A Randomized Controlled Trial of the Subchondroplasty® Procedure with Arthroscopy versus Arthroscopy Alone for Treatment of Bone Marrow Lesions in the Knee (PRESERVE—Knee Study)

Multicenter, Prospective, Single-Blinded, Two-Arm Study

Protocol No.: KC.CR.I.AM.16.1
Protocol Date: 23 October 2020
Version: 5.0
Americas

STUDY SPONSOR

Zimmer Biomet

Clinical Affairs

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Warsaw, IN 46580

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1.0 General Information

TITLE

A Randomized Controlled Trial of the Subchondroplasty® Procedure with Arthroscopy versus Arthroscopy Alone for Treatment of Bone Marrow Lesions in the Knee (PRESERVE—Knee Study)

PROTOCOL NUMBER

KC.CR.I.AM.16.1

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2.0 Protocol Signature Page

I have read and understand "A Randomized Controlled Trial of the Subchondroplasty® Procedure with Arthroscopy versus Arthroscopy Alone for Treatment of Bone Marrow Lesions in the Knee (PRESERVE—Knee Study)" (KC.CR.I.AM.16.1), and will conduct the study in accordance with this protocol, all attachments and amendments, applicable Food and Drug Administration regulations, HIPAA, local regulations, and the policies of the reviewing IRBs/REBs and institutions where the study will take place.

Principal Investigator:

_____

(Print Name)

_____

(Signature) (Date)

_____

(Site Name)

_____

(Site Address)

3.0 Protocol Synopsis

Study Title	A Randomized Controlled Trial of the Subchondroplasty® Procedure with Arthroscopy versus Arthroscopy Alone for Treatment of Bone Marrow Lesions in the Knee (PRESERVE—Knee Study)
Short Title	PRESERVE (Prospective Randomized Evaluation of Subchondroplasty Effectiveness, Pain Relief, and Economic ValuE in the Knee)—Knee Study
Protocol Number	KC.CR.I.AM.16.1
Sponsor	Zimmer Biomet Clinical Affairs 345 East Main Street Warsaw, IN 46580 484-467-7047
Manufacturer	AccuFill® Bone Substitute Material ETEX Corporation 55 Messina Drive Braintree, MA 02184 USA Subchondroplasty® (SCP®) Surgical Instrumentation Zimmer Knee Creations 841 Springdale Dr. Exton, PA 19341 USA
Study Device	AccuFill® Bone Substitute Material Subchondroplasty® (SCP®) Surgical Instrumentation
Treatment Groups	Treatment: Subchondroplasty® (SCP®) with Arthroscopy Control: Arthroscopy
Number of Study Sites	Up to 25 study sites in the U.S. and Canada
Study Population	Subjects with a single bone marrow lesion (BML) of the tibia, single BML of the femur, or adjoining BML's of the tibia & femur, in the same compartment
Clinical Phase	Post-Market Clinical Follow-Up (PMCF)

Study Design	Multi-center, prospective, randomized, single-blinded, two-arm study, originally to include 134 subjects treated with SCP + Arthroscopy and 67 subjects with arthroscopy alone. Randomization will be within site and whether the bone lesion is unipolar or bipolar. Enrollment was stopped early when an interim analysis demonstrated that the study was unlikely to meet its primary endpoint due to an unexpectedly high success rate in the arthroscopy only group.
Inclusion/Exclusion Criteria	Candidates must meet ALL of the following: 1) Voluntary signature of the IRB/REB approved Informed Consent, 2) Male or female subjects between the ages of 30 to 75 years, 3) Body Mass Index ≤ 40 (BMI=kg/m^2), 4) Has experienced pain in study knee for at least 3 months, 5) Kellgren-Lawrence grade 1-3 Osteoarthritis, as reviewed on preoperative XR imaging, in the study knee, 6) BML is confirmed on T2 weighted or Proton Density MR Imaging by presence of white signal, 7) Single BML of tibia, single BML of femur, or adjoining BML's of tibia & femur, in the same compartment, extending to the articular surface of the joint, 8) Surgical candidate for knee arthroscopy due to mechanical symptoms, meniscus tear, loose body and/or synovitis, 9) Must record a response, at the preoperative study visit, of moderate to extreme pain for any one of the KOOS Pain Scale questions, P2 through P9, 10) Index knee alignment is defined radiographically as one of the following: Neutral, ≤ 6° mechanical varus, or ≤ 6° mechanical valgus, 11) Ligaments in the study knee are stable, 12) The contralateral (non-study) knee is stable and functional, 13) Is refractory to conservative non-surgical management a) having failed 2 or more of the following: hyaluronic acid injection, corticosteroid injection, NSAIDs, physical therapy, bracing, activity modification, or minimal surgical intervention (e.g., arthroscopy,

	debridement/chondroplasty, and/or loose body removal) b) and is ≥ 3 months from the start of treatment (these treatments can continue up to the time of the randomized procedure; injections to be completed per Section 10.4.7), 14) Must be physically and mentally willing and able, in the Investigator's opinion at the time of enrollment, to be compliant with the protocol - including all follow-up visits, survey completion, weight-bearing restrictions, and post-operative rehabilitation. Candidates will be excluded if they meet ANY of the following: 1) BML caused by acute trauma less than 3 months prior to enrollment, 2) Clinical and/or radiographic disease diagnosis of the index knee that includes any of the following: a) Kellgren-Lawrence Grade 4 Osteoarthritis with complete loss of joint space (bone-on-bone) or subchondral bone collapse, b) Rheumatoid arthritis, or history of septic or reactive arthritis, c) Gout or a history of gout or pseudogout in the affected knee, d) Has more than two clinically relevant BMLs in the index knee, e) Osteochondritis dissecans of the knee with significant bone loss, f) Collapse of subchondral bone, g) Clinically relevant BML located at ACL/PCL insertion, h) MRI evidence of frank ligament instability, 3) Passive knee flexion < 110° or flexion contracture > 30°, 4) History of systemic diseases which could contribute to secondary arthropathies (e.g., sickle cell disease, hemochromatosis, or autoimmune disease), 5) Has a neuromuscular, neurosensory, or musculoskeletal deficiency that limits the ability to perform objective functional assessment of either knee, 6) If diabetic, blood glucose over 200 mg/dL at time of enrollment,

	7) Current daily tobacco or high nicotine product user or < 3 months from nicotine cessation, 8) Presents a high surgical risk due to unstable cardiac and/or pulmonary disease, 9) Has HIV or other immunodeficient state including subjects on immunosuppressant therapies, or has significant illness (metastasis of any type) that decreases the probability of survival to the 2 year endpoint, 10) Is at substantial risk for the need of organ transplantation, such as renal insufficiency, 11) Is pregnant or breast-feeding at the time of surgery, 12) Has a history of any invasive malignancy (except non-melanoma skin cancer), unless treated with curative intent and with no clinical signs or symptoms of the malignancy for 5 years, 13) Has primary bone tumor in the knee area, 14) Anticipates having a lower extremity surgery other than the investigational surgery during the course of the study, 15) Is participating concurrently in another clinical trial, or has participated in a clinical trial within 30 days of surgery, 16) Is receiving prescription pain medication other than NSAIDs or acetaminophen for conditions unrelated to the index knee condition, chronic use of anticoagulants, or taking oral or inhaled corticosteroids, 17) Active joint infection or history of chronic joint infection at the surgical site, 18) Prior total meniscectomy of index knee, 19) Has primarily patellofemoral symptoms, 20) Is indicated for concomitant procedures (i.e., microfracture, subchondral drilling, cartilage allograft, ligament or tendon repair, distal realignment/osteotomy, root repair) in the index knee, with the exception of incidental loose body removal, debridement, synovectomy, osteophyte removal in locations other than adjacent to BMLs, and/or partial meniscectomy, 21) Has contraindications for Magnetic Resonance Imaging (MRI), 22) Is receiving worker's compensation or is currently involved in litigation relating to the index knee,

	23) Has a history of substance abuse.
Pre-Operative Evaluation	Initial study procedures include baseline evaluation of medical history, knee history, and each of the assessments and measures that will be applied longitudinally, including: • Knee Physical Examination • X-ray series • MRI • Use of pain medications • Subject-reported outcomes: o EQ-5D o KOOS o Numeric Pain Scale o Healthcare Utilization Survey

Study Procedure	Each subject will be randomized to one of two procedure groups, as follows. Group 1 subjects (n=134) will undergo: • Arthroscopy to include synovectomy, partial meniscectomy, loose body removal and/or debridement • Subchondroplasty® to inject AccuFill® into bone marrow lesion(s) Group 2 subjects (n=67) will undergo: • Arthroscopy to include synovectomy, partial meniscectomy, loose body removal and/or debridement • Superficial skin incision at the site(s) of typical AccuPort® portal access points for SCP procedures to treat BMLs For both groups, surgical documentation of meniscus status, procedures performed and BML details will be recorded.
Telephone Follow-up Interviews	Subjects will be contacted via telephone for follow-up interviews at 6 weeks, 3, 6, 9, 12, 18 and 24 months. • Assessment of post-operative complications, adverse events, re-operation, and revision • Subject-reported outcomes at 6 weeks, 3, 6, 12, 18 and 24 months: o KOOS o Numeric Pain Scale • Subject-reported outcomes at 9 months: o KOOS Pain Scale o
Study Objectives	The primary objective of this study is to demonstrate superiority of Subchondroplasty with arthroscopy compared to arthroscopy alone for treatment of bone marrow lesions in the knee. • Superiority will be evaluated in terms of composite clinical success (CCS) requiring freedom from subsequent secondary surgical intervention (SSSI) and among those free from SSSI, a clinically meaningful reduction in self-reported pain based on a validated measure of subject-reported pain. • Conditional on showing superiority in terms of CCS, superiority in terms of improved ADL will then be tested as

	a conditional endpoint. Secondary objectives include: • Evaluation of other subject-reported outcomes measures; • Evaluating the safe profile by determining the incidence and time to resolution of post-operative complications and adverse events; • Comparing the incidence and time to subsequent secondary surgical intervention including re-operation and revision; and • Evaluating the use of healthcare resources and impact on productivity, where available.
Materials and Methods	Case report forms will be completed in-office or hospital at the Study Admit/Pre-Operative and Operative intervals. Subjects will be contacted via telephone for follow-up interviews at the 6 week, 3 month, 6 month, 9 month, 12 month, 18 month, and 24 month intervals. Post-Operative case report forms will be collected either by phone during these telephone interviews or by direct completion by the subject utilizing electronic patient reported outcomes (ePRO).
Statistical Considerations & Methodology	The primary measure of clinical success is a composite clinical success (CCS) endpoint requiring: • Freedom from secondary subsequent surgical intervention (SSSI); and • Among subjects free from SSSI; an improvement in KOOS pain of at least 10 points. First, superiority will be statistically tested at 12 months using $\alpha=0.01$. If $p\leq0.01$, then it will be concluded that S+A is superior to AA in terms of the primary endpoint and the conditional hypothesis of superiority in terms of ADL improvements will be tested, also at $\alpha=0.01$. If $p>0.01$ at month 12, the same hypotheses will be tested at month 24 using $\alpha=0.04$, thereby controlling the overall study type 1 error rate to no more than 0.05 according to the Bonferroni inequality. If $p\leq0.04$ at month 24, it will be concluded that S+A is superior to AA in terms of the primary endpoint and the conditional hypothesis of superiority in terms of ADL improvements will then be tested at $\alpha=0.04$. The conditional superiority test for improvements in ADL will be tested using one-sided contrasts derived from a mixed model for repeated measures (MMRM) for change in KOOS ADL among subjects free from SSSI. A stratified blocked randomization will be used to assign subjects to either Subchondroplasty with arthroscopy or to arthroscopy

	alone in a 2:1 ratio. Individual sets of blocks will be determined stratified by study site and lesion polarity status (unipolar vs bipolar). Adverse events, serious adverse events, and surgical complications occurring from the time of surgery until the completion of the study will be recorded and tabulated by group. Summaries will consist of counts and percentages to describe the distribution of each safety endpoint.
Sample Size	For testing the primary superiority hypothesis as defined above and assuming true CCS rates of 0.80 and 0.60 for S+A and AA, respectively, a total of 174 subjects (116 and 58, respectively) are needed for 80% power. This value is increased by 15% to 201 to account for losses-to-follow-up.
Length of Study	Maximum subject participation is expected to be 29 months. Subject participation can start up to 90 days prior to the study surgical procedure and will continue up to 26 months (24 months +/- 2 months) after the study surgical procedure. Subject recruitment lasted 42 months (May 2017-November 2020), for a total study duration of approximately 66 months (until November 2022).
Standards	The PMCF is compliant with the below: • ISO 14155: 2020 - Clinical investigation of medical devices for human subjects - Good clinical practice. The Declaration of Helsinki (DoH) - Ethical principles for medical research involving human subjects.

4.0 Abbreviations

AA	Arthroscopy Alone
ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
BML	Bone Marrow Lesion
BSM	Bone Substitute Material
CCS	Composite Clinical Success
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
HA	Hyaluronic Acid
ICC	Interclass Correlation Coefficient
ICRS	International Cartilage Repair Society
IFU	Instructions for Use
IKDC	International Knee Documentation Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
KOOS	Knee Injury and Osteoarthritis Outcome Score
LCL	Lateral Collateral Ligament
MCL	Medial Collateral Ligament
MCID	Minimal Clinically Important Distance

MDC	Minimal Detectable Change
MRI	Magnetic Resonance Image
NSAID	Non-steroidal Anti-inflammatory Drug
OA	Osteoarthritis
PCL	Posterior Cruciate Ligament
PP	Per Protocol
PMCF	Post-Market Clinical Follow-Up
REB	Research Ethics Board
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCP	Subchondroplasty
SSSI	Secondary Subsequent Surgical Intervention
TKA	Total Knee Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale

5.0 Introduction

5.1 Clinical Background

Subchondral bone defects, sometimes called bone marrow lesions (BMLs), are MRI-visible defects that can be seen on fat-suppressed MRI sequences (T2FS, PDFS, etc.) where they appear as a hazy white area against the background of darker bone. Pathologists have shown that BMLs represent a healing response to trauma such as micro trabecular fractures of the subchondral bone [1]. BML defects have been highly correlated with pain symptoms in the knee [2, 3]. However, BMLs and their impact on knee pain and function went relatively unrecognized in the orthopedic literature until 2011 [4].

Treatment options for BMLs have been limited in the past. For degenerative or chronic BMLs, treatments have included core decompression, extracorporeal shock wave therapy and pharmaceuticals [5]. While core decompression seeks to directly stimulate the bone through a surgical procedure, it does not fill the voids and defects in the bone and is not widely used to treat BMLs in the knee. Subchondroplasty® is a procedure first described in 2007 to fill subchondral osseous defects associated with bone marrow lesions using an injectable bone substitute material (BSM), AccuFill® [6]. AccuFill is an injectable, self-

setting, macro-porous, osteo-conductive, calcium phosphate bone graft substitute material that is intended for use to fill bony voids or gaps of the skeletal system of the extremities, spine (i.e. posterolateral spine), and the pelvis that are not intrinsic to the stability of the bony structure. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. AccuFill is a bone graft substitute that resorbs and is replaced with new bone during the healing process. AccuFill has unique properties that allow it to flow through the osseous defects in trabecular bone and then set up hard at body temperature [7]. Two year results from a clinical study on 66 subjects considering TKA has shown improvements in subject reported pain and function with only 30% of subjects undergoing revision to TKA at 2 years [8]. The goal of this study is to evaluate the clinical outcomes associated with the on-label use of AccuFill during the Subchondroplasty procedure with arthroscopy compared to arthroscopy alone in subjects with bone marrow lesions in the knee.

5.2 Product Description

The Subchondroplasty® (SCP®) Procedure targets and fills bone defects with AccuFill® BSM utilizing an arthroscopic / percutaneous approach as follows. Preoperatively, the BML bone defect is identified on fat-suppressed MRI, and the approach and trajectory is planned based on defect location. Using intraoperative fluoroscopy, the bone defect is localized relative to MRI findings. The appropriate AccuPort® Delivery Cannula is drilled to the bone defect. AccuFill® BSM is then injected into the subchondral bone defect. The calcium phosphate (CaP) fills the edematous void and hardens within the BML. Per Appendix B. Recommended Surgical Technique Guide, surgeons are not to overfill the defect site. Over pressurizing the AccuPort device may lead to extrusion beyond the site of intended application and damage surrounding tissues. Surgeons are to remove any excess material from the subcutaneous tissue at the entry point by gently expressing and irrigating the material. Surgeons should blot any excess material from the surgical wound as needed. The CaP is resorbed over time and replaced with new bone during the healing process.

The knee arthroscopy may be performed prior to or after the Subchondroplasty procedure. In either case, the arthroscope should be placed into the joint after injection of the BSM to check for possible material extravasation. Using standard arthroscopic surgery techniques, skin incisions are made for the insertion of arthroscopic instrumentation. Debridement of the meniscal/chondral area or synovium is performed as necessary.

Per Appendix A. Package Insert, AccuFill and Subchondroplasty Instrumentation should only be used by surgeons familiar with the material, appropriate surgical techniques, and bone repair procedures. The Subchondroplasty Procedure and knee arthroscopy are intended to be performed by surgeons. Furthermore, per Appendix B., each surgeon should exercise his or her own independent judgment in the diagnosis and treatment of an individual patient, and aforementioned information does not purport to replace the comprehensive training surgeons have received. As with all surgical procedures, the technique used in each case will depend on the surgeon's medical judgment as the best treatment for each patient. Results will vary based on health, weight, activity and other

variables. Not all patients are candidates for this product and/or procedure.

5.3 Preclinical Studies

Preclinical studies in established animal models were used to evaluate safety of AccuFill for treatment of bone defects. A rabbit bilateral lateral femoral condyle defect model (4.8 mm diameter x 6 mm length cylindrical defect) through 24 weeks demonstrated that AccuFill caused bone induction and osteointegration at the implant sites, and was well tolerated.

No significant adverse events or indications of infections or rejections of the AccuFill material were observed in the preclinical evaluations of AccuFill. Studies demonstrated bone induction, osteointegration and potential for use as a bone void filler.

5.4 Clinical Studies

Davis, et al. [9] presented a retrospective review of 50 subjects with a mean follow-up of 14.6 months after Subchondroplasty for BMLs in the knee. Eighty-eight percent (88%) of subjects reported improvement in pain and 72% reported improvement in pain free walking distance. Four (4) subjects (8%) were revised to TKA.

Another retrospective study evaluated the effectiveness of Subchondroplasty in treating osseous defects in subjects reporting pain with documented BMLs associated with advanced knee OA [8]. Data were collected from a consecutive subject series (N=66) who underwent Subchondroplasty combined with arthroscopy, performed at a single center by one surgeon. The study reported significant improvements in both pain and function, as measured by the visual analog scale (VAS) and the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, through 2 years post-operative follow-up. Given that arthroscopic debridement alone has been previously shown to yield insignificant pain relief beyond 6 months post-op [10], the results suggest that Subchondroplasty is a promising approach for the treatment of osseous defects associated with BMLs in subjects with knee OA.

5.6 Regulatory Overview of Subchondroplasty

The Subchondroplasty® procedure will be performed using two commercially available devices. The regulatory status of each component of the system is described below:

1. AccuFill® Injectable Calcium Phosphate – Class II device; 510(k) Number K093447 - Calcium Salt Bone Void Filler Device, cleared by FDA. The package insert provides product description, indications, and usage information. (Appendix A). AccuFill Injectable Bone Substitute Material, 5cc Part Number: 201.050.
2. SCP® Surgical Instrumentation – These are Class I manual surgical instruments. Per 21 CFR 888.4540, manual surgical instruments are premarket exempt. AccuPort® Side-Delivery Cannula, 11 ga., 120mm Part Number: 307.032. AccuPort® End-Delivery Cannula, 11 ga., 120mm Part Number: 307.034.

AccuFill is an injectable, self-setting, macro-porous, osteo-conductive, calcium phosphate bone graft substitute material that is intended for use to fill bony voids or gaps of the skeletal system of the extremities, spine (i.e. posterolateral spine), and the pelvis that are not intrinsic to the stability of the bony structure. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. AccuFill is a bone graft substitute that resorbs and is replaced with new bone during the healing process.

This study will evaluate the on-label use of AccuFill during the Subchondroplasty procedure.

5.7 Risk Analysis

This study was designed to assure that the benefits and knowledge gained by studying clinical outcomes associated with Subchondroplasty for treatment of BMLs in the knee outweigh the potential risks to the subjects. Arthroscopic surgery is a well-established procedure that is utilized regularly as standard of care. The Subchondroplasty procedure utilizes FDA-cleared implants and pre-market exempt instruments that are used according to their cleared indications. The primary risks involved in this study are those that are normally experienced during these surgical procedures as detailed below. Alternative treatment options may require more invasive surgical therapy to treat the painful knee, up to and including, a total knee arthroplasty.

5.7.1 Potential Clinical Benefits

Because this study will be conducted in patients already planning to undergo a non-invasive surgical procedure, the study protocol will not impart significant benefits beyond the benefit of the surgical procedure itself.

5.7.2 Potential Arthroscopic Surgical Risks

Risks of surgical intervention include those risks currently associated with arthroscopic surgical interventions in the knee. These risks include intra-articular adhesions (scar tissue), superficial and/or deep wound infection, nausea and/or vomiting, bleeding, knee pain, muscle weakness, and postoperative blood clot (hematoma). Meniscal tear and plica formation may occur. There are possibilities of wound re-opening, deep vein thrombosis (blood clot), pulmonary embolus (lung clot), vascular or nerve injury and an allergic response to the anesthetic or medications. Some additional risks related to local anesthesia are swelling, pain, bleeding, bruising, nerve pain and loss of sensation in the skin and ligament around the knee.

5.7.3 Potential Subchondroplasty Surgical Risks

Risks associated with subchondral implantation of AccuFill may include tissue thinning over implant site, tenderness/redness/edema, seroma/hematoma, infection, swelling/fluid collection and loss of contour. Migration, extrusion, dehiscence, fracture and sloughing of AccuFill can occur as a result of excessive trauma. Neurovascular injury may occur due to surgical trauma.

5.7.4 Methods to Minimize Risk

Methods to minimize risks include inclusion and exclusion criteria that recruit only appropriate subjects into the study. Potential subjects who may be at increased risk of experiencing an adverse reaction will not be enrolled.

Study subjects will be monitored post-operatively to assess the surgical site for any acute and chronic adverse reactions to ensure proper medical treatment can be administered. Validated and standardized outcome scales and surveys will be used to collect subjects' data. Experienced orthopedic surgeons will participate as investigators and have experienced staff to perform the study procedures including post-operative rehabilitation.

6.0 Study Objectives & Endpoints

6.1 Study Objectives

The primary objective of this study is to determine whether Subchondroplasty with arthroscopy is superior to arthroscopy alone for treatment of bone marrow lesions in the knee. Superiority will be evaluated in terms of composite clinical success (CCS) requiring freedom from subsequent secondary surgical intervention (SSSI) and among those free from SSSI, a clinically meaningful reduction in self-reported pain based on a validated measure of subject-reported pain. Conditional on showing superiority in terms of CCS, superiority in terms of improved ADL will then be tested as a conditional endpoint.

Secondary objectives include evaluation of other subject-reported outcomes measures; evaluating the safety profile by determining the incidence and time to resolution of post-operative complications and adverse events; comparing the incidence and time to subsequent secondary surgical intervention including re-operation and revision; and evaluating the use of healthcare resources and impact on productivity.

6.2 Primary Endpoint

The primary measure of clinical success is a composite clinical success (CCS) endpoint requiring:

- Freedom from secondary subsequent surgical intervention (SSSI); and
- Among subjects free from SSSI; an improvement in KOOS pain of at least 10 points.

For the purpose of this study, SSSI will include any partial or total joint arthroplasty or any bone grafting or bone substitute procedure in the study knee.

The 10 point threshold is consistent with ICRS recommendations for the use of changes in the KOOS pain score in responder endpoints [11].

6.3 Secondary Endpoints

Secondary endpoints include evaluation of:

1) Comparison of mean change in KOOS subscale scores (Pain, ADL, Symptoms, Sports and Recreation, Quality of Life)

2) Longitudinal comparison of KOOS subscales over 12 to 24 months post-surgery
3) Comparison of mean Numeric Pain, EQ-5D and Global Satisfaction scores, where available
4) X-ray evaluation of joint space narrowing, osteophyte and cyst formation and subchondral sclerosis, where available
5) MRI analysis of bone marrow lesion variables, where available
6) Incidence and time to resolution of post-operative complications and adverse events
7) Incidence and time to joint injections, where available
8) Incidence and time to re-operations and revisions
9) Number of visits to healthcare providers, diagnostic or treatment procedures, and support devices; use of pain medication; and days of productivity lost, where available

7.0 Study Design

This is a multicenter, prospective, single-blinded, two-arm, randomized study. Enrolled subjects will have a single BML of the tibia, single BML of the femur, or adjoining BMLs of tibia and femur, as long as the BMLs are in the same compartment of the knee. Subjects will also be surgical candidates for knee arthroscopy due to mechanical symptoms, meniscus tear, loose body and/or synovitis.

A stratified blocked randomization will be used to assign subjects to either Subchondroplasty with arthroscopy or to arthroscopy alone in a 2:1 ratio. Individual sets of blocks will be determined within study site and lesion polarity status (unipolar vs bipolar).

Subjects will be consented within 90 days prior to surgery and take part in follow-up visits for two years following surgery. A preoperative visit (with exception of MR imaging) will occur within 60 days prior to surgery. Telephone follow-up interviews will be done at 6 weeks, 3 months, 6 months, 9 months, 18 months and 24 months post-surgery. Target enrollment is 201 subjects, to include 134 subjects in the treatment group (SCP + Arthroscopy) and 67 subjects in the control group (Arthroscopy alone).

Enrollment was stopped early when an interim analysis demonstrated that the study was unlikely to meet its primary endpoint due to an unexpectedly high success rate in the arthroscopy only group. Follow-up will continue for all subjects enrolled through the 24 month visit to allow further monitoring of outcomes related to revisions, reoperations, adverse events, and to collect KOOS assessments and numeric pain scores.

Subjects will complete the study at the 24 month follow-up visit. For the purposes of this protocol, a revision will be defined as any partial or total joint arthroplasty or any bone fixation, bone grafting or bone substitute procedure in the same compartment in the study knee.

8.0 Subject Selection Criteria

8.1 Inclusion Criteria

Candidates must meet ALL of the following:

1) Voluntary signature of the IRB/REB approved Informed Consent,
2) Male or female subjects between the ages of 30 to 75 years,
3) Body Mass Index ≤ 40 (BMI=kg/m^2),
4) Has experienced pain in study knee for at least 3 months,
5) Kellgren-Lawrence grade 1-3 Osteoarthritis in the study knee, as reviewed on preoperative XR imaging,
6) BML is confirmed on T2 weighted or Proton Density MR Imaging by presence of white signal,
7) Single BML of tibia, single BML of femur, or adjoining BMLs of tibia & femur, in the same compartment, extending to the articular surface of the joint,
8) Surgical candidate for knee arthroscopy due to mechanical symptoms, meniscus tear, loose body and/or synovitis,
9) Must record a response, at the preoperative study visit, of moderate to extreme pain for any one of the KOOS Pain Scale questions, P2 through P9,
10) Index knee alignment is defined radiographically as one of the following: Neutral, ≤ to 6° mechanical varus, or ≤ 6° mechanical valgus,
11) Ligaments in the study knee are stable,
12) The contralateral (non-study) knee is stable and functional,
13) Is refractory to conservative non-surgical management
    a) having failed 2 or more of the following: hyaluronic acid injection, corticosteroid injection, NSAIDs, physical therapy, bracing, activity modification, or minimal surgical intervention (e.g., arthroscopy, debridement/chondroplasty, and/or loose body removal)
    b) and is ≥ 3 months from the start of treatment (these treatments can continue up to the time of the randomized procedure; injections to be completed per Section 10.4.7),
14) Must be physically and mentally willing and able, in the Investigator's opinion at the time of enrollment, to be compliant with the protocol, including all follow-up visits, survey completion, weight-bearing restrictions, and post-operative rehabilitation.

8.2 Exclusion Criteria

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

1) BML caused by acute trauma less than 3 months prior to enrollment,
2) Clinical and/or radiographic disease diagnosis of the index knee that includes any of the following:
    a. Kellgren-Lawrence Grade 4 Osteoarthritis with complete loss of joint space (bone-on-bone) or subchondral bone collapse,
    b. Rheumatoid arthritis, or history of septic or reactive arthritis,
    c. Gout or a history of gout or pseudogout in the affected knee,
    d. Has more than two clinically relevant BMLs in the index knee,
    e. Osteochondritis dissecans of the knee with significant bone loss,
    f. Collapse of subchondral bone,
    g. Clinically relevant BML located at ACL/PCL insertion,
    h. MRI evidence of frank ligament instability,
3) Passive knee flexion < 110° or flexion contracture >30°,
4) History of systemic diseases which could contribute to secondary arthropathies (e.g., sickle cell disease, hemochromatosis, or autoimmune disease),
5) Has a neuromuscular, neurosensory, or musculoskeletal deficiency that limits the ability to perform objective functional assessment of either knee,
6) If diabetic, blood glucose over 200 mg/dL at time of enrollment,
7) Current daily tobacco or high nicotine product user or < 3months from nicotine cessation,
8) Presents a high surgical risk due to unstable cardiac and/or pulmonary disease,
9) Has HIV or other immunodeficient state including subjects on immunosuppressant therapies, or has significant illness (metastasis of any type) that decreases the probability of survival to the 2 year endpoint,
10) Is at substantial risk for the need of organ transplantation, such as renal insufficiency,
11) Is pregnant or breast-feeding at the time of surgery,

12) Has a history of any invasive malignancy (except non-melanoma skin cancer), unless treated with curative intent and with no clinical signs or symptoms of the malignancy for 5 years,

13) Has primary bone tumor in the knee area,

14) Anticipates having a lower extremity surgery other than the investigational surgery during the course of the study

15) Is participating concurrently in another clinical trial, or has participated in a clinical trial within 30 days of surgery,

16) Is receiving prescription pain medication other than NSAIDs or acetaminophen for conditions unrelated to the index knee condition, chronic use of anticoagulants, or taking oral or inhaled corticosteroids,

17) Active joint infection or history of chronic joint infection at the surgical site,

18) Prior total meniscectomy of index knee,

19) Has primarily patellofemoral symptoms,

20) Is indicated for concomitant procedures (i.e., microfracture, subchondral drilling, cartilage allograft, ligament or tendon repair, distal realignment/osteotomy, root repair) in the index knee, with the exception of incidental loose body removal, debridement, synovectomy, osteophyte removal in locations other than adjacent to BMLs, and/or partial meniscectomy,

21) Has contraindications for Magnetic Resonance Imaging (MRI),

22) Is receiving worker's compensation or currently involved in litigation relating to the index knee,

23) Has a history of substance abuse.

9.0 Study Procedures

9.1 Screening and Enrollment

Potential subjects will be screened from each investigator's subject population. Subjects in this group will be screened for eligibility based on the inclusion and exclusion criteria described in Sections 8.1 and 8.2. The Study Site will maintain a Subject Screening Log to track all screened subjects, including subjects who do not meet the study criteria and those who decline to participate. For subjects who do not meet the study criteria, the reason for ineligibility will be recorded on the log; however, their eligibility criteria should not be entered into the Electronic Data Capture (EDC) System.

Subjects will not be invited to participate in the study until after approval of the protocol by the reviewing IRB/REB. Subjects will be considered enrolled in the study if they meet

the pre-surgery inclusion and exclusion criteria, sign a consent form, and undergo a randomized study procedure. The Study Site will maintain a Subject Enrollment Log for all enrolled subjects.

9.2 Informed Consent

All study subjects are required to undergo the process of Informed Consent and sign an Institutional Review Board (IRB) or Research Ethics Board (REB) approved Informed Consent Form, compliant with 21 CFR Part 50-Protection of Human Subjects, and in accordance with institutional policies. The Informed Consent Form must be signed prior to the conduct of any protocol-specific procedures or data collection. Informed consent may be obtained up to 90 days prior to surgery.

If the Study Site does not have an IRB/REB of record, a central IRB/REB may be utilized upon approval by Zimmer Biomet.

9.3 Preoperative Procedures

Preoperative procedures include a knee examination, documentation of medical and knee history and pain medication use, collection of baseline X-rays, and completion of subject-reported outcomes surveys. All preoperative procedures are to be completed within 60 days prior to the study surgery; this includes X-ray images. A preoperative MRI will also be included in the study analysis. The MR images may be obtained up to 90 days prior to surgery and according to the Image Acquisition Protocol (Appendix C). The Schedule of Events is listed in **Table 1**.

9.3.1 The knee examination is to be conducted during a preoperative visit including evaluations of laxity, alignment, range of motion, effusion and passive motion deficit as appropriate for the subject's condition.

9.3.2 The preoperative visit will also include collection of basic demographic information and medical history, current use of prescription and over-the-counter pain medication, and a detailed history of all knee-related injuries, treatment and surgeries.

9.3.3 A baseline series of knee x-rays are to be obtained prior to surgery. This series is to include:

- Long Standing AP View
- Lateral View
- PA Fixed Flexion (Bilateral) View
- Skyline/Sunrise View

The Image Acquisition Protocol (Appendix C) describes the views and parameters in detail.

The preoperative x-ray files are to be submitted to the central imaging laboratory, per the Image Transfer Protocol (Appendix D).

9.3.4 The Institution's MRI Department is to obtain the preoperative images

described and prepare the standard imaging report within 90 days prior to the surgery. The investigator shall obtain a copy of this report and the images. The MRI files are to be submitted to the central imaging laboratory per the Image Transfer Protocol (Appendix D).

MR examinations are to be performed on a 1.5 or 3.0 T MR. The following sequences are to be applied:

- Three Plane Localizer
- Coronal Proton Density Sequence with Fat Saturation
- Coronal Short Tau Inversion Recovery (STIR)
- Sagittal T1 Weighted
- Sagittal Proton Density Sequence with Fat Saturation
- Sagittal 3D SPGR (Spoiled Gradient) Sequence with Fat Saturation
- Axial Proton Density Sequence with Fat Saturation

The Image Acquisition Protocol (Appendix C) describes the examination protocol in detail. If the institution utilizes an MR device that is not listed on or compatible with the Image Acquisition Protocol, Zimmer Biomet will arrange for an alternate protocol to be provided by the central imaging laboratory.

9.3.4 The subject is to complete a series of surveys and scales regarding their clinical outcomes at the time preceding surgery, including pain, range of motion, and activities. These scales include:

- The Knee Injury and Osteoarthritis Outcomes Score (KOOS)
- EQ-5D
- Numeric Pain Scale
- Healthcare Utilization Survey

9.3.5 Use of any preoperative injections within the past year into the index knee should be recorded on the Healthcare Utilization Form during the baseline visit. Potential subjects can continue to receive injections preoperatively, with no washout period. Injections however should not be given within 2 weeks prior to the baseline visit and if given, should be done after completion of subject reported outcome forms.

9.4 Randomization Procedures

The surgeon will be blinded to the treatment group until the time of surgery to avoid potential selection bias during the screening process. The subject will be blinded to the treatment group throughout the study. The research coordinator will input the subject's Inclusion/Exclusion criteria into the Electronic Data Capture System, once all criteria has been confirmed, and select that the subject is ready to randomize when appropriate. Subjects may be randomized prior to surgery to allow for OR set-up. However, randomization should be performed as close to the time of surgery as possible to reduce the risk of randomization failures due to cancelled procedures.

9.5 Operative Procedures

9.5.1 Arthroscopy Control Procedure

All operative procedures are to be performed under aseptic conditions according to the institution's standards. After randomization, subjects assigned to the Arthroscopy control group will undergo arthroscopy of the study knee with one or more of the following procedures:

- Partial meniscectomy
- Lavage
- Debridement
- Loose body removal
- Synovectomy
- Removal of osteophytes in the notch or locations other than those adjacent to BML(s)

No cartilage repair procedures other than debridement should be performed. Osteophytes adjacent to the target BML(s) identified on MRI should not be treated. Additionally, for subjects with meniscal root injuries, root repairs should not be performed.

Superficial skin incision(s) should be created at the typical AccuPort® access point(s) as if the subject had undergone SCP. The incisions should be closed in the typical fashion.

9.5.2 Subchondroplasty Procedure

After randomization to the study group, subjects assigned to the SCP + Arthroscopy group will undergo the Subchondroplasty portion of the procedure before or after the Arthroscopy portion per the surgeon's discretion. All operative procedures are to be performed under aseptic conditions according to the institution's standards. The same Arthroscopic procedures reported above for Arthroscopy Control subjects should be performed for Subchondroplasty + Arthroscopy subjects. The Subchondroplasty surgical technique is described in detail in Appendix B, with the required steps outlined below.

- The preoperative MRI should be used in planning the access point, trajectory and depth of the AccuPort® cannula(s) for accessing the location of the BML(s).
- AccuPorts should be placed using fluoroscopic guidance.
- Use of the SCP Navigation guide is optional.
- AccuFill should only be mixed with saline, for consistency between subjects.
- Appropriate volume of AccuFill should be used to adequately fill the area(s) of BML(s) taking care not to over-pressurize or overfill the defect. Multiple fluoroscopic images should be taken during injection to check for extravasation of material.
- Any extravasation of material into surrounding soft tissues should be

thoroughly irrigated at the time of the procedure.

- An arthroscopic examination of the joint should be performed after injection to check for any material in the joint space. Any material found should be evacuated from the joint utilizing suction and lavage.

9.5.3 Surgical Documentation

The investigator is to dictate detailed operative notes that include the measures listed below, or have paper copies of the Surgical Documentation Case Report Forms completed during surgery to serve as source documents. Arthroscopic and Fluoroscopic images should also be retained in the study files.

Surgical Documentation

- Randomization Allocation
- OR Time
- SCP Procedure Time (if applicable)
- Anesthesia Type
- Intraoperative Adverse Events
- Documentation of Cartilage Lesions
    - Location: femur, tibia, or patella; surface;
    - ICRS Grade
    - Lesion Size, if ICRS Grade 3 or 4
- List of Concomitant Arthroscopic Procedures
- Documentation of Remaining Meniscus Status
- Documentation of SCP Injection (if applicable)
    - Type of AccuPort(s) used (end target, side target, etc.)
    - Volume of AccuFill injected
- Part and Lot numbers of AccuFill, AccuPort(s) and AccuMix used (if applicable)

9.6 Perioperative Pain Management, Postoperative Procedures and Assessments

Perioperative pain management is important in maintaining blinding of subjects. Perioperative pain management protocols may be determined per investigator and institution preference but should be consistent between treatment groups at each site to ensure subject blinding.

During the immediate postoperative period, the investigator's standard postoperative care procedures should be followed. All adverse events and complications are to be assessed and recorded on the **Adverse Event Form,** per Section 11.0 Safety Management—Medical Events/Adverse Events.

Rehabilitation should be performed as part of a 3 to 6 month program, depending on the progress of the individual subject. The Recommended Rehabilitation Protocol is found in Appendix E.

9.7 Telephone Follow-Up Interviews

Telephone follow-up interviews are scheduled at 6 weeks, 3, 6, 9, 12, 18 and 24 months following the date of surgery. Each interview will include screening for Adverse Events, Serious Adverse Events, and reoperations that have occurred since the last follow-up interval and completion of a subset of subject reported outcomes surveys..

A Subject Stipend may be offered to the subject at the completion of each follow-up visit, if in accordance with the institution's policies, and if the subject has completed the full visit, Sections 9.7.1 – 9.7.2**.** The stipend is provided to defray costs of travel, parking and missed time from work.

Follow-up visits are detailed in **Table 1. Schedule of Events**. All visits are to occur within the windows described in **Table 1.**

9.7.1 Subject Reported Outcome Surveys

The study's Electronic Data Capture System can be configured to send an email notification to subjects at the beginning of each visit window with a reminder that they need to complete the KOOS Pain Scale or KOOS and Numeric Pain Scale surveys. This email will contain a method to allow the subjects to complete their surveys electronically via the EDC's electronic subject reported outcomes (ePRO) system. Prior to conducting the phone interview, the Study Coordinator will check to confirm whether these surveys have been completed electronically or not. If they have not been completed, the Study Coordinator will fax, email or mail a copy of the applicable surveys to the subject with instructions for completion or initiate another reminder from the ePRO system. Mailed surveys will be sent with a stamped, return envelope. Any subject survey forms that are not collected via the database's ePRO system are to be maintained in the subjects' study files as source documents.

9.7.2 Telephone Interviews

The Study Coordinator will schedule a call with the subject within the visit window.

During the call, the subject is to be queried regarding the occurrence of any Adverse Events and Serious Adverse Events, per Section 11.0 Safety Management—Medical Events/Adverse Events. Any adverse event that results in reoperation or revision is to be recorded as a Serious Adverse Event.

The subject is to be queried regarding any reoperations of the index knee. All reoperations are to be documented using the Surgical Reoperation Form, per Section 10.4.2.

If the subject has not already completed the applicable PROs, these subject reported outcome surveys may be completed during the telephone interview. The Study Coordinator is to read each question and record the answer given.

The Study Coordinator is to document the phone interview, including any completion of outcome measures over the phone, in the subjects' study files.

Table 1. Schedule of Events

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Procedures	**Study Admit/ Pre-operative**	**Operative**	**6 Weeks**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**18 Months**	**24 Months**
Visit Window	≤60 days Prior to Surgery		±10 Days	±30 Days	±30 Days	±30 Days	±2 Mos	±2 Mos	±2 Mos
Informed Consent[1]	X								
Inclusion & Exclusion Criteria	X								
Demographic Form	X								
Knee Examination	X								
Knee History	X								
Medical History	X								
Pain Medications	X								
X-Ray Series	X								
MRI[1]	X								
Telephone Follow-Up			X	X	X	X	X	X	X
Screen for Adverse Events[2]		X	X	X	X	X	X	X	X
KOOS Knee Survey	P		P	P	P	P[3]	P	P	P
Numeric Pain Scale	P		P	P	P		P	P	P
EQ-5D	P								
Healthcare Utilization	P								
Return to Work									
Surgical Documentation		X							
Serious Adverse Event[2]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation[2]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Surgical Reoperation[4]			(X)	(X)	(X)	(X)	(X)	(X)	(X)
Study Exit[5]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

X Investigator completed forms
P Subject completed forms
[1]Informed Consent and Baseline MRI to be done within 90 days of study enrollment.
[2] Case Report Forms to be completed if/when event occurs.
[3] KOOS Pain Subscale *only* at 9 month visit
[4] Surgical Reoperation form will be completed if the investigator performs any procedure on the index knee regardless of whether the subject's change in condition is related to the initial study procedure.
[5] Study Exit form will be completed if the subject is no longer participating in the study for any reason.

10.0 Reporting

10.1 Activities Required Prior to Initiation of the Study

10.1.1 Clinical Trial Agreement (CTA) and Financial Arrangements

A fully executed (signed by all required parties) CTA must be on file with the Sponsor prior to any investigator participating in this study. This agreement must explain the financial arrangement with the investigative site.

10.1.2 Institutional Review Board/ Research Ethics Board Protocol Approval

This study protocol must be submitted to and approved by the Investigator's Institutional Review Board (IRB) or Research Ethics Board (REB). A copy of the IRB or REB approval letter must be submitted to the Sponsor. The letter should identify the following:

- Protocol name and/or number.
- Date of IRB or REB meeting (if available).
- Date of approval.
- Date of expiration.
- Signature of IRB or REB.

10.1.3 ClinicalTrials.gov Registration

The Sponsor will be responsible for registering this study on www.ClinicalTrials.gov if required by local and national regulations.

10.2 Clinical Data Collection/Submission

10.2.1 Summary of Case Report Form Data Collection

Study data will be collected on source documents which may include study-specific worksheets provided by the Sponsor.

The following source document/CRF completion guidelines should be followed:

- Complete carefully and accurately.
- Complete header information consistently across all case report forms for each individual study subject (when study-specific CRFs are used).
- Be sure that data on the source documents match that which is entered through the electronic data capture (EDC) system.
- Use the study subject's unique Case ID number assigned as instructed. Do not provide information that is not requested on the CRFs.

- Ensure that all fields are completed. For fields completed by the subject, efforts should be made to obtain any missing responses prior to the subject completing their visit.

10.2.2 Data Submission

Completed CRFs will be submitted directly to the Sponsor by electronic data capture and submission via a method approved by the Sponsor. Every effort must be made to ensure data submission to the Sponsor is made within 30 days of the visit completion.

10.2.3 Quality Assurance of Data

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All electronic systems used to create, modify, maintain, or transmit electronic study records will be validated. The Sponsor will maintain quality control systems, in accordance with the Sponsor's policies and procedures.

10.3 Investigator Reporting Responsibilities

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of data reported to the Sponsor in accordance with this protocol. The Investigator or Designee will provide periodic reports to their IRB or REB as required to maintain IRB or REB approval throughout the study, and will provide any required final reporting to the IRB or REB upon study completion/termination. A copy of all IRB or REB re-approval letters must be submitted to the Sponsor. If the IRB or REB terminates or suspends its approval of the study, the Investigator or Designee will suspend study-related activities and will promptly notify the Sponsor. The Investigator should also promptly provide written reports to the Sponsor and the IRB or REB regarding any changes significantly affecting the conduct of the study, and/or increasing risk to the subjects.

10.4 Management of Intercurrent Events

10.4.1 Failure to Obtain Informed Consent

Study data will not be collected until the Informed Consent has been signed and dated by the candidate. If a candidate does not wish to participate (does not sign and date the Informed Consent), data for that candidate will not be collected for this study.

10.4.2 Surgical Reoperation or Revision

A reoperation of the index knee or revision of the SCP injection site may be performed at the discretion of the Investigator (e.g., due to progressive pain or disability, clinical or radiographic evidence of potential graft failure, etc.). A reoperation is defined as any surgical procedure on the index knee. For the

purposes of this protocol, a revision will be defined as any partial or total joint arthroplasty or any bone fixation, bone grafting or bone substitute procedure in the same compartment in the study knee.

The investigator is to dictate detailed operative notes that include the measures listed below, or have paper copies of the Surgical Reoperation Form completed during surgery to serve as a source document.

10.4.3 Surgical Reoperation Documentation

- Reason for Surgery
- Postoperative Diagnosis
- OR Time
- Anesthesia Type

All reoperations should be documented on an Adverse Event Form and the surgery documented on the Surgical Reoperation Form.

In the event that a revision occurs (defined as any partial or total joint arthroplasty or any bone fixation, bone grafting or bone substitute procedure in the same compartment in the index knee), the subject will be excluded from any future per protocol (PP) analysis of secondary endpoints, but should continue to be followed through the two-year endpoint for ITT analysis. An Adverse Event Form and Surgical Reoperation Form will be completed.

In the event that a reoperation occurs that does not involve revision of the BML site(s), an Adverse Event Form and Surgical Reoperation Form will be completed, and the subject will continue to be followed in the study per protocol. If possible, reoperations should not be performed within 6 weeks of the 12 and 24 month visits.

10.4.4 Subject Cross-over Between Treatment Groups

Subjects that display a lack of improvement in their baseline KOOS pain score by at least 10 points for at least two consecutive follow-up intervals, starting with the 3 and 6 month visits, or for any two consecutive visits thereafter, or subjects who show a trending decline in their KOOS pain score (as confirmed through an independent review of the case, see Section 10.4.5 below) may be considered for an additional procedure. The earliest a subject can be considered for an additional procedure is the 6 month follow-up visit. Subjects originally in the arthroscopy alone group may cross-over and be treated with Subchondroplasty with Arthroscopy, should they meet the aforementioned criteria, as determined by independent review. These subjects should not be unblinded until after the independent review's determination and will continue to be followed in the study per protocol through the 2 year endpoint.

10.4.5 Independent Review of Worsening Cases and Potential Cross-over Treatment

If any subject displays a lack of improvement or trending decline in their KOOS

pain scores as described in Section 10.4.4, the site shall submit documentation of the case to an independent, blinded review process for final determination of subject decline prior to unblinding the subject.

The independent review will be conducted by one or more physicians independent of the study and the clinical sites.

Information to be submitted to the independent review process will include all KOOS pain scores collected for the study and may include subject and knee history, pain medication and therapy use, as well as adverse event information, if applicable. Information submitted shall contain no indication of the treatment group to which the subject was assigned.

The independent review will result in a final documented assessment of subject decline irrespective of subject randomization. Once the assessment is received by the site, additional treatment options will be discussed with both groups of subjects prior to unblinding by the Investigator. If the subject was randomized to the Arthroscopy only group, they may proceed with the cross-over procedure in accordance with the protocol requirements and the assessment made during independent review.

10.4.6 Unblinded Subjects

If a subject has become unblinded due to meeting Section 10.4.5 worsening criteria but has not been revised or has been unblinded for any other reason, they should continue to be followed through the two-year endpoint for ITT analysis. All study procedures will continue to be completed. A Protocol Deviation Form will be required for any subject who has become unblinded, unless they have undergone the cross-over procedure or an additional intervention per protocol.

10.4.7 Postoperative Injections

Subjects should not receive cortisone injections before the 3 month follow-up visit and should not receive hyaluronic acid (HA) injections prior to the 6 month visit. Injections should not be given within 2 weeks prior to a postoperative visit and when given, should be done after completion of subject reported outcome forms. Subjects receiving postoperative knee injections will continue to be followed per the study protocol.

10.4.8 Missed Follow-up Visits

Investigators are to ensure that all follow-up visits are completed and are done within the window indicated in **Table 1**. If a visit is missed or occurs outside of the window, a Protocol Deviation Form is to be completed.

In the event of difficulty in scheduling a subject, at least three attempts of follow-up contact should be completed at each follow-up visit. Should the subject continue to be unresponsive at the 2 year follow-up visit, at least two telephone contacts should be attempted and documented and a certified letter mailed, prior to

considering the subject lost to follow-up. Once loss to follow-up is definitively established, a Study Exit Form is to be completed to properly withdraw the subject from the study.

10.4.9 Unscheduled Office Visits

Investigators may see the subjects, at their professional discretion, outside of the visits described in the study protocol. If an adverse event (AE) is reported during an unscheduled visit, the AE should be documented in the same manner as for a study visit, per Section 11.0 Safety Management—Medical Events/Adverse Events. No additional data collection or Case Report Forms are required at the unscheduled visit.

10.5 Protocol Deviations and Violations

10.5.1 Investigators acknowledge that they are not permitted to deviate from this Protocol, except in emergency circumstances.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor or reviewing IRB/REB. Such deviations will be recorded and reported to the Sponsor and reviewing IRB/REB as soon as possible.

All protocol deviations and violations shall include a corrective and preventive action plan to assist in the limiting of deviations from the Protocol in the future.

10.5.2 All protocol deviations (i.e. any change, divergence or departure from the procedures or protocol) shall be recorded with an explanation for the deviation on the Protocol Deviation Form. A simple protocol deviation does not impact the subjects' rights, safety, or well-being, or the completeness, accuracy or reliability of the study data. Deviations shall be reported by the Investigator to Zimmer Biomet within 30 days. Zimmer Biomet will analyze the information and assess the significance. Deviations must also be reported to the reviewing IRB/REB per policy.

Any deviations to inclusion or exclusion criteria must be submitted to Zimmer Biomet in writing, per section 10.5.4 and the reviewing IRB/REB, where applicable, for analysis and approval prior to subject enrollment.

10.5.3 All protocol violations (i.e. any deviation from the protocol that may impact the subjects' rights, safety, or well-being, or the completeness, accuracy or reliability of the study data, or a deviation from FDA or IRB/REB regulations or standards) shall be reported to Zimmer Biomet within 24 hours and to the reviewing IRB/REB per policy. A Protocol Deviation Form shall be completed that includes a full explanation of the event and outcome.

The Investigator will assist Zimmer Biomet in corresponding with the reviewing IRB/REB, where appropriate, to determine the appropriate course of action.

10.5.4 Protocol waivers/exceptions may be granted by the Sponsor on a case by

case basis as per request from sites. A description and rationale for the exception request should be put in writing on a Protocol Waiver/Exception Request Form. A Site Investigator will be required to sign off on the form, as well as a Sponsor Approver, prior to the enrollment of a subject or known deviation from the protocol. Should a deviation or violation be performed without prior written approval from all parties, the Investigator may be terminated from the study. Any deviation or violation from the protocol should be captured on a Protocol Deviation Form.

10.6 Withdrawal and Study Re-Entry

Subjects may withdraw or be withdrawn at any time during the course of the study, per subject request or at the discretion of the investigator. Investigators may withdraw a subject due to non-compliance with the protocol or follow-up visit schedule, occurrence of adverse events, death, or other reasons per their professional opinion. The date and reason for subject withdrawal is to be documented on the **Study Exit Form**.

If a subject is withdrawn or terminated due to medical safety considerations because of an adverse event, the adverse event must be followed by medical attention until the investigator determines the event is chronic or clinically stable and all study data related to the event recorded.

When a subject withdraws or is withdrawn, all study procedures completed and data collected prior to the date of withdrawal will be submitted to the Sponsor and included in the study database, unless the subject requests otherwise in writing.

Should a subject who previously chose to withdraw or were considered lost-to-follow-up wish to re-enter the study, a new Informed Consent will be required. The site may resume scheduled follow-up visits according to their follow-up schedule.

Since the pre-determined sample size includes an additional 27 patients to account for lost-to follow-up, subjects that are withdrawn from the study will not be replaced.

11.0 Safety Management—Medical Events/Adverse Events

Adverse events that occur either intraoperatively or during the follow-up phase of the study protocol are to be recorded on an Adverse Event Form whether noted by the Investigator or the subject. Sites should report only those adverse events that are related to the implant (AccuFill), Subchondroplasty Instrumentation (AccuPort Cannulas), or study procedure (Subchondroplasty and/or Arthroscopy), or those that are considered serious. Sites should also take into consideration the possibility of a temporal relationship between a potential adverse event and the study implant, instrumentation or procedure. Any events that are pre-existing (prior to surgery) are not considered adverse events, unless a pre-existing complication or event has changed in severity or intensity during the study period.

11.1 Event Classification

Adverse Event (AE):

An adverse event is any untoward medical occurrence, unintended disease or injury, or

untoward clinical signs (including abnormal laboratory findings) in subjects whether or not related to the investigational medical device. This definition includes events related to the AccuFill implant or Subchondroplasty Surgical Instrumentation as well as those related to the Subchondroplasty Procedure.

Serious Adverse Event (SAE):

A Serious Adverse Event is any adverse event that:

a. led to death.
b. led to serious deterioration in the health of the subject, that either resulted in:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. led to fetal distress, fetal death or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, *with the exception of a lower extremity surgical procedure*, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE):

An Adverse Device Effect is an adverse event related to the use of the AccuFill implant or SCP Surgical Instrumentation (AccuPort Delivery Cannulas). This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment implantation, installation, or operation, or any malfunction of the medical device, as well as any event resulting from use error or from intentional misuse of the medical device.

For the purposes of this study protocol, all AEs will be assessed for relationship to the AccuFill implant or SCP Surgical Instrumentation. Any AEs considered to be possibly, probably, or definitely related to the implant or SCP Surgical Instrumentation will be considered as potential ADEs in study analysis and/or reporting.

Serious Adverse Device Effect (SADE):

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

An Unanticipated Serious Adverse Device Effect is a serious adverse device effect that is not identified in nature, severity, or degree of incidence in Appendix A. Package Insert.

Device Deficiency

A Device Deficiency is defined as an inadequacy of a medical device with respect to its

identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labeling.

11.2 Adverse Event Data Collection

The Adverse Event Form will collect the following:

- Description of Complication (Diagnosis)
- Date of Onset
- Status of Adverse Event or Date of Resolution
- Severity/Intensity of Symptoms
    - Mild: Event/symptom is transient and well tolerated by the subject.
    - Moderate: Event/symptom causes discomfort and interferes with routine activities of the subject.
    - Severe: Event/symptom interferes considerably with the routine activities of the subject or causes inability to work.
- Relationship to Study Surgical Procedure (Subchondroplasty and/or Arthroscopy)
    - Not Related: The adverse event is clearly NOT related to the surgical procedure: the AE follows no known or suspected pattern of response, and an alternative cause is present.
    - Possibly Related: The adverse event may be related to the surgical procedure. The AE follows a suspected pattern of response, or is otherwise logically related to the surgical procedure; however, an alternative cause is present.
    - Probably Related: The adverse event is likely related to the surgical procedure. The AE follows a known or suspected pattern of response or is otherwise logically related to the surgical procedure, but an alternative cause may be present.
    - Definitely Related: The adverse event is directly related to the surgical procedure such that is no alternative cause.
- Relationship to Implant (AccuFill) or Instrumentation (AccuPort Cannulas)
    - Not Related: The adverse event has no temporal or other relationship to the administration of the implant: follows no known or suspected pattern of response and an alternative cause is present.
    - Possibly Related: The adverse event may be related to the implant. The AE has a temporal relationship to the administration of the implant, follows a suspected pattern of response, or is otherwise logically related to the implant; however, an alternative cause is present.
    - Probably Related: The adverse event is likely related to the implant. The AE follows a known or suspected pattern of response or is otherwise logically related to the implant, but an alternative cause may be present.
    - Definitely Related: The adverse event is clearly related to the implant: the adverse event has a temporal relationship to the

administration of the implant, follows a known pattern of response, or is otherwise logically related to the implant and no alternative cause is present

- Treatment
- AE Outcome

The outcome is in relationship to the Adverse Event, not the treatment rendered for the event (if any).

- Recovered: The adverse event has been resolved and/or no further treatment is required to treat the reported condition or illness.
- Recovered with Sequelae: The adverse event has been resolved, however they have retained pathological conditions resulting from the prior disease or injury.
- Not Recovered, Ongoing: Treatment or diagnostic studies were prescribed for the adverse event and the outcome of the adverse event is not yet known.
- Lost-to-Follow-up: The outcome of the adverse event cannot be assessed as the subject has been lost-to-follow-up.
- Chronic, Clinically Stable: The adverse event will most likely never be resolved. The subject "tolerates" the illness or condition as a matter of life.
- Death: The outcome indicates the subject died as a direct result of the reported adverse event.

11.3 Events Followed to Resolution

Any adverse event considered by the Investigator to be possibly, probably or definitely related to the Subchondroplasty procedure and/or AccuFill should be followed over the study period until resolution or until the Investigator determines the event is chronic or clinically stable.

11.4 Serious Adverse Events

If an AE is determined to be serious (i.e. an SAE), the Investigator(s) will determine the relationship of the adverse event to the procedure(s), device, or any commercial products used during the period of the study and complete an **Adverse Event Form**. Death is considered to be an outcome of an Adverse Event and documented on the Adverse Event Form. The actual cause of death (rather than the term "death") should be recorded on the form. All SAEs will be followed until resolution or the Investigator judges the event to be chronic or stable.

11.5 Safety Reporting

All Adverse Events and Serious Adverse Events will be reported on an Adverse Event Form to the Sponsor as soon as possible after the Investigator first learns of the event.
The Investigator must report all SAEs that meet the criteria below to a Zimmer Biomet Study Representative within twenty-four (24) hours after becoming aware of the incident:

- Definitely, probably or possibly related to the Study Procedure(s) and/or Study Implant AND unexpected

The Investigator is responsible for notifying their IRB/REB of all Adverse Events, including SAEs, in accordance with local regulations and institutional policies.

If an Unanticipated Serious Adverse Device Effect (USADE) is identified by the Sponsor, it will be promptly reported to concerned Investigators and regulatory authorities as required by applicable regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will report the USADE to their IRB/REB or EC.

Device deficiencies resulting in an adverse event will be documented on the Adverse Event form. Device deficiencies that could have led to a medical occurrence but did not lead to an adverse event will be reported to the sponsor within 48 hours of becoming aware of the event. The sponsor will process the device deficiency according to local complaint reporting procedures.

12.0 Assessment of Safety

All reports of Adverse Events will be entered into the study database and evaluated by the Sponsor on a regular basis throughout the study. These reports will be made available to the Investigator for preparation of IRB/REB continuing review reports, when requested.

Individual and aggregated events will be reviewed for consistency with expected events, for both severity and rate of incidence. Individual events or trends in events that appear to impact subject safety are reviewed by Zimmer Biomet management to determine if a change in the protocol or termination of the study is warranted. These decisions will be promptly communicated to all Investigators and local IRBs/REBs.

13.0 Compliance

13.1 Statement of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Clinical investigation of medical devices for human subjects — ISO 14155:2020 Good Clinical Practice, and any regional or national regulations, as appropriate. The clinical investigation will not begin until all necessary approvals/favorable opinions are obtained from the appropriate IRB or REB or regulatory authority, as appropriate. Should an IRB or REB or regulatory authority impose any additional requirements, they will be followed. Information regarding the study and study data will be made available via publication on clinicaltrials.gov. Additionally, the results of this study will be offered for publication at the conclusion of the study, if participating investigators believe the data warrants publication in an appropriate journal.

13.2 Protocol Amendments

Any proposed amendments to this protocol must be submitted in writing, with a justification for the amendment, and approved by the Sponsor prior to implementation. All Sponsor-initiated protocol amendments will be documented in writing, including the date

and justification for the change, and communicated in a timely manner to the investigators. All amendments are to be approved by the reviewing IRB/REB prior to implementation, if required according to the local and/or national laws/regulations.

13.3 Monitoring Procedures

Prior to initiating the clinical study, the Sponsor may conduct a site evaluation visit to ensure the Investigator(s) and study staff understands the study protocol and requirements and have adequate time and resources to implement and conduct the study. Prior to study initiation, the Investigator must have a fully executed CTA and IRB or REB approval of the study protocol and the study Informed Consent.

During the course of the study, the Sponsor will conduct periodic central monitoring and maintain contact with the study staff to monitor compliance and evidence of adverse events, in accordance with the Sponsor's policies and procedures. The Sponsor will address any identified non-compliance with the executed CTA, study protocol, and applicable regulatory requirements.

If onsite monitoring visit(s) are deemed appropriate by the Sponsor, the Investigator will permit representatives of the Sponsor's monitoring team to have direct access to inspect all source data/documents, study documents/binders, study subject case report forms, corresponding sections of study subject medical/hospital records, and any other documents relevant to the study.

14.0 Statistical Considerations and Methodology

14.1 Primary Efficacy Endpoint Analysis

The primary measure of clinical success is a composite clinical success (CCS) endpoint requiring:

- Freedom from secondary subsequent surgical intervention (SSSI); and
- Among subjects free from SSSI; an improvement in KOOS pain of at least 10 points.

For the purpose of this study, SSSI will include any partial or total joint arthroplasty or any bone fixation, bone grafting or bone substitute procedure in the same compartment in the study knee.

14.2 Hypotheses

The primary hypotheses to be tested are symbolically represented as:

$$\mathbf{H_o: CCS(S+A) \leq CCS(AA) \text{ VS } H_a: CCS(S+A) > CCS(AA)}$$

Where CCS(S+A) and CCS(AA) are equal to the probabilities of achieving composite clinical success for subjects undergoing Subchondroplasty with arthroscopy (S+A) compared to arthroscopy alone (AA). First, superiority will be statistically tested at 12 months using $\alpha=0.01$. If $p \leq 0.01$, then it will be concluded that S+A is superior to AA in terms of the primary endpoint and the conditional hypothesis of superiority in terms of ADL improvements will be tested, also at $\alpha=0.01$. If $p>0.01$ at month 12, the same

hypothesis will be tested at month 24 using α=0.04, thereby controlling the overall study type 1 error rate to no more than 0.05 according to the Bonferroni inequality. If $p \leq 0.04$ at month 24, it will be concluded that S+A is superior to AA in terms of the primary endpoint and the conditional hypothesis of superiority in terms of ADL improvements will then be tested at α=0.04. The superiority hypotheses involving CCS will be tested using one-sided normal approximation tests. The conditional superiority test for improvements in ADL will be tested using one-sided contrasts derived from a mixed model for repeated measures (MMRM) for change in KOOS ADL among subjects free from SSSI.

14.3 Selection of KOOS Threshold

As described by the ICRS Recommendation Document [11], the KOOS was developed in 1994-1995 as an extension of the WOMAC Osteoarthritis Index with the purpose of evaluating short-term and long-term symptoms and function in people with knee injury and OA. The KOOS includes 42 items in 5 separately scored subscales: Pain, Other Symptoms, Activities of Daily Living (ADL), Function in Sport and Recreation (Sport/Rec), and Knee-related Quality of Life (QOL). Each subscale is scored from 0 to 100 on a worst to best scale. Evidence supports the use of the KOOS for several orthopedic interventions such as autologous cartilage repair and microfracture, ACL reconstruction, meniscectomy, and total knee replacement. The KOOS has been used to evaluate other interventions, including tibial osteotomy, physical therapy, nutritional supplementation, and glucosamine supplementation. The KOOS is used in many large-scale databases, including the prospective registries on ACL reconstruction in Norway, Sweden, and Denmark; the MOON database in the United States; and the National Institutes of Health– sponsored Osteoarthritis Initiative following 5000 subjects at risk of OA, or with OA, for 5 years. Data from the latter study are freely available at www.oai.ucsf.edu. Normative data from the general population and from men and women having ACL reconstruction have been published.

In the reliability evaluation of the KOOS for people with articular cartilage lesions, test-retest was assessed over 2 days. The ICCs (Intraclass Correlation Coefficients) ranged from 0.87 to 0.95 for the 5 sub- scales, and the internal consistency ranged from 0.74 to 0.95. The minimal detectable change (MDC) for the Pain subscale was estimated to be equal to 6. When determining the effectiveness of an intervention, the proportion of individuals who achieve a minimal clinically important difference (MCID) should be considered. This was estimated to be 8-10 points for the KOOS subscales. Since the MDC is smaller than the MCID, it is shown that the KOOS Pain subscale has sufficient test-retest reliability to detect the suggested MCID. The MDC for the ADL subscale is 7.

The use of the KOOS Pain subscale in the primary composite clinical success endpoint, followed by the conditional testing of the KOOS ADL subscale is consistent with the ICRS Recommendation Document. “Although there is appeal in a single score for simplicity’s sake, reporting outcomes in separate sub-scales helps in interpreting the outcome of clinical studies and can assist subjects in their understanding of the expected course of their recovery over a number of outcomes”. “The recommended method for addressing such multiplicity issues is hierarchical testing of endpoints—that is, the primary endpoint is

tested first; if this is statistically significant, the secondary endpoint is tested, and so on. When an endpoint is statistically insignificant, no further endpoints are tested. The hierarchy of endpoints should of course be defined *a priori* and be described in the study protocol."

14.4 Study Number Assignment

Subject ID number assignment is done when the subject has met study criteria, signed the informed consent form, scheduled a surgery date and Inclusion/Exclusion has been entered into the Electronic Data Capture System. The Subject ID number will be the first two digits of the site number followed by a three-digit patient number, automatically assigned by the Electronic Data Capture System after entering the Inclusion/Exclusion form. Informed consent may occur up to 90 days prior to or at the time of the study procedure, however all other enrollment criteria should be completed within 60 days. A Randomization ID will be assigned at the time of randomization just prior to the procedure.

14.5 Sample Size Determination

For testing the primary superiority hypothesis as defined above and assuming true CCS rates of 0.80 and 0.60 for S+A and AA, respectively, a total of 174 subjects (116 and 58, respectively) are need for 80% power. This value is increased by 15% to 201 to account for losses-to-follow-up (134 S+A and 67 AA).

14.6 Analysis of Secondary Endpoints

The following secondary endpoints will be examined:

1) Comparison of mean change in KOOS Pain, ADL, Symptoms, Sports and Recreation, Quality of Life Subscale scores
2) Longitudinal comparison of KOOS subscales over 12 to 24 months post-surgery
3) Comparison of mean Numeric Pain, EQ-5D and Global Satisfaction scores, where available
4) X-ray evaluation of joint space narrowing, osteophyte and cyst formation and subchondral sclerosis, where available
5) MRI analysis of bone marrow lesion variables, where available
6) Incidence and time to resolution of post-operative complications and adverse events
7) Incidence and time to joint injections, where available
8) Incidence and time to re-operations and revisions
9) Number of visits to healthcare providers, diagnostic or treatment procedures, and support devices; use of pain medication; and days of productivity lost, where available.

14.7 Safety Endpoints

Assessment of the safety profiles will be based on the incidence and seriousness of adverse events associated with the treatment.

Adverse event rates will be summarized by type of AE and for specific AEs in two ways:

1) Per subject using counts and percentages,

2) By event, summarizing event counts by visit interval over time.

Device and procedure related events will be summarized by seriousness. Events listings will be provided that include details such as relatedness, severity, onset and resolution status for all events and for relevant subsets of events such as serious events and related events.

Additional tables presenting a survey of the incidence rates by treatment groups will be drawn up for the following classifications and items:

- Premature Termination, Serious Adverse Events and Causal Relationship
- Separate Presentation of Serious Adverse Events

14.8 Analyses Populations

Subjects will be assigned a subject ID number after verification that they met the preliminary study criteria, have signed the informed consent form, scheduled a surgery date and Inclusion/Exclusion has been entered into the Electronic Data Capture System. A Randomization ID will be assigned just prior to the time of surgery.

The **intent-to-treat (ITT)** population is defined as subjects who complete the preoperative procedures and are randomized just prior to the time of surgery. The final determinations of inclusion and exclusion criteria and stratum assignment are made during surgery. The allowable exclusions will be any subject who does not meet inclusion or exclusion criteria based on surgeon review. Preoperative and surgical data will be collected from these subjects, along with the reason for the subject being excluded from the study. However, the subject will be exited and will not continue for follow-up. The baseline analyses and analyses of population characteristics will be performed on the ITT group.

The **modified ITT (mITT)** population is defined as subjects who meet all inclusion and exclusion criteria and have an arthroscopy with SCP or arthroscopy alone as outlined in Section 9.5. The modified ITT population will be used for the primary and secondary efficacy analyses and safety analyses.

The **per-protocol (PP)** population is all subjects who are assigned a study number, receive treatment as randomized per the study procedure and complete the study according to the protocol. Exclusions for the per-protocol analysis population include, but are not limited to, protocol violations and any actions that compromise the efficacy of the procedure. The primary variables analyses will be done on this population to determine if study findings would have differed with the inclusion of the excluded subjects.

14.9 Missing Data

A tipping point sensitivity analysis will be conducted in which missing values in each group are separately assumed to be either successes or failures. Treatment group differences will be computed based on all possible combinations of assigning success or

failure to the primary overall success endpoint to the subjects in the two groups. For example, one scenario will be that all missing S+A device observations are failures and all missing AA observations are successes. The next scenario would have one success and the remaining missing values as failure for S+A and all missing AA controls as successes. For each scenario, the one-sided normal approximation p-value will be determined. These results will be plotted using a dot plot with the number of missings assumed as failures for S+A on the x-axis and the number of missing assumed as failures for AA controls on the Y-axis. The dots will be color coded to indicate whether or not the primary statistical conclusion changes under each individual scenario. If the fraction of scenarios in which the statistical conclusion changes is small, the primary results will have been shown to be robust against assumptions concerning missingness. Therefore, the primary hypothesis test will be conduct using the mITT analysis set in conjunction with the tipping point sensitivity analysis to account for mITT subjects who are not evaluable for primary CCS (either at 12 months or 24 months). If the fraction of missing data is larger than 10%, then multiple imputation (MI) will be performed in order to provide a comparison that includes all mITT subjects in order to further assess the potential impact of missing data. The MI will be implemented using SAS Proc MI and MIANALYZE and based on a monotonic missing value pattern.

14.10 Poolability, Stratified Analyses, and Covariates

Site poolability will be evaluated using a random effects meta-analysis approach using the R package metafor to implement the analysis. True effects are assumed to be normally distributed with mean m and variance t^2.

By imposing a specified distribution on the site-to-site variability, i.e. a normal distribution with mean m and variance t^2, sensitivity to small sample sizes in individual sites is reduced and the parameters reflecting the magnitude of site-to-site variability are naturally derived. The quantitative measure of the magnitude of heterogeneity is I^2. I^2 is the fraction of t^2 that is due to effect size heterogeneity, as opposed to sampling variance. Fractions 25% and less are considered small. If there is significant site to site variability, the impact on this variability will be evaluated using a random effects logistic regression.

Primary endpoints and selected secondary endpoints will be subjected to stratified analyses in order to evaluate poolability and heterogeneity of device group differences. Stratifications will include age (<55 vs ≥ 55 years), gender, body mass index (<30 vs ≥ 30 kg/m^2), femoral vs tibial primary lesion, and unipolar vs bipolar lesion polarity status.

Analyses will focus on determining if clinically significant group differences exist for variables that potentially have important associations with clinical outcomes.

Identification of such variables will be based on clinical significance and not statistical significance since the study was not powered to detect any specific magnitude of difference between randomized groups. Nonetheless, conventional p-values for baseline group differences will be provided for descriptive purposes only and as a visual aid in identifying covariates worthy of further consideration. Variables for which clinically significant group differences are observed that are also associated with outcomes will be utilized as covariates in supporting analyses design to characterize how relative efficacy may vary

across subgroups. Additionally, using data from the investigational device only, a failure risk analysis will be performed starting with the same set of baseline covariates with the possible addition of procedure and device specific variables.

14.11 Reporting Deviations from the Statistical Plan

Any deviations from the statistical plan will be noted in the final study report.

15.0 Quality Control & Quality Assurance

The study is conducted in accordance with the Declaration of Helsinki and the ISO 14155:2020.

The Investigator will be required to permit representative(s) of the Sponsor's monitoring team to inspect all Case Report Forms and corresponding sections of the study patients' office records and/or hospital original medical records. These audits will be done for quality assurance purposes, i.e. verifying adherence to the Clinical Investigation Plan and the completeness and accuracy of the data being entered on the Case Report Forms.

The Clinical Investigation Plan will be provided to all participating study centers. The Investigators will be fully trained in the proper reporting and submission of trial data prior to patient enrollment. Completed Case Report Forms will be reviewed before entering the data into a central database by the Sponsor.

The Clinical Study Manager is responsible for generating data queries for missing or unclear data if needed. It is the responsibility of the Clinical Study Manager to ensure data quality.

There are regular meetings between the Investigators and Zimmer Biomet Clinical Affairs staff. Written correspondence to all sites is used to inform the Investigators of routine study details and to update them on study status.

16.0 Suspension, Termination, and Closeout of the Clinical Investigation

16.1 Completion of the Clinical Investigation

The clinical investigation will be considered complete when the last visit of the last subject is complete.

16.2 Suspension or Premature Termination of the Clinical Trial

Should the trial be terminated prematurely or suspended for any reason, the Sponsor will inform the Clinical Study Sites of the termination or suspension and the reason(s) for the termination or suspension. Individual IRBs/REBs will be informed promptly and provided with reasoning for the termination or suspension by the Sponsor or by the Clinical Study Site, as specified by the applicable regulatory requirement(s).

Clinical Study Sites should promptly inform subjects of the suspension or termination and should assure appropriate follow-up for the subjects.

16.3 Suspension or Premature Termination of a Clinical Study Site

A Clinical Study Site may be suspended or prematurely terminated in the case of the following events:

- Enrollment expectations have not been met
- Protocol violations have occurred that may result in study subjects being put at risk or that render the study data unreliable or invalid
- Monitoring at the Clinical Study Site has shown noncompliance with the protocol
- Failure to comply with any applicable federal or provincial law, regulation or requirement or any failure to comply with a requirement of the applicable IRB/REB
- Per IRB/REB discretion
- By request of the Clinical Study Site or Zimmer Biomet

For any early termination of study participation at a Clinical Study Site, subject enrollment and follow-up will be discontinued.

For cases in which termination is due to protocol violations that may result in study subjects being put at risk or that may render the study data unreliable or invalid, the Clinical Study Site Investigator must cease enrolling subjects immediately and report the termination of the study (and reasons) to appropriate regulatory authorities.

17.0 Data Handling and Record Keeping

17.1 Data Collection

Data will be recorded using an electronic data capture (EDC) platform provided by Zimmer Biomet. Zimmer Biomet personnel will provide access, training and user support to all sites. Investigative sites will be required to have broadband internet access with standard firewall protection features.

Data are to be recorded utilizing subjects' source documentation, which includes medical records, operative and clinic notes, ancillary services reports, subject surveys and in some cases Case Report Forms. The subject-completed surveys are considered source documentation for this information. This may include electronically collected ePRO surveys where the direct data entry of survey data by the subject constitutes electronic source, paper surveys completed and submitted by the subject, or paper surveys completed on behalf of the subject by the site coordinator during phone interviews. Case Report Forms or certified copies of Case Report Forms may also serve as source documentation when the information is in addition to what is typically entered into a subject's medical record (e.g. fields documenting SCP time on the Surgical Documentation Form). Any Case Report Forms used as source documentation are to be labeled as such and made part of the subjects' case histories. Data are to be recorded accurately and in a timely manner following each event.

Questions regarding the content of the forms should be directed to the Zimmer Biomet Study Representatives.

17.2 Data Submission

eCRFs are submitted electronically following completion of each form. If there is missing or out-of-range information, the system will give immediate feedback to the individual making the entry and allow for correction and/or the assignment of a data query.

Submitted forms will undergo review by Zimmer Biomet personnel and questions or requests for corrections will be sent to the site via the EDC's electronic data query system. All corrections are to be made by the site coordinator within the EDC system as well as any needed corrections to paper CRFs following GCP guidelines. Zimmer Biomet personnel will review corrected information in the study database.

17.3 Data Locking

Once all eCRFs have been completed and are free of any automatic or manual queries, forms will be signed off by each site's Investigator and the data will be locked by the Data Manager. Only once all data has been locked will final analysis of the data begin.

18.0 Records and Reporting

18.1 Disclosure of Health Information

The use or disclosure of all protected health information will comply with the Health Insurance Portability and Accountability Act (HIPAA). Any information provided to Zimmer Biomet will be identified only by a subject ID and date of surgery. All information will be treated with strict adherence to professional standards of confidentiality and will be filed at Zimmer Biomet under adequate security and restricted accessibility by clinical personnel.

At the discretion of the Sponsor, a representative of Zimmer Biomet may visit a site to ensure proper conduct of the study in terms of collection and recording of data and maintaining records. Representatives of Zimmer Biomet should be allowed access to relevant study materials, including source documents of data collected as part of this study. Every precaution will be taken to protect the privacy of research subjects and the confidentiality of their personal information when using or disclosing protected health information (PHI), or when requesting PHI from others. Reasonable efforts will be made to limit the disclosures to the minimum necessary to accomplish the intended purpose of the use, disclosure, or request. Zimmer Biomet strictly complies with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Rules.

18.2 Maintenance of Records

The Investigator is to maintain a copy of all study records and source documentation, including signed Informed Consent Forms and HIPAA Authorization, for a minimum of 15 years following the latter of: (1) the date the Study is terminated or completed; or (2) the date such records are no longer required for purposes of supporting the completion of

the Protocol. This time period may be greater if required by reviewing IRB or institutional policies. Measures shall be taken to prevent accidental or premature destruction.

19.0 Materials and Supplies

19.1 Study Materials

Zimmer Biomet will provide each investigative site with an Investigator Notebook including the protocol, paper copies of case report forms and logs, study tools, and subject stipend cards (if applicable to site). The Zimmer Biomet Study Representatives are available to provide additional supplies upon request.

19.2 Subchondroplasty Products

The AccuFill bone substitute material and Subchondroplasty Instrumentation is to be ordered through a Zimmer Biomet Study Representative; these materials will be provided to the site as in-kind product as indicated in the site specific budget. Specific information on the products used will be recorded on study Case Report Forms as well as Study Product Accountability Logs, including part and lot numbers. Any unused product will be returned to the Sponsor.

20.0 Publication Policy

Both the Clinical Investigator and the Sponsor have the right to publish or allow the results of the clinical trial to be published. Further details regarding publication are described in the Clinical Trial Agreement with the investigational site.

21.0 Document History

Revision Number	Date	Description of Change	Person in Charge of Change
2.0	20 September 2017	Zimmer Knee Creations, Inc. has revised the July 11, 2016 Protocol with the following major modifications : the study title, protocol number, version number and date has been added to each page of the protocol following the cover page; Section 9.5.2 Subchondroplasty Procedure has been revised to include that the AccuFill product should only be mixed with saline; Section 9.5.2 Subchondroplasty Procedure, Arthroscopy Time has been removed as a measure to be collected; Section 10.1.1 Surgical Reoperation Documentation has been revised so that certain measures are no longer required to be collected; Section 10.2 Subjects Cross-over Between Treatment Groups has been revised so that all subjects, even those with a reoperation, will now be followed through the 2 year endpoint; Appendix B has been updated per Zimmer Knee Creations, Inc. marketing; Appendices C and D have been updated per Contract Research Organization, Medical Metrics, Inc.; additionally, formatting and page numbers have been updated.	Lynsey Boyle
3.0	24 May 2018	Zimmer Knee Creations, Inc. has revised the September 20, 2017 Protocol with the following major modifications : the study version number and date has been updated on each page of the protocol following the cover page; Section 3.0 Protocol Synopsis and Section 8.2 Exclusion Criteria has additional clarification language added to exclusion criteria 2a; Section 9.3 Preoperative Procedures has revised language surrounding the preoperative X-ray imaging and an added sentence on timing of preoperative injections; Section 10.2 Subject Cross-over	Lynsey Boyle

		Between Treatment Groups has been revised for clarification and to allow cross-over as early as 6 months post-treatment; Appendix B Recommended Surgical Technique Guide has been updated to the latest version of the surgical technique guide; Kellgren Lawrence Grade and Knee Alignment as assessed by the study investigator at each site have been added as fields to the Inclusion/Exclusion Criteria CRF.	
3.1	20 February 2019	Zimmer Biomet has revised the May 24, 2018, Version 3.0 Protocol with the following major modifications: • The study version number and date has been updated on each page of the protocol following the cover page; • Section 3.0 Protocol Synopsis has been modified where the number of sites has increased from 10-15 to up to 25 study sites.	Lynsey Boyle
4.0	23 July 2019	Zimmer Biomet has revised the February 20, 2019, Version 3.1 Protocol with the following major modifications: • The study version number and date has been updated on each page of the protocol following the cover page; • Zimmer Knee Creations, Inc. will now be referred to as Zimmer Biomet; • Section 3.0 Protocol Synopsis has been modified where a short title of PRESERVE—Knee Study has been added where PRESERVE stands for Prospective Randomized Evaluation of Subchondroplasty Effectiveness, Pain Relief, and Economic ValuE in the Knee; • Additional language has been added to clarify eligibility criteria in Section 3.0 Protocol Synopsis as well as Section 8.0 Subject Selection Criteria; • Per Sections 7.0 Study Design, 13.4	Lynsey Boyle

		Study Number Assignment and Table 1. Schedule of Events, informed consent may now be obtained up to 90 days prior to surgery; • Section 3.0 Protocol Synopsis, Section 7.0 Study Design, Section 9.7 Telephone Follow-up Interviews and Table 1. Schedule of Events now include a 9 month telephone follow-up interview where the KOOS Pain Scale will be collected; • A definition for REB—Research Ethics Board has been added to Section 4.0 Abbreviations and throughout the protocol for those sites who will be using a REB instead of an IRB. • Section 10.1 Protocol Waiver/Exception Requests has been added to include information regarding protocol waivers/exceptions; • Section 10.3 Subject Cross-over Between Groups has been revised; • Section 10.4 Independent Review of Worsening Cases and Potential Cross-over Treatment has been added to include information regarding a new independent review board for potential cross-over cases; • Section 10.5 Unblinded Subjects has been added to include information regarding unblinded subjects; • Section 11.0 Adverse Event Reporting has additional detail and language added regarding adverse events.	
5.0	23 October 2020	Zimmer Biomet has revised the July 23, 2019, Version 4.0 Protocol with the following major modifications: • The study version number and date has been updated on each page of the protocol following the cover page;	Lynsey Boyle

		• Section 1.0 General Information includes the following changes:
		  o The study title and protocol number has been added;
		  o Study sponsor contact information has been updated, as Patrick Reischling is no longer the appropriate contact;
		  o Contract Research Organization, IMARC Research, Inc. has been added;
		• Section 3.0 Protocol Synopsis includes the following changes:
		  o Sponsor contact information has been added;
		  o Manufacturer information has been added for both AccuFill BSM and SCP Surgical Instrumentation;
		  o Study device has been edited to include SCP Surgical Instrumentation;
		  o Clinical Phase, Post-Market Clinical Follow-Up, has been added;
		  o Materials and methods section has been added;
		  o Length of study section has been added;
		  o Study standards have been added;
		• Section 4.0 Abbreviations now includes the abbreviation for Adverse Device Effect, Electronic Data Capture, Electronic Patient Reported Outcomes, Post-Market Clinical Follow-Up and Serious Adverse Device Effect;
		• Section 3.0 Protocol Synopsis, Section 7.0 Study Design, Section 9.7 Follow-Up Visits at the Study Site, Section 9.7 Telephone Follow-	

		up Interviews and Table 1. Schedule of Events have been edited as post-operative, follow-up clinic evaluations requiring subjects to attend in person visits will no longer occur; all follow-up visits will now be conducted by telephone and will only include the KOOS and Numeric Pain Scale, with the exception of the 9 month visit, where only the KOOS Pain Scale will be collected; • Per Sections 3.0 Protocol Synopsis and 7.0 Study Design, study enrollment has been stopped due to interim data analysis results demonstrating that the study is unlikely to meet its primary endpoint; • Section 10.0 has been changed from Management of Intercurrent Events to Reporting and now includes details for activities required prior to the initiation of the study, clinical data collection/submission, Investigator reporting responsibilities, management of intercurrent events, and subject withdrawal and study re-entry; • Adverse Event Reporting in Section 11.0 has been updated as Safety Management—Medical Events/Adverse Events, where event classification and AE outcome definitions have been added; • Clinical Investigation Compliance information has been added in Section 13.0 to include a statement of compliance, protocol amendments and monitoring procedures; • Section 15.0 has been added to provide details for quality control and quality assurance;	

		• Suspension, termination and closeout of the Clinical Investigation has been detailed in the added Section 16.0; • Section 17.3 has been added to include information regarding data locking; • The publication policy, Section 20.0, has been edited as details regarding publication are described in the CTA with each individual investigational site.	

22.0 References

1. Eriksen, E.F. and J.D. Ringe, Bone marrow lesions: a universal bone response to injury? Rheumatol Int, 2012. 32(3): p. 575-84.

2. Felson, D.T., et al., The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med, 2001. 134(7): p. 541-9.

3. Hofmann, S., et al., Painful bone marrow edema of the knee: differential diagnosis and therapeutic concepts. Orthop Clin North Am, 2004. 35(3): p. 321-33, ix.

4. Sowers, M., et al., Associations of anatomical measures from MRI with radiographically defined knee osteoarthritis score, pain, and physical functioning. J Bone Joint Surg Am, 2011. 93(3): p. 241-51.

5. Eriksen, E.F., Treatment of bone marrow lesions (bone marrow edema). Bonekey Rep, 2015. 4: p. 755.

6. Sharkey, P.F., et al., Subchondral bone marrow lesions associated with knee osteoarthritis. Am J Orthop (Belle Mead NJ), 2012. 41(9): p. 413-7.

7. Colon, D.A., et al., Assessment of the injection behavior of commercially available bone BSMs for Subchondroplasty® procedures. The Knee, 2015. http://dx.doi.org/10.1016/j.knee.2015.06.017.

8. Cohen, S.B. and P.F. Sharkey, Subchondroplasty for Treating Bone Marrow Lesions. J Knee Surg, 2015.

9. Davis, A., et al., Short-Term Outcomes of the Subchondroplasty Procedure for the Treatment of Bone Marrow Edema Lesions in Patients with Knee Osteoarthritis, in The American Orthopaedic Society for Sports Medicine Annual Meeting 2015: Orlando, FL.

10. Thorlund, J.B., et al., Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. BMJ, 2015. 350: p. h2747.

11. Roos, E.M., et al., ICRS Recommendation Document: Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects. Cartilage, 2011. 2(2): p. 122-136.

23.0 Appendices

A. Package Insert
B. Recommended Surgical Technique Guide
C. Image Acquisition Protocol
D. Image Transfer Protocol
E. Recommended Rehabilitation Protocol