

Protocol: 004  
Version Date: January 2017

# Autologous Conditioned Plasma (ACP) Intra-articular (IA) Injections for Knee Osteoarthritis (OA)

## Investigational Plan

### Study Sponsor

**ARTHREX INC**  
1370 Creekside Boulevard  
Naples, Florida 34108 USA

### Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH), the Code of Federal Regulations (CFR) 812 Investigational Device Exemption, 21CFR50, Protection of Human Subjects, 21 CFR 56 Institutional Review Board, 21 CFR 54 Financial Disclosure, and the investigational plan as outlined below. All personnel involved in the conduct of this study have completed human subject's protection training. (i.e.: CITI, GCP)

## LIST OF ABBREVIATIONS

ACI	Autologous Chondrocyte Implantation
ACP	Autologous Conditioned Plasma
AE	Adverse Event
CBC	Complete Blood Count
CFR	Code of Federal Regulation
CRA	Clinical Research Associate
EDC	Electronic Data Collection
FDA	Food and Drug Administration
GF	Growth Factors
HA	Hyaluronic Acid
IA	Intra-Articular
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
NSAID	Non-Steroidal Anti-Inflammatory
OA	Osteoarthritis
OATS	Osteochondral Autograft Transfer System
PAR	Protease-Activated Receptor
PRP	Platelet Rich Plasma
PE	Physical Exam
SAE	Serious Adverse Event
RBC	Red Blood Count
UADE	Unanticipated Adverse Device Effect
WOMAC	Western Ontario an McMaster Universities
WBC	White Blood Count

## Protocol Signature Page

Protocol: 004

### Autologous Conditioned Plasma (ACP) Intra-articular (IA) Injections for Knee Osteoarthritis (OA): A Pivotal Trial

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to the ICH (GCP), 21CFR 812 Investigational Device Exemptions, 21CFR50 Protection of Human Subjects, 21CFR56 Institutional Review Board, 21CFR54 Financial Disclosure and applicable national and local regulations whichever provide the greater protection of the individual. I agree to collect and report all study data according to this protocol.

Investigational Site Name

Primary Clinical Investigator – Print Name

Location (City, Country)

Primary Clinical Investigator Signature

Date (MM – DD – YYYY)

Sub-Investigator Name –Print Name

Sub-Investigator Name / Signature

Date (MM – DD – YYYY)

Sub-Investigator Name –Print Name

Sub-Investigator Name / Signature

Date (MM – DD – YYYY)

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## 1 Protocol Summary

<b>Title:</b>	Autologous Conditioned Plasma (ACP) Intra-Articular (IA) Injections for Knee Osteoarthritis (OA):
<b>Study Design:</b>	<p>This study is a prospective, multicenter (up to 5 sites), randomized, double blind, two-arm study. Ninety (90) patients will be randomized to receive a three single weekly intra-articular (IA) injection of either ACP (n=60) or Phosphate buffered saline (n=30). To evaluate the effectiveness of ACP (three weekly doses IA of 3-6 ml of ACP injected into the knee from baseline through 6 months) to treat Knee OA. Subjects will remain blinded to treatment throughout the study.</p> <p>All patients will have a screening visit and three treatment visits one week apart (visit 2/Week 0, visit 3/Week 1, and Visit 4/Week 2), followed by four follow-up visits; Visit 5/2 months (60 days), Visit 6/3 months (90 days) and Visit 7/6 months 180 days) after the 1st treatment visit.</p> <p>Patients will have a follow-up visit at Visit 8/12 month (365 days) after the 1<sup>st</sup> treatment visit. Note: Once the <b>last patient</b> has reached their 6 month (180 days) Visit, an analysis of the primary endpoint will be performed based on 6-month outcomes.</p> <p>All subjects will continue to be followed out to 12 month (365 days) post-treatment. When the last patient reaches the 6-month time point, all available data will be reported to FDA.</p>
<b>Investigational Arm:</b>	ACP Treatment: Three IA injections of 3-6 mL ACP at 1-week intervals.
<b>Control Arm:</b>	Three Normal Saline IA injections of 3-6 mL at 1-week intervals.
<b>Primary Endpoint:</b>	Change in WOMAC Pain score from baseline to 6 months.
<b>Primary Hypotheses:</b>	ACP treatment is superior to control in terms of mean change from baseline to 6 months (180 days) in the WOMAC Pain score.
<b>Study Success Criterion:</b>	This study will be achieve its study success criterion if it is demonstrated that the mean improvement in WOMAC Pain score from baseline to 6 months (180 days) is significantly larger for ACP treatment compared to saline control with a 1-sided $p \leq 0.025$ .

**Conditional Endpoint:** If superiority in WOMAC Pain score improvement is established, the study is designed to provide additional evidence of superiority in terms on improvements in WOMAC Function score from baseline to 6 months (180 days).

**Conditional Hypotheses:** ACP treatment is superior to control in terms of mean change from baseline to 6 months (180 days) in the WOMAC Function score. No multiplicity adjustment is necessary when testing the conditional hypothesis.

**Secondary Endpoint:** The following will be evaluated as secondary endpoints in descriptive analyses: WOMAC Total (Pain, Function, Stiffness) Scores 2 (60 days), 3 (90 days) and 12 month (365 days) and changes to these time points. WOMAC Stiffness Score at Month 6 (180 days) and changes to Month 6.

**Safety Endpoints:** Adverse events will be compared between ACP treatment and the control in terms of both per patient incidence and total.

**Timeline:**

First Subject In:	7/2016
Last Enrollment (90 subjects):	7/2017
12 month follow-up:	7/2018

**Study Population:** Male and female patients between the ages of 18 and 70 years old, with at least 6 weeks of symptomatic OA of the tibio-femoral or patella-femoral compartment of the target knee, as evidenced by radiographs and continued pain.

**Inclusion Criteria:** General:

1. The subject is  $\geq 18$  to 70 years of age.
2. The subject presents with complaints of continued pain of target knee for at least 6 weeks.
3. The subject has documented radiographic evidence of OA in the tibio-femoral or patella-femoral compartment of the target knee (Kellgren-Lawrence Grades II-III), using radiographs performed within 24 weeks of screening.
4. The subject has a WOMAC pain score of at least 8 out of 20 and at least moderate pain (a score of 2) for at least 2 questions on activities.

**Exclusion Criteria:** General:

1. Grade I and IV on the target knee Kellgren-Lawrence grading scale



2. Subject has clinically 3+ effusion of the target knee (stroke test grading system).
3. Subject has significant ( $> 10^0$ ) valgus or varus deformities as evidenced by standard of care X-ray.
4. Subject has had systemic or IA injection of corticosteroids in any joint within three months prior to screening.
5. Viscosupplementation in any joint in the past six months.
6. Subject which, in the investigator's opinion, has an increased risk for post procedure bleeding (e.g., bleeding disorder or taking anticoagulants except low-dose aspirin).
7. Subject had prior open surgery on the target knee within 12 months or knee arthroscopy within 6 months
8. Subject has inflammatory disease of either knee other than OA.
9. Subject which, in the investigator's opinion, has underlying medical conditions that could interfere with the evaluation of the outcome.
10. Subject with positive pregnancy test, or breast feeding.
11. Subject with plans to participate in other clinical trial involving medical or surgical intervention in the next 12 months.
12. Subject with any condition (including cognitive impairment) that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.
13. Subject has rheumatoid arthritis or gout
14. Subject has history or a current infection at the affected joint.
15. Subject with plans to undergo any elective orthopedic surgery in the next 12 months.
16. Subject requires pain management therapy (with the exception of acetaminophen) not related to the target knee.

## 2 Introduction

### 2.1 Background

Arthritis is a very prevalent disease all over the world, and the United States is no exception. Between 2010 and 2012, 52.5 million adults in the US ages 18 and over (which is 22.7% of the total adult population in the US) were diagnosed with some form of arthritis. Out of the total adult population in the US, 49.7% of those ages 65 or over had an arthritis diagnosis.<sup>1</sup> Furthermore, by 2030, the number of adults in the US with doctor-diagnosed arthritis is expected to rise to almost 67 million people.<sup>2</sup>

The prevalence of doctor-diagnosed arthritis by race and gender between 2010 and 2012 was: 35.7 million whites, 7.5 million Hispanic adults, 6.2 million blacks, 2.6 million Asians and 420,000 adults of other races. Additionally, between 2010 and 2012, the prevalence of doctor-diagnosed arthritis out of the total US population was 26% for adult women and 19.1% for adult men. Lastly, the prevalence of doctor-diagnosed arthritis from 2010-2012 in the total US population was 7.3% for ages 18-44 and 30.3% for ages 45-64.<sup>1</sup>

Knee OA is a condition where articular cartilage at the knee is worn away, leading to severe pain for the patient. This pain can lead to decreased mobility and inability to function. Therefore, as the population gets older and lives longer, the number of people with OA will increase significantly.

OA can be classified as either primary or secondary. Primary OA is usually diagnosed when an underlying cause cannot be found.<sup>3</sup> Secondary OA, however, indicates there is some underlying cause, such as an endocrine or metabolic disorder, trauma, malformation, or some genetic cause.<sup>4</sup> The clinical manifestation of OA is the destruction of cartilage, and this can be affected by the synovial membrane, the subchondral bone, and the meniscus. Prior to the destruction of cartilage, the balance of anabolic cytokines such as TGF- $\beta$ 1, bone morphogenic protein-7 (BMP-7), and IGF-1, and catabolic cytokines such as IL-1 $\beta$  and TNF- $\alpha$  in the joint space is disturbed.<sup>5</sup> When OA becomes a significant issue, it is usually found that the catabolic cytokines play a much larger role in creating cartilage degradation.

Many groups have investigated what risk factors could be predictive for OA, such as age, weight, gender, and genetics.<sup>6-8</sup> However, there is no major consensus on which risk factor is the best indicator of OA, if at all. Due to its uncertain disease etiology and progression, as well as the pain it causes, the need for an effective OA treatment that allows patients to go back to normal function as quickly as possible is important.

## 2.2 Treatment Options

The current non-surgical standard of care for OA is treatment with substances that provide pain relief. The most common type of injection is corticosteroids such as triamcinolone, methylprednisolone, and betamethasone, which are designed to dissolve slowly to provide pain relief. As shown in clinical studies, corticosteroids can provide long-term pain relief equal to or better than placebo (saline) for up to 24 weeks.<sup>9</sup> The effect of corticosteroids in OA is evident in a study that showed a decrease in the amount of macrophages and lymphocytes in the synovial tissue, with an increase in new fibroblasts and collagen.<sup>10,11</sup> However, another study found that even though macrophages are reduced, this does not come with a decrease in MMPs.<sup>10,12</sup>

Since knee synovial fluid contains HA, many companies have also pursued viscosupplementation or injection of gels such as HA into the knee. HA is isolated from chicken combs or produced from bacteria, and this HA is injected into the joint for pain relief. Exogenous HA can reduce pain through several different mechanisms – by inhibiting inflammatory mediators such as IL-1 $\beta$ , binding to neuropeptides that shield pain receptors, stimulating production of new endogenous HA, and decreasing production of MMPs which can destroy cartilage.<sup>13</sup> HA with differing molecular weights (from 500-730 kDa to 6000 kDa) have been produced, and all have had success in clinical studies to receive FDA approval in the United States. In pooled comparisons between HA and placebo for OA, results indicated that there were significant differences in pain and physical function between 1 to 4 weeks, but that these measurements were similar by 14 weeks.<sup>13</sup> Studies that measured HA vs. corticosteroid injections found a significant difference in pain relief for the corticosteroids compared to HA from 0 to 4 weeks, but that HA had a significant improvement in pain relief compared to corticosteroids from 5 to 13 weeks.<sup>13</sup>

Even though corticosteroids and HA have been successful in treating OA, there has been a movement towards treating OA with natural or autogenous substances. PRP is a mixture of platelets at a higher concentration than whole blood, mixed with blood plasma, and red and white blood cells in some cases. When injected, the platelets in PRP become activated and release GFs and cytokines which modify the healing process of the damaged or modified tissues. Using this autologous therapy, there are no concerns with allergic or immunogenic responses to the patient, unlike the possibility with allogeneic, xenogeneic, or alloplastic substances.

Since PRP is being proposed as a therapy for OA, the effect of platelets on pain reduction needs to be explored. When platelets are activated, in addition to releasing GFs, they release serotonin and histamine, known activators in the nociceptive and inflammatory processes, respectively. However, when activated by thrombin, these cytokines do not appear to have major effects on either process to increase pain.<sup>14</sup> Therefore, it is not believed that PRP itself contributes to pain. Protease-activated receptor-4 (PAR<sub>4</sub>) is a newly discovered receptor released

from platelets when activated by thrombin or trypsin; it is very analgesic and has anti-nociceptive properties.<sup>15</sup> This receptor is a candidate for the proposed decrease in pain when PRP is injected.

## **2.3 Investigational Treatment**

PRP is an autologous treatment in which blood is drawn from a patient and is spun down to produce a separation of platelets and plasma from WBCs and RBCs. The platelets and plasma are then recovered after centrifugation and re-injected into the patient's body at or near the site of injury or damage. This technique has seen increased use in Orthopaedic and sports medicine in the past 10 years.

## **2.4 History of Development**

The concept of PRP was developed in the blood banking field. A newspaper article from January 9, 1961 stated that, at the time, PRP could increase the supply of donated human platelets and plasma in blood banks by up to 30 times over current supply.<sup>16</sup> The American Red Cross set the definition of PRP as at least  $5.5 \times 10^{10}$  platelets per 50 mL of plasma. Since the average platelet concentration in humans is between 150000-450000 platelets per  $\mu\text{L}$ , this leads to a definition of PRP concentration as 2X to 7X over baseline.<sup>17</sup> This fits the definition of PRP as being any concentration of platelets over baseline whole blood.

When PRP is clotted, it is an autologous version of allogeneic fibrin glue or fibrin sealant,<sup>18</sup> which has a history of use since the 1900s,<sup>19,20</sup> primarily for haemostasis during surgeries. However, PRP did not receive recognition clinically until the mid-1990s, mostly in dentistry. The seminal paper in the field was published in 1998 by Dr. Robert Marx.<sup>21</sup> He used PRP, at a 3X concentration over baseline, in combination with cellular marrow grafts from the ilium. A significant increase in new bone was seen in the cellular marrow with PRP group vs. marrow alone at 6 months. Other studies since the Marx paper have focused on the use of PRP in dentistry.<sup>22,23</sup> Many other clinical studies have focused on the use of PRP for various orthopedic and sports medicine applications.<sup>24-26</sup>

## **2.5 ACP Definition and Biological Description**

In December 2008, Arthrex received 510K clearance (#BK070069) for the ACP double syringe system. The system is used to facilitate the safe and rapid preparation of autologous PRP from a small sample of blood at the patient's point of care. The indication is that the PRP can be mixed with autograft and allograft bone prior to application to an orthopedic surgical site as deemed necessary by the clinical use requirements. Arthrex Inc. is seeking to expand this indication for the use of PRP to be injected into the knee for the treatment of OA. This study is designed to investigate the safety and effectiveness of ACP in treating pain in subjects with primary OA of the knee.

There are many biological factors in ACP which combine to create an optimal healing environment for OA. Table 1 below highlights the prominent GFs and cytokines involved in the OA healing process. Many studies have shown the importance of these GFs and cytokines, both in the pathogenesis and possible resolution of OA.<sup>5,27-29</sup> These growth factors and cytokines are found in PRP, and specifically in ACP.<sup>30,31</sup>

Factor	Name	Effects/Activities
PDGF-AB	Platelet-derived growth factor AB	Cell proliferation and mitogenesis
TGF-β1	Transforming growth factor-beta1	Extracellular matrix (ECM) synthesis, cell proliferation
VEGF	Vascular endothelial growth factor	Angiogenesis, cartilage metabolism
IL-10	Interleukin-10	Prevention of IL-1β and TNF-α activity
IL-1ra	Interleukin-1 receptor antagonist	Prevention of IL-1β and TNF-α activity
IL-1β	Interleukin-1 beta	Cartilage degradation and inflammation
TNF-α	Tumor necrosis factor-alpha	Cartilage degradation and inflammation

## 2.6 Dosing and Frequency

The volume of ACP after the whole blood is centrifuged will vary between individuals. In this study, the rationale for a dosage between 3-8 mL with an injection frequency of once a week for 3 weeks is based on previous studies, as listed in the table below. These studies used either a plasma-based PRP system similar in platelet and WBC concentration to ACP, or actual ACP which is also a plasma-based PRP system. The other studies, however, use buffy coat-based PRP systems with a higher WBC concentration than ACP. They have longer times in between injections due to the extra inflammation caused by the additional WBCs in the buffy coat-based PRPs.

Study – Author	Year	PRP Volume	Dosage Frequency	Purpose
<u>“IA injection of an autologous PRGF for the treatment of knee OA: a retrospective cohort study” – Sanchez et al<sup>32</sup></u>	<u>2008</u>	<u>6-8 mL</u>	<u>3 weekly injections</u>	<u>OA IA injection</u>
<u>“Comparison between HA and PRP, IA infiltration in treatment of gonarthrosis” – Cerza et al (unpublished)<sup>33</sup></u>	<u>2011</u>	<u>5.5 mL</u>	<u>4 weekly injections</u>	<u>OA IA injection</u>
“PRP: IA knee injections produced favorable results on degenerative cartilage lesions” – Kon et al <sup>34</sup>	2010	5 mL	3 injections every 21 days	OA IA injection
“Injection of PRP in patients with primary and secondary knee OA” – Sampson et al <sup>35</sup>	2010	~6 mL	3 injections every 4 weeks	OA IA injection
“PRP IA knee injections for the treatment of degenerative cartilage lesions and OA” – Filardo & Kon et al <sup>36</sup>	2011	5 mL	3 injections every 21 days	OA IA injection
“PRP IA injection vs. viscosupplementation as treatments for cartilage pathology: from early degeneration to OA” – Kon & Mandelbaum et al <sup>37</sup>	2011	5 mL	3 injections every 2 weeks	OA IA injection

## 2.7 Alternative Practices and Procedures

Alternative practice and procedures include nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injection of corticosteroids; avoidance of activities that cause joint pain; exercise; physical therapy; weight loss; and removal of excess fluid from the knee. For patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement are also alternative treatments.

## 3 Study Design, Endpoints and Criteria

### 3.1 Study Design

This study is primarily investigating the effectiveness ACP IA in patients with OA of the knee in reducing pain.

This study is a prospective, multicenter, double blind, clinical study with up to 5 sites, approximately 90 subjects who are candidates for IA ACP treatments for knee OA. Ninety (90) subjects will be randomized to receive three single weekly intra-articular (IA) injection of either ACP (n=60) or Phosphate buffered saline (n=30).

To evaluate the effectiveness of three weekly doses IA of 3-6 ml of ACP injected into the knee from baseline through 6 months (180 days).

All patients will have a screening visit and three treatment visits one week apart (Visit 2 / Week 0, Visit 3 / Week 1, and Visit 4/ Week 2), followed by three follow-up visits; Visit 5/ 2 months (60 days) Visit 6/ 3 months (90 days) and Visit 7/ 6 month (180 days) after the 1st treatment visit.

Patients will have an additional follow-up Study visit at Visit 8/ 12 month (365 days ) after the 1<sup>st</sup> treatment visit. Note: Once the **last patient** has reached their 6 month Visit (180 days), an analysis of the co-primary endpoints will be performed based on 6-month (180 days) outcomes. Subjects will remain blinded to treatment throughout the study.

### 3.2 Study Hypotheses and Endpoints

#### 3.2.1 Primary Effectiveness Hypotheses for Pain:

ACP treatment is superior to control in terms of mean change from baseline to 6 month (180 days) in the WOMAC Pain score.

#### 3.2.2 Conditional Effectiveness Hypotheses for Function:

The study is designed to permit an additional labeling claim beyond reduction in pain while maintaining control of type 1 error. The additional labeling claim concerns improvement in patient function. This will be measured using change from baseline to Month 6 (180 days) in the WOMAC Function score. In order to control type 1 error for this study, these two hypotheses were hierarchically specified. First, the primary endpoint concerning WOMAC pain will be tested. If

the 1-sided p-value  $\leq 0.025$ , it will be concluded that the investigational treatment is superior to control in terms of pain reduction and the study will be considered as having met its Study Success criterion. In this case, additionally, the treatment group difference in mean change from baseline to Month 6 (180 days) will also be tested for the WOMAC Function score using a 1-sided p-value  $\leq 0.025$ . Testing of the conditional endpoint is contingent on demonstrating superiority in terms of WOMAC pain and it is not intended to require superiority in both WOMAC Pain and WOMAC Function for Study Success.

### **3.2.3 Primary and Conditional Endpoints:**

The primary and conditional endpoints of WOMAC Pain and Function will be assessed at 6 months (180 days) post-treatment. All subjects will continue to be followed out to 12 months (365 days) post-treatment. When the last patient reaches the 6-month (180 days) time point, all available data will be reported to FDA. Note: Subjects will remain blinded to their randomized treatment throughout the study.

### **3.2.4 Secondary Endpoints:**

WOMAC Total, (Pain, Function, Stiffness) Scores 2 (60 days), 3 months (90 days) and 12 months (365 days) and changes to these.

WOMAC Stiffness Score at Month 6 (180 days) and changes to Month 6 (180 days).

### **3.2.5 Safety Endpoint**

Adverse events will be compared between ACP treatment and the control in terms of both per patient incidence and total.

## **3.3 Study Population**

The investigator will invite prospective patients to enroll in the study that meet the inclusion/exclusion criteria and have signed the informed consent.

## **3.4 Study Subject Eligibility Criteria**

Candidates must meet all eligibility criteria to be eligible for study participation:



### 3.4.1 Inclusion Criteria

1. The subject is  $\geq 18$  to 70 years of age.
2. The subject present with complaints of continued pain of primary knee for at least 6 weeks.
3. The subject has documented radiographic evidence of OA in the tibio-femoral or patella-femoral compartment of the target knee (Kellgren-Lawrence Grades II-III), using radiographs performed within 24 weeks of screening.
4. The subject has a WOMAC pain score of at least 8 out of 20 and at least moderate pain (a score of 2) for at least 2 questions on activities

### 3.4.2 Exclusion Criteria

1. Grade I and IV on the target knee Kellgren-Lawrence grading scale
2. Subject has clinically 3+ effusion of the target knee (stroke test grading system).
3. Subject has significant ( $> 10^0$ ) valgus or varus deformities as evidenced by standard of care X-ray.
4. Subject has had systemic or IA injection of corticosteroids in any joint within three months prior to screening.
5. Viscosupplementation in any joint in the past six months.
6. Subject which, in the investigator's opinion, has an increased risk for post-procedure bleeding (e.g., bleeding disorder or taking anticoagulants except low-dose aspirin).
7. Subject had prior open surgery on the target knee within 12 months or knee arthroscopy within 6 months
8. Subject has inflammatory disease of either knee other than OA.
9. Subject which, in the investigator's opinion, has underlying medical conditions that could interfere with the evaluation of the outcome.
10. Subject with positive pregnancy test, or breast feeding.
11. Subject with plans to participate in other clinical trial involving medical or surgical intervention in the next 12 months.
12. Subject with any condition (including cognitive impairment) that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.
13. Subject has rheumatoid arthritis or gout
14. Subject has a history of or a current infection at the affected joint.
15. Subject with plans to undergo any elective orthopedic surgery in the next 12 months.
16. Subject requires pain management therapy (with the exception of acetaminophen) not related to the target knee.

### **3.5 Kellgren Lawrence Grades of OA**

1 = Possible osteophytes only

2 = Definite osteophytes and possible joint space narrowing

3 = Moderate osteophytes and/or definite narrowing of the joint space

4 = Large osteophytes and severe joint space narrowing and/or bony sclerosis

### **3.6 Stroke Test Grading System**

Zero = No Wave produced on downstroke

Trace = Small wave on medial side with downstroke

1 + = Larger bulge on medial side with downstroke

2+ = Effusion spontaneously returns to medial side after upstroke (no downstroke necessary)

3 + = So much fluid that it is not possible to move the effusion out of the medial aspect of the knee.

Please reference Appendix 2-2 Knee Exam: Stroke Test Grading.

### **3.7 WOMAC**

The WOMAC index is a 24-item questionnaire completed by the patient focusing on joint pain, stiffness, and loss of function related to OA of the knee. The WOMAC pain score ranges from 0 to 20, the WOMAC stiffness score ranges from 0-8, and the WOMAC physical function score ranges from 0 to 68. The overall WOMAC score is the sum of these components, and ranges from 0 to 96. Each of these scores is often normalized to a 100 point scale. For the overall score and each of its components, higher scores indicate greater disability.

### **3.8 Allowed Concomitant Medications and Prohibited Treatments**

Only acetaminophen is permitted for pain while in the study. NSAIDs and other non-acetaminophen pain medication are not permitted for the first 6 months of the study. Oral steroids, steroid injections and Viscosupplementation injections are not permitted for the first 6 months (180 days) of the study.

### **3.9 Screen Failures**

Screen failures are those subjects who have signed the informed consent, but are not eligible to start treatment following the Screening/Baseline assessments. A log of all subjects screened for the study but not entered into the study will be

maintained by each investigational site. The reason(s) for screen failure will be recorded on the log.

### **3.10 Withdrawal Criteria**

Potential reasons for discontinuation may include, but are not limited to:

Subject Withdrawal: Subject participation in a clinical trial is voluntary. The subject may discontinue participation (refuse all subsequent testing and follow-up procedures) at any time without penalty or loss of benefits.

Investigator Termination: The investigator may terminate the subject's participation without regard to the subject's consent if the investigator believes it is medically necessary and in the best interest of the subject.

Lost to Follow-up: The subject does not complete the 6 month follow-up but has not "officially" withdrawn from the study. Failure to return for follow-up visits is not a criterion for withdrawal. In order to consider a subject lost to follow-up, site personnel should make all reasonable efforts to locate and establish communication with the study subject. All attempts should be documented within the source documents, indicating date, time, method, and site personnel. A minimum of three documented attempts should be made without response from the study subject in order to classify a subject as lost to follow-up. Should subject discontinuation occur, the reason(s) for discontinuation must be documented in the source documents along with notification to Arthrex Inc. or designee. Subjects who withdraw or are discontinued from the study will not be replaced.

### **3.11 Study Duration**

The study enrollment period will be approximately 12 months (365 days). The co-primary endpoints will be assessed at 6 months (180 days) post-treatment. Patients will continue to be followed out to 12 months (365 days) post-treatment until the last patient reaches the 6-month (180 days) time point. Therefore, the overall study duration will be approximately 24 months.

### **3.11 Unscheduled Visits**

Unscheduled visits may occur due to changes in subject circumstances that require immediate attention. (e.g., adverse event: increased or uncontrolled pain requiring treatment).

### **3.12 Subject Compensation**

Each subject who returns for each follow-up visit within the protocol required time frame will receive a reasonable compensation to offset the cost of meals, transportation, parking, and other such expenses, as approved by the IRB.

Compensation is provided to the subject by the investigational site. Compensation amounts are specified in the Informed Consent and the Clinical Trial Agreement.

## 4 Risk Analysis

### 4.1 Benefits

The Arthrex ACP system allows rapid and efficient concentration of platelets and growth factors from autologous blood for use at the treatment site. The unique double syringe allows for convenient and safe handling as the whole preparation process takes place in a closed system. The ACP system is more affordable, easier to use, and has quicker procedure time when compared to other conventional PRP devices. WBCs and RBCs are NOT concentrated within the ACP system. These cells can cause a detrimental effect on the healing process due to release of derivative proteins and reactive oxygen species.

If the procedure is successful, possible benefits may include significant decrease your knee pain, improvement in knee function and range of motion. It is not guaranteed that subject's condition will improve as a result of participating in this study and may receive no direct benefit at all.

### 4.2 Risks and Mitigations

Since ACP is autologous and prepared from a patient's own blood, there are no issues with transmission of diseases such as human immunodeficiency virus (HIV), hepatitis, or Creutzfeldt-Jacob disease (CJD or "mad cow" disease). Also, any immunogenic issues that could occur with allograft or xenograft preparations should not be a problem.<sup>23,38</sup>

The potential risks associated with the ACP double syringe system can be split into two groups:

- Preclinical – double syringe operation, and centrifugation
- Clinical – delivery of ACP and the subsequent effects of ACP in the body

From the preclinical side, the primary concern is associated with the function and ease of use of the syringe, such as difficulty drawing blood through the syringe, or difficulty depressing the plunger. The risk to the patient, as a result of this is an additional needle stick. Arthrex has implemented appropriate manufacturing assembly steps, user training, and product testing procedures to ensure that the syringes meet customer requirements. Arthrex confirms that no other measures are necessary to mitigate risk.

From the clinical side, the procedure requires a peripheral blood draw as well as an IA injection. Potential risks to the patient can include: deep and superficial infections; allergies and other reactions; development of a hematoma; damage to blood vessels and nerve damage resulting in pain or numbness; and delayed wound healing. These risks can be mitigated by making sure that only trained personnel carry out all the blood draws and IA injections.

## 5 Device Description

### 5.1 Device Description

The Arthrex ACP® double syringe is a specially designed outer syringe which holds approximately 16 mL of liquid. The syringe is made of polypropylene, a well-known biocompatible material used for a wide variety of medical devices. Within this outer syringe, a smaller syringe is connected over a Luer-lock (hub) female connector. At the distal end of both syringes there is a male luer-lock connector (nozzle) for fitting the female connector (hub) or adaptor for connection to a syringe or cannula. A threaded screw cap (containing the Luer-lock nozzle) at the distal end of the outer syringe can be removed to allow the user to fill the outer syringe (Figure 5.1.1).



Figure 5.1.1

ACP double syringe with cap

The special design of the double syringe facilitates the rapid preparation of autologous PRP and concentrated PPP from a small sample of blood.

A Rotofix 32 A bench top centrifuge is used to centrifuge the double syringe (Figure 5.1.2). After centrifugation, the special design of the double syringe allows for the transfer of the supernatant (ACP) from the outer syringe into the smaller, inner syringe, under aseptic condition (Figure 5.1.3).



Figure 5.1.2

Rotofix 32 A bench top centrifuge



Figure 5.1.3

Supernatant (ACP) is aseptically transferred into the small, inner syringe



ACP Kit Series I – IDE-ABS-10011-IDE

Component #	Description	Qty
ABS-10014U	Double Syringe	1
REF-645	Double Syringe Luer Cap	1
REF-337	Tourniquet – Disposable, Latex-Free	1
REF-338	Alcohol Pads	1
REF-01530	Butterfly Needle Infusion Set, 19G	1
REF-340	Gauze Sponge, 2x2 in.	1
C12690-01	Band-Aid, Latex-Free	1
REF-443	Hypodermic Needle, 22G, 1.5"	1
	Patient Labels (inside kit)	2

## 5.2 Principle of Device Operation

The ACP® double syringe system is designed to facilitate the rapid preparation of autologous PRP from a small sample of blood. After centrifugation, the special design of the double syringe allows for



the transfer of the supernatant from the outer syringe into the inner, smaller syringe under aseptic condition.

A butterfly needle is used to withdraw approximately 16 mL of patient blood. The butterfly needle is removed and a screw cap is placed on the syringe. The double syringe is put into one bucket of the bench top centrifuge (Rotofix 32 A) for 5 min. at 1500 rpm.

Thereafter, the supernatant is transferred to the inner syringe under aseptic condition by pressing the wings of the double syringe together. See Figure 5.2.1 below for reference.

Figure 5.2.1 Principle of Operation



The ACP Kit contains the necessary components to facilitate blood draw



Withdraw blood using provided butterfly needle



Centrifuge 1500 rpm for 5 min



Transfer plasma into smaller syringe and unscrew



ACP ready for use

### 5.3 Analytical Study

An analytical study was conducted to determine the amount of GFs, thrombocytes/platelets (T), erythrocytes/RBCs (E), and leukocytes/WBCs (L) present in ACP.

The density of the blood cells, triglycerides, and 7 selected GFs in ACP were compared to whole blood drawn from 12 healthy test subjects and centrifuged using the ACP double syringe System.

The GFs were determined on the basis of the whole blood samples and plasma samples using ELISA kits (R&D Systems, Inc.). A blood cell count was also performed (Bioscientia Labs, Germany).

Table 5.3.1 Analysis overview

Sample	Analysis
Whole blood	E, L, T
Whole blood plasma	GFs and triglycerides
ACP	E, L, T

#### Results:

The density of thrombocytes in the ACP was increased 2-fold compared to whole blood. The concentration of the leucocytes and erythrocytes in the ACP was 10% and 1% of the whole blood, respectively.

The concentration of all GFs in the ACP was significantly higher than in the whole blood.

The triglyceride values of the ACP do not differ from those for the whole blood.

See Table 5.3.2 for a complete list of the test results.

Table 5.3.2 Results of the ACP analysis

Cell Count		Whole Blood	ACP (Autologous Conditioned Plasma)
Thrombocytes (T) [10E3 / µl]	Mean	242	550
	SD	62	126
Erythrocytes (E) [10E6 / µl]	Mean	4,97	0,05
	SD	0,24	0,01
Leukocytes (L) [10E3 / µl]	Mean	7,11	0,69
	SD	1,67	0,83
Growth Factors		Whole Blood Plasma	ACP
IGF-I [ng/ ml]	Mean	121	122
	SD	50	51
EGF [pg/ ml]	Mean	113	396
	SD	116	112
VEGF [pg/ ml]	Mean	32	130
	SD	40	124
PDGF-AB [pg/ ml]	Mean	2467	30979
	SD	2210	8525
PDGF-BB [pg/ ml]	Mean	1760	4529
	SD	2042	1458
TGF-b-1 [pg/ ml]	Mean	36506	92824
	SD	38380	21504
TGF-b2 [pg/ ml]	Mean	98	197
	SD	128	131
Triglyceride [mg/ ml]	Mean	506	466
	SD	126	171

## 6 Study Procedures

### 6.1 Subject Recruitment, Consent and Enrollment

The investigator or designee should review all prospective subjects' medical histories to screen for eligibility.

#### 6.1.1 Subject Recruitment

The investigator will provide patients who present to his practice with symptomatic knee pain and Radiographic evidence of OA in the tibio-femoral or patella-femoral compartment of the target knee (Kellgren-Lawrence Grades II- III), the opportunity to be considered as a candidate for this trial. Pre-procedure screening to confirm the diagnosis is not considered part of the study; however the informed consent form will advise the subject that their medical history records used to confirm diagnosis and X-rays will be incorporated into the study record. If all X-ray required for inclusion have not been done or present in medical records within 24 weeks of screening, they must be taken prior to randomization. These X-rays include:

- Weight bearing hip to ankle Anterior –Posterior (AP) of the involved knee (extremity)
- Standing AP of both knees in extension
- Standing Posterior-Anterior (PA) weight bearing of both knees at 45 degrees of flexion
- Supine lateral of the involved knee
- Sunrise view of both knees

#### 6.1.3 Consent

The investigator will prepare an informed consent form (ICF) in accordance with this study protocol and all regulatory requirements (21 CFR Part 50) using the sample informed consent form provided by the sponsor. Changes to the ICF and amended ICF(s) must be approved by Arthrex's Clinical Research prior to submitting to IRB. A copy of the final IRB-approved ICF or amended ICF(s) must be maintained as part of the study file.

The subject candidate will be introduced to the study by the investigator. Interested patients will have the study thoroughly explained to them by the investigator and/or site coordinator. Additionally, informed consent forms will be provided to the patient so they may take home and review with significant others if desired. The informed consent process includes ensuring all of the patient's questions are answered. Once the subject decides if they want to participate in the clinical trial,

the site will obtain a signed consent from the subject and make arrangements to schedule them for Visit 2.

Prior to any study procedures, all subjects must document their consent for study participation and authorization for use and disclosure of health information by signing the IRB approved Informed Consent form.

#### **6.1.4 Subject Status**

Only those patients who meet the inclusion / exclusion criteria and who have signed the informed consent for the trial and proceeded to Visit 1 will have a status of “Screened”. Subjects that are screened but do not meet inclusion/exclusion criteria will be considered, “Screen failed.” Once the subject is treated (has either randomized treatment) they will be considered “treated”.

Subjects that are treated (has either randomized treatment) and do not complete the follow final visit will be considered “early termination”. Subjects that complete Visit 8/12 months (365 days) will be considered complete.

Subjects receiving treatment, but not meeting all inclusion / exclusion are considered treated, and will be followed per the protocol but will be considered protocol deviations.

### **6.2 Study Visits**

For this study all subjects will have a screening visit and three treatment visits to receive a series of intra-articular injections one week apart. Subjects will then return for follow-up visits at 2 months (60 days), 3 months (90 days), 6 months (180 days) and 12 months (365 days) post-treatment 1<sup>st</sup> injection.

#### **6.2.1 Screening Visit 1 (-7 to -2 days)**

Once the subject has signed the informed consent and prior to treatment, he/she will have the following data collected and procedures conducted:

- Medical history/Demographics
- Physical exam (Temperature, heart rate and blood pressure)
- Radiograph(s) (if not part of medical record) refer to section 6.1.1
- Urine pregnancy test (for females with childbearing potential)
- Concomitant Analgesics/Treatment review
- WOMAC survey (pain, stiffness, function)
- Inclusion/exclusion criteria review
- Kellgren-Lawrence grading
- Strokes Test Grading

- Inform subjects that they will return for visit 2 to receive their 1<sup>st</sup> IA injection and then to return at 1 week and 2 weeks for an additional IA injection. Additionally, inform that they will need to return for visits at 2, 3 and 6 months post-treatment 1<sup>st</sup> injection.

### **6.2.2 Treatment: Visit 2 (Day 0)**

All subjects will have the following procedures at visits 2 prior to randomization:

- Concomitant Analgesics/Treatment review
- Inclusion /Exclusion review
- Whole Blood and ACP collected for analysis

#### **6.2.2.1 Randomization**

Once confirmed that the subject has met all the inclusion/exclusion criteria, the principal investigator will be permitted to proceed to randomization of the subject. An automated Internet-based randomization system will ensure concealed randomization of eligible consenting subjects. Subjects will be randomized to one of 2 treatment groups.

**6.2.2.2** Investigational Arm: Three IA injections of 3-6 mL ACP at 1 week intervals. (n=60)

**6.2.2.3** Control Arm: Three IA injections of 3-6 mL Normal Saline at 1 week intervals. (n=30)

*Note: The volume of PRP produced during the ACP procedure differs per individual; therefore we are providing a range as noted in earlier justification. Additionally, the amount of Normal Saline will be determined by the volume of PRP produced during the ACP procedure, except the control subjects will receive only the same volume of Normal Saline as produced by their own blood during the ACP procedure.*

#### **6.2.2.4 Venipuncture and Blood collection**

Refer to Venipuncture and Blood Collection Procedure (Appendix 2-3)

#### **6.2.2.5 Processing ACP**

Refer to Venipuncture and Blood Collection Procedure (Appendix 2-3)

#### **6.2.2.6 Blinding Procedure:**

Subject blinding will be maintained by drawing blood from all subjects, then preparing and administering both treatments (ACP and Normal Saline) in a concealed, opaque syringe.

Blinding will be maintained by a separate clinician(s) designated to blind the syringes (i.e.: Laboratory Technician) from the staff designated to collect/assess patient outcomes and designated to administer the treatments (Investigator/ Sub-Investigator).

The subject, the evaluating physician, and coordinator will be blinded until 12 (365 days) months.

Refer to Blinding Procedure (Appendix 2-5)

#### **6.2.2.7 IA Injection Procedure**

Refer to Intra-articular Injection (Appendix 2-4)

#### **6.2.2.8 Adverse event/device events**

- Assess subjects during treatment for adverse events as defined in section 7.
- Assess for complications as defined in section 7.

#### **6.2.2.9 Patient Management Plan**

Instruct patient on the following:

1. He/she may experience transient pain, swelling, and/or effusion of the injected joint after IA injection.
2. Pronounced pain and extensive swelling should be reported to the physician.
3. He/she should avoid strenuous activities or prolonged weight-bearing for approximately 48 hours.
4. He/she should be able to resume baseline activities after 48 hours.

### **6.3 Study Visits**

#### **6.3.1 Treatment Visits**

**All subjects enrolled in the study will have the following procedures at visit 3 (1 week +/- 3 days) & visit 4 (2 weeks +/- 3 days):**

- WOMAC survey (pain, stiffness, function)
- Concomitant Analgesics/Treatment review
- Adverse event assessment /device complications as defined in Section 7
- Venipuncture, processing, blinding and IA procedure.
- Refer to Visit 3 and 4 Venipuncture and Blood Collection Procedure (Appendix 2-3)
- Refer to Blinding Procedure (Appendix 2-5)



- Refer to Visit 2, 3 and 4 Intra-Articular Injection (Appendix 2-4)

**6.3.2 Follow-Up Visit 5 [2 months (60 days)+/- 7 days], Visit 6 [3 months (90 days)+/- 7 days] & Visit 7 [6 months (180 days) +/- 14 days]**

- WOMAC survey (pain, stiffness, function)
- Concomitant Analgesics/Treatment review
- Adverse event assessment

**6.3.3 Visit 8 (12 months (365 days) +/- 30 days)**

- WOMAC survey (pain, stiffness, function)
- Concomitant Analgesics/Treatment review
- Adverse event assessments

## 7 Adverse Events

### 7.1 Definitions

#### 7.1.1 Adverse Events

An adverse event (AE) is any undesirable experience (e.g., sign, symptom, illness, clinically significant abnormal laboratory value, or other medical event) occurring in a subject during the course of the study, whether or not it is related to the investigational treatment or procedure.

An AE does include a/an:

- Exacerbation of a pre-existing illness
- Increase in frequency or intensity of a pre-existing episodic event or condition
- Condition detected or diagnosed after study device use even though it may have been present prior to the start of the study treatment.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study

An AE does not include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, transfusion); the condition that leads to the procedure is considered an AE
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions)
- The disease or disorder being studied, or sign or symptom associated with the disease or disorder, unless the disease, sign or symptom is more severe than expected based on the subject's condition and/or requires intervention.

#### 7.1.2 Serious Adverse Events

A serious AE is one that:

- led to death,
- led to serious deterioration in the health of a subject that:
  - resulted in a life-threatening illness or injury,
  - resulted in permanent impairment of a body structure or body function,
  - required inpatient hospitalization or prolongation of existing hospitalization,

- resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function, or
- led to fetal distress, fetal death or a congenital anomaly or birth defect.

The following clarifications are provided for the serious AEs:

- Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. The definition does not include an event that, had it occurred in a more severe form, might have caused death.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered a serious AE.
- “Inpatient” hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a causality or emergency room.
- Important medical events that may not result in death, or be life-threatening, however based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- It is significant for any other reason.

### **7.1.3 Anticipated Adverse Events:**

Anticipated AEs are those events that are reasonably expected to occur as a result of the subject’s disease state or treatment. For this study, anticipated AEs associated with the procedure or post-procedure include, but are not limited to, the following;

1. Infections, both deep and superficial.
2. Allergies and other reactions to device materials.
3. Hematoma.
4. Arthralgia
5. Joint stiffness
6. Joint effusion
7. Joint swelling
8. Joint warmth
9. Injection site pain
10. Blood vessel damage
11. Nerve damage
12. Arthritis
13. Arthropathy
14. Gait disturbance

### 7.1.4 Unanticipated Adverse Device Events

An Unanticipated Adverse Device Effect (UADE) is defined as any serious AE on the study subject's health or safety, or any life-threatening problem or death caused by or associated with the treatment, if, the effect, problem or death was not previously identified in this Investigational Plan or Instructions for Use in its nature, frequency, or severity. UADEs may also include other serious problems associated with the treatment that affect the rights or welfare of study subjects.

## 7.2 Adverse Event Documentation

AE information will be collected on all subjects. All AEs must be reported in the source documents and in the Electronic Data Collection (EDC) database. AEs will be evaluated by the investigator and differentiated by:

- Serious, as defined in Section 8.1.2
- Severity of the event, defined as:
  - Mild: Awareness of signs and symptoms, but easily tolerated; are of minor irritant type, causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.
  - Moderate: Discomfort severe enough to cause interference with usual activities; requiring treatment, but not extended hospitalization or intensive care for the subject.
  - Severe: Incapacitating with inability to do work or usual activities; signs and symptoms may be systemic in nature or require medical evaluation and/or treatment; requiring additional hospitalization or intensive care (prolonged hospitalization).
- Relatedness to the device or procedure, defined as:
  - Unrelated: AE is due to the underlying disease state or concomitant medication or therapy not related to the study-specific treatment or procedures.
  - Probably not Related: AE had minimum or no temporal relationship to the study-specific treatment or procedures and/or more likely alternative etiology exists.
  - Possibly Related: AE had a strong temporal relationship to the study-specific devices or procedures and alternative etiology is equally or less likely compared to the potential relationship to the study-specific treatment or procedures.
  - Probably Related: AE had a strong temporal relationship to the study-specific treatment or procedures and another etiology is unlikely.

- Unknown: Relationship of the AE to the study-specific devices or procedures and alternative etiology is unknown.

### **7.3 Adverse Event and Unanticipated Adverse Device Effect Reporting**

At every subject encounter, the investigator will determine if there has been an adverse event since the last encounter.

For this study, serious adverse events must be reported to Arthrex or designee within 24 hours of event discovery by the site and entered into the EDC database. At the time of the initial report, the outcome (resolution status) may not be known. Updated information must be entered into the EDC database until final resolution of the event.

UADEs must also be reported by the investigator to the approving IRB as soon as possible, but not later than 10 working days after the investigator first learns of the effect. The sponsor must report to the FDA, all reviewing IRBs, and participating investigators within 10 working days of notification from the investigator of a UADE.

The monitor will provide medical surveillance on adverse events and will evaluate all Serious Adverse Events (SAEs)

### **7.4 Device Complications**

For this study all device malfunctions including ; unable to pull up outer syringe, unable to pull up inner syringe, damaged parts, cracked parts, packaging – device/component missing, packaging – broken in package, leaking, air mixed with blood, piece broke from device , frozen or other will be collected and reported on associated eCRF.

### **7.5 Safety Monitoring**

As the study sponsor of this clinical study, Arthrex Inc. will be responsible to monitor it for safety. In the circumstance where UADEs or serious AEs occur due to a procedure, Arthrex, Inc., will convene a review committee which will determine any unreasonable risk to subjects or if the study should be reviewed for modification or early termination.

## 8 Statistical Method and Sample Size Calculation

### 8.1 Primary Effectiveness Hypothesis for Pain

The primary effectiveness hypothesis for this study is that ACP treatment is superior to control in terms of mean change from baseline to Month 6 in the WOMAC Pain score. Symbolically, the null and alternative hypotheses may be expressed as follows:

$$H_0: \delta(\text{pain})_{\text{ACP}} - \delta(\text{pain})_{\text{Control}} \leq 0$$

$$H_a: \delta(\text{pain})_{\text{ACP}} - \delta(\text{pain})_{\text{Control}} > 0$$

Where  $\delta(\text{pain})_{\text{ACP}}$  and  $\delta(\text{pain})_{\text{Control}}$  are the expected mean changes from baseline to Month 6 in the WOMAC Pain score among patients in the ACP and control groups, respectively.

### 8.2 Conditional Effectiveness Hypothesis for Function

The study is designed to permit an additional labeling claim beyond reduction in pain while maintaining control of type 1 error. The additional labeling claim concerns improvement in patient function. This will be measured using change from baseline to Month 6 in the WOMAC Function score. In order to control type 1 error for this study, these two hypotheses were hierarchically specified. First, the primary endpoint concerning WOMAC pain will be tested. If the 1-sided p-value  $\leq 0.025$ , it will be concluded that the investigational treatment is superior to control in terms of pain reduction and the study will be considered as having met its Study Success criterion. In this case, additionally, the treatment group difference in mean change from baseline to Month 6 will also be tested for the WOMAC Function score using a 1-sided p-value  $\leq 0.025$ . Testing of the conditional endpoint is contingent on demonstrating superiority in terms of WOMAC pain and it is not intended to require superiority in both WOMAC Pain and WOMAC Function for Study Success.

The conditional effectiveness hypothesis for this study is that ACP treatment is superior to control in terms of mean change from baseline to Month 6 in the WOMAC Function score. Symbolically, the null and alternative hypotheses may be expressed as follows:

$$H_0: \delta(\text{function})_{\text{ACP}} - \delta(\text{function})_{\text{Control}} \leq 0$$

$$H_a: \delta(\text{function})_{\text{ACP}} - \delta(\text{function})_{\text{Control}} > 0$$

Where  $\delta(\text{function})_{\text{ACP}}$  and  $\delta(\text{function})_{\text{Control}}$  are the expected mean changes from baseline to Month 6 in the WOMAC Function score among patients in the ACP and control groups, respectively.

Formal testing of the conditional endpoint will only take place if the null hypothesis involving the primary endpoint is rejected at 1-sided  $\alpha=0.025$ . In that case, the null hypothesis concerning the conditional endpoint will be tested, also at 1-sided  $\alpha=0.025$ . By structuring the hypothesis testing hierarchically and by the ‘closed testing principle’ no multiplicity adjustment is necessary.

## 8.3 Statistical Methods for Testing Superiority

### 8.3.1 MMRM

Superiority testing will be performed using a mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) Model.<sup>39</sup> The MMRM approach is a direct likelihood approach requiring specialized statistical software. For this study, all MMRM parameters will be estimated using SAS PROC MIXED. The MMRM model is notable for its inclusion of all available data from all eligible subjects and does not require their exclusion as in complete case analysis or arbitrary assignment of some value as in Last Observation Carried Forward (LOCF). Inclusion of outcome data from time points earlier than Months 6 informs the implicit imputation of missing Month 6 values through the covariance matrix used to model the random effects.

The random effects in the MMRM model will be based on the so-called ‘unstructured covariance matrix’ in which variances over time are allowed to vary as are the pair-wise correlations over time.

The values over time will include all WOMAC scores, namely at each of the 3 follow-up time points, visit 5 / 2 months, visit 6 / 3 months, and visit 7 / 6 months.

All WOMAC values will be included in the analysis even if they are obtained out-of-window. However, the fraction of out-of-window visits will be summarized at each time point.

The contrast indicated by the primary hypotheses above,  $\delta(\text{pain})_{\text{ACP}} - \delta(\text{pain})_{\text{Control}}$  will be estimated as the treatment group contrast from baseline to Month 6 in the WOMAC score derived from the MMRM. The null hypothesis is that the true value of this contrast is equal to zero. The same approach will be taken for the WOMAC Function score if superiority in pain relief is demonstrated.

### 8.3.2 Covariates in MMRM

The MMRM model must contain an indicator variable for treatment group, a categorical time factor, and treatment group by time interaction. It is also necessary to include the baseline value of the WOMAC outcome variable (either pain or function) so that significance levels will apply equally to values over time and to changes from baseline. Often a factor for site is included in the MMRM to account for randomization within site. Given the modest sample size and in

response to FDA Advisory items c.1.b (dated July 23, 2015), site will not be included in the primary MMRM. Instead, the impact of site heterogeneity on estimated treatment group differences will be evaluated in supporting analyses by introducing an additional random effect as described below.

It is often considered useful to include additional baseline covariates in order to further reduction of potential bias due from missing values. Candidate variables include age, gender, BMI, and prior analgesic use. However, in response to FDA Advisory item c.1.b, these variables will not be included in the primary MMRM model. Instead, additional baseline covariates will be added to the model in exploratory analyses only if any of these variables appear with clinically significant imbalance between treatment groups. The purpose of these analyses would to be determine the extent to which such imbalance impacts on estimated treatment group differences and associated significance levels.

### 8.3.3 Details Concerning the MMRM

As stated above, the covariance matrix for MMRM is an unstructured covariance matrix in which each of the 3 variances (2 months, 3 months, and 6 months) are free to vary as are the 6 pairwise covariances. That is, the covariance matrix for the MMRM will not include any random effects per se, but accounts for correlations among errors by specifying the form of the covariance matrix. The MMRM employs an unstructured covariance in order to produce inferences that are valid under the so-called ‘missing at random’ (MAR) assumption which is more generally true than the ‘missing completely at random’ assumption that is required for validity of analyses restricted to complete cases.

The longitudinal model will be specified as a repeated measures model that expresses the WOMAC score as a linear function of treatment, time, treatment-by-time interaction, and a covariate of the baseline pain measurement.

The model can be mathematically expressed as:

$$Y_i = X_i\beta + e_i$$

- $Y_i$  is change from baseline to Month 6 in WOMAC Pain or Function scores
- $\beta$  is a vector of fixed-effect regression parameters which includes:
  - $\mu$ , the overall mean
  - $\theta$ , the treatment effect
  - $\tau$ , a vector of post-baseline time effects
  - $\eta$ , a vector of treatment-by-time interaction effects,
  - $\phi$ , a vector of covariate effect parameters that only includes baseline WOMAC score but in general could include additional baseline variable,
- $X$  is a design matrix for the fixed effects, and
- $e$  is the error vector with
  - $E(e) = 0$  and



$$\circ \text{Var}(\mathbf{e}) = \sigma_e^2 \mathbf{V}_{\text{unstructured}}.$$

The specific model to be used may be expressed as:

$$Y = b_{int} + b_{base} + b_T + b_{2M} + b_{3M} + b_{6M} + b_T b_{2M} + b_T b_{3M} + b_T b_{6M}$$

With parameters as explained below.

<u>Parameter</u>	<u>Represents</u>
$Y$	Change from baseline
$b_{int}$	Model intercept
$b_{base}$	Baseline value
$b_T$	Indicator for Active Treatment
$b_{2M}, b_{3M}, b_{6M}$	Indicator for each visit
$b_T b_{2M}, b_T b_{3M}, b_T b_{6M}$	Indicators allowing varying treatment differences at each visit

From this model estimates of treatment effect at specific visits and specifically at Month 6 difference may be obtained as follows.

$$T_{M6} = b_{int} + b_{base} + b_T + b_T b_{M6}$$

$$S_{M6} = b_{int} + b_{base}$$

$$\Delta_{M6} = T_{M6} - S_{M6} = b_T + b_T b_{M6}$$

Where e.g.  $T_{M6}$  and  $S_{M6}$  are the expected changes from baseline to Month 6 in the WOMAC scores in the active and sham control groups, respectively, in terms of these model parameters, the superiority hypotheses are:

$H_0: \Delta_{M6} = 0$   $H_1: \Delta_{M6} > 0$  when larger values reflect improvement or

$H_0: \Delta_{M6} = 0$   $H_1: \Delta_{M6} < 0$  when smaller values reflect improvement

The following SAS Proc Mixed statements provides the test for this null hypothesis. The key results is listed among the results provided by the 'slice' option of the LSMEANS statement. One of these will provide the treatment group contrast at Month 6.

```
proc mixed data=dataset method=ml;
  class patid trt time;
  model womac_pain = trt time trt*time womac_pain_bl / s chisq;
```

```
repeated time / type=un subject=patid;  
lsmeans trt*time / slice=time;  
run;
```

The Month 6 treatment group contrast, the p-value associated with the null hypotheses and 95% two-sided confidence interval will be derived from the MMRM in order to test the superiority hypotheses for the primary endpoint and co-primary endpoints.

## 8.4 Sample Size Analysis

### 8.4.1 Primary Superiority Test

The power for the MMRM tests were approximated by the power for the corresponding two-sample t-test using industry standard software.<sup>40</sup> Power for the t-test is a function of the magnitude of the treatment group difference relative to the standard deviation of change scores. Preliminary data to evaluate clinical effect size was available from the safety and efficacy pilot study (BB-IDE 14796). In 15 patients per group, the mean (SD) WOMAC Pain Total score for the ACP and control groups at 6 months post-treatment were 2.5 (3.6) and 9.1(3.2) respectively. At screening, the baseline mean (SD) values were 10.2 (1.8) and 10.5 (2.0). Therefore, the large difference at Month 6 is not explainable by baseline differences. These data imply a treatment group difference in mean improvements equal  $[10.2 - 2.5 = 7.7]$  minus  $[10.5 - 9.1 = 1.4] = 6.3$  in favor of ACP and a standard deviation of approximately equal to 3.4. This standard deviation also applies to change from baseline if the correlation between baseline and change scores is equal to 0.5. Given the small sample size of the pilot study, a 95% two-sided confidence interval for the true difference was determined to be (-9.0 to -4.2) in order to account for the uncertainty in estimated treatment group mean differences. Specifically, on the basis of the pilot study, a superiority treatment group differences as small as -4.2 cannot be statistically ruled out. Therefore, as -4.2 represents a conservative estimate of the treatment group difference for purpose of sample size analysis. Under these assumptions, the standardized mean difference (Cohen's effect size) is equal to 1.235. This effect size is typically considered very large. Cohen's benchmark for a large effect size in the behavioral sciences is 0.80. In order to mitigate against any potential bias present in the preliminary study, the expected effect size is further reduced from 1.235 to 0.80. From another perspective, a treatment group difference of -4.2 in mean improvements is clinically significant as follows. The mean WOMAC Pain prior to surgery is slightly more than 10 (range 0 to 20). Therefore, a treatment group difference of -4.2 in the mean improvement in WOMAC Pain score represents about a 40% treatment group difference in the mean percent improvements. A group difference

in mean percentage changes so large is likely clinically significant given the known reliability and validity of the WOMAC Pain score.

Randomization will be 2:1 in order to increase precision when characterizing the safety profile of the investigational treatment. We assume a one-sided type 1 error of  $\alpha=0.025$  and a standardized mean difference of 0.80 and determined that a total sample size of  $N=78$  (52 ACP and 26 control) patients are required for 90% power. **This value is increased by 15% to  $N=90$  (60 ACP and 30 control)** to account for potential loss-to-follow-up or other exclusions from the primary effectiveness analysis set.

### 8.4.2 Conditional Superiority Test

Among 15 patients per group, the mean (SD) WOMAC Function score for the ACP and control groups at 6 months post-treatment were 7.9 (11.7) and 31.3 (12.0), respectively. At screening, the baseline mean (SD) values were 32.1 (9.5) and 31.4 (10.2). Therefore, the large difference at Month 6 is not explainable by baseline differences. These data imply a treatment group difference in mean improvements equal  $[31.1-7.9=23.2]$  minus  $[31.3-31.4=-0.1] = 23.3$  in favor of ACP and a standard deviation approximately equal to 11.9. Given the small sample size of the pilot study, a 95% two-sided confidence interval for the true difference was determined to be  $(-31.9 \text{ to } -14.9)$ . Therefore, the pilot study cannot rule out treatment group differences as small as -14.9 and so -14.9 represents a conservative estimate of the treatment group difference for purpose of sample size analysis

Under these assumptions, the standardized mean difference (Cohen's effect size) is equal to  $14.9/11.9=1.25$  which is nearly the same as observed for WOMAC Pain scores. For the same reason stated above, the study will be designed to detect an effect size of 0.80 with 90% power and the same final sample size of  $N=78$  (52 ACP and 26 control) patients increased by 15% to  $N=90$  (60 ACP and 30 control) to account for potential loss-to-follow-up or other exclusions is assumed.

## 8.5 Secondary Endpoints

The following will be summarized in descriptive analyses:

- WOMAC Stiffness Score at Month 6 and changes to Month 6
- WOMAC Total, (Function, Pain, Stiffness Scores) at 2 (60 days), 3 (90 days), and 12 months (365 days) and changes to these time points.

There will be no adjustment for multiplicity for the secondary endpoints.

## 8.6 Concomitant Analgesics/Treatment

Use of medication for joint pain will be recorded at each study visit according to, category (OTC NSAID, prescription NSAID, acetaminophen, and narcotic). The

use of analgesic at 6 months (180 days) will be evaluated as an exploratory endpoint in the descriptive analyses. The data collected will include medication name and the total daily dose. Additionally, concomitant treatments (e.g., physical therapy) will be recorded at each evaluation visit.

## 8.7 Safety Endpoints

The primary safety endpoints for this study are based on adverse events. Details regarding analyses of adverse events are provided below. Briefly, adverse event endpoints will include, but are not limited to, the following patient specific endpoints:

- Any adverse event (per patient)
- Any treatment related AE
- Any serious AE
- Any serious AE that is treatment related
- Patient death

Specific endpoints such as discomfort and pain, erythema, swelling, bruising, hemorrhage, and papules will be compared between treatment groups in terms of both per patient incidence rates and total counts. Fisher's exact tests will be used to provide descriptive comparisons between incidence rates. Counts of AEs will be displayed overall and over time.

## 8.8 Other Elements of Analysis Plan

### 8.8.1 Analysis Sets

The following analysis sets are defined:

*Intent-to-treat (ITT)*: The ITT analysis set will include all randomized patients.

*Modified Intent-to-treat (mITT)*: The mITT analysis set will include all patients with any exposure to a study treatment (active or placebo), where patients will be classified by the group in which they are randomized, regardless of the treatment received; and who have at least one WOMAC assessment subsequent to randomization. Primary, secondary, and exploratory effectiveness analyses will be conducted in the mITT analysis set. It is necessary to only include patients with at least one post randomization WOMAC assessment for use in the MMRM. Baseline carried forward is likely to produce substantial bias in estimated treatment differences. It is reasonable to expect that baseline carried forward bias is substantial and perhaps even larger than might be expected from excluding a very small number of patients with no follow-up subsequent to randomization. For this reason, baseline carried

forward will not be conducted. It is acknowledged that if there are more than a very small percentage of patients with no follow-up subsequent to randomization, results from this clinical trial may not be adequately interpretable to provide sufficient evidence of effectiveness depending upon the robustness of primary analyses and the consistency of supporting analyses.

*As Treated (AT):* The AT analysis set will include all patients randomized with any exposure to a study treatment (active or placebo), where patients will be classified by the treatment actually received. Safety analyses will be performed in the AT analysis set. If there are no patients receiving the incorrect treatment, then this analysis set will be identical to mITT.

*Per protocol (PP):* The PP analysis set will include subjects with no major protocol deviations. In particular, the PP analysis will exclude patients that start but do not complete all injections associated with a study treatment. The PP analysis set will also exclude patients with major violations of inclusion or exclusion criteria or who receive confounding concomitant medication expected to significantly impact the primary outcome measure. Secondary effectiveness analyses will be performed using the PP analysis set.

The primary and conditional hypotheses will also be tested using the ITT analysis set and in an analysis set restricted to complete cases using the same MMRM. Comparison among results from these three analyses will provide FDA the capability of determining robustness of conclusions relative to assumptions regarding missing data. In the case of no missing data, these three analyses are identical. Therefore, it will be a study goal to minimize the number of patients with early termination and missing data for other reasons as the most important way of addressing this issue.

### **8.8.2 Randomization and Blinding**

A site stratified, randomized block randomization will be performed such that within each block, patients will be allocated to either ACP or control in a 2:1 randomization ratio. Patients, physicians, and study personnel will be blinded to treatment until end of the study to prevent bias in estimated treatment differences.

### **8.8.3 Description of baseline characteristics**

Demographic and baseline characteristics will be tabulated and compared between the investigational group and control group. Variables to be compared will include baseline knee assessment, disease severity, age, gender, Body Mass Index (BMI), weight and height, race and ethnicity, disease histories, and concomitant medications and therapies.

Descriptive p-values will be determined using Wilcoxon rank sum tests for continuous measures and chi-square or exact tests for categorical variables. However, focus will be on clinical significance of group differences and only secondarily on p-values, since these p-values are not associated with planned comparison. If there are clinically significant group differences for any baseline variable, then supporting analyses will include adding these covariates to the MMRM used in primary superiority testing and evaluating the impact of the imbalance on primary findings.

#### **8.8.4 Description of Effectiveness Outcome**

WOMAC Pain, Function, Stiffness, and Total scores and the as well as change scores will be summarized at each planned follow-up visit [Pre-Op, 1 Week, 2 Weeks, 2 Months (60 days), 3 Months (90 days), 6 Months (180 days), and 12 Months (365 days)] using means, standard deviations, medians, minimum, and maximum values. Standardized effect sizes (mean difference divided by the standard deviation of differences) will be computed at each time point for each continuous measure in order to facilitate assessment of group differences across measures as well as time. Pooled t-tests and Wilcoxon rank sum tests will be provided as additional descriptive measures. There will be no imputation of missing values for secondary endpoint and exploratory endpoints and no control for type I error in the set of exploratory endpoints. Graphical displays of selected endpoints will be provided to provide visual assessments of group differences over time.

#### **8.8.5 Site Poolability**

A random effects model for site to site heterogeneity among treatment group differences in mean improvement in WOMAC Pain score will be evaluated. If important heterogeneity is observed, further analyses will be performed aimed at determining the source of this heterogeneity and its impact on estimates of treatment group differences.

#### **8.8.6 Treatment of Missing Data**

All patients contributing at least one follow-up WOMAC Total score will be included in the primary superiority test through the use of the mixed model for repeated measures (MMRM) in the mITT analysis set. In this way patients with incomplete follow-up are retained and contribute to the primary superiority test.

As noted elsewhere, FDA has previously recommended to not include many baseline covariates in the MMRM due to the modest sample size. Therefore, the only baseline covariates available for implicit imputation of changes from baseline to Month 6 (180 days) is the baseline value itself and treatment group. It follows then, that for the ITT analysis, the MMRM will implicitly impute missing changes from baseline to Month 6

(180 days) for patients with no follow-up data as the within treatment group mean change score modified by the effect of the baseline value

## **8.7 Subgroup Analyses**

Primary and selected secondary effectiveness analyses and selected adverse event comparisons will be stratified according to site subject demographics and baseline characteristics.

## **8.8 Safety Analysis**

Assessment of safety will be based primarily on the incidence and severity of complications and adverse reactions associated with the treatment. Adverse event rates will be summarized by type of AE and for specific AEs in two ways: 1) per patient using counts and percentages and 2) by event, summarizing event counts by visit interval over time. Treatment and procedure related events will be summarized by severity. Events listings will be provided that include details such as relatedness, severity, onset and resolution status will be provide for all events and for relevant subsets of events such as serious events and related events. All safety endpoints will be summarized separately for investigational and control groups. Incidence rates for grouped and individual adverse events will be compared using counts, percentages, and descriptive Fisher's exact test nominal p-values. Grouped adverse events will include events at least possibly related to study treatment and serious adverse events.

## **8.9 Adverse events counts over time**

The numbers of specific adverse events occurring pre-discharge and for each study interval will summarized separately for each relevant cohort. Counts of systemic adverse events will be summarized on a per patient basis. All other adverse events will be summarized on a per procedure basis.

### **8.9.1 Adverse event detail listings**

Adverse events listings will be provided for all patients exposed to a study treatment and will provide details regarding adverse event type, relation to procedure, action taken, and clinical outcome. Separate listings will be constructed for adverse events with "definite" relationship to the treatment, "severe" adverse event, "severe treatment-related", serious adverse events, and for all adverse events. The listing for all adverse events will be sorted by adverse event type.

Additional listings will be provided that include all adverse events among procedures requiring revision, removal, or replacement and all adverse events among patients who died.

## 9 Study Administration

### 9.1 Role of the Study Sponsor

As the study sponsor of this clinical study, Arthrex, Inc., has the overall responsibility for the conduct of the study, including assurance that the study meets and is conducted within the regulatory requirements specified by each reviewing regulatory authority. In this study, Arthrex Inc. will have certain direct responsibilities and may delegate other responsibilities.

### 9.2 General Duties

Arthrex Inc. will be responsible for submitting the Investigational Device Exemption (IDE) application to FDA and ensuring IRB approval prior to shipping study product to sites. Additionally, Arthrex Inc. is responsible for ensuring investigators are properly trained on the study product, conducting and ensuring proper clinical site monitoring and subject informed consent is obtained. Arthrex Inc. will also supply qualified clinical sites with study product/devices that obtain IRB approval for this study.

As the study sponsor of this clinical study, Arthrex Inc. will be responsible to monitor it for safety. In the circumstance where unanticipated adverse device Events or serious adverse events occur due to a procedure, Arthrex, Inc., will convene a review committee which will determine any unreasonable risk to subject or if the study should be reviewed for modification or early termination.

Arthrex Inc. or designee is responsible for providing quality data that satisfies regulations and informing the study investigators of unanticipated adverse device events and deviations from the protocol as appropriate. Arthrex Inc. or designee will prepare written reports and a final report.

### 9.3 Subject Confidentiality

During the investigation, confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access. Subject confidentiality will be maintained throughout the clinical study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification number will be assigned that allows identification of all data reported for each subject. Subject names should be maintained separately from case report forms whenever possible.

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 as confidential and that the subject's privacy is guaranteed.



## **9.4 Selection of Investigators**

Arthrex, Inc. will select qualified investigators, who have orthopedic qualifications and experience in treating osteoarthritis including intra-articular (IA) injections. All qualified Investigators must sign a study agreement. Arthrex will provide the investigators with the information they need to conduct the study properly.

In the selection of study investigators, the Sponsor requires each investigator to have adequate experience with the investigational product, and to demonstrate a commitment to subject safety and consistency through adherence to study protocols. The Sponsor will closely monitor compliance with the protocol throughout the study.

## **9.5 Supplemental Applications**

As appropriate, Arthrex, Inc. will submit changes to the investigational plan to the appropriate regulatory authorities. The sponsor will notify the site when there are changes in the investigational plan. Each investigator is required to submit the amendment to their IRB to obtain re-approval.

## **9.6 Submitting Reports**

Arthrex Inc. will submit all applicable reports required by the FDA. This includes Serious Unanticipated Adverse Device Effect (UADE), withdrawal of IRB or regulatory approval, current investigators list, annual progress reports, recall information, and final reports. The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) 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” (21 CFR 812.3(s)).

Investigative site personnel will notify Arthrex Inc. or designee as soon as possible but no longer than 24 hours of any UADE or death. Investigational site personnel will notify Arthrex, Inc. or designee of any withdrawal of IRB approval within 5 days. Arthrex Inc. or designee will also assist in the preparation of annual progress reports and a final report for the IRB.

## **9.7 Maintaining Records**

The investigational site will maintain copies of correspondence, data, shipment of devices, all adverse events, and other records related to the clinical trial. Investigational site will maintain records related to the clinical trial for a period no less than 2 years following the date a marketing application is approved for the device for the indication for which it is being investigated; or, if no application is

to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. The investigational site shall notify Arthrex, Inc. before disposing of the clinical trial records.

## **9.8 Institutional Review Board (IRB) Approval**

The protocol, informed consent form, and authorization for the use and disclosure of health information (HIPAA) must be reviewed and approved by the respective IRB and Arthrex Inc. or designee before subject enrollment. Changes to the informed consent must be approved in writing by Arthrex Inc. or designee in addition to the IRB (as applicable) before the change is implemented.

Prior to site activation, a signed copy of the IRB approval letter addressed to the investigator must be submitted to Arthrex Inc. or designee, certifying trial approval. Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB and forwarding copies of the approval letters to Arthrex Inc. or designee. The original letters are to be kept on file at the site.

## **9.9 Investigator Agreement and Financial Disclosure**

The principal investigator at each site will sign the investigator's agreement before beginning the study, as required by federal regulations. The principal investigator agrees to be responsible for conducting the investigational study in accordance with the signed agreement, the investigational protocol, and all applicable FDA regulations.

In accordance with federal regulations, all investigators will be required to sign a Financial Disclosure form, which certifies the investigator's and his/her immediate family's financial interest in Arthrex Inc. and study outcomes. Investigators must inform Arthrex Inc. or designee of any changes to the information within the financial disclosure throughout the course of the study and for a period of two (2) years after the device is approved by the FDA or the study is terminated, whichever is later.

## **9.10 Study Monitors and Visits**

Arthrex shall select monitors qualified by training and experience to monitor the investigational study in accordance with FDA regulations for IDE studies including 21 CFR 812.21, CFR 50, 21 CFR 54, 21 CFR 56, this investigational plan, HIPPA, and Good Clinical Practice (GCP). The qualifications of monitors will be on file at Arthrex Inc. and will follow Arthrex Inc.'s standard operating procedures and the written monitoring plan for this study. All monitors (Arthrex Clinical Research or designee) will have training on the monitoring plan, monitoring plan amendments, associated documents (e.g., standard operating procedures or other documents referenced in the monitoring plan).

Arthrex Clinical Research or designee monitoring activities objective is to prevent or mitigate issues with study conduct, data collection/reporting and subject safety.

Arthrex Clinical Research monitor will review critical data remotely via the EDC and/or data reports routinely. Critical data includes:

- protocol eligibility including medical history, physical and enrollment.
- safety assessments / Adverse Events/device effects
- investigational product accountability
- study endpoints –WOMAC scores
- concomitant medications
- deviations

Arthrex Clinical Research team will review site trial file in eTMF (e.g. VEEVA) ongoing basis. Sites will be required to upload all regulatory site files in the Arthrex Clinical Research team will review /quality checks on all uploaded site completeness, accuracy and version control. The eTMF will contain the following documents:

- Clinical trial agreement (executed initially and all amendments)
- Curriculum vitae for each research team member on delegation log will be signed and updated every 2 years.
- Delegation of authority log-for each member of the research team performing study related activities.
- Financial disclosure statement
- Investigation product accountability logs, labels, DFUs and packing slips
- Good Clinical Practice Certificate/CITI (e.g. initial and updates) for all members of research team.
- IRB Documentation (initial approvals, continuing reviews, change in research, ICF , advertisement and reporting requirements)
- Medical license (investigators, nurses, PA current with all renewals)
- Non-subject Deviation log
- Pre-screening logs
- Protocol signature page
- Research team training documents (investigator meeting, procedure training, Veeva, EDC Certificate, protocol updates)

Arthrex Clinical Research monitors or designees will query (via EDC/email/phone) research sites if issues or questions are identified during remote monitoring. Unresolved issues may identify the need to increase the frequency of on-site monitoring.

Arthrex Clinical Research monitors or designees will visit each clinical site routinely (after the 1<sup>st</sup> subject is enrolled and every 8 -12 weeks) to perform on site monitoring. The monitors will be reviewing 100% of the critical data in the EDC database and verifying with source documents (i.e. the electronic medical record, professional notes, laboratory reports, study-specific worksheets, etc.).

In the event that information in the EDC database does not match the corresponding information on the source document, the study monitor will generate an electronic data query for site resolution. The study monitor may request further documentation, such as clinic notes or lab reports, when adverse events or complications are identified and reported.

Critical data includes:

- Informed consent process-see section 6.1.2
- Protocol eligibility including medical history, physical and enrollment-see section 6.1.3
- Randomization/blinding process-see section 6.2.2.1 & 6.2.2.4
- Safety assessments / Adverse Events/device effects-see section 7.0
- Investigational product accountability
- study endpoints –WOMAC scores-see section 3.7
- concomitant medications-see section 8.6
- deviations-see section 9.17

Additionally, the study site will be evaluated for study conduct, timeliness of data form completion and data accuracy.

Arthrex Clinical Research monitors or designees review findings with Investigator, /research team during site visits. These findings will include study updates, training as needed, action items and at a minimum if present., “identified non-compliance” (e.g., ICF process issues, protocol eligibility issues, AE reporting issues, data collection of critical endpoint issue and deviations).

Repeated site non-compliance will be documented and subject to a corrective action plan. If a corrective action plan is not followed, the clinical site may be withdrawn from the study by the sponsor.

Arthrex’s site monitor will forward a follow up letter with findings from site visit, open action items and pending issues that must be addressed before the next monitoring visit.

### **9.11 Investigational Site Qualification**

Investigational sites will be qualified and selected by Arthrex's CRA based on investigator qualification, research staff expertise and availability, subject availability, and overall site reputation. The site qualification will be scheduled to include time with the Investigator, study coordinator, and other study personnel. Areas of discussion include review of personnel training, investigator qualifications, and adequacy of potential subject pool, FDA-regulated study experience, and this study's specific requirements for procedures and equipment, and a review of staffing and equipment availability and appropriateness. A written follow-up letter will be submitted to the Investigator documenting any concerns and/or completion of study activities during the pre-study visit.

### **9.12 Investigational Site Training**

Study conduct-specific training of clinical trial personnel is the responsibility of study manager, the study monitor, and/or the site personnel. Study training will occur before the first device use. The investigator is responsible for ensuring that his/her staff conducts the study according to protocol. To ensure compliance with the Investigational Plan and regulatory requirements as well as accurate data collection, site training will include a detailed review of this Investigational Plan, Electronic Data Collection (EDC), AE reporting, device handling and inventory, monitoring logistics, and regulatory requirements.

Arthrex's Clinical Research personnel will ensure that site study personnel:

- Submit this Investigational Plan to their IRB for appropriate review and obtain written approval for the conduct of the study prior to consenting any subject for this study;
- Maintain all study correspondence, this Investigational Plan, and all related and required records on file at their facility, and
- Confirm the investigator understands his/her full responsibility for the study investigation at their individual medical practices, clinics, or medical facilities.

#### Procedure Training

All Investigators and site personnel participating in the study will receive device-specific detailed training from Arthrex personnel.

All training will be conducted and documented prior to first use of the study device. Hands-on training will be conducted prior or during the first treatment.

### **9.13 Investigator Responsibility for Study Conduct**

Study investigators will ensure that all work and services they provide will be conducted in compliance with the signed investigator agreement, the investigational plan, and applicable federal regulations for IDE studies and

HIPAA, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for control of investigational devices/product. It is the responsibility of each site principal investigator to provide the current study protocol to all sub-investigators and other staff responsible for study conduct, as well as provide for the training of all sub-investigators or other staff involved in the conduct of this research. Specific responsibilities are listed in the Investigator Agreement and include:

- That informed consent is obtained in accordance with 21 CFR Part 50.
- That there is IRB approval prior to commencement of study activities at the site.
- That investigational device/product is only to be used with subjects under the investigator's supervision.
- That they disclose to sponsor sufficient accurate financial information to allow applicant to submit accurate disclosure statement under 21 CFR Part 54.
- To prepare and submit to Arthrex Inc. or designee and IRB complete, accurate and timely reports on this investigation when necessary, according to 21 CFR 812.50. Types of reports to be submitted include reports pertaining to Unanticipated Adverse Device Effects, withdrawal of IRB approval, and deviations from the investigational plan. The investigator is required to submit an annual report to his/her IRB with a copy to Arthrex Inc. or designee.
- That upon completion or termination of clinical investigation at sponsor's request, investigator shall return remaining supply of investigational product/device or otherwise dispose of the device as the sponsor directs.
- That upon completion of the trial, a final written report to the reviewing IRB, within three (3) months of completion or termination of the study. The final report must include:
  - Device name
  - Number of subjects screened, enrolled, withdrawn and completed
  - Number of devices received, used and returned
  - Summary of all adverse events (anticipated and unanticipated)
  - Summary of serious adverse events
  - Summary of all protocol deviations
  - Brief statement of results, outcomes and conclusions.
- Maintain records and reports (see Records below) on file at the investigational site for a minimum of two (2) years after the later of either the completion/termination of the investigational study or the date the investigational product receives market approval for the indication being

studied. They may be discarded only upon approval from Arthrex. The principal investigator must contact Arthrex's CRA before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. In addition, Arthrex must be contacted if the investigator plans to leave the investigational site to ensure that arrangements for a new investigator or records transfer are made prior to investigator departure.

- Records

Records to be maintained by the investigator in the designated investigational center's Regulatory Binder include:

- Investigational plan and all amendments
- Signed Investigator Agreement
- Signed Financial Disclosure
- IRB approval letter including all versions of the consent and HIPAA (for US sites) or the country-specific requirement authorization form(s)
- IRB Membership list or Letter of Assurance
- All correspondence relating to the study between the site and Arthrex.
- CVs and professional licenses for all investigators
- Site personnel signature and responsibility list
- Clinical monitor sign-in log
- Subject Screening/Enrollment log
- Investigational device inventory log including: date, quantity, and lot numbers of all devices, identification of all persons the device was used on and final disposition.

The following records must be maintained for each subject enrolled in the study:

- Signed Consent Form and Authorization for the Use and Disclosure of Health Information
- Compete, accurate, and current data collection forms
- AE reports and any supporting documentation
- Protocol deviations
- Complete medical records, including procedure reports, lab reports, professional notes, etc.
- Records pertaining to subject death during the investigation (including death records, death certificate, and autopsy report if performed).

Arthrex reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study at any time.

## **9.14 Investigational Site Termination**

Arthrex reserves the right to terminate an investigational site for any of the following reasons:

- Failure to secure subject informed consent or Authorization for the Use and Disclosure of Health Information prior to study enrollment.
- Failure to report Unanticipated Adverse Device Events within 24 hours of discovery to Arthrex and/or designee and ten days (to the IRB) of learning of the event.
- Failure to report serious adverse device events within 24 hours of discovery to Arthrex and/or designee.
- Repeated investigational plan violations.
- Repeated failure to appropriately complete case report forms.
- Failure to enroll an adequate number of subjects.
- Loss of or unaccounted for investigational product inventory.
- Administrative decision by the company.

## **9.15 Final Monitoring Visit**

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits, the data collection and queries have been completed, and no additional information is required of the site for data management / statistical review), a final study close-out visit will be conducted by the Study Monitor. The study monitor will verify disposition of investigational devices and review regulatory documents to confirm that the investigator's regulatory files are current and complete, and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include, but are not limited to: long-term retention of study files, possibility of site audits, publication policy, and verification that the investigator will notify the IRB regarding study closure. A final follow-up letter will be drafted and submitted to the Investigator to document that all investigational plan-related activities have been completed and that the clinical study is completed and may be closed at the site.

## **9.16 Protocol Amendments**

All protocol amendments must be approved by Arthrex Inc. All amendments must have FDA approval in addition to IRB approval.

## **9.17 Protocol Deviations**

A study deviation is defined as any event where the clinical investigator or site personnel did not conduct the study according to the protocol.



Any deviations from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to the Arthrex Inc. or designee within 48 hours of occurrence and the respective IRB as soon as possible, but in no later than five (5) calendar days after the emergency occurs.

All deviations will be reported to Arthrex Inc. or designee.

Subject specific deviations will be reported in the EDC.

Study deviations are as follows:

- Informed Consent Form (ICF)
  - Wrong ICF version signed
  - Other deviation related to informed consent version.
- Protocol
  - Study procedure not done per protocol
  - Study procedure or visit not done
  - Study procedure or visit Out of study window
  - Other procedure not done per protocol
- Eligibility
  - Subject did not meet eligibility criteria
  - Other deviation related to eligibility criteria
- Source Document
  - Missing or incomplete source document
  - Other deviation related to source document
- Regulatory
  - Subject enrolled without IRB approval
  - Other deviations related to Regulatory

Non-subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an investigator agreement, improper storage and IP accountability etc.), will also need to be reported to the sponsor. Investigators will adhere to procedures for reporting study deviations to their IRB in accordance with their IRB reporting policies and procedures.

FDA regulations require that investigators maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol.

## **9.18 Publication**

The publication of the principal results from any single center experience within the trial is not permitted, and any exceptions to this rule require the prior approval from Arthrex, Inc.

## **9.19 Audits / Inspections**

In the event a site is audited or inspected by the IRB or, FDA, the investigator should notify the sponsor immediately. The investigator will provide all requested information to the auditor or inspector.

## Appendix 2-1 Schedule of Events

ACP IA FOR KNEE OA SCHEDULE OF EVENTS	Screening	Treatment Visits				Follow –up Visits			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
	Day -2 to 07	Day 0	Week 1 +/- 3 days	Week 2 +/- 3 days	2 months +/- 7 days	3 months +/- 7 days	6 months +/- 14 days	EOS or 1year +/- 30 days	
Informed Consent	X <sup>1</sup>								
History & Demographics	X <sup>2</sup>								
Physical Exam (VS) • Knee Exam • Kellgren-Lawrence Grading • Strokes Test Grading	X <sup>3</sup>								
Concomitant Medication/Therapy	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	
WOMAC	X <sup>5</sup>		X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	
Enrollment  Pregnancy (urine)  Radiograph	X <sup>6</sup>	X <sup>6</sup>							
Randomization		X							
Visit	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	X <sup>7</sup>	
Treatment		X <sup>8</sup>	X <sup>8</sup>	X <sup>8</sup>					
AE		X <sup>9</sup>	X <sup>9</sup>	X <sup>9</sup>	X <sup>9</sup>	X <sup>9</sup>	X <sup>9</sup>	X <sup>9</sup>	
Deviation	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	
Completion								X <sup>11</sup>	
Heme Profile		X <sup>12</sup>							

**1. Informed Consent process is conducted and the form is signed prior to any study related procedures.**

2. Medical & Surgical History and Demographics are collected at Screening
3. Physical Exam (including Knee exam, Kellgren-Lawrence & Strokes Test) is done at screening
4. Pain medication and therapy review are collected at screening and reviewed at each study visit
5. WOMAC is completed at screening visit to confirm Inclusion Criteria # 4
6. Available Inclusion/Exclusion Criteria is collected at screening and confirmed at V2 (Day 0) prior to randomization. Radiographs to confirm Inclusion #3 and exclusion #1 and 3. Radiographs are done prior to Randomization, if not complete and part of subject's medical historical medical record. Urine pregnancy is done at screening as when applicable.
7. Visit Data collected all study Visits.
8. Treatment form is collected at V2, V3 & V4.
9. Adverse Events are collected as applicable at V2 thru V8.
10. Deviations are collected at each V1 thru V8.
11. Study Completion is done at Visit 8 or sooner if discontinues prior to Visit 8.
12. Whole blood and ACP collected for analysis.

## Appendix 2-2 Knee Exam: Stroke Test Grading

## Knee Exam: Stroke Test Grading

### Reliability of the Stroke Test for Identifying Knee Joint Effusion

Test and Study Quality	Description and Positive Findings	Population	Interexaminer Reliability
Stroke test <sup>29</sup> ●	Patient is supine and has knee in full extension. Starting at the medial tibiofemoral joint line, the examiner strokes upward two or three times toward the suprapatellar pouch in an attempt to move the swelling within the joint capsule to the suprapatellar pouch. The examiner then strokes downward on the distal lateral thigh, just superior to the suprapatellar pouch, toward the lateral joint line. Positive if fluid is observed on the medial side of the knee and quantified using a 5-point scale	75 patients referred to an outpatient physical therapy clinic for treatment of knee dysfunction for which effusion testing was deemed appropriate by the treating therapist	$\kappa = .64 (.54, .81)$

Stroke Test Grading Scale<sup>20</sup>

Grade	Test Result
Zero	No wave produced on downstroke
Trace	Small wave on medial side with downstroke
1+	Larger bulge on medial side with downstroke
2+	Effusion spontaneously returns to medial side after upstroke (no downstroke necessary)
3+	So much fluid that it is not possible to move the effusion out of the medial aspect of the knee



[c/sportinjuriesandwellness.tawa.blogspot.com/2009/12/orthopedic-test-south-stroke-test.html](http://c/sportinjuriesandwellness.tawa.blogspot.com/2009/12/orthopedic-test-south-stroke-test.html)

[https://books.google.com/books?id=6BwAAC8AJsgpg7A345d&pg=PA345&q=Nct0r%27%24Hncoc49okroixam&source=bl&sig=273sdUKD3aigwQDvbnIMY-fSjWmo5gTg9G95o&hl=en&as\\_ssk&as\\_dsc=UkWhUtwipaficucPMAHKMDh4CHYU3pxQC8ABHDAAARvwagqg&oeq=otter+AgLOn%20Nct0r%27%24okroik%20xam&f=false](https://books.google.com/books?id=6BwAAC8AJsgpg7A345d&pg=PA345&q=Nct0r%27%24Hncoc49okroixam&source=bl&sig=273sdUKD3aigwQDvbnIMY-fSjWmo5gTg9G95o&hl=en&as_ssk&as_dsc=UkWhUtwipaficucPMAHKMDh4CHYU3pxQC8ABHDAAARvwagqg&oeq=otter+AgLOn%20Nct0r%27%24okroik%20xam&f=false)

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Stroke Test  
Version 1: May 2016



## Appendix 2-3 ACP Venipuncture and Blood Collection Procedure:

Protocol Version: August 1, 2016

### ACP Study Instructions for Visit 2 Sample and Treatment Preparation and Processing

(Procedure tool should be kept in secure area and available only to the study personnel)

<b>I. <u>Gather All Supplies and Notify Personnel</u></b>	
8 Labels	2- 16 gauge needles
3-ACP Series 1 Kits	2 Red top tubes without activator
500cc bag of ACD-A	Centrifuge
1-20cc Syringe	vial of normal saline for IA injection

- A. Gather all supplies listed above
- B. Prior to starting the treatment procedure the subject should be randomized in the EDC by authorized personnel.
- C. After randomization, the blinding person should be contacted to be available for blinding the treatment syringes after the syringes are prepared.
- D. The authorized Investigator should be available for treatment and should ensure treatment is administered with 30 minutes of the blood draw.

**Label all syringes and tubes prior to blood draw**

### II. Preparing Syringes & Labels: (done prior to blood draw)

#### A. Syringe for CBC analysis of ACP:

1. Prepare ACP double syringe (Series I kit) by priming the large outer and small inner syringes by pulling each plunger completely back and forth. Then, make sure the inner syringe is secure by tightening.
2. Draw up 1.5 cc ACD-A into double syringe.
3. Label ACP double syringe with Subject Identification and *CBC Analysis of ACP*
4. Label a Red Top tube with subject Identification and *CBC Analysis of ACP*.

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5. Have an additional label with subject Identification and *CBC Analysis of ACP* ready for the inner syringe after processing.

**B. Syringe for IA injection:**

1. Prepare the ACP syringes for IA injection (Series I Kit) by priming the large outer and small inner syringes by pulling each plunger completely back and forth.
2. Then, make sure the inner syringe is secure by tightening.
3. Label ACP double syringe with subject Identification and *ACP for IA injection*.
4. Make additional label for inner syringe after processing with subject ID and *ACP for IA Injection*.

**C. Syringe for CBC analysis of whole blood:**

1. Draw up 1.5 cc ACD-A into 20 cc syringe.
2. Label syringe with Subject Identification and *CBC Analysis of Whole Blood*.
3. Label one Red Top tube with subject Identification and *CBC Analysis of Whole Blood*.

**D. Normal Saline Syringe for IA injection:**

1. Remove inner ACP syringe for IA injection (Series I Kit) by drawing up 6 ml of normal saline (NS).
2. Label with subject identification and *NS for IA Injection*.

**III. Blood draw for Each Sample and Treatment****A. CBC sample of ACP:**

1. Cleanse site and perform venipuncture with butterfly needle.

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2. Attach Syringe that is labeled for CBC analysis of ACP (ACP double syringe with 1.5 cc ACD-A) to butterfly needle.
3. Slowly withdraw by pulling back on the wings that are colored red.
4. Fill the syringe to the maximum of whole blood at a rate of 1cc every two seconds. Kink tubing prior to removing syringe from butterfly tubing. Seal the syringe with the red (luer) cap.



5. Gently invert syringe to allow mixing of anticoagulant. Set sample aside for processing.

**B. ACP Sample for IA injection:**

1. Record blood draw time for ACP Sample for IA Injection.
2. Attach the Syringe labeled for *ACP IA injection* (ACP double syringe no additive) to butterfly needle.
3. Slowly withdraw by pulling back on the red wings.
4. Fill the syringe to the maximum of whole blood at a rate of 1cc every two seconds. Kink tubing prior to removing syringe from butterfly tubing. Seal the syringe with the red (luer) cap. Set sample aside for processing.

**C. CBC sample of Whole Blood:**

1. Attach Syringe that is labeled for *CBC Analysis of Whole Blood* (20cc syringe with 1.5 cc ACD-A) to butterfly needle.
2. Slowly withdraw by pulling back the plunger.
3. Fill the syringe to 16cc at a rate of 1cc every two seconds. Kink tubing prior to removing syringe from butterfly tubing.
4. Gently invert syringe to allow mixing of anticoagulant.
5. Inject sample into one red top vacutainer with 16 gauge needle (this tube is labeled with subject Identification and *CBC analysis of whole blood*) Note: discard excess blood.
6. Send to local laboratory for CBC analysis.

**\*If not sent to lab immediately, place specimens on rocker\***



Protocol Version: August 1, 2016

#### IV. ACP Sample and Treatment Processing

##### A. Centrifugation

1. Place both double syringes (Syringe for CBC Analysis of ACP & ACP Syringe for IA injection) containing the whole blood in buckets of centrifuge with red luer cap facing down, place in opposite buckets. Note: syringes must be in opposite buckets and contain the same amount of fluid to maintain balance.
2. Run the centrifuge at 1500 rpm for 5 minutes. Remove the syringes, taking care to keep it in an upright position to avoid mixing the plasma and red blood cells. Note: if sample mixes or coagulates the syringe must be discarded and the blood draw repeated.



##### B. Prepare the Syringe for IA injection:

1. In order to transfer the ACP from the outer syringe into the inner syringe, slowly push down on the outer syringes red wings, while slowly pulling up the plunger of the inner syringe.
2. Unscrew smaller syringe, place a capped injection needle (20-25 gauge) on small syringe, label with subject ID and *ACP IA Injection* and set it aside.
3. Document the amount processed in the syringe intended for injection.

##### C. Prepare Normal Saline Syringe for Injection

1. Place a capped injection needle (20-25 gauge) on the syringe.

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2. The saline amount must equal the ACP treatment amount. Discard the extra saline from the syringe labeled *Normal Saline for Injection*.
3. Provide the blinding personnel with both the syringes for Injection of ACP and normal saline with the same volume of fluid.

**\*If fluid is noted in the cap or needle of processed ACP or normal saline, the needle should be replaced to avoid unblinding.\***

**\*Please Note – To avoid unblinding to treatment, do not push fluid to the tip of the needle.\***

*Authorized Investigator should inject the treatment within 30 minutes from blood draw time recorded for “ACP Sample for IA Injection.” See IA injection instructions for Injection procedure.*

**Please note: Depressing the syringe to remove air and push fluids up to the tip to avoid embolisms is not needed.**

#### **D. Prepare Sample of ACP for CBC Analysis**

1. In order to transfer the ACP from the outer syringe into the inner syringe, slowly push down on the outer syringe red wings, while slowly pulling up the plunger of the inner syringe.
2. Unscrew smaller syringe, place a capped 16 gauge needle on small syringe. Label syringe with subject Identification, *CBC analysis of ACP*.
3. Inject sample into red top vacutainer (this tube is labeled with subject Identification and *CBC analysis of ACP*).
4. Send to local laboratory for CBC analysis.

**\*If not sent to lab immediately, place specimens on rocker\***

*All device complications are to be reported to your site monitor. The site research team should document the details of complication in subject's source documents. Here are some examples of complications that can occur.*

- Unable to pull up outer syringe
- Unable to pull up inner syringe
- Damaged
- Cracked
- Packaging – device/component missing
- Packaging – broken in package

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**ACP Venipuncture and Blood Collection Procedure Visit 3 & 4****(Procedure tool should be kept in secure area and available only to the study personnel)**

<b>I. Gather All Supplies and Notify Personnel</b>	
2-ACP Series I Kit	Centrifuge
1-20cc Syringe	1 vial of normal saline for IA injection

- A. Gather all supplies listed above
- B. Prior to starting the treatment procedure the subject should be randomized in the EDC by authorized personnel.
- C. After randomization, the blinding person should be contacted to be available for blinding the treatment syringes after the syringes are prepared.
- D. The authorized Investigator should be available for treatment and should ensure treatment is administered with 30 minutes of the blood draw.

**II. Preparing Syringes & Labels: (done prior to blood draw)****Label all syringes and tubes prior to blood draw**

- A. **Syringe for IA injection (ACP):** prepare the ACP syringes for IA injection (Series I Kit) by priming the large outer and small inner syringes by pulling each plunger completely back and forth. Then, make sure the inner syringe is secure by tightening. Label ACP double syringe with subject Identification and ACP for IA injection.
- B. **Syringe for IA injection (Normal Saline):** prepare the inner ACP syringe for IA injection (Series I Kit) by drawing up 7 ml of normal saline (NS) with subject identification and NS for IA injection.

**III. Blood draw**

- Cleanse site and perform venipuncture with butterfly needle.
- Attach Syringe for IA injection (ACP double syringe no additive) to butterfly needle.

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**ACP Venipuncture and Blood Collection Procedure Visit 3 & 4**

- Slowly withdraw by pulling back on the wings that are colored red.
- Fill the syringe to with maximum of whole blood at a rate of 1cc every two seconds and seal the syringe the red (luer) cap.
- Refer to ACP processing

**IV. ACP Processing**

- Place Syringe for IA injection containing the whole blood in bucket of centrifuge. Place the counterbalance in the opposite bucket. **Note:** the syringe and counterbalance must be in opposite buckets to maintain balance.
- Run the centrifuge at 1500 rpm for 5 minutes. Remove the syringe, taking care to keep it in an upright position to avoid mixing the plasma and red blood cells.

**Syringe for IA injection:**

- In order to transfer the ACP from the outer syringe into the inner syringe, slowly push down on the outer syringes red wings, while slowly pulling up the plunger of the inner syringe.
- Unscrew smaller syringe, place a capped injection needle (20-25 gauge) on small syringe, label with subject ID and "ACP Injection" and set it aside.
- Document the amount processed in the syringe intended for injection.

If sample mixes or clots, obtain another sample, do not re-spin.

**Note:**

Subjects randomized to the Normal Saline group will receive the same amount of normal saline as the amount of ACP processed. (3-6 ml)

Subjects randomized to ACP will receive the maximum amount of ACP processed.(3-6ml)

Provide the blinding personnel with both the syringe of ACP and normal saline with the same volume of fluid. Discard extra normal saline if subject's ACP processed is less than 6 ml prior to providing to blinding personnel.

**Authorized Investigator should deliver treatment within 30 minutes. See IA injection instructions.**

Protocol Version: January 1, 2017

**ACP Venipuncture and Blood Collection Procedure Visit 3 & 4**

**\*If fluid is noted in the cap or needle of processed ACP or normal saline, the needle should be replaced to avoid unblinding.\***

**\*Please Note – To avoid unblinding to treatment, do not push fluid to the tip of the needle.\***

## Appendix 2-4 Intra-Articular Injection Procedure: Visits 2, 3 & 4

### ACP Study Instructions for Visits 2, 3 and 4 Intra-Articular Injection

\* The Clinical Investigator will personally operate the study device and may not delegate this duty

#### Supplies

1 Blinded Syringe (20-25 gauge) with subject ID & Group on it  
Antiseptic solution of choice



1 Place subject in supine position, affected knee slightly bent with the help of a popliteal cushion. Disinfect skin with alcohol, betadine solution, chlorhexidine or antiseptic of choice.



2 Topical anesthetic can be used to locally anesthetize the skin prior to injection. Prepare the ACP as directed in the directions for use with a minimum injection volume of 3 cc and a maximum of 6 cc. Use injection needle of choice ranging from 20 – 25 gauge.



3 Insert the needle angled toward the medial joint line of the knee into the soft spot between the patella and femur. This will be next to where the line going through the lateral patellar edge and the line going through the superior pole of the patella meet.



4 Dispense the ACP into the joint cavity. If meeting resistance upon injection, redirect the needle as the needle is probably within soft tissue. Note, if an effusion exists before ACP is administered, the effusion should be aspirated before the ACP injection is given. **Do not use the same syringe for removing fluid and injection randomized treatment.**



5 After the injection is complete, place a bandage over the injection site. Monitor the subject for 10 minutes post injection in order to ensure absence of adverse reactions.

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### ACP Study Instructions for Visits 2, 3 and 4 Intra-Articular Injection

**Patient Management Plan** - Instruct patient on the following:

1. He/she may experience transient pain, swelling, and/or effusion of the injected joint after IA injection.
2. Pronounced pain and extensive swelling should be reported to the physician.
3. He/she should avoid strenuous activities or prolonged weight-bearing for approximately 48 hours.
4. He/she should be able to resume baseline activities after 48 hours.

## Appendix 2-5 Blinding Procedure

Protocol Version: February 1, 2016

### ACP Blinding Procedure Visit 2, 3 & 4

**(Blinding Procedure tool should be kept in secure area and available only to the study personnel)**

<b>Supplies:</b>	
1 syringe with normal Saline (clearly marked with subject ID)	• 1-2 black finger cots and 1-2 white finger cots
1 syringe with ACP (clearly marked with subject ID)	• 1-2 patient labels
<b>Opaque biohazardous container</b>	

#### Blinding Procedure:

The blinding person will run the randomization report in Medrio for the subject prior to preparing the syringe for blinding.

The blinding should be done in a separate secure place where the Randomized treatment will not be un-blinded or in view to others.

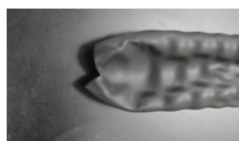
The blinding personnel will be provided with both the syringe with ACP (clearly marked with subject ID) and a syringe with normal saline with the same volume of fluid.

The blinding personnel will discard the syringe the subject was not randomized to in **opaque biohazard container** prior to leaving blinding area to avoid inadvertent un-blinding

**Note: If fluid is noted in cap or needle of the processed ACP or normal saline, the needle should be replaced to avoid unblinding**

Prepare Randomized Treatment:

- Place a black finger cot and cut a **tiny portion** of the finger tip off, just enough for the capped needle to pass through.



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Protocol Version: February 1, 2016

#### ACP Blinding Procedure Visit 2, 3 & 4

- Take the black finger cot and draw it over the capped needle and the syringe until the syringe is fully covered.
- Take a white finger cot and cut a tiny portion of the finger tip off, just enough for the capped needle to pass through.



- Take the white finger cot and draw it over the capped needle and the syringe, covering the black finger cot, until the syringe is fully covered.



- Clearly mark with subject ID and group 1 or group 2
- The blinding personnel will provide the syringe to the Investigator designated to do the IA injection.

## Appendix 2-6 Case Report Forms

### ACP\_Pivotal\_Test

Visit Date at Visit 1 - Screening, Visit 2 - Day 0, Visit 3 - Week 1 (+/- 3 days), Visit 4 - Week 2 (+/- 3 days), Visit 5 - 2 months (+/- 7 days), Visit 6 - 3 months (+/- 7 days), Visit 7 - 6 months (+/- 14 days), Visit 8 - 1 year (+/- 30 days), Unscheduled

Visit Date  [Now](#)

## ACP\_Pivotal\_Test

### Inclusion Criteria at Visit 1 - Screening

1. The subject is  $\geq 18$  to 70 years.  
☐ Yes ☐ No
2. The subject present with complaints of continued pain of primary knee for at least 6 weeks.  
☐ Yes ☐ No
3. The subject has documented Radiographic evidence of OA in the tibio-femoral or patella-femoral compartment of the target knee (Kellgren-Lawrence Grades II-III), using radiographs performed within 24 weeks of screening.  
☐ Yes ☐ No
- 3a. Which knee is a candidate for the ACP procedure?  
☐ Right ☐ Left
- 3b. Specify Indication:  
☐ Symptomatic OA of the tibio-femoral compartment of the target knee  
☐ Symptomatic OA of the patella-femoral compartment of the target knee
- 3c. Date of Radiograph
4. The subject has WOMAC pain score of at least 8 out of 20 and at least moderate pain (a score of 2) for at least 2 questions on activities.  
☐ Yes ☐ No

## ACP\_Pivotal\_Test

### Exclusion Criteria at Visit 1 - Screening

1. Grade I or IV on the knee Kellgren-Lawrence grading scale  
☐ Yes ☐ No
2. The subject has clinically apparent 3+ effusion of the target knee (stroke test grading system)  
☐ Yes ☐ No
3. The subject has significant > 10° Valgus or Varus deformities as evidence by standard of care X-ray  
☐ Yes ☐ No
4. Subject has had systemic or IA injection of corticosteroids in any joint within three months prior to screening.  
☐ Yes ☐ No
5. Viscosupplementation in any joint in the past six months.  
☐ Yes ☐ No
6. Subject has an increased risk for post-surgical bleeding (e.g., bleeding disorder or taking anticoagulants except low-dose aspirin).  
☐ Yes ☐ No
7. Subject had prior open surgery on the target knee within 12 months or arthroscopy within 6 months.  
☐ Yes ☐ No
8. Subject has inflammatory disease of either knee other than OA.  
☐ Yes ☐ No
9. Subject with any condition medical conditions that could interfere with the evaluation of the outcome.  
☐ Yes ☐ No
10. Subject with positive pregnancy test, or breast feeding  
☐ Yes ☐ No
11. Subject with plans to participate in other clinical trial involving medical or surgical intervention in the 12 months.  
☐ Yes ☐ No
12. Subject with any condition (including cognitive impairment) that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.  
☐ Yes ☐ No
13. Subject has rheumatoid arthritis or gout.  
☐ Yes ☐ No
14. Subject has history or current infection at the affected joint.  
☐ Yes ☐ No
15. Subject with plans to undergo any elective orthopedic surgery in the next 12 months.  
☐ Yes ☐ No

## ACP\_Pivotal\_Test

### History and Demographics at Visit 1 - Screening

**1. Date of Birth:**

**Age**

**2. What is subject's gender?**

☐ Male ☐ Female

**3. Please indicate all that apply:**

☐ Native American Indian

☐ Asian or Pacific Islander

☐ Black or African-American

☐ White/Caucasian

☐ Hispanic/Latino

☐ Non-Hispanic or Latino

☐ Other (specify)

**Specify:**

**4. Allergies:**

**5. Does subject have potential to become pregnant?**

☐ Yes

☐ No

**Specify:**

**Pregnancy Test Result:**

☐ Positive

☐ Negative

**6. Is subject breastfeeding?**

☐ Yes

☐ No

**Specify:**

**9. Has Subject had systemic or IA injections of corticosteroids in any joint within the last three months?**

☐ Yes ☐ No

**10. Has Subject had Viscosupplementation in any joint in the past six months?**

☐ Yes ☐ No

## ACP\_Pivotal\_Test

	Medical Disorder	Specify:	Date Diagnosed	Actively Treated?
1	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No
2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No

More rows: 1 5 10

## Surgery History

	Type of Surgery	Date of Surgery
1	<input type="text"/>	<input type="text"/>
2	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>

More rows: 1 5 10

## ACP\_Pivotal\_Test

## Physical Examination at Visit 1 - Screening,Unscheduled

BP - Systolic  mmHG BP - Diastolic  mmHG Temp  F

Height  inches Weight  pounds

	Specify:	Abnormalities?	If Yes, Specify:
1 <input type="text" value="General Appearance &amp; Mental Status"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>
2 <input type="text" value="Integumentary"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>
3 <input type="text" value="Cardiovascular"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>
4 <input type="text" value="Respiratory"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>
5 <input type="text" value=""/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>
6 <input type="text" value="Musculoskeletal"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>
7 <input type="text" value="Other"/>	<input type="text"/>	<input type="radio"/> Yes <input type="radio"/> No	<input type="text"/>

**Knee Exam****Stroke Test:**

- ☐ Zero No Wave produced on downstroke
- ☐ Trace Small wave on medial side with downstroke
- ☐ 1 + Larger bulge on medial side with downstroke
- ☐ 2+ Effusion spontaneously returns to medial side after upstroke (no downstroke necessary)
- ☐ 3 + So much fluid that it is not possible to move the effusion out of the medial aspect of the knee.

**Deformity:**

- ☐ > 10° Valgus
- ☐ ≤ 10° Valgus

**Deformity**

- ☐ > 10° Varus
- ☐ ≤ 10° Varus

**Kellgren-Lawrence Grades:**

- ☐ Grade 1 - Possible osteophytes only
- ☐ Grade 2 - Definite osteophytes and possible joint space narrowing
- ☐ Grade 3 - Moderate osteophytes and/or definite narrowing of the joint space
- ☐ Grade 4 - Large osteophytes and severe joint narrowing and/or bony sclerosis

## ACP\_Pivotal\_Test

### Laboratory Results - Heme Profile at Visit 2 - Day 0

#### Heme Profile:

	Whole Blood	Result	ACP	Result
1 WBC (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
2 RBC (mil/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
3 Hgb (gm/dL) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
4 Hct (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
5 MCV (80-100 fL) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
6 MCH (pg) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
7 MCHC (gm/dL) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
8 RDW-CV (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
9 Platelet (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
10 Neut % (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
11 Lymph % (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
12 Mono % (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
13 Eos % (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >
14 Baso % (%) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="text"/> <input type="radio"/> < <input type="radio"/> >



## ACP\_Pivotal\_Test

15	Neut Abs# (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="radio"/> <	<input type="text"/>
					<input type="radio"/> >	
16	Lymph Abs# (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="radio"/> <	<input type="text"/>
					<input type="radio"/> >	
17	Mono Abs# (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="radio"/> <	<input type="text"/>
					<input type="radio"/> >	
18	Eos Abs# (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="radio"/> <	<input type="text"/>
					<input type="radio"/> >	
19	Baso Abs# (thou/cumm) ▼	<input type="checkbox"/> ND	<input type="text"/>	<input type="checkbox"/> ND	<input type="radio"/> <	<input type="text"/>
					<input type="radio"/> >	

## ACP\_Pivotal\_Test

Pre-Randomization at Visit 2 - Day 0

Subject eligible to be randomized? ☐ Yes ☐ No

## ACP\_Pivotal\_Test

Randomization at Visit 2 - Day 0

Date Informed Consent signed

### **Randomization information below will be generated by system:**

Please update subject ID and group to what appears below;  
return to subject homepage, update subject information link is at bottom of page.

Subject ID:

Treatment:

## ACP\_Pivotal\_Test

Treatment at Visit 2 - Day 0, Visit 3 - Week 1 (+/- 3 days), Visit 4 - Week 2 (+/- 3 days)

01. Procedure Side

☐ Left ☐ Right

02. Blood draw time

03. Volume of Plasma after centrifuge for IA Injection

 CC

04. Syringe blinded to group

05. Was topical anesthesia used

☐ Yes (specify on medication log)☐ No

06. Effusion fluid aspirated

☐ Yes ☐ No cc

07. Time of IA injection

08. Injection was given at the soft spot between patella and femur

☐ Yes☐ No

Specify:

09. What was the volume of treatment injected?

 cc

## ACP\_Pivotal\_Test

10. Were there any device complications during the IA procedure

☐ Yes

☐ No

If Yes, specify

☐ Unable to pull up outer syringe

☐ Unable to pull up inner syringe

☐ Damaged

☐ Cracked

☐ Packaging - Device/component missing

☐ Packaging - Broken in package

☐ Leaking

☐ Air mixed with blood

☐ Piece broke from device

☐ Frozen

☐ Other

Specify:

Series I Kit Part #

Lot #

Quantity Used:

1

11. Were there any Adverse Events during procedure?

☐ Yes (complete AE form)

☐ No

## ACP\_Pivotal\_Test

WOMAC at Visit 1 - Screening, Visit 3 - Week 1 (+/- 3 days), Visit 4 - Week 2 (+/- 3 days), Visit 5 - 2 months (+/- 7 days), Visit 6 - 3 months (+/- 7 days), Visit 7 - 6 months (+/- 14 days), Visit 8 - 1 year (+/- 30 days), Unscheduled

WOMAC Scoring: 0=none, 1=mild, 2=moderate, 3=severe, 4=extreme

For each WOMAC@ dimension, a subscale score is calculated by simple summation:

Pain = 0-20

Stiffness = 0-8

Physical function = 0-68

### Section A PAIN

Think about the pain you felt in your knee caused by your arthritis during the last 48 hours.

QUESTION: **How much pain have you had...**

1. when walking on a flat surface?  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
2. when going up or down stairs:  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
3. at night while in bed? (that is - pain that disturbs your sleep)  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
4. while sitting or lying down?  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
5. while standing?  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

### Section B STIFFNESS

Think about the stiffness (not pain) you felt in your knee caused by the arthritis during the last 48 hours.  
 Stiffness is a sensation of **decreased** ease in moving your joint.

6. How **severe** has your stiffness been **after you first woke up** in the morning?  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day**?  
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

### Section C DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your knee during the last 48 hours.  
 By this we mean **your ability to move around and take care of yourself**.

QUESTION: **How much difficulty have you had...**

## ACP\_Pivotal\_Test

8. when going down the stairs?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC 8 CAL

9. when going up the stairs?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC9 CAL

10. when getting up from a sitting position?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC10 CAL

11. while standing?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC11 CAL

12. when bending to the floor?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC12 CAL

13. when walking on a flat surface?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC13 CAL

14. getting in or out of a car, or getting on or off a bus?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC14 CAL

15. while going shopping?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC15 CAL

16. when putting on your socks or panty hose or stockings?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC16 CAL

17. when getting out of bed?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC17 CAL

18. when taking off your socks or panty hose or stockings?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC18 CAL

19. while lying in bed?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC19 CAL

20. when getting in or out of the bathtub?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC20 CAL

21. while sitting?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC21 CAL

22. when getting on or off toilet?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC22 CAL

23. while doing heavy household chores?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC23 CAL

24. while doing light household chores?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

WOMAC24 CAL

WOMAC Total

## ACP\_Pivotal\_Test

WOMAC Score at Visit 1 - Screening, Visit 3 - Week 1 (+/- 3 days), Visit 4 - Week 2 (+/- 3 days), Visit 5 - 2 months (+/- 7 days), Visit 6 - 3 months (+/- 7 days), Visit 7 - 6 months (+/- 14 days), Visit 8 - 1 year (+/- 30 days), Unscheduled

WOMAC Scoring: 0=none, 1=mild, 2=moderate, 3=severe, 4=extreme

For each WOMAC® dimension, a subscale score is calculated by simple summation:

Pain = 0-20

Stiffness = 0-8

Physical function = 0-68

Subject's responses for WOMAC for this visit entered in EDC? ☐ Yes ☐ No

### Section A PAIN

PAIN1

PAIN2

PAIN3

PAIN4

PAIN5

**Total PAIN**

### Section B STIFFNESS

STIFF6

STIFF7

**Total STIFFNESS**

### Section C DIFFICULTY PERFORMING DAILY ACTIVITIES

PFTN8

PFTN9

PFTN10

PFTN11

PFTN12

PFTN13

PFTN14

PFTN15

PFTN16

PFTN17

PFTN18

PFTN19

PFTN20

PFTN21

PFTN22

PFTN23

PFTN24

**Total DIFFICULTLY PERFORMING  
DAILY ACTIVITIES**

**WOMAC TOTAL**

## ACP\_Pivotal\_Test

Completion at Completion

### A. Trial Completion

**Did the subject complete the trial?**

☐ Yes; provide Date of Last Visit.

☐ No; provide Date of Discontinuation and complete Section B.

Date of Last Visit

Date of Study Discontinuation

### B. Primary Reason for Discontinuation

Check **one** primary reason:

## ACP\_Pivotal\_Test

Specify Criteria not met:  
(Select all that apply)

- ☐ Inclusion 1
- ☐ Inclusion 2
- ☐ Inclusion 3
- ☐ Inclusion 4
- ☐ Inclusion 5
- ☐ Exclusion 1
- ☐ Exclusion 2
- ☐ Exclusion 3
- ☐ Exclusion 4
- ☐ Exclusion 5
- ☐ Exclusion 6
- ☐ Exclusion 7
- ☐ Exclusion 8
- ☐ Exclusion 9
- ☐ Exclusion 10
- ☐ Exclusion 11
- ☐ Exclusion 12
- ☐ Exclusion 13
- ☐ Exclusion 14
- ☐ Exclusion 15
- ☐ Other; specify

Specify:



## ACP\_Pivotal\_Test

### Inclusion Criteria

1. The subject is  $\geq 18$  to 70 years of age.
2. The subject present with complaints of continued knee pain of primary knee for at least 6 weeks.
3. The subject has documented radiographic evidence of OA in the tibio-femoral or patella-femoral compartment of the target knee (Kellgren-Lawrence Grades II-III), using radiographs performed within 24 weeks of screening.
4. The subject has a WOMAC pain score of at least 8 out of 20 and at least moderate pain (a score of 2) for at least 2 questions on activities.

### Exclusion Criteria

1. Grade I and IV on the knee Kellgren-Lawrence grading scale.
2. Subject has clinically 3+ effusion of the target knee (stroke test grading system).
3. Subject has significant ( $> 10^\circ$ ) valgus or varus deformities as evidenced by standard of care X-ray.
4. Subject has had systemic or IA injection of corticosteroids in any joint within three months prior to screening.
5. Viscosupplementation in any joint in the past six months.
6. Subject has an increased risk for post-surgical bleeding (e.g., bleeding disorder or taking anticoagulants except low-dose aspirin).
7. Subject had prior open surgery on the target knee within 12 months or knee arthroscopy within 6 months.
8. Subject has inflammatory disease of either knee other than OA.
9. Subject with underlying medical conditions that could interfere with the evaluation of the outcome.
10. Subject with positive pregnancy test, or breast feeding.
11. Subject with plans to participate in other clinical trial involving medical or surgical intervention in the next 12 months.
12. Subject with any condition (including cognitive impairment) that, in the opinion of the investigator, might interfere with the evaluation of the study objectives.
13. Subject has rheumatoid arthritis or gout.
14. Subject has history or a current infection at the affected joint.
15. Subject with plans to undergo any elective orthopedic surgery in the next 12 months.

## ACP\_Pivotal\_Test

### Adverse Events at Adverse Events

ADVERSE EVENTS : Any undesirable medical occurrence in a clinical investigational subject. This occurrence may or may not have a causal relationship with study device. Any condition that is recorded as preexisting, unless there is a change in nature, severity or degree of incidence, is not an AE.

Device Related?	AE Type: AE Classification:	AE Description:	Onset Date	Stop Date	AE Onset?	Causality Assessment Code	Severity Code (Select one)	Serious? In this AE?	Serious Code (Select one)	If Serious Code 3 selected, specify:	Specify:	Apply Action Taken/Treatment Code (Select all that apply)	Outcome Code (Select one)	Narrative:
1	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Anticipated (Applies to device) <input type="radio"/> Unanticipated			<input type="checkbox"/>	<input type="radio"/> 1 = Unrelated <input type="radio"/> 2 = Probable <input type="radio"/> 3 = Possibly related <input type="radio"/> 4 = Probably related <input type="radio"/> 5 = Unknown	<input type="radio"/> 1 = Mild <input type="radio"/> 2 = Moderate <input type="radio"/> 3 = Severe	<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> 1 = Fatal <input type="radio"/> 2 = Led to serious deterioration of subject that resulted in: <input type="radio"/> 3 = Fetal distress/fetal death or congenital abnormality or birth defect <input type="radio"/> 4 = Other; specify <input type="radio"/> 5 = Life-threatening illness or impairment of body function <input type="radio"/> 2a = Permanent impairment of body function <input type="radio"/> 2b = Inpatient hospitalization or existing hospitalization <input type="radio"/> 2c = Medical intervention to prevent injury or permanent impairment (	<input type="radio"/> 1 = None <input type="radio"/> 2 = Discontinuation of therapy <input type="radio"/> 3 = Non-intervention <input type="radio"/> 4 = Surgical intervention <input type="radio"/> 5 = Subject removed <input type="radio"/> 6 = Subject discontinued <input type="radio"/> 7 = Ongoing & improving <input type="radio"/> 8 = Ongoing & unchanged <input type="radio"/> 9 = Ongoing & deteriorating <input type="radio"/> 10 = Death	<input type="radio"/> 1 = Recovered <input type="radio"/> 2 = Recovered w/ separate <input type="radio"/> 3 = Recovered w/ ongoing <input type="radio"/> 4 = Recovered w/ ongoing & improving <input type="radio"/> 5 = Recovered w/ ongoing & unchanged <input type="radio"/> 6 = Recovered w/ ongoing & deteriorating <input type="radio"/> 7 = Recovered w/ ongoing & death			

More rows: 1 5 10

## ACP\_Pivotal\_Test

### Medication/Therapy at Concomitant Medications

Medication/Concomitant Therapy	Dose	Units	Specify:	Frequency	Specify:	Route	Specify:	Indication/Reason (Specify area of body and primary complaint)	Start Date	Stop Date
1										<input type="checkbox"/> Ongoing

More rows: 1 5 10

**ADVERSE EVENTS** : Any undesirable medical occurrence in a clinical investigational subject. This occurrence may or may not have a causal relationship with Study device. Any condition that is recorded as preexisting, unless there is a change in nature, severity or degree of incidence, is not an AE.

Device Related?	AE Type:	AE Classification:	AE Description:	Onset Date	Stop Date	AE Ongoing?	Causality Assessment Code (Select one)	Severity Code (Select one)	Serious? Is this a serious AET?	Serious Code	If Serious Code 2 selected, specify:	Specify:	Apply Action Taken/Treatment Code (Select all that apply)	Outcome Code (Select one)	Narrative:
1	<input type="radio"/> Anticipated (applies to procedure or device)	<input type="radio"/> Anticipated				<input type="checkbox"/>	<input type="radio"/> 1 = Unrelated <input type="radio"/> 2 = Probably not related <input type="radio"/> 3 = Possibly related <input type="radio"/> 4 = Probably related <input type="radio"/> 5 = Unknown	<input type="radio"/> 1 = Mild <input type="radio"/> 2 = Moderate <input type="radio"/> 3 = Severe	<input type="radio"/> 1 = Yes <input type="radio"/> 2 = No	<input type="radio"/> 1 = Fatal <input type="radio"/> 2 = Led to serious deterioration in the health of the subject that resulted in death or a body function <input type="radio"/> 3 = Fatal distress; mental death or congenital abnormality or birth defect <input type="radio"/> 4 = Other; Specify	<input type="radio"/> 1a = Life-threatening illness or injury <input type="radio"/> 2b = Permanent impairment of body function or a body function <input type="radio"/> 2c = Impairment, hospitalization or prolongation of existing condition <input type="radio"/> 3 = Significant medical intervention to prevent life threatening illness; injury or permanent impairment	<input type="radio"/> 1 = None <input type="radio"/> 2 = Concomitant <input type="radio"/> 3 = Non-interventive <input type="radio"/> 4 = Surgical <input type="radio"/> 5 = Intervention <input type="radio"/> 6 = Removed <input type="radio"/> 7 = Subject discontinued	<input type="radio"/> 1 = Recovered completely <input type="radio"/> 2 = Recovered <input type="radio"/> 3 = Stable <input type="radio"/> 4 = Improving <input type="radio"/> 5 = Impairment <input type="radio"/> 6 = Subject unchanged <input type="radio"/> 7 = Deteriorating <input type="radio"/> 8 = Death		

ACP\_Pivotal\_Test  
Protocol Deviation at Protocol Deviations

Associated Visit	Date of Deviation	Deviation Description	Deviation Code	Deviation Classification	Deviation Classification	Deviation Classification	Deviation Classification	Deviation Classification	Deviation Classification	Deviation Classification	Specify:	Corrective Action Taken to Prevent Recurrence	Resulted in AE?	Meets IDE Reporting Req.	IDE Reporting Date	
1													<input type="radio"/> Yes <input type="radio"/> No	<input type="radio"/> Yes <input type="radio"/> No		
<input type="radio"/> Visit 1																
<input type="radio"/> Visit 2																
<input type="radio"/> Visit 3																
<input type="radio"/> Visit 4																
<input type="radio"/> Visit 5																
<input type="radio"/> Visit 6																
<input type="radio"/> Visit 7																
<input type="radio"/> Visit 8																
<input type="radio"/> Unscheduled or Between visits																
<input type="radio"/> NA																

More rows: 1 5 10

## ACP\_Pivotal\_Test

### Visit Details at Visit 2 - Day 0

1. Has the subject received additional therapy for their target knee since their last visit?

☐ None

☐ Occupation therapy

☐ Other; non-drug injections, specify

☐ Medication (document on Concomitant Medication Form)

Specify:

2. Please confirm that concomitant medications and/or treatments were reviewed with subject during Visit and documented on Concomitant Medications.

☐ Yes

☐ No

## ACP Pivotal Test

Visit Details at Visit 3 - Week 1 (+/- 3 days), Visit 4 - Week 2 (+/- 3 days), Visit 5 - 2 months (+/- 7 days), Visit 6 - 3 months (+/- 7 days), Visit 7 - 6 months (+/- 14 days), Visit 8 - 1 year (+/- 30 days), Unscheduled

1. Has the subject received additional therapy for their target knee since their last visit?

- ☐ None
- ☐ Occupation therapy
- ☐ Other; non-drug injections, specify
- ☐ Medication (document on Concomitant Medication Form)

Specify:

2. Please confirm that concomitant medications and/or treatments were reviewed with subject during Visit and documented on Concomitant Medications.

- ☐ Yes
- ☐ No

3. Has the subject had any Adverse Events since their last visit?

- ☐ Yes
- ☐ No

If, 'YES', document any Adverse Events on AE form.

4. Was WOMAC completed

- ☐ Yes
- ☐ No

ACP\_Pivotal\_Test  
Device Accountability Log at Device Accountability Log

Part # IDE-ABS-10011

Lot Number	Number of Devices Received	Date Received	Received by Initials	Number of Devices Dispensed	Date Dispensed	Subject ID	Number of Devices Returned or Discarded	Reason Discarded/Returned (Loaner Return #) if applicable	Dispensed, Discarded, or Returned Initials	Current Balance of Devices
1	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

More rows: 1 5 10

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