A Randomized Controlled Trial Evaluating Edema and ROM Using Negative Pressure Therapy Over Closed Incisions and Surrounding Soft Tissue Versus Standard Surgical Dressings in Bilateral Total Knee Arthroplasty: A Pilot Study (The ENABLE Trial)	
NCT Number	NCT04712019
Protocol Date	07 December 2020

A Randomized Controlled Trial Evaluating Edema and ROM Using Negative Pressure Therapy Over Closed Incisions and Surrounding Soft Tissue Versus Standard Surgical Dressings in Bilateral Total Knee Arthroplasty: A Pilot Study (The ENABLE Trial)

PROTOCOL NUMBER	KCI.PREVENA.RESTOR.ARTHRO.2019.01
SPONSOR	KCI Manufacturing Unlimited Company 25/28 North Wall Quay Dublin 1 Ireland
PROTOCOL VERSION/DATE	Version 2.0, 07 December 2020

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Study Synopsis	
TITLE:	**A Randomized Controlled Trial Evaluating Edema and ROM Using Negative Pressure Therapy Over Closed Incisions and Surrounding Soft Tissue Versus Standard Surgical Dressings in Bilateral Total Knee Arthroplasty: A Pilot Study (The ENABLE Trial)**
PROTOCOL NUMBER:	KCI.PREVENA.RESTOR.ARTHRO.2019.01
TYPE AND PHASE:	Post-market, prospective, randomized, controlled
STUDY PRODUCT(S):	PREVENA RESTOR™ Incision Management System with PREVENA RESTOR ARTHRO•FORM™ Dressing vs. Standard silver-containing dressing
STUDY OBJECTIVE(S):	The primary objective of this study is to compare the effects of the PREVENA RESTOR ARTHRO•FORM™ Incision Management System to standard silver-containing dressings on lower limb swelling after bilateral primary total knee arthroplasty.
STUDY DESIGN:	This is a randomized, controlled, prospective, global, multicenter study performed at approximately 10 sites.
PRIMARY ENDPOINT:	The primary endpoint is the percent change in lower limb volume, as calculated based on manual circumference measurements, 5-7 days after bilateral TKA when using the PREVENA RESTOR ARTHRO•FORM™ Incision Management System compared to the control.
SECONDARY ENDPOINTS:	The secondary endpoints are as follows: • Percent change in lower limb volume, as calculated based on manual circumference measurements, from baseline to visits 4, 5, and 6 • Percent change in circumferences from baseline to visits 3-6 that are measured at:

	○ 10 cm above the center of the patella ○ at the center of the patella ○ 10 cm below the center of the patella ○ at the ankle; 1 cm above the medial malleolus • Change in knee flexion angle from baseline to visits 3-6 • Change in knee extension angle from baseline to visits 3-6 • Change of total ROM degrees, defined as the flexion angle minus the extension angle, from baseline to visits 3-6 • The incidence of SSCs by visits 5 and 6 • Scar cosmesis assessment at visits 3-6 • The average pain in each leg in the last 24 hours, using an NPRS (numerical pain rating scale) of 0-10 (daily for 4 weeks post-surgery, then weekly for weeks 5-12) • The worst pain in each leg in the last 24 hours, using an NPRS of 0-10 (daily for 4 weeks post-surgery, then weekly for weeks 5-12).
SAFETY ENDPOINT:	The Safety Endpoint is the subject incidence of Adverse Events and Serious Adverse Events, including subsequent emergency department visits or subsequent hospitalizations/interventions for either knee.
NUMBER OF SUBJECTS PLANNED AND DURATION OF PARTICIPATION:	Approximately 52 subjects will participate in this study. The total duration of participation may include up to 42 days of screening, day of surgery, and up to 13 weeks post-surgery. Total duration of participation will be up to 134 days.
NUMBER OF STUDY SITES:	This will be a multicenter study conducted at approximately 10 study sites.
INCLUSION CRITERIA:	The subject: • is at least 22 years of age on the date of informed consent. • can independently provide informed consent.

	• requires and is scheduled to undergo a simultaneous, bilateral, primary TKA. • is willing and physically capable of undergoing a simultaneous, bilateral, primary TKA with or without replacement of the patella. • is willing and able to return for all scheduled study visits.
EXCLUSION CRITERIA:	The subject: • is pregnant or lactating. • has signs of an infection in the area of either knee or has signs of a systemic infection at the time of surgery. • is a chronic opioid user, defined per the CDC guidelines as opioid use for >3 months, at the time of enrollment. • has a current diagnosis of lymphedema in either leg. • has signs, symptoms, or a current diagnosis of venous insufficiency in either leg, as determined by the investigator's review of the subject's medical history. • has a history of clotting disorder or prior history of deep vein thrombosis • will undergo a unilateral TKA. • will undergo a staged, bilateral TKA. • has had previous knee replacement surgery. • has received a corticosteroid injection into either knee within 30 days of surgery. • undergoes a simultaneous, bilateral TKA with a planned different incision type on each knee (eg, midline incision vs. medial parapatellar incision). • has known sensitivity to the study product components (drape and/or dressing materials in direct contact with the closed incision or skin). • has known sensitivity to silver. • is enrolled in another interventional clinical study. • has skin cancer localized at or in proximity to the incision site.

	• does not have access to an electronic device (smartphone, iPad, or computer) on a daily basis to complete online assessments. • has condition(s) that, in the opinion of the investigator, cause the subject to be an overall health risk that is unsuitable for the surgery. • has condition(s) that, in the opinion of the investigator, will impact study endpoints (eg, hemophilia or autoimmune disorders) or the ability to comply with study procedures. Intra-op Criteria The subject: • does not receive a "total" knee replacement for first knee. For example, a partial or uni-compartmental knee replacement is performed • has a surgical incision that would preclude placement of either dressing onto the knee • has a TKA resulting in a muscle flap
STUDY EVALUATION/VISIT SCHEDULE:	The duration of study participation for each subject is as follows: • Screening Period: up to 42 days (Day -42 to Day 0) • Day of Surgery – Bilateral, primary TKA procedures • Treatment Period: 2 weeks (12-14 days, but no longer than 14 days), with dressing change and assessment at 1 week (5-7 days) • Follow-up: 6 weeks (± 1 week) and 12 weeks (± 1 week) after surgery The maximum participation duration per subject is up to 134 days.
SAMPLE SIZE AND STATISTICAL METHODOLOGY:	**Sample Size Determination** Pichonnaz et al measured the limb volume utilizing the truncated cone method.[1] The mean volume percentage difference from baseline to Day 8 post-surgery was 11.9%, with a standard deviation of 8.2% at Day 8. In 2016, Pichonnaz et al

	used the same method to evaluate the lower limb volume and the mean percentage difference from baseline to postoperative Day 7 was 15.3%, with a standard deviation of 6.5% at Day 7.[2] Assuming in our study the control group has a percent change of 13.6% in volume from baseline to post-surgery Day 5-7, while the PREVENA RESTOR group has a percent change of 8% in the same period, given the standard deviation is 9.2% in both groups, a total of ***52 subjects*** (assuming 15% dropout rate) are needed to achieve 80% power based on a two-sample t-test with a type I error rate of 0.05.
	
	Analysis Sets
	
	The following analysis sets will be used:
	
	• Intention-to-treat (ITT) Analysis Set – The ITT Set will consist of all randomized subjects. Subjects/Knees will be analyzed according to the treatment allocated at randomization for that particular knee (right or left)
	  ○ In the event each treatment is allocated to a knee different than that to which they were randomized, the subject/knee will be counted under the treatment received as long as the subject receives each treatment once (one treatment per knee).
	  ○ In the event subjects receive the same treatment in both knees, each knee will be counted once in each unique treatment group according to the treatment allocated as per the randomization and will not be counted twice under the same treatment group.
	• Per-Protocol (PP) Analysis Set – The PP Set will include all subjects and/or knees in the ITT Analysis Set with no disqualifying protocol deviation(s) that would impact the interpretation of the primary endpoint. The disqualifying protocol deviation(s) for exclusion from this set will be defined and documented prior to database lock.
	• Safety Analysis Set – The Safety Analysis Set will consist of all subjects and/or knees that received any study treatment-related procedures. Subjects/Knees will be analyzed according to the treatment received in each knee.
	
	Analysis Methods

	A general linear mixed model repeated measures analysis (MMRM) will be used to analyze the primary endpoint with covariates: site, study visit, treatment, knee side (left/right), baseline lower limb volume, baseline BMI category (<30 kg/m2, ≥ 30 kg/m2), and treatment by study visit.

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SIGNATURE PAGE

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PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT OF PROTOCOL

I confirm that I have read the protocol entitled: "A Randomized Controlled Trial Evaluating Edema and ROM Using Negative Pressure Therapy Over Closed Incisions and Surrounding Soft Tissue Versus Standard Surgical Dressings in Bilateral Total Knee Arthroplasty: A Pilot Study (The ENABLE Trial)" Version 2.0, dated 07 December 2020. I understand the protocol and agree to conduct the study according to the procedures therein in accordance with applicable local government regulations, institutional research policies and procedures, the International Council for Harmonisation principles of Good Clinical Practice, and in the spirit of the Declaration of Helsinki concerning medical research in humans.

Site Name:_____ **Site #:**_____

Principal Investigator Name: _____

Signature: _____ **Date:** _____

ABBREVIATIONS

3D	three-dimensional
ASLR	active straight leg raising
AUC	area under curve
AE	adverse event
BMI	Body Mass Index
CFR	Code of Federal Regulations
ciNPT	closed incision negative pressure therapy
cm	Centimeter
CRF	case report form
CSR	Clinical Study Report
eCRF	electronic case report form
EC	Ethics Committee
ED	emergency department
GCP	good clinical practice
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IDE	investigational device exemption
IFU	instructions for Use
IRB	Institutional Review Board
ITT	intention-to-treat
KCI	Kinetic Concepts Incorporated
KSKSS	Knee Society Knee Scoring System
ml	Milliliter
mmHg	millimeters of mercury
NPRS	numerical pain rating scale
PHI	personal health information
PRO	patient-reported outcome

QoL	quality of life
RCT	randomized, controlled trial
ROC	receiver operating characteristics
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SSC	surgical site complication
SSI	surgical site infection
UADE	unanticipated adverse device effect
USA	United States of America
TEAE	treatment-emergent adverse event
THA	total hip arthroplasty
TKA	total knee arthroplasty

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1. INTRODUCTION

Total knee arthroplasty (TKA), which is the third most common surgical procedure performed in the United States of America (USA),[3] is performed to provide pain relief, restore joint function, and provide joint stability and durability.[4] Enhanced recovery after TKA is focused on pain management and return to ambulation.[5] Therefore, primary postoperative goals for TKAs involve mitigating postoperative swelling (ie, increased limb volume resulting from fluid accumulation) and reestablishing adequate range of motion (ROM), including knee flexion and extension. Previous studies have shown that postoperative limb volume increases approximately 15% from the time of surgery to post-surgical Day 7 or 8.[1;2] ROM initially declines following TKA and then improves for a period before plateauing.[6;7] For example, one study showed that the postoperative knee flexion angles improved for up to 12 months, but flexion angle improvement slowed between six months and 12 months at 119 degrees (119°) and 123°, respectively.[6] Another study showed improvement in postoperative knee flexion angle plateauing after approximately three months at 112°.[7] This protocol is designed to assess whether postoperative surgical incision management modalities differentially affect lower limb swelling following TKA. The effects of postoperative surgical incision management modalities on knee ROM following TKA will also be evaluated.

1.1. Background

1.1.1. Overview of TKA

The standard incision type for TKA, also known as total knee replacement, is either a midline incision or a medial parapatellar incision. However, other incision types may be necessary for patients with at-risk incisions due to local causes (eg, previous incision present) or general causes (eg, prolonged corticosteroid use or diabetes mellitus).[8] The goal of these incisions is to provide adequate space for the replacement of a damaged knee joint with an artificial joint, or prosthesis.[4;9] The most common knee prosthesis is non-constrained, whereby the patient's ligaments and muscles stabilize the prosthesis; however, prostheses can also be semi-constrained (patient ligaments removed and

prosthesis provides some stability) or fully constrained, or "hinged".[9] During the procedure, the patella, if not replaced, may or may not be resurfaced, and ligamentous releases may be required for adequate balance.[4] Options for holding the knee replacement prosthesis in place include cementing the prosthesis to the bones with polymethylmethacrylate, non-cementing procedures that allow bone growth into the prosthesis, or hybrid fixation that combines cemented and non-cemented procedures.[4;9] After placing the prosthesis, allowing cement to dry (if applicable), and copious saline lavage to remove any debris, the wound is closed in layers, starting with the retinaculum, then the fat and subcutaneous tissue, and finally the skin.[4] Although wound closure of knees in flexion has recently been suggested to lead to favorable clinical outcomes, there is not currently enough evidence to determine whether any specific degree of flexion used during closure impacts ROM or other clinical outcomes.[10]

1.1.2. Postoperative Surgical Incision Management Following TKA

The focus of postoperative surgical incision management for TKAs and other surgical procedures has been to reduce surgical site complications (SSCs), including surgical site infections (SSIs) – SSIs have been reported as the third most common cause of non-revision reoperations in patients that had undergone a previous TKA, accounting for 12% of non-revision reoperation.[11] This focus stems from patients with post-TKA SSCs having a significantly increased probability of subsequent major surgeries and a significantly increased probability of deep infection when compared to patients without SSCs.[12] Two classes of postoperative surgical incision management modalities have recently been demonstrated to lower SSCs in patients undergoing TKAs when compared to standard surgical dressings: silver-containing dressings and closed incision negative pressure therapy (ciNPT).

1.1.2.1. Silver-containing dressings

Silver has been incorporated (eg, bound, coated, or impregnated) into various types of dressings, including but not limited to polyethylene mesh dressings, charcoal dressings, hydrofiber dressings, and hydrocolloid dressings.[13] These silver-containing dressings

have antibacterial effects by delivering silver ions to the wound or incision site, and the antimicrobial efficacy of the dressings can be influenced by the silver content and the dressing formation.[13] In a previous randomized, controlled trial (RCT) and a case-control study of joint arthroplasties, including TKAs, the use of silver-containing dressings resulted in significantly fewer SSCs and greater patient satisfaction when compared to dressings that did not contain silver.[14;15] Similarly, an RCT comparing silver-containing dressings to dressings without silver after closure of minimally invasive TKAs reported significantly longer wear times, lower number of dressing changes, higher patient comfort, and greater ease of use when using the silver-containing dressing.[16]

1.1.2.2. Closed incision negative pressure therapy

Incisional negative pressure therapy, which was introduced in 2006[17], involves the application of negative pressure wound therapy on clean, post-surgically closed incisions. Based on early results of incisional negative pressure therapy, a second-generation closed incision negative pressure therapy (ciNPT) system (PREVENA™ Incision Management System) was released in 2010 to enhance the postoperative rehabilitation process.[18;19] Since its initial release, a meta-analysis of RCTs assessing SSIs, including an RCT concerning total hip arthroplasties (THAs) and TKAs, revealed a highly significant effect in favor of ciNPT when compared to traditional dressings such as sterile gauze, absorbent dressings, or silver-containing dressings.[20] Similarly, a meta-analysis of comparative studies assessing SSIs in lower extremity surgeries, including THAs and TKAs, showed a highly significant effect in favor of ciNPT when compared to traditional dressings.[20] A retrospective, comparative study reported that arthroplasty patients (THA or TKA) treated with ciNPT had significantly fewer SSCs when compared to patients treated with silver-containing dressings after closure; however, the incidence of SSCs in low-risk patients (a risk factor score < 2) did not significantly differ between those treated with ciNPT or silver-containing dressings.[21]

Two studies, including a small RCT[22], have compared the effectiveness of ciNPT with conventional dry dressings in preventing SSCs after TKAs, and neither study found a statistically significant difference between treatments with respect to the incidence of

SSCs.[22;23] However, in the RCT, patient-reported Quality of Life (QoL) scores for wound leakage and wound protection were significantly better for patients treated with ciNPT compared to those treated with conventional dry dressings.[22]

In 2019, the PREVENA RESTOR™ Incision Management System, which incorporates all the key design elements of PREVENA™ Therapy (ie, utilizes a negative pressure therapy unit, with fluid collection canister, that delivers -125 mmHg and a dressing composed of open reticulated foam and wicking skin interface layer), was released. This system contains uniquely shaped dressings that are designed for various incision types (linear, non-linear, intersecting and/or multiple incisions) and various anatomical locations, such as articulating joints. The PREVENA RESTOR™ Dressings cover a larger area of the soft tissue surrounding the surgical site.

1.2. Rationale for Studying the Specific Population/Condition

Ample leg strength and ROM of the knee joint, along with sufficient ROM of the hip and ankle joints, enable normal ambulation and other daily living activities (eg, getting into and out of bathtubs and tying shoelaces), with more strength and higher degrees of ROM being necessary for more advanced movements (eg, crouching with or without rotation).[24] Previous studies have shown that changes in knee extension strength and knee flexion ROM are significantly correlated with patient ambulation (eg, changes in gait speed) after TKA, and knee swelling post-TKA has been significantly correlated with reduced knee extension strength.[25] Swelling of the lower limb can also be an indicator of more serious health issues such as deep vein thrombosis or joint effusion/haemarthrosis, which are conditions that would potentially require hospital readmittance[26], and lastly, swelling of the lower limb lasting beyond 1 week and difficulty with daily living activities have been significantly correlated with patient dissatisfaction after TKAs.[27]

A major goal for healthcare practitioners following TKA is to mitigate swelling and restore knee ROM and leg strength. Postoperative outcomes after TKA can be positively impacted by peri-operative interventions, and there is a growing interest in the use of modern wound dressings as part of enhanced recovery.[28;29] Although ciNPT manages

the environment of closed surgical incisions, in part, by reducing edema, there have been limited studies assessing the effects of ciNPT on postoperative swelling or other postoperative outcomes (eg, knee ROM) that impact enhanced recovery goals after TKA.

1.3. Rationale for Study Design

To have the highest possible level of evidence, a prospective, multi-center RCT was the study design chosen. Silver-containing dressings were selected as the comparator since they are routinely used for the management of closed incisions after TKA, and there are several studies concerning the effectiveness of silver-containing dressings for the prevention of SSCs after TKAs (see **Section 1.1.2.1**). A simultaneous, bilateral procedure was also chosen for the study design, which reduces the number of patients needed for the study and reduces the intraindividual variability. This type of procedure also exposes the subjects to less anesthesia and has fewer days hospitalized, although there are some risks reported of certain cardiopulmonary complications (eg, cardiac arrhythmia or pulmonary embolism) when compared to unilateral TKAs.[30] The proposed study is designed to evaluate differences in lower limb swelling, as measured volumetrically, in subjects undergoing simultaneous, bilateral TKA when ciNPT is used to manage the closed incision and surrounding soft tissue, as compared to silver-containing dressings. It is hypothesized that ciNPT will mitigate post-surgical lower limb swelling after TKA surgery. The follow-up period of 6-12 weeks, with an assessment of lower limb swelling as early as 5-7 days after surgery, was selected due to published studies showing that lower limb swelling occurs within 2-8 days after TKA surgery[1] and that knee ROM improves after TKA but can begin plateauing at 3 months in some cases (see **Section 1**).[6;7]

1.4. Study Products

The following devices and dressings will be the therapies for the two treatment groups:

- PREVENA RESTOR ARTHRO•FORM™ System (**Table 1**), including:

- The PREVENA PLUS™ 125 Therapy Unit – 14 Day, which delivers continuous negative pressure at -125 mmHg through the dressing to the incision site for up to 14 days.
- The PREVENA PLUS™ 150mL Canister, where exudate from the incision is collected and stored.
- The PREVENA™ Patch Strips, which may be used to help seal leaks around the dressing.
- Any PREVENA ARTHRO•FORM™ Dressing

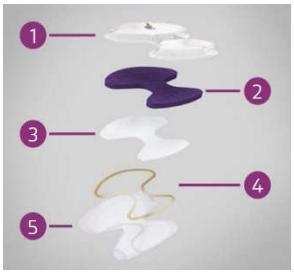
- Any silver-containing dressing

1.4.1. PREVENA RESTOR ARTHRO•FORM™ System

The PREVENA RESTOR ARTHRO•FORM™ System, which incorporates all the functional elements of ciNPT, contains uniquely shaped dressings that are designed to facilitate anatomical adaptability better and to expand the ciNPT coverage area to help manage the incision over a larger soft tissue envelope. The dressings contain the following components (**Table 1**):

- a polyurethane film shell that encapsulates the foam bolster and interface layer
- a polyurethane ether foam bolster that covers the interface layer
- a polyester fabric interface layer that wicks fluid from the skin surface
- a hydrocolloid that outlines the perimeter of the interface layer to help secure the dressing to the skin and minimize leaks
- a polyurethane film with acrylic adhesive, which provides adhesion of the dressing to the skin surrounding the closed incision

Table 1: PREVENA RESTOR ARTHRO•FORM™ Incision Management System.

Name/Description	Picture/Diagram
PREVENA RESTOR ARTHRO•FORM™ System • PREVENA PLUS™ 125 Therapy Unit -14 Day • PREVENA RESTOR ARTHRO•FORM™ Dressing	
PREVENA PLUS™ 150ml Canister	
PREVENA RESTOR ARTHRO•FORM™ Dressing Components 1. Polyurethane film shell 2. Polyurethane ether foam 3. Polyester fabric interface layer 4. Hydrocolloid 5. Polyurethane film with acrylic adhesive	

1.4.2. Regulatory Status – United States

The PREVENA RESTOR™ Incision Management System is a 510(k)–cleared, Class II device (K181507) with the following indication for use.

> *The PREVENA RESTOR™ Incision Management System is intended to manage the environment of surgical incisions that continue to drain following sutured or stapled closure by maintaining a closed environment and removing exudate via the application of negative pressure wound therapy.*

For those knees of subjects in this study that are randomized into the Treatment arm, the PREVENA RESTOR ARTHRO•FORM™ Incision Management System will be applied using the PREVENA PLUS™ 125 Therapy Unit (14-day) and a PREVENA RESTOR ARTHRO•FORM™ Dressing.

For this study, the PREVENA RESTOR™ Incision Management System will be used in accordance with its cleared labeling and indications for use and is, therefore, exempt from the investigational device exemptions (IDE) regulation because it meets the conditions for an exempt investigation as provided in 21 CFR 812.2 (c) (2). The system's indications, contraindications, warnings, precautions, and instructions can be found in the PREVENA RESTOR™ Incision Management System Instructions for Use (IFU) document.

1.4.3. Regulatory Status – Australia

The PREVENA RESTOR™ Incision Management System is a Class IIa device licensed under ARTG318254 with the following indication for use.

> *The PREVENA RESTOR™ Incision Management System is intended to manage the environment of closed surgical incisions and surrounding intact skin in patients at risk for developing post-operative complications, such as infection, by maintaining a closed environment via the application of a negative pressure wound therapy system to the incision. The PREVENA RESTOR™ Incision Dressing skin interface layer with silver reduces microbial colonization in the fabric.*

For those knees of subjects in this study that are randomized into the Treatment arm, the PREVENA RESTOR ARTHRO•FORM™ Incision Management System will be applied using the PREVENA PLUS™ 125 Therapy Unit (14-day) and a PREVENA RESTOR ARTHRO•FORM™ Dressing.

For this study, the PREVENA RESTOR™ Incision Management System will be used in accordance with its cleared labeling and indications for use. The system's indications, contraindications, warnings, precautions, and instructions can be found in the PREVENA RESTOR™ Incision Management System Instructions for Use (IFU) document.

2. STUDY OBJECTIVES

The primary objective of this study is to compare the effects of the PREVENA RESTOR ARTHRO•FORM™ Incision Management System to standard silver-containing dressings on lower limb swelling after bilateral primary total knee arthroplasty.

3. STUDY DESIGN

3.1. Design Summary

This randomized, controlled, prospective, global, multicenter study will enroll subjects undergoing simultaneous, bilateral, primary TKA. The study will enroll approximately 52 subjects (104 randomized knees) from approximately 10 sites. Each enrolled subject will receive ciNPT after surgery for one knee, and the other knee will receive a standard silver-containing post-surgical dressing.

The knee randomized to the ciNPT treatment arm will receive a PREVENA RESTOR ARTHRO•FORM™ Dressing in conjunction with the PREVENA PLUS™ 125 Therapy Unit for a duration of 12 to 14 days post-surgery, with a change of the PREVENA RESTOR ARTHRO•FORM™ Dressing at 5-7 days.

The knee randomized to the SOC treatment arm will receive a standard silver-containing dressing for 12-14 days with a dressing change and assessment at 5-7 days. Silver-containing dressings should be changed per the product IFU or as deemed necessary by the investigator or investigator-designated attending physician during the 12-14 day treatment period.

Subjects will be seen during Screening (no more than 42 days before TKA), on the day of surgery, one week after surgery (a minimum of 5 days to a maximum of 7 days), at 2 weeks after surgery (a minimum of 12 days to a maximum of 14 days post-surgery), at a 6-week follow-up visit (day 35 to 49), and at a 12-week follow-up visit (day 77 to 91). Subjects may participate in additional unscheduled visits as required during the study if

evaluation of either knee is required. Unscheduled visits may be initiated by either the investigator or the subject.

3.1.1. PREVENA RESTOR ARTHRO•FORM™ Dressing

Closed incision NPT will be applied to the clean, closed surgical wound immediately following closure and randomization. The dressing will be applied on Day 0 and changed on post-surgical Day 5-7. Closed incision NPT will be discontinued, and the dressing will be removed by Day 14.

3.1.2. Standard silver-containing dressing

Standard silver-containing dressings will be applied to the clean, closed surgical wound immediately following closure and randomization. The dressing will be applied on Day 0 and changed on Day 7 or as deemed necessary by the investigator (or investigator designee). If subsequent dressings are applied, the final dressing must be removed by Day 14.

3.1.3. Duration of Study Participation

The duration of study participation for each subject is as follows:

- Screening Period: up to 42 days (Day -42 to Day 0)
- Day of Surgery - Bilateral TKA procedures
- Treatment Period: 2 weeks (12-14 days, but no longer than 14 days), with dressing change and assessment at 1 week (5-7 days)
- Follow-up: 6 weeks (± 1 week) and 12 weeks (± 1 week) after bilateral TKA

The maximum participation duration per subject is up to 134 days.

3.2. Primary Endpoint

The primary endpoint is the percent change in lower limb volume, as calculated based on manual circumference measurements, 5-7 days after bilateral TKA when using the PREVENA RESTOR ARTHRO•FORM™ Incision Management System compared to the control.

3.3. Secondary Endpoints

The secondary endpoints are as follows:

- Percent change in lower limb volume, as calculated based on manual circumference measurements, from baseline to visits 4, 5, and 6
- Percent change in circumferences from baseline to visits 3-6 that are measured at:
    - 10 cm above the center of the patella
    - at the center of the patella
    - 10 cm below the center of the patella
    - at the ankle; 1 cm above the medial malleolus
- Change in knee flexion angle from baseline to visits 3-6
- Change in knee extension angle from baseline to visits 3-6
- Change of total ROM degrees, defined as the flexion angle minus the extension angle, from baseline to visits 3-6
- The incidence of SSCs by visits 5 and 6
- Scar cosmesis assessment at visits 3-6
- The average pain in each leg in the last 24 hours, using an NPRS (numerical pain rating scale) of 0-10 (daily for 4 weeks post-surgery, then weekly for weeks 5-12)
- The worst pain in each leg in the last 24 hours, using an NPRS of 0-10 (daily for 4 weeks post-surgery, then weekly for weeks 5-12).

3.4. Exploratory Endpoints

The exploratory endpoints are as follows:

- the percent change in lower limb volume, as calculated based on three-dimensional (3D) imaging, from baseline to visits 3-6

- Knee-related QoL questionnaire (new Knee Society Knee Scoring System) at visits 4, 5, and 6
- Ability to perform a straight leg raise at visits 4, 5, and 6

Additional exploratory endpoints may be added and will be detailed in the statistical analysis plan (SAP).

3.5. Health Economic Endpoints

The health economic endpoints are as follows:

- Total length of hospitalization
- Subsequent emergency department (ED) visits related to either knee and reason (eg, edema or pain)
- Subsequent hospitalization related to either knee and reason (eg, edema or pain)
- Subsequent clinic visits (unscheduled) related to either knee and reason (eg, edema or pain).

Additional health economic endpoints may be added and will be detailed in the statistical analysis plan (SAP).

3.6. Safety Endpoint

The Safety Endpoint is the incidence of Adverse Events and Serious Adverse Events, including subsequent emergency department visits or subsequent hospitalizations/interventions for either knee.

4. STUDY PROCEDURES AND ASSESSMENTS

4.1. Informed Consent

The investigator, or designee, will discuss the purpose of this study with potential subjects. Each individual will review the Informed Consent Form (ICF) approved by the local Institutional Review Board (IRB) or Ethics Committee (EC). The ICF must be signed

according to IRB/EC requirements before the subject can undergo any study-related procedures. Informed consent will be obtained under these conditions:

- Subjects must be made aware of the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected in language that is understandable to the subject.
- Subjects must be given the opportunity to ask the investigator questions and must be provided time to consider participation in the study.
- ICFs will be written in a manner that is non-technical and understandable to the subject.
- Subjects will not be led to believe that they are waiving their legal rights to release the investigator, sponsor, study site, or any of their agents from liability for negligence.
- Subjects will be asked to sign and date the ICF indicating their informed consent to participate in the study.
- The investigator's responsibilities during the ICF process include:
    - screening out potential subjects who may not be able or willing to comply with the study protocol.
    - discussing with potential subjects to ensure they understand the purpose of the study, the study procedures that will be required, and the risks and benefits known or that can be reasonably predicted or expected.
    - answering all questions from potential subjects.
    - ensuring that subjects have signed the ICF before undergoing any study-related assessments.
    - confirming that the study-site representative performing the informed consent process has signed the informed consent form, if required.
    - ensuring that each subject receives a copy of the signed ICF.

4.2. Inclusion/Exclusion

In order to be considered for randomization, a subject must meet all eligibility criteria and be assessed no more than 42 days before surgery. Subjects who do not meet all eligibility criteria will not be eligible for randomization, will discontinue from the study, and will be considered a screen failure. Inclusion and exclusion criteria will be reconfirmed immediately prior to surgery if visit 1 and visit 2 are on different dates.

4.2.1. Inclusion Criteria

The subject:

- is at least 22 years of age on the date of informed consent.
- can independently provide informed consent.
- requires and is scheduled to undergo a simultaneous, bilateral, primary TKA.
- is willing and physically capable of undergoing a simultaneous, bilateral, primary TKA with or without replacement of the patella.
- is willing and able to return for all scheduled study visits.

4.2.2. Exclusion Criteria

The subject:

- is pregnant or lactating.
- has signs of an infection in the area of either knee or has signs of a systemic infection at the time of surgery.
- is a chronic opioid user, defined per the CDC guidelines as opioid use for >3 months, at the time of enrollment.
- has a current diagnosis of lymphedema in either leg
- has signs, symptoms, or a current diagnosis of venous insufficiency in either leg, as determined by the investigator's review of the subject's medical history.
- has a history of clotting disorder or prior history of deep vein thrombosis

- will undergo a unilateral TKA
- will undergo a staged, bilateral TKA
- has received a corticosteroid injection into either knee within 30 days of surgery
- undergoes a simultaneous, bilateral TKA with a planned different incision type on each knee (eg, midline incision vs. medial parapatellar incision).
- has known sensitivity to the study product components (drape and/or dressing materials in direct contact with the closed incision or skin).
- has known sensitivity to silver.
- is enrolled in another interventional clinical study.
- has skin cancer localized at or in proximity to the incision site.
- does not have access to an electronic device (smartphone, iPad, or computer) on a daily basis to complete online assessments.
- has condition(s) that, in the opinion of the investigator, cause the subject to be an overall health risk that is unsuitable for the surgery.
- has condition(s) that, in the opinion of the investigator, will impact study endpoints (eg, hemophilia or autoimmune disorders) or the ability to comply with study procedures.

4.2.3. Intra-Operative Exclusion Criteria

Randomization occurs immediately after completion of the first total knee arthroplasty surgery. Prior to randomization, the following criteria should be assessed to determine if randomization should occur or the subject becomes a screen failure.

The subject:

- does not receive a “total” knee replacement for first knee. For example, a partial or uni-compartmental knee replacement is performed

- has a surgical incision that would preclude placement of either dressing onto the knee
- has a TKA resulting in a muscle flap

4.3. Premature Study Termination

If the study is terminated prematurely or suspended, study subjects and the IRB/EC will be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator. If applicable, regulatory authorities and the personal physicians of the subjects will also be informed.

4.3.1. By Sponsor

The sponsor reserves the right to discontinue the clinical study for business or ethical reasons at any time, such as, but not limited to:

- Information regarding the study product causes doubt as to the benefit/risk ratio.
- Changes in medical practice limit utility of the data obtained from the study.

The sponsor reserves the right to terminate a study at a site at any time, including but not limited to any of the following reasons:

- Investigator(s) lack of compliance with the approved study protocol, lack of oversight, and/or not following applicable regulatory or IRB/EC guidelines in conducting the study
- Incidence or severity of AEs indicates a potential health hazard or poses an unreasonable risk to the study participants
- Subject enrollment is unsatisfactory
- Fraud or misconduct

4.3.2. By IRB/EC

The IRB/EC may choose to discontinue the study at the site for which they granted approval. If the IRB/EC discontinues the study, the investigator will report a withdrawal of IRB/EC approval to the study sponsor within five (5) working days.

4.4. Subject Withdrawal or Termination

4.4.1. Reasons for Withdrawal or Termination

Subjects may withdraw from participation in the study at any time upon request.

The investigator may choose to terminate the participation of a subject from the study with or without their consent for any of the following reasons:

- Adverse events
- Noncompliance
- For any reason that may, in the opinion of the investigator, negatively affect the safety or well-being of the subject

Subjects with the following surgical outcomes will be withdrawn from the study.

- Subject does not undergo a bilateral TKA procedure
- Subject does not receive a “total” knee replacement for each knee. For example, a partial or uni-compartmental knee replacement is performed on one or both sides
- Subject has a surgical incision that precludes placement of either dressing onto the appropriately randomized knee
- Subject has a TKA resulting in a muscle flap

An investigator must terminate participation of a subject from the study for any of the reasons indicated in section 4.17.

4.4.2. Handling of Withdrawal or Termination

Every effort should be made to complete assessments required for the primary endpoint and safety endpoints prior to the subject withdrawal.

For subjects who are lost to follow-up, the investigator will make attempts to collect at least the vital status (eg, whether the subject is alive) before formally withdrawing the subject from the study. Prior to considering a subject lost to follow-up, at least two documented attempts should be made to contact the subject through all available routes, and a certified letter should be sent to the permanent address on file.

Once the subject withdraws from the study, both knees will be considered withdrawn. A subject may not withdraw only one knee from the study. No further study evaluations will be performed, and no additional data will be collected. The investigator may retain and continue to use any data collected before withdrawal. The subject will not be replaced.

If for any reason the subject is withdrawn by the investigator from this study, the investigator will inform the subject and the sponsor.

4.5. Demographics and Subject Characteristics

The following demographic data and subject characteristics will be collected and documented after the subject signs the ICF:

- Age
- Sex
- Race / Ethnicity
- Vital signs (height/weight)
- Comorbidities

4.6. Medical and Surgical History

The research staff will collect medical and surgical history for each subject. If the screening visit and surgery occur on different days, the medical and surgical history will be updated (if changes have occurred) at the surgical visit.

4.7. Laboratory Assessment for Pregnancy

Serum or urine assessment for human chorionic gonadotropin (hCG) to determine pregnancy status in female subjects of child-bearing potential will be conducted. This

assessment will need to be captured on the day of surgery. If the pregnancy test is positive, the subject will not be eligible for the study and will be considered a screen failure. Women who have had documented surgical sterilization by a medically accepted method (eg, tubal ligation, hysterectomy, or oophorectomy) or are post-menopausal, defined as not having menstruation for > 12 months, will be excluded from this laboratory assessment.

4.8. Randomization and Subject Numbering

Consented subjects will be assigned a unique subject identifier. Study data will be reported according to this unique subject identifier.

Subjects who satisfy all inclusion criteria and none of the exclusion criteria will be eligible for randomization, which will occur upon closure of the first knee in the bilateral procedure. Randomization of each knee to the treatment arm or the control arm will be centralized, electronic, and web-based.

If a screened subject does not meet all inclusion criteria or meets any exclusion criteria, the subject will be considered a screen failure.

4.9. Lower Limb Volume

Lower limb volume for each leg will be calculated using two different methods. The first will be the Partial Frustum Model method[31], using measurements of circumference taken above and below the patella. The circumferences of each limb will be measured at the center of the patella, every 5 cm from the center of the patella to 15 cm superior to the patella (ie, 3 measurements), every 5 cm from the center of the patella to 20-30 cm inferior to the patella (ie, no less than 4 but no more than 6 measurements). Additionally, the circumference 1 cm above the superior edge of the medial malleolus will also be measured for each leg; however, the measurement taken 1 cm above the malleolus should not overlap with the most inferior measurement taken below the patella. There will be a total of nine (9) to 11 measurements per leg. The volume of each leg segment (between two measures of circumference) will then be calculated using a formula for a

truncated cone, and the sum of all segments will then be calculated to determine lower limb volume.

The second method for calculating lower limb volume will utilize a mobile 3D imaging system (LymphaTech) that combines an infrared depth sensor with a tablet computer using proprietary software. 3D imaging will be performed by the investigator or investigator designee according to the User Guide documentation that accompanies the tablet computer that is provided to the investigators. Briefly, the subject will stand with their feet shoulder-width apart on a flat surface with an approximately 1 meter radius of free space on all sides. The investigator will then scan both legs by slowly walking around the subject while keeping the camera pointed at the subject and moving the camera up and down to capture a 3D rendering (ie, image) of the entirety of both legs. During the scan, the subject should remain as still as possible, and the lower limbs should be free of any materials that will distort the image (eg, clothing covering the area). Once the 3D rendering is obtained and inspected for quality, lower limb volume will be calculated using scan measurements from the mid-thigh to the ankle of each leg, excluding the gluteal fold region of each leg, the heel/ankle region of each leg, and the feet.

4.10. Knee Range of Motion

ROM is the full movement of the joint, measured as an increased or decreased angle (ie, degrees) between the bones of the limb at the joint. ROM for the knee includes flexion (bending) and extension (straightening). A completely straight knee will have a joint measure of 0º while a fully bent knee (without crouching) will have about 135º of flexion. For this study, the flexion and extension angles of each knee will be captured using a goniometer with the subject lying flat, in the supine position. ROM will be calculated as the difference between the flexion angle and the extension angle. Both active ROM, whereby the subject flexes and extends the joint without assistance, and passive ROM, whereby the investigator or investigator designee flexes and extends the joint, will be captured.

4.11. Patient Reported Outcomes (PRO) Assessment: Knee Society Knee Scoring System (KSKSS)

The KSKSS is a validated system that combines an objective physician-derived component with a subjective patient-derived component to evaluate pain relief, functional abilities, satisfaction and fulfillment of expectations. The score prioritizes the patient perspective to better track patient expectations, satisfaction, and activity levels. Two variations of the form exist: a preoperative evaluation completed prior to surgery and a postoperative evaluation administrated after surgery.[32]

Aside from a section on demographics, the questionnaire is divided into 4 scoring sections:

1. Objective components consisting of:
    - Alignment
    - Instability
    - Joint Motion
    - Symptoms
2. Patient expectations
3. Patient satisfaction
4. Functional components consisting of:
    - Walking and Standing
    - Standard Activities
    - Advanced Activities
    - Discretionary Activities

In this study, each knee will be independently scored using the KSKSS.

4.12. Pain Assessments

Pain will be captured daily for the first 4 weeks post-surgery and then weekly for weeks 5-12. In addition, a baseline pain assessment associated with each knee will be captured at screening and recorded by the investigator or investigator designee. After surgery, the pain associated with each leg will be electronically recorded using an ePRO system as part of the EDC. Subjects will receive reminders (eg, phone calls, e-mails, or ePRO system reminders) to log-in by computer or use an app to complete their pain assessments.

For all pain assessments, subjects will evaluate their average pain and their worst pain associated with each leg for the previous 24hr period using the numerical pain rating scale (NPRS), which ranges from 0 (no pain) to 10 (extremely painful).

4.13. Surgical Procedures and Assessments

4.13.1. Bilateral TKA Procedure

The surgical procedure will be performed in accordance with the investigator's standard practice; however, the incision type for each knee should be the same. For the method of closure, types such as sutures, staples, steri-strips, and skin glue are allowed; however, skin closure using any type of plastic closure device (eg, Zipline sutures) is restricted. The following information regarding the TKA procedure will be documented:

- Order of knee surgery (right vs. left)
- Administration of tranexamic acid preoperatively or intraoperatively
- Surgical approach
- Method of Closure (each knee)
- Length of incision
- Anesthesia start and stop time

4.13.2. Application of Dressings

4.13.2.1. ciNPT

For the knee randomized to receive ciNPT, a PREVENA RESTOR ARTHRO•FORM™ Dressing will be applied over the closed incision immediately after incision closure and cleansing of the application site. Any surgical drains must be routed under the skin beyond the dressing boundary and function independently from the ciNPT. The dressings should not be lifted or prematurely removed after application for reasons other than those related to the device, such as a malfunction or leak alarm. If the dressing is lifted for any reason, a new dressing must be applied; do not re-adhere the same dressing. For the delivery of negative pressure, a PREVENA PLUS™ 125 Therapy Unit will be attached to the dressing tubing, and ciNPT will be initiated in the operating room. If the dressing leaks and a seal cannot be maintained, replacement of the PREVENA RESTOR ARTHRO•FORM™ Dressing is acceptable and will be documented. In the event that the therapy unit malfunctions at any time during treatment, a replacement unit may be used. The dressing will be applied on Day 0 and changed on post-surgical Day 5-7. When removing the dressing, it should always be removed parallel/in-line with the incision and never across the incision line. After changing the dressing, ciNPT will be reapplied for the remainder of the treatment period until 12-14 days of treatment are completed. Treatment removal is addressed in Section 4.14.1.

4.13.2.2. Standard silver-containing dressings

For the knee randomized to the control arm, a silver-containing dressing will be applied over the closed incision immediately after incision closure and cleansing of the application site. Silver-containing dressings will be applied following the product IFU, and the dressing may be replaced as needed throughout the treatment period according to the IFU. At a minimum, the dressing will be removed and changed at the Day 5-7 visit. After re-application of the silver containing dressing at the Day 5-7 visit, treatment will continue until 12-14 days of treatment are completed. Treatment removal is addressed in Section 4.14.2.

4.14. Treatment Removal

4.14.1. PREVENA RESTOR ARTHRO•FORM™ Dressing

All subjects should receive ciNPT on the appropriately randomized knee for a duration of 12-14 days post-surgery. Closed incision negative pressure therapy (ciNPT) will be discontinued no later than 14 days after surgery, and the PREVENA RESTOR ARTHRO•FORM™ Dressing will be removed. The PREVENA RESTOR ARTHRO•FORM™ Dressing should be removed parallel/in-line with the incision and never across the incision line. If a subsequent dressing is required, a gauze dressing may be used.

4.14.2. Standard silver-containing dressing

All subjects should receive a standard silver-containing dressing on the appropriately randomized knee for a duration of 12-14 days post-surgery. If a subsequent dressing is required, a gauze dressing may be used.

4.15. Post-Operative Assessments

It is recommended that all post-operative assessments occur during the afternoon (local time), if possible, to control for time-of-day effects on the primary and secondary endpoints. The time of day for each postoperative visit will be recorded. In addition, it is recommended that subjects do not undergo physical therapy activities on the day of follow-up visits before completing assessments in order to achieve more accurate measures of swelling, range of motion, and straight-leg-raise tests. If PT is to occur on the same day of a follow-up visit, it is recommended that it occurs after the visit.

4.15.1. Surgical Site Complications

The investigator will examine both legs and both incisions of the subject for any evidence of surgical site complications. SSCs will be assessed in the following categories, and interventions to resolve the SSC will be captured:

- Superficial or Deep Incisional Surgical Site Infection (SSI)
- Full thickness skin dehiscence

- Seroma or hematoma requiring drainage or surgery
- Skin necrosis
- Continued drainage determined by an Investigator's visual inspection of the incision after completion of the study treatment period and removal of the study treatment dressing.
- Other complication that requires intervention
    - Investigator will define type of complication

4.15.2. Scar Cosmesis Assessment

The assessments of scar quality in this study will be performed by the investigator or investigator-designated physician for each knee using the Manchester Scar Scale.[33] This visual analog scale includes clinical assessment of the scar color, contour, texture, and distortion.

4.15.3. Straight Leg Raises

Assessments of active straight leg raising (ASLR), which is used to evaluate pain provocation and the ability to load the quadriceps muscle after TKA, will be performed independently for each leg in this study. While lying flat in a supine position on a firm surface (eg, an exam table), subjects will be asked to raise their leg 20 cm off of the flat surface without any assistance. The ability to perform the straight leg raise will be scored for each leg using a six-point scale previously described by Mens et al: 0 = not difficult at all; 1 = minimally difficult; 2 = somewhat difficult; 3 = fairly difficult; 4 = very difficult; 5 = unable to do.[34]

4.15.4. Health Economics Assessment

Information related to additional hospital admissions, procedures, emergency room visits and/or follow-up care after the subject's TKA during the study period will be documented at all post-surgery visits, including unscheduled visits. Data to be collected will include:

- Hospital admissions related to either knee since previous study visit (the knee that caused the admission will be documented)
    - If admitted, length of the hospital stay
    - Procedures performed on either knee
    - Medications used to treat the cause of admission (ie, the knee)
- Emergency Department (ED) visits related to either knee since previous visit (specify which knee necessitated ED visit)
    - Procedures performed related to either knee
    - Medications used to treat the cause of admission (ie, the knee)

4.16. Concomitant Medications

Concomitant medications will be collected from the time of treatment application through the end of the study. The medication name, start date, end date, and indication will be reported.

Medications required to be reported include:

- Medications required to treat pre-existing health conditions that are active during the study period
- Diuretics
- Anticoagulants (eg, tranexamic acid, acetylsalicylic acid, anti-thrombotic agents, etc)
- Steroids
- Medications used to treat adverse events
- All medications that are used as prophylactic agent(s)

4.17. Prohibited Procedures and Treatments

Skin closure using any type of plastic closure device (eg, Zipline sutures) is restricted in this study. In addition, re-application of ciNPT using a PREVENA ARTHRO•FORM™

Dressing or any other PREVENA™ Dressing is **prohibited** after the treatment period. For the control arm, silver-containing dressings should be removed no later than 14 after surgery, and re-application of any silver-containing dressing past post-operative Day 14 is **prohibited**.

Subjects who undergo a subsequent surgery involving the initial TKA within the 12 weeks must withdraw from the study prior to the subsequent procedure.

Subjects who are in need of a TKA revision on either knee within the 12 weeks of the original study procedure must withdraw from the study prior to the subsequent procedure.

Cross-over therapy is not permitted during the study. Subjects receiving cross-over therapy after completing the original study treatment on either knee (ie, therapy from the arm in which each knee was not initially treated) must withdraw from the study. The reason for withdrawal will be documented.

4.18. End of Study

Subjects may withdraw or be discontinued from this study at any time (**Section 4.4.1**). The investigator may discontinue a subject's study participation if the investigator feels it is in the best interest of the subject.

The following information will be documented at the End of Study:

- Last day of study participation
- Completion status – Did the subject complete the study (Yes/No)?
- Reason for study discontinuation

5. VISIT SCHEDULE AND DESCRIPTION OF STUDY VISITS

5.1. Schedule of Visits

Procedure Description	Visit 1 Screening	Visit 2 Day of Surgery			Visit 3 Mid-Treatment Follow-up	Visit 4 End of Treatment	Visit 5 Midterm Follow-up	Visit 6 Long Term Follow-up	Unscheduled
		Pre-Op	Intra-Op	Post-Op					
Visit Windows	**Day -42 to 0**	**Day 0**	**Day 0**	**Day 1**	**Day 5-7**	**Day 12-14**	**Day 35-49**	**Day 77-91**	
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X[1]							
Demographics and Subject Characteristics	X	X[1]							
Medical and Surgical History	X	X[1]							
Knee Society Knee Score	X				X	X	X	X	X
Lower Limb Volume – Circumference measurements (manual and 3D)		X			X	X	X	X	X
Range of Motion		X			X	X	X	X	X
Pain Assessment		X		X[4]					X
Laboratory Assessment for Pregnancy		X[2]							
Bilateral TKA Procedure			X						
Intra-op exclusion criteria			X						
Randomization			X[3]						

ENABLE TRIAL

Procedure Description	Visit 1 Screening	Visit 2 Day of Surgery			Visit 3 Mid-Treatment Follow-up	Visit 4 End of Treatment	Visit 5 Midterm Follow-up	Visit 6 Long Term Follow-up	Unscheduled
		Pre-Op	Intra-Op	Post-Op					
Visit Windows	**Day -42 to 0**	**Day 0**	**Day 0**	**Day 1**	**Day 5-7**	**Day 12-14**	**Day 35-49**	**Day 77-91**	
Application of Treatment			X						
Concomitant Medication			X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X
Removal of Study Treatment					X[5]	X			
Scar cosmesis assessment					X	X	X	X	X
Straight Leg raises					X	X	X	X	X
Health Economic Assessments					X	X	X	X	X
SSC Assessments					X	X	X	X	X
End of Study								X	X[6]

[1] If visit 1 and visit 2 occur on different days, assessments will be reviewed and updated if changes have occurred.

[2] For women of child-bearing potential

[3] Upon surgical closure of 1st TKA but before initiating 2nd TKA on the contralateral knee.

[4] Daily post-op pain collection will start the day following bilateral TKA by ePRO.

[5] Dressings will be removed, and a new dressing placed after assessments completed.

[6] If the subject is withdrawn early.

5.2. Description of Study Visits

5.2.1. Screening/ Days -42 to 0

The following procedures and assessments will be performed and documented in the subject's medical records/source notes:

- Informed consent
- Inclusion and exclusion criteria
- Demographics and subject characteristics
- Medical and surgical history
- KSKSS (for each knee)

5.2.2. Day of Surgery/Pre-op/Day 0

The following procedures and assessments will be performed and documented:

- Inclusion and exclusion criteria confirmation immediately prior to randomization
- Demographics and subject characteristics update, if the Screening visit and surgery occur on different days
- Medical and surgical history update, if the Screening visit and surgery occur on different days
- Laboratory assessment for pregnancy
- Lower limb volume (for each leg), before surgery
- Range of Motion (for each knee), before surgery
- Pain assessment

5.2.3. Day of Surgery/Intra-op/Day 0

- Bilateral TKA
- Intraoperative exclusion criteria

- Randomization
- Application of treatment
- Concomitant medications
- AE assessment and serious adverse event (SAE) reporting after randomization

5.2.4. Day of Surgery/Post-op/Day 1

- ePro access granted post-op Day 1 for pain assessments
- Concomitant medications
- AE assessment and serious adverse event (SAE)

5.2.5. Mid-Treatment / Days 5-7

The following procedures and assessments will be performed and documented:

- Dressing change/removal of the dressing
- Lower limb volume (for each knee) by measuring lower limb circumferences
- KSKSS (for each knee)
- Range of Motion (for each knee)
- Scar cosmesis assessment (for each knee)
- Straight leg raises (for each leg)
- SSC assessment (for each knee)
- Concomitant Medications
- AE assessment and SAE reporting
- Health Economics assessments

5.2.6. End of Treatment / Days 12-14

The following procedures and assessments will be performed and documented:

- Removal of Dressing
- Lower limb volume (for each knee) by measuring lower limb circumferences
- KSKSS (for each knee)
- Range of Motion (for each knee)
- Scar cosmesis assessment (for each knee)
- Straight leg raises (for each leg)
- SSC assessment (for each knee)
- Concomitant Medications
- AE assessment and SAE reporting
- Health Economics assessments

5.2.7. Follow-up Visits - Midterm/ Days 35-49 and Long Term/ Days 77-91

The following procedures and assessments will be performed and documented:

- Lower limb volume (for each knee) by measuring lower limb circumferences
- KSKSS (for each knee)
- Range of Motion (for each knee)
- Scar cosmesis assessment (for each knee)
- Straight leg raises (for each leg)
- SSC assessment (for each knee)
- Concomitant Medications
- AE assessment and SAE reporting
- Health Economics assessments
- End of Study, after long term follow-up

5.2.8. Unscheduled Visits

Outside of scheduled study visits, if the subject needs to be assessed by the investigator for any reason related to either knee, the following procedures and assessments will be performed and documented in the subject's medical records/source notes:

- Lower limb volume (for each knee) by measuring lower limb circumferences
- KSKSS (for each knee)
- Range of Motion (for each knee)
- Scar cosmesis assessment (for each knee)
- Straight leg raises (for each leg)
- SSC assessment (for each knee)
- Pain assessment
- Concomitant medications
- AE assessment and SAE reporting
- Health Economics
- End of study, if a subject is withdrawn early

6. RISKS ASSOCIATED WITH STUDY PARTICIPATION

Participation in the clinical investigation presents low risks to subjects. Some risks are generalized and are listed below:

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue	• Epidermal (skin) stripping • Contusion (bruising) • Maceration • Minor soft tissue damage • Local cutaneous reaction (i.e., redness, rash, significant pruritis, urticaria) • Minor bleeding • Pain
Other	• Bleeding complications (associated with the surgical procedure, concomitant therapy, and co-morbidities) • Localized infection • Exposure related infection • First-degree burn (if the device gets warm) • Minor desiccation (due to dressing leak) • Moderate soft tissue damage (i.e., due to trip hazard, tubing entanglement) • Deterioration of the wound (due to lack of visibility of incision site through dressing) • Physical discomfort

7. SAFETY AND ADVERSE EVENTS

7.1. Definitions

7.1.1. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including clinically significant abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

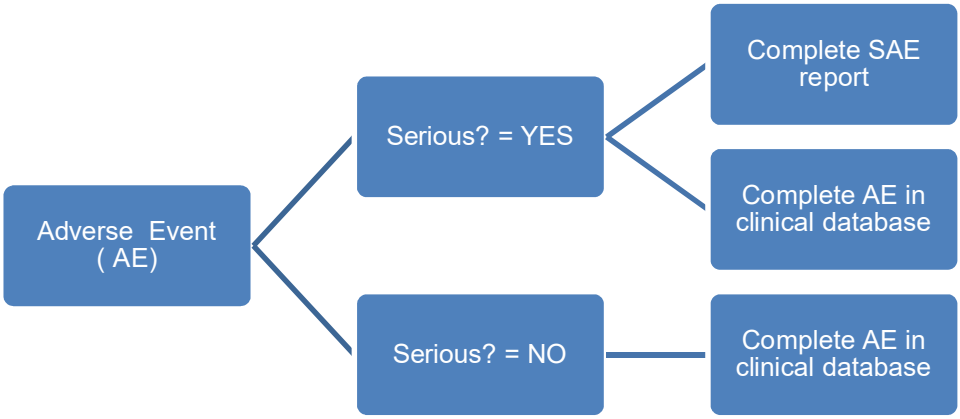
7.1.2. Serious Adverse Event (SAE)

An AE is considered serious if it results in any of the following outcomes:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage
- Other important medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

7.2. Classification



7.2.1. Relationship to Study Treatment

The investigator will assess the relationship of the AE as:

- **Related** to the study product: any AE for which there is a reasonable possibility that the study product caused the AE. The sponsor will review all SAEs for expectedness.
- **Not Related** to the study product: when it is determined that there is no relationship between the AE and the use of the study product.

7.2.2. Severity

The investigator will assign severity as:

- **Mild** – asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- **Moderate** – minimal, local, or non-invasive intervention indicated
- **Severe** – medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling

7.3. AE Reporting Procedures

The investigator is responsible for monitoring the safety of all subjects enrolled in the study and reporting AEs as described in this protocol.

7.4. AE Collection/Reporting Period

The AE collection/reporting period will begin after the subject has been randomized. Investigators should assess for AEs at each visit. In addition, study subjects should be instructed to report any AE that they experience to the investigator.

All AEs, regardless of perceived relationship to study product, will be reported and documented in a timely manner. In addition, the worsening of a medical condition previously reported in the medical history should also be recorded as an AE.

The AE description will include the nature of the experience (AE term), the start date, the end date, the severity of each sign or symptom, the seriousness of the event or experience, relationship to study treatment, the course of action taken, and the outcome of the experience. It will be indicated if the AE caused the subject to be discontinued from the study.

7.5. SAE Reporting to Sponsor

The SAE collection/reporting period will begin after the subject has been randomized. SAEs will be reported via the sponsor's SAE Report Form. This form should be completed by the investigator, or designee, and submitted (fax or email) to the sponsor within 24 hours of the investigator becoming aware of the event. The sponsor's SAE e-mail inbox is available for SAE reporting 24 hours per day and is monitored during normal business hours.

7.6. UADE Reporting - Unanticipated Adverse Device Effect (UADE)

A UADE is any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated

serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The sponsor will immediately conduct an evaluation of the received SAEs to determine whether the event meets the UADE definition. If the event is determined to be a UADE, sponsor will report the results of the evaluation to all regulatory agencies overseeing the project and to participating investigators.

If the sponsor determines that the event presents an unreasonable risk to the study subjects, the sponsor will terminate all clinical studies or parts of studies presenting risk as soon as possible.

7.7. Follow-up Period for Ongoing AEs

Treatment-related AEs (serious and non-serious) that are ongoing at the final study visit will be followed up to 30 days to assess resolution or stabilization. All unrelated AEs will be considered closed at the time the subject completes participation in the study.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Sets

The following analysis sets will be used:

- Intention-to-treat (ITT) Analysis Set – The ITT Set will consist of all randomized subjects. Subjects/Knees will be analyzed according to the treatment allocated at randomization for that particular knee (right or left)
    - In the event each treatment is allocated to a knee different than what they were randomized to, the subject/knee will be counted under the treatment received as long as the subjects receives each treatment once (one treatment per knee).
    - In the event subjects receive the same treatment in both knees, each knee will be counted once in each unique treatment group according to the

treatment allocated as per the randomization and will not be counted twice under the same treatment group.

- Per-Protocol (PP) Analysis Set – The PP Set will include all subjects and/or knees in the ITT Analysis Set with no disqualifying protocol deviation(s) that would impact the interpretation of the primary endpoint. The disqualifying protocol deviation(s) for exclusion from this set will be defined and documented prior to the final database lock.
- Safety Analysis Set – The Safety Analysis Set will consist of all subjects and/or knees that received any on study treatment-related procedures. Subjects/Knees will be analyzed according to the treatment received in each knee.

8.2. Planned Analysis and Data Summaries

8.2.1. General Analysis Techniques

In general, summaries of endpoints will consist of descriptive statistics. Data will be summarized by treatment group, overall and/or by visit, if applicable. Due to each subject serving as their own control and receiving both treatments (one treatment per knee), the same subjects will be counted once within each treatment group according to the treatment received and/or randomized in for each knee. Subjects who only have one knee treated will only be counted in the treatment group that the knee received. Data processing, tabulation of descriptive statistics, and any graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, details will be included in the clinical study report (CSR).

Summaries of continuous variables will display the number of subjects and/or knees with available data (n), the mean, median, standard deviation, minimum, and maximum values at each time point. For categorical variables, the number and percentage of subjects and/or knees that are in each category will be provided. The denominator for percentages will be all relevant subjects and/or knees in a particular analysis, including those for whom data are not reported or missing.

Formal statistical testing will be conducted utilizing two-sided tests at a significance level of 0.05. Corresponding 95% confidence intervals (CIs) will be presented for appropriate endpoints.

Additional analyses to characterize the safety and/or efficacy may be conducted. These additional analyses will be included in the Statistical Analysis Plan. Any ad hoc summaries/analyses conducted after database lock will be included in the CSR and labeled as *ad hoc*.

8.2.2. Subject Disposition

Summaries of disposition will be tabulated by treatment group and overall. At a minimum, the following summaries containing the number of subjects and percentage of subjects will be included for subjects:

- Included each analysis set
- Provided informed consent
- Randomized and treated
- Discontinued early from the study for any reason, along with the reason for discontinuation (if the reason is an AE, the system organ class and preferred term)
- Completed the study as planned

Subject disposition also will be described in a flowchart (CONSORT diagram).

8.2.3. Demographic and Baseline Characteristics

Demographic characteristics (eg, age, sex, race, and ethnicity), baseline characteristics, and other disease characteristics may be summarized by treatment arm and overall.

8.2.4. Analysis of Primary Endpoint

The primary endpoint is the percent change in lower limb volume, as calculated based on manual circumference measurements, 5-7 days after total knee arthroplasty (TKA) when using the PREVENA RESTOR ARTHRO•FORM™ Incision Management System

compared to the control. The lower limb volume is calculated using the Frustum formula[35;36]:

$$Volume = \sum \pi\left({x_{(i+1)}}^2 + {x_i}^2 + x_i \cdot x_{(i+1)}\right)\left(\frac{h}{3}\right)$$

where x_i and x_{i+1} are the circumferences of two consecutive sections along the limb, and h is the length of the interval between the two measurements on the limb. The lower limb volume is determined by calculating the sum of the volumes of all sections. The percent change of the lower limb volume is defined as the difference of lower limb volume from baseline (pre-op) to postoperative Day 5-7, divided by the baseline measurement of lower limb volume, multiplied by 100.

A general linear mixed model repeated measures analysis (MMRM) will be used to analyze the primary endpoint with covariates: site, study visit, treatment, knee side (left/right), baseline lower limb volume, baseline BMI category (<30 kg/m^2, ≥ 30 kg/m^2), and treatment by study visit. Knee side will serve as a repeated-measure factor to account for the correlations between left knee and right knee on the same subject, and the subject variable will also be specified to identify those observations that are to be correlated. Raw means, LS Means, including 95% confidence intervals, will be presented by treatment group. The ITT analysis set will be used for the primary analysis.

8.2.4.1. Sensitivity Analyses of Primary endpoint

- The primary analysis will be repeated on the Per-Protocol analysis set.
- The primary analysis will be repeated on the ITT analysis set to explore the following covariate: treatment, site, visit, baseline lower limb volume, surgical approach, and length of incisions.
- Additional sensitivity analyses may be conducted to explore other characteristics that may impact the lower limb volume. All analyses will be outlined in the Statistical Analysis Plan.

8.2.5. Analysis of Secondary Endpoints

All secondary endpoints will be summarized by treatment group on the ITT population. Raw means and changes from baseline will be displayed by treatment group, as appropriate.

The following continuous endpoints:

- Percent change in lower limb volume, as calculated based on manual circumference measurements, from baseline to visits 4, 5, and 6
- Percent change in circumferences from baseline to visits 3-6 that are measured at:
    - 10 cm above the center of the patella
    - at the center of the patella
    - 10 cm below the center of the patella
    - at the ankle; 1 cm above the medial malleolus
- Change of knee flexion angle from baseline to visits 3-6
- Change of knee extension angle from baseline to visits 3-6

Change of total ROM degrees, defined as the flexion angle minus the extension angle, from baseline to visits 3-6 will be analyzed using a mixed model repeated measures analysis (MMRM) with the same covariates outlined in the primary analysis. General linear mixed models and/or paired t-tests at each week may also be performed.

The average pain and worst pain in each leg in the last 24 hours using an NPRS (numerical pain rating scale) of 0-10 (daily for 4 weeks post-surgery, then weekly for weeks 5-12) will be analyzed in the following two ways:

- An AUC, or area under the receiver operating characteristics (ROC) curve, will be calculated for daily pain scores for each knee using a general linear mixed model with site, treatment, and knee side (left/right) included in the model as

covariates while adjusting for correlations from the within-subject comparisons over time. A model with an AUC of at least 0.70 will be considered adequate.[37]

- Weekly pain scores (average pain scores for each week (weeks 1-4) and reported weekly pain scores (weeks 5-12) will be analyzed using an MMRM with site, week, treatment, knee side (left/right), and treatment by week included in the model as covariates while adjusting for correlations from the within-subject comparisons over time. The covariance structure will be selected based on the lowest Akaike Information Criterion value. Raw means, LS Means, including 95% confidence intervals, will be presented by treatment group.

A Chi-square, McNemar's, or Fisher's test as appropriate will be used to analyze the following endpoints:

- The incidence of SSCs by visits 5 and 6
- Scar cosmesis assessment at visits 3-6

Additional details will be specified in the Statistical Analysis Plan.

8.2.6. Exploratory Analyses

The exploratory endpoints are as follows:

- the percent change in lower limb volume, as calculated based on three-dimensional (3D) imaging, from baseline to visits 3-6
- Knee-related QoL questionnaire (new Knee Society Knee Scoring System) at visits 4, 5, and 6
- Ability to perform a straight leg raise at visits 4, 5, and 6

Any additional exploratory endpoints and all exploratory endpoint analyses will be outlined in the SAP. Because the analyses are exploratory, no adjustment will be made for multiple comparisons.

8.2.7. Analysis of Safety Endpoint

All safety results will be presented based on the Safety Analysis Set. All TEAEs will be summarized by treatment arm. Subject incidence of TEAEs will be summarized by treatment arm and by MedDRA (Version 23 or higher) system organ class and preferred term. For each coded medical term, the proportion of subjects who experience at least one treatment-emergent:

- adverse event(s);
- adverse event(s) related to treatment
- serious adverse event(s);
- serious adverse event(s) related to treatment
- adverse event(s) by severity (mild, moderate, severe);
- adverse event(s) leading to treatment/study discontinuation, or
- serious adverse event(s) leading to treatment/study discontinuation will be reported.

A listing of death(s), subjects who died of any cause during the study, will be presented.

8.3. Additional Statistical Details

8.3.1. Sample Size Determination

Pichonnaz et al measured the limb volume utilizing the truncated cone method. The mean volume percentage difference from baseline to Day 8 post-surgery was 11.9%, with a standard deviation of 8.2% at Day 8.[1] In 2016, Pichonnaz et al used the same method to evaluate the lower limb volume and the mean percentage difference from baseline to postoperative Day 7 was 15.3%, with a standard deviation of 6.5% at Day 7.[2] Assuming in our study the control group has a percent change of 13.6% in volume from baseline to post-surgery Day 6-8, while the PREVENA RESTOR group holds a percent change of 8% in the same period, given the standard deviation is 9.2% in both groups, a total of ***52***

subjects (assuming 15% dropout rate) are needed to achieve 80% power based on a two-sample t-test with a type I error rate of 0.05.

8.3.2. Randomization

All subjects who meet all inclusion criteria and no exclusion criteria will be randomized in a 1:1 ratio to receive the PREVENA RESTOR ARTHRO•FORM™ Incision Management System or the control in either right or left knee. Each subject will receive both treatments (one treatment per knee). A randomization schedule, including randomization numbers and treatment assignments, will be generated and maintained centrally in the web-based clinical database management system. Once randomized, a subject's assignment cannot be altered or changed; a subject should not be randomized twice. The randomization schedule will be kept blind to any person who is involved in the daily operations of the study. It will only be accessible to the study biostatisticians who generate and review the schedule, and the vendor's team members (if an EDC vendor is utilized) who are involved in reviewing the schedule and uploading the schedule.

8.4. Open-Label Study Reporting Results

All precautions will be taken to avoid introducing any form of bias during the conduct of the study. While the study is ongoing, summary statistics by treatment arms across all sites may be limited to a small group not involved in the daily operations of the study. Treatment arms may be masked in the summary reports or outputs (tables, listings, and figures) if needed. Summary statistics during the conduct of the study will not be shared with investigators and clinical sites. Upon study completion, the full results will be shared with all investigators and clinical sites.

8.5. Interim Analysis

No interim analysis is planned for this study.

8.6. Statistical Analysis Plan and Changes in Analyses

A Statistical Analysis Plan (SAP) containing full details of the statistical analyses and execution will be prepared for this study. The SAP (SAP) will be finalized prior to locking

the study database and the final analysis. Any changes from the planned analyses in this protocol or SAP will be noted in the Clinical Study Report (CSR).

9. HANDLING OF STUDY PRODUCTS

Study product receipt, use, dispensation, destruction, and return records will be maintained throughout the study.

Upon receipt of product, the investigator or designee will inventory the shipment and immediately notify the sponsor if the study product or other study supplies are missing. The monitor will verify that study product documentation is maintained appropriately during monitoring visits.

At the completion of the study, there will be a final reconciliation of study product shipped, used, and unused. Any unused study product and associated supplies will be returned to the sponsor.

10. DATA HANDLING AND RECORD KEEPING

10.1. Investigator/Study Site Training

The investigator and site staff will be trained on the protocol, the study products, and any specialized procedures prior to enrolling subjects into the study. The sponsor will provide support to site staff for any questions or concerns related to study products and procedures. The sponsor will not have any influence on subject medical care.

10.2. Electronic Case Report Form (eCRF) and Source Documents

Source documents include all information in original records, certified copies of original records, observations, or other activities necessary for the reconstruction and evaluation of the study. All source documents should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of the data.

Data from source documents of each subject will be entered into the subject's electronic case report form (eCRF). Guidance for eCRF completion will be provided and reviewed with the site staff prior to receiving study product.

10.3. Monitoring of Study Data

The data will be entered into the clinical study database by Investigative site staff and verified for accuracy by a sponsor representative. The investigator will allow access to their clinical study records for periodic on-site monitoring visits by a designated sponsor representative, with the understanding that the representative is bound by professional secrecy and will not disclose a subject's identity or personal medical information. The representative will review eCRFs for completeness during on-site monitoring visits, and after the eCRFs are submitted; any discrepancies will be resolved with the investigator or designee, as appropriate.

10.4. Data Handling

The sponsor is responsible for compilation and verification of the clinical study data, retention of the clinical study database, performance of statistical analysis, and preparation of the CSR.

10.5. Records Retention

The study site will maintain all study documentation and institute measures to prevent the accidental or premature destruction of any data and/or documents related to the study.

After formal discontinuation or completion of the study, the investigator will retain all clinical study documentation for a minimum of two (2) years from the date the investigation is terminated or completed or in accordance with the regulations in effect for the jurisdiction where the site is located. The investigator will contact the sponsor prior to the destruction of any study records.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Good Clinical Practice (GCP)

This study is to be conducted according to applicable national regulations where the study is being conducted, international standards of good clinical practice (GCP) such as the International Council for Harmonisation guidelines, and institutional research policies and procedures.

11.2. Ethical Considerations

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. Approving IRB/ECs will be provided all relevant study documentation to safeguard the rights, safety, and well-being of subjects as mandated. Participating investigators will obtain IRB/EC approval of the study prior to initiation at their sites. The protocol, IFUs, informed consent, written information given to subjects, safety updates, and any revisions to these documents will be provided to the IRB/EC by the investigator.

11.3. Subject Informed Consent

Written informed consent will be obtained from a potential subject after the study has been fully explained and prior to the conduct of any study-related procedures. Obtaining informed consent is a process that must be documented in compliance with GCP, IRB/EC, and other applicable regulatory requirements. The investigator is responsible for continuing an open conversation with the subject about their continued participation in the study. The sponsor will conduct periodic monitoring to ensure informed consent is obtained for each subject prior to any study procedures.

11.4. Confidentiality

Information collected about subjects during the study will be kept confidential and managed according to the requirements of the IRB/EC, Health Insurance Portability and Accountability Act of 1996 (HIPAA), and any additional requirements as required by the country/regulatory agency where the study is taking place.

In the event that a subject revokes an authorization to collect or use Personal Health Information (PHI), the investigator retains the ability to use all information collected prior to the revocation of subject authorization.

11.5. Clinical Trial Registration

A description of this study will be available on http://www.ClinicalTrials.gov and any other designated public study registry as required by applicable local and federal regulations. The description of the study that is made available will not include information that identifies subjects. At most, the website will include a summary of the results of the study and will be available for public review at any time. If required, the study may also be listed on additional clinical trial websites as required by the country/regulatory agency.

11.6. Auditing and Inspecting

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

The investigator will permit study-related monitoring, audits, and inspections of all study-related documents (eg, source documents, regulatory documents, data collection instruments, study data) by the IRB/EC, sponsor or its designee, and government regulatory bodies.

12. PUBLICATION PLAN

The publication policy for this study will be addressed in a separate agreement.

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