DUROLANE®

13DUR503

A 26 WEEK PROSPECTIVE OPEN LABEL CLINICAL STUDY EVALUATING A SINGLE INTRA-ARTICULAR INJECTION OF DUROLANE® 3ML FOR TREATMENT OF OSTEOARTHRITIS PAIN OF THE SHOULDER

Protocol Amendment 02

Date: 20Mar15

SPONSOR INFORMATION PAGE

Sponsor:

Bioventus LLC

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Durham, NC 27703

USA

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In some countries, the clinical trial sponsor may be the local Bioventus affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information for Unanticipated Adverse Events (UAE) and Adverse Device Effect (UADE):

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable Canadian regulations and ICH guidelines.

Investigator Printed Name

Investigator Signature

Date

2. SYNOPSIS

Name of Sponsor/Company:
Bioventus LLC

Name of Investigational Product:
DUROLANE®

Name of Active Ingredient:
Hyaluronic Acid

Title of Study:
A 26 Week Prospective Open Label Clinical Study Evaluating a Single Intra-Articular Injection of DUROLANE® 3mL for Treatment of Osteoarthritis Pain of the Shoulder

Principal Investigator(s): Michael McKee, MD

Phase of Development: EU Post-Marketing Commitment

Trial Objectives:

Primary:

To evaluate the efficacy of a single intra-articular (IA) injection of DUROLANE® 3mL given for the relief of pain in the treatment of symptomatic osteoarthritis (OA) of the shoulder followed over a 26-week time period

Secondary:

To evaluate the efficacy of a single IA injection of DUROLANE® 3mL given for treatment of symptomatic OA of the shoulder followed over a 26-week time period for

- shoulder pain at night
- shoulder range of motion
- shoulder pain rescue medication use

To evaluate the safety and tolerability of a single IA injection of DUROLANE® 3mL over a 26-week time period

Trial Assessments:

Effectiveness:

Primary:

Shoulder pain on movement (SPOM) visual analogue scale (VAS) (0-100mm)

Secondary **:**

- Shoulder pain at night (SPAN) VAS (0-100mm)
- American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form (*physician range of motion and patient self-evaluation VAS pain*

today and activities of daily living only) (Richards, et al.,1994)

- Patient Global Assessment (PGA) VAS (0-100mm)
- Shoulder pain rescue medication diary

Safety:

- Adverse events
- Concomitant medications
- Physical exams, as needed

Methodology:

Open label, prospective, single cohort study

Number of Subjects (planned):

A minimum of 36 subjects will be enrolled.

Diagnosis and main criteria for inclusion:

Pain due to mild to moderate osteoarthritis in the shoulder

Investigational Product, dosage and mode of administration:

DUROLANE® 3mL single IA injection

Duration of treatment and study participation:

Subjects will receive a single injection and participation will be approximately 28 weeks (including an up to 2 week screening period)

Eligibility Criteria:

Inclusion

1. Females or males between the ages of 19 and 85 years of age
2. Diagnosis of glenohumeral osteoarthritis (GH-OA), confirmed by radiographs taken within the previous six months, with GH-OA being the primary source of pain; OA in the contralateral shoulder is permissible provided that OA symptoms are greater in the trial shoulder
3. Shoulder pain on movement (SPOM) visual analogue scale (VAS) (0-100mm) score ≥50mm for the study shoulder
4. Must be willing to discontinue use of oral and topical analgesia other than rescue use of acetaminophen for the study shoulder. Must also be willing to discontinue rescue medication for at least 24 hours before each visit
5. Abstinence from any IA or peri-articular injections for the shoulder during the course of the trial, except for the assigned Investigational Product
6. Patients with chronic shoulder pain lasting more than 6 months without clinically significant improvement in shoulder pain over the past one month

7. Pain at least 50% of the days during the previous month
8. Patients who have failed conventional therapy including but not limited to the following: nonsteroidal anti-inflammatory drugs (NSAIDs); one or more intra-articular or local peri-articular steroid injections and physiotherapy (a minimum of one month of previous physiotherapy treatment is required)
9. Patients with a retained active range of motion (ROM) of at least 30% in all directions to rule out frozen shoulder (>30° for abduction with scapula fixed, >30° for external rotation, and >20° for internal rotation)
10. Cooperative and able to communicate effectively with the Investigators
11. Must agree not to participate in any other clinical research (interventional) studies while participating in this study
12. Body mass index (BMI) ≤ 35 kg/m^2
13. English literacy and ability to understand and complete all informed consent procedures

Exclusion

1. Significant pain from other joints or low back pain requiring chronic ongoing analgesic therapy
2. Presence of one or more conditions besides OA that could confound pain and functional assessments in the study shoulder
3. Clinically-apparent tense effusion or gross misalignment or instability in the study shoulder
4. Shoulder x-ray findings of acute fractures, severe loss of bone density, avascular necrosis and/or severe deformity
5. Surgery of the study joint within the previous 12 months.
6. Treatment with NSAIDs or any pain management medications (including topical agents for the study shoulder) during the last week (or five half-lives of the drug, whichever is longer) prior to Baseline Visit.
7. Inability to tolerate acetaminophen for rescue medication use.
8. Use of acetaminophen or any other analgesics during the 24 hours preceding the baseline visit.
9. IA or local peri-articular corticosteroid injections to the study joint or shoulder within the previous three months; or to any other joint within the previous month; or any oral corticosteroid within the previous month. Steroid inhalants are permitted if the patient has been on a stable regimen for the past month and remains on this regimen throughout the course of the trial
10. IA injections with hyaluronic acid in the study shoulder within the last 9 months
11. Previous allergic reaction to a HA or local anesthetic such as lidocaine.

12. Treatment with glucosamine/chondroitin sulfate initiated within the past three months, or dosage not stable for the past three months
13. Change in physical therapy for the study shoulder within one month preceding screening, or expected change in physical therapy during the study
14. Planned surgical procedure during the study period.
15. Previous history or presence of septic arthritis in study joint
16. Active skin disease or infection in the area of the injection site
17. Alcohol or drug abuse as determined by the Investigator or use of alcohol for control of pain
18. Use of illicit drugs including cannabis
19. Systemic inflammatory condition or autoimmune disease or infection such as rheumatoid arthritis, inflammatory arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, gout/ acute pseudo gout or any other connective tissue disease
20. Uncontrolled hypothyroidism
21. Use of aspirin (acetylsalicylic acid) as analgesic (up to 325 mg/day for anticoagulant treatment is permissible)
22. Any medical condition which in the opinion of the investigator makes the patient unsuitable for inclusion (e.g., severe progressive chronic disease, malignancy, bleeding disorder, fibromyalgia)
23. Pregnant or breast-feeding woman or woman of child-bearing potential not practicing adequate contraception.
24. Subjects that in the opinion of the investigator are unsuitable for inclusion (e.g., subjects not likely to avoid other therapies, subjects not likely to stay in the study or with plans to relocate during the study period, or subjects likely to be unreliable)
25. Concurrent participation in any other clinical study or participation within the preceding 30 days

Statistical Methods:

General:

There is a single pre-planned hypothesis test for the primary variable. There are no pre-planned hypotheses tests for secondary or exploratory efficacy variables or safety variables. Any inferential statistic for these variables is exploratory. All variables will be summarized using descriptive statistics such as sample size, mean, standard deviation, median, minimum and maximum and frequencies, i.e. counts and percents.

Effectiveness:

Primary Variable:

- VAS (0-100mm) SPOM over weeks 0, 6, 12, 18 and 26

Primary hypothesis:

Ho: VAS SPOM over weeks 6, 12, 18 and 26 ≥ VAS SPOM at week 0 (baseline)
Ha: VAS SPOM over weeks 6, 12, 18 and 26 < VAS SPOM at week 0 (baseline)

Primary hypothesis statistical test method:

A mixed effect repeated measures (MERM) regression will be used. VAS SPOM will be the dependent variable. The weeks 0 (baseline), 6, 12, 18, and 26 visits will be a fixed effect covariate. Subjects will be random effects. The correlation structure will be unstructured. If convergence is problematic then an alternative covariance structure will be necessary. A contrast will be constructed to test the hypothesis of a VAS SPOM reduction from baseline.

Trial success criteria:

If the weeks 6, 12, 18, and 26 VAS SPOM least square mean versus week 0 (baseline) VAS SPOM least square mean contrast achieves the 0.05 type I error level of statistical significance this trial will be considered a success.

Secondary variables:

The weeks 0, 6, 12, 18 and 26:

- SPAN VAS (0-100mm)
- ASES patient self-evaluation (PSE) Shoulder Score Index (SSI): (range: 0-100)
- PGA VAS (0-100mm)
- Shoulder pain rescue medication consumed (unit: average mg per week)

The weeks 0, 6, 12, and 26:

- ASES physician assessment (PA) range of motion (ROM): 5 questions (right and left, active and passive; total 10 assessments) (unit: degrees)

Exploratory ASES variables (patient self-evaluation only):

The weeks 0, 6, 12, 18 and 26:

- ASES PSE pain today: VAS (range: 0-10cm)
- ASES PSE activity of daily living: 10 questions (range: 0,1,2,3)

Safety variables:

Over the entire study:

- MedDRA coded adverse events
- WHO coded concomitant medications
- Physical exams (range: 0,1,2,3)

Sample Size:

The sample size was estimated for a repeated measures ANOVA using method MOT2 in nQuery Advisor 7.0 statistical software. A sample size of 29 will be capable of detecting a reduction in mean VAS pain on movement score of 15 mm (25% reduction from a baseline mean of 60mm) over the course of the study with 80% power under the following assumptions:

Type I error rate, α,	= 0.05
Standard deviation within time point	= 25 mm
Correlation between visits	= 0.5
Mean VAS (0-100mm) results at:	
0 weeks (baseline)	= 60 mm
6 weeks	= 55 mm
12 weeks	= 50 mm
26 weeks	= 45 mm

A minimum of 36 subjects will be enrolled into the study to allow the power of the study to be maintained in the case of a drop-out rate of up to 20%.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND SPECIALIST TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
ASES	American Shoulder and Elbow Surgeons
BMI	Body mass index
CDRH	Center for Devices and Radiological Health
CFB	Change from Baseline
CRF	Case Report Form
CTA	Clinical Trial Agreement
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	Glenohumeral
GH-OA	Glenohumeral Osteoarthritis
Ha:	Alternative hypothesis
Ho:	Test hypothesis
HA	Hyaluronic Acid
IA	Intra-Articular
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
Investigational Product	DUROLANE Hyaluronic Acid, Stabilized Single Injection
MDD	Medical Device Directives
MedDRA®	Medical Dictionary for Regulatory Activities
MERM	Mixed Effect Repeated Measures
MW	Molecular Weight

Abbreviation or Specialist Term	Explanation
N	Number (typically refers to subjects)
NASHA	Non Animal derived Stabilized Hyaluronic Acid
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
PA	Physician Assessment
PGA	Patient Global Assessment
PSE	Patient Self Evaluation
REB	Research Ethics Board
ROM	Range of Motion
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SPAN	Shoulder Pain at Night
SPOM	Shoulder Pain on Movement
SS	Study Shoulder
SSI	Shoulder Score Index
UADE	Unanticipated Serious Adverse Device Effect
US	United States
VAS	Visual Analog Scale
WHO	World Health Organization

5. INTRODUCTION

5.1. Background Information

The glenohumeral (GH) joint, commonly known as the shoulder joint, is a ball-and-socket joint made up of the top rounded head portion of the humerus and the concave surface on the lateral portion of the scapula, known as the glenoid. In the normal GH joint, the head of the humerus and the glenoid articulate smoothly. This smooth efficient joint motion is facilitated by the presence of cartilage, which surrounds the articular portion of the bones.

With age and normal wear and tear, degeneration of the cartilage takes place in many joints of the body. As the cartilage begins to deteriorate, the smooth surface becomes asymmetric, and the bone becomes exposed, allowing the unprotected surfaces of the bones in the joint to interact causing pain, swelling and loss of function. Over time bone spurs can form, further magnifying the asymmetric interaction of these joint surfaces. Degenerative changes in the GH joint can be characterized as GH osteoarthritis (GH-OA), which can be painful and debilitating and can compromise the functional capacity to perform activities of daily living.

For diagnostic purposes, a subject with GH-OA is identified using standard shoulder radiographs. Radiographic findings consistent with this condition include GH joint-space narrowing, subchondral bony sclerosis, osteophyte formation, glenoid bone erosion, and posterior humeral head displacement.

Initial treatment for GH-OA includes activity modification and nonsteroidal anti-inflammatory drugs (NSAIDs). Physical therapy can be utilized to maintain motion and strength, but it should be carefully monitored to prevent symptomatic aggravation. Corticosteroid injections are frequently administered for treatment of shoulder pain and have been effective in clinical trials. However, guidelines of the American Academy of Orthopaedic Surgeons suggest that such injections are not routinely recommended for patients with GH-OA. In addition, the potential risk of damage to the collagen matrix of tendons and ligaments suggests caution in the use of corticosteroid injections, especially with repeated administrations over time. Ultimately, shoulder replacement surgery may be indicated in advanced cases of GH-OA that have failed conservative management.

DUROLANE® is a clear, transparent, viscous gel of highly purified non-animal HA derived via a bacterial fermentation process (Agerup, et al., 2005). The gel is manufactured by Q-Med, a division of Galderma, AB (Uppsala, Sweden) using NASHA™ technology, a proprietary process that is designed specifically to provide stabilization of the HA. In this process, the natural entanglements that exist in normal HA are combined with the introduction of a minute (~1%) number of synthetic cross-links to create a three-dimensional gel network. Mechanical sieving is used to prepare NASHA gel particles of approximately 300µm. DUROLANE product is a suspension of NASHA gel particles in phosphate buffered saline with a concentration of 20mg/mL.

The product is distributed as a 1mL or 3mL glass syringe. The content of the syringes is sterilized by moist heat; the outside of the syringe is not sterile. The shelf life of DUROLANE is 36 months. The device has undergone extensive pre-clinical testing to demonstrate its safety and to characterize its properties related to the NASHA gel structure.

The three mL version of DUROLANE has been marketed outside of the United States since 2001 for use in knee and hip OA. The product was originally introduced into the European market and since that time, it has been granted marketing authorization in Canada and select markets of the Middle East, Asia, and Latin America. In 2010, indications were expanded within the EU to include pain relief associated with OA in joints of all sizes (except temporomandibular and facet) and in the treatment of post-arthroscopic pain. A 1mL product was concurrently introduced as DUROLANE SJ to meet the injection needs of smaller joints. Durolane is currently marketed in the EU for use in hip, knee, ankle, fingers and toes.

This study is part of the post-approval commitment to BSi, the European Notified Body which granted the expanded indications of the product in 2010. Specifically, it aims to evaluate the effectiveness of a single IA injection of DUROLANE 3mL given for the relief of pain in patients with diagnosed and symptomatic shoulder osteoarthritis followed over a 26-week time period as measured by VAS pain on movement. It also seeks to evaluate the product's safety and tolerability.

5.1.1. Pre-Clinical Documentation

The composition of DUROLANE is very similar to a product manufactured by Q-Med for correction of facial wrinkles and folds, Restylane® (NASHA 20 mg/mL). Therefore, the biocompatibility of DUROLANE is primarily based on data obtained for Restylane (Restylane IFU, 2011). The biocompatibility tests for Restylane were performed in accordance with current requirements for medical devices, i.e., FDA/CDRH guidance document G95-1 and the ISO standard 10993 for biological evaluation of medical devices (CDRH, 2013). The overall conclusion of these studies was that Restylane fulfilled the current biocompatibility requirements for medical devices (Q-Med, 2004). The clinical safety of both products is well documented.

As of today, more than 10,000,000 treatments have been given with Restylane and approximately 350,000 treatments with DUROLANE®. The clinical safety of both products is well documented.

Two pre-clinical studies of DUROLANE in rabbits were conducted at the University of Calgary, Canada. The first study was a single IA injection study with a three-week follow-up. In the second study, follow-up doses were given six weeks and 12 weeks after the first injection. In both studies DUROLANE (0.25 mL) was injected intra-articularly in the right knee joint and the same volume of saline was injected into the left knee joint. Assessments included general health of the rabbits and histopathological evaluation which showed no untoward changes or any other adverse reactions. The results indicated that DUROLANE was well tolerated and no safety concerns were noted (Q-Med, 2000).

An additional preclinical study was carried out in Sweden to investigate the IA duration of ^{14}C-labeled DUROLANE in a rabbit model. This study shows that DUROLANE has a half-life of 32 days in the rabbit knee joint, which is much longer compared to half-lives reported in the literature data on HA and other modified HA products (Edsman, et al., 2011).

5.1.2. Clinical Documentation of HA use in Shoulder Studies

There have been 12 studies on the effect of intra-articular HA in reducing pain and improving functional outcome in patients with shoulder pathologies published to date. Of these, seven included patients with osteoarthritis (Leardini, et al., 1988; Brander, et al., 2010; Tagliafico, et al., 2011; Noel, et al., 2009; Blaine, et al., 2008; Merolla, et al., 2011; Silverstein, et al., 2007; Kwon et al., 2013). The rest were indicated for shoulder periarthritis/adhesive capsulitis, rotator cuff tear arthropathy and hemophilic chronic arthropathy (Rovetta, et al., 1998; Fernández-Palazzi, et al., 2002; Lee, et al., 2009; Calis, et al., 2006; Itokazu, et al., 1995).

Of the 12 shoulder HA studies published to date, seven were prospectively documented as a single cohort study (Noel, et al., 2009; Silverstein, et al., 2007; Itokazu, et al., 1995), one was saline controlled (Blaine, et al., 2008), three were active treatment controlled (corticosteroid and physiotherapy arms) (Calis, et al., 2006) and one was a controlled study investigating guided and unguided injection techniques (Lee, et al., 2009).

Within these studies, five different HA products were used: Hyalgan (Blaine, et al., 2008); Hylan G-F 20 (Brander, et al., 2010; Noel, et al., 2009; Merolla, et al., 2011; Silverstein, et al., 2007); Orthovisc (Calis, et al., 2006); Synvisc (Fernández-Palazzi, et al., 2002; unknown HA (Leardini, et al., 1988; Tagliafico, et al., 2011; Rovetta, et al., 1998; Lee, et al., 2009; Itokazu, et al., 1995). Both Hylan G-F 20 and Orthovisc are indicated for use in the shoulder within the EU. The other products appear to be off-label application for use in the shoulder, although as described, favorable results were achieved in this joint.

Therapeutic regimes ranged from one to 8 injections at intervals from 3 days to 1 month between injections with injection volumes of 1-2mL (volume was not identified in one study) using needle sizes where specified of 18G – 23G.

In total 802 patients, treating 805 shoulder joints with HA have been reported in twelve studies. Seventy-two patients (73 shoulders) were treated with corticosteroid as active control; 221 patients (221 shoulders) received saline control; 21 patients (21 shoulders) received physiotherapy; and 20 patients (20 shoulders) performed stretching exercise as therapy.

All studies that evaluated clinically meaningful patient outcomes relating to symptoms reported improvement in the HA groups over baseline. Uncontrolled studies demonstrated significant improvements in pain and function outcomes out to six months over baseline. The controlled studies provide favorable evidence for the effectiveness of HA in comparison to physiotherapy, intra-articular saline or intra-articular corticosteroid.

It is of note that the large Level 1 study reported significant results in pain reduction over saline controls only in patients with OA with no associated pathologies, such as rotator cuff tears and/or adhesive capsulitis (Blaine, et al., 2008). The retrospective controlled trial by Merolla et al. echoes this finding. The study reported lower clinical advantages in patients with greater degree of OA and rotator cuff tears (Merolla, et al., 2011). This data does not appear to be in discordance with the adhesive capsulitis study by Calis et al. (Calis, et al., 2006) as rotator cuff problems were excluded in this study and presence of OA of the shoulder was not mentioned, therefore it is not clear if these patients did or did not have OA of the shoulder in addition to a diagnosis of adhesive capsulitis. This study revealed significant effects of HA in pain and function outcomes at three months over baseline (although physical therapy overall appeared to be the best treatment overall).

Five articles dealing with intra-articular infiltration of HA in patients with shoulder OA were prospectively documented as a single cohort. Two studies resulted in a total of 69 patients who improved on VAS pain after 3 months; improvement is considered statistically significant and clinically relevant (Brander, et al., 2010; Noel, et al., 2009). Silverstein et al did not provide the statistical difference or range for VAS pain, and cannot be pooled (Silverstein, et al., 2007). Leardini et al described a series of heterogeneous group of patients with several types of shoulder pain-inducing pathology. On all measures of treatment effectiveness, including joint mobility, pain, and analgesic consumption, the patients showed rapid and significant improvement (Leardini, et al., 1988). Tagliafico et al treated 30 patients with cuff tear arthropathy (all patients with advanced shoulder OA) showing statistically significant improvement in VAS and Constant scores in the first 4 month follow-up with a complete relapse to the same VAS pain as pre-injection at 6 months after treatment (Tagliafico, et al., 2011).

No trends in favor of any one of the preparations were identified. It is of note that the study by Noel at al. (Noel, et al., 2009) demonstrated that a single injection of HA, as compared to two injections, resulted in superior responder rates (although patient populations for single and two injections was different).

A 2010 meta-analysis of HA use in chronic shoulder conditions (Saito, et al., 2010) considered saline controlled clinical studies (which included corticosteroid controlled studies). The meta-analysis concluded that HA injection is effective in relief of pain and is a safe alternative therapy for chronic painful shoulder. Improvement in pain outcomes, and total functional scores was noted with standardized mean differences of 0.39 (95% CI 0.26-0.53) and 0.36 (95% CI 0.01-0.71), respectively. No improvement in shoulder range of movement was found. Lastly it was noted that HA injection was modestly more effective than corticosteroid injection.

Adverse events were not considered or reported in five studies (Merolla, et al., 2011; Rovetta, et al., 1998; Calis, et al., 2006) and no adverse events were reported in the study conducted by Leardini et al and Itokazu et al (Itokazu, et al., 1995).

Blaine et al (Blaine, et al., 2008), reported the adverse events most likely to be considered to be related to the study treatment were injection-site pain. This occurred in 3.2% of patients receiving five HA injections as compared to 1.4% of patients receiving three HA injections (+ two saline injections) and 1.4% in the saline control group (five

saline injections). Tagliafico et all noted no safety concerns during the study except mild vagal reactions in 1/30 patients (3%) which occurred in association with the percutaneous procedure (Tagliafico, et al., 2011). Overall, all treatments were considered to be well tolerated (Leardini, et al., 1988; Brander, et al., 2010; Tagliafico, et al., 2011; Blaine, et al., 2008; Itokazu, et al., 1995). Serious adverse events were less frequent in both the HA groups than the saline control group. Noel et al., (2009) observed ten adverse events in eight patients that were all mild to moderate injection site pain.

Time to resolution was not noted in the publication. Silverstein et al., (2007) reported that no adverse events were considered related to the study device and no local pain or swelling or injection site irritation was observed.

Taken together, the data reported indicate the safety and effectiveness of a number of HA preparations and therapeutic regimes in the treatment of different forms of OA of the shoulder and possibly in degenerative conditions such as adhesive capsulitis.

5.2. Rationale

Osteoarthritis (OA) is a disease of the synovial joints characterized by the loss of cartilage, subchondral sclerosis, cyst formation, joint deterioration and new bone (osteophytes) formation around the joint. In addition, the properties of synovial fluid, to act as a shock absorber and lubricant for the joint surfaces, are impaired (Balazs, et al., 1993). In the shoulder joint, osteoarthritis is a common disorder that leads to pain, progressive loss of function and diminished quality of life. Glenohumeral osteoarthritis usually presents as gradual pain and loss of motion in patients older than 50 years (Self, 2002; Iannotti, et al., 2005; Stevenson, et al., 2002). A history of arthritis, previous shoulder surgery, pain, crepitus, and decreased motion is consistent with the diagnosis.

Currently, no curative therapy is available for osteoarthritis, and thus the overall goals of management are to reduce pain and prevent disability. Traditional treatments for OA include simple analgesics, NSAIDs, IA corticosteroid injections, physiotherapy, activity modification, weight reduction, orthotics, and surgery (Hochberg, et al., 2012). NSAIDs have proven therapeutic efficacy, but have been noted to have important adverse effects such as gastrointestinal bleeding, liver or kidney toxicity, and cardiac disorders. In addition the economic burden of providing medical treatment for adverse events (AEs) of NSAIDs has been estimated to be more than US $4 billion a year. Intra-articular corticosteroid injections, although useful for moderate to severe OA not responsive to conservative treatments, is contraindicated in diabetics and osteoporotic patients or those at risk. Normally, all other treatment options should be fully exploited prior to surgical management of OA, which is expensive, painful, and not risk-free. Taking into consideration that chronic use of some oral pain medications may be contraindicated, a locally-delivered therapy with no known drug interactions and an excellent safety profile is a valuable treatment option for patients.

Hyaluronic acid is an important component of synovial fluid and cartilage matrix and contributes to the homeostasis of the joint environment. Various clinical trials in the recent years have shown that hyaluronic acid replacement showed significant improvement compared with baseline (Colen, et al., 2012). The OARSI (Osteoarthritis

Research Society International) has concluded that intra-articular injection of hyaluronic acid may be useful in patients with knee or hip OA. Hyaluronic acid can be used in patients with contraindications to NSAIDS and corticosteroids or in patients not suitable for operative treatment. Hyaluronic acid (HA) is a polysaccharide secreted into the normal joint space by type B synoviocytes or fibroblasts, and it has viscoelastic properties for lubrication and chondroprotective effects. Recent studies of human synoviocytes from osteoarthritic joints have revealed that exogenous hyaluronic acid stimulates de novo synthesis of hyaluronic acid (Smith, et al., 1987), inhibits release of arachidonic acid, and inhibits interleukin-1α-induced prostaglandin E2 synthesis by human synoviocytes, which reduces the anti-inflammatory response (Yasui, et al., 1992). Hence, replenishing the hyaluronic acid component of normal synovial fluid may play a role in supplementing the elastic and viscous properties of synovial fluid (Balazs, 1993; Balazs, 1982), which may help relieve signs and symptoms related to OA and improve shoulder function.

Recently a large (660 subjects) randomized, double-blind, multicenter trial was conducted in the United States to compare the HA product Hyalgan® (HA) (Sanofi-Aventis) to saline injections over a 6-month period for the treatment of chronic shoulder pain. Based on radiographic criteria, subjects were stratified at baseline into two major groups: those with GH osteoarthritis (GH-OA) (60%) and those without GH-OA (40%). Using MRI and other clinical criteria, subjects were further sub-categorized by presence of adhesive capsulitis and rotator cuff pathology at baseline. The subjects were randomized into one of three treatment groups: five injections of saline, five injections of HA, or three injections of HA and two injections of saline. The intent to treat (ITT) longitudinal analysis revealed the five HA injection group and the three HA plus two saline injection group improved significantly more than the group receiving five saline injections over the 6-month period. There were no significant differences between the groups receiving three or five HA injections. Although all groups demonstrated improvements from baseline, the greatest treatment benefit was seen in the group of patients with GH-OA. In addition, statistically significant improvement in pain was observed in the OA group, regardless of the presence of other shoulder pathologies including rotator cuff tears or adhesive capsulitis. The improvement in pain in the non-OA group was not statistically different from the saline control group. These findings suggest HA's therapeutic effect on the shoulder was related to the presence of OA and not to other pathologies such as rotator cuff tears. The safety profile was favorable, with a low incidence of injection site pain (<1%) and no significant differences in pain between the HA and saline groups.

HA product injections exert their therapeutic effects on pain by a non-pharmacologic mechanism, are not associated with any catabolic actions on the joint tissue, and have been repeatedly administered over several years in both the knee and hip. DUROLANE has been proven to be an effective treatment for OA in the knee with a low percentage of adverse events (AEs). Because DUROLANE has demonstrated a successful history of pain relief in the knee with a very low rate of AEs, we believe it will demonstrate similar effectiveness for pain relief in the shoulder.

The purpose of this study is to assess whether the use of a HA-containing synovial fluid substitute (DUROLANE®) will relieve pain and result in an improvement of joint function

in patients presenting with persistent shoulder pain due to OA. It also seeks to evaluate its safety and tolerability. Clinical trials with DUROLANE and other HAs have shown a sustained response to treatment up to 26 weeks at least (Agerup, et al., 2005; Edsman, et al., 2009). Using this as a basis, the effectiveness and safety assessments for this study will be collected over 26 weeks.

In conclusion, the results of this study should support the current indications in the EU, specifically, for symptomatic treatment associated with mild to moderate osteoarthritis pain in the shoulder joint.

5.3. Potential Risks and Benefits

5.3.1. Potential Risks

5.3.1.1. Risks Associated with the Use of DUROLANE

There is a lack of published data related to the use of viscosupplementation for joints other than the hip and knee (e.g. ankle, shoulder, temporal mandibular joint, etc.). The majority of the reported adverse reactions in DUROLANE clinical studies of the knee and hip were described as transient pain, swelling and/or stiffness locally in the joint. It is unclear if these adverse reactions were related to the injection procedure or DUROLANE. These adverse reactions were mild or moderate in intensity and only occasionally required treatment with analgesics. A review of the literature related to the use of other HA preparations in other joints did not reveal any additional unique AEs (Durolane IFU, 2012). The type of adverse reactions associated with the use of DUROLANE in shoulder are likely to be the same as those observed in hip and knee.

The differences in physical and chemical properties between DUROLANE and other HA preparations have been assessed not to influence the safety and tolerability when injected intra-articularly (Q-Med, 2012). The risks associated with the IA injection will be minimized by only allowing clinicians to participate who have adequate education and are experienced in the delivery of IA shoulder therapies.

As with any treatment, unexpected reactions may occur. The study contains an exclusion criterion for those subjects with a previous history of an allergic response to a HA-based product. However, should a reaction occur, the subjects will be informed to contact the study site immediately and be given immediate advice about any necessary medical treatment.

Many subjects with shoulder pain receive treatment with anti-inflammatory drugs. Subjects who decide to take part and are receiving anti-inflammatory drugs must stop such treatment for a time sufficient for the given medication to clear the body (at least 5 half-lives of drug activity) before the shoulder injection is made and refrain from using such medications during the rest of the study period. This may increase the risk that study subjects experience shoulder or other bodily pain. However, to mitigate such risk, all subjects will be allowed to take rescue medication (acetaminophen) during the study for such pain. Other analgesics are prohibited.

All subject use of rescue medication will be recorded in the CRF.

5.3.1.2. Risks Associated with Injection

Certain risks are specifically associated with insertion of a needle into the IA joint space, irrespective of the device. Such risks include bleeding, infection, and joint injury, all of which are rare.

The risks associated with IA injections can be minimized by choosing appropriate technique, and ensuring accurate needle placement into the IA joint space. Image guidance of the needle (via ultrasound or fluoroscopy) is allowed but not required in this study. Additionally, strict aseptic procedures should be maintained during the procedure to reduce the risk of infection.

5.3.2. Known Potential Benefits

Taking part in this study may improve the subject's shoulder OA pain.

Information from this study may help Investigators learn more about symptomatic shoulder OA, treatment for persistent shoulder pain or help identify who is more likely to benefit from DUROLANE treatment.

This information may help future patients with shoulder OA pain.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Study Objectives

6.1.1. Primary Objective

To evaluate the efficacy of a single intra-articular (IA) injection of DUROLANE 3mL given for the relief of pain in the treatment of symptomatic osteoarthritis (OA) of the shoulder followed over a 26-week time period.

6.1.2. Secondary Objectives

To evaluate the efficacy of a single IA injection of DUROLANE 3mL given for treatment of symptomatic OA of the shoulder followed over a 26-week time period for:

- shoulder pain at night
- shoulder range of motion
- shoulder pain rescue medication use

To evaluate the safety and tolerability of a single IA injection of DUROLANE 3mL over a 26-week time period

6.2. Study Outcome Measures

6.2.1. Primary Outcome Measures

The primary outcome measure is the Shoulder Pain on Movement (SPOM) VAS (0-100mm) scale.

6.2.2. Secondary Outcome Measures

Secondary outcome measures will include the Shoulder pain at night (SPAN) VAS (0-100mm) scale, American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment (which includes range of motion and patient self-evaluation of pain today and activities of daily living), Patient Global Assessment (PGA) VAS (0-100mm) scale and Shoulder pain rescue medication diary.

Safety and tolerability of DUROLANE 3mL will be assessed through the collection of concomitant medications, SAEs and AEs related to the injection procedure and the device. Physical exams will be performed as needed. Consumption of rescue medication will be collected via subject diaries.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a prospective, open-label, single-cohort study to evaluate pain and function outcomes and safety following a single IA injection of DUROLANE 3mL in subjects with symptomatic shoulder OA. The study will be performed at one site in Canada with potential to add additional sites to boost recruitment, if required.

Adult subjects who have been clinically diagnosed with symptomatic mild to moderate OA of the shoulder that meet the inclusion and exclusion criteria will be recruited after providing written informed consent. Patients reporting pain per the SPOM VAS (0-100mm) scale ≥50mm and radiographic evidence of OA will be screened for eligibility. Subjects should be willing to discontinue use of oral analgesia, other than acetaminophen use. Subjects with significant pain from other joints (neck, hand, hip, knee, ankle), or report of >20mm on SPOM VAS (0-100mm) scale for the contralateral shoulder, will not be eligible to enroll in the study.

The study will consist of a screening visit, a Baseline Visit (Week 0) during which an IA shoulder injection will be given and follow-up clinic visits at Week 6, Week 12, and Week 26 after the Baseline Visit. There will be a telephone contact at Week 18 to collect efficacy assessments (excluding the physician range of motion assessment), adverse events, concomitant and rescue medication use.

The effectiveness assessments (excluding range of motion) are completed by the patient and the same evaluating investigator should preferably see the patient at all visits including the eligibility check at the screening visit.

7.2. Number of Subjects

In total, approximately 39 subjects will be screened and 36 subjects will be enrolled for up to 29 evaluable subjects.

7.3. Treatment Assignment

This is an open-label, single-treatment study. Qualified subjects will be assigned to DUROLANE 3mL only.

7.4. Study Schedule

Written informed consent will be obtained from prospective subjects prior to enrollment to the study. The assessments to be done at each visit are shown in Table 2. In case of any withdrawal (subject drop-out before the completion of the intended follow-up period), the date and reason for withdrawal will be collected in the CRF.

Table 2: Schedule of Events

Activities	Visit 1 (screening) Week -1 to -2 (≤ 14 days)	Visit 2 (baseline) Week 0 (Day 0)	Visit 3 Week 6 (±7 days)	Visit 4 Week 12 (±7 days)	Visit 5 (telephone contact) Week 18 (±7 days)	Visit 6 (final study visit) Week 26 (±7 days)
Informed consent	X					
Review of inclusion/exclusion criteria	X	X				
Demographics	X					
Medical history, including shoulder OA	X					
X-ray of the study shoulder	X[1]					
Review of concomitant medications/therapies	X	X	X	X	X	X
Physical examination including height and weight, vital signs	X	X	[2]	[2]		X
Physical examination of the study shoulder (SS)	X	X	X	X		X
Physical examination of the contralateral shoulder	X	X				
Washout of analgesics	X[3]	X[3,4]	X[4]	X[4]	X[4,6]	X[4]
Urine pregnancy test		X[5]				
VAS Shoulder pain on movement – contralateral shoulder	X	X				
VAS Shoulder pain on movement – SS	X	X	X	X	X[6]	X
VAS Shoulder pain at night – SS		X	X	X	X[6]	X
VAS Patient global assessment		X	X	X	X[6]	X
ASES Patient self-evaluation (VAS pain today and ADL only) – SS		X	X	X	X[6]	X
ASES Physician assessment range of motion only – SS		X	X	X		X
Dispense Week 18 VAS pain, PGA, and ASES patient self-evaluation forms				X		
Intra-articular shoulder injection		X				
Instruct subject on rescue medication use	X	X	X	X	X	
Dispense shoulder pain rescue medication diary	X					
Review shoulder pain rescue medication diary and record intake on CRF		X	X	X	X	X
Review and report adverse events (AEs)		X	X	X	X	X
Collect shoulder pain rescue medication diary						X

1. If a radiograph was not taken within 6 months of the screening visit, then a radiograph must be taken as standing x-rays in the anterior-posterior and lateral plane views. Radiographs must be read by a local radiologist or the orthopaedic surgeon.
2. As clinically indicated.
3. At least 5 half-lives of current analgesic must have passed before Baseline Visit to confirm eligibility.
4. No acetaminophen is to be taken for 24 hours before each study visit (Weeks 0, 6, 12, 18, 26). No other analgesic is to be taken during the course of the study.
5. Urine pregnancy test will be performed on all females of childbearing potential.
   At the Week 12 visit VAS pain, PGA, and ASES patient self-evaluation forms will be dispensed to the subject to be completed at the time of the Week 18 telephone contact.

7.4.1. Screening Visit

The prospective subject must be informed about the study both orally and in writing, and the ICF must be signed prior to initiation of any study related procedure. Inclusion into this study requires literacy in English sufficient to complete the informed consent process and ability to complete effectiveness assessment forms. A study number will be assigned chronologically to each subject screened per the Screening and Enrollment log. Based on a chart review and discussion with the subject, the following demographic data will be recorded in the CRF: anonymized subject initials, gender, date of birth, ethnic origin, weight, and height. Medical history, including OA history and concurrent diseases will be queried and recorded on the CRF. The assessments of OA history at the screening visit will consist of: duration of diagnosed shoulder OA (i.e., time since

diagnosis), duration of persistent shoulder pain, OA in joints other than the shoulder, clinically-significant pain from other parts of the body than the shoulder, and history of prior medications and interventions for shoulder OA (including IA injections, surgical procedures, and any traumatic injury). Concomitant medications and non-pharmacological treatment of shoulder OA will be recorded in CRF logs.

A full physical examination including vital signs, height and weight will be conducted. Physical examination of both shoulders will be performed. Evidence of joint inflammation, as reflected by clinically-tense effusion and tenderness on palpation will exclude the subject from the study.

Radiographs of the study shoulder will be performed, if a radiograph taken within six months of the screening visit does not exist. Assessment of radiographs will be made by either the Study Investigator or the local radiologist. The SPOM VAS (0-100mm) assessment will be completed for both shoulders. A pain score ≥50mm is required for the study shoulder and must be ≤20mm for the contralateral shoulder to be eligible.

For eligibility, symptomatic OA of the contralateral shoulder should be responsive to acetaminophen and not require any protocol prohibited therapies that would confound measurement of pain in the study shoulder. Also, low back pain requiring chronic ongoing analgesic therapy is an exclusion criterion.

The subject will receive, as part of the informed consent, a written explanation of shoulder OA and the anticipated AEs associated with DUROLANE injection. Subjects should also be informed about medications which are permitted and medications which are prohibited during the study period (see Appendix 2). In addition, subjects should be informed about post-injection procedures (see Section 9.4.6).

Acetaminophen will be purchased by the research subject as needed. The research site staff will provide written instructions that the dose should not exceed 4g/day and no analgesics are to be taken 24 hours prior to any study visit. No other analgesic medication is permitted during study participation. A shoulder pain rescue medication diary will be provided to record intake of rescue medication and other concomitant medications used throughout study participation. The shoulder pain rescue medication diary will have written instructions on how to record use of rescue and concomitant medications. In addition, instructions on rescue medication dosing and wash-out periods prior to study visits will also be provided.

Screen failures will be recorded in the Screening Log, including a clear description for screen failure rationale. For subjects determined to be eligible, the date of enrollment will be entered into the Enrollment Log.

7.4.2. Enrollment/Baseline

No more than two weeks after the screening visit, the subject will return to the clinic for the Baseline Visit. This visit must take place after at least five half-lives of pre-screening analgesic medication have elapsed and the assessment of radiographs by the radiologist or study investigator.

Subjects should be queried about his/her use of analgesics during the previous 24 hours and the shoulder pain rescue medication diary checked and rescue medication

consumption recorded on the CRF. If acetaminophen was used in the previous 24 hours, the visit MUST be rescheduled.

If an analgesic other than acetaminophen was used prior to the visit, ensure the appropriate wash-out period (i.e., at least five half-lives) was observed, and if otherwise, reschedule the visit. If a reschedule that ensures appropriate wash-out of analgesic would fall outside the visit window, then the subject will be excluded from the study and recorded as screen failure in the Screening Log.

A urine pregnancy test should be performed for all women of childbearing potential. A positive result excludes the subject from the study. Pregnancy after enrollment must be communicated to the investigator. No other mandatory clinical chemistry or hematology tests will be performed during this study.

Before administering the study injection, SPOM VAS (0-100mm) ASES pain on movement assessment will be completed for both shoulders. A pain score ≥50mm is required for the study shoulder and no more than 20mm for the contralateral shoulder to be eligible. The SPAN VAS (0-100mm), ASES patient self-evaluation (VAS pain today and activities of daily living only), ASES physician ROM assessment will be completed for the study shoulder only. The PGA (0-100mm) will also be completed at this visit.

A full physical examination including vital signs, height and weight will be conducted. Physical examination of both shoulders will be performed. The investigator will determine if the study shoulder has a clinically-apparent tense effusion or signs of misalignment or instability. If it has either, then the subject must be excluded.

The inclusion/exclusion criteria will be verified. If a subject fails any of these inclusion/exclusion criteria the subject should be recorded as a screen failure in the Screening and Enrollment Log and will be excluded from the study.

Subjects will be informed about possible anticipated AEs following the IA injection. The shoulder pain rescue medication diary will be reviewed and any necessary counseling regarding use of rescue and other concomitant medication will be given as needed. The shoulder pain rescue medication diary will be returned to the subject at each visit starting from the Screening Visit to record intake of rescue medication and other concomitant medications.

Instructions on how to take acetaminophen as rescue medication will be provided. The subject will again be reminded that the acetaminophen intake should not exceed 4g/day and that none is to be taken 24 hours prior to any study visit. Subjects will also again be reminded that no other analgesia should be used during study participation.

If for any reason, injection is not possible during the Baseline Visit (Week 0), the injection may be rescheduled for up to two days after the Baseline Visit provided it is within 14 days from the Screening Visit. Subsequent study visits will be based on calendar days from the date of the Day 0 injection. Eligibility must be reconfirmed prior to injection.

Thereafter, at Investigator’s discretion, topical anesthesia (using ethyl chloride or lidocaine spray) or subcutaneous lidocaine may be given followed by the IA injection of DUROLANE. If effusion is found in the shoulder upon needle placement in the joint

space, it must be removed (arthrocentesis) before DUROLANE is injected. The amount of fluid removed will be documented in the CRF. The injection procedure will be conducted by the Investigator. See Section 9.4 for more details.

Image-guidance may be used to ensure proper IA placement of the treatment with the assumption that the investigator is experienced with the use of the type of imaging used.

To monitor for possible injection procedure-related events, subjects should remain at the study site for 30 minutes following injection. Acetaminophen to relieve post-injection pain is allowed. All subjects should be informed about post-injection procedures (see Section 9.4.6).

7.4.3. Follow-up Visits (Weeks 6, 12 and 18)

Weeks 6 and 12: Subjects will return to the clinic for Visit 3 (Week 6) and Visit 4 (Week 12) after the baseline injection of DUROLANE. The SPOM VAS (0-100mm), SPAN VAS (0-100mm), ASES patient self-evaluation (VAS pain today and activities of daily living only), and ASES physician ROM assessment will be completed for the study shoulder only. The PGA (0-100mm) will also be completed at this visit. If clinically indicated, a full physical examination will be performed.

Week 18: Patients will receive a follow-up telephone call from the research staff at Visit 5 (Week 18) after the baseline injection of DUROLANE. The subject will be asked to complete the SPOM VAS (0-100mm), SPAN VAS (0-100mm), and ASES patient self-evaluation (VAS pain today and activities of daily living only) for the study shoulder. The PGA (0-100mm) will also be completed at this visit. All efficacy assessments will be returned to the study site by mail.

At all visits: Subjects will be queried about any AEs since the last visit. The subject diary for rescue and other concomitant medications will be reviewed and any necessary counseling regarding use of rescue and other concomitant medication will be given as needed. Use of rescue medication and concomitant medication since last visit will be recorded on the CRF. Instructions that the acetaminophen dose should not exceed 4g/day and that the 24-hour wash-out prior to any study visit will be discussed with each subject at length. The subject shall also be reminded that no other analgesia should be used.

Return the shoulder pain rescue medication diary to subjects at each clinic visit (excluding Week 18), unless a replacement is needed. This enables the subject to record their intake of rescue medication and other concomitant medications used between clinic visits.

7.4.4. Final Study Visit (Week 26)

Subjects will return for the final visit of the study, Visit 6, 26 weeks after injection of DUROLANE at baseline. The SPOM VAS (0-100mm), SPAN VAS (0-100mm), ASES patient self-evaluation (VAS pain today and activities of daily living only), and ASES physician ROM assessment will be completed for the study shoulder. The PGA (0-

100mm) will also be completed at this visit. A full physical examination will be performed.

Subjects will be queried about any AEs since the last visit. The diary for rescue and other concomitant medications will be reviewed for use of rescue medication and concomitant medication since the last visit will be recorded on the CRF. The shoulder pain rescue medication diary will be collected at the Final Study Visit.

7.4.5. Early Withdrawal

The End of Study form will be completed for all subjects, including withdrawals. For subjects who wish to withdraw from the trial, monitoring of outcome measures by registered mail must be offered. All assessments scheduled for the Week 26 visit must be completed for early withdrawals. Completion of the questionnaires will document data on the safety and efficacy of the injection throughout the study.

For subjects who wish to withdraw completely and are not amenable to being followed and for other subjects who had to be discontinued prematurely, the primary reason for discontinuation must be recorded.

Subjects lost to follow-up are defined as those who are unrecoverable for the final Week 26 visit assessments.

7.4.6. Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the site Investigator. The date and reason for the unscheduled visit will be recorded in the source documentation and CRF.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects will be recruited from outpatient clinics. Referrals from general practitioners and extended scope practitioners such as physiotherapists will be accepted. A Dear Healthcare Provider letter and/or an advertisement (approved by the REB) in a local newspaper may be used if considered appropriate.

Informed consent will be administered to the potential subjects prior to screening. Each patient must have met all eligibility criteria before the IA injection is given at the Baseline Visit.

8.1. Subject Inclusion Criteria

1. Females or males between the ages of 19 and 85 years of age
2. Diagnosis of glenohumeral osteoarthritis (GH-OA), confirmed by radiographs taken within the previous six months, with GH-OA being the primary source of pain; OA in the contralateral shoulder is permissible provided that OA symptoms are greater in the trial shoulder
3. Shoulder pain on movement (SPOM) visual analogue scale (VAS) (0-100mm) ≥50mm for the study shoulder
4. Must be willing to discontinue use of oral and topical analgesia other than rescue use of acetaminophen for the study shoulder. Must also be willing to discontinue rescue medication for at least 24 hours before each visit
5. Abstinence from any IA or peri-articular injections for the shoulder during the course of the trial, except for the assigned Investigational Product
6. Patients with chronic shoulder pain lasting more than 6 months without clinically significant improvement in shoulder pain over the past one month
7. Pain at least 50% of the days during the previous month
8. Patients who have failed conventional therapy including but not limited to the following: nonsteroidal anti-inflammatory drugs (NSAIDs); one or more intra-articular or local peri-articular steroid injections and physiotherapy (a minimum of one month of previous physiotherapy treatment is required)
9. Patients with a retained active range of motion (ROM) of at least 30% in all directions to rule out frozen shoulder (>30° for abduction with scapula fixed, >30° for external rotation, and >20° for internal rotation)
10. Cooperative and able to communicate effectively with the Investigators
11. Must agree not to participate in any other clinical research (interventional) studies while participating in this study
12. Body mass index (BMI) ≤ 35 kg/m^2
13. English literacy and ability to understand and complete all informed consent procedures

8.2. Subject Exclusion Criteria

1. Significant pain from other joints or low back pain requiring chronic ongoing analgesic therapy
2. Presence of one or more conditions besides OA that could confound pain and functional assessments in the study shoulder
3. Clinically-apparent tense effusion or gross misalignment or instability in the study shoulder
4. Shoulder x-ray findings of acute fractures, severe loss of bone density, avascular necrosis and/or severe deformity
5. Surgery of the study joint within the previous 12 months.
6. Treatment with NSAIDs or any pain management medications (including topical agents for the study shoulder) during the last week (or five half-lives of the drug, whichever is longer) prior to Baseline Visit.
7. Inability to tolerate acetaminophen for rescue medication use.
8. Use of acetaminophen or any other analgesics during the 24 hours preceding the baseline visit.
9. IA or local peri-articular corticosteroid injections to the study joint or shoulder within the previous three months; or to any other joint within the previous month; or any oral corticosteroid within the previous month. Steroid inhalants are permitted if the patient has been on a stable regimen for the past month and remains on this regimen throughout the course of the trial
10. IA injections with hyaluronic acid in the study shoulder within the last 9 months
11. Previous allergic reaction to a HA or local anesthetic such as lidocaine.
12. Treatment with glucosamine/chondroitin sulfate initiated within the past three months, or dosage not stable for the past three months
13. Change in physical therapy for the study shoulder within one month preceding screening, or expected change in physical therapy during the study
14. Planned surgical procedure during the study period.
15. Previous history or presence of septic arthritis in study joint
16. Active skin disease or infection in the area of the injection site
17. Alcohol or drug abuse as determined by the Investigator or use of alcohol for control of pain
18. Use of illicit drugs including cannabis
19. Systemic inflammatory condition or autoimmune disease or infection such as rheumatoid arthritis, inflammatory arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, gout/ acute pseudo gout or any other connective tissue disease

20. Uncontrolled hypothyroidism
21. Use of aspirin (acetylsalicylic acid) as an analgesic (up to 325 mg/day for anticoagulant treatment is permissible)
22. Any medical condition which in the opinion of the investigator makes the patient unsuitable for inclusion (e.g., severe progressive chronic disease, malignancy, bleeding disorder, fibromyalgia)
23. Pregnant or breast-feeding woman or woman of child-bearing potential not practicing adequate contraception.
24. Subjects that in the opinion of the investigator are unsuitable for inclusion (e.g., subjects not likely to avoid other therapies, subjects not likely to stay in the study or with plans to relocate during the study period, or subjects likely to be unreliable)
25. Concurrent participation in any other clinical study or participation within the preceding 30 days

8.3. Screen Failures

A screen failure is a subject who signed the ICF, but never received treatment with Investigational Product. Screen failure reasons will be documented in the Screening and Enrollment logs and all study assessments completed through determination of ineligibility will be documented.

8.4. Subject Compliance

Subject compliance describes how well the subject follows the prescription of the treatment and instructions of dosing. As the Investigator will give the treatment to the subject at the center, no other measurements of subject compliance will be performed.

8.5. Subject Withdrawals

8.5.1. Reasons for Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The Principal Investigator also may withdraw subjects from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the Sponsor. Subjects also may be withdrawn if the Sponsor or site REB terminates the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of subjects who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in subjects' study records. In the event that subjects who voluntarily withdraw from the study wish to re-join the study, they may resume follow-up through their originally scheduled study exit date, pending consultation with the Sponsor.

Use of analgesics other than rescue medication (acetaminophen) for pain management is not allowed. Increased acetaminophen usage may signal worsening of the disease under study or of a pre-existing disease other than shoulder pain. Investigator plans to

withdraw a subject for any reason must be communicated to the Sponsor. Subjects' safety must always take precedence. The Sponsor must be informed within 24 hours of all study subjects who are withdrawn due to an AE.

8.5.2. Handling of Withdrawals

If the patient consents, monitoring for subject reported outcomes and for any AE should continue via certified letter within the prescribed study visit window. For subjects who do not wish to be followed but had an AE which, according to the Investigator's assessment, is related to the use of the Investigational Product and remains ongoing at the time of the withdrawal, the AE must be followed until the event resolves or is assessed by the Investigator to be "chronic" or "stable".

8.6. Study Pause

Following a decision from the Sponsor, study enrollment may be suspended at any time on medical grounds. Examples of these findings are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. In the event of enrollment suspension, the Sponsor will promptly inform the investigator/hospital, the competent authorities and research ethics committee, stating the reasons for this decision.

8.7. Termination of Study

The Sponsor reserves the right to end the study at any time prior to inclusion of the intended number of subjects, but intends to exercise this right only for valid scientific or administrative reasons.

After such a decision, all delivered unused Investigational Product and other study materials must be collected without delay and the CRFs completed.

9. INVESTIGATIONAL PRODUCT

9.1. Investigational Product Description

DUROLANE is a clear, transparent, viscous gel of highly purified non-animal hyaluronic acid derived via a bacterial fermentation process. The content of the syringes are sterilized by moist heat, the outside of the syringe is not sterile.

9.2. Investigational Product Packaging and Labeling

Commercially-available DUROLANE 3mL will be used as Investigational Product. The Investigational Product is manufactured, packaged, and labeled by Q-Med.

9.3. Investigational Product Storage and Stability

The expiry dates are indicated on the package. The syringes should be stored at up to 30°C, protected from sunlight and freezing. The storage of Investigational Product at the study site must be kept separate from other supplies and in a secure location. Packages/syringes must be opened by designated personnel only. Once the package/syringes have been opened, the sterile barrier is broken. Opened packages/syringes should not be re-used. The shelf life of DUROLANE is 36 months.

9.4. Investigational Product Administration

9.4.1. General Instructions

The treatment will be injected by the Investigator or treating physician into the study shoulder of each subject. Use of imaging is optional. The recommended needle size for the IA injection for the shoulder is between18 to 22 G with appropriate length. The needle is not provided in the investigational product package.

The Investigational Product is intended for single use and strict aseptic administration technique must be followed. The contents of the syringe must be used immediately after the syringe has been removed from its packaging.

Strict aseptic technique must be followed. The injection site should be disinfected carefully according to standard medical practice. Disinfectants containing quaternary ammonium salts, such as benzalkonium chloride, which may induce precipitation of HA, should be avoided.

The date, whether complete or incomplete device contents were administered, and which shoulder was treated will be recorded in the CRF by the Investigator. After having made the injection, the syringe and packages should be discarded in an appropriate manner.

9.4.2. Injection of DUROLANE

The injections will be performed by Investigators who are very well experienced with this type of administration. He or she will have previously chosen the most appropriate injection route based on the anatomy of the subject's shoulder.

Remove the pre-filled 3mL syringe from its packaging and use only if the packaging has not been opened or damaged. The Investigational Product is intended for single use and strict aseptic administration technique must be followed.

Syringes used for aspiration prior to injection and needles for injection of Investigational Product will be supplied by the sites. Required sizes of needles will be in the range of 18 to 22G with appropriate length.

9.4.3. Anesthetization of the Injection Site

Anesthetization of the injection site is not required. However, the Investigator or treating physician may administer at his/her discretion a topical anesthetic (e.g., ethyl chloride or lidocaine spray) or subcutaneous lidocaine as part of the injection procedure.

9.4.4. Use of Imaging Guidance

Injection by image guidance is at the discretion of the Investigator. Use of image guidance will be recorded in the CRF.

9.4.5. Arthrocentesis

The presence of clinically-apparent tense effusion in the study shoulder will exclude the subject from inclusion in the study. If effusion is found in the shoulder upon needle placement in the joint space, it must be removed (arthrocentesis) before study/reference product is injected.

Strict aseptic technique must be followed. The same needle will be used for arthrocentesis and the IA injection. Needles from 18 to 22G will be supplied by each study site and the study personnel will choose an appropriate needle.

Gentle aspiration will be performed prior to injection of the study treatment for each subject in an attempt to ascertain that the needle has been placed within the joint space. Any joint fluid will be withdrawn using an empty 20mL syringe (supplied by each study site) and the volume of the aspirated fluid will be recorded in the CRF.

Leaving the needle in the joint space, the aspiration syringe will be removed and replaced by the pre-filled 3mL syringe containing DUROLANE. Care must be taken when exchanging syringes to avoid displacement of the needle and to ensure the syringe with Investigational Product is securely attached prior to injection.

9.4.6. Post-Injection Care

To monitor for possible injection procedure-related events, subjects should remain at the study site for 30 minutes following injection.

The subjects should be encouraged to rest the injected joint as much as possible for at least 24 hours. Subjects are allowed to return to work, but strenuous activities and driving long distances should be avoided the first 48 hours after injection.

Subjects should be informed that there could be pain associated with the injection procedure. For post-injection pain management, subjects should rest and apply ice at the injection site for 20-minute intervals, if needed. In the event of persistent pain, the subject may take recommended rescue medication (see Section 10). All pharmacological and non-pharmacological treatments of post-injection pain must be captured in the CRF.

9.4.7. Documentation of Treatment Procedure

All procedures will be carefully documented in the medical notes and in the CRF. The subject number, date and time of injection, study shoulder, needle size, possible use of topical, subcutaneous and intra-articular anesthetics, arthrocentesis volume, volume of Investigational Product (3mL) injected and possible technical or medical problems with the injection will be recorded in the CRF by the Investigator.

After the injection, the syringe and packages should be discarded according to approved institutional disposal policy. An Investigational Product Dispensing Log is to be maintained by the site.

9.4.8. Reporting Technical Complaints

All technical complaints regarding the Investigational Product are to be reported to the Sponsor promptly.

AEs and other clinical findings prior, during or immediately post-injection must be recorded. Subjects experiencing pain and swelling at the study shoulder or any other AEs will be instructed to contact the study staff.

9.5. Investigational Product Accountability

The product will be released to each Investigator (or pharmacy located at the study site) after approvals of the protocol have been received from the REB and the Clinical Trial Agreement (CTA) has been finalized and signed by the study site.

The Investigator must ensure that the Investigational Product is kept under secure conditions, with access limited to those authorized by the Investigator per the Delegation of Authorities Log.

The Investigational Products must be traceable from the manufacturer to their use in subjects and the Investigator must maintain accurate product accountability records, i.e., documentation of deliveries and return of Investigational Product between the Sponsor or their representative and the Investigator, and documentation of administration of product to the subject.

A log will be kept of all Investigational Product received from the Sponsor. In addition, dispensing logs will be maintained including the date, amount dispensed, and the

subject receiving Investigational Product. Logs for all accountability procedures are provided by the Sponsor.

When the study is completed, all unused investigational product at each study site must be returned to the Sponsor for destruction, with proper documentation, unless otherwise instructed by the Sponsor.

Products deliberately or accidentally destroyed during shipment or at a study site should be accounted for and documented. Used syringes should be destroyed according to the procedures at the clinic. Disposal of hazardous material, i.e., syringes and needles, must conform to applicable laws and regulations. The Investigational Product must not be used outside the study.

10. CONCOMITANT MEDICATIONS /TREATMENTS

Except as noted below, concomitant medications or other treatments or procedures may be given at the discretion of the Investigator when medically necessary. All concomitant therapy used during the study, should be recorded in the CRFs, by the name (generic name for pharmacological therapy), start and end date, and indication.

The restrictions on treatments and the specified time periods prior to and during the study are provided in the inclusion/exclusion criteria. Except for analgesic given for management of persistent post-injection pain and for short-term relief of pain other than shoulder pain, the Investigator should contact the Sponsor prior to implementation of these therapies. All such therapy used during the study is to be recorded in the CRF.

For rescue medication, subjects will be instructed to take as needed of acetaminophen not to exceed 4g/day. Subjects will be required to purchase this for themselves as needed. A shoulder pain rescue medication diary will be provided to the subject at the screening visit to record intake of rescue medication. The diary will be reviewed at baseline, Week 6, Week 12, Week 18 (via phone) and Week 26. Any use of rescue medication since last visit will be recorded in the CRF.

Acetaminophen is also the preferred analgesic for other types of body pains while the subject is in the study. Usage will be documented in the subject's shoulder pain rescue medication diary and Concomitant Medications CRF page.

Any concomitant medications, including over-the-counter (OTC) medications, administered during the study are also to be recorded in the CRF and in the shoulder pain rescue medication diary.

11. CLINICAL EVALUATIONS

11.1. Demographics (Screening Visit)

The demographic data will consist of: subject study number, sex, age, race, ethnicity, height, weight, body mass index, and child-bearing potential for females.

11.2. Medical and Medications History (Screening Visit/Baseline Visit)

Medical history and concurrent diseases will be reviewed. History will be obtained from interview and review of medical records. History of analgesic use will be elucidated, an appropriate wash-out period will be prescribed and Baseline Visit will be scheduled for the end of this period, and within 14 days of the screening visit.

11.3. Concomitant Medications (All Visits)

Any therapies for other diseases that are considered necessary for the subject's welfare may be given at the discretion of the Investigator. All concomitant therapy used during the study, should be recorded in the CRFs by the name (generic name for pharmacological therapy), the start and end date, and indication.

Acetylsalicylic acid up to 325mg per day is allowed during the study as thrombosis prophylaxis. Acetylsalicylic acid for analgesic purposes is not allowed. The prohibition for taking any analgesic 24 hours before a visit also applies.

No other product under investigation may be used concomitantly with the Investigational Product.

11.4. Non-pharmacological treatment (All Visits)

Non- pharmacological therapy will be noted in the CRF. This may include but are not limited to:

- resting the shoulder joint
- physical therapy
- range-of-motion exercises
- appropriate application of ice and moist heat
- patient education
- self-management programs
- personalized social support through telephone contact
- aerobic and muscle-strengthening exercises
- occupational therapy
- joint protection and energy conservation

- assistive devices for activities of daily living

New therapies may not be initiated during the study. See Appendix 2 .

11.5. Physical Examination of Shoulder (All Visits)

The physical examination of the study shoulder at screening will include assessment for joint inflammation seen as joint effusion and/or tenderness on palpation. The skin over the study shoulder will also be observed for any infection.

11.6. Pregnancy Test (Baseline Visit)

At the Baseline Visit, a urine pregnancy test should be performed for all women of childbearing potential to be processed locally. A positive result excludes the subject from the study. No other mandatory clinical chemistry or hematology tests will be performed during this study.

12. ASSESSMENT OF EFFICACY

The choice of outcome measures in this study is based on recommendations on measures to be used in clinical studies on OA of the shoulder. Effectiveness assessments will be completed by subjects at each scheduled study visit at Week 6, Week 12, Week 18 and Week 26 after the injection visit.

The primary efficacy assessment will be the VAS (0-100mm) shoulder pain on movement. A Visual Analog Scale (VAS) is a measurement instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot be objectively recorded. A VAS is a horizontal line, 100mm in length, anchored by word descriptors (i.e., no pain, worst pain imaginable) at each end. For this study, the subject will mark the line at the point that they feel represents their perception of his or her pain in the last 24 hours. The VAS score is determined by measuring in millimeters from the left end of the line to the point that the subject marks (Burckhardt, et al., 2003; Johnson, 2005; Paul-Dauphin, et al., 1999)

The secondary efficacy variables will include the VAS (0-100mm) shoulder pain at night, American Shoulder and Elbow Surgeons patient self-evaluation (VAS pain today and activities of daily living only), ASES physician ROM assessment, and PGA. In addition to the efficacy assessments described above, the consumption of rescue medication will be accessed.

In this study the SPOM, SPAN, ASES patient self-evaluation (VAS pain today and activities of daily living only) and PGA are completed by the patient at each study visit. The ASES physician ROM is completed by the Investigator. The same evaluating investigator should preferably see the patient at all visits in order to present the questionnaires for the patient in a uniform way throughout the study. If more than one investigator has assessed any patient at any time-point during the study, it should be documented in the CRF.

At baseline all efficacy assessments have to be performed before the study product is injected. All assessments should be made without comparing the data from the assessments at previous visits.

12.1. Shoulder Pain on Movement (SPOM) VAS (0-100mm) (All Visits)

The SPOM VAS (0-100mm) scale will be completed both for the study shoulder and the untreated shoulder on the screening visit to exclude significant pain on the contralateral shoulder that might affect pain assessments.

The self-administered SPOM VAS (0-100mm) scale will contain the instruction below for the subject:

“How severe has your pain on movement been in the last 24 hours? Place a vertical mark in the line below to indicate how severe your pain has been.”

12.2. Shoulder Pain at Night (SPAN) VAS (0-100mm) (All Visits)

The self-administered SPAN VAS (0-100mm) scale will contain the instruction below for the subject:

“How severe has your pain at night been in the last 24 hours? Place a vertical mark in the line below to indicate how severe your pain has been.”

12.3. American Shoulder and Elbow Surgeons (ASES)

In 1993 the American Shoulder and Elbow Surgeons society (ASES) adopted a standardized form for the assessment of shoulder function. The ASES form contains a patient self-evaluation section and a physician assessment section. The form is used to measure baseline shoulder function and is applicable to all subjects regardless of their diagnoses.

12.3.1. ASES Range of Motion (ROM) (Screening, Baseline, Week 6, Week 12 and Week 26)

The ASES physician-administered ROM will contain instructions for the assessment of the subject’s shoulder active range of motion (measured in degrees) for the movements of abduction, extension, forward elevation, external rotation, internal rotation, cross-body adduction will be taken using a 41 cm universal goniometer.

12.3.2. ASES Patient Self-Evaluation (All Visits)

The ASES patient self-evaluation (PSE) portion contains a VAS for pain today and instability and a questionnaire for activities of daily living (ADL). In this study, patients will only complete the VAS pain today and activities of daily living only sections of the patient self-evaluation form. The ADL questionnaire is marked on a four-point ordinal scale that can be converted to a cumulative ADL index. A Shoulder Score Index (SSI) can then be derived from the VAS pain today score and the cumulative ADL score.

The patient self-evaluation section consists of eleven items divided into two areas:

1. Pain (one item): The question asked is: “How bad is your pain today?” the patient’s response to the pain today question is marked on a 0-10cm (equal to 0-100mm) VAS scale anchored with verbal descriptors at 0 (No pain at all) and 100mm (Pain as bad as it can be).

2. Function (ten items): the items in the function area assess activities of daily living (1. put on a coat, 2. sleep on your painful or affected side, 3. wash back/do up bra in back, 4. managing toilette, 5. comb hair), demanding activities (6. reach a high shelf, 7. lift 10 pounds above shoulder, 8. throw a ball overhand) and general activities (9. do usual work, 10. do usual sport). The possible responses are 0 (unable to do), 1 (very difficult to do), 2 (somewhat difficult), and 3 (not difficult).

12.4. Patient Global Assessment (PGA) (All Visits)

The VAS Patient Global Assessment (PGA) asks a patient to rate on a scale how they feel overall. The scale goes from 0 (zero) to 10. Only the two extremes have text: level 0 is defined as “Very poor” and level 100 as “Excellent”.

The self-administered PGA will contain the instruction below for the subject:

“Considering all the ways your target shoulder affects you, how are you doing today?”

The subject should mark the alternative that he/she finds appropriate (Pincus, et al., 1989).

12.5. Recorded Use of Rescue Medication

Subjects will be advised to take acetaminophen as rescue medication for study shoulder pain as required. Acetaminophen intake will be recorded in the shoulder pain rescue medication diary which will be transcribed on the CRF.

13. ASSESSMENT OF SAFETY

All AEs which occur during the course of the subject's involvement in the clinical investigation shall be appropriately recorded and reported to ensure their continuing safety. The Medical Devices Regulations SOR/98-282 and the Guidance Document for Mandatory Problem Reporting for Medical Devices provides guidance for Post-Market Vigilance Reporting and sets out specific requirements for the management of AEs. Each type of AE is subject to different reporting requirements.

All AEs must be followed until they are resolved or the study has ended. In addition, all serious, as well as, non-serious AEs with a causal relationship to the device under investigation and/or its usage must continue to be followed until resolved or until the Investigator assesses them as chronic or stable, even if the subject's participation in the study is otherwise completed. See Appendix 3 for more details.

14. STATISTICS

14.1. Methods

14.1.1. General

There is a single pre-planned hypothesis test for the primary variable. There are no pre-planned hypotheses tests for secondary or exploratory efficacy variables or safety variables. Any inferential statistic for these variables is exploratory. All variables will be summarized using descriptive statistics such as sample size, mean, standard deviation, median, minimum and maximum and frequencies, i.e. counts and percents. All other analyses details will be described in a statistical analysis plan (SAP).

14.1.2. Safety

The incidences of all AEs and serious AEs, complaints and complications will be monitored for all subjects that signed an informed consent. However, safety analysis shall be carried out on those subjects that were enrolled into the study and received the DUROLANE 3mL injection (the Safety Population). Since this is a single arm study there are no inter-group comparisons. Nevertheless, all events will be reviewed by the Investigator and categorized in terms of both severity and the likelihood that these events were caused as a result of using DUROLANE 3mL. Enrollment will be paused for thorough review in the event of any serious AE deemed to be as a direct result of using the treatment.

Below are general considerations for summary and display of AEs and concomitant medications. Additional safety analyses will be described in a SAP.

Adverse Events

- AEs will be coded using the current MedDRA dictionary.
- All AEs will be summarized by MedDRA primary system organ class (SOC) and preferred term (PT). If a subject has more than one occurrence of the same preferred term then they will be counted only once in a summary table for that preferred term.
- A listing by subject of all AEs will be provided. Listings of serious AEs and AEs leading to discontinuation will also be provided.

Concomitant Medications

- Concomitant medications will be coded using the WHO dictionary.
- All concomitant medications will be summarized by WHO generic term. If a subject has more than one occurrence of the same generic term then they will be counted only once in summary tables for that generic term.
- A listing by subject of all concomitant medications will be provided.

Physical Exams (*performed as needed*):

- A listing by subject of all abnormal physical exams will be provided.

14.1.3. Efficacy

14.1.3.1. Primary Variable

VAS (0-100mm) SPOM over weeks 0, 6, 12, 18 and 26

14.1.3.2. Primary hypothesis

Ho: VAS SPOM over weeks 6, 12, 18 and 26 ≥ VAS SPOM at week 0 (baseline)
Ha: VAS SPOM over weeks 6, 12, 18 and 26 < VAS SPOM at week 0 (baseline)

14.1.3.3. Primary hypothesis statistical test method

A mixed effect repeated measures (MERM) regression will be used. VAS SPOM will be the dependent variable. The weeks 0 (baseline), 6, 12, 18, and 26 visits will be a fixed effect covariate. Subjects will be random effects. The correlation structure will be unstructured. If convergence is problematic then an alternative covariance structure will be necessary. A contrast will be constructed to test the hypothesis of a VAS SPOM reduction from baseline.

14.1.3.4. Trial success criteria

If the weeks 6, 12, 18, and 26 VAS SPOM least square mean versus week 0 (baseline) VAS SPOM least square mean contrast achieves the 0.05 type I error level of statistical significance this trial will be considered a success.

The mean VAS result at baseline is estimated to be 60 mm and that, a reduction in VAS result of 25%, i.e., 15 mm, will be achieved. The magnitude of the improvement in VAS was assumed to be equal between successive time points, i.e. the VAS results of 60, 55, 50 and 45 mm are expected at baseline, and Weeks 6, 12, 18 and 26, respectively.

The magnitude of what is considered a minimally clinically meaningful change from an individual patient perspective has been cited in the literature as 10-22% from baseline to endpoint following a given treatment as reported on the VAS instrument (Erich, et al., 2000; Dworkin, et al., 2008; Angst, et al., 2002). In this context, the established trial success criteria of a 25% reduction in pain from baseline values represents a clinically meaningful change in patients' pain as it exceeds this threshold range.

14.1.3.5. Secondary variables

The weeks 0, 6, 12, 18 and 26:

- VAS (0-100mm) SPAN
- ASES patient self-evaluation (PSE) Shoulder Score Index (SSI): (range: 0-100)
- VAS (0-100mm) PGA

- Shoulder pain rescue medication consumed (unit: average mg per week)

The weeks 0, 6, 12, and 26:

- ASES physician assessment (PA) range of motion (ROM): 5 questions (active and passive; total 10 assessments) (unit: degrees)

14.1.3.6. Exploratory variables

Exploratory ASES variables (patient self-evaluation only):

The weeks 0, 6, 12, 18 and 26:

- ASES PSE pain today: VAS (range: 0-10cm)
- ASES PSE activity of daily living: 10 questions (range: 0,1,2,3)

14.2. Sample Size Considerations

The sample size was estimated for a univariate one-way repeated measures ANOVA using method MOT2 in nQuery Advisor 7.0 statistical software. A sample size of 29 will be capable of detecting a reduction in mean VAS pain on movement score of 15 mm (25% reduction from a baseline mean of 60mm) over the course of the study with 80% power under the following assumptions:

Type I error rate, α,	= 0.05
Standard deviation within time point	= 25 mm
Correlation between visits	= 0.5
Mean VAS (0-100mm) results at:	
0 weeks (baseline)	= 60 mm
6 weeks	= 55 mm
12 weeks	= 50 mm
26 weeks	= 45 mm

Hence, when the sample size is 29, a single-group repeated measures analysis of variance with a 0.05 significance level will have at least 80% power to detect a difference in means across the 4 time-points for the individual subjects characterized by an effect size of 0.1 (i.e., a Variance of means, $V=\sum(\mu_i-\mu)^2/M$, of 31.25, a standard deviation at each time-point of 25 mm, and a constant between time-point correlation of 0.5).

Assuming a 20% drop-out rate a minimum of 36 subjects will be enrolled to maintain 80% power. It is noted that the sample size estimation does not include the week 18 time point.

14.3. Planned Interim Analyses

There are no planned interim analyses.

14.4. Statistical software

The analysis will be conducted using SAS® version 9.3 or higher statistical software.

15. STUDY DATA

Investigators should protect the source data of this clinical research to ensure a subject's rights and confidentiality. The investigator must give the monitor/auditor/inspector access to all relevant source documents to confirm their consistency with the CRF entries so source data and progression can be authenticated. If any data cannot be traced from source documents, investigators should help the monitor/auditor/inspector to confirm further information's quality control.

The Principal Investigator/Institution shall permit study-related monitoring, audits, REB review and regulatory inspections, and shall provide direct access to the source data/medical record as legally required.

The Sponsor shall verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). During the monitoring, the data recorded in the CRFs by the Investigator will be checked for consistency with the source documents/medical record by the study monitor (source data verification). Any discrepancies of data shall be documented, clarified by the Investigator in source documents and explained in the monitoring reports.

To be able to make source data verification, information about each subject's participation in the study must be detailed in the medical record.

The Source Data Location Log specifies what data that should be available in the medical record.

The Source Data Location Log should also specify the data for which the CRF serves as the source document. Such data only need to be recorded into the CRF and are typically associated with protocol-specific procedures and not with normal clinical care practice. For this type of study data, the Investigator would not be expected to duplicate the information into the medical record.

15.1. Study Monitoring

This study will be regularly monitored by the sponsor. To ensure compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements, the sponsor representative is responsible for monitoring that sites conduct the study according to the protocol, standard operating procedures, and other written instructions and regulatory guidelines. Monitoring visits by the sponsor representative will be arranged in advance, at a mutually-acceptable time, with site personnel. The site personnel must allow sufficient time for the sponsor representative to review CRFs and relevant source documents and queries. During recruitment, monitoring shall take place regularly according to a schedule planned jointly by the sponsor and the Investigator per the study monitoring plan. During these monitoring visits, the sponsor representative shall check the subject's information and consent forms, verify the completed CRF, compare the data recorded on these forms with the source data (verify there is no missing, incorrect, illegible data), and ensure that the study is conducted in compliance with the

trial protocol and Good Clinical Practice as put forth in the ICH Guidelines. The Investigator and/or his/her team must be available to answer questions and or resolve data clarifications. During this interview, the Investigator will also be available to make any corrections to the CRFs (these will be clearly marked and the amendment must be dated and signed by the Investigator).

The verification of data recorded in CRFs compared with the source data will cover at least the following data:

- Date of signing of the consent form by the subject,
- Confirmation of the diagnosis of the indication required for the study,
- Inclusion/Exclusion Criteria check,
- Participation of the subject in this study must be mentioned in his or her medical file,
- Outcome measures,
- Any adverse event, serious or not, observed or reported by the subject,
- Concomitant treatments.

The sponsor representative shall verify the correct use of the investigational product.

At the end of the study, a final inspection is carried out during which the sponsor representative shall finalize the monitoring, update the paperwork, verify the remaining products, and organize the return of these products to the Sponsor.

The sponsor representative will verify at each review, that all AEs observed during the study have been reported promptly to the Sponsor and/or REB, if applicable.

15.2. Audits and Inspections

Quality assurance audits of this trial may be conducted by the sponsor or a mandated auditor. GCP audits can also be performed by the authorities. The quality assurance auditor should have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation that is relevant to this clinical trial.

The Sponsor may organize an audit inspection to ensure the successful completion of the study and to verify the documents related to the study. The Investigator shall be informed of the results of this audit.

In addition, representatives from a Competent Authority, Research Ethics Board, or appointed Notified Body may inspect the trial center at any time. The Investigator shall immediately inform the Sponsor as soon as he or she is aware that an audit will take place.

The investigator is responsible to ensure the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Copies of the CRF will be provided for use and maintained for recording data for each subject enrolled in the study. Data reported in the

CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained. The investigator must provide formal approval of all subject information in the CRFs and changes to the CRFs to endorse the final submitted data for the subjects for which he or she is responsible. The audit trail entry shall show the user's identification information and the date and time of any corrections.

CRFs should be completed in a timely manner and every effort should be made to have forms completed and up-to-date in anticipation of a visit by the Sponsor's monitor or designee. Specific instructions will be provided to each site. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it should be documented as such.

CRF completion may be delegated to other study personnel; however, such delegation must be documented in writing. If, for any reason, certain data are lacking to complete an individual report form, the investigator will provide a written statement explaining the reasons for the lack of data.

Sponsor or designee will retain the CRF data and corresponding audit trails.

15.3. Inspection of Records

Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the investigational product storage area, investigational product stocks, investigational product accountability records, subject charts and study source documents, and other records relative to study conduct.

15.4. Retention of Records

The Investigator and Sponsor must retain essential study documents until at least five years after the last marketing approval of the investigational product, or 15 years after the conduct of the study is complete, whichever is longer. In this case, the Investigator is required to keep documents for 15 years. For discontinued product, the essential documents will be retained until at least two years have elapsed since the formal discontinuation (via notification of the appropriate regulatory agency). The Investigator will retain these documents for a longer period if required by the applicable local laws.

If an Investigator is unable to hold these records in his or her archives, the Investigator must ask the Sponsor for permission to make alternative arrangements. If an Investigator leaves the institution at which the study was conducted, another responsible party must be designated to maintain the records. Details of these arrangements must be documented in writing to the Sponsor.

16. ETHICS

16.1. Ethical Standards

The trial will be carried out in accordance with the principles stated in the Declaration of Helsinki (5th revision, 2000), and in accordance with ICH-GCP, ISO 14155, and applicable regulatory requirements.

16.2. Research Ethics Board (REB)

The Sponsor or designee will supply all necessary information to the Investigator for submission of the protocol and consent form to the REB for review and approval. The Investigator agrees to provide the REB all appropriate material. The trial may not commence until the Investigator has obtained appropriate REB approval. A copy of the approval letter and approved consent form must be submitted to the Sponsor. The Investigator will request from the REB a composition of the members reviewing the protocol and informed consent.

The Investigator is responsible for checking what reporting procedures are applicable for his/her REB regarding serious AEs and other reports, and to comply with such reporting procedures during the study period. The Sponsor will notify the site when the REB may be notified of study completion. The Investigator is responsible for notifying the REB when the study ends. This includes study discontinuation, whether it is permanent or temporary. The Investigator shall then send a copy of the site REB's acknowledgement of study completion to the Sponsor.

The Investigator will discuss any proposed protocol changes with the Sponsor and no modifications will be made without prior written approval by the Sponsor, except where clinical judgment requires an immediate change for reasons of subject welfare. The REB will be informed of any amendments to the protocol or consent form, and approval, when appropriate, will be obtained before implementation. No protocol amendments are allowed without REB approval.

16.3. Written Informed Consent

The Principal Investigator or his/her designated representative, is responsible for obtaining informed consent from each subject prior to initiation of any study procedures, including screening assessments, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The subject must be informed about his/her right to withdraw from the study at any time, and that such withdrawal will not affect his/her future medical care, treatment or benefits to which the subject is otherwise entitled.

In obtaining and documenting informed consent, the investigator should comply with any applicable regulatory requirements, and should adhere to ICH-GCP and the Declaration of Helsinki.

Before informed consent is obtained the subject should be allowed ample time and opportunity to read the subject information, to enquire about details of the trial, and to decide whether or not to participate.

If the subject wishes to participate, the written ICF should be completed as appropriate and then signed and personally dated by the subject and the Investigator or authorized designee who conducted the informed consent discussions. The Investigator will countersign and date if a designee conducted the informed consent. A copy of the signed and dated written informed consent and any other written information must be provided to the subject prior to participation in the trial. Similarly, the subject should also receive copies of any consent form updates or new information during the trial.

The Investigator will confirm the receipt of informed consent from each subject by a recording in the CRF. The signed ICFs shall be filed in the Investigator File for possible future audits and inspections.

If the investigator uses a device without obtaining informed consent, the investigator shall submit a protocol deviation report indicating the circumstances for the occurrence to the Sponsor and to the reviewing REB within applicable timelines after the use occurs.

16.4. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. All CRFs identify subjects through unique subject identifiers and subject initials. No date of birth, subject names, addresses or contact details will be transferred to the Sponsor.

16.5. Study Discontinuation Notification

In the event of premature termination or suspension of the study, the Sponsor will promptly inform the investigator / hospital, the Competent Authorities and ethics board, stating the reasons for this decision. The subjects will be informed as soon as possible by the Investigator of study discontinuation. Any unresolved AE will be reviewed per Section 13. The Sponsor or authorized representative will schedule site close-out visit as soon as practicable.

Following the completion of the study, Sponsor or authorized representative will conduct a closeout visit to ensure that all data queries have been resolved, any protocol deviations are documented appropriately, all possible study data have been retrieved,

that study treatment and clinical supplies have been/will be properly returned to the Sponsor and that the Investigator has copies of all study-related data/information on file.

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APPENDICES

APPENDIX 1. PERMITTED TREATMENTS/MEDICATIONS

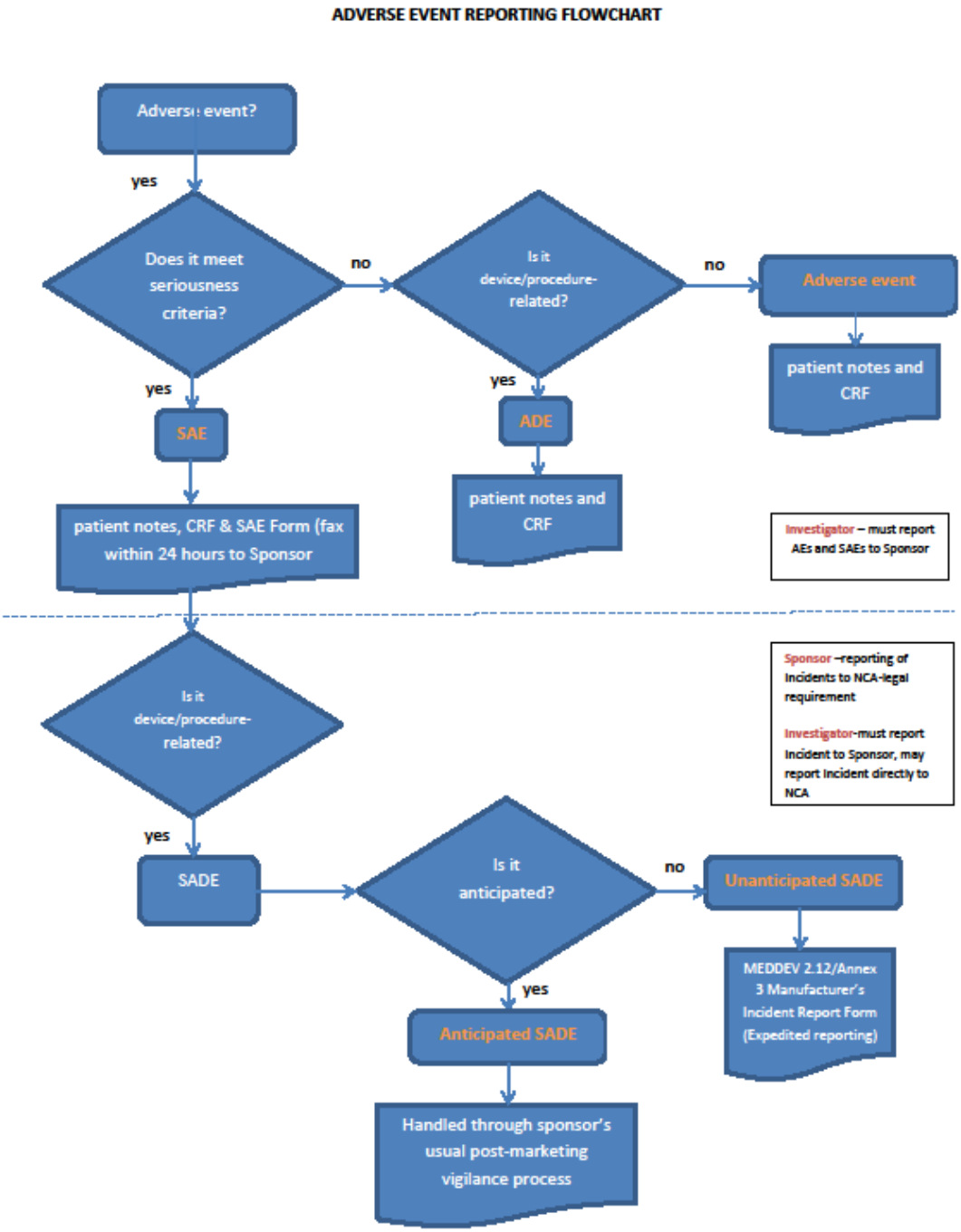
Treatments Allowed	Restrictions
Any treatment for a pre-existing condition, outside the study indication.	Subject has to have met the inclusion/exclusion criteria. Treatment must not be listed as prohibited.
Rescue medication: Acetaminophen	Not to exceed 4g/day and not taken within 24 hours prior to visit.
Low dose ASA anticoagulant therapy	Not to exceed 325mg/day
Topical corticosteroids for skin irritations	Allowed at any site other than the study shoulder
Inhaled corticosteroids for pulmonary disease	None
Nonpharmacologic therapy (including physical therapy)	Allowable if started before Screening, not to be initiated or substantially altered during the study except for discontinuation

APPENDIX 2. PROHIBITED TREATMENTS/MEDICATIONS

Prohibited Treatments/Medications	Restriction
Pain medications other than acetaminophen	Beginning at screening and lasting throughout the duration of the trial (or study discontinuation)
Chronic use of narcotics	
Systemic corticosteroids (oral or injected)	
Any planned surgical procedure	
Heparin or anti-vitamin K (e.g., crystalline warfarin) anticoagulant therapy	
Viscosupplementation injected into any joint other than as required by the protocol	
Local corticosteroid injection into any joint or periarticular structure	Within 3 months prior to Screening
Previous IA injection/s with hyaluronic acid in the study shoulder	Within 9 months prior to Screening
Any investigational drug, device or biologic	Within 30 days prior to Screening and lasting throughout the duration of the trial (other than as required by the protocol)
Physical therapy for the lower extremities	May not be initiated during the study

APPENDIX 3. DEVICE SAFETY AND VIGILANCE GUIDELINES

APPENDIX 4. ADVERSE EVENT REPORTING FLOWCHART



APPENDIX 5. INSTRUCTIONS FOR USE

APPENDIX 6. OSTEOARTHRITIS CLASSIFICATION SYSTEMS

Osteoarthritis is diagnosed if subject presents with shoulder pain plus ≥3 of 6 clinical findings:

1. age>50 years

morning stiffness>30 minutes duration

crepitus on active motion

tenderness of the bony margins of the joint

bony enlargement noted on examination

a lack of palpable warmth of the synovium