Protocol Title: **A Prospective Study of a Single Intra-Articular Injection of Autologous Protein Solution in Females with Primary Patellofemoral Osteoarthritis**

Protocol Number: **APSS-55-00**

Study Sponsor: **Zimmer Biomet**
Biologics
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CLINICAL PROTOCOL APPROVAL PAGE

The signatories have read and understood the clinical protocol and agree to conduct the clinical investigation in compliance with this protocol:

Protocol approved by Scientific Affairs Zimmer Biomet Biologics
Krista Toler, M.S., MBA
Scientific Affairs Manager
Zimmer Biomet Biologics

Krista Toler, M.S., MBA Date

Protocol approved by Research Zimmer Biomet Biologics
Jennifer Woodell-May, PhD.
Director of Research
Zimmer Biomet Biologics

Jennifer Woodell-May, PhD Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site and supervise all testing of the device involving human subjects
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Zimmer Biomet Biologics.
- To conduct the study in compliance with ISO 14155-2011, the ethical principles that have their origin in the Declaration of Helsinki, any regional or national regulations, as appropriate, and any additional requirements imposed by the Independent Ethics Committee (IEC) or regulatory authority, as appropriate.
- To ensure that the requirements for obtaining informed consent from each subject are met. Not to implement any changes to the protocol without written agreement from Zimmer Biomet Biologics and prior review and written approval from my (IEC) except when necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study device, as described in this protocol and any other information provided by Zimmer Biomet Biologics.
- That I am aware of, and will comply with, good clinical practice and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Zimmer Biomet Biologics device and have been trained on their study-related duties and functions as described in the protocol.
- To not begin the study until the required approval/favorable opinion from the IEC or regulatory authority has been obtained.

Signature

Peter Verdonk, MD, PhD Date

STUDY CONTACT INFORMATION

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STUDY SYNOPSIS

Protocol Number:	APSS-55-00
Title:	A Prospective Study of a Single Intra-Articular Injection of Autologous Protein Solution (APS) in Females with Primary Isolated Patellofemoral Osteoarthritis (PFOA)
Sponsor:	Zimmer Biomet Biologics
Name of Product:	nSTRIDE APS Kit with Anticoagulant Citrate Dextrose Solution-Formula A (ACD-A)
Device Description:	The APS Kit with ACD-A is a self-contained, sterile-packaged, single-use, disposable device designed to isolate anti-inflammatory cytokines and growth factors from whole blood. The device system is to be used at the point of care to create an autologous protein solution. This device system consists of 2 parts: the APS Cell Separator and the APS Concentrator. The APS Cell Separator separates the cellular components from plasma and red blood cells in whole blood. The cell suspension is then loaded into the APS Concentrator, which uses filtration through polyacrylamide beads to concentrate the cytokines in the injectable output.
Intended Use:	The nSTRIDE APS Kit with ACD-A is designed to be used for the safe and rapid preparation of APS from a small sample of blood at the patient's point of care. The APS is to be injected intra-articularly for the treatment of osteoarthritis (OA).
Study Center:	The study will be conducted at a single center in Antwerp Belgium.
Sample Size:	50 subjects
Study Populations:	Females with isolated and symptomatic PFOA who have failed at least 1 prior conservative PFOA therapy (e.g. physiotherapy, simple analgesics, intra-articular injection)
Study Objectives:	**Primary Objective** The primary objective of this study is to evaluate clinical outcomes following a single injection of nSTRIDE APS in females with isolated PFOA **Secondary Objectives** A secondary objective of this study is to document the duration of treatment effect following nSTRIDE injection. Additionally blood chemistry characterize, erythrocyte sedimentation rate, C-reactive Protein, thyroid hormones T3, T4 and TSH, luteinizing hormone, and follicle stimulating hormone and analyze them with respect to clinical improvements in PFOA. This study will also allow for the

	documentation of clinical outcomes and treatment effect following a second injection of APS to treat PFOA.
Study Design and Procedures:	This single-center prospective follow-up will evaluate the effectiveness of a single dose of APS in females with isolated and symptomatic PFOA which failed at least 1 prior conservative PFOA therapy (e.g. physiotherapy, simple analgesics, intra-articular injection). This will be accomplished by assessing pain, other symptoms, activity, function of daily living, function of sports and recreations and knee related quality of life using the Knee Injury and Osteoarthritis Outcome Score (KOOS), the Kujala Anterior Knee Pain Symptom Questionnaire (KAKPAQ), the UCLA Activity Score, and numeric rating scales (NRS) for pain, function, and stiffness. Patients will also be evaluated for general quality of life using the EQ-5D-3L. Adverse events (AEs) related to the pathology, the nSTRIDE APS device or the procedure will be recorded. This study will also allow for the documentation of the same parameters following a second injection of APS to treat PFOA. Subjects will provide informed consent and be screened for eligibility (i.e., they will meet inclusion and exclusion criteria) within 2 months of treatment. If subjects meet the inclusion and exclusion criteria they will be eligible for treatment and for participation in the study. On the day of treatment but prior to treatment subjects' demographics and osteoarthritic pathology will be documented. Subjects will complete baseline KOOS, KAKPAQ, NRS, EQ-5D-3L and UCLA activity questionnaires. Following the acquisition of baseline data, subjects will have their blood drawn for processing into nSTRIDE APS and measurement of blood chemistry. Subjects will receive a single intra-articular injection into the knee(s). If both knees are included in the study, both knees will be initially treated on the same date. Follow-up assessments will be conducted at 1, 3, 6, and 12-months post injection; all subjects will complete KOOS, KAKPAQ, NRS, UCLA Activity Score, and EQ-5D-3L questionnaires. The investigative center will complete the Follow-up form and collect knee related AE information. Follow-up assessments may consist of a structured telephone interview, electronic self-report or, *if standard of care*, an office visit. Subjects will remain in the study until they complete the 12-month follow-up assessments. Under the conditions including but not limited to, a more invasive knee

	procedure, or voluntary withdrawal of consent, the subject's study participation will be terminated.
Study Duration:	The maximum study duration for each subject is estimated to be 14 months. Time will be up to 2 months prior to treatment and follow-up 12 months post injection.
Inclusion Criteria:	• Female • Primary PFOA in one or both knees as diagnosed by the treating physician • Objective evidence of PFOA on one or both of a radiograph or MRI taken within 1year of treatment. • From 40-65 years of age, inclusive at time of injection • Failed at least 1 prior conservative PFOA therapy (e.g. physiotherapy, simple analgesics, intra-articular injection). Willing and able to comply with the study procedures • Signed informed consent form
Exclusion Criteria:	• Any systemic inflammatory condition (e.g., rheumatoid arthritis) • Active malignancy at time of injection • Pregnant at time of injection • Lactating at the time of injection • Knee joint infections or skin diseases or infections in the area of the injection site. • Leukemia, metastatic malignant cells, or who are receiving chemotherapeutic treatment • Participating in another device or drug study
Schedule of Assessments:	• Informed Consent (within 2 months of treatment) • Confirm eligibility; Treatment • Post-injection assessments: – 1 month (30 days ±7 days) – 3 month (91 days ±14 days) – 6 month (182 ±21 days) – 12 month (365 ±28 days)
Assessment Tools:	• Knee Injury and Osteoarthritis Outcome Score • Kujala Anterior Knee Pain Assessment Questionnaire • Numeric Rating Scale (pain, stiffness, function) • UCLA Activity Score • European Quality of Life 5 Dimensions 3 Levels

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Abbreviations and Terms

ACD-A	Anticoagulant Citrate Dextrose Solution, Solution A
ACS	Autologous Conditioned Serum
ADE	Adverse Device Effect
AE	Adverse Event
APS	Autologous Protein Solution
CIP	Clinical Investigation Plan
CRF	Case Report Forms
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Levels
FDA	Food and Drug Administration (US)
HA	Hyaluronic Acid
ICF	Informed Consent Form
I/E	Inclusion/Exclusion
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
IL-1,IL-6, IL-8	Interleukin 1, Interleukin-6, Interleukin-8
IL-1ra	IL-1 receptor antagonist
KAKPAQ	Kajula Anterior Knee Pain Assessment Questionnaire
KOOS	Knee Injury and Osteoarthritis Outcome Score
MDD	Medical Device Directive
NRS	Numeric Rating Scale
OA	Osteoarthritis
PETG	Polyethylene terephthalate
PFOA	Patellofemoral Osteoarthritis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
sIL-1RI, sIL-1RII	Soluble forms of IL-1 receptor
sTNF-RI,sTNF-RII	Soluble forms of TNFα receptor
T3, T4, TSH	Thyroid hormones
TNFα	Tumor Necrosis Factor alpha
UCLA	University of California Los Angles

1 INTRODUCTION

Osteoarthritis (OA) is a degenerative and disabling articulating joint disease that affects both young, active patients and the elderly (1-4). Surgical intervention is a widely used and clinically successful option for treatment of severe degenerative OA. However, success rates for treating less severe OA vary. Current treatment options include nonsteroidal anti-inflammatory drugs, corticosteroid injections, and hyaluronic acid (HA) injections. Although these treatments may be effective in temporary pain relief for some OA patients, they do not address the biological mechanisms causing the disease (5). OA is characterized by chronic pain, cartilage degradation, loss of subchondral bone remodeling, and varying degrees of synovial inflammation. OA pain is a complex response resulting from the interplay between inflammation, anatomic pathology, articular cartilage innervation, nerve sensitization, and psychological factors. Inflammation associated with OA results in joint stiffness and pain; patients may experience local warmth, tenderness, and effusion (6). Although OA is classified as a non-inflammatory disease, inflammation is implicated in many symptoms and the progression of OA. Pro-inflammatory cytokines are involved in OA development (7-12). Cytokines such as interleukin (IL)-1, tumor necrosis factor alpha (TNFα), IL-6, and IL-8 are integral in the initiation and maintenance of inflammation by mediating cell-to-cell interactions (13). Of these, IL-1 has been proposed to play a key role (14-16). The cytokines associated with inflammation in OA, primarily IL-1 and TNFα, are also implicated in cartilage matrix breakdown (17-19). These cytokines induce cells in the joint to produce matrix metalloproteinases that in turn are responsible for degradation of the cartilage matrix (20). The interactions between chondrocytes in articular cartilage, synovium, and IL-1 and TNFα result in a positive feedback loop that further increases inflammation and cartilage breakdown associated with increasing limitation in cartilage repair. IL-1, TNFα, IL-6, and IL-8, along with nerve growth factor, also lead to nerve sensitization and stimulation (21).

Both IL-1 and TNFα are implicated in inflammation and cartilage breakdown, thus inhibition of these cytokines may be an effective therapy by limiting inflammation and matrix degradation. The anti-inflammatory cytokine interleukin-1 receptor antagonist (IL-1ra), a competitive IL-1 receptor antagonist, blocks the signaling activity of IL-1 and has no signal-inducing activity itself (22-24). Soluble forms of the IL-1 cell receptor competitively bind with IL-1 and reduce IL-1 biologic activity (25). Additionally, soluble forms of the cell receptors for TNFα, known as sTNF-RI and sTNF-RII, can bind to TNFα preventing it from binding to a surface receptor and thus inhibiting cell signaling (26). These anti-inflammatory cytokines are present systemically, but not in the concentrations or locations that may be clinically beneficial in the treatment of knee OA.

The nSTRIDE APS Kit is designed to produce an autologous protein solution (APS). APS contains concentrated levels of anti-inflammatory cytokines including IL-1ra, sIL-1RII, sTNF-RI, and sTNF-RII and of anabolic cytokines for cartilage, including insulin-like growth factor 1 and transforming growth factor β1 (27). A method of balancing these cytokines by injection of autologous conditioned serum (ACS) has been explored. ACS is an autologous acellular plasma serum containing proteins. The ACS also contains up-regulated levels of anti-inflammatory cytokines and has shown promise when compared to HA or saline for the treatment of OA (28).

In summary, inflammatory and catabolic cytokines are strongly implicated in the OA degenerative process and inhibition of their action may be clinically beneficial. Anti-inflammatory and anabolic cytokines found in whole blood may also reduce or reverse the degenerative process. Appropriate processing of whole blood substantially increases the concentrations of anti-inflammatory and anabolic cytokines. Thus, a likely mechanism of action of APS in reducing symptomatic OA and reducing or reversing the degenerative impact of inflammatory and catabolic cytokines is the introduction of greater than normal levels of anti-inflammatory and anabolic cytokines in a targeted fashion.

2 NSTRIDE APS KIT DESCRIPTION

The nSTRIDE APS Kit is a self-contained, sterile packaged, single-use, disposable device used at the point of care to concentrate anti-inflammatory cytokines and growth factors from whole blood. The device is to be used at the point-of-care to create an autologous solution. The nSTRIDE APS Kit with Anticoagulant Citrate Dextrose Solution – Formula A (ACD-A) contains two polymer blood processing devices and a 30 milliliter (ml) vial of Anticoagulant Citrate Dextrose Solution – Formula A (ACD-A). The first of the two devices is the nSTRIDE Cell Separator. It is a plastic tube containing a tuned-density buoy and separates cellular components of whole blood when appropriately cycled in a centrifuge. The cell suspension produced is further processed by the second of the two devices, the nSTRIDE Concentrator. This device is a plastic tube containing polyacrylamide beads to further concentrate the cell suspension and produce an injectable output, the APS.
Sixty milliliters (mL) of anticoagulated whole blood (55mL blood drawn into 5 mL ACD-A) are injected into the APS Cell Separator. The device is centrifuged for 15 minutes; the plasma is discarded and the cell concentrate is resuspended and transferred to the Concentrator containing the acrylamide beads. The device is centrifuged for 2 minutes and the final product (output) is removed. The output (APS) is approximately 2.5mL and is intended to be administered via an intra-articular injection.

APS contains high concentrations of anti-inflammatory molecules, and it has been shown to block inflammation and prevent cartilage degradation in vitro. In a prospective, randomized, controlled equine clinical study, APS reduced pain and improved function in horses with osteoarthritis.

The components of the device are listed in the table below.

Component Name	Part Number
nSTRIDE APS Kit	800-3000ST

The overall device classification is as follows:

Device Classification:	Class IIb, as defined in Annex IX of the Council Directive 93/42/EEC Concerning Medical Devices, i.e., Medical Device Directive (MDD)
Sterilization:	The APS device is supplied as a sterile single-use unit.

Intended Use:

The nSTRIDE APS Kit with ACD-A is designed to be used for the safe and rapid preparation of APS from a small sample of blood at the patient's point of care. The APS is to be injected intra-articularly for the treatment of knee osteoarthritis.

Contraindications:
APS should not be injected in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site. Please refer to the Instructions for Use (IFU) for a complete list of contraindications (Appendix 1).

Manufacturing, Packaging and Labeling
The investigational device is made primarily out of the raw material Cyrolite Med 2 acrylic-based multipolymer compound, which is manufactured at Cyro Industries (Rockaway, NJ). All of the device components are manufactured and/ or assembled at Advanced Engineering Inc.(Huntington, IN). Components are injection molded on a 50-80 ton horizontal Nissei screw type injection molding machine and then assembled in a clean room environment under ISO 13485 and FDA guidelines. The complete assembled parts are packaged at Advanced Engineering Inc. in a clean room environment in a PETG Tray and sealed with a Tyvek lid. The sealed package is shipped to Steris Inc. (Libertyville, IL) for gamma sterilization and received back at Advanced Engineering Inc. for final inspection. The sterilized device packages are then kitted into the final carton, shrink wrapped in plastic in a clean room environment and shipped complete to Zimmer Biomet Inc. (Warsaw, IN).
The APS devices will be labeled in accordance with local regulations for device labeling.

Device Supply, Storage, and Accountability
The APS Kit with ACD-A will be supplied by Zimmer Biomet Biologics. The device can be stored at room temperature. The nSTRIDE device is CE marked for this indication and no special restrictions are necessary.

3 RATIONALE

Clinical trials have, in general, formally demonstrated the effectiveness and safety of various autologous therapies for the treatment of knee OA. Differences in the processing of autologous therapies can yield substantial differences in the resulting output. Thus, making generalizations regarding the effectiveness across these autologous therapies is more complicated. Each autologous therapy requires independent efficacy evaluation. nSTRIDE APS has been shown to decrease pain, increase function and have a favorable safety profile in a pilot trial[1].
Further, demonstration of the treatment effects in patellofemoral OA (PFOA), an important subset of knee osteoarthritis is lacking. This study will evaluate a population of female patients with PFOA in which treatment with other modalities provides limited/short lived relief with the hope that APS treatment will provide and extend relief to these patients. The study will document the treatment effects and timeline of treatment effects for nSTRIDE APS following a single injection (per symptomatic knee).

[1] A Pilot Study of a Single Intra-articular Injection of Autologous Protein Solution (APS) in Patients with Osteoarthritis (OA) of the Knee. (2014) Data on file Biomet Biologics

4 STUDY OBJECTIVES

The study objectives will document treatment effects, changes in quality of life, and treatment complications in female patients with PFOA following a single APS injection into the knee(s).

4.1 Study Objectives

4.1.1 Primary Objective

The primary objective of this study is to assess clinical outcomes such as pain, other symptoms, function of daily living, function of sports and recreation, and other knee related quality of life measures of a single nSTRIDE APS injection in females with isolated PFOA. This will be accomplished by tracking these outcome measures for up to 12 months post injection.

4.1.2 Secondary Objectives

Secondary objectives include documenting the duration of treatment effect following nSTRIDE APS injection and characterization of various blood components with respect to clinical improvement in PFOA. This study will also allow for the documentation of clinical outcomes and treatment effect following a second injection of APS to treat PFOA.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The following clinical endpoints will be assessed:

- The time from the initial nSTRIDE injection to subsequent nSTRIDE injection(s) or other intrusive treatment.
- For each of the five KOOS subscales, (Symptoms, Pain, Quality of Life (QoL), Function, Sports and Recreational Activities) and at each post-injection time point the change from baseline up to 12 months.
- The change from baseline in patellofemoral pain and instability measured by the KAKPAQ at each post-injection time point up to 12 months.
- The change from baseline in knee pain, stiffness and function measured by the NRS at each post-injection time point up to 12 months.
- The change from baseline in subject activity as measured by the UCLA Activity Score at each post-injection time point up to 12 months.
- The change from baseline in quality of life as measured by the EQ-5D at each post-injection time point up to 12 months.

4.2.2 Secondary Outcome Measures

The following secondary endpoints will be assessed at 1, 3, 6 and 12 month.

<u>Clinical endpoint:</u>

- Composite of the primary endpoint following a second injection of APS.

- Composite of the primary endpoint in relationship to the various blood components.

Safety endpoint:

- Incidence of treatment and knee related events
- Incidence of device or procedure related events

5 RISK EVALUATION

5.1 Potential Risks to Study Patients

Risks to patients in the study include risks associated with a blood draw, aspiration of joint fluid, and injection of a solution into the knee. These include allergic reaction to anesthesia, pain, stiffness, bleeding, bruising, infection, deep venous thrombosis, scar tissue formation, thrombotic complications or nerve/nervous systems damage. These possible risks may occur with any blood draw, aspiration, or joint injection procedure. Possible risks associated with the injection of APS include worsening pain and/or knee function, effusion, and infection. Another potential risk is possibility of injecting the APS of one patient into another patient when processing more than one donor at a time. This risk could be associated with the possibility of an inflammatory reaction by the patient receiving the injection and/or transmission of blood-borne pathogens. There are no known specific risks due to the device itself.

5.2 Methods to Minimize Risks

The inclusion/exclusion criteria will assure that any subject who may be at increased risk from participating in this study will not be enrolled.

This device will be used and administered only by trained healthcare professionals who are experienced in the study procedure and treatment

Sticker labels are included in each kit to identify the subject associated with each syringe, device, and sample. The use of these labels will reduce the risk of sample mix-up. Additionally, processing only one subject's blood in the centrifuge at a time would eliminate the risk.

5.3 Potential Benefits of the Procedure

The potential benefit of APS in the treatment of PFOA is that it may provide symptomatic pain relief, help restore knee function and delay the necessity of more invasive procedures.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a single center, one arm, prospective, outpatient study evaluating the effectiveness of a single nSTRIDE APS injection per symptomatic knee. The target population for this study is female patients with PFOA who have failed at least 1 prior conservative PFOA therapy (e.g. physiotherapy, simple analgesics, intra-articular injection). The target population is further refined in that, potential subjects must meet all of the inclusion criteria and none of the exclusion criteria below (6.3.2.).

During the pre-treatment visit and prior to any study specific procedures that are not standard of care, the subject will have the study explained to them and will be asked to give written informed consent. The subject will be preliminarily assessed for study eligibility on any criteria that are obtained through means that are standard of care. The subject will be asked to abstain from analgesics for 48 hours prior to the treatment visit, which will be scheduled within 2 months of the pre-treatment visit and signed informed consent.

At the pre-treatment visit, subjects formally complete the screening assessment (inclusion / exclusion criteria), including demographics, medical history, knee exam and, as needed, a pregnancy test. Upon eligibility confirmation, patients will be asked to respond to a battery of subject reported outcome measures including the KOOS, KAKPAQ, NRS, UCLA Activity Score, and EQ-5D-3L questionnaires. A blood sample of sufficient size to test for several hormones will be obtained.

Upon completion of all questionnaires the subject will receive the treatment injection(s). A subject with bilateral PFOA in whom both knees are treated must be injected on the same date for the subject to be enrolled in the study. If any intra-articular injection other than nSTRIDE APS (in index knees[s]) is necessary during the study interval the subject will be exited from the study (see 6.3.6).

At 1-, 3-, 6-, and 12-months after treatment subjects will complete questionnaires including, the KOOS, KAKPAQ, NRS, UCLA Activity Score, and EQ-5D-3L online. Subjects will be asked to abstain from analgesics for 48 hours prior to completing the questionnaires. The investigative center will complete the Follow-up form and collect knee related AE information. Follow-up assessments may consist of a structured telephone interview, electronic self-report or, *if standard of care*, an office visit.

6.2 Duration of Study and Subject Participation

This study will enroll up to 50 subjects over 12 months. Subject participation will be approximately 14 months from time of recruitment to study completion at 12 months post injection.

Subjects will participate in the study until they complete the 12 month post treatment assessments (per protocol)

Subjects who do not complete the study per protocol may be exited from the study in the following manner:

- Subject voluntarily withdraws consent.
- Subject lost-to-follow-up
- Subject receives additional knee injection(s) other than nSTRIDE APS in index knee(s)
- Subject receives more than two nSTRIDE APS injection(s) in index knee(s)
- Subject undergoes other invasive treatment of the index knee(s)
- Subject death

Subjects have the right to withdraw from the study at any time, for any reason or no reason, without jeopardizing their medical care.

6.3 Study Visit Details

A schedule of assessments to be performed at each visit is presented below:

			Post-Treatment Follow-Up					
	Pre-Treatment	Treatment	1 Month (30 days ± 7 days)	3 Month (91 days ± 14 days)	6 Month (182 days ±21 days)	12 Month (365 days ± 28 days)	2nd injection[4]	Study Exit
Informed Consent	X							
Inclusion / Exclusion	X							
Medical History	X							
Knee Exam	X							
Pregnancy Test[1]	X							
Follow-up[2]			X	X	X	X	X	
Demographics	X							
KOOS	X		X	X	X	X		
KAKPAQ	X		X	X	X	X		
NRS	X		X	X	X	X	X	
UCLA Activity Score	X		X	X	X	X		
EQ-5D-3L	X		X	X	X	X		
Routine Laboratory Test	X							
Procedure Details		X					X	
Adverse Events[3]		X	X	X	X	X	X	X
Study Completion								X

[1] If needed.

[2] Follow-up will be completed online or in the hospital (if standard of care) for KOOS, KAKPAQ, NRSs, UCLA Activity Score, and EQ-5D-3L

[3] If applicable, knee related events only.

[4] Subjects who are receiving an additional injection of nSTRIDE will complete a Patient Questionnaire (NRS). The site will complete a Follow-up, Procedure and Adverse Event form, if applicable.

6.3.1 Informed Consent

Prior to participation in this study, the completion of any required non-standard of care procedures or collection of any study specific data, the patient must complete an informed consent process and sign and date the informed consent form. Designated center staff will explain the purpose of the registry, data to be collected, how data will be used, time and travel commitments and other expectations of a registry subject. The subject will be given the opportunity to discuss the study with the investigator, including any medical aspect of their disease or the study treatment. If the subject decides to participate he/she will sign and date the informed consent form along with the Investigator and other staff participating in the consent process and the treatment visit will be scheduled. A copy of the ICF will be given to the subject.

6.3.2 Pre-treatment

After completing the informed consent, eligibility for the study will be confirmed and documented.

Inclusion Criteria

Subjects will be assessed to ensure they meet all of the inclusion criteria to be eligible for study enrollment:

1. Patient must be female
2. Isolated PFOA in one or both knees as diagnosed by the treating physician
3. Objective evidence of PFOA on one or both of a radiograph or MRI taken within 1 year of treatment
4. From 40-65 years of age, inclusive at time of injection
5. Failed at least 1 prior conservative PFOA therapy (e.g. physiotherapy, simple analgesics, intra-articular injection).
6. Willing and able to comply with the study procedures
7. Sign informed consent form

Exclusion Criteria

Subjects will be assessed to ensure they do not meet all of the exclusion criteria to be eligible for study enrollment:

1. Any systematic inflammatory condition (e.g. rheumatoid arthritis)
2. Active malignancy at time of injection
3. Pregnant at time of injection
4. Lactating at time of injection
5. Knee joint infections or skin diseases or infections in the area of the injection site
6. Leukemia, metastatic malignant cells, or who are receiving chemotherapeutic treatment
7. Participation in another device, biologic or drug study

Prior to treatment, each subject's Medical History and Demographics will be collected. Knee examination will be performed to the extent required to confirm inclusion / exclusion criteria.

As applicable, a pregnancy test will be completed to confirm inclusion / exclusion criteria.

Subject Reported Outcomes

The following baseline assessments will be completed prior to treatment and after final confirmation of eligibility:

- KOOS
- KAKPAQ
- NRS (for pain, stiffness, and function)
- UCLA Activity Score
- EQ-5D-3L

Routine Laboratory Test

After confirmation of eligibility criteria and collection of baseline information the subject will have blood drawn for analysis. A blood sample sufficient to allow for analysis of the following will be taken:

- Erythrocyte sedimentation rate
- C-reactive protein
- Thyroid hormones – T3, T4 and TSH
- Luteinizing hormone
- Follicle stimulating hormone

6.3.3 Treatment

The treatment visit should be completed within 2 months (60 days) after signed informed consent. The subject will be asked to abstain from analgesics for 48 hours prior to treatment.

Blood Draw and APS Preparation

To produce the APS volume, draw 5 ml of ACD-A into a 60 ml syringe. Attach syringe to an 18-gauge butterfly apheresis needle and prime with ACD-A. Draw 55 ml of whole blood into the syringe and gently mix. This will produce 60 ml of anti-coagulated blood. Inject the 60 ml of anti-coagulated whole blood into the nSTRIDE Cell Separator. Place the nSTRIDE Cell Separator and a counterbalance (or second sample) into the centrifuge and run for 15 minutes at 3200 RPM. Using a 30 ml syringe, remove the plasma from the nSTRIDE Cell Separator and discard appropriately. Using a 10 ml syringe, extract 2 ml of the cell concentrate from the nSTRIDE Cell Separator and suspend the cells by shaking the syringe and nSTRIDE Cell Separator for 30 seconds

while the nSTRIDE Cell Separator and syringe are attached. Extract remaining cell concentrate into the syringe. Inject the cell concentrate into the upper chamber of the nSTRIDE Concentrator which contains polyacrylamide beads. Spin the paddle on the nSTRIDE Concentrator to mix the cell concentrate and beads. Place the nSTRIDE Concentrator and counterbalance (or second sample) into the centrifuge and spin for 2 minutes at 2000 RPM. Using another 10 ml syringe, extract the final APS product. The first APS volume should be used for the treatment injection. For further details of processing whole blood to APS, consult the training material or contact the sponsor directly.

If both knees will be treated, two portions of nSTRIDE APS may be made concurrently using two separate kits.

Injection Procedure
The APS (approximately 2.5mL) is intended to be administered as a single injection into the knee joint. The general procedure for injection(s) is as follows:

1. Prepare knee(s) per investigators standard protocol for knee injections
    a. ***Investigator will avoid injecting any anesthetic into the joint space to avoid diluting the APS***
2. Insert an 18-22 gauge needle into the joint space
3. Attach an empty syringe to the needle and aspirate and discard all available joint fluid
    a. ***This step must be completed to remove all available fluid so the injected APS is not diluted in the joint space***
    b. ***Aspiration will be completed on all treated knees without exception***
4. Remove the aspiration syringe and attach the syringe containing the APS
5. Inject the approximately 2.5mL of APS into the joint space

The position of the knee (e.g. extended or bent) and needle approach to the joint space (e.g. lateral or medial) is at the discretion of the person performing the injection.

The subject should be instructed not to exceed pre-injection activity levels for 14 days.

Procedure Details and complications or immediate post-injection AEs will be recorded.

6.3.4 Post-Treatment Follow-Up
Follow-up assessments will be conducted at 1-, 3-, 6-, and 12-months after treatment. The follow-up assessments times and windows are defined below. All follow-up assessments should be conducted within the appropriate time window.

- 1 month (30 days ±7 days)
- 3 month (91 days ±14 days)
- 6 month (182 days ±21 days)

- 12 month (365 ±28 days)

Follow-up visits may consist of a structured telephone interview, electronic self-report or, *if standard of care*, an office visit. The investigative center will contact the subject to complete the Follow-up form and collect knee related AE information. The subject will be asked to complete the following Patient Questionnaires:

- KOOS
- KAKPAQ
- NRS (for pain, stiffness, and function)
- UCLA Activity Score
- EQ-5D-3L

6.3.5 Second Injection

As determined by the treating physician, each subject unresponsive to the first injection may receive a second injection of nSTRIDE APS within the 12-month time frame, but not earlier than 3 months. During the visit of the second injection the site will complete a Follow-up and Adverse Event form, if applicable. The subject will be asked to complete a Patient Questionnaire (i.e., Numeric Rating Scales) prior to the injection and the site will complete an additional Procedure form for each additional injection.

Subjects may receive up to two procedures in each knee but will remain time indexed to the initial procedure. Repeat procedures will be performed in the same manner as the initial procedure. If both knees are included in the study, both knees will be initially treated on the same date.

If the subject received an additional nSTRIDE injection they will be followed according to section 6.3 and the subject will continue participation in the study.

6.3.6 Study Exit

Subjects will participate in the study until they complete the 12 month post injection assessments. When the 12 month assessment has been collected, subject participation in the study will be considered completed. Subjects who exit the study in this fashion will be considered complete per protocol.

Subjects who do not complete the study per protocol may be exited from the study in the following manner:

- Subject voluntarily withdraws consent.
- Subject lost-to-follow-up
- Subject receives additional knee injection(s) other than nSTRIDE APS in index knee(s)
- Subject receives more than two nSTRIDE APS injection(s) in index knee(s)
- Subject undergoes other invasive treatment of the index knee(s)

- Subject death

Once a subject's study participation ends a study exit form will be completed to document the circumstances of subject's exit.

If subject withdraws consent, center should attempt to document the reason for withdrawal.

If subject is exited due to lost-to-follow-up, dates of the three times email reminders were sent should be recorded.

If the subject exits subsequent to other invasive treatment, the type of treatment should be recorded.
If both limbs are included in the study, both limbs will exit the study at the same time such that an intrusive treatment other than nSTRIDE in either limb will result in the exit of both limbs.

If subject exits subsequent to death the date and cause of death should be recorded.

6.4 Description of Assessments and Other Forms
6.4.1 Informed Consent
The informed consent form will, in writing understandable to the subject, describe the study and its purpose. It will outline the potential benefits and the potential risks as well as what alternative procedures may be available. The confidentially of the subject's participation will be confirmed and the confidentiality of the subject's data and the study data will be described. Any compensation or lack thereof as well as any anticipated expenses will be disclosed. Subject will be informed that any new findings which may affect their participation will be disclosed. As applicable circumstances under which the investigator or the sponsored may terminate the study will be explained. All applicable local laws must be respected while obtaining subject's informed consent.

6.4.2 Demographics
Demographics collected will include but are not limited to height, weight, age, and length of knee pathology,

6.4.3 Medical History
Information regarding systemic inflammatory conditions, currently active malignancy, pregnancy, lactation status, leukemia and current chemotherapeutic drug use will be obtained.

6.4.4 Knee Exam
A knee exam will be performed, and the results will be used to determine subject eligibility.

6.4.5 Images (Radiograph or MRI)
A knee radiograph (or MRI) may be used for objective evidence of PFOA. The X-ray or MRI must have been taken within 1 year of the injection procedure. As standard of care it is expected that one or both of these image studies will be available. If images are not available eligibility cannot be determined.

6.4.6 Clinical Lab Tests
On the day of the procedure a sufficient amount of blood will be taken for analysis of the following:

- Erythrocyte sedimentation rate
- C-reactive protein
- Thyroid hormones – T3, T4 and TSH
- Luteinizing hormone
- Follicle stimulating hormone

6.4.7 Inclusion/Exclusion Criteria
This lists all of the criteria the subject must meet to be eligible for the study. All questions must be answered “Yes” for all inclusion criteria and “No” for all exclusion criteria for a subject to be eligible for the study.

6.4.8 Pregnancy Test
Diagnostic clinical test which determines pregnancy status.

6.4.9 Knee Injury and Osteoarthritis Outcome Score (KOOS)
The KOOS is a validated instrument which measures knee pain and function using five subscales: pain, symptoms, function in daily living, function in sport and recreation, and quality of life. The instrument consists of 42 standardized questions each having 5 point Likert response scale.

6.4.10 Kujala Anterior Knee Pain Assessment Questionnaire (KAKPAQ)
The KAKPAQ is a reliable and valid measurement of patellofemoral pain and instability. The weighted questionnaire examines 13 domains, including pain and functionality.

6.4.11 Numeric Rating Scales (pain, stiffness, and function [NRS])
The NRS is a validated measure of pain. The NRS is an 11 point Likert type scale anchored by 0 “no pain” and 10 “worst possible pain”. Subjects rate their average pain over the last 24 hours. Likewise subjects rate their stiffness and function on an 11 point Likert type scale.

6.4.12 European Quality of Life 5 Dimensions 3 Levels (EQ-5D-3L)
The EQ-5D-3L is a validated instrument which assesses an individual’s current health status and heath related quality of life. The EQ-5D-3L assess five dimensions, mobility,

self-care, usual activities, pain/discomfort, and anxiety/depression over three levels of severity.

6.4.13 UCLA Activity Score
The UCLA Activity Score is a validated measure of subject activity. Subjects rate their current activity level from “wholly inactive” to “regularly participate in impact sports”.

6.4.14 Adverse Event Form (AE)
AE[2] forms will document a description of the AE, onset and resolution dates, severity, seriousness, treatment, and relatedness to the device and the procedure. The form will also document whether the event was anticipated or unanticipated.

Possible AEs associated with the joint fluid aspiration and injection procedure include worsening of pain and/or knee function, effusion, burning sensation, swelling, erythema, and infection.

6.4.15 Study Exit Form
This form will document the termination of a subject’s study participation and capture the reason for the exit from the study.

6.4.16 Protocol Deviation Form
This form will document the deviations from the study protocol.

[2] Adverse Events (AEs) can be reported as one main diagnosis (like fever), instead of recording many symptoms in different AEs

7. STATISTICAL CONSIDERATIONS

As a study to track treatment effects following APS injections for knee OA, the planned statistical analyses are exploratory in nature. Data analysis may be conducted intermittently as needed or as requested by investigators without a power penalty and consist primarily of summary statistics and inferential statistics for changes in dependent measures over time.
Specific data analyses include but are not limited to:

- **Demographics** and other pro-treatment characteristics will be summarized and characterized with appropriate descriptive statistics including error measures. Statistics may include mean, mode, median, range, inter-quartile range, minimum, maximum, frequency, cumulative frequency percentage and cumulative percentage. Results may be presented in a narrative and graphically.
- **Subject reported outcome measures** will be summarized and thoroughly characterized with the appropriate descriptive statistics including error measures. Statistics may include mean, mode, median, range, inter-quartile range, minimum, maximum, frequency, cumulative frequency percentage and cumulative percentage. Results may be presented in a narrative and graphically. These measures will also be analyzed using inferential statistics to assess changes over time. As appropriate a repeated measure ANOVA or Wilcoxon signed rank test will be completed for each outcome measure. If a significant trend is identified, significance among time points may be further explored using the appropriate pair-wise comparisons. In all cases a p-value equal to or less than 0.05 will be considered significant. No corrections for multiple pair-wise comparisons will be made.
- **Clinical Lab results** will be summarized and characterized with the appropriate descriptive statistics. Statistics may include mean, mode, median, range, inter-quartile range, minimum, maximum, frequency, cumulative frequency percentage and cumulative percentage. Clinical lab results will also be analyzed for correlation with positive clinical outcomes.
- **Missing data** will be ignored in statistical calculations while using the appropriate n (sample size) for any given statistic or test.
- Patients who signed informed consent but did not receive the study treatment will not be included in the analyses.

8 MONITORING PLAN

The investigators will allow onsite inspection of subjects' source documentation as requested by the sponsor or required by an IEC, IRB or regulatory authorities. Monitoring activities may take place at the trial center or any ancillary facility where study conduct takes place. The investigators will provide access to all source documentation and adequate work space. The investigators will be available to the sponsor, IEC, IRB or other regulatory authorities to discuss study issues as requested.

Data monitoring will occur at the sponsor's discretion and consistent with sponsor's quality policies and in all cases where data irregularities are identified. As needed intermittent monitoring visits will be conducted to compare data entered into the database to an unsystematically selected sample of the subjects' source documents. Monitoring efforts will be expanded if the sample suggests irregularities.

9 DATA MANAGEMENT AND RECORD RETENTION

Case report forms will be used to record demographic, procedural, and follow-up data. The subject data collected will be entered into a secure database by the clinician, designated staff or subjects (for online assessment completion). Subject data stored in the study database will be identified by the subject number and possibly subject initials. The unique number will identify the subject and will be included on all case report forms. Authorized representatives of the sponsor (i.e. the monitor[s], the auditor[s], the IEC will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, as needed, to monitor the conduct of the study. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access. The information obtained in this study may be published in scientific journals or presented at scientific meetings, however, the identity of individual participants will not be revealed. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

The investigators will maintain all study records for the minimum time required in the country in which the study is conducted.

10 AMENDMENTS TO THE STUDY PLAN

Investigators will not modify, change or otherwise amend the protocol without prior written consent of the sponsor. As applicable, if a protocol amendment substantially alters the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continued participation in the study, the subject should generally be re-consented on an updated and approved (as required by local law and regulation) ICF. New procedures or processes which substantially alter the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continued participation the study will not be implemented until an approval or favorable opinion has been granted by the reviewing IEC or IRB, as applicable.

11 DEVIATIONS TO THE STUDY PLAN

Investigators are not allowed to deviate from this CIP without prior authorization by the sponsor except under emergency situations when necessary to preserve the rights, safety or well-being of study patients.

Deviations and non-compliances will be recorded together with an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of patients shall be reported to the sponsor and IEC as required and as soon as possible.

If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the IEC to determine a suitable course of action.

Deviations from the CIP will be documented on the appropriate form.

12 STATEMENT OF COMPLIANCE

This protocol has been developed and the study will be run in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013). Further the study will be run in compliance with ISO 14155 (2nd ed) 2011. Both investigators and sponsor will conduct this study in accordance with any applicable local or regional laws and regulations.

Investigators will neither conduct procedures specific to the study nor collect subject data without prior approval or favorable opinion of any IEC or IRB under whose jurisdiction the conduct of this study falls. It is acknowledged that in some geographic areas IEC or IRB review and approval of study data collection activities may not be required.

During the conduct of study activity, the investigators and the sponsor shall act in accordance with any further requirements as imposed by an IEC, IRB or other regulatory agency.

13 SUSPENSION OR TERMINATION OF THE STUDY

The study may be terminated at any time by the sponsor, however, follow-up of all enrolled patients will continue through the 12-month follow-up. The study will be closed and the data will be archived according to the appropriate regulations.

14 ADVERSE EVENT AND SEFETY REPORTING

14.1 Definitions

Adverse Event

An AE is any knee related untoward medical occurrence in a subject receiving nSTRIDE APS; it does not necessarily have to have a causal relationship with nSTRIDE APS. An AE can therefore be any knee related unfavorable and unintended sign (including abnormal laboratory finding), symptom, or condition temporally associated with the use of nSTRIDE APS whether or not considered related to nSTRIDE APS.

Only events that occur during or after treatment can be considered AEs. An unanticipated AE is one that is not part of the normal disease profile and has not been previously documented in information about the device.

Serious Adverse Event (SAE)

An SAE is an AE that leads to 1 of the following conditions:

- Death
- Serious deterioration in the health of the subject that results in 1 of the following situations:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or a body function
  - Medical or surgical intervention to prevent permanent impairment to body structure or body function
  - Inpatient hospitalization or prolongation of existing hospitalization
- Fetal distress, fetal death, or a congenital abnormality or birth defect

Adverse Device Effect (ADE)

An ADE is an AE that is considered, upon assessment by the primary clinical investigator, related to the study device.

Serious Adverse Device Effect

A serious ADE is one that has resulted in any of the consequences characteristic of an SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

14.2 Adverse Event Assessments

All knee related AEs, including the following will be documented on and adverse event form and assessed by the primary clinician with respect to relatedness, severity, and seriousness.

- Observed or volunteered problems
- Complaints
- Physical signs and symptoms
- Medical condition which occurs during the study, having been absent at baseline
- Medical condition present at baseline, which appears to worsen during the study

Each AE record will include a description of the event, date of onset, date of resolution, severity, treatment as applicable, relationship to study device, or procedure and seriousness. Each AE must be recorded separately.

Severity will be assessed using the following definitions:

- Mild: Aware of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or do usual activity

Relationship to the study device or procedure will be assessed by the investigator using the following definitions:

- Definitely Not: Evidence exists that the AE definitely has a cause other than the study procedure (e.g., pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
- Unlikely: A temporal relationship exists between the event onset and study procedure. Although the AE may appear unlikely to be related to the study procedure, it cannot be ruled out with certainty; and/or the event cannot be readily explained by the subject's clinical state or concomitant therapies.
- Likely: A temporal relationship exists between the event onset and the study procedure, and appears with some degree of certainty to be related based on the event symptoms and the nature of the study procedure. It cannot be readily explained by the subject's clinical state or concomitant therapies.
- Definitely: Strong evidence exists that the study procedure caused the AE. There is a temporal relationship between the event onset and the study procedure. There is strong mechanistic evidence that the event was caused by the study procedure. The subject's clinical state and concomitant therapies have been ruled out as a cause.

Seriousness, If the AE meets any of the SAE criteria mentioned in section 14.1, it is regarded as serious.

14.3 Adverse Event Reporting

All AEs will be documented as described above and entered into the EDC system.

As needed, reporting of AEs outside of study collection will be completed according to local laws and regulations.

Device deficiencies must be reported to Zimmer Biomet within 2 business days using the Product Experience Report.

15 CLINICAL STUDY ADMINISTRATION AND INVESTIGATORS

15.1 Approval and Agreements

The sponsor and the principal investigator for this clinical research center shall agree to this document and any modifications. A justification for any modifications will be documented. Signing the signature page provided within this document will indicate approval and agreement with the protocol and methods of modifying the protocol.

15.2 Investigators

The principal investigator's, qualifications and contact information will be updated and maintained by the sponsor. The name(s) and address(es) of other institutions involved in the clinical investigation as well as a complete list of monitors along with their contact information will also be maintained by the sponsor.

16 OTHER ETHICAL CONDUCT

16.1 IEC Approval

Prior to initiation of the study, the chairman or the recording secretary of the IEC charged with the responsibility of approving the investigation must sign the IEC approval form, and a copy of the approval will be retained by the sponsor.

16.2 Informed Consent

Prior to the performance of any study-specific procedures, the subject will have undergo a thorough informed consent procedure as described above (6.3.1).

The ICF includes all of the relevant elements currently required by European regulations (ISO 14155), the Declaration of Helsinki of 1964, and its subsequent revisions.

16.3 Patient Compensation for Injury

All subjects participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

17 CONFIDENTIALITY

The information contained herein is provided to you in confidence and should not be disclosed to others, without written authorization from Zimmer Biomet Biologics, except to the extent necessary to obtain informed consent from those persons to whom the device will be administered.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will not be supplied to the sponsor. Subject data will be stored in a computer database by the sponsor, maintaining confidentiality. Subjects in this database, will be identified by subject number. This number will identify the subject and will be included on all case report forms. Authorized representative of the sponsor (i.e. the monitor[s], the auditor[s], the IEC, and regulatory authorities) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access. Identities of individuals participating in clinical research will be kept as confidential as is possible within the law. While the information obtained in clinical studies may be published in scientific journals or presented at scientific meetings, the identity of participants will not be revealed.

18 REPORTING

At the completion of this study, the sponsor will analyze the data, generate a final report, and forward the report to all investigators. The investigators will submit a copy of the report to the reviewing IEC.

The sponsor will notify the accredited IEC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last subject's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited IEC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited IEC and the Competent Authority.

19 PUBLICATION POLICY

All data, results and any intellectual property derived from the data or results of the study are the property of the sponsor. The sponsor may use the data as they deem necessary, such as for submissions to governmental regulatory authorities, disclosure to other investigators and scientific communications. Sponsor will engage investigators to actively participate in scientific communication production at the sponsor's discretion. The sponsor recognizes the right of the investigators to publish data and results derived from the study. However, prior to submitting for publication, presentation, using for instructional purposes, or otherwise disclosing results obtained from the study, the investigators agree to allow the sponsor a period of at least 30 days to review the proposed publication or disclosure prior to its submission for publication or other disclosure. Publications or disclosures of study results shall not include confidential information belonging to the sponsor. If the proposed publication/disclosure risks the sponsor's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed for a sufficient time to allow the sponsor to seek patent protection of the invention. This statement does not give the sponsor any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of the sponsor's confidential information. The Investigators may also request data summaries of all data in the study. These requests will be fulfilled at the sponsor's discretion. If the written contract for study conduct includes publication provisions inconsistent with this statement, then that contract's publication provisions shall apply rather than this statement.

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APPENDIX A: Manufacturer's Instructions for Use

Biomet Biologics
56 East Bell Drive
P.O. Box 587
Warsaw, Indiana 46581 USA

01-50-1489
Revision C
Date: 2013-07

NStride Autologous Protein Solution (APS) Kit with ACD-A

ATTENTION ADMINISTERING PERSONNEL

Not For Sale In The U.S.A.

NOTE: FOR SINGLE USE ONLY. Discard the entire disposable kit after one use, using acceptable disposal method for products potentially contaminated with blood.

DESCRIPTION
NStride Autologous Protein Solution (APS) with ACD-A (Anticoagulant Citrate Dextrose Solution, Solution A, USP)
The NStride Autologous Protein Solution (APS) Kit with ACD-A aids separation of the patient's own blood components by density through the use of a Biomet Biologics centrifuge.

The NStride Autologous Protein Solution (APS) Kit with ACD-A permits autologous protein solution (APS) to be rapidly prepared from a small volume of the patient's blood that is drawn at the time of treatment.

APS contains high concentrations of anti-inflammatory molecules, and it has been shown to block inflammation and prevent cartilage degradation in vitro. In a prospective, randomized, controlled equine clinical study, APS reduced pain and improved function in horses with osteoarthritis.

MATERIALS
Blood-draw components, when supplied in this kit, are packaged, labeled and sterilized as indicated by the manufacturer's labeling. All components in this kit are latex free. The materials used for needles, syringes, tubing, connectors, and concentration device consist of medical grade polymers, elastomers and stainless steels suitable for use in medical devices.

ACD-A (Anticoagulant Citrate Dextrose Solution, Solution A, USP) is manufactured and supplied by Citra Labs LLC, Braintree, MA. For further information regarding ACD-A Anticoagulant, please contact the supplier at 1-800-299-3411.

The ACD-A included in this system is only for use with the NStride Autologous Protein Solution (APS) kit. NOT FOR DIRECT INTRAVENOUS INFUSION.

INDICATIONS FOR USE
NStride Autologous Protein Solution (APS) with ACD-A (Anticoagulant Citrate Dextrose Solution, Solution A, USP)
The NStride Autologous Protein Solution (APS) Kit with ACD-A is designed to be used for the safe and rapid preparation of autologous protein solution (APS) from a small sample of blood at the patient's point of care. The APS is to be injected intra-articularly for the treatment of osteoarthritis.

CONTRAINDICATIONS
- Do not inject APS in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.
- NStride Autologous Protein Solution (APS) Kit is not for use in patients with systemic inflammatory conditions.
- NStride Autologous Protein Solution (APS) is not intended for use in patients with leukemia, metastatic malignant cells, or who are receiving chemotherapeutic treatment.

WARNINGS AND PRECAUTIONS
General

1. Use proper safety precautions to guard against needlestick injury. Discard used needles in "sharps" containers.
2. Follow manufacturer instructions when using centrifuge. Use only a Biomet Biologics centrifuge (NStride – IEC centrifuge or The Drucker Company centrifuge). Outcomes using centrifuges from other manufacturers are unknown.
3. The administering personnel are to be thoroughly familiar with the equipment and the procedure prior to using this device. Strict aseptic administration technique must be followed.
4. Do not use sterile components in this device system if package is opened or damaged.
5. STERILE CONTENTS. Single use device. Do not reuse. Use contents of NStride Autologous Protein Solution (APS) Kit immediately after its packaging is opened.
6. Only use prepared APS intra-articularly, as directed. NOT FOR DIRECT INTRAVENOUS INFUSION.
7. Use prepared APS within 4 hours after drawing blood from patient. The safety and effectiveness of frozen stored APS has not been established.
8. FOR AUTOLOGOUS USE ONLY. Do not use APS allogeneically.
9. CAUTION: Injection of additional fluids into the knee in conjunction with APS may dilute APS and affect its safety and effectiveness.
10. Remove all synovial fluid or effusion before APS injection.

Information for Patients

1. The patient is to be made aware of general risks associated with treatment and the possible adverse effects.
2. Transient pain, swelling and/or effusion of the injected joint may occur after intra-articular injection of APS.
3. As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged weight-bearing activities following the intra-articular injection.

Use in Specific Populations

1. **Pregnancy:** The safety and effectiveness of APS has not been established in pregnant women.
2. **Nursing Mothers:** It is not known if APS affects the content of human milk. The safety and effectiveness of APS has not been established in lactating women.
3. The safety and effectiveness of APS has not been established in children.
4. The safety and effectiveness of APS has not been established in patients with a very high body mass index (BMI > 40).
5. The safety and effectiveness of APS has not been established in patients with severe osteoarthritis (Kellgren-Lawrence grade IV).

POSSIBLE ADVERSE EFFECTS FROM BLOOD DRAW AND INTRA-ARTICULAR INJECTION
1. Damage to blood vessels, hematoma and/or infection.
2. Temporary or permanent nerve damage that may result in pain or numbness.
3. Early or late post-injection infection.
4. Acute swelling and/or burning sensation at injection site.

STERILITY
The NStride Autologous Protein Solution (APS) device system is sterilized by exposure to a minimum dose of 25 kGy gamma irradiation. ACD-A is sterilized by the supplier using steam sterilization. Do not re-sterilize. Do not use after expiration date. Do not use any component from an opened or damaged package. Single Use Only.

INSTRUCTIONS FOR USE
Precaution: Use strict aseptic technique throughout the following procedures.
Precaution: Do not use NStride Autologous Protein Solution (APS) kit with ACD-A if the package has been opened or damaged. Store in original packaging.
Precaution: The NStride APS kit is intended for single use. The contents of the kit must be used immediately after they have been removed from their packaging. Inject the full APS product into one knee only. If treatment is bilateral, a separate NStride APS kit must be used for each knee. Discard any unused APS.

PROCEDURE ONE: Use the NStride Cell Separator to collect the cells.
1. **DRAW:** Draw 5ml of anticoagulant into 60 ml syringe, attach to 18-gauge apheresis needle and prime it with anticoagulant. Slowly draw