A Pivotal Study Comparing Two Injections of MONOVISC to Two Injections of Saline in Patients with Osteoarthritis of the Hip

SHORT TITLE: The MONOVISC Hip OA IDE Study

Protocol Number 15-MVH-01

Version 4: 30-OCTOBER-2017

Amendment 3

Clinical Sponsor:

DePuy Synthes Mitek Sports Medicine

325 Paramount Drive

Raynham, MA 02767

Investigator Signature Page

I certify that I have read and understand the following clinical study protocol "A Pivotal Study Comparing Two Injections of MONOVISC to Two Injections of Saline in Patients with Osteoarthritis of the Hip". I agree to comply with the protocol in accordance with 21 CFR Parts 812, 50, 54, 56 as well as Good Clinical Practices (GCP) and ISO 14155 and the relevant articles of the Declaration of Helsinki, using the investigational products, as indicated. All data relevant to the clinical evaluation and regarding the subject response and safety will be documented and forwarded to DePuy Synthes Mitek Sports Medicine.

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Signature of Principal Investigator: **Date**

Printed Name

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1.0 STUDY SUMMARY

Clinical Sponsor	DePuy Synthes Mitek Sports Medicine
Title	A Pivotal Study Comparing Two Injections of MONOVISC to Two Injections of Saline in Patients with Osteoarthritis of the Hip
Short Title	The MONOVISC Hip OA IDE Study
Protocol Number	15-MVH-01
Active Treatment	Two (2) intra-articular injections of 4 ml MONOVISC, separated by 1 month
Control Treatment	Two (2) intra-articular injections of 4 ml saline, separated by 1 month
Study Design	Prospective, multicenter, randomized (2:1), controlled, double-blind, superiority study
Study Population	Subjects suffering from mild to moderate hip osteoarthritis pain
Number of Subjects	Up to 560
Number of Sites	Up to 40 (U.S., Europe, Canada)
Enrollment Timeframe	Approximately 2.5 years (30 months)
Subject Follow-up	26 weeks (180 days)
Study Objective	To determine the difference in pain and functional improvement between the active and control treatments
Endpoints:	**Primary:** Walking pain change from baseline at 26 weeks (WOMAC A1). *The WOMAC questionnaire used in this study will be administered in the NRS (Numerical Rating Scale) format.* The primary endpoint analysis will be based upon a longitudinal model of all primary endpoint (WOMAC A1 change from baseline) data from 2 weeks through 26 weeks; the adjusted means at 26 weeks from this longitudinal model will be compared. **Secondary:** • Walking pain change from baseline at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A1 score. **Tertiary:** • Walking pain at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A1 score. • Area-under-curve (AUC) analysis of walking pain change from baseline using longitudinal model over time comparing treatment vs. control • Pain at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A (pain) score.

	• Pain improvement from baseline at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A (pain) score. • Total WOMAC (pain, function, stiffness) score at the 2, 4, 8, 16 and 26 week time points. • Improvement from baseline in Total WOMAC (pain, function, stiffness) score at the 2, 4, 8, 16 and 26 week time points. • OMERACT-OARSI responder rate at the 2, 4, 8, 16 and 26 week time points. • Patient Global Assessment (PGA) at the 2, 4, 8, 16, and 26 week time points. • SF-12 outcomes at study defined time-points • Rescue medicine consumption (acetaminophen) from baseline through week 26 **Safety:** • Comparison of adverse events between MONOVISC and saline groups.
Sample Size Justification:	A sample size was calculated that would provide 80% power for demonstrating superiority in WOMAC A1 (walking pain) change from baseline at 26 weeks; it is anticipated that there will be a difference of at least 0.6 NRS between MONOVISC and Saline subjects, and that both groups will have a standard deviation of 2.2 NRS. The required sample size is 477 with 2:1 randomization (318 MONOVISC / 159 Saline). This was increased to 374 MONOVSIC / 186 Saline (560 patients total) to accommodate up to 15% attrition.
Interim data analysis:	The primary endpoint will be assessed after 74 MONOVISC and 37 Saline Subjects have completed their 26 week visit. The study will be terminated if the separation (point estimate) between MONOVISC and saline is less than 0.4 NRS for the primary endpoint of WOMAC A1 walking pain change from baseline in both the Per Protocol Analysis Set for the 26 week interval and the As Treated Analysis Set for the 26 week interval. Enrollment will continue throughout the time preceding and during the interim analysis.

1.1 TIME AND EVENTS SCHEDULE

Visit #	1	2	3	4	5	6	7	
Interval	**Patient Screening**	**Baseline * & Injection #1 Day 0**	**Day 14**	**Injection #2 Day 28**	**Day 60**	**Day 120**	**Day 180**	**Unscheduled visit**
Range		**Within 30 days of screening***	**±3 Days**	**±7 Days**	**±14 Days**	**±14 Days**	**±21 Days**	**N/A**
Informed Consent	X	X**	X**	X**	X**	X**	X**	X**
Demographics & Medical History	X							
General Exam	X	X	X	X	X	X	X	X
Pregnancy Test***	X							
Randomization		X						
Hip X-ray (within 6 months of screening)	X							
Injection MONOVISC OR Injection Saline		X		X				
NRS Walking Pain	X							
WOMAC - NRS		X	X	X	X	X	X	X
Patient Global Assessment		X	X	X	X	X	X	X
SF-12		X	X	X	X	X	X	X
Medication Status (patient diary)			X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X
Adverse Events / Secondary Procedures		X^	X^	X^	X^	X^	X^	X^

* All baseline evaluations and Injection #1 must be completed on the say day
** Re-consent only as required by EC/IRB
*** Female subjects only

^ AE evaluation during injections (Visits 1 & 4) will be performed by Injecting Investigator. Non-injection AE evaluation during follow up visits will be performed by Blinded Investigator.

2.0 INTRODUCTION

2.1 Background

Intra-articular injections of hyaluronic acid (HA), commonly referred to as viscosupplementation, have been an FDA approved therapy for knee osteoarthritis since 1997. These products are indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen). Currently there are five HA products on the US market that are indicated as 3-5 injection therapies, with injections given one week apart (Orthovisc, Euflexxa, Supartz, Hyalgan, and Synvisc). Three products are indicated as single injection therapies (MONOVISC, GelOne, and Synvisc One).

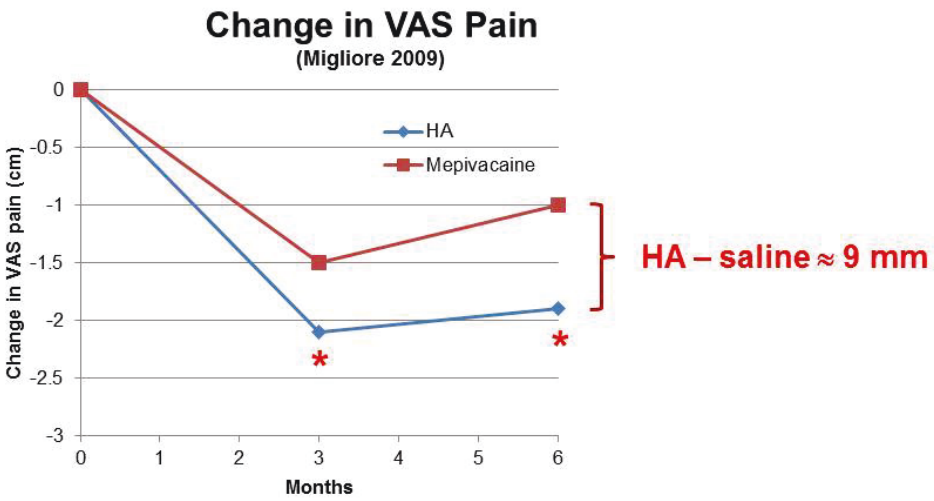
Surprisingly, while weekly injections are considered the standard for multiple injection HA products for knee OA, the literature offers no evidence that this regimen is optimal. The history of viscosupplementation, which began with the treatment of thoroughbred racehorses, suggests that weekly injections evolved out of convenience, rather than through clinical optimization of injection timing. *The present study will use monthly, rather than weekly, HA injections for the treatment of osteoarthritis of the hip.*

2.1.1 Hyaluronic Acid Therapy for Hip Osteoarthritis

Several randomized, controlled clinical trials have been published on the use of intra-articular injections of hyaluronic acid (HA) for the treatment of hip osteoarthritis (1-6). Study designs are inconsistent with regards to number of injections (ranging from 1 to 3), timing of injections (weekly, biweekly, or monthly), and clinical comparator (saline, steroid, standard of care, multiple HA products). The HA formulations used in these studies also vary considerably (cross-linked vs non-cross-linked, HA concentration, HA molecular weight).

Two published trials have attempted to demonstrate efficacy of a single HA injection in comparison to saline (Richette 2009, Atchia 2011). In both trials, the efficacy of a single HA injection was not significantly different from that of the saline comparator. Moreover, the small improvement of HA over saline was of such small magnitude that even a much larger trial would not have been able to detect a statistically or clinically meaningful difference.

Qvistgaard (2006) reported encouraging results using a series of three ultrasound-guided HA injections in comparison to steroid and saline injections. While most multi-injection HA products are FDA approved for weekly injections, this study employed three HA injections separated by two weeks. Similarly, Spitzer (2010) used two biweekly injections of HA to demonstrate comparable efficacy to corticosteroid injection, with patients that had more advanced disease responding better to the HA therapy. Migliore (2009) reported the most promising results to date for HA injections in the hip, using two injections of HA separated by one month. Compared to the intra-articular anesthetic comparator, improvement from baseline pain for patients treated with HA was significantly greater, despite a relatively small patient population (22 HA/20 control). VAS pain improvement for both groups is shown below, and was significant at both the 3 and 6 month time points.



The studies described above suggest that multiple injections of intra-articular HA could show significant efficacy in the treatment of hip OA. Results also suggest that increasing the time between injections from the current one-week standard may provide more long term pain relief. However, the impact of HA injectate composition remains uncertain. Published studies report HA formulations having a wide range of HA concentrations (8 – 15 mg/ml). Molecular weight also varies considerably. Qvistgaard et. al. used Hyalgan, which has a molecular weight range of 0.5-0.73 million Daltons. Spitzer used Synvisc, which comprises a fluid component with HA molecular weight of 6 million Daltons and a crosslinked gel component with essentially infinite molecular weight. Migliore used a non-crosslinked HA (Hyalubrix) with a molecular weight range of 1.5 – 3.2 million Daltons. Both Hyalgan and Synvisc contain HA derived from rooster combs, while Hyalubrix contains HA derived from bacterial fermentation.

MONOVISC™ is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen). It contains bacterially derived HA having a concentration of 22 mg/ml, giving it a significantly higher concentration than other HA products that have been used in hip OA trials. Its HA molecular weight range of 1.0 – 2.9 MDa is similar to that used in the successful trial by Milgliore et al. For knee OA, MONOVISC is indicated as a single injection therapy, with additional treatments administered every six months.

*For the present hip OA study, **two monthly** injections of MONOVISC will be administered.*

3.0 BENEFITS / RISKS

3.1 Benefits

Intra-articular injections of MONOVISC and other hyaluronic acid viscosupplements have shown significant clinical benefits for many knee osteoarthritis patients. It is anticipated that such benefits may result from the use of MONOVISC to treat hip OA pain.

3.2 Risks

Any intra-articular injection poses potential risks, and the procedures in this trial are no exception. However, subjects should incur no additional risks compared to injections of other frequently injected products, such as corticosteroids or diagnostic contrast agents.

Adverse events associated with single intra-articular knee injections of MONOVISC can be found in the MONOVISC Package Insert (7). These events are expected to be similar for hip injections. In the clinical trial for MONOVISC, adverse events that were related to the injection treatment were:

- injection site pain/swelling
- joint stiffness / swelling / effusion
- arthralgia, or aggravated osteoarthritis
- pain in extremity
- synovitis
- contusion
- subcutaneous nodule
- Baker's cyst

The above risks may be elevated in the present study since the protocol calls for two injections of MONOVISC rather than one injection.

Adverse events not related to the index knee for MONOVISC were:

- arthralgia
- headache
- pain in extremity
- upper respiratory tract infection
- back pain

The frequency of all of the above AEs for MONOVISC was similar to the AEs for the saline group (7).

Other risks associated with intra-articular hip injections, regardless of treatment, include:

- temporary injection site pain, swelling or tenderness
- temporary stiffness of the hip
- malfunction of the syringe and/or needle

In rare instances, side effects could include:

- an allergic reaction to the fluoroscopic imaging contrast agent. Symptoms could include redness or inflammation at the injection site or inside the hip joint, hives or itching.

- an allergic reaction to the local anesthetic (lidocaine). Symptoms could include redness or inflammation at the injection site or inside the hip joint, hives or itching.
- injection site infection
- neurovascular, cartilage, or bone damage resulting from the injection itself

Finally, there is a low risk associated with radiation from the X-ray evaluation required for inclusion in the study. There is also a low risk from the radiation during fluoroscopy-guided injections

4.0 Objectives and Hypotheses

The primary objective of this study is determine whether two intra-articular injections of MONOVISC, separated by 1 month, are superior to two intra-articular injections of physiologic saline, separated by 1 month, in relieving hip osteoarthritis pain, as determined by reduction in walking pain change from baseline.

We hypothesize that two (2) monthly injections of MONOVISC will be an effective treatment regimen for hip OA patients.

5.0 Study Device

The proposed device for this study is MONOVISC High Molecular Weight Hyaluronan. It is currently FDA approved for the treatment of osteoarthritis of the knee. Its primary component is hyaluronic acid (HA), a polysaccharide which is naturally found in the synovial fluid of articulating joints. The synovial fluid in osteoarthritic joints has been shown to have deficiencies in HA concentration and rheological properties when compared to fluid from non-arthritic joints (8). Replenishment of HA through intra-articular injections, often referred to as viscosupplementation, has been demonstrated in multiple trials to relieve pain in patients with mild-to-moderate osteoarthritis pain. In these trials, HA has demonstrated an excellent safety profile.

MONOVISC is a sterile, non-pyrogenic, clear, viscoelastic solution of hyaluronic acid contained in a single use 5 ml glass syringe (see image below). The concentration of HA in MONOVISC is 22 mg/ml, with a molecular weight range of 1.0 – 2.9 MDa. The injectate volume is 4 ml. The glass syringe can be fitted with a needle (18-20 gauge) prior to injection.

The MONOVISC and saline injections will be provided in identical 5 ml syringes, with labeling to conceal the identity of the syringe contents from the patient and the Investigators.

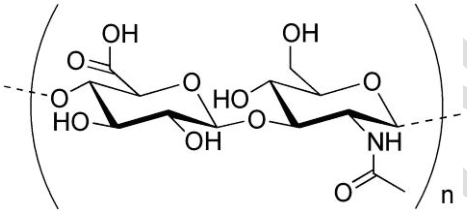
5.1 Indication for Use

MONOVISC is being investigated for the treatment of pain in patients with mild to moderate osteoarthritis (OA) of the hip.

5.2 Component Materials

5.2.1 Hyaluronic Acid

Hyaluronic acid (HA), also known as hyaluronan or hyaluronate, is a high molecular weight glycosaminoglycan (GAG) composed of continuously repeating molecular sequences of glucuronic acid and N-acetyl-glucosamine(8). The molecular structure of hyaluronic acid is shown below.



As the repeat unit comprises a disaccharide, HA can also be described as a polysaccharide. HA is usually manufactured as the sodium salt because of the presence of a carboxylic acid group in the glucuronic acid moiety. Saline is used instead of pure water as the solvent for HA to impart isotonicity. The HA contained in MONOVISC is produced by fermentation of the bacterium *streptococcus equi.* It is lightly crosslinked using a proprietary crosslinker.

HA is common to many tissues of the body, including extracellular matrix, vitreous humor, and synovial fluid. In cartilage, it is part of the proteoglycan aggregate that is responsible for maintaining the high water content of cartilage. It is the most prominent component of synovial fluid, in which its functions are believed to include lubrication of the cartilage surface and shock absorption during physical activity. In the arthritic joint, the concentration and molecular weight of endogenous hyaluronic acid are decreased by 33% to 50%, thereby diminishing its ability to help maintain normal joint biomechanics, which in turn can lead to the hallmark signs of pain and loss of function in weight-bearing joints such as the knee and hip (8). Thus, the goal of intra-articular therapy with HA is to help restore synovial fluid that has lost its viscoelastic properties (9).

6.0 Study Design

This study is a prospective, multi-center, double-blinded, randomized, controlled, superiority study comparing intra-articular injections of MONOVISC High Molecular Weight Hyaluronan with intra-articular injections of physiologic saline. The study will take place at up to 40

investigational sites, primarily in the United States. Additional sites may be added in Canada and/or Europe. Subjects will be randomized through a 2:1 schema to receive either two (2) injections of 4 ml of MONOVISC, separated by 1 month (active treatment), or two (2) monthly injections of 4 ml of saline, separated by 1 month (control treatment).

Subjects will return for follow-up visits at 2, 4, 8, 16, and 26 weeks after the first injection.

The primary endpoint will be pain during walking (WOMAC A1) change from baseline at the 26 week time point.

An interim analysis of the primary endpoint will be conducted after 74 MONOVISC and 37 saline subjects have received both injections of MONOVISC or saline and completed their per protocol 26 week follow up visit. A stopping rule for futility will be implemented, such that the study will be terminated if the improvement of MONOVISC over saline (change from baseline) is less than 0.4 on a 10 point Numerical Rating Scale (NRS) in both the Per Protocol Analysis Set for the 26 week interval and the As Treated Analysis Set for the 26 week interval. If the improvement of MONOVISC over saline (change from baseline) is more than 0.4 NRS in either of these analysis sets, the study will continue to completion.

6.1 Rationale

While hyaluronic acid therapy for knee OA has been FDA approved since 1997, HA injections for hip OA are still not an approved indication. Per FDA guidelines, the efficacy of HA therapy in the hip must be demonstrated in a clinical trial before it can be designated as an approved indication. As mentioned previously, several small studies have shown promise, despite inconsistencies in methodology and HA formulation.

6.2 Injection Regimen

The intra-articular HA injection regimen in the present study represents a departure from conventional HA dosing. Rather than a single injection of HA or a series of weekly HA injections, a regimen of *two (2) HA injections separated by one (1) month* will be implemented in this study.

Injections must be given using image guidance to insure delivery of MONOVISC into the hip joint. Either ultrasound or fluoroscopy may be used. ***However, each site should use the same image guidance method for all patients treated at that site.***

6.3 Study Population

This study will be restricted to adult patients with mild to moderate hip osteoarthritis, as measured by Kellgren/Lawrence score. Up to 560 patients will be treated in a 2:1 randomization scheme. Such patients have been shown to derive the greatest benefit from HA therapy in previous studies of patients with knee OA, and are the indicated patient population for currently marketed HA therapies. Only patients with K-L Grades 2 and 3 hip OA will be included in the trial, such that beginning and end stage OA patients are excluded. Also, only patients reporting NRS walking pain of ≥ 4 and ≤ 8 will be included. These pain states were chosen to exclude patients with only minimal pain that can be addressed with conservative therapy, as well as those with end stage disease that are not likely to respond to HA therapy.

6.4 Follow-up

The study is designed for a follow-up period of six (6) months (26 weeks), based on the efficacy observed for HA in the knee, and in pilot studies of HA in the hip. The earliest time point is two weeks after the first injection, and is intended to capture early pain relief.

6.5 Comparator / Control

The comparator for this study is physiologic saline, which is the vehicle for the HA in Monovisc. Saline has been the standard control arm for viscosupplementation studies.

6.6 Endpoints

The clinical endpoints for this study are chosen to assess pain relief and functional improvement in the hip.

The choice of walking pain improvement as the primary endpoint was based on previous studies, both in the knee and hip, suggesting that HA impacts walking pain more than other pain states captured in the WOMAC instrument. Also, pain during and after walking is a major impediment to regular exercise for OA patients. By targeting walking pain change from baseline as an endpoint, this study design can potentially demonstrate indirect effects on overall patient health.

Endpoints for the study are as follows:

Primary:

Walking pain change from baseline at 26 weeks (WOMAC A1 – NRS format).

The WOMAC questionnaire used in this study will be administered in the NRS (Numerical Rating Scale) format.

The primary endpoint analysis will be based upon a longitudinal model of all primary endpoint (WOMAC A1 change from baseline) data from 2 weeks through 26 weeks; the adjusted means at 26 weeks from this longitudinal model at 26 weeks will be compared.

Secondary:

- Walking pain change from baseline at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A1 score.

Tertiary:

- Walking pain at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A1 score.
- Area-under-curve (AUC) analysis of walking pain change from baseline using longitudinal model over time comparing treatment vs. control.
- Pain at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A (pain) score.
- Pain improvement from baseline at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A (pain) score.
- Total WOMAC (pain, function, stiffness) score at the 2, 4, 8, 16 and 26 week time points.

- Improvement from baseline in Total WOMAC (pain, function, stiffness) score at the 2, 4, 8, 16 and 26 week time points.
- OMERACT-OARSI responder rate at the 2, 4, 8, 16 and 26 week time points.
- Patient Global Assessment (PGA) at the 2, 4, 8, 16, and 26 week time points.
- SF-12 outcomes at study defined time-points
- Change in work status
- Rescue medication consumption (acetaminophen) from baseline through week 26

Safety:

- Safety of the therapy will be assessed by comparing the incidence of adverse events in the treated vs the control group through 26 weeks post-injection, including AEs that occur during injection.

7.0 STUDY POPULATION

The study population will comprise adult subjects seeking treatment for osteoarthritis pain of the hip. Up to 560 patients will be treated in a 2:1 randomization scheme. Subjects will be considered enrolled in the study when they have met the inclusion/exclusion criteria and signed the informed consent form.

7.1 Inclusion Criteria

Candidates may be included if they meet **ALL** of the following:

1. Male or female ≥ 30 years old
2. Body Mass Index (BMI) ≤ 35
3. Clinical or radiographic diagnosis of hip osteoarthritis in the target hip, with a Kellgren-Lawrence (K/L) grade of 2 or 3.
4. Walking pain NRS ≥ 4 and ≤ 8.
5. Willing to discontinue all pain medications (except rescue medication) for 7 days prior to the first study injection and for the duration of the study.
6. Willing to discontinue rescue medication for 48 hours prior to the first study injection.
7. Willing to discontinue rescue medication for 48 hours prior to all follow-up visits
8. Ability to tolerate acetaminophen (e.g. Tylenol).
9. Must be physically and mentally willing and able to comply with pre and post-treatment scheduled clinical and radiographic evaluations
10. Must voluntarily sign the Institutional Review Board approved Informed Consent Form.
11. Must agree not to initiate cannabis therapy during the trial study period.

7.2 Exclusion Criteria

Candidates will be excluded if they meet **ANY** of the following:

1. Radiographic evidence of osteonecrosis in the target hip
2. NRS walking pain ≥ 3 the contralateral hip

3. Clinically diagnosed osteoarthritis in either knee resulting in walking pain greater than NRS 5.
4. Dependence on external stabilization for walking (e.g. cane, crutches, walker, etc.)
5. Pain associated with lower back disorders that cannot be differentiated from target hip pain
6. Major dysplasia or congenital abnormality
7. Diagnosis of fibromyalgia
8. Primary inflammatory arthropathy, or any other condition affecting the joint, including rheumatoid arthritis or gout in the target hip
9. Any musculoskeletal condition that could impede efficacy measurement of the target hip
10. Any major surgery, arthroplasty, or arthroscopy of the lower extremities in the past 6 months, or planned surgery during the study
11. Infection of the injection site area
12. Chronic skin disorders that could interfere with injection site evaluation
13. Patients with asthma who require systemic use of corticosteroids
14. Septic arthritis in any joint in the past 12 weeks
15. For all patients: known hypersensitivity to hyaluronan, lidocaine, or acetaminophen
16. For patients undergoing fluoroscopic injection guidance: known hypersensitivity to iodine-based fluoroscopic contrast agents, shellfish, or iodine
17. Intra-articular steroid injection of the target hip within the last 3 months or hyaluronan injection of the target hip within the last 26 weeks
18. Systemic corticosteroids within the last 12 weeks
19. Glucosamine and/or chondroitin sulfate within last 4 weeks
20. Currently on anticoagulation therapy, including aspirin therapy of > 81 mg/day (e.g. one daily “baby aspirin”).
21. Uncontrolled diabetes mellitus.
22. Pregnant or breast feeding, or plan to be pregnant during the course of the study
23. Any significant illness (metastasis of any type) that decreases the probability of the subject’s survival to the 26 week endpoint
24. Patients unwilling/unable to complete a pain/function and quality of life questionnaires
25. Significant trauma to the index hip within 26 weeks of screening
26. Is receiving workman’s compensation, or is currently involved in litigation relating to hip osteoarthritis
27. Is receiving prescription pain medication for conditions unrelated to hip osteoarthritis
28. Chronic use of narcotics
29. Unwilling to return for follow-up visits as described in this protocol
30. Otherwise determined by the investigator to be medically unsuitable for participation in this study

8.0 Study Procedures

8.1 Patient Screening (Visit #1)

A qualified member of the Investigator’s team will meet with the potential subject and review the patient’s medical history to screen for study eligibility. Prior to performing any screening procedures, the patient must sign the Informed Consent Form.

Clinical Assessment:

A complete history will be documented on the Demographic / Physical History CRF. Data collected will include but not be limited to:

- Date of birth, gender, ethnicity, race, height, weight
- History of concurrent or previous medical illness
- History of previous treatment received to the index hip

Evaluation Assessment by either the ***Injecting*** *or* ***Blinded*** Investigator (see section 12.1.1):
A complete evaluation will be documented on the Screening CRF. Data collection and procedures will include:

- General medical exam
- Work status

Each subject will assess their current level of pain during walking using the Numerical Rating Scale (NRS). If the patient reports a walking pain score ≥ 4 and ≤ 8, they may be eligible for the study.

8.2 X-ray Imaging

Patients that meet all non-radiographic inclusion/exclusion criteria must have X-rays to determine the severity of osteoarthritis in the target hip. Weight bearing, anterior-posterior (A-P) pelvic images of the hip will be acquired according to an image acquisition protocol (IAP) and transferred to a third-party imaging vendor using an image transfer protocol (ITP). Alternatively, A-P X-rays collected within 6 months prior to patient screening may be submitted using the ITP. The imaging vendor will provide a Kellgren-Lawrence (K/L) score for the patient. The K/L score will be entered in the X-Ray CRF. If all imaging criteria are met, they will be eligible to participate in the trial.

8.3 Washout Periods / Medications

Subjects will be advised that the only pain medication that they are allowed to take during this study will be acetaminophen (e.g. Tylenol), with doses not to exceed 4,000 mg/day. This should be considered rescue pain medication, and should be taken only as needed.

All subjects will be asked to refrain from taking any pain medication, except for rescue medication, for 7 days (washout period) prior to their first injection, and no pain medication of any kind should be taken for 48 hours prior to the first injection. These washout periods allow for adequate baseline pain evaluation. Subjects will be asked to keep a Medication Diary beginning after their first injection, and for the duration of their follow-up visits.

All subjects will be asked to refrain from taking any pain medication for 48 hours preceding each clinical follow-up visit to allow for adequate pain evaluation (wash-out).

8.4 Patient Compensation

Funding will be made available for patient stipends to help defray transportation and other costs associated with the follow-up visits (e.g. mileage, parking, public transportation). A maximum of $50 per visit will be allowable for each visit.

8.5 Baseline / Randomization / Injection #1 (Day 0, Visit #2)

Baseline assessment, patient randomization and Injection #1 must be performed within 30 days of the screening visit, and should be performed on the same day

The following will be performed after the subject has signed the EC/IRB approved Informed Consent form:

A review and reconfirmation of the Inclusion/Exclusion criteria obtained at the initial screening visit will be completed by a designated member of the study team. Confirmation that subject has complied with the washout period for all pain medications for a period of at least 7 days, and 48 hours for acetaminophen, will be documented. In addition, if subject is a female of childbearing potential, she must have a negative pregnancy test, or document her inability to become pregnant (e.g. surgically sterile). Confirmation of K-L grade 2/3 hip OA should be performed before the baseline visit. Subjects who maintain study qualification will be randomized to receive either MONOVISC or Saline.

Evaluation Assessment by either the ***Injecting*** *or* ***Blinded*** Investigator (see section 12.1.1):
A complete evaluation will be documented on the Screening CRF. Data collection and procedures will include:

- General medical exam
- Work status
- Current medication consumption

Each subject will then complete the following self-report questionnaires:

- Western Ontario MacMaster (WOMAC)
- Patient Global Assessment (PGA)
- SF-12

8.5.1 Randomization & Injection

Prior to the start of the study, a computer generated random list of treatment assignments (Master Randomization List) will be created using a 2:1 schema to either MONOVISC or saline injection, and patient kits of MONOVISC and saline will be sequentially numbered according to this list. Investigational sites will be provided with an initial, sequentially numbered quantity of kits to be used, and as these kits are utilized, additional quantities of sequentially numbered kits can be ordered by the site. With this randomization scheme, each study subject will be associated with a unique kit number, and the order of randomized subjects at each investigational site will be distinct. The syringe contents will be physically blinded. However, due to the difference in syringe plunger pressure required to eject MONOVISC compared to saline, the Investigator performing the injections will likely know whether they are injecting MONOVISC or saline. As such, a designated Injecting Investigator will be responsible for the injection of either MONOVISC or saline. Non-injecting Blinded Investigators will perform all follow-up evaluations to ensure that blinding is maintained. However, Injecting Investigators may participate in screening and pre-injection baseline evaluations.

Final enrollment anticipated:

- 374 subjects receiving two 4-mL injections of MONOVISC, separated by 1 month (active treatment)

- 186 subjects receiving two 4-mL injections of saline, separated by 1 month (control)

All clinical research and biostatistics personnel at DePuy Synthes Mitek Sports Medicine will remain blinded to treatment assignment until the end of the study. An employee within Strategic Medical Affairs will be designated to maintain the Master Randomization, to facilitate any medical safety reviews, if necessary, and to facilitate the planned interim futility analysis. This individual will be authorized to unblind a site for any patient in the event of an Adverse Event that requires treatment.

The Injecting Investigator will obtain the next sequentially numbered patient kit from the secure storage area. The kit will not contain any labeling to indicate whether the patient is receiving MONOVISC or Saline. If the Investigator discovers the presence of a condition at the time of injection that would render the subject ineligible for study participation, the subject should not be injected and will be considered a screen fail; the patient kit will be returned to the storage area to be used with the next study subject. The ineligible subject should then receive the standard of care as determined by the enrolling Investigator. The reason for subject ineligibility will be documented on the Screening and Enrollment Log.

Prior to injection, sterile drapes or other suitable means should be used to block the patient's view of the injection and the imaging monitor. Under fluoroscopic or ultrasound guidance, the patient will receive an intra-articular hip injection of either MONOVISC or saline. Injection technique should follow established procedures for IA hip injection, such as those used for injections of corticosteroid or imaging contrast agents. Details of a typical image-guided injection procedure are described in Appendix C.

> *During intra-articular hip injections, it is common to use extension tubing to connect the syringe to the needle. However, due to the high viscosity of MONOVISC, it can be very difficult to inject the solution through such tubing. Moreover, some of the injected liquid can remain in the tubing rather than being injected into the joint.* ***For these reasons, extension tubing should not be used for the intra-articular injections in this study.***

The Injecting Investigator will evaluate and report any Adverse Events that occur as part of the injection procedure.

Identical post-injection instructions will be given to all subjects, regardless of randomization. Patients will be advised to refrain from rigorous physical activity for 48 hours post-injection. All subjects will be permitted to take acetaminophen (e.g. Tylenol) only (through the 26 week follow-up visit) if necessary, for the control of injection site pain or for general joint pain, at a maximum rate of 4000 mg in a 24 hour period. Acetaminophen use will be monitored at each subsequent follow-up visit as self-reported by the subject (Sec. 8.3)

8.6 Follow-Up Visits – No injections (Visits 3, 5, 6 & 7)

Post-injection follow-up visits, with no injections, will occur on Days 14 ± 3, 60 ± 14, 120 ± 14, and 180 ± 21 (Visits 3, 5, 6 and 7). At each visit, each subject will complete the following self-report questionnaires:

- Western Ontario MacMaster (WOMAC)
- Patient Global Assessment (PGA)
- SF-12

The patient will also submit their completed patient diary for evaluation.

Evaluation Assessment by ***Blinded Investigator only:***
A complete evaluation will be documented on the follow-up CRFs. Data collection and procedures will include:

- Work status
- History of concurrent or previous medical illness
- Medication review
- Adverse events / secondary procedures

8.7 Injection #2 (Day 28 ± 7, Visit #4)

Prior to the second injection of MONOVISC or saline, each subject will complete the following self-report questionnaires:

- Western Ontario MacMaster (WOMAC)
- Patient Global Assessment (PGA)
- SF-12

The patient will also submit their completed patient diary for evaluation.

Evaluation Assessment by ***Blinded Investigator only:***
A complete evaluation will be documented on the Follow-up CRF. Data collection and procedures will include:

- Work status
- History of concurrent or previous medical illness
- Medication review
- Adverse events / secondary procedures

After completion of questionnaires and evaluation assessment, the patient will receive the 2nd injection of either MONOVISC or saline from the same product kit that was utilized for the 1st injection, using procedures employed for the first injection. The injection must be performed by an *Injecting Investigator*. The Injecting Investigator will also evaluate and report any Adverse Events that occur as part of the injection procedure.

8.8 Unscheduled Visit Procedures

If an unscheduled visit falls between the injection procedure and Week 26, the evaluation assessment must be performed by a ***Blinded*** Investigator. Evaluation assessment should not be performed if the unscheduled visit is deemed unrelated to the study treatment, or is considered a Standard of Care visit.

The patient will also submit their completed patient diary for evaluation.

Evaluation Assessment by ***Blinded Investigator only:***

A complete evaluation will be documented on the Follow-up CRF. Data collection and procedures will include:

- Work status
- History of concurrent or previous medical illness
- Medication review
- Adverse events / secondary procedures

8.9 Study Period

Enrollment for the study is anticipated to require approximately 30 months (up to 560 patients). Each patient's participation will be at least 26 weeks from the time of the initial injection until their final follow up visit. Therefore, the estimated total duration for the study will be approximately 36 months.

9.0 ADVERSE EVENT REPORTING

9.1 Anticipated Adverse Events

These are immediate post-injection or peri-injection events that are changes from the baseline condition of the Subject, but are expected events resulting from the treatment. If these events occur, they should be recorded in the Subject's medical record.

9.2 Adverse Events

An Adverse Event is any untoward medical occurrence in a subject, regardless if there is a relationship between the adverse events and the study devices.

At each evaluation of the subject enrolled in a clinical investigation, the Investigator determines whether any adverse events (AE) have occurred, and determines their relationship to the study devices or procedure.

All adverse events, study device malfunctions and other product issues must be recorded in the medical records and entered into electronic Case Report Forms (eCRFs) within two weeks of awareness the AE occurred. Upon entry of an AE into the eCRF, designated members of the DePuy Synthes Mitek clinical team will receive an email alert describing the AE.

9.3 Serious Adverse Events

Serious Adverse Events (SAEs) are defined as any adverse event that:

1. Led to a death,
2. Led to a serious deterioration in the health of the subject that,
    a. Resulted in life-threatening illness or injury,
    b. Resulted in permanent impairment of a body structure or a body function,
    c. Required hospitalization or prolongation of existing hospitalization
    d. resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function,
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization and/or medical intervention for pre-existing conditions, or a procedure required by the protocol, without serious deterioration in health, is not considered to be a serious adverse event.

Investigator must submit to DePuy Synthes Mitek any SAEs occurring during the study as soon as possible, but within 72 hours, after being notified of the event and provide additional information if required by DePuy Synthes Mitek. All SAEs need to be followed until the event is resolved (with or without sequelae). The Medical Monitor of this study will decide if more follow-up information is needed (via electronic queries) in case the event is not resolved at study completion.

The Investigator notifies his/her EC/IRB of all SAEs occurred at his/her site (and any additional information as required by EC/IRB).

9.4 Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Investigator must report to DePuy Synthes Mitek, either verbally or by eCRF entry, any UADE that occurs during the study within 72 hours after becoming aware of the event. Reporting by eCRF entry will trigger an email alert to DePuy Synthes Mitek. Investigator must provide additional information if required by DePuy Synthes Mitek to confirm that the event is a UADE. DePuy Synthes Mitek Sports Medicine will notify all participating Investigators and EC/IRBs of the UADE within 10 working days after confirmation of the event.

DePuy Synthes Mitek Sports Medicine will submit every year (unless otherwise indicated by the EC/IRB) to all participating Investigators an update of all study devices related, site reported and adjudicated SAEs. A letter summarizing the study status, enrollment figures, any safety concerns as well as any recommendation will accompany the updates.

9.5 Duration of Follow-up After Adverse Events

The Investigator should ensure that adequate medical care is provided to any subject for any adverse events, including clinically significant laboratory values, related to the study.

All adverse events related to the subject's participation in the study should be followed until the condition has resolved, or in the case of permanent impairment until the condition stabilizes and clinical outcome has been ascertained.

9.6 Reporting an Adverse Event

Adverse events are reported from the start time of the injection procedure until the subject's study participation has ended (i.e. completion of study or withdrawal of consent). All AEs must be followed until the AE has resolved, stabilized, or the study has been completed.

The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine its relationship to the investigational products or any protocol mandated procedures involved in the clinical study.

The following categories of adverse event severity are to be used:

Mild	Awareness of sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae,
Moderate	Interferes, but does not hinder, the subject's usual activity and may require treatment,
Severe	Symptom(s) causing severe discomfort and significant impact on the subject's usual activity and requires treatment or intervention.

The causal relationship should be rated as follows:

Unrelated	The event is definitely not associated with product application
Unlikely	The temporal sequence between product application and the event is such that the relationship is unlikely,
Possible	The temporal sequence between product application and the event is such that the relationship is not unlikely or the subject's condition or concomitant therapy could have caused the AE,
Probable	The temporal sequence is relevant or the event abates upon product application completion or the event cannot be reasonably explained by the patient's condition,
Related	The temporal sequence is relevant and the event abates upon product application completion or reappearance of the event on repeat product application (re-challenge).

Adverse events will be reported by the Investigator to DePuy Synthes Mitek Sports Medicine via the Adverse Events CRF.

10.0 EARLY DISCONTINUATION

10.1 Reasons for Early Discontinuation

Possible reasons for early discontinuation may include, but are not limited to the following:

- Withdrawal of consent: Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the patient study files;
- Physician discretion: The Investigator may choose to withdraw a subject from the study if there are safety concerns;
- Adverse event: Adverse event or serious adverse event may not lead to subject discontinuation from the study. When the investigator decided to discontinue the subject, subject must be

followed until the adverse event resolves or until a stable clinical endpoint is reached;

- Death;
- Early study termination: DePuy Synthes Mitek Sports Medicine can decide to discontinue the study prematurely for various reasons, and/or
- Lost to follow-up: All subjects should be encouraged to return for all scheduled clinical follow-ups. If a subject is unable to return for mandatory clinical visits, 3 separate telephone calls or email messages should be made to attempt to bring the subject back into the clinic for follow-up visits. All attempts at contact should be documented in the source documents. If the subject does not respond to 3 telephone calls or emails, the Investigator must send a registered letter to the subject. If the subject does not respond to the registered letter and further contact is not made, then the subject will be considered to have missed the scheduled visit. If the aforementioned contact efforts are unsuccessful over two study intervals the subject will be considered lost to follow-up and an End of Study case report form must be completed.

10.2 Study Early Discontinuation

DePuy Synthes Mitek Sports Medicine reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, non-compliance, or unsatisfactory enrollment with respect to quality or quantity. The study may also be discontinued on the basis of the interim data analysis, as described in Section 6: **Study Design.**

If the study is prematurely terminated or suspended, DePuy Synthes Mitek Sports Medicine or its representatives will inform the Investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The ED/IRB should also be informed and provided with reason(s) for the termination or suspension by DePuy Synthes Mitek Sports Medicine or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused investigational products and other material in accordance with Sponsor procedure for the study.

10.3 Subject Early Discontinuation

Every subject should be encouraged to remain in the study until they have completed the protocol-required 26 week follow-up period. If the subject discontinues prematurely from the study, the reason for discontinuation must be documented in the source documents and site files, and submitted via CRF.

Subjects who have discontinued prematurely will be included in the analysis of results; however they will not be replaced.

11.0 STATISTICAL METHODOLOGY / DATA MANAGEMENT

The following sections provide a general description of the statistical plan for the analysis of study data. A separate Statistical Analysis Plan (SAP) document that provides greater detail on data derivations and the analyses to be performed will be developed prior to the planned interim analysis. The SAP will be developed no later than 90 days following enrollment of the first

patient in the study. The SAP will reflect the protocol and any amendments that have been implemented at the time the SAP is finalized. Any deviations from the final SAP will be noted in the final clinical summary report.

11.1 Study Design

This study is a prospective, multi-center, double-blinded, randomized controlled trial comparing the treatment group (MONOVISC) to a control (Saline) for the purpose of demonstrating superiority. It is planned that a total of N=560 subjects will be enrolled using a 2:1 randomization (374 MONOVISC and 186 Saline). An interim analysis of the primary endpoint will be conducted after 74 patients in the MONOVISC arm and 37 patients in the Saline arm have completed their 26 week per protocol follow up visit. The study will be terminated if the mean WOMAC A1 pain change from baseline difference (MONOVISC minus Saline) is less than 0.4 in both the Per Protocol Analysis Set for the 26 week interval and the As Treated Analysis Set for the 26 week interval. If this difference is greater than 0.4 in favor of MONOVISC in either the Per Protocol Analysis Set for the 26 week interval or the As Treated Analysis Set for the 26 week interval, the study will continue to completion. Enrollment will continue throughout the time preceding and during the interim analysis.

Further description of the study design can be found in Section 6.0 above.

11.2 Treatment Assignment

The treatment groups in this study are:

> MONOVISC: Two intra-articular injections of MONOVISC High Molecular Weight Hyaluronan, separated by 1 month (active treatment).
>
> Saline: Two injections of 4 ml saline, separated by 1 month (control treatment).

Subjects will be randomized in a 2:1 ratio to receive either treatment with MONOVISC or treatment with Saline. Block randomization (random blocks of size 3 or 6) will be used to create a Master Randomization List, and patient kits of MONOVISC and saline will be sequentially numbered according to this list. With this randomization scheme, each study subject will be associated with a unique kit number, and the order of randomized subjects at each investigational site will be distinct. Prior to initiation of the study, investigational sites will be provided with an initial, sequentially numbered quantity of kits to be used, and as these kits are utilized, additional quantities of sequentially numbered kits can be ordered as needed through an electronic re-order system. The kit will not contain any labeling to indicate whether the patient is receiving MONOVISC or Saline. After the first injection, the remaining syringe will be returned to the storage site for the second injection.

All clinical research and biostatistics personnel at DePuy Synthes Mitek Sports Medicine will remain blinded to treatment assignment until the end of the study. An employee within Strategic Medical Affairs will be designated to maintain the Master Randomization, to facilitate any medical safety reviews, if necessary, and to facilitate the planned interim futility analysis.

11.3 Levels of Significance

Unless otherwise stated, confidence intervals will be 2-sided 95% confidence intervals, and *p*-values will also be 2-sided; *p*-values below 0.05 will be deemed to be statistically significant. Unless otherwise stated, there will be no adjustment of significance levels because of testing multiple hypotheses.

A primary endpoint interim analysis will be conducted after 74 patients in the MONOVISC arm and 37 patients in the saline arm have completed their 26 week follow-up visit to determine whether or not to stop the trial early for futility. This analysis will be based solely on the primary efficacy endpoint, and the trial will stop early if the mean WOMAC A1 pain difference (MONOVISC minus Saline) change from baseline is less than 0.4 in both the Per Protocol Analysis Set for the 26 week interval and the As Treated Analysis Set for the 26 week interval. Since this interim analysis does not have an early stopping rule for success, the final primary endpoint analysis will be conducted with a 2-sided *p*-value threshold of 0.05 for determining study success (no penalty for having conducted the interim analysis with futility stopping rule). Subject enrollment will continue during the interim analysis period.

11.4 Interval Windows

The study windows are presented in the Time and Event Schedule (Section 1.1).

For analysis purposes, the baseline/screening evaluation is to be done within 30 days prior to the first injection; the first injection is considered to be day 0. The 2, 4, 8, 16 and 26 week visits will occur in the time intervals (days) indicated in the following table:

Study Interval Windows [days]						
Baseline/ Screening	Injection	2 Week	4 Week	8 Week	16 Week	26 Week
-30 to 0	Day 0 (by definition)	11 to 17	21 to 35	46 to 74	105 to 134	159 to 201

11.5 Handling of Missing Data

The primary efficacy endpoint analysis will be conducted on the modified intent to treat (MITT) analysis set, which consists of all primary endpoint data on all As Treated subjects (regardless of whether or not there were protocol deviations associated with the data) for the 2, 4, 8, 16 and 26 week visits. In this MITT Analysis Set, primary endpoint data for the 26 week visit will be imputed with multiple imputation methodology (missing primary endpoint data for the 26 week visit will be imputed).

A supportive primary endpoint analysis will be conducted on the Per Protocol Analysis Set for Longitudinal Analysis, with no imputation for missing data. Aside from any other sensitivity analysis purposes, all other analyses will utilize only actual subject data which are collected; no imputation of missing data will be performed.

11.6 Endpoints

Primary Endpoint:

The primary efficacy endpoint in this study is the WOMAC A1 (walking pain) score (response options 0 through 10, where 0 indicates no pain and 10 indicates worst possible pain) change from baseline at 26 weeks.

The primary efficacy analysis is a superiority comparison of MONOVISC vs. saline in WOMAC A1 pain score change from baseline at 26 weeks. The primary endpoint analysis will be based upon a longitudinal model of all primary endpoint data from 2 weeks through 26 weeks; the adjusted means at 26 weeks from this longitudinal model at 26 weeks will be compared.

Secondary Endpoints:

- WOMAC A1 Pain change from baseline at the 2, 4, 8, and 16 week time points as measured by WOMAC A1 pain score.

Tertiary Endpoints:

- Walking pain at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A1 score.
- Area-under-curve (AUC) analysis of walking pain change from baseline using longitudinal model over time comparing treatment vs. control.
- Pain at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A (pain) score.
- Pain improvement from baseline at the 2, 4, 8, 16 and 26 week time points as measured by WOMAC A (pain) score.
- Total WOMAC (pain, function, stiffness) score at the 2, 4, 8, 16 and 26 week time points.
- Improvement from baseline in Total WOMAC (pain, function, stiffness) score at the 2, 4, 8, 16 and 26 week time points.
- OMERACT-OARSI responder rate at the 2, 4, 8, 16 and 26 week time points.
- Patient Global Assessment (PGA) at the 2, 4, 8, 16, and 26 week time points.
- SF-12 outcomes at study defined time-points
- Rescue medicine consumption (acetaminophen) from baseline through week 26

Safety:

- Safety of the therapy will be assessed by comparing the incidence of adverse events in the treated vs the control group through 26 weeks post-injection, including AEs that occur during injection.

11.7 Hypotheses

The primary endpoint analysis will be to demonstrate that the mean WOMAC A1 pain change from baseline for MONOVISC is significantly better than the mean WOMAC A1 pain change from baseline for Saline at 26 weeks after the first injection. The null (H_o) and alternate (H_A) hypotheses for this test of superiority are as follows:

$$H_o: \mu_{MONOVISC} \geq \mu_{Saline}$$
$$H_A: \mu_{MONOVISC} < \mu_{Saline},$$

where $\mu_{MONOVISC}$ is the mean WOMAC A1 pain change from baseline for MONOVISC at 26 weeks, and μ_{Saline} is the mean WOMAC A1 pain change from baseline for Saline at 26 weeks.

Decision Criterion: The primary endpoint analysis will be based upon a longitudinal model of all primary endpoint data from 2 weeks through 26 weeks; the adjusted means at 26 weeks from

this longitudinal model at 26 weeks will be compared. The decision will be made to reject the null hypotheses Ho and conclude the alternative hypothesis H_A if the WOMAC A1 pain change from baseline adjusted mean for MONOVISC is less than the WOMAC A1 Pain change from baseline adjusted mean for Saline at 26 weeks, and the two sided p-value for the comparison of these adjusted means at 26 weeks is less than 0.05, or equivalently, if the entire 2-sided 95% confidence interval for the WOMAC A1 pain change from baseline adjusted mean difference (MONOVISC minus Saline), based upon the longitudinal model estimates, is less than 0. This primary efficacy endpoint analysis will be conducted on the MITT analysis set.

11.8 Analysis Sets

A detailed accounting of all enrolled Subjects will be documented with the following analysis sets.

Intent to Treat (ITT) Analysis Set
The Intent to Treat (ITT) Analysis Set consists of all subjects who are enrolled into the study. subjects in the ITT dataset but in whom treatment is not attempted with either MONOVISC or saline will be listed along with the reason for not being treated.

Safety Analysis Set
The Safety Analysis Set consists of all randomized subjects who are enrolled into the study, in whom treatment is attempted with either MONOVISC or saline. Subjects will be analyzed according to the treatment which is attempted.

As Treated (AT) Analysis Set for Each Study Defined Time Point

For each follow-up time point (the 2, 4, 8, 16 and 26 week visits), the As Treated (AT) Analysis Set (for the interval) will consist of all Safety Analysis Set subjects who have a follow-up visit within the interval in which WOMAC A1 pain data were collected. Reasons for not having WOMAC A1 pain follow-up in the interval will be documented (including deaths, withdrawals of consent, and Subjects who are past due for follow-up in the interval).

Modified Intent to Treat (MITT) Analysis Set (for Longitudinal Analysis)
All primary endpoint data from all As Treated Analysis Sets for the 2, 4, 8, 16 and 26 week visits will be combined into a dataset upon which longitudinal analysis for the primary endpoint can be conducted. In this MITT analysis set, primary endpoint data for the 26 week visit will be imputed with multiple imputation methodology.

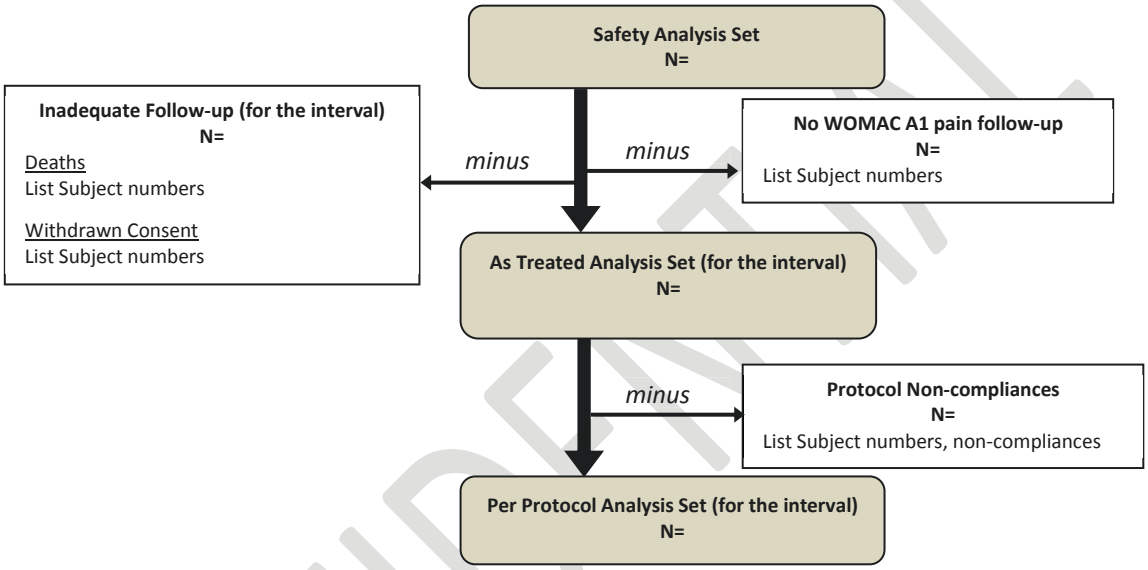
Per Protocol (PP) Analysis Set for Each Study Defined Time Point

For each follow-up time point (the 2, 4, 8, 16 and 26 week visits), the Per Protocol (PP) Analysis Set (for the interval) will consist of As Treated Analysis Set subjects (for the interval), excluding protocol violations which are deemed to have possibly affected the scientific validity of the data. Note that some subjects may have data excluded from a particular Per Protocol Analysis Set for an interval (for example, if they used acetaminophen within 48 hours prior to a study visit), or from all Per Protocol Analysis Sets for all intervals (for example, if they failed an inclusion/exclusion criterion that is deemed to possibly affect the scientific validity of the data).

Per Protocol Analysis Set for Longitudinal Analysis
All primary endpoint data from all Per Protocol Analysis Sets for the 2, 4, 8, 16 and 26 week visits will be combined into a dataset upon which longitudinal analysis for the primary endpoint can be conducted.

For each follow-up time point, a flowchart as depicted below will be created. This flowchart will present the Safety Analysis Set, the As Treated Analysis Set for the interval, and the Per Protocol Analysis Set for the interval. This diagram will indicate all protocol violations, deaths, withdrawals of consent, and Subjects who are past due for follow-up in the interval.

Flow Diagram for [ ]-Week Study Interval



A Medically Trained Professional and a Biostatistician at DePuy Synthes will review and confirm all protocol non-compliances prior to the planned interim analysis (if possible), and also prior to final dataset lock.

11.9 Sample Size Justification

The sample size was determined based on the primary endpoint, which is a superiority comparison of WOMAC A1 pain change from baseline at 26 weeks for MONOVSIC Subjects compared to Saline Subjects. Although it is planned to conduct the primary endpoint analysis with a longitudinal model, and to compare the WOMAC A1 pain change from baseline adjusted means at 26 weeks from this longitudinal model, the sample size was established based upon estimates for a t-test comparison of 26 week means for simplicity. Specifically, it is anticipated that the mean difference in WOMAC A1 pain change from baseline means will be at least 0.6 (where the mean for MONOVISC subjects is less than the mean for Saline Subjects), and that the standard deviation in WOMAC A1 pain change from baseline at 26 weeks will be approximately 2.2 in both groups. This standard deviation of 2.2 is consistent with published studies by Spitzer (2010) and Qvistgaard (2006); also, 2.2 is approximately ¼ of the maximum anticipated range of WOMAC A1 pain change from baseline, which would be an estimate of the standard deviation from data which are normally distributed. Using a two-tailed t-test and assuming a 2:1 randomization, the required sample size to yield 80% statistical power was estimated to be 318 MONOVISC and 159 Saline. With an anticipated attrition rate of 15%, the total study population was increased to be 560 patients (374 MONOVISC, 186 Saline). The sample size estimate was calculated with the following SAS code:

SAS Code for Power Estimation:
WOMAC A pain at 26 weeks

```
proc power;
      twosamplemeans
      meandiff= .6
      stddev=2.2
      groupweights=(2 1)
      power= .8
      alpha=0.05
      sides=2
      ntotal=.;
run;
```

The primary efficacy endpoint analysis will be conducted on the modified intent treat (MITT) Analysis Set with the handling of missing data at 26 weeks as described in Section 11.5 above. A supportive analysis will be conducted on the Per Protocol Analysis Set for Longitudinal Analysis.

11.10 Analysis Plan

All statistical processing will be performed using SAS® Version 9.2 or higher, unless otherwise noted. A separate Statistical Analysis Plan (SAP) document that provides greater detail on data derivations and the analyses to be performed will be developed within 90 days after the first patient is enrolled.

Summary tables will be provided for subject demographics and baseline variables for the Safety Analysis Set, the As Treated Analysis Set at 26 weeks, and the Per Protocol Analysis Set at 26 weeks. Safety endpoints (adverse events) will be summarized on the Safety Analysis Set. Effectiveness endpoints will be summarized at each protocol-specified evaluation time point on the Per Protocol Analysis Set for the time point. Analyses will be conducted on pooled data from all sites. For the primary endpoint data at 26 weeks, a 2-way ANOVA test with interaction term will be conducted to confirm the homogeneity of 26 week data across sites. The primary endpoint analysis will be conducted with a longitudinal model on the MITT Analysis Set using PROC MIXED and an antedependence covariance structure to model the correlation between visits. A supportive analysis of the primary endpoint analysis will be conducted on the Per Protocol Analysis Set for Longitudinal Analysis with the same PROC MIXED model.

Descriptive statistics for dichotomous/categorical variables will include the number and percentage of subjects. Fisher's exact test 2-sided *p*-values will be provided for the comparison of dichotomous variables, including adverse event rates, to facilitate clinical judgment. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum, and maximum. *P*-values for comparing continuous endpoints will be provided to facilitate clinical judgment; these will be 2-sided *p*-values based upon the t-distribution.

If Age, Gender, or pre-injection WOMAC A1 pain score are found to be significantly different ($p<0.05$) across treatment groups in the As Treated Analysis Set at 26 weeks, then an ANCOVA sensitivity analysis will be conducted for the primary endpoint analysis (on the MITT Analysis Set, with Age, Gender, and pre-injection WOMAC A1 pain as covariates).

11.11 Plans for Interim Analysis

An interim analysis of the primary endpoint will be conducted after 74 subjects in the MONOVISC arm and 37 patients in the saline arm have entered the Per Protocol Analysis Set at 26 weeks. An early stopping rule for futility will be implemented in which the study will be terminated if the WOMAC A1 pain score change from baseline difference (MONOVISC minus Saline) is less than 0.4 in both the Per Protocol Analysis Set for the 26 week interval and the As Treated Analysis Set for the 26 week interval. If this difference is greater than 0.4 (which favors MONOVISC) in either the Per Protocol Analysis Set for the 26 week interval or the As Treated Analysis Set for the 26 week interval, the study will continue to completion.

11.12 Reporting

After all subjects have completed the primary endpoint (26 week) follow-up visit, a clinical study report will be provided to FDA for review. Trial results will also be posted on www.clinicaltrials.gov.

12.0 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Investigator Responsibilities

12.1.1 Blinded Investigator

The Investigator that may screen and enroll subjects, but will not inject patients. He/she will be blinded to randomization and will be responsible for subject follow-up data collection and assessment of endpoints.

12.1.2 Injecting Investigator

Injecting Investigator: The Investigator that actively treats (injects) enrolled subjects in the sequential order of patient kits which have been provided will not be blinded to treatment assignment due to obvious tactile differences in MONOVISC vs saline injections. The injecting Investigator may be an orthopedic surgeon, sports medicine specialist, rheumatologist, physiatrist, or primary care physician approved to participate in the study by the Clinical Sponsor, DePuy Synthes Mitek Sports Medicine. To maintain blinding, the injecting Investigator may not participate in subject follow-up data collection. *However, he/she may participate in patient screening, enrollment and baseline evaluation. He/she may also assess, report and treat adverse events that may occur as part of the injection procedures. He/she may also treat adverse events that are reported by the blinded investigator during follow-up visits.*

12.1.3 Clinical Research Coordinator (CRC)

A designated coordinator will be identified at each clinical site. The CRC will act as the liaison between the enrolling (blinded) Investigator and the injecting (un-blinded) Investigator. He/she will facilitate the completion of all required documentation, ensure subject follow-up compliance and maintain the study inventory, etc. The CRC will be blinded to study treatment assignment.

12.2 Good Clinical Practice

The study will be conducted in accordance with the GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study device as described in the protocol and Investigational Device Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data

collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.3 Financial Disclosure Forms (FDF)

All Investigators will be required to complete a Financial Disclosure Form prior to participating in the study. One year after study completion, the Investigators will be required to complete an updated FDF.

12.4 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The EC/IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where initial and annual EC/IRB approval has been obtained. Furthermore, the study must not begin until the EC/IRB approval letter is received by DePuy Synthes Mitek Sports Medicine. In addition, a copy of the ED/IRB approval letter must be filed on site in the Investigator's study files.

The protocol, Investigational Device Brochure, informed consent, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the EC/IRB by the Investigator. When applicable, amendments to the protocol will be submitted for EC/IRB review before implementation.

12.5 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with GCP and all applicable regulatory requirement(s).

12.6 Subject Confidentiality

In order to maintain subject privacy, all eCRFs, study device accountability records, study reports and communications will identify the subject by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority (ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.7 Protocol Compliance

The Investigator(s) agree to conduct the study in accordance with the study protocol. Prior to beginning the study, the Investigator(s) must sign the Investigator Agreement and the Protocol Signature Page. Modifications to the protocol should not be made without agreement of the Investigator, DePuy Synthes Mitek Sports Medicine, and FDA. Changes to the protocol will require written EC/IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The EC/IRB may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the

EC/IRB. DePuy Synthes Mitek Sports Medicine will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

12.8 Direct Access to Source Data

The study will be monitored by DePuy Synthes Mitek Sports Medicine or its designee. Monitoring will be done by personal visits from a representative of DePuy Synthes Mitek Sports Medicine (site monitor) and will include on-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax). Regulatory authorities, the EC/IRB, and/or DePuy Synthes Mitek Sports Medicine's quality assurance group may request access to all source documents, eCRFs, the Device Accountability Record, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

12.9 Case Report Form Completion

An electronic data capture system, compliant to 21 CFR Part 11, will be used to collect data from this study.

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status. The Investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the CRF to endorse the recorded data.

12.10 Record Retention

The Investigator will maintain all study records according to GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs. Study documentation includes, but is not limited to, the following:

- Source data, informed consents and enrollment logs
- Device accountability records and device shipment receipts of all devices shipped to the center
- The Investigator will maintain a Device Accountability Record for all investigational devices received, used, or returned during this study
- Correspondence with the EC/IRB, DePuy Synthes Mitek Sports Medicine, Food and Drug Administration (FDA), monitor, or other Investigators
- Study protocol and any amendments issued
- Protocol and Informed Consent approvals from the EC/IRB
- Investigator agreements and curricula vitae of Investigator(s), and the site personnel signature form

12.11 Investigator Reports

The Investigator(s) is required to complete the following reports:

1. Unanticipated Adverse Device Effects – A report, either verbal or by eCRF entry, must be submitted to the Sponsor regarding any UADE that occurs during the study within 72 hours after becoming aware of the event. Investigator must provide additional information if required by DePuy Synthes Mitek to confirm that the event is a UADE.
2. Withdrawal of EC/IRB Approval – Notification must be sent to the Sponsor within 5 working days
3. Informed Consent – A report of any use of the investigational device without a signed Informed Consent form must be forwarded to the Sponsor and the EC/IRB with 5 working days of the occurrence
4. Investigational Plan Deviations – Emergent deviations must be forwarded to the EC/IRB and the Sponsor as soon as possible and within 5 working days of the event. All other deviations require pre-approval of the Sponsor. Any departures from the protocol must be fully documented in the CRF and source documentation
5. Progress Reports – Annual progress reports must be forwarded to the EC/IRB and the Sponsor
6. Final Report – A copy of the final study report must be filed with the EC/IRB and the Sponsor within 3 months of completion of the study
7. Principal Investigator(s) may delegate a qualified associate(s) to complete one or more of the above functions. However, the Principal Investigator retains the overall responsibility for subject safety, proper conduct of the study including obtaining subject consent, compliance with this study plan, and the collection of all required data

13.0 SPONSOR OBLIGATIONS

13.1 Investigator(s) Training

DePuy Synthes Mitek Sports Medicine will select only Investigator(s) with extensive experience in intra-articular hip injections. The protocol will be reviewed with the Investigator(s) and their study personnel at the Site Initiation Visit. Furthermore, they will be instructed on how to complete the study documentation.

13.2 Study Monitoring

Study monitoring will be carried out in compliance with FDA regulations (21CFR 812) and all GCP guidelines, and will be consistent with the sponsor's internal monitoring procedures.

13.3 Liability and Insurance

DePuy Synthes Mitek Sports Medicine has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

14.0 ETHICS COMMITTEES (EC), INSTITUTIONAL REVIEW BOARDS (IRB) AND REGULATORY REQUIREMENTS

14.1 EC/IRBs

The protocol, informed consent form and other applicable study-related documents must be submitted to the appropriate EC/IRB and written approval must be obtained and submitted to DePuy Synthes Mitek Sports Medicine prior to enrolling any subjects.

The Investigator will promptly report to the EC/IRB any change in the designation of Principal Investigator role and all unanticipated problems involving risks to human subjects and will not make any changes in the research plan without EC/IRB approval, except when necessary to eliminate immediate hazards to human subjects. Those amendments involving significant risk or change require EC/IRB approval and written documentation of this approval must be submitted to the DePuy Synthes Mitek.

The Investigator must report to the EC/IRB at least yearly on the progress of the investigation. A letter from the EC/IRB should document continuing EC/IRB review. Notification to the EC/IRB by the Investigator within 3 months after completion, termination, or discontinuation of the study at the specific site must be documented.

Other Investigator responsibilities to the EC/IRB and DePuy Synthes Mitek include the following:

- During the conduct of the study, submit progress reports to the EC/IRB as required.
- Report unexpected adverse device effects (UADE) that occur during the study to the EC/IRB and DePuy Synthes Mitek.
- As required, obtain approval from the EC/IRB for protocol amendments and for revisions to the informed consent or subject recruitment advertisements.
- Provide EC/IRB with any other information it requests before or during the conduct of the study.
- Maintain a file of study-related information that includes all correspondence with the EC/IRB.
- Notify EC/IRB within 3 months after study completion, termination or discontinuation.

- Notify DePuy Synthes Mitek, within 24 hours, of withdrawal of approval by the reviewing EC/IRB.

14.2 Informed Consent

Each subject (or a legally authorized representative) must sign and date the EC/IRB approved Informed Consent (and other locally required documents) after the nature of the study has been fully explained, and prior to performance of any study-related activity or procedure, that is not standard of care.

The voluntary process of obtaining written informed consent confirms the subject's willingness to participate in the study. All aspects of the study must be explained to the subject prior to signing the informed consent. The Investigator and/or designee must clearly document the process of obtaining informed consent in the subject clinical record. It is the Investigator's responsibility to ensure that the informed consent process is performed in accordance with FDA, ISO 14155 and EC/IRB requirements. The Informed Consent Form template for this study can be found in Appendix D.

14.3 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code (site number and subject number) will be used that allows identification of all data reported for each subject.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the subject's privacy is guaranteed.

14.4 Protocol Amendments

As appropriate, DePuy Synthes Mitek will submit changes in the protocol to the investigators, the appropriate regulatory authorities and EC/IRBs. EC/IRB approval and Regulatory Authority / FDA approval are required for all substantial amendments prior to implementation of any changes to study procedures.

An amendment is regarded substantial when they are likely to have a significant impact on:

- The safety or physical or mental integrity of the subjects;
- Scientific value of the trial;
- Conduct or management of the trial;
- Quality or safety of an investigational medical product used in the trial.

14.5 13.5 Protocol Deviations

A protocol deviation is defined as a divergence from a specific element of a protocol (e.g., missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria).

Investigators are required to obtain prior approval from the medical monitor before initiating deviations from protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in study files. Prior approval is generally not expected in situations where unforeseen circumstances are

beyond the Investigator's control, (e.g., subject did not attend scheduled follow-up visit); however, the event is still considered a deviation.

Deviations shall be reported to the DePuy Synthes Mitek regardless of whether medically justifiable, preapproved by the Medical Monitor, or taken to protect the subject in an emergency. Subject specific deviations will be reported in the eCRFs. Investigators will also adhere to procedures for reporting study deviations to their EC/IRB in accordance with their specific EC/IRB reporting policies and procedures. Regulations (ISO 14155, 21 CFR 812) require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol.

15.0 PUBLICATION POLICY

At the conclusion of the study, a multicenter manuscript will be prepared for publication in a reputable scientific journal. The publication of the principal results from any single-site experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of DePuy Synthes Mitek Sports Medicine. The analysis of other pre-specified and non-pre-specified endpoints will be performed by Data Management. Such secondary analyses, as well as other proposed investigations, will require the approval of DePuy Synthes Mitek Sports Medicine. For purposes of timely abstract presentation and publication, secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of DePuy Synthes Mitek Sports Medicine.

16.0 DEVICES

16.1 Investigational Device Accountability

Investigational devices will be packaged, randomized, stored and distributed to sites by an approved and qualified vendor, Fisher Clinical Services (FCS).

All received investigational devices will be inventoried and accounted for throughout the study on an ongoing basis. The Investigator and/or trained designee will maintain adequate records of the receipt, use, disposition and return of the investigational devices. These investigational devices must be kept in a secure location with restricted access and stored according to the conditions outlined in the IFU. In all circumstances, the investigational device is intended for use by the Investigator or Sub-Investigator for subjects consented for participation in this clinical study only.

An accountability log will be used by each site to acknowledge receipt of all investigational devices and to record the disposition of all investigational devices on an ongoing basis throughout the course of the study. Detailed written instructions regarding this device accountability process will be provided and the study monitor will review the investigational device accountability at each monitoring visit for as long as devices are stored on site.

In addition, the following paper study documents must be maintained as well:

- Packing slips provided with each investigational device shipment (signed and dated);
- Accountability records of each subject that received an investigational device (this may include source documents and/or package labels of investigational/commercial products used);
- All forms documenting the investigational devices return process;

- All shipment-related forms.

16.2 Return of Study Devices

All unopened and unused (e.g., expired), opened and unused, damaged, mislabeled or mechanically malfunctioning investigational devices (including saline controls) must be returned to Fisher Clinical Services. The appropriate form(s) must be completed and the device must be returned by courier to FCS at an address specified by DePuy Synthes Mitek Sports Medicine. Furthermore, the reason for each returned investigational device must be reflected in the accountability system as well.

Detailed instructions for return will be provided separately by DePuy Synthes Mitek Sports Medicine and explained thoroughly during the site initiation visit.

16.3 Device Complaint

Device Complaints consist of the following:

- The study device is damaged;
- The study device is mislabeled;
- The study device is mechanically malfunctioning.

A Device Malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended.

It is important that all malfunctioning investigational devices are returned to DePuy Synthes Mitek Sports Medicine per instructions provided in the Study Manual and the return process will be explained thoroughly during the site initiation visit. In case of any device complaints, the site must notify DePuy Synthes Mitek Sports Medicine as soon as possible. In case of a device malfunction, the Investigator will report the relevant information regarding the device malfunction in the appropriate eCRF in addition to notifying DePuy Synthes Mitek Sports Medicine.

APPENDICES

17.0 APPENDIX A: Definitions

PATIENT REPORTED OUTCOME CASE REPORT FORMS

NRS: Numerical Rating Scale. The patient reports an integer pain score between 0 and 10, with 1 being no pain and 10 being worst pain imaginable.

SF-12: The Short Form-12 was designed to measure general health status from the patient's point of view. The SF-12 is a multi-purpose, short-form health survey with only 12 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-12 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

WOMAC: The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was developed in 1982 at Western Ontario and McMaster Universities and is widely used in the evaluation of Hip and Knee Osteoarthritis. The WOMAC is available in over 65 languages and has been linguistically validated. It is a self-administered questionnaire consisting of 24 items divided into 3 subscales: pain (5 items), stiffness (2 items) and physical function (17 items). The WOMAC takes approximately 12 minutes to complete. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

WOMAC A: The pain subscale of the WOMAC questionnaire

WOMAC A1: The first question of the WOMAC A questionnaire that addresses pain during walking.

PROTOCOL DEVIATION

A protocol deviation is defined as an incident where the Investigator or site personnel did not conduct the study according to the investigational plan, protocol or the Investigator agreement.

Any deviation from patient inclusion and exclusion criteria or patient informed consent procedures, or any deviation from a protocol requirement such as incomplete/inadequate patient testing procedures, follow-ups performed outside specified time windows, etc.

18.0 APPENDIX B: References

1) Spitzer, A.I. et al, Hylan G-F 20 improves hip osteoarthritis: a prospective, randomized study, The Physician and Sports Medicine, 2(38): 35-47 (2010)

2) Migliore, A. et al, Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix®) injections versus local anesthetic in osteoarthritis of the hip, Arthritis Research & Therapy, 11(6) (2009)

3) Qvistgaard, E. et al, Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline, Osteoarthritis & Cartilage, 14(2): 163-70 (2006)

4) Richette, P. et al, Effect of hyaluronic acid in symptomatic hip osteoarthritis, Arthritis & Rheumatism, 60(3): 824-30 (2009)

5) Tikiz, C. et al, Comparison of low and high molecular weight viscosupplementation in the treatment of hip osteoarthritis, Clinical Rheumatology, 24: 244-50 (2005)

6) Atchia, I. et al, Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis, Annals of the Rheumatic Diseases, 70: 110-116 (2011)

7) MONOVISC Package Insert

8) Balazs, EA, Denlinger JL: Viscosupplementation: A new concept in the treatment of osteoarthritis. Journal of Rheumatology, 20 (Suppl 39): 3-9 (1993)

9) Strauss, EJ, Hart JA, Miller MD et al. Hyaluronic acid viscosupplementation and osteoarthritis, Am J Sports Med.; 37(8):1636-1643 (2009)

10) Nichols, AW, Complications associated with the use of corticosteroids in the treatment of treatment of athletic injuries, Clinical Journal of Sports Medicine, 15 (5) (2005)

11) Horn, M. et al, Intra-articular corticosteroid/local anesthetic hip injections and rapidly progressing joint degeneration, 2015 AAOS Annual Meeting, Paper #179

12) Qvistgaard, E. et al, Guidance by ultrasound of intra-articular injections in the knee and hip joints, Osteoarthritis & Cartilage, 9(6): 512-17 (2001)

19.0 APPENDIX C: Image guided hip injection technique

Intra-articular injections into the hip joint will be administered under fluoroscopic or ultrasound guidance using standard techniques, such as currently used for intra-articular injection of corticosteroids. *Sterile drapes or other suitable means should be used to block the patient's view of the injection procedure and the imaging monitor.* The target injection site is the femoral neck, just below the femoral head and inside the joint capsule. The specific approach angle for the injection will be at the discretion of the injecting Investigator. A typical injection procedure is as follows:

The patient is placed in the supine position with the target hip rotated internally 15-20°. The patient should be draped with only the injection site exposed. The skin at the injection site should be prepped using a 1% betadine solution. The soft tissues around the injection site may be anesthetized prior to IA injection using a local injection (e.g. lidocaine) or a topical refrigerant anesthetic (e.g. ethyl chloride). Under guidance, an 18-20 gauge needle will be inserted anteriorly towards the anterior-inferior joint capsule, approximately 8-10 cm below the inguinal ligament and just below the femoral head, taking care to avoid the femoral artery. Needle placement in the capsule is illustrated in Figures 1 and 2. ***Extension tubing that connects the needle to the syringe should not be used.*** If using fluoroscopic guidance, a small amount of fluoroscopic contrast agent (0.5 to 1.0 ml) should be injected through the needle to verify intra-articular placement. If using ultrasound guidance, a small volume of air (up to 0.5 ml) may be injected to verify IA positioning. If pooling of the contrast agent or air around the needle tip is observed, the needle should be repositioned. When contrast agent or air is successfully injected into the joint, intra-articular placement is confirmed.

Figure 1: Injection technique for hip, shown here using ultrasound guidance to inject the left hip (12).

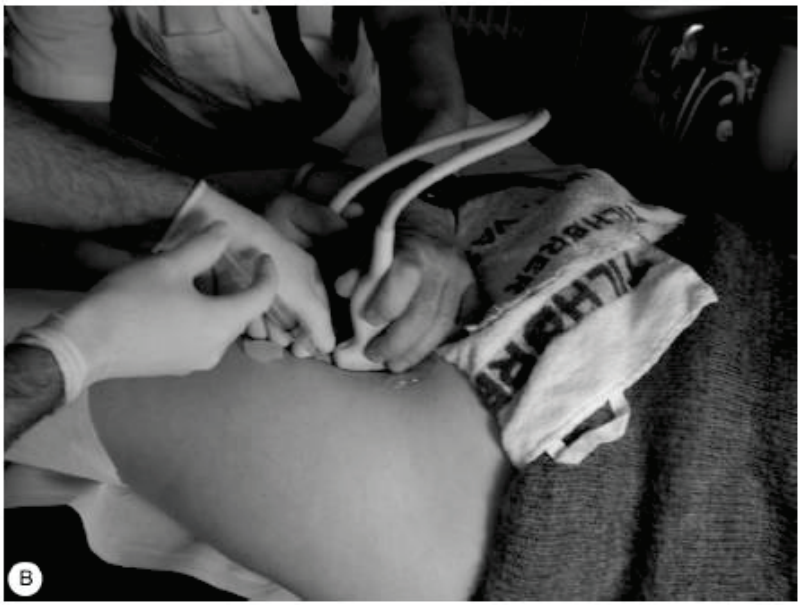
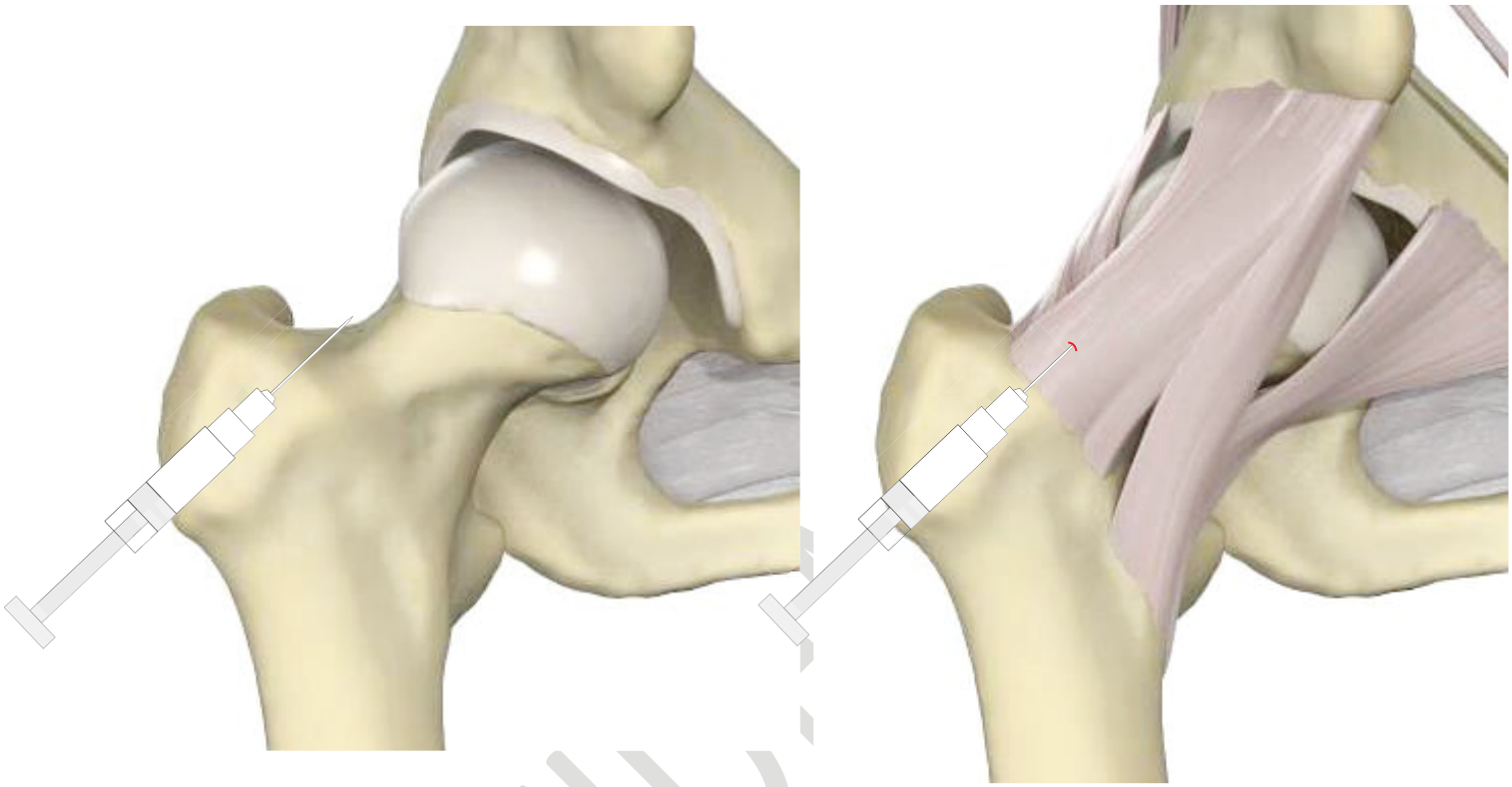


Figure 2: Target needle placement at the femoral neck, shown with and without ligamentous anatomy.



Following confirmation of intra-articular needle placement, the joint may be aspirated to remove osteoarthritic synovial fluid. Finally, 4 ml of either MONOVISC or saline should be injected into the joint. *Intra-articular* anesthetic should NOT be administered as part of the injection procedure.

Following the injection, the patient should be advised to maintain a low level of physical activity for the next 24 hours. Cold therapy and/or acetaminophen may be prescribed to address short term injection site pain.

20.0 APPENDIX D: INFORMED CONSENT FORM

STUDY TITLE: A Pivotal Study Comparing Two Injections of MONOVISC to Two Injections of Saline in Patients with Osteoarthritis of the Hip

Protocol Number 15-MVH-01

SHORT STUDY TITLE: The MONOVISC Hip OA Study
STUDY SPONSOR: DePuy Synthes Mitek Sports Medicine
CLINICAL SITE:
PRINICPAL INVESTIGATOR NAME:

PLEASE READ THIS INFORMATION CAREFULLY AND MAKE SURE THAT YOU UNDERSTAND IT BEFORE SIGNING YOUR NAME TO THE FINAL PAGE

SHOULD YOU TAKE PART IN THIS STUDY?

This form tells you about this research study. You can choose whether or not you want to take part in it. You do not have to take part in the study. Reading this form should help you choose if you want to take part in the study. If at any time you have any questions, feel free to ask the person talking to you about The MONOVISC Hip OA Study.

WHY IS THE STUDY BEING DONE?

This study is being done to determine the effectiveness of MONOVISC for the relief of pain and symptoms of osteoarthritis of the hip. Specifically, the study will determine if MONOVISC is more effective than a placebo treatment when delivered as intra-articular injections (injected directly into the hip joint). In this case, the placebo will be a dilute solution of salt water (saline).

WHY ARE YOU BEING ASKED TO TAKE PART?

You are being asked to be in this study because you have osteoarthritis (OA) in your hip, which your doctor believes is causing your hip pain, stiffness, or reduced function. If you choose to be in this study, you will receive two intra-articular injections of either

MONOVISC or saline, separated by one month. MONOVISC is not currently approved by the United States Food and Drug Administration (FDA) for the treatment of hip OA. However, it is FDA approved for the treatment of knee OA. Your study doctor feels that you might be a good candidate for this study.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 560 people with pain due to hip OA will take part in this study. This study is randomized, meaning that there is a chance that your will get MONOVISC injections and a chance that you will get saline injections. Specifically, you will have a 67% chance of getting MONOVISC injections in this study, and a 33% chance of getting saline injections in this study.

About 374 people will get MONOVISC injections in the study and about 186 people will get saline injections.

WHAT IS INVOLVED IN THE STUDY?

You are being asked to take part in this study at <*Insert Institution Name/Research Site*> , the hospital or medical center where your injections and follow-up visits will occur.

This study will investigate a product called MONOVISC High Molecular Weight Hyaluronan for the treatment of hip osteoarthritis. MONOVISC is a clear, colorless liquid solution. It is a highly viscous solution, meaning that it has a thick consistency similar to that of honey. The main ingredient of MONOVISC is hyaluronic acid (HA), also known as hyaluronan. Hyaluronic acid is a naturally occurring substance that is found in many body tissues, including the skin, eye, and cartilage. It is also an important component of synovial fluid. Synovial fluid is a liquid that bathes the tissues inside articulating joints, such as the knee, hip, shoulder and ankle. This fluid helps lubricate the cartilage in the joint, making it easier for the joint to flex. It is also believed to function as a shock absorber, thereby helping to protect the cartilage from damage and injury. In patients with osteoarthritis, the amount of HA in the synovial fluid is often reduced, which can contribute to pain, stiffness, and loss of function in the osteoarthritic joint. Intra-articular injections

of HA (injected directly into the joint) can help replenish synovial fluid HA, and have been shown in many clinical studies to help reduce pain and restore mobility to patients with osteoarthritis of the knee. We hypothesize that HA injections into the hip could have similar positive effects for hip OA patients.

Your physician will perform two (2) injections directly into your hip joint, with one month between the two injections. For both injections, either fluoroscopy or ultrasound imaging will be used to help the physician accurately guide the needle into the hip joint. The injection procedures will be identical to those currently in use for the injection of other compounds for the treatment of hip OA, such as corticosteroids.

If your doctor uses fluoroscopic guidance, a small amount of contrast agent will be injected into the joint prior to the MONOVISC or saline injection. This contrast agent is easy to see on the fluoroscopy monitor, and will enable the physician to determine accurately the placement of the tip of the needle inside the joint. Similarly, if ultrasound guidance is used, a small amount of air or water may be injected into the joint prior to the MONOVISC or saline injection to ensure accurate needle placement.

During this study, you will only be allowed to take acetaminophen (e.g. Tylenol) to control your hip pain. This is called your "rescue medication" and should only be taken as needed. You should not take more than 4000 mg per day. Prior to your first injection, you should not take any pain medications, except acetaminophen, beginning 7 days prior to the injection. Also, beginning 48 hours prior to your first injection you should not take *any pain medications at all*. This is called a *washout period* and is intended to make sure that you have as little pain medication in your system as possible when you begin your treatment. By doing this, we can assess your true level of hip pain without any treatment, and helps ensure that we can accurately measure the effectiveness of your hip injections in treating your OA pain. You may resume rescue medication following your injection.

You will need to attend follow-up visits at 2, 4, 8, 16 and 26 weeks after your first injection during this study. Your second injection will be given at the 4-week visit. You should not

take any pain medications, including acetaminophen, for 48 hours prior to each visit, for similar reasons to the pre-treatment washout period. Again, this helps ensure that your pain relief from the injections is assessed accurately. At each of these visits, you will be asked to fill out questionnaires about your recent levels of pain, function, and stiffness, and about your overall medical health and wellbeing. These questionnaires are designed to assess your level of pain and functional impairment, your overall health and wellbeing, the medications you have been taking, and any side effects you have experienced.

At each of these visits, you will be asked to fill out questionnaires about your recent levels of pain, function, and stiffness, and about your overall medical health and wellbeing. For example, you will be asked to rate your level of pain or stiffness when doing certain activities, such as walking, standing, or climbing stairs, or at certain times of the day. You will be asked to rate how much difficulty you have in performing certain tasks, such as getting out of a chair or getting dressed. You will also be asked to report any side effects that you may have experienced from your injections.

You will be asked to keep a diary of the amount of acetaminophen you take, and how often you take it, to control your hip pain.

If you choose to be a part of this study, you will need to go to each study visit and follow your study doctor's instructions. You must also tell your study doctor immediately if there are any changes in your health while participating in this study. If you choose to stop being part of the study, your study doctor will plan for your continued medical care in accordance with standard clinical practice.

If you have a serious medical problem during the course of the study, please notify your study doctor as soon as possible and he/she will follow-up with you until the problem has resolved, or until he/she feels that it has stabilized.

HOW LONG WILL I BE IN THE STUDY?

You will be in this study for at least 6 months.

WHAT ARE THE RISKS OF THE STUDY?

As with any intra-articular (IA) injection, injections into the hip joint carry some level of risk. Most of these risks are anticipated to be minor and temporary.

In previous studies using a single (1) intra-articular knee injection of MONOVISC into the knee joint, the following adverse events sometimes occurred:

- injection site pain/swelling
- joint stiffness / swelling / effusion
- arthralgia (joint pain), or aggravated osteoarthritis
- pain in extremity
- synovitis (inflammation of the inner lining of the knee)
- contusion (bruising)
- subcutaneous nodule (just underneath the skin)
- Baker's cyst (a bulge in the back of the knee)

The above risks may be slightly elevated in this study, since you will receive two (2) injections of MONOVISC rather than one (1) injection.

Adverse events that were deemed unrelated to the treatment of the knee included:

- arthralgia (joint pain)
- headache
- pain in extremity
- upper respiratory tract infection
- back pain

The occurrence of all of the above adverse events for MONOVISC was similar to the adverse events for the control (saline) group.

Other risks associated with intra-articular hip injections, regardless of treatment, include:

- temporary injection site pain, swelling or tenderness

- temporary stiffness of your hip
- malfunction of the syringe and/or needle

In rare instances, side effects could include:

- an allergic reaction to the imaging contrast agent that may be injected into your joint if your physician uses fluoroscopy to guide the injection. Symptoms could include redness or inflammation at the injection site or inside the hip joint, hives or itching.
- an allergic reaction to the local anesthetic (lidocaine) that may be injected into your joint as part of the injection procedure. Symptoms could include redness or inflammation at the injection site or inside your hip joint, hives or itching.
- injection site infection
- neurovascular, cartilage or bone damage resulting from the injection itself

There is a low risk associated with radiation from the X-ray evaluation required for inclusion in the study. There is also a low risk from the radiation during fluoroscopy-guided injections

To ensure that you are fully able to complete the study and attend all follow up visits, you should not be pregnant or nursing, or have plans to become pregnant, during this study.

Finally, participation in this study may also involve unforeseeable risks. Your doctor will be able to answer any questions you may have about the risks identified above.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you choose to be in this study, you may experience a significant improvement in your hip pain and/or your ability to participate in physical activities. You may have better mobility and a better quality of life with less pain in your hip. However, there may be no

benefits from participating in this study. Your hip osteoarthritis symptoms may not change or could become worse than before your injections.

The results of the study may be beneficial to the research and medical community. The information we learn from this study may help us to better treat future patients who need treatment for your condition.

ALTERNATIVE PROCEDURES

There are other methods for treating hip osteoarthritis. These include acetaminophen (e.g. Tylenol), NSAIDs (e.g. ibuprofen, naproxen, Celebrex), physical therapy, weight loss, hip joint injections of corticosteroid injections, dietary supplements (e.g. glucosamine and/or chondroitin sulfate), opioids (e.g. Percocet, Oxycodone) and total joint replacement. Your Study Doctor will explain the alternative treatments that are available to you as well as their potential benefits and risks.

VOLUNTARY PARTICIPATION IN THIS STUDY

Your participation in this study is absolutely voluntary. If you do not want to participate within this study or if you decide to stop the study before you complete your follow-up, your decision to do so will have no negative impact on your future or subsequent treatment. A decision to stop the study will not involve penalty or loss of benefits to which you are otherwise entitled. The study may be stopped by a regulatory authority or the Sponsor. Additionally, your doctor may decide to stop your participation in the study, with or without your consent, for medical reasons. He/she will tell you in writing if they have decided to stop your participation in this study. Your doctor will be available if you have any questions regarding your participation in this study.

COSTS AND COMPENSATION

No matter which group you are assigned to, your injection treatments and follow up visits will be paid for by DePuy Synthes Mitek Sports Medicine. You or your insurance

company will be billed for any additional costs that you would have incurred if you were receiving an injection therapy that is already currently in use to treat hip OA, such as corticosteroids.

No matter what group you are assigned to, you will not have to pay the fees for tests required for this study that are not a part of regular medical care for your disease. The company paying for the study will pay for these tests.

The Study Sponsor will not pay for surgeries, procedures, treatments or doctor's visits that are not defined by this study, or that occur after you have ended your participation in this study. An itemized copy of your hospital bill may be sent to the Study Sponsor. This information will be used to look at the cost of your surgery, hospital stay, and other health-economic information. Only your initials and study ID will be given to the study sponsor on this itemized bill.

The Investigator and/or the institution is receiving payment from DePuy Synthes Mitek Sports Medicine to perform the study and/or to recruit participants. The Investigator may have financial arrangements with DePuy Synthes Mitek Sports Medicine or DePuy Synthes beyond the payment for the fees related to the study, and that the study participant may inquire as to those arrangements.

PAYMENT FOR PARTICIPANT

Funding will be available to compensate you for transportation and other costs associated with your follow-up visits. Your doctor will provide you with details about compensation.

TREATMENT AND COMPENSATION FOR INJURIES

If you are injured as a result of being in this study, necessary medical care, which may include emergency treatment, follow-up care, and professional services, will be available to you. Neither your Study Doctor nor DePuy Synthes Mitek Sports Medicine have plans to provide payment or free medical treatment beyond what is necessary to treat your injury. In the event that you believe you have been injured because of taking part in this study, it is important that you contact your study doctor to review the matter with you. Neither the hospital, nor the Federal Government has any programs to provide compensation for persons participating in research projects who may experience injury. You and/or your health plan will be billed for the cost of this care. If your insurance does not pay for your care, or pays only a portion of the cost of such care, you may be billed for any unpaid amounts. By signing this form, you do not waive your rights to seek other legal remedies or release any person from liability for negligence.

CONFIDENTIALITY

Your privacy is important. All information collected during this study will be kept private. Your identity as a participant in this study will remain strictly confidential.

Authorized representatives of this institution, the US Food and Drug Administration (FDA) or other regulatory agency, and the Study Sponsor or its representatives can view your files to make sure that the information provided to them is correct. However, the information received and reviewed by the Study Sponsor or its representatives will not include your name or personal data that will allow your identification. You will only be identified in the study by a study-specific code. If results of this study are published, you will not be identified by name or other personal information.

If you consent to participate in this clinical research study, you will be asked to sign a form that allows the <*Insert Institution Name/Research Site*> to use and disclose your personal information for purposes of the study. For example, the form will allow the <*Insert Institution Name/Research Site*> to share your information with the study staff, with the Institutional Review Board (IRB) or Ethics Committee (EC) and study oversight staff, with other researchers and scientists working on this study, and with any other people who will

need access to your personal information in order to conduct the study. Once information has been disclosed, it could be re-disclosed and no longer protected by federal privacy laws.

The form will also permit the <*Insert Institution Name/Research Site*> to share your personal information with the Study Sponsor, and with those who help the study sponsor manage the study. Your personal information will usually be shared on study forms without your name, except when your name is necessary to make sure that the information on the study forms is accurate.

Your name will not be reported in any publication. Only the data obtained as a result of your participation in this study will be made public. Because this study involves devices that are regulated by the US FDA and other regulatory agencies, individuals from these regulatory agencies may inspect/review records identifying you as a subject in this study.

The medical record is maintained by your Study Doctor or hospital, as applicable, and will be subject to state and federal laws and regulations concerning confidentiality of medical records.

If your contact information changes and your Study Doctor or your Study Doctor's research staff cannot communicate with you during the study follow-up period, your name and most recent contact information may be shared with a missing subject locator service to help obtain your current contact information. This contact information will be shared with your Study Doctor and your Study Doctor's research staff so that you may be contacted to ensure your safety and to collect study data.

This authorization does not have an expiration date. You may change your mind and revoke (take back) this authorization at any time. Even if you revoke this authorization, the Sponsor and the site's clinical, administrative, and research staff may still use or disclose health information they already have obtained about you as necessary to maintain the integrity of this study.

ADDITIONAL INFORMATION

You or your legal representative will be notified in a timely manner of any new information that develops over the course of this study that may affect your willingness to participate in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

FOR FURTHER INFORMATION

If you would wish to obtain more information regarding this study or its risks, advantages, or medical alternatives, please contact the Study Doctor (Investigator). You should also inform the Study Doctor if you have been injured or hospitalized for any reason during the study.

Contact Information

Investigator: _____ Study Coordinator: _____

Telephone: _____ Telephone: _____

For more information about your rights as a study subject contact: <*Insert IRB/EC contact details*>

DOCUMENTATION OF CONSENT

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered to my satisfaction. I agree to take part in this study.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

_____

_____

Date Participant's Signature

I have fully explained to _____ the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____

_____

Date Principal Investigator or Representative's Signature

Include the following section, if the presence of a witness is required at time of consent.

_____

_____

Date Witness' Signature

THE SUBJECT OR HIS OR HER PERSONAL REPRESENTATIVE MUST BE PROVIDED A COPY OF THIS FORM IN ITS ENTIRETY AFTER IT HAS BEEN SIGNED.