankle, metatarsal phalangeal (MTP) and lumbar facet joints. The devices are sodium hyaluronate (HA) based devices used for viscosupplementation of synovial joints. The review comprises both published and unpublished clinical data on Suplasyn, Suplasyn *m.d.,* Suplasyn 1-Shot and GO-ON ONE themselves, including two post market studies and post market surveillance (PMS) data on the devices.

This clinical evaluation has been performed in accordance with the requirements of Annex X, MDD, and with European Commission Guideline MEDDEV 2.7/1.

The purpose of this clinical evaluation is to:

- document that there is sufficient clinical evidence to demonstrate conformity with the Essential Requirements Annex I Section 1, 3, 6 and 6a of MDD 93/42/EEC covering clinical performance and clinical safety;
- identify aspects that need to be addressed systematically during PMS, e.g. in post market clinical follow-up studies (PMCF Studies) required under the MDD and with European Commission Guideline MEDDEV 2.12/2, PMCF. Typically, these aspects include estimation of residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding long-term performance, safety under wide-spread use).
- verify if the benefit/risk profile, undesirable side-effects and risk mitigation measures are still
    - compatible with a high level of protection of health and safety and acceptable according to current knowledge/ the state of the art;
    - correctly addressed in the information materials supplied to support the device;
    - correctly addressed by the current PMS plan;
- verify if existing claims are still justified;

1.2 Process used to perform clinical evaluation

This clinical evaluation follows the five basic stages described in MEDDEV 2.7/1, section 6.3:

- Define scope and plan the clinical evaluation (Stage 0);
- Identification of pertinent data (standards and clinical data) (Stage 1);
- Appraisal of each individual data set, in terms of its scientific validity, relevance, and weighting (Stage 2);

- Analysis of the data, whereby conclusions are reached about the compliance with Essential Requirements (ER1, ER 3, ER 6 and ER 6a) on performance and safety of the device, including overall clinical risk-benefit, instructions for use (IFU), residual risks, uncertainties or unanswered questions and Post Market Surveillance (PMS) requirements (Stage 3); and,
- Finalise the Clinical Evaluation Report (CER) (Stage 4)

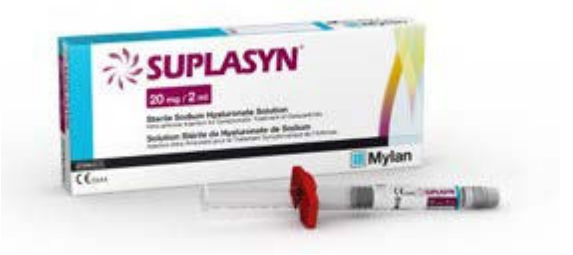
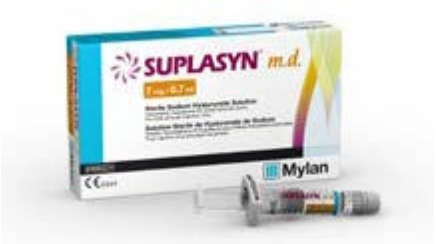
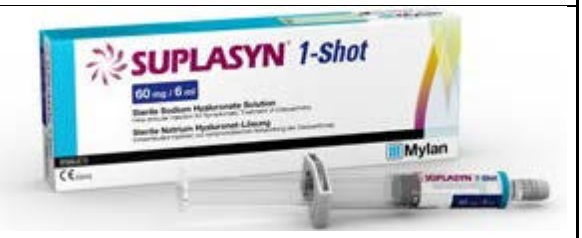
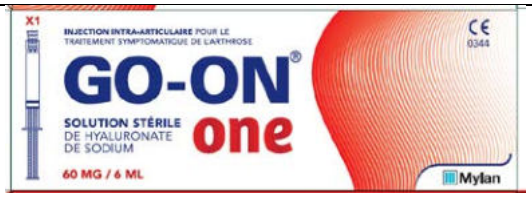
2 SCOPE OF THE CLINICAL EVALUATION

2.1 Device Overview

The devices are composed of sterile sodium hyaluronate solution 10 mg/mL. Suplasyn, Suplasyn 1-Shot & GO-ON ONE are indicated for the symptomatic treatment of osteoarthritis. Suplasyn *m.d.* is indicated as a supplement for small synovial joints.. For the purposes of this report, Suplasyn, Suplasyn *m.d.,* Suplasyn 1-Shot and GO-ON ONE, will be collectively referred to as the devices.

In accordance with the guidance document "Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices Version 1.21 (01-2019)" Section 4.2, in the EU the devices are classified as medical devices as their primary mode of action is mechanical; increased elastoviscosity of the synovial fluid following injection of HA provides shock absorption and lubrication during movement of the joint allowing greater movement with less pain. As such, the devices are classified as class III medical devices. As per rule 8 of MDD Annex IX they are implantable devices that are totally introduced into the human body through surgical intervention and are intended to have a biological effect or to be wholly or mainly absorbed. Also, as the Sodium Hyaluraonate used in the manufacture of the devices utilisies animal derived materials rendered non-viable during the manufacturing process, rule 17 is also applicable.

The Suplasyn devices are available in the following presentations:

DEVICE	FINISHED PRODUCT CODE	PRESENTATION	IMAGE
Suplasyn	0137	2 ml solution in a 3 ml syringe	
Suplasyn *m.d.*	0166	0.7 ml solution in a 1.25 ml syringe	
Suplasyn 1-Shot	0203	6 ml solution in a 10 ml syringe	
GO-ON ONE			

The GMDN code for the devices is 44757: A sterile viscous/elastic solution or gel (e.g., comprised of hyaluronic acids and their polymeric derivatives) intended to 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.

2.2 Manufacturer

The legal manufacturer of the devices is Mylan Institutional located at Inverin, Co. Galway, Ireland.

Mylan Institutional develops and manufactures high quality, sterile injectable products suitable for a range of therapeutic categories including oncology, cardiovascular, anti-infectives and anaesthesia/pain management. Their product range includes two medical device families containing HA that are manufactured at the manufacturing facility in Galway. The device families include the Suplasyn range of devices for the treatment of osteoarthritis and Cystistat® for the treatment of interstitial cystitis, presented in syringe and vial format respectively.

2.3 Device History

The Suplasyn devices are marketed worldwide, with the exception of the U.S.

Suplasyn was first CE marked and placed on the European market in October 1998 and Health Canada issued a product license in July 1999. Suplasyn *m.d.* was CE marked in November 2003. Suplasyn and Suplasyn *m.d.* have also been registered in the following countries/territories:

Suplasyn has been registered in the following countries / territories: Albania, Algeria, Armenia, Bolivia, Chile, Colombia, Costa Rica, Egypt, Hong Kong, Indonesia, Iran, Israel, Jamaica, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Mexico, Morocco, Oman, Peru, Philippines, Qatar, Russia, Saudi Arabia, South Africa, Taiwan, Thailand, Turkmenistan, Ukraine, United Arab Emirates and Uzbekistan.

Suplasyn *m.d.* has been registered in the following countries / territories: Albania, Costa Rica, Hong Kong, Malaysia, Morocco, Oman, Philippines, Qatar, Taiwan, Thailand, Turkmenistan and Ukraine.

Suplasyn 1-Shot was first CE marked and placed on the European market in February 2010. Suplasyn 1-Shot has also been registered in the following countries/territories:

Albania, Bolivia, Chile, Colombia, Costa Rica, Egypt, Hong Kong, Indonesia, Iran, Israel, Jordan, Kuwait, Lebanon, Macau, Malaysia, Mexico, Morocco, Oman, Peru, Philippines, Qatar, Russia, Saudi Arabia, South Africa, Thailand, Turkmenistan, Ukraine and United Arab Emirates.

GO-ON ONE was approved as a brand extension in January 2019.

To date worldwide sales of Suplasyn devices have exceeded 6 million devices. A breakdown of the sales data by device and market is included in the annual PMS reports held on file at Mylan Institutional.

This is an update to the Clinical Evalution Report 18-RAR-001. There have been no design changes to the devices since the completion of 18-RAR-001 Rev 001 and the previous clinical evaluation reports; Suplasyn and Suplasyn *m.d.* Clinical Evaluation Report 13-RAR-003 and Suplasyn 1-Shot Clinical Evaluation Report 09-RAR-004 & 09-RAR-004 Addendum 1.

2.4 Detailed Device Description

The devices are comprised of a clear, colourless sterile aqueous solution containing 10 mg/ml of HA in phosphate-buffered saline. The purified, non cross-linked HA has a molecular weight (MW) of 500-1000kDa, and is produced by fermentation. The details of the devices, the syringe size, fill volume and administration schedule can be found in Table 1.

Table 1: Suplasyn, Suplasyn *m.d.*, Suplasyn 1-Shot & GO-ON ONE Device Details

Product	Syringe Size	Fill Volume	Injection Administration Schedule into the Joint
Suplasyn	3 mL	2 mL	3 to 6 weekly injections
Suplasyn *m.d.*	1.25 mL	0.7 mL	3 weekly injections
Suplasyn 1-Shot	10 mL	6 mL	Singe injection
GO-ON ONE (*alternative brand name for Suplasyn 1-Shot*)	10 mL	6 mL	Single Injection

The composition of the devices is outlined in Table 2.

Table 2 : Device Composition

Component	Quantity mg/ml	Function
Sodium Hyaluronate	10	Active Ingredient
Sodium Chloride	8.5	Buffer (Inactive)
Sodium Dihydrogen Phosphate Dihydrate	0.05	Buffer (Inactive)
Disodium Hydrogen Phosphate Dodecahydrate	0.6	Buffer (Inactive)
Sodium Hydroxide 0.01M	q.s. as required	pH adjustor
Hydrochloric Acid 0.1M	q.s. as required	pH adjustor
Water for Injection	q.s.	Solvent

The devices are equivalent in their materials of composition and only differ by injection regime and administration volume. All devices are supplied sterile in a syringe. They are

intended for single use and for administration in a clinical setting by a physician only, in accordance with the instructions for use that accompany the device.

The devices do not contain any medicinal or blood products.

Casein hydrolysate is used as a nutritive source in the fermentation media used to manufacture the HA raw material used in the devices. Porcine enzymes are used in the manufacture of the casein hydrolysate. The HA raw material is highly purified during the production process and complies with EU Regulation No 722/2012, as well as EN ISO 22442 parts 1-3. In addition it also meets the requirements for human medicinal products (EMA/410/01). Further details are available in the Design Dossier.

No other animal tissues are utilised in the manufacture of the device therefore the risks associated with the animal derived materials used in the production of HA have been reduced as far as possible in compliance with EU Regulation No 722/2012 for medical devices manufactured utilising tissues of animal origin, EN ISO 22442-1 for the application of risk management, EN ISO 22442-2 for controls on sourcing, collection and handling, and EN ISO 22442-3 for the validation of the elimination and/or inactivation of viruses and TSE .

2.5 Mechanism of Action

Suplasyn achieves its therapeutic effect through viscosupplementation, a process whereby an injection of exogenous HA is administered into synovial joints, restoring the normal physiological and normal rheological environment in osteoarthritic joints. Viscosupplementation also decreases pain and discomfort, allowing more extensive movement of the joint. By restoring the viscoelastic quality (lubrication and shock adsorption) of synovial fluid, the primary mechanism of action of the Suplasyn devices is therefore a mechincal effect. In addition, there is evidence to suggest that viscosupplementation has disease modifying ancillary effects, such as reduction of synovial inflammation, protection

against cartilage erosion and promotion of HA production. Injected HA is cleared from the joint in less than one day, but the benefits of a single treatment cycle can last several months and can increase the viscosity and decrease the clearance time from the joint [12, 16 & 17].

2.6 Intended therapeutic and/or diagnostic indications and claims

The following are excerpts from the IFUs supplied with the devices. Example of the IFU for Suplasyn, Suplasyn *m.d.* and Suplasyn 1-Shot containing English text are provided in Appendix I (1-3). Instructions for use are provided according to local language requirements, the English text is translated in accordance with Mylan Institutional Standard Operating Procedures.

2.6.1 Indications

Suplasyn, Suplasyn 1-Shot and GO-ON ONE are indicated for the symptomatic treatment of osteoarthritis (OA). Suplasyn has been shown to be beneficial in osteoarthritis for the management of pain and improvement in physical function of joints. More than one joint may be treated at the same time.

Suplasyn *m.d.* is indicated for use as a supplement for small synovial joints. Suplasyn *m.d.* has been shown to be beneficial in osteoarthritis for the management of pain and improvement in physical function of joints.

2.6.2 Contraindications/precautions

The devices have the following contraindications/precautions:

- Do not administer to patients with known hypersensitivity reactions
- Respect usual precautions and contraindications for any intra-articular injection
- Do not inject intra-vascularly

- Should not be used in patients presenting an inflammation/irritation of the joint, since adverse events more commonly occur in patients with already existing joint inflammation/irritation.
- As no clinical evidence is available on the use of Hyaluronic Acid in children, pregnant and lactating women, treatment with the devices is not recommended in these patients
- The patient should rest the joint 24-48 hours after the injection and avoid any strenuous activity over the full course of the treatment
- Transient short duration pain may occur following intra-articular introduction. The affected joint may show a mild local reaction like pain, feeling of heat, hyperthermia, redness, effusion, irritation, and swelling/inflammation. If these symptoms occur, rest the affected joint and apply ice locally. Symptoms subside within days for most of the patients.
- In some cases, mild local reactions such as pain, irritation, swelling/joint inflammation and effusion may be significantly enhanced and much more severe as an expression of hypersensitivity. In such cases, a therapeutic intervention could be necessary (e.g. aspiration of joint fluid).
- Local adverse reactions could be accompanied by systemic reactions such as fever, chills, or cardiovascular reactions, and in rare cases anaphylactic reactions.
- In extremely rare circumstances, rash/itching, urticaria, synovitis, and a drop in blood pressure have been reported following the administration of Suplasyn.
- Discontinue use if adverse reactions are experienced.
- Avoid using the devices with sterilising or sanitising agents containing quaternary ammonium salts solutions.

2.6.3 Dosage and Administration

Suplasyn, Suplasyn 1-Shot and GO-ON ONE: Depending upon joint size, up to 6 ml may be administered intra-articularly.

Suplasyn:

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

Suplasyn 1-Shot & GO-ON ONE:

Intended for single administration.

Suplasyn *m.d.*:

Depending upon joint size, up to 0.7 ml may be administered intra-articularly. The recommended schedule is 1 injection per week for three weeks, but additional injections may be administered depending on the patient's clinical condition. More than one joint may be treated at the same time.

Use strict aseptic technique. Discard any unused portion of the syringe. To use the pre filled syringe, remove the Luer lock cap, attach a suitable cannula (recommended is 21 – 25 G depending on joint) and secure it by turning slightly. GRADUATION ON THE SYRINGE LABEL IS TO BE USED AS A GUIDE ONLY.

2.6.4 Claims

The Suplasyn promotional materials claim that Suplasyn administration results in the fast improvement of pain, long-lasting improvement of functionality and sustained significant improvement of quality of life.

3 CLINICAL BACKGROUND, CURRENT KNOWLEDGE, STATE OF THE ART

3.1 Literature search methodology and results for the current knowledge and state of the art

The search methodology used to identify papers relevant to the state of the art is provided in Appendix A and Appendix B. The articles were also reviewed to collect information related to:

- The interest of using such technology,
- The possible alternatives,
- Potential advantages and disadvantages of the different options.

The results are documented in Appendices E1 and E2 Search Results and summarized in Section 4.3 Clinical Data from the Literature. A summary of clinical context is described in Section 3.5.

3.2 Applicable standards and guidance documents

The devices have been designed and developed with consideration of relevant harmonised European and other International standards to ensure that the design, manufacture, packaging and labelling are in accordance with the current state of the art and meet the ERs of the MDD. A full list of standards with which the devices comply is maintained in the Design Dossier.

The literature searches identified recent guidelines on current management strategies for OA, which includes intra-articular HA as treatment for pain relief and joint mobility restoration[1-11].

3.3 Risk Management File and Instructions for Use

The following Risk Management Files are applicable:

- Suplasyn, Suplasyn *m.d.*, Suplasyn 1-Shot and GO-ON ONE Risk Management File (incorporating the risk management report), Rev 05

The Instructions for Use provided in Appendix I are applicable to the devices:

- Suplasyn
- Suplasyn *m.d.*
- Suplasyn 1-Shot

The risk mangement documents and instructions for use, are maintained within the quality system at Mylan Institutional. Copies of the documents are included in the Design Dossier.

3.4 Summary of preclinical studies

The devices have been developed in accordance with documented processes to ensure that they are designed, manufactured, packaged and labelled in accordance with the current state of the art and to meet all the relevant ERs of the MDD. Full details of the design verification and validation activities are provided in the Design Dossier.

3.5 State of the Art for the Suplasyn devices

3.5.1 Design Concept

The devices were developed for the symptomatic treatment of osteoarthritis (OA).

Hyaluronic acid (HA) forms the base of a wide range of saccharide biopolymers (glycosaminoglycan), which are important components of extracellular tissue structures, including cartilage and synovial fluid. HA is a normal component of the synovia and plays a central role in maintaining the physiological internal environment of the joint.

The primary role of synovial fluid is protective, by limiting axial forces on the articular surface and decreasing friction between joint surfaces. HA enhances the elastoviscositic nature of synovial fluid. Due to its HA content, synovial fluid can behave as a viscous fluid during slow joint movements or as an elastic shock absorber during rapid joint movements. HA is also responsible for protecting the collagen fibrils and cells of articular surfaces, synovial tissue, capsule, and ligaments from mechanical damage [*12, 13*].

HA is produced by chondrocytes in the cartilage and by synoviocytes and synovial fibroblasts in the synovium. People with OA have lower levels of hyaluronic acid in their synovial fluid. In normal synovial fluid, the HA concentration is 2-3 mg/ml (MW 4-5 million Da) whereas in knee OA (KOA), the concentration is 0.2-2 mg/ml (MW 0.5-4 million Da). This results in a decrease in rheological properties and elastoviscosity of the joint fluid. The decrease in concentration and MW of HA in synovial fluid inhibits cartilage functionality and may promote joint diseases including OA of the knee, hip and smaller joints, such as the TMJ[*12, 14*].

Viscosupplementation is the process whereby an injection of exogenous HA is administered into synovial joints, which can increase joint viscosity, HA MW and restore normal

rheological environment in osteoarthritic joints. By restoring the viscoelastic quality (lubrication and shock adsorption) of synovial fluid the primary mechanism of action of the devices is therefore a mechincal effect. In addition, there is also evidence that suggests that viscosupplementation has a disease modifying secondary effect, such as reduction of synovial inflammation, protection against cartilage erosion and promotion of HA production. Injected HA is cleared from the joint in less than one day, but the benefits of a single treatment cycle can last several months and can increase the viscosity and decrease the clearance time from the joint[16]. Viscosupplementation has been proposed to increase the benefit to the patient in terms of pain and function but can also increase the risk of transient local reactions arising from the method of administration [12-16].

Exogenous HA available for viscosupplementation is formulated as different MW preparations; low (range 500 – 730 kDa), intermediate (800 – 2000 kDa) and high MW (average 6000 kDa) and also includes cross-linked formulations of HA[17].

Viscosupplementation using HA is believed to improve OA symptoms by restoring rheological properties, and inhibiting the activity of neuropeptides and pro-inflammatory mediators secreted by the synovial cells that cause pain [17].

3.5.2 Prevalence of Osteoarthritis (OA)

OA is the most common form of joint disease and among the top 10 causes of disability worldwide. OA affects over 250 million people worldwide with an estimated 9.6% of men and 18% of women of 60 or older having symptomatic OA. A reported 4.4 million people exhibit radiographic evidence of OA in the UK. Increases in life expectancy and ageing populations are expected to make OA the fourth leading cause of disability by 2020 [4, 12, 15, 35]. OA risk factors include both genetic and environmental components [13, 15, 18]. Symptoms of OA include pain that typically worsens with weight bearing and activity (which tend to improve

with rest) as well as joint stiffness, inflammation of the synovial capsule and loss of joint function. Radiographically, the disease may show evidence of joint space narrowing, synovial thickening and the presence of osteophytes [14, 15]. On physical examination, people with OA often have tenderness on palpation, bony enlargement, crepitus on motion, and/or limitation of joint motion. Unlike the case with rheumatoid arthritis and other inflammatory arthritis, inflammation if present, is usually mild and localized to the affected joint. Although the causes of OA are not completely understood, biomechanical stresses affecting the articular cartilage and subchondral bone, biochemical changes in the articular cartilage and synovial membrane, and genetic factors are all important in its pathogenesis [4, 18].

OA mostly affects the knee, hip, ankle, lower back and hand. Disease progression commonly involves the whole joint, leading to inharmonious functioning of tissue components, and consequently to abnormal stress transition [4, 15].

Knee OA is the principal large joint to be affected and accounts for 83% of all joints affected by OA. Prevalence of OA of the knee, is estimated at 24% in the general adult population, with a higher prevalence in women and more severe OA manifesting in women over the age of 55 [8, 15, 19]. The annual cost attributable to OA of the knee is immense. There is therefore a burden on health from both morbidity and cost. Within the knee joint, the most common radiographic OA pattern of involvement is combined tibiofemoral and patellofemoral changes [4].

Hip OA is the second most frequent form of OA affecting a large joint, with a prevalence of 11 - 27%, with men showing a higher prevalence of radiographic hip OA. It is one of the main causes of functional disability and pain in adults aged 55 years and older [4, 19, 20].

OA of the hand is a common condition in people aged 55 years and over, especially in postmenopausal females. Within the hand, OA of the first carpometacarpal joint, or basal joint of the thumb, is a common, painful, and debilitating disease. It has been reported that up to

41% of the population eventually show radiographic evidence of hand OA, with only 5-9% with symptomatic OA. OA of the trapeziometacarpal or thumb carpometacarpal (CMC) joint, also called rhizarthrosis, most commonly occurs in women over 50 years of age and is often bilateral. The age-adjusted prevalence of radiographic OA of the first CMC joint has been reported to be 7% for men and 15% for women. Among men and women older than 40 years, the radiological prevalence is 21% and as high as 35% among post-menopausal women. The risk of hand OA is doubled in obese patients [4, 12, 21].

Symptomatic ankle arthritis affects 1-4% of the younger population, and is less prevalent than hip or KOA [22, 35].

3.5.3 Aetiology and Pathogenesis

OA is a whole joint disease with cartilage destruction being the main factor in its pathogenesis. Additional factors include synovitis, subchondral bone remodelling (thickening, bone collapse, bone cysts), degeneration of ligaments and menisci, and hypertrophy of the joint capsule. The aetiology of OA is multifactorial and includes generalised constitutional factors (e.g. aging, sex, obesity, heredity, reproductive variables), local adverse mechanical factors (e.g. trauma, occupational and recreational usage, intense physical activity, alignment, muscle weakness, anatomical and orthopaedic disorders) and pathological factors (e.g. metabolic disorders, joint infection, crystal deposition and a bone turnover and blood clotting disorders) [12-15, 18]. In OA, the HA in the synovial fluid decreases in concentration and MW, resulting in a decrease in rheological properties and elastoviscosity. These changes increase the susceptibility of cartilage to injury [12, 16].

Among the OA of peripheral joints, KOA is the most common form followed by the hip. Knee and hip OA pain symptoms worsen with motion, and as the condition progresses, the activities of daily living are increasingly limited making even walking difficult. Physical disability arising from pain and loss of functional capacity increases the risk of further morbidity and mortality [4].

Hand OA is a common disorder frequently causing pain and impaired function with subsequent reduction in health related quality of life. The most common presenting complaints are pain and limitations in gripping and pinching objects [21, 23].

OA of the TMJ is one of the most common forms of temporomandibular disorders. This disorder shows a variety of clinical symptoms such as pain, joint sound, stiffness, irregular jaw movement and joint tenderness. It is commonly believed that articular inflammations, the degradation of extracellular matrix of cartilage and bone destruction are the main pathologic events of OA in the TMJ [24].

The aetiology underpinning ankle arthritis is primary idiopathic in 7% of cases, inflammatory arthritis such as rheumatoid arthritis or gout in 12%, and post-traumatic in 70% of cases [22].

3.5.4 Diagnosis

There is no single sign, symptom, or test that can diagnose OA. Instead, the diagnosis is based on a consideration of several factors, including the characteristic symptoms of OA and the results of laboratory tests, x-rays, joint aspiration and/or magnetic resonance imaging (MRI) [4, 11, 18, 20].

- Laboratory Tests

  These may be recommended to help diagnose OA by ruling out conditions with similar symptoms.

- Imaging Tests

  Imaging is recommended in atypical presentations to confirm diagnosis of OA or for alternative or additional diagnoses. In cases where there is unexpected rapid

progression of symptoms or change in clinical characteristics, imaging is recommended for disease monitoring.

Radiographic imaging is useful to provide an objective measure for OA and may include the 0-4 Kellgren-Lawrence (KL) score which considers a person with ≥ 2 as having radiographic disease. Additional definitions include the Croft or Altman scores and other based on specific radiographic evaluation scores and parameters like joint space width, definite osteophytes, joint space narrowing and bone sclerosis.

Other types of imaging tests, such as ultrasound and MRI may be used to detect damage to cartilage, ligaments, and tendons, which cannot be seen on x-ray.

Formal diagnostic criteria are often used to diagnose OA in specific joints.

3.5.4.1 OA of the Knee

The criteria for diagnosis of OA of the knee include the presence of osteophytes and knee pain in addition to following:

- Age greater than 45 years
- Activity related joint pain
- Morning stiffness lasting less than 30 minutes
- Crackling or grating sensation (crepitus)
- Bony tenderness of the knee
- Bony enlargement of the knee
- No detectable warmth of the joint to the touch

Laboratory tests and x-rays are often used in addition to these criteria to detect OA features in the knee.

3.5.4.2 OA of the Hip

The diagnosis of OA in the hip relies on the results of laboratory tests and x-rays. The criteria include the presence of hip pain plus at least two of the following characteristics:

- A normal erythrocyte sedimentation rate (ESR)
- The presence of bony outgrowths (osteophytes) on x-rays
- The presence of joint space narrowing on x-rays, indicating a loss of cartilage

3.5.4.3 OA of the Hand

The criteria for OA of the hand include the presence of hand pain, aching or stiffness and at least three of the following characteristics:

- Bony enlargement of at least 2 or more of 10 selected joints
- Bony enlargements of two or more distal interphalangeal (DIP) joints
- Fewer than three swollen metacarpophalangeal (MCP) joints
- Deformity of at least 1 of the 10 selected joints

OA of the hand can often be diagnosed on the basis of these criteria alone, and laboratory tests and x-rays may be unnecessary.

3.5.5 Treatment

The goals of OA treatment are pain reduction and improvement of function, with the following overall objectives of management [3, 12, 18]:

- Educate the patient about OA and its management
- Alleviate pain
- Improve function and decrease disability
- Improve quality of life

- Prevent or delay progression of the disease and its consequences

Current treatments aim at alleviating the symptoms of OA by several different methods combining non-pharmacological and pharmacological treatment modalities [4, 12, 13, 15, 18, 19, 21, 25].

3.5.5.1 Non-pharmacological treatments

e.g. education, exercise, lifestyle changes, weight reduction, physical therapy, biomechanical interventions

Biomechanical interventions, such as knee braces and foot orthoses, may be associated with an improvement in pain, joint stiffness, physical function and use of drugs with minimal adverse effects. However, the use of some interventions, such as walking sticks, may be inappropriate in individuals with multi-joint OA as this may increase weight-bearing load on other affected joints [6, 14].

Exercise including strength training, active range of motion exercise and aerobic activity is associated with short-term benefits for pain and physical function for patients with knee OA. Water based exercise demonstrated short term benefits for function and quality of life in knee and hip OA, but only minor benefit for pain [6].

Weight reduction shows improvement in pain and physical disability when a rate of 0.25% per week is achieved [6].

The above interventions represent a core set of initial treatment measures. Clinically, core therapies are usually insufficient to fully control symptoms of OA as the disease progresses and should be combined with additional non-pharmacological and pharmacological therapies [8].

3.5.5.2 Pharmacological treatments

e.g. analgesics, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), [COX]-2-specific inhibitors, symptomatic slow acting drugs for OA (SYSADOAs) such as glucosamine and chondroitin sulphate, opioids such as tramadol, and topical treatments such as capsaicin and methyl salicylate.

Oral analgesics such as paracetamol are associated with pain relief. However, there is no significant evidence that suggests improvement in stiffness or physical function. Paracetamol is also associated with gastrointestinal side effects which may increase the risk of hospitalisation resulting from gastro intestinal perforation, ulceration and bleeding with high dose treatment (>3g/day). Long term consumption of paracetamol may also cause mild loss of renal function, increase incidence of hypertension and increase risk of multi-organ failure [5, 6].

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with superior pain relief when compared to paracetamol. However, gastro intestinal perforation, ulceration and bleeding are also higher in patients treated with NSAIDs when compared to paracetamol. COX-2 specific inhibitors have comparable to better tolerability to non-COX-2 selective NSAIDs, with serious adverse effects also being comparable. Topical NSAIDs have comparable efficacy to oral NSAIDs and are associated with lower gastro-intestinal adverse events but higher risk of dermatological adverse events. [5, 6].

Glucosamine is associated with moderate pain relief and there is some evidence to suggest a significant decrease in joint space narrowing of the knee in the short term, but no significant effects on joint space narrowing in the knee or hip after 24 months therapy. Similarly chondroitin sulphate is associated with pain relief and a small but significant decrease in joint space narrowing per year. Both glucosamine and chondroitin sulphate have a positive safety profile as they have comparable adverse events to placebo [5, 8].

Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOAs) are associated with a better safety profile when compared to NSAIDs, therefore NSAIDs may be appropriate in patients with more severe pain and in particular if the SYSADOA has failed in effective symptom control. The use of SYSADOAs may also decrease NSAID use if used as a background therapy [8].

The last pharmacological intervention for severely symptomatic patients is the use of weak opioids. Opioids are associated with pain relief and moderate improvements in physical function, but are also associated with frequent side effects such as nausea, constipation, dizziness, somnolence and vomiting [5, 8].

3.5.5.3 Invasive interventions

e.g. intra-articular injections of corticosteroids, viscosupplementation, and advanced therapies to initiate tissue regeneration such as biomaterials, natural matrices, synthetic polymers, platelet rich plasma (PRP) and stem cells.

In cases where NSAID use is contraindicated, or if a patient is still symptomatic despite use of NSAIDs or is severely symptomatic, intra-articular treatment may be applied [8].

Intra-articular corticosteroids are associated with short term relief of pain (up to 4-6 weeks) but no significant improvement in physical function or stiffness. Intra-articular HA provides comparable pain relief to intra-articular corticosteroids up to 4 weeks, but is more effective 5-13 weeks post injection. Intra-articular HA is not associated with serious safety issues but transient side-effects such as pain and swelling at the injection site, with the exception of cross-linked higher MW intra-articular HA (in particular, Hylan-GF 20), which has been associated with pseudoseptic reactions. Intra-articular HA is more appealing for long-term use when compared to NSAIDs due to the better safety profile and no known medication interactions [5, 6, 8, 12, 13].

Intra-articular HA injection i.e. viscosupplementation, is a well-established treatment option for OA and is included in the professional guidelines for the treatment of the disease. Recent evidence based guidelines, such as the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), Osteoarthritis Research Society International (OARSI) and American Medical Society for Sport Medicine (AMSSM) Guidelines, support the use of viscosupplementation with HA particularly for knee and hip OA [6, 8, 9]. Intra-articular HA has been reported to be relatively safe with sustained effects up to 6 months. Intra-articular HA induces longer-lasting pain control, when compared to intra-articular corticosteroids, may delay total joint replacement and may be a good alternative to NSAID use in older patients and those at greater risk for NSAID-induced adverse effects [2, 3, 5, 8]. The OARSI guidelines, 2014[6] recommend physician and patient interaction to determine whether intra-articular HA treatment may have merit in the context of their individual characteristics, co-morbidities and preferences. The guidelines state though that treatment for multiple-joint OA (defined as symptomatic OA of the knee in addition to other joints such as the hip, hand, and spine), intra-articular HA is not appropriate. European League Against Rheumatism (EULAR) recommendations suggest that the use of imaging may improve accuracy of viscosupplementation administration particularly for joints that are difficult to access[11]. Some guidelines [1, 4, 7, 10] do not recommend the use of intra-articular HA injections for the treatment of OA, however, the guidelines from Royal College of Physicians take economic considerations into account. Another limitation is that the guidelines are developed based on meta-analyses and systematic reviews where data between high and low MW HA is not differentiated, it is based on products with different dosing regimens and therefore efficacy is difficult to interpret. Viscosupplementation therapeutic modality is based on the physiologic importance of hyaluronan in synovial joints. Its therapeutic goal is to restore viscoelasticity of synovial hyaluronan, decrease pain, improve mobility, and restore the natural protective function of hyaluronan in the synovial joints. The short term mode of action of viscosupplementation is believed to be based on the pain relieving effects 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 synovial flow and subsequently the metabolic and rheological homeostasis of the joint [12, 13, 15] .

While treatment modalities such as PRP are more recent developments, there is some evidence to suggest that PRP has beneficial effects in younger patients with mild OA. Intra-articular PRP is associated with minor transient side-effects such as pain, swelling and mild effusion. The use of biomaterials and stem cells are an emerging technology aimed at tissue regeneration. These technologies are still under evaluation but remain a feasible approach for future OA treatment [*12, 15*].

There are now also several cell-based therapies available to complement the various surgical techniques described below, including autologous osteochondral transplantation (OATS), mosaicplasty autologous chondrocyte implantation (ACI), matrix-induced autologous chrondrocyte implantation (MACI) and matrix-induced autologous stem cell implantation (MASI). However, it should be noted that autologous osteochondral transplantation,despite remaining a valid option, has been linked with a significant amount of complications [35].

3.5.5.4 Surgical interventions

e.g. lavage, debridement, arthrodesis for certain joints such as joints of the hand, ligament reconstruction, arthroplasty.

When all other treatment modalities have failed, and there is a significant loss in quality of life, surgical intervention is required [*8*].

Lavage and debridement of the knee have shown no benefit in pain relief, improvement in function or reduction in stiffness. Arthroplasty is associated with improvements in pain and function. When comparing unicompartmental knee arthroplasty (UKA), total knee arthroplasty (TKA) and high tibial osteotomy, UKA was associated with a lower level of

complications such as deep vein thrombosis, lower revision rates and quicker recovery [5, 8, 36]. Furthermore, robotic-assisted UKA has led to improved survivorship [36].

3.6 Risk Analysis

The following risks associated with the use of the devices have been identified:

- Local inflammation reaction including pain, irritation, swelling, effusion, redness, feeling of heat, impaired motion, synovitis.
- Systemic reactions such as rash, itching, fever, chills, urticaria, allergic reactions, vomiting, diarrhoea, sleepless nights, drop in blood pressure and lower leg venous thrombosis.
- Joint infection.
- Injection not done in the intra-articular space.
- Inflammatory reaction due to intra-articular injection itself.

No delayed or prolonged effects associated with the use of the devices have been identified.

These risks are sufficiently evaluated and, where appropriate, mitigated as far as possible.

One risk from review of the risk management document was identified as not being reduced to an acceptable level but was determined to have a risk level of "Tolerable" post-mitigation.

- Lack of aseptic conditions during administration. This risk is considered to be acceptable as it is associated with poor administration technique or aseptic technique not being used during administration. It is not specific to the device and the risk cannot be reduced further by Mylan Institutional.

Overall it was concluded that the risks associated with the use of the devices, from a safety perspective, is low and outweighs the established clinical benefit of the devices.

Risk evaluation is documented in the following document contained within the Design Dossier:

- Suplasyn, Suplasyn *m.d.*, Suplasyn 1-Shot and GO-ON ONE Risk Management File (incorporating the risk management report), Revision 05

4 CLINICAL EVALUATION OF THE SUPLASYN DEVICES

4.1 Type of evaluation

The devices were first CE marked in 1998 and have since been marketed throughout Europe. This clinical evaluation is based on scientific literature that has been published for all of the Suplasyn devices, PMCF Studies and PMS for the subject devices.

The data included in this CER include data on the actual clinical use of the devices and represent use as per the indications for use stated by the manufacturer.

Equivalence to a similar device is not being claimed as part of this clinical evaluation.

4.2 Data generated and held by the manufacturer

No pre-market clinical data was generated by the manufacturer on the devices.

4.2.1 Post market clinical studies

Two post-market clinical investigations have been completed for the devices, as summarised below. See Appendices C1 and C2 for full details of these studies.

- A multicentre observational survey of 3,614 patients was conducted in Germany to obtain practice relevant data on the safety, onset of effect and performance of Suplasyn (2 ml) in patients with OA of the larger joints. The majority of patients suffered from OA of the knee (86%). The remainder of patients suffered from OA of the hip (9%) or shoulder (3%). Data was missing for 2% of patients participating in the study. Patients were symptomatic for an average period of 24 months (range: 0 – 600) at the start of treatment and received an average of 5 intra-articular injections of 2 mL Suplasyn at weekly intervals. Some (13%) patients had previously been treated intra-articularly with HA. The

majority of patients (58%) experienced an improvement in symptoms after the third injection (8% after 1 injection, 20% after 2 injections, 30% after 3 injections) while 38% of patients required a 4th or 5th injection before an improvement in symptoms was experienced.

The intensity of pain at rest and in motion was evaluated before and after treatment. The number of patients experiencing moderate to severe pain at rest decreased from 26% to 6% while the number of patients experiencing no pain at rest increased from 29.7% to 63.1%. The number of patients experiencing moderate to severe pain in motion decreased from 77% to 19% while the number of patients experiencing no pain in motion increased from 1.1% to 26.2%. These results demonstrate the success of treatment in particular for pain in motion. Patient quality of life before and after treatment was evaluated by measuring the impairment of day to day activities before and after treatment. Prior to treatment average rating for impairment of day to day activities was moderate (2.0), this reduced to slight (1.0) after treatment. Prior to treatment 68% of patients rated impairment as moderate or severe whereas post treatment this number reduced to 20%. These results demonstrate that treatment with Suplasyn has a positive impact on patient quality of life. Post treatment 69.7% patients reported a significant improvement in symptoms and 19.9% patients reported moderate improvement. Only 3.4% patients reported no improvement in symptoms post treatment. Physician rating of effectiveness of Suplasyn was "good" or "very good" for 86% patients (very good = 48%, good = 38%). Tolerance was rated as "very good" by 85.3% of physicians and 83.7% of patients indicating the safety of Suplasyn; this data is supported by a low incidence of reported side effects.

Side effects such as swelling, redness, itching, pain and effusion were documented for 0.5% patients. No serious adverse events (SAEs) were reported. The data gathered during this Post Market Study supports the safety and performance claims of Suplasyn injection for the treatment of symptomatic OA in large joints.

- In May 2010 a multicentre post market study (ASKOT) was initiated for Suplasyn 1-Shot. The ASKOT study evaluated the acceptability and safety in real-life conditions and in the

context of a regular treatment scheme of a viscoelastic solution of HA for intra-articular injection in the treatment of OA.

This was an international multicentre (Germany, Spain, Czech Republic and Slovakia) non interventional, observational study that covered a population of patients followed up in rheumatology for KOA.

A total of 411 patients were included in the study between May 26th 2010 and March 15th 2011. The mean age of the population was 62 years ± 13.8 with a majority of women (64%). All patients had a diagnosis of either unilateral or bilateral KOA (23% cases for the latter) with a mean of 3.6 years since diagnosis and an average of 29 cases of breakthrough pain per patient annually.

All patients received an intra-articular injection of Suplasyn 1-Shot. Half of the patient population received concomitant treatment with analgesics and /or anti-inflammatory medication. Non pharmacological treatments were prescribed in one third of the population such as physiotherapy, acupuncture, strapping etc.

Patients were followed up at 7 days, 3 months and 6 months post injection. The primary endpoint of the study was safety at 7 days post injection. The secondary endpoints were severity of symptoms at 3 and 6 months follow up assessed by: pain (10 cm visual analogue scale (VAS)), Lequesne algofunctional index, patient satisfaction and medico economic impact.

Only 10 adverse reactions were reported in the study. Of these events 7 were considered to be related or possibly related to the treatment and involved joint pain and/or swelling. All occurred within 2 days of the injection and all resolved without treatment except the use of ice and NSAID in one case.

There was a significant reduction in pain (VAS) and Lequesne index at 3 and 6 months compared to baseline. 86.7% of patients reported an improvement at 3 months post injection and 80.6% at 6 months. There were also improvements in the medico economic indicators with reductions in doctors' visits, sick days and hospitalization at 6 months compared to the 3 month period before the injection.

The study showed that the increased volume of administration (three times more than a conventional Suplasyn 2 ml injection) did not have any effect on the safety or patient satisfaction of the injection. The AEs reported, which were restricted to minor and transient local events, did not require specific treatment and occurred with a frequency comparable to that described for the 2 ml dose of Suplasyn.

The study confirmed the efficacy of a single injection and maintenance of the therapeutic benefit over a period of 6 months.

4.2.2 PMS data

The PMS data includes a review of the clinical risks reported to the manufacturer and the number of devices distributed as summarised below. PMS is conducted annually and full reports containing a detailed breakdown of the data are held on file at Mylan Institutional.

An internal review of the sales versus complaints data since 2008 has been completed. A summary of the data, results of an analysis and a breakdown of the reportable incidents are provided as follows.

As shown in the table below, between 2008 and 2018, a total of 6,373,550 of the Suplasyn devices (Suplasyn, Suplasyn *m.d* and Suplasyn 1-Shot) were sold; the percentage of vigilance reportable events versus sales is negligible at 0.001%.

Table 3: Sales, adverse events and vigilance data.

YEAR	TOTAL NUMBER* SOLD OF SUPLASYN DEVICES	TOTAL NUMBER OF ADVERSE EVENTS	TOTAL NUMBER* OF VIGILANCE REPORTABLE EVENTS	RECALLS
2008	971,568	388	29	0
2009	793,384	29	2	0
2010	352,578	13	1	0
2011	495,567	12	0	0
2012	485,621	4	1	0
2013	538,332	4	1	0
2014	622,234	11	0	0
2015	512,052	14	0	0
2016	399,126	0	0	0
2017	529,229	3	0	0
2018	673,859	3	0	0
TOTAL	**6,373,550**	**481**	**34**	**0**

Unit devices
Note that to date no units of GO-ON ONE (alternate brand name for Suplasyn 1-Shot) have been sold.

A summary of the vigilance reportable events is provided in Table 4.

Table 4: Summary of Vigilance Reportable Events

YEAR	NUMBER OF VIGILANCE REPORTABLE EVENTS	DESCRIPTION	%*
2008	1	General weakness	0.2
	27	Swollen knee	5.6
	1	Circulatory complaints	0.2
2009	1	Numb feeling in leg – patient suffered a fall and fracture of hip due to numb feeling in legs, not directly related to device	0.2
	1	Knee pressure	0.2
2010	1	Agglutinations in the wrist	0.2
2012	1	Pulmonary embolism – the patient was elderly with unknown past medical history; this event occurred after discontinuation of treatment with Suplasyn	0.2
2013	1	Extreme hip pain after injection	0.2
2014	0	N/A	0
2015	0	N/A	0
2016	0	N/A	0
2017	0	N/A	0
2018	0	N/A	0

This is as a percentage of the total number of reported adverse events reported rather than total sales

4.2.3 Vigilance Reporting and Recalls

Between 2008 and 2018, a total of 34 incidents were reported to Regulatory Authorities following use of the Suplasyn devices. A significant decrease in reportable events was observed after 2008, as detailed in Tables 3 and 4.

During the period of 2008 to 2018, there were no recalls of the Suplasyn devices.

Vigilance databases publish details of safety issues affecting devices sold in their respective countries in the form of medical device alerts and field safety notices. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) and Switzerland SwissMedic Recalls and FSCA (Field Safety Corrective Action) databases were searched up to February 2019 using the search terms; Suplasyn, Mylan, Bioniche, hyaluronic acid, hyaluronan and sodium hyaluronate. These searches did not retrieve any results relevant to the Suplasyn devices. Full details of the search criteria can be found in Appendix G.

4.3 Clinical data from the literature

Systematic literature searches were used to retrieve published clinical data relevant to the devices for the purposes of inclusion in this clinical evaluation report. The searches were designed to retrieve literature on the use of the Suplasyn devices. See Appendices D1 & D2 and Appendices E1 & E2 for details of the searches conducted and search results.

A total of 267 articles were identified in the systematic search of published literature in relation to the devices. These papers were subject to the selection process described in Appendix A and Appendix B. In the first step a review was conducted based on the title and abstract if available. A total of 43 papers were identified as potentially relevant. In the second step the full text of each article was obtained and reviewed against the acceptance criteria. In addition details of study design and location were compared to identify any duplicated or overlapping

data sets (i.e. data from the same clinical study published in different papers). At the end of the second step, 36 papers remained for review and appraisal. Of the 36 articles, 11 are clinical guidelines and 12 articles provide reviews related to the state of the art and current knowledge (23 total articles). 13 articles provide clinical data supporting performance and safety for the Suplasyn devices. A summary and appraisal of the clinical data identified for the Suplasyn devices is provided in the next section.

4.4 Analysis of the clinical data

4.4.1 Discussion in relation to safety (MDD ER 1)

Suplasyn and Suplasyn *m.d.* have been commercialized in the EU since 1998 and 2003 respectively and Suplasyn 1-Shot since 2010. Up until the end of 2018, 6,373,550 devices have been sold, 481 adverse events have been received and 34 incidents have been reported. The 34 reportable incidents consist of 27 cases of swollen knee, and only 1 reporting each of general weakness, circulatory complaints, numbness, knee pressure, wrist agglutination, pulmonary embolism and hip pain.

An analysis of market feedback was also made through various databases as described in Section 4.2.3. No relevant results relating to the devices were retrieved.

The clinical risks identified in the literature include pain at injection site, localized swelling/ oedema, exudate, pruritus/itching, effusion, postoperative discomfort, erythema and nausea [16, 21, 24, 26-29]. All adverse events were minor or transient and resolved within a few days. There were no serious adverse events reported in the literature.

The adverse events identified in the PMCF studies were consistent with those identified in the literature and included transient and minor local events such as joint swelling, erythema,

itching, pain and effusion. No serious adverse events were identified. The side effects associated with the use of Suplasyn 1-Shot were comparable in severity and frequency with those associated with the 2 ml dose of Suplasyn.

The following, previously unidentified, additional risks have therefore been identified in this CER: general weakness, circulatory complaints, numbness, knee pressure, wrist agglutination, pulmonary embolism, exudate and nausea. These clinical risks are transient and minor side effects that are inherent with HA products of this type, and those that are administered by intra-articular injection. Mylan will continue to monitor these additional risks for increased occurrence.

The devices are intended for use by a physican only who is likely to be familiar with administration of intra-articular HA due to the widespread use of such devices. The instructions for use identify the potential side-effects as transient and local reactions. User risks have been addressed as far as possible within the risk analyses for the devices. No further mitigation or training on the use of the devices is required.

4.4.2 Performance (MDD ER 3)

The clinical data provided in Sections 4.2 and 4.3 support the performance of the devices for the symptomatic treatment of OA. A total of 13 clinical trials from the published literature and two post market clinical follow-up studies support the efficacy of the devices when used to treat knee, hip, shoulder, and small synovial joints such as the TMJ, thumb, MTP joint, ankle and lumbar facet joint.

Knee OA (KOA)

Treatment of KOA has been evaluated by six studies from the published literature *(16, 26-28, 30, 31)*. Clinical performance of the devices were quantified using clinical outcome measures including VAS pain index, knee society score (KSS), Lequesne index, Western Ontario and

McMaster Universities (WOMAC) scale, 12-item Short Form questionnaire (SF-12), and range of motion (ROM).

Suplasyn administered via three intra-articular injections was evaluated in three studies. At 1 month follow-up, in a cohort of 4,519 patients, pain at rest and walking decreased as did morning stiffness and stiffness at rest [27]. A significant improvement in weight bearing pain was reported following a seventh cycle of treatment (each cycle consisted of three intra-articular injections of 2 ml, each administered over three consecutive weeks) in the 1,971 patients studied [16]. Significant improvement in pain and function in 296 patients was also reported at 3 and 6 months following treatment when compared to 3 months prior to treatment with Suplasyn [31].

Suplasyn 1-Shot was evaluated in three studies. At three - six weeks follow-up, 75% of the 95 treated patients reported a relief of symptoms associated with KOA [26]. In another study, in a cohort of 20 patients, 50% of patients reported favourable clinical response at 1 week and 60% reported the same at 4 and 8 weeks follow-up [30]. In a cohort ot 214 patients, improvement in function and reduction in pain was reported at 2-3 weeks following treatment. These effects were sustained up to 4-6 weeks following administration of Suplasyn 1-Shot. The most common reasons patients provided for preference of the single injection product over the multiple-administration products were single administration, comfort and lower risk of infection [28].

The PMCF ASKOT study (Section 4.2.1) also evaluated Suplasyn 1-Shot used to treat 411 patients with KOA. A significant reduction in VAS pain and Lequesne index at 3 and 6 months follow-up was reported.

Hip OA

Treatment of hip OA was evaluated in one study published in the literature using Suplasyn. Hip function was evaluated using the Harris Hip Score (HHS) in 13 patients. Significant

improvement in hip function was reported at 3 months in 66.7% of treated hips. Continued significant improvement was seen at 6 months, with a reported 73% overall success rate of hip viscosupplementation [32].

Shoulder OA

Treatment of patients with unilateral OA of the acromio-clavicular (AC) shoulder joint was evaluated in one study published in the literature using Suplasyn. Pain and function was evaluated using VAS, ROM, impingement testing and WOMAC-VAS in 682 patients. Significant improvements in pain and function were reported. Resting VAS pain between the first and final series of treatment (treatment series ranged from 6-9) demonstrated a significant improvement for each series and was similar for both first and last series [29].

Further evidence for the efficacy and safety of Suplasyn has been gathered via post-marketing activities in a total of 3,614 patients. The PMCF study (Section 4.2.1) evaluating Suplasyn used for treatment of large joints such as the knee, hip and shoulder OA reported an improvement in symptoms in majority of patients. Patients experienced improvements in pain at rest and in motion and a positive impact on quality of life.

OA of small synovial joints

Treatment of smaller synovial joints was evaluated in five studies published in the literature. These included the TMJ, thumb, ankle, lumbar facet joint and MTP joint.

Treatment of TMJ OA using Suplasyn was evaluated in a cohort of 25 patients using the VAS pain index and maximum voluntary mouth opening (MVMO) scores. The results demonstrated a significant functional improvement at 3 months follow-up which were sustained up to six months. A significant decrease in function was then observed from 6 to 12 months. A significant decrease in pain was also reported at 3 months follow-up with no significant changes from 3 to 6 months. While a significant increase in pain score was then observed between 6 to 12 months indicating worsening pain from the 6 month mark, the final

12 month pain score was still significantly lower than that at 1 month, which demonstrated that pain relief had been sustained up to 12 months from baseline, supporting a conclusion that HA treatment improved symptoms of pain. The study compared the HA treatment effects with PRP treatment and results demonstrated that while HA had sustained effects up to 6 months, PRP effects were seen up to 12 months [(24)].

Treatment of ankle OA using Suplasyn was evaluated in 50 patients for changes in pain and function using the foot and ankle outcome scores (FAOS) scale. Follow up was conducted at 6 and 12 months following administration of treatment. Statistically significant improvements were reported in FAOS scores, and specifically for pain, daily living, sports and recreational activities and quality of life scores [(22)].

Treatment of lumbar facet joint arthritis using Suplasyn was evaluated for changes in pain VAS scores and Oswestry Disability Questionnaire (ODQ) scores for disability and function in 13 patients. At a 6 week follow-up, and following one injection treatment there was no statistically significant improvement in disability or pain scores. The authors suggested that this may have been due to the fact that the patients were treated and evaluated after a single injection of Suplasyn [(33)].

Treatment of thumb OA using Suplasyn *m.d.* was evaluated for improvements in the VAS pain and functional index for hand osteoarthritis (FIHOA) functionality scores in 48 patients. The pain and functionality scores were significantly improved at 3 and 6 months. When treatment with HA was compared to a corticosteroid, better functional results were observed with HA. There was no difference in incidence of minor or transient effects between the group treated with HA and that treated with corticosteroid [(21)].

Suplasyn *m.d.* was used to treat OA of the first MTP joint in a cohort of 498 patients with pain and function evaluated using VAS at rest and weight-bearing. There was a significant improvement in both rest and weight-bearing pain indices at both the first and second series

and last series of treatment. HA injections were found to be highly satisfactory at each series (*34*).

In addition to the clinical data available for the device, the PMS data presented for the last 10 years for the Suplasyn devices demonstrates that there are no concerns of the devices failure to perform.

In conclusion, the clinical data evaluated in this report demonstrates that the devices achieve the performances claimed by the manufacturer for symptomatic treatment of osteoarthritis. The devices have been evaluated for use in larger joints, including the knee, hip and shoulder, and smaller joints, such as the TMJ, thumb, ankle and MTP with positive results. The single administration regime of Suplasyn 1-Shot has been shown to have comparable efficacy and safety profiles when compared to the multiple administration regime of Suplasyn.

4.4.3 Requirement on Acceptability of Side effects (MDD ER 6)

The complications or side effects associated with the use of the devices reported in this clinical evaluation are minor and transient in nature. The rates of incidence of these are relatively low as demonstrated in the clinical literature:

The rates of incidence of side effects for Suplasyn 1-Shot when used to treat KOA were: 2.1% for pain at injection site (*26*), 1.1% for localised swelling (*26*), 4.7% for knee oedema (*28*) and 1.7% for pain and/or swelling (PMCF ASKOT study).

A 1.7% rate of incidence of side effects for Suplasyn when used to treat KOA was reported with side effects including oedema, exudate, pruritus, redness, pain, effusion, and erythema (*16, 27*).

A 2% rate of incidence of side effects for Suplasyn when used to treat OA of the AC shoulder joint was reported with side effects including pain at the injection site, erythema at the injection site and nausea [29].

Use of Suplasyn to treat knee, hip and shoulder OA was associated with a 0.5% incidence of side effects which included swelling, redness, itching, pain and effusion (German PMCF study).

Incidence of side effects for Suplasyn used to treat TMJ OA were 60% (15/25) for pain during injection and 32% (8/25) for post-operative discomfort [24]. These are transient side effects that are associated with treatment. The high incidence noted in this study may be due to the location of the joint.

Suplasyn *m.d.* when used to treat thumb OA was associated with 10.4% incidence of minor to moderate pain after injection and 6.3% incidence of swelling [21].

There were no systemic or serious side effects/adverse events reported in the clinical data evaluated in this report. Studies with longer term follow up of ≥ 3 months, did not identify any prolonged or delayed side effects [16, 21, 22, 24, 31, 32].

The PMS data for the Suplasyn devices shows a negligible rate of < 0.01% adverse events when compared to number of sales.

In conclusion, the combination of the clinical data and PMS data provides sufficient evidence to demonstrate that the Suplasyn devices are well tolerated and are not associated with unacceptable side effects.

4.4.4 Risk/benefit profile (MDD ER 1)

Suplasyn and Suplasyn *m.d.* have been commercialized in Europe, since 1998 and 2003 respectively and Suplasyn 1-Shot since 2010. The devices are also marketed worldwide with the exception of the U.S. More than 6,000,000 devices have been sold worldwide, and a sufficient amount of clinical data published over the last 10 years has been retrieved which suitably supports the safety and performance of the devices.

In the context of this clinical evaluation report, the Suplasyn devices have been evaluated in the literature with approximately 12,469 patients with OA of the knee, hip, shoulder, TMJ, thumb, ankle, MTP and lumbar facet joints. Suplasyn has been evaluated in approximately 11,183 patients, Suplasyn *m.d.* in 546 patients and Suplasyn 1-Shot in 740 patients.

The clinical risks and complications identified consist of minor and transient effects inherent with HA products of this type and those administered by intra-articular injection. The devices benefit patients by providing pain relief and improvements in function for up to 6 months. When considering alternative treatments, guidelines state that intra-articular HA induces longer lasting pain control when compared to intra-articular corticosteroids, may delay total joint replacement and may be a good alternative to NSAID use in older patients and those at greater risk for NSAID-induced adverse effects [2, 3, 5, 8]. In terms of more recently introduced treatments for OA, such as intra-articular injection of ATMPs (including PRPs and stem cells), the clinical evidence is insufficient to draw definitive conclusions. However, one article comparing the use of platelet-rich plasma (PRP) and HA in the treatment of temporomandibular joint (TMJ) osteoarthritis (OA), concluded that PRP performed better than HA in the treatment of TMJ-OA during long-term follow-up in terms of pain reduction and increased interincisal distance [24]. These latest treatment areas should therefore continue to be monitored closely.

Based on these conclusions, the performance and safety data identified in this clinical evaluation, demonstrate that:

- the Suplasyn devices perform as intended by the manufacturer in the clinical setting;
- the Suplasyn devices do not pose unacceptable safety concerns in the clinical setting;
- the side-effects associated with the Suplasyn devices are acceptable when compared to the state of the art; and
- any risks associated with clinical use of the Suplasyn devices are acceptable when weighed against the benefits to the patient.

4.5 Summary and appraisal of clinical data from the clinical literature

A total of 36 papers were included in the CER.

Thirteen of these papers provide clinical data for the Suplasyn range of devices, met the acceptance criteria for inclusion and were subjected to the appraisal process. All 13 papers scored >30 and were considered suitable for inclusion in this clinical evaluation to support the safety and performance of the devices. Details of the appraisal and appraisal results are provided in Appendix F. Summaries of the 13 clinical studies are provided in Table 5 below, including study design, patient population, injection administration, follow-up, results, adverse events/complications and conclusions. The clinical data from the published literature comprises 13 clinical studies evaluating the Suplasyn devices involving 12,469 patients. All studies were prospective or prospective observational studies.

A total of 27 of the 36 papers met the acceptance criteria for inclusion and were included in this clinical evaluation to support the state of the art/clinical background.

The following table summarizes the clinical data collected and their contribution to clinical performance, safety and/or state of the art for the Suplasyn devices.

Table 5: Literature data contribution to the clinical evaluation.

References (See Section 9)	Authors	Contribution		
		Safety	Performance	State of the Art
Published clinical data				
(1)	NICE 2014			x
(2)	Zhang et al. 2007			x
(3)	Zhang et al. 2008			x
(4)	Royal College of Physicians of London, 2008			x
(5)	Zhang et al. 2010			x
(6)	McAlindon et al. 2014			x
(7)	Hochberg et al. 2012			x
(8)	Bruyere et al. 2014			x
(9)	Trojian et al. 2016			x
(10)	Jevsevar et al. 2013			x
(11)	Sakellariou et al. 2017			x
(12)	Ayhan et al. 2014			x
(13)	Fibel et al. 2015			x
(14)	Schiraldi et al. 2016			x
(15)	Ondresik et al. 2017			x
(16)	Petrella et al. 2010	x	x	x
(17)	Maheu et al. 2016			x
(18)	Pereira et al. 2015			x
(19)	Fernandes et al. 2013			x
(20)	Cibulka et al. 2017			x
(21)	Monfort et al. 2015	x	x	x
(22)	Murphy et al. 2017		x	x
(23)	Punzi et al. 2012			x
(24)	Hegab et al. 2015	x	x	x

References (See Section 9)	Authors	Contribution		
		Safety	Performance	State of the Art
Published clinical data				
(25)	Manara et al. 2013			x
(26)	van Lindhoudt et al. 2013	x	x	
(27)	Gydek et al. 2011	x	x	
(28)	Miśkowiec et al. 2016	x	x	
(29)	Petrella 2008	x	x	
(30)	Habib et al. 2014		x	
(31)	Mazières et al. 2007		x	
(32)	Gaston et al. 2007	x	x	
(33)	Cleary et al. 2008	x	x	
(34)	Petrella	x	x	
(35)	Pereira et al. 2018			x
(36)	Christ et al. 2018			x

Table 6: Summary of articles included to support safety and performance

REFERENCE	STUDY DESIGN	FOLLOW UP AND EVALUATION	RESULTS, DISCUSSION AND CONCLUSIONS
(*16*) Petrella et al. (2010)	**Design** Prospective observational controlled study **Patient Population** N=3697 Patients with knee OA Avian HA Group (Synvisc) N=1726 Mean Age (SD): 64.22 years (7.43) M/F: 725/1001 Non Avian HA Group (Suplasyn) N=1971 Mean Age (SD): 65.76 years (6.68) M/F: 861/1110 **Dates** 1997 - 2007	**Products** Avian HA Group: Synvisc Non-Avian HA Group: Suplasyn 2ml **Administration** 2 ml one week apart over three consecutive weeks. Cycles of treatment were separated by at least 26 weeks. Up to 10 cycles were recorded. **Evaluation** Assessment was made using VAS at rest and with weight-bearing pain (0–10 cm), numbers of medications taken, patient satisfaction with treatment using a 5-point categorical scale (1 = Not Satisfied, 5 = Extremely Satisfied). **Endpoints** Resting VAS for pain	**Key Results Performance** There were no differences in reduction of resting pain between groups between the first and tenth consecutive series of HA injections; however, there was a significantly greater improvement in weight-bearing pain ($P < 0.01$) favouring non-avian HA after the seventh series. **Key Results Safety** There were also a significantly greater number of AEs (4.8% versus 1.7%; $P < 0.01$) in the avian compared to non-avian HA treated patients. AEs included (in descending order of prevalence): pain, effusion, erythema – over 80% of AEs being pain. There were no SAEs. **Conclusions** Both avian HA and non-avian HA improve pain in patients with OA of the knee. Some difference in weight-bearing pain favouring non-avian HA was seen later in the treatment cycle while a significantly greater number of AEs was observed in the avian HA treated patients.
(*21*) Monfort et al. (2015)	**Design** Prospective, randomised controlled study	**Products** HA group: Suplasyn *m.d.* Betamethasone group: Betamethasone disodium phosphate	**Key Results Performance** FIHOA and VAS scores decreased significantly for both groups after treatment; scores were all below baseline values at follow-up visits.

	Patient Population N=88 Mean age (SD): 62.8 years (8.7) M/F: 11/77 Patients with OA of the thumb Defined inclusion/exclusion criteria HA group: N=48 Betamethasone group: N=40 **Dates** January 2005 to December 2009	**Follow Up** 7, 14, 30, 90 and 180 days **Administration** 3 injections at 7-day intervals. **Evaluation** Pain index score assessed using a 10 point VAS scale with 0 indicating absence of pain and 10, the worst pain possible. Functionality was evaluated using the FIHOA based on a physician administered questionnaire on 10 daily activities using the hands. Uses a 4 point verbal scale ranging from 0 – possible without difficulty to 4 – impossible. **Endpoints** VAS Pain score Clinical improvement using the FIHOA	Median difference of FIHOA score was greater in the HA group. Changes from baseline were -4 and -3 at 90 days and 180 days follow-up compared to -1 at 90 and 180 days follow-up in the betamethasone arm. Patients with FIHOA ≥ 5 and VAS score ≥ 5 at baseline demonstrated better improvement in the HA group. A significantly greater difference in FIHOA was observed after the first treatment in the HA group and a significant difference in mean VAS score was observed in the HA group at final assessment. **Key Results Safety** Minor or moderate pain after IA injection (n=5 in HA group and n=5 in betamethasone group) and swelling (n=3 in HA group and n=2 in betamethasone group). No SAEs reported. **Conclusions** Both HA and betamethasone were effective and well-tolerated for the management of rhizarthrosis. HA was more effective over time and more efficiently improved functionality and pain in patients with more severe symptoms.
(*22*) Murphy et al. (2017)	**Design** Prospective **Patient Population** N=50 Mean age (SD): 49 years (8) (range: 30 to 70 years) M/F: 25/25 Patients with OA of the ankle	**Products** Suplasyn 2 ml **Follow Up** 6 and 12 months following injection **Administration** 3 injections at 2 week intervals **Evaluation**	**Key Results Performance** Statistically significant improvement in FAOS score from baseline to follow up (P=0.0001). Statistically significant improvement in pain domain score from baseline to follow up (P=0.005). Statistically significant improvement in daily living domain score from baseline to follow up (P=0.0001). Statistically significant improvement in sports and recreational activities domain score from baseline to follow up (P=0.048). Statistically significant improvement in quality of life domain score from baseline to follow up (P=0.005).

	Defined inclusion/exclusion criteria **Dates** January 2014 to January 2015	Patient's subjective opinion on the influence of their foot and ankle on their activities using the FAOS. Uses a scale of 0-100 with 100 indicating no symptoms and 0 indicating severe symptoms and disability. **Endpoints** Ankle function using FAOS	**Conclusions** Findings in the present prospective cohort study, concluded that viscosupplementation with intra-articular injection of HA is a useful conservative therapy for osteoarthritis of the ankle.
(*24*) Hegab et al. (2015)	**Design** Prospective randomised controlled study **Patient Population** N=50 Patients with TMJ OA Defined inclusion/exclusion criteria PRP Group N=25 Mean age (SD): 39 years (5.0) M/F: 10/15 HA Group N=25 Mean age (SD): 38.2 years (4.4) M/F: 11/14	**Products** HA Group: Suplasyn 2ml **Follow Up** 1,3,6 and 12 months **Administration** PRP Group: 3 IA injections of 1 ml PRP once a week for 3 consecutive weeks HA Group: 3 IA injections of 1 ml HA once a week for 3 consecutive weeks **Evaluation** Pain index score assessed using a 10 point VAS scale with 0 indicating absence of pain and 10, the worst pain possible. **Endpoints** MVMO Pain index scores	**Key Results Performance** In the HA group, significant improvements in median MVMO were observed at 3 months and from 3 to 6 months. From 6 to 12 months, a statistically significant decrease in the median MVMO was observed (40 and 39 mm respectively). Improvements were maintained for 6 months post-operatively and then began to decrease until the end of the study. The PRP group exhibited significantly lower median MVMOs than the HA group after 1, 3 and 6 months. After 12 months, the PRP group exhibited significantly higher median MVMO than the HA group. PRP group had significantly higher median pain scores than the HA group after 1, 3 and 6 months. After 12 months PRP group exhibited significantly lower median pain score than did the HA group. The HA group exhibited a significant decrease in median pain score after 3 months (6.9 at baseline to 3.0 at 3 months), and no significant change from 3 to 6 months. From 6 to 12 months, a significant increase in the median pain score was observed (median pain score 0.0 and 2.0 respectively). However, at 12 months, the median pain score was significantly lower than that at 1 month. The PRP Group exhibited a significantly greater prevalence of joint sounds than the HA group after 1 month. After 3, 6, and 12 months, no significant differences were observed between the groups. In the HA group, a significant decrease in joint sound was seen after 3 months. From 3 months to 6 months and from 6 to 12 months, no significant

	Dates November 2011 – March 2013		changes were seen in prevalence of joint sounds. At 12 months, prevalence of joint sounds was lower than that at 1 month. **Key Results Safety** Injection associated complications comprising of pain during injection and postoperative discomfort (HA group: 15 and 8 respectively, PRP group: 22 and 19 respectively) was observed. Incidence of complications was greater in the PRP group. **Conclusions** Long term follow up (12 months) indicated that PRP performed better than the HA group in the treatment of TMJ-OA in terms of pain reduction and increased interincisal distance. However, the HA group demonstrated improvements earlier and the benefit in terms of pain relief and improved function were seen up to 6 months post treatment. HA is also associated with fewer side effects and is less costly.
(*26*) van Linthoudt et al. 2013	**Design** Prospective observational study **Patient Population** N= 95 Patients with unilateral or bilateral knee OA M/F: 29/66 Mean age (SD): 66 years (11.7) Range: 35 – 92 years **Dates** September – December 2010	**Products** Suplasyn 1-Shot **Follow up** 6 weeks 78% patients completed the 6 week follow up. **Evaluation** Analgesics efficacy (semi quantitative scale from unchanged to excellent improvement), subjective and clinical tolerance.	**Key Results Performance** 79% of patients showed improvement at 3 weeks. There was no difference in improvement between those patients who had previously been treated with HA injections (44%) and those treated for the first time. **Key Results Safety** Three AEs were reported; pain at the injection site (2 cases) which resolved without treatment and localized swelling (1 case) which resolved after treatment with NSAID. **Conclusions** In this unselected population with OA of the knee, the Suplasyn 1-Shot injection relieved approximately 75% of patients between three to six weeks. The study showed that a single administration of larger volume HA gave identical results to those achieved by repeated injections, while reducing the number of intra-articular procedures..

(*27*) Gydek et al. (2011)	**Design** Prospective observational study **Patient Population** N= 4519 Patients with unilateral and bilateral OA of the knee M/F: 1853/2666 Mean age (SD): 54.2 years (13.2) **Dates** January 2007 – June 2008	**Products** Suplasyn **Follow up** 30 days **Administration** Three intra-articular injections **Evaluation** Intensity of symptoms before and after treatment was measured. This included: • Pain at rest and pain during walking (VAS score) • Change in pain intensity • Morning stiffness • Pain after ascending stairs and walking on the surface level • Change in range of motion	**Key Results Performance** Pain at rest and walking decreased from 3.4 and 5 before treatment to 1.5 and 2.2 respectively after treatment. Morning stiffness intensity scores decreased from 3.5 before treatment to 1.8 after treatment. Score of stiffness at rest decreased from 3 to 1.5. **Key Results Safety** No SAE were reported. 1.6% of patients had an AE such as edema, exudate, pruritus, redness and pain. **Conclusions** The study confirmed high efficacy and good tolerance of Suplasyn in the treatment of knee OA. Due to adverse reaction related to the treatment with NSAIDs, treatment with HA is increasingly considered as the therapy of choice in patients suffering from OA.
(*28*) Miśkowiec et al. (2016)	**Design** Prospective **Patient Population** N=214 M/F: 103/111 Patients with knee OA	**Products** Suplasyn 1-Shot **Follow Up** 2-3 weeks and 4-6 weeks following injection **Administration** Single administration **Evaluation**	**Key Results Performance** Initial KSS Score was at the level of 66.0±5.63, after 2-3 weeks it reached the value of 77.64±5.61, and after 4-6 weeks a value of 78.79±5.00. Pain severity measured with the VAS score was 5.93±1.05 before the treatment and 2.32±0.87 and 2.08±0.79 after 2-3 weeks and 4-6 weeks, respectively. Reasons for preference for single injection product over product administered in 3 injections included single administration, comfort, lower risk of infection were the most common answers in 62% of patients.

	Defined inclusion/exclusion criteria	Pain index using the VAS scale Knee joint function using the KSS **Endpoints** Pain Knee function	**Key Results Safety** Knee oedema developed in 10 cases, these resolved within several days under treatment with cooling pads. **Conclusions** The study confirms positive effects of HA, with decreased pain severity and improved joint function observed in patients treated with Suplasyn 1-Shot. The study shows a high efficacy and good tolerance of Suplasyn 1-Shot in the treatment of KOA. A very important feature of the product is an extremely low incidence of side effects. The study also confirmed that Suplasyn 1-Shot used in the treatment of knee joint arthritis is an effective, safe and well tolerated agent.
(*29*) Petrella 2008	**Design** Prospective **Patient Population** N=682 Mean age (SD): 57 (10) years M/F: 416/266 Patients with unilateral OA of the AC shoulder joint **Dates** 1999 to 2007	**Products** Suplasyn 2ml **Follow Up** 4 weeks post-treatment and similarly with each successive treatment series **Administration** 3 weekly intra-articular injections, patients received a range of 6-9 treatment series every 37±7 weeks. **Evaluation** Pain and function evaluated using VAS and ROM and impingement testing and WOMAC-VAS for pain, stiffness and disability. Patient global satisfaction evaluated using a 5-point categorical scale. **Endpoints** Pain and function outcomes Patient global satisfaction	**Key Results Performance** Significant improvement in all indices of pain and function were observed using the WOMAC and VAS response to clinical testing. Resting VAS pain improved similarly between the first and final series (7.4±2 to 2.1±2, $p<0.05$, compared to 7.1±1.6 to 1.9±1.5, $p<0.05$ respectively). Injections were highly satisfactory (4±1) with no difference between the first and last series. **Key Results Safety** Fourteen minor AEs reported including pain at the injection site, erythema of the injection site and nausea. **Conclusions** Suplasyn injections resulted in a significant improvement in pain, stiffness and disability over at least 6 consecutive series, with very few AEs and was highly satisfactory to patients.

		AEs	
(*30*) Habib et al. (2014)	**Design** Prospective randomised controlled study **Patient Population** N=40 Patients with knee OA Defined inclusion/exclusion criteria IA corticosteroid injection (IACI) Group N=20 Mean age (SD): 53.3 years (13.1) M/F: 12/8 Intra-articular injection (IAI) Group N=20 Mean age (SD): 50.9 (11.8) M/F:15/5	**Products** IACI Group: Methylprednisolone acetate (Depo-Medrol, Pfizer) IAI Group: Suplasyn 1-Shot (60mg) **Follow up** 1, 2, 3, 4 and 8 weeks **Administration** Single administration **Evaluation** Secondary adrenal insufficiency (SAI) was evaluated using the ACTH stimulation test following IA injections. Clinical response was deemed favourable if a reduction of >30 points on the VAS scale for pain (0 – no pain to 100 – worst pain ever experienced) was observed **Endpoints** SAI VAS for pain	**Key Results Performance** SAI was detected in five patients in Group 1, observed between week 2 and week 4. None of the patients in Group 2 had SAI. A favourable clinical response was observed in 85% of Group 1 patients and 50% of Group 2 patients in week 1. In Group 2, favourable clinical responses were seen in 60% of patients in both weeks 4 and 8. **Key Results Safety** None reported. **Conclusions** Suplasyn 1-Shot was shown to have a favourable and steady clinical response between 4 to 8 weeks and was not associated with SAI.

(*31*) Mazières et al. (2007)	**Design** Observational, multicentre study **Patient Population** N=296 Mean age (SD): 69 years (10) M/F: 104/192 Patients with knee OA Defined inclusion/exclusion criteria **Dates** April 2003 – Jan 2004	**Products** Suplasyn **Follow Up** 3 and 6 months following last injection **Administration** 3 HA injections at 1 week intervals **Evaluation** Radiographic analysis for structural lesions Lequesne index Pain and function subscores using the WOMAC scale using a 5 point Likert format. Quality of life using physical and mental components of SF-12 **Endpoints** Pain and function using Lequesne index, WOMAC and SF-12.	**Key Results Performance** The Lequesne index was significantly lower at 3 and 6 months than at 3 months prior to treatment (P<0.0001). WOMAC pain and functional impairment scores were significantly decreased at 3 and 6 months compared to 3 months prior to treatment (P<0.0001). SF-12 physical and mental scores showed significant improvement at 3 and 6 months compared to 3 months prior to treatment (P<0.0001). **Conclusions** The costs of KOA 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.
(*32*) Gaston et al. (2007)	**Design** Prospective open study **Patient Population** N=13 patients, 15 hips Mean age: 64 years (range 51-85 years) M/F: 8/5 Patients with hip OA.	**Products** Suplasyn 2ml **Follow Up** 3 and 6 months **Administration** 3 injections at 1 week intervals **Evaluation**	**Key Results Performance** At 3 months, mean HHS increased to 63.6 from 52.9 at baseline in 10 hips (significant improvement P<0.05). One hip showed no change and 4 showed a worsening in HHS and were subsequently recommended for total hip replacement. At 6 months, mean HHS in 11 hips was 73.3 and all hips continued to show an improvement over the pre-injection score (significant improvement P<0.001). Overall success rate of hip viscosupplementation was 73%. Analysis of radiographic data demonstrated that those with less radiographic changes had trend towards an increased benefit from viscosupplementation when compared to those with substantial radiographic changes who did not

	Defined inclusion/exclusion criteria	Hip function scores evaluated using the HHS scored as a total out of 100, with 100 representing normal hip function. **Endpoints** Hip function	benefit from viscosupplementation and were subsequently recommended for total hip replacement. **Key Results Safety** No complications or AEs were recorded. **Conclusions** Viscosupplementation performed under fluoroscopic guidance is an effective and safe method of treating hip OA and appears to be more effective in those with less radiographic changes of OA.
(*33*) Cleary et al. (2008)	**Design** Prospective pilot study **Patient Population** N=13 M/F: 6/7 Patients with lumbar facet joint arthritis Defined inclusion/exclusion criteria **Dates** May 2005 to October 2005	**Products** Suplasyn 2ml **Follow Up** 6 weeks post-injection **Administration** Single injection **Evaluation** Pain using the VAS scale Function using the ODQ **Endpoints** Pain Disability and function	**Key Results Performance** There was no statistically significant improvement in disability or pain scores in the group as a whole (P>0.05). **Key Results Safety** No complications or AEs associated with the procedure. **Limitations** Limited efficacy may be due to the fact that patients were treated and evaluated after a single injection of HA. Possibly, better results could be achieved by administering an optimal regimen, and perhaps a comparative study of various regimens would be of interest. **Conclusions** Preliminary results from this pilot study do not demonstrate any benefit of viscosupplementation in the management of symptomatic lumbar facet arthropathy.
(*34*) Petrella	**Design** Prospective **Patient Population** N=498	**Products** Suplasyn *m.d. (*0.7 ml) **Follow Up**	**Key Results Performance** Significant improvement in weight bearing pain indices were observed at first,second and third series. Results for weight bearing pain improved significantly pre and post injection in the first series (8.3 vs 3.1, P<0.05), in

	Mean age (SD): 61 (12) years Patients with OA of the 1st metatarsal phalangeal (MTP) joint	Following first series of treatment and prior to subsequent series. **Administration** 3 weekly intra-articular injections, patients received at least 2 series of treatment (2-7) over 5 years. There was an interval of 33±11 weeks between series. **Evaluation** Pain and function evaluated using VAS at rest and weight-bearing **Endpoints** Pain and function Patient satisfaction AEs	the second series (7.9 vs 2.1cm, P<0.05) and in the third injection series (6.8 vs 2.2, P<0.05). There was a small but non-significant reduction in VAS rest pain between the first and last series. HA injections were highly satisfactory at each series. **Key Results Safety** No SAEs reported. **Conclusions** Intra-articular injection of HA into the small joint of the foot produced significant pain reduction, with no SAEs over a long-term follow up.

5 CONCLUSIONS

In respect of the requirement in Directive 93/42/EEC amended by 2007/47/EC, for clinical evidence to be provided for the safety and effectiveness of the devices, it is considered that:

a) The benefit/risk profile is acceptable according to current knowledge / the state of the art in the medical fields concerned and according to available medical alternatives.
b) The information materials supplied by Mylan Institutional, including the IFU and promotional materials, as well as the intended purpose and risk reduction measures are deemed adequate.
c) The devices, including the IFU, were evaluated and are considered suitable for the intended users and intended use.
d) The claims made by the manufacturer in the IFU and other information materials are supported by available clinical data.
e) The clinical data, the information materials supplied by the manufacturer and the risk management documentation for the device under evaluation are consistent.
f) The devices are not associated with an unacceptable level of complaints or side-effects.
g) The PMS / PMCF plan in regards to the device is appropriate. The devices are well established devices given the duration on the market place. PMS is conducted annually in accordance with IRLGWY-SOP-QA-GEN-0040.

Accordingly it is concluded that the risk of the devices failing to achieve acceptable levels of clinical performance and safety are low and are outweighed by the established clinical benefits of the devices.

As such, Essential Requirements 1, 3, 6 and 6a of Directive 93/42/EEC, concerning clinical evidence of the safety and performance of the devices, are considered to be satisfied.

6 DATE OF THE NEXT CLINICAL EVALUATION

This clinical evaluation report will be updated at a minimum every 3 years based on the established use of the devices. This clinical evaluation will also be updated when new post-market surveillance information becomes available that impacts the benefit/risk profile of the device.

Post-market surveillance data as part of the quality system is continually compiled by the manufacturer as per an established quality management system. Device-related adverse events and complaints are recorded with the explicit purpose of identifying and investigating any residual risks associated with the use of the device. PMS data is reviewed annually. Clinical literature searches are conducted as part of this activity and the results are an input into PMS. If the results of a clinical literature search or PMS activities determine that there is new information that may impact on the benefit/risk profile of the device then the clinical evaluation report will be updated.

As the devices have been in wide-spread use for a number of years with no significant new risks having been identified, there is no need for any further PMCF studies to be conducted.

The devices have been on the market for a considerable number of years. In addition, there is significant availability of published and unpublished data to support the continued use of the device. The devices are therefore deemed to be well-established. As such the clinical evaluation report will be updated every three years. However, if new information becomes available that impacts the benefit/risk profile of the device the clinical evaluation report will be updated.

7 QUALIFICATION OF THE RESPONSIBLE CONTRIBUTORS

Function	Name	Role
COMPILER		
Senior Regulatory Consultant EMERGO	Karen Hill	Search of databases, review of literature returned and compilation
Senior Specialist, Regulatory Affairs Mylan Institutional	Bernadette Griffin	Supported literature search and regulatory review
APPROVED BY		
Regulatory Affairs Director Mylan Institutional	Suzanne Spence	Regulatory review
Clinical Expert Mylan Institutional	Dr. Alex Aguilera	Clinical expert review

The contributors' qualifications are included in Appendix H.

8 REFERENCES

1. Clinical Guideline [CG177]. Osteoarthritis: care and management. February 2014. .
2. Zhang W., Moskowitz R. W., Nuki G., Abramson S., Altman R. D., Arden N., Bierma-Zeinstra S., Brandt K. D., Croft P., Doherty M., Dougados M., Hochberg M., Hunter D. J., Kwoh K., Lohmander L. S., Tugwell P., OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 15, 981-1000 (2007).
3. Zhang W., Moskowitz R. W., Nuki G., Abramson S., Altman R. D., Arden N., Bierma-Zeinstra S., Brandt K. D., Croft P., Doherty M., Dougados M., Hochberg M., Hunter D. J., Kwoh K., Lohmander L. S., Tugwell P., OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 16, 137-162 (2008).
4. National Collaborating Centre for Chronic C., *in Osteoarthritis: National Clinical Guideline for Care and Management in Adults*. (Royal College of Physicians (UK) Royal College of Physicians of London., London, 2008). Section 1 pages 3-10 and Section 3 pages 19-21. Referenced pages included. Full document can be found on file at Mylan Institutional.
5. Zhang W., Nuki G., Moskowitz R. W., Abramson S., Altman R. D., Arden N. K., Bierma-Zeinstra S., Brandt K. D., Croft P., Doherty M., Dougados M., Hochberg M., Hunter D. J., Kwoh K., Lohmander L. S., Tugwell P., OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 18, 476-499 (2010).
6. McAlindon T. E., Bannuru R. R., Sullivan M. C., Arden N. K., Berenbaum F., Bierma-Zeinstra S. M., Hawker G. A., Henrotin Y., Hunter D. J., Kawaguchi H., Kwoh K., Lohmander S., Rannou F., Roos E. M., Underwood M., OARSI guidelines for the non-

surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 22, 363-388 (2014).

7. Hochberg M. C., Altman R. D., April K. T., Benkhalti M., Guyatt G., McGowan J., Towheed T., Welch V., Wells G., Tugwell P., American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis care & research* 64, 465-474 (2012).
8. Bruyere O., Cooper C., Pelletier J. P., Branco J., Luisa Brandi M., Guillemin F., Hochberg M. C., Kanis J. A., Kvien T. K., Martel-Pelletier J., Rizzoli R., Silverman S., Reginster J. Y., An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 44, 253-263 (2014).
9. Trojian T. H., Concoff A. L., Joy S. M., Hatzenbuehler J. R., Saulsberry W. J., Coleman C. I., AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes. British journal of sports medicine 50, 84-92 (2016).
10. Jevsevar D. S., Brown G. A., Jones D. L., Matzkin E. G., Manner P. A., Mooar P., Schousboe J. T., Stovitz S., Sanders J. O., Bozic K. J., Goldberg M. J., Martin W. R., 3rd, Cummins D. S., Donnelly P., Woznica A., Gross L., The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. Pages 770 – 853 (2013). Referenced pages included. Full document can be found on file at Mylan Institutional.
11. Sakellariou G., Conaghan P. G., Zhang W., Bijlsma J. W. J., Boyesen P., D'Agostino M. A., Doherty M., Fodor D., Kloppenburg M., Miese F., Naredo E., Porcheret M., Iagnocco A., EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. *Ann Rheum Dis* 76, 1484-1494 (2017).

12. Ayhan E., Kesmezacar H., Akgun I., Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World journal of orthopedics 5,* 351-361 (2014).

13. Fibel K. H., Hillstrom H. J., Halpern B. C., State-of-the-Art management of knee osteoarthritis. World journal of clinical cases 3, 89-101 (2015).

14. Schiraldi C., Stellavato A., de Novellis F., La Gatta A., De Rosa M., Hyaluronan viscosupplementation: state of the art and insight into the novel cooperative hybrid complexes based on high and low molecular weight HA of potential interest in osteoarthritis treatment. *Clinical cases in mineral and bone metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases* 13, 36-37 (2016).

15. Ondresik M., Azevedo Maia F. R., da Silva Morais A., Gertrudes A. C., Dias Bacelar A. H., Correia C., Goncalves C., Radhouani H., Amandi Sousa R., Oliveira J. M., Reis R. L., Management of knee osteoarthritis. Current status and future trends. *Biotechnology and bioengineering* 114, 717-739 (2017).

16. Petrella R. J., Cogliano A., Decaria J., Comparison of avian and nonavian hyaluronic acid in osteoarthritis of the knee. *Orthop Res Rev* 2, 5-9 (2010).

17. Maheu E., Rannou F., Reginster J. Y., Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Semin Arthritis Rheum* 45, S28-33 (2016).

18. Pereira D., Ramos E., Branco J., Osteoarthritis. *Acta Medica Portuguesa* 28, 99-106 (2015).

19. Fernandes L., Hagen K. B., Bijlsma J. W., Andreassen O., Christensen P., Conaghan P. G., Doherty M., Geenen R., Hammond A., Kjeken I., EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Annals of the rheumatic diseases* 72, 1125-1135 (2013).

20. Cibulka M. T., Bloom N. J., Enseki K. R., Macdonald C. W., Woehrle J., McDonough C. M., Hip Pain and Mobility Deficits-Hip Osteoarthritis: Revision 2017. J Orthop Sports Phys Ther 47, A1-A37 (2017).

21. Monfort J., Rotés-Sala D., Segalés N., Montañes F. J., Orellana C., Llorente-Onaindia J., Mojal S., Padró I., Benito P., Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: Results of a 6-month single-masked randomized study. *Joint Bone Spine* 82, 116-121 (2015).

22. Murphy E. P., Curtin M., McGoldrick N. P., Thong G., Kearns S. R., Prospective Evaluation of Intra-Articular Sodium Hyaluronate Injection in the Ankle. *Journal of Foot and Ankle Surgery* 56, 327-331 (2017).

23. Punzi L., Frallonardo P., Campana C., Ramonda R., State of art in managing hand osteoarthritis. *Osteoarthritis and Cartilage* 20, S6-S7 (2012).

24. Hegab A. F., Ali H. E., Elmasry M., Khallaf M. G., Platelet-rich plasma injection as an effective treatment for temporomandibular joint osteoarthritis. *Journal of Oral and Maxillofacial Surgery* 73, 1706-1713 (2015).

25. Manara M., Bortoluzzi A., Favero M., Prevete I., Scire C. A., Bagnato G., Bianchi G., Ceruso M., Checchia G. A., D'Avola G. M., Di Giacinto G., Frediani B., Lombardi A., Mannoni A., Mascheroni G., Matucci Cerinic M., Punzi L., Richelmi P., Scarpellini M., Torretta F., Migliore A., Ramonda R., Minisola G., Italian Society for Rheumatology recommendations for the management of hand osteoarthritis. *Reumatismo* 65, 167-185 (2013).

26. Van Linthoudt D, .Gasser U.E., Evaluation of the analgesic efficacy and short-term tolerance of a single 6 ml injection of hyaluronic acid (Suplasyn 1-Shot) on osteoarthritis of the knee. *DOLOR* 28, 89-92 (2013).

27. Gydek A., Kowiec K., Wordliczek J., Liszka H., Effectiveness and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis. *Przeglad lekarski* 68, 307-310 (2011).

28. Miśkowiec K., Gądek A., Jurecka A., Sówka J., Ślusarski J., Liszka H., Wordliczek J., Effectiveness and safety of intra-articular use of hyaluronic acid (Suplasyn 1-Shot) in the treatment of knee osteoarthritis. *Przegląd lekarski* 73, 221-223 (2016).

29. Petrella R., Hyaluronic acid in the treatment of osteoarthritis of the shoulder (2008). *Canadian Centre for Activity and Aging, the University of Western Ontario, London, Ontario, Canada*.

30. Habib G., Jabbour A., Artul S., Hakim G., Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: A randomized controlled study. *Clinical Rheumatology* 33, 99-103 (2014).

31. Mazières B., Bard H., Ligier M., Bru I., Giret d'Orsay G., Le Pen C., Medicoeconomic evaluation of hyaluronic acid for knee osteoarthritis in everyday practice: The MESSAGE study. *Joint Bone Spine* 74, 453-460 (2007).

32. Gaston M. S., Tiemessen C. H., Philips J. E., Intra-articular hip viscosupplementation with synthetic hyaluronic acid for osteoarthritis: efficacy, safety and relation to pre-injection radiographs. *Arch Orthop Trauma Surg* 127, 899-903 (2007).

33. Cleary M., Keating C., Poynton A. R., Viscosupplementation in lumbar facet joint arthropathy: A pilot study. *Journal of Spinal Disorders and Techniques* 21, 29-32 (2008).

34. Petrella R., Hyaluronic acid in the treatment of osteoarthritis of the small joint. *Canadian Centre for Activity and Aging, the University of Western Ontario, London, Ontario, Canada*

35. Pereira H, Cengiz IF, Vilela C, Ripoll PL, Esprequeira-Mendes J, Oliveira JM, Reis RL, Niek van Dijk C. Emerging Concepts in Treating Cartilage, Osteochondral Defects, and Osteoarthritis of the Knee and Ankle. *Adv Exp Med Biol. 1059:25-62 (2018).*

36. Christ AB, Pearle AD, Mayman DJ, Haas SB. Robotic-Assisted Unicompartmental Knee Arthroplasty: State-of-the-art and Review of the Literature. *J Arthroplasty, 33:1994-2001 (2018).*

9 VERSION HISTORY

DOCUMENT REF./REV. #	DCR	DESCRIPTION
18-RAR-001 / Rev 1	18DCR145	New report (Revision 1)
18-RAR-001 / Rev 2	19DCR174	Update of report to support recertification activities.