Protocol

Post-market, Randomized, Open-Label, Multicenter, Study to Evaluate the Effectiveness of Closed Incision Negative Pressure Therapy versus Standard of Care Dressings in Reducing Surgical Site Complications in Subjects with Revision of a Failed Total Knee Arthroplasty (PROMISES)

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PROTOCOL NUMBER	KCI.PREVENA.2017.01
SPONSOR	KCI USA, Inc. 6203 Farinon Drive San Antonio, Texas 78249 Fax: 210.255.6760
STUDY PRODUCTS	ActiV.A.C.® Therapy Unit **or** Prevena Plus™ 125 Therapy Unit **in combination with** Prevena™ Incision Dressing
ORIGINAL PROTOCOL VERSION/DATE	Version 3.0, 6-Oct-18

TITLE:	Post-market, Randomized, Open-Label, Multicenter, Study to Evaluate the Effectiveness of Closed Incision Negative Pressure Therapy versus Standard of Care Dressings in Reducing Surgical Site Complications in Subjects with Revision of a Failed Total Knee Arthroplasty (PROMISES)
PROTOCOL NUMBER:	KCI.PREVENA.2017.01
TYPE AND PHASE:	Post-market, prospective, randomized, open-label
STUDY PRODUCT(S):	ActiV.A.C.® Therapy Unit **or** Prevena Plus™ 125 Therapy Unit **and** Prevena™ Dressing
STUDY OBJECTIVE(S):	The goal of this study is to evaluate surgical site complications (SSCs) in subjects undergoing a revision of a failed total knee arthroplasty (TKA) when closed incision negative pressure therapy (ciNPT) is used to manage the closed incision, as compared to standard of care dressing.
STUDY DESIGN:	This is a post-market, prospective, randomized, open-label, multicenter, controlled study. Subjects randomized to the ciNPT treatment arm will have a Prevena™ Dressing placed over the sutured incision immediately after surgery. Negative pressure therapy will be delivered by the ActiV.A.C.® or Prevena Plus™ 125 Therapy Units up to the maximum optimal use condition specified in the Instructions for Use (IFU) document of the selected Prevena™ Dressing but no shorter than five days post-surgery. Subjects randomized to the standard of care treatment arm will receive Aquacel® Ag Surgical incision dressing, or another equivalent silver-impregnated dressing, up to the maximum number of days specified in the IFU but no shorter than five days post-surgery, not inclusive of other negative pressure wound therapy devices or dressings for the duration of the study. Subjects will be regularly evaluated for SSCs through 90 days after the TKA revision.
PRIMARY ENDPOINT:	The primary endpoint is the subject incidence of Investigator-assessed surgical site complications within 90 days of TKA revision.

SECONDARY ENDPOINTS:	The two secondary endpoints for this study are the 90-day subject incidence of Investigator-assessed surgical site infection (superficial or deep) and the 90-day subject incidence of Investigator-assessed deep surgical site infection.
SAFETY ENDPOINT:	The safety endpoint is the subject incidence of adverse events.
NUMBER OF SUBJECTS PLANNED and DURATION OF PARTICIPATION:	The study will randomize approximately 440 subjects from approximately 15 sites in a 1:1 ratio to receive either ciNPT or standard of care after a revision TKA. The duration of study participation for each subject is as follows: o Screening: 30 days prior to and including day of TKA revision (Day 0) o TKA revision o Treatment Period: According to the IFU document included with the selected dressing but no shorter than five days post-surgery. o Post Operation and Follow-up: through 90 days after TKA revision The maximum participation duration per subject is 134 days.
NUMBER OF STUDY SITES:	It is anticipated that approximately 15 study sites in North America will participate and each site will randomize and treat subjects in both treatment groups.
INCLUSION CRITERIA:	The subject must meet all the following inclusion criteria: o is at least 22 years of age on the date of informed consent o is able to provide their own informed consent o requires a TKA revision defined as one of the following: ▪ a one-stage aseptic revision procedure

	▪ a one-stage septic exchange procedure (requiring removal of all hardware) for acute postoperative infection ▪ removal of cement spacer and re-implantation procedure ▪ open reduction and internal fixation of peri-prosthetic fractures o has one or more of the following: ▪ a body mass index (BMI) greater than 35 kg/m^2 ▪ a requirement for the use of blood thinners other than acetylsalicylic acid (ASA) after surgery ▪ history of or current peripheral vascular disease ▪ the presence of lymphedema in the operative limb ▪ insulin-dependent diabetes mellitus ▪ current tobacco use or previous history of smoking and quitting within the past 30 days ▪ a history of prior infection of the operative site ▪ current use of immunomodulators or steroids ▪ current or history of cancer or hematological malignancy (excluding localized skin cancer) ▪ rheumatoid arthritis ▪ current renal failure or dialysis ▪ malnutrition as determined by the investigator ▪ liver disease as determined by the investigator ▪ status post solid organ transplant ▪ HIV

	○ is willing and able to return for all scheduled study visits ○ if female and of child-bearing potential, has a negative urine or serum pregnancy test at screening and day of revision surgery ○ has undergone a TKA revision resulting in a closed surgical incision
EXCLUSION CRITERIA:	The subject must not meet any of the following criteria: ○ is pregnant or lactating ○ will undergo a bilateral TKA within the same operative visit ○ will undergo a bilateral TKA in which the first TKA surgery is on the knee selected for study ○ will undergo a staged bilateral TKA in which the TKA revision surgery for the knee under study occurs within 30 days of the first TKA procedure ○ was previously randomized in this protocol ○ has a systemic active infection at the time of revision not including chronic viral infections such as HIV or hepatitis ○ has a remote-site skin infection at the time of revision ○ was tattooed on the area of the incision within 30 days prior to randomization ○ 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 currently enrolled in another investigational trial that requires additional interventions ○ is planned to be enrolled in another investigational trial that requires additional interventions at any time during the study

	○ has localized skin cancer around the incision site ○ has a surgical incision that precludes placement of dressing ○ has a TKA revision resulting in a muscle flap ○ has a TKA revision resulting in the placement of a spacer ○ has an incision drainage and debridement procedure only ○ has a surgical incision closed with skin glue
STUDY EVALUATION/ VISIT SCHEDULE:	Subjects will be seen during Screening (no more than 30 days before TKA revision), at the TKA revision, at the weekly study treatment visits (a minimum of 5 days to a maximum number of days indicated in the Instruction for Use document for the selected dressing), the Midterm Follow-up visit (day 30 to 45), the Long Term Follow-up visit (day 90 to 104), or as initiated by either the Investigator or the subject (Unscheduled). All subjects will be followed for 90 days for outcomes regardless of the treatment received.
SAMPLE SIZE AND STATISTICAL METHODOLOGY:	The incidence rates of SSC are different for septic and aseptic revisions; the assumed SSC rate is 33% for septic and 6.9% for aseptic. This study plans to enroll at least 50% septic revisions overall. These enrollment rates lead to an assumed pooled SSC rate of 20% in the standard of care dressing arm. Assuming an overall type 1 error rate of 0.05, with a two-sided hypothesis test, the study will have at least 80% power to detect a difference of 10% (50% reduction) in SSCs in the ciNPT arm with 199 subjects in each treatment arm, with one interim analysis at about 50% of the evaluable subjects for a total of 398 subjects using the likelihood ratio test. With an estimated 5%-10% loss, a non-binding interim analysis for superiority at approximately 50% of the evaluable subjects using O'Brien-Fleming method for monitoring boundaries, the planned sample size will be inflated for potential loss of follow-up for a total of 440 subjects.

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SIGNATURE PAGE

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PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT OF PROTOCOL

I confirm that I have read the protocol entitled: “Post-market, Randomized, Open-Label, Multicenter, Study to Evaluate the Effectiveness of Closed Incision Negative Pressure Therapy versus Standard of Care Dressings in Reducing Surgical Site Complications in Subjects with Revision of a Failed Total Knee Arthroplasty (PROMISES)” Version 3.0, dated 6-Oct-18. 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 Federal Drug Administration Code of Federal Regulations, the International Conference on Harmonisation principles of Good Clinical Practice, and in the spirit of the Declaration of Helsinki concerning medical research in humans.

PRINCIPAL INVESTIGATOR NAME:

_____

SITE NAMES AND IDENTIFICATION NUMBERS:

_____

PRINCIPAL INVESTIGATOR SIGNATURE:

_____

DATE:_____

ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AJRR	American Joint Replacement Registry
ANCOVA	Analysis of Covariance
ASC/AST	Active Surveillance Culture/Testing
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
ciNPT	closed incision negative pressure therapy
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
DB	database
DEHP-free PVC	(Di(2-ethylhexyl)phthalate-free polyvinyl chloride
eCRF	Electronic Case Report Form
fSAP	final Statistical Analysis Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
IFU	Instructions for Use
iSAP	interim Statistical Analysis Plan
ISS	Injury Severity Score
ITT	intention-to-treat
IV	intravenous
KCI	Kinetic Concepts, Inc.
KOOS	Knee injury and Osteoarthritis Outcome Score
mITT	modified Intention-to-Treat
mmHG	millimeters of mercury

mPP	modified Per-Protocol
NHSN	National Healthcare Safety Network
NPWT	negative pressure wound therapy
NSAID	non-steroidal anti-inflammatory drug
OR	operating room
PHI	personal health information
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	Quality of Life
RCT	randomized clinical trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	standard of care
SSC	surgical site complication
SSI	surgical site infection
TEAE	treatment-emergent adverse event
THA	total hip arthroplasty
TKA	total knee arthroplasty
UADE	Unanticipated Adverse Device Effect

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1. INTRODUCTION

1.1. Background Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) was first introduced for the treatment of acute and chronic open wounds more than 25 years ago. This therapy has become a common and effective adjunct to wound healing, as evidenced by its use among surgeons and clinicians all over the world. NPWT is used in treating both open and closed wounds. Problems associated with wound healing frequently lead to infection, wound dehiscence, and additional procedures.

Hyldig *et al.* performed a meta-analysis combining the results from ten randomized clinical trials (RCTs) which compared NPWT against standard post-operative dressings among 1089 patients undergoing procedures requiring closed surgical incisions such as hip and knee arthroplasty, sternotomy, spinal fractures, abdominal wounds, and breast reconstruction.[1] Each study measured and reported at least one of the following wound complications: dehiscence, infection, or seroma. Most trials included in the meta-analysis were published in a peer-reviewed journal, however, three trials contributing 697 patients (64%), provided the results used in the meta-analysis via personal communication.

While the results of the meta-analysis showed NPWT to be effective in reducing the risk of seroma formation (relative risk and 95% CI: 0.48 [0.27,0.84]) and would infection (0.54 [0.33,0.89]) compared to the standard dressings, the effect on wound dehiscence did not reach statistical significance (0.69 [0.47,1.01]). The results of this meta-analysis should be interpreted cautiously. Heterogeneity among the studies included in the meta-analysis prevents general conclusions or recommendations across all closed surgical incisions. Also, the majority of the patient-data (64%) included in the meta-analysis came from un-published results communicated directly with the study authors.

In a multi-center, prospective RCT in patients with high-risk lower extremity fractures (calcaneus, pilon, and tibial plateau) Stannard *et al.* showed a lower frequency of infection and dehiscence among fractures in patients randomized to the NPWT group (14 [9.9%] and12 [8.5%]) compared to the fractures in patients randomized to the standard post-operative dressing group (23 [18.8%] and 20 [16.4%]).[2] The study population consisted of 249 patients; 130 patients with 141 fractures randomized to NPWT and 119 patients with 122 fractures randomized to standard of care.

In a prospective, single-center study of obese patients undergoing cardiac surgery via sternotomy, patients allocated to NPWT had a lower rate of infection (4%) than those treated with standard of care (16% p-value= 0.0266)[3]. Retrospective studies also found lower rates of infection for patients with surgical incisions treated with NPWT compared to standard of care. [4;5]

Innovations and successes with NPWT have led to the development of devices that simplify and provide options for the application of NPWT, such as ActiV.A.C.® Therapy Unit in conjunction with the Prevena™ Peel & Place Dressing and the Prevena Plus™ Customizable™ Dressing for closed incisions. Closed incision negative pressure therapy (ciNPT) is now used as an adjunct therapy in all types of closed incisions, including incisions resulting from knee replacement surgery.

1.2. Total Knee Arthroplasty and Revision

Replacement of a knee joint with a prosthesis, or Total Knee Arthroplasty (TKA), is an increasingly common surgical procedure in the United States. In a study using the Nationwide Inpatient Sample, US Census data, and National Health Expenditure data from 1993 through 2010, Kurtz and colleagues found steady growth of both primary and revision TKAs between 2000 and 2010. They concluded that the economic downturn did not substantially affect the growth trends for these procedures in the United States (2014).[6] As a large percentage of the population ages, the number of these procedures is expected to increase.

A TKA may fail for a variety of reasons causing pain, swelling, stiffness, and instability. When a TKA fails, a second surgery (revision) may be performed, where some or all parts of the original prosthesis are replaced. The most common reasons for TKA revision include infection, aseptic loosening, instability, mechanical complications, wear, and fracture. [7-11] The 2014 annual report from the American Joint Replacement Registry (AJRR) considered TKA revisions for 639 patients and finds that infection and inflammatory reaction (27.2%) were the most frequently reported causes of TKA revision and that among revisions with complete data, 43% occurred within 3 months post primary TKA. Although the revision has the same goal as the primary TKA – to relieve pain and improve function – revision surgery is longer and more complex, requires extensive planning, and requires the use of specialized implants and tools to achieve the desired result.

Among patients undergoing orthopedic surgeries, including TKA and revisions, published literature shows that patients with multiple co-morbidities, such as obesity, diabetes, dyspnea, hypertension, and smoking are at an even higher risk for infections than patients without co-morbidities.[11-13] Infections can cause prolonged hospital stays, can create significant burden on the healthcare system, and can result in substantial morbidity and quality of life (QoL) deterioration for the patient. [14]

A reduction in the occurrence of these negative and costly outcomes by closed incision negative pressure therapy (ciNPT) would have a significant benefit for TKA revision patients.

1.3. Review of Medical Literature – ciNPT in TKA

A retrospective study of revision TKAs and total hip arthroplasties (THAs) with 138 patients (30 treated with ciNPT and 108 patients with antimicrobial dressings) undergoing procedures by a single surgeon, found that patients treated with ciNPT developed fewer overall wound complications (6.7% vs. 26.9%) and fewer surgical site infections (3.3% vs. 18.5%) as compared to patients whose wounds were treated using antimicrobial dressings.[15]

The authors concluded that ciNPT decreases the incidence of surgical site complications – including dehiscence, suture granuloma, prolonged drainage, and surgical site infections – and may have the potential to lower the need for another reoperation in this population of TKA and THA revision patients.

1.4. Conclusion

Surgical Site Complications (SSCs) arising from aseptic and septic TKA revisions, particularly surgical site infection, are well documented in the literature, with patient co-morbidities further impacting the rate of SSCs. The use of ciNPT has been shown to reduce complication rates related to closed surgical incisions in a variety of indications. An interest in exploring the benefits of ciNPT in orthopedic closed incisions is growing, such as impact on deep infection and dehiscence. There is a need for higher level evidence from a large, randomized, well-controlled study. This study will assess how ciNPT impacts the rate of SSCs and the components in patients undergoing TKA revision after primary TKA compared to the rate of complication associated with standard of care surgical wound dressings.

1.5. Study Products

The following devices and dressings will provide the ciNPT system used for this study in comparison to standard of care (SOC) surgical dressings. The system consists of any United States Food and Drug Administration (FDA)-cleared Prevena™ Incision Management System dressing, including but not limited to:

- Prevena™ Peel & Place™ Dressings (section 1.5.3), or
- Prevena Plus™ Customizable™ Dressing (section 1.5.4)

applied at the time of the surgery and one of the following negative pressure pumps:

- ActiV.A.C.® Therapy Unit (section 1.5.2.1), or
- Prevena Plus™ 125 Therapy Unit (section 1.5.2.2).

The products provide surgical incision management via the application of negative pressure wound therapy over an incision site that has been surgically closed with sutures or staples.

1.5.1. Regulatory status

The Prevena Plus™ Incision Management System was cleared by the United States FDA via a 510(k) clearance affirming that the system is substantially equivalent in terms of indication and technology to the predicate device, the Prevena™ Incision Management System. The system's indications, contraindication, warnings, precautions, and instructions for use can be found in the Prevena Plus™ Therapy System Clinician Guide.[16] The Prevena Plus™ Incision Management System is intended to manage the environment for 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.

1.5.2. Negative Pressure Wound Therapy Units

The Therapy Unit creates a negative pressure vacuum of the closed surgical incision and causes exudate to be pumped into a collection canister attached to the unit. The Therapy Units described in this section were designed to be used in conjunction with any Prevena™ Dressings used in this study immediately after the dressing is applied to the subject's closed incision.

Both Therapy Units are lightweight, portable, electric and battery-powered devices that the surgeon will attach to the dressing immediately after it is applied to the subject's closed incision. Subjects will maintain the Therapy Unit after being discharged from the hospital. The unit will be programmed to deliver continuous 125 mmHg negative pressure for the duration of the ciNPT treatment.

1.5.2.1. ActiV.A.C.®

The ActiV.A.C.® Therapy Unit (Figure 1) delivers continuous negative pressure to a wound in the selectable range of 25 mmHg to 200 mmHg. It weighs 2.4 pounds, has alarm notifications, and a 14-hour battery. A 300 mL canister is attached to the device to collect wound fluid.

Figure 1. ActiV.A.C.® Therapy Unit

1.5.2.2. Prevena Plus™ 125

The Prevena Plus™ 125 Therapy Unit (Figure 2) delivers continuous negative pressure at 125 mmHg for up to seven days. A 150 mL canister is attached to the device to store exudates away from the incision site. Audible and visual alerts notify subjects and Investigators of leaks, full canister, and low battery.

Figure 2. Prevena Plus™ 125 Therapy Unit

1.5.3. Prevena™ Peel & Place™ Dressing

The Prevena™ Peel & Place™ dressing is an integrated one-piece dressing that is applied to the closed surgical incision without sizing or cutting. The foam dressing has an integrated pressure indicator to ensure adequate negative pressure and Prevena™ patches used to seal leaks at the time of application. Each dressing has a V.A.C.® Therapy Unit Connector to allow connection to the therapy unit. The dressings are designed for linear incisions and are constructed of 3 layers, as described in Table 1 and shown in Figure 3.

Table 1. Prevena™ Peel & Place™ Dressing Description

Layer/Material	Function
Skin Interface layer (Subject skin contacting)	
Wicking Interface Fabric (polyurethane-coated polyester fabric with 0.019% silver)	Placed directly over the incision. Wicks fluid away from the skin/tissue; contains silver ions to reduce potential for contamination of the fabric with microbes.
Polyurethane film with acrylic adhesive	Secures dressing to application site
Foam Bolster (Subject skin noncontacting)	
Polyurethane foam with pigment violet 23	Manifolds negative pressure to the surgical incision area through the underlying interface fabric
Polyurethane film shell	Maintains the negative pressure environment in conjunction with the therapy unit
PIMS Pressure Pad with Sterile Tubing (Subject skin noncontacting)	
Polyurethane film with acrylic adhesive	Connects dressing to the therapy unit, transfers negative pressure and removes exudate
DEHP-free PVC, medical grade	

Figure 3. Prevena™ Peel & Place™ Dressing

1.5.4. Prevena Plus™ Customizable™ Dressing

The Prevena Plus™ Customizable™ Dressing is designed to be altered such that the dressing can cover closed surgical incisions of different sizes and shapes.

The dressing is fitted with SENSAT.R.A.C.™ Pad and connector enabling attachment to the Therapy Units (Section 1.5.2). The dressing comes with V.A.C.® Drapes used to cover the dressing and hydrocolloid sealing strips used to create a continuous adhesive seal around the dressing. The Prevena Plus™ Customizable™ Dressing is constructed of three layers, as described in Table 2 and shown in Figure 4.

Table 2. Prevena Plus™ Customizable™ Dressing Description

Layer/Material	Function
Skin Interface layer (Subject skin contacting)	
Wicking Interface Fabric (polyurethane-coated polyester fabric with 0.019% silver)	Placed directly over the incision. Wicks fluid away from the skin/tissue; contains silver ions to reduce potential for contamination of the fabric with microbes.
Polyurethane film with acrylic adhesive	Secures dressing to application site on subject
Hydrocolloid Ring (Subject skin contacting)	
Hydrophilic polymer ring attached to the outside edge of the foam bolster	Assists with dressing application and helps reduce dressing leaks
Foam Bolster (Subject skin non-contacting)	
Polyurethane foam with pigment violet 23	Manifolds negative pressure to the surgical incision area through the underlying interface fabric
Polyurethane film shell	Maintains the negative pressure environment in conjunction with the therapy unit
Pressure Pad with Sterile Tubing (Subject skin non-contacting)	
Polyurethane film with acrylic adhesive	Connects dressing to the therapy unit, transfers negative pressure and removes exudate
DEHP-free PVC, medical grade	

Figure 4. Prevena Plus™ Customizable™ Dressing

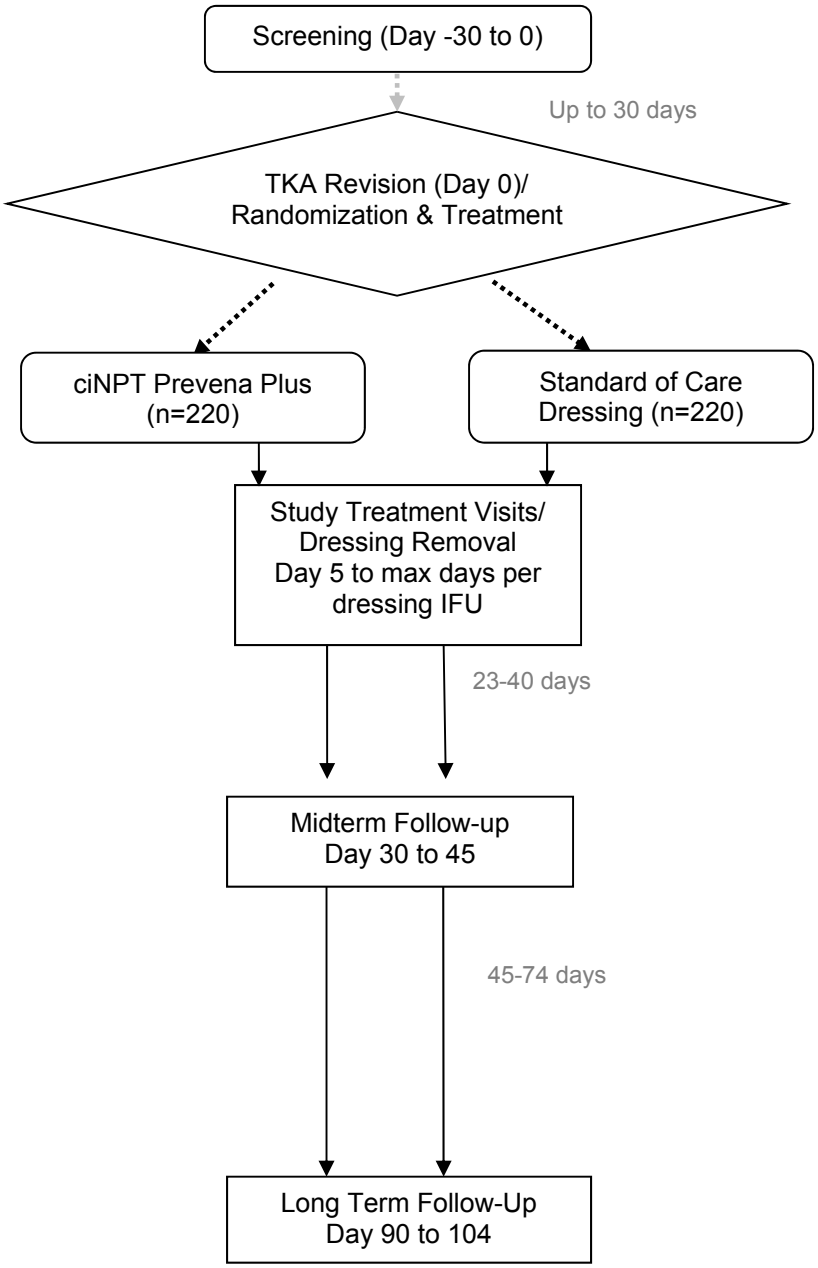
2. STUDY OBJECTIVES

The goal of this study is to evaluate surgical site complications (SSC) in subjects undergoing a revision of a failed total knee arthroplasty when ciNPT is used to manage the closed incision, as compared to standard of care dressing. The individual components for SSC (section 4.11.1) will also be assessed by collecting data associated with each complication. Safety and quality of life will also be evaluated.

3. STUDY DESIGN

3.1. Study Schematic

Figure 5. Study Schematic



3.2. Design Summary

This post-market, prospective, randomized, open-label, multicenter, controlled study will evaluate the effectiveness of closed incision negative pressure therapy (ciNPT) compared to standard of care (SOC) surgical dressing in reducing the surgical site complications (SSCs) in subjects with revision of a failed total knee arthroplasty (TKA).

The study will randomize approximately 440 subjects from approximately 15 sites in a 1:1 ratio to receive either ciNPT or SOC after a revision TKA. Subjects randomized to the ciNPT treatment arm will receive the placement of a Prevena™ Dressing in conjunction with ActiV.A.C.® or Prevena Plus™ 125 Therapy Units for a duration consistent with the Instructions for Use (IFU) document for the selected dressing but no shorter than five days post-surgery. Subjects randomized to the SOC treatment arm will receive Aquacel® Ag Surgical incision dressing, or another equivalent silver-impregnated dressing, up to the maximum number of days specified in the IFU but no shorter than five days post-surgery, not inclusive of other negative pressure wound therapy devices or dressings for the duration of the study.

Subjects will be seen during Screening (no more than 30 days before TKA revision) at the TKA revision, at weekly study treatment visits (a minimum of 5 days to a maximum number of days indicated in the Instruction for Use document for the selected dressing), the Midterm Follow-up visit (day 30 to 45), the Long Term Follow-up visit (day 90 to 104), or as initiated by either the Investigator or the subject (Unscheduled). All subjects will be followed for 90 days for outcomes regardless of the treatment received.

3.3. Duration of Study Participation

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

- Screening: 30 days prior to and including day of TKA revision (Day 0)
- TKA revision
- Treatment Period: According to the IFU document included with the selected dressing but no shorter than five days post-surgery
- Post Operation and Follow-up: through 90 days after TKA revision

The maximum participation duration per subject is 134 days.

3.4. Primary Endpoint

The primary endpoint is the subject incidence of Investigator-assessed surgical site complications (SSCs) within 90 days of TKA revision. SSCs include any of the following:

- Superficial Surgical Site Infection (SSI)
- Deep SSI
- Full thickness skin dehiscence
- Seroma or hematoma requiring drainage or surgery
- Skin necrosis
- Continued drainage

Specific details regarding SSC determination and measurement can be found in section 4.11.1.

3.5. Secondary Endpoints

The two secondary endpoints for this study are the 90-day subject incidence of Investigator-assessed:

- Any SSI (superficial or deep)
- Deep SSI only

3.6. Exploratory Endpoints

Exploratory endpoints in this study are self-reported, except where indicated, and include:

- Worst pain last 24 hours
- Average pain in last 24 hours
- Knee-Related Quality of Life – as assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS)
- Function in Sport and Recreation (KOOS)
- Function in Daily Living (KOOS)
- Pain (KOOS)
- Other Symptoms (KOOS)
- Mental health – as assessed by PROMIS Global 10 t-score
- Physical health – as assessed by PROMIS Global 10 t-score

- Investigator-assessed:
  - 30-Day subject incidence of SSC
  - 45-Day subject incidence of SSC

3.7. Safety Endpoint

The safety endpoint is the subject incidence of adverse events.

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). The subject and the Investigator (or medically licensed sub-Investigator), must both sign and date the ICF before the subject can undergo any study-related procedures. The subject's 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.
- 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, KCI, the study site, or any of their agents from liability from 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, and
- ensuring that subjects have signed the ICF prior to undergoing any study-related assessments, and
- ensuring that each subject receives a copy of their signed ICF.

4.2. Inclusion/Exclusion

In order to be considered for randomization, a subject must meet all pre-operative eligibility criteria, assessed no more than 30 days prior to the planned TKA revision, and the intra-operative eligibility criteria assessed on the day of 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.

4.2.1. Pre-Operative Inclusion Criteria

The subject:

- is at least 22 years of age on the date of informed consent
- is able to provide their own informed consent
- requires a TKA revision defined as one of the following:
  - a one-stage aseptic revision procedure
  - a one-stage septic exchange procedure (requiring removal of all hardware) for acute postoperative infection
  - removal of cement spacer and re-implantation procedure
  - open reduction and internal fixation of peri-prosthetic fractures
- has one or more of the following:
  - a body mass index (BMI) greater than 35 kg/m^2
  - a requirement for the use of blood thinners other than acetylsalicylic acid (ASA) after surgery
  - history of or current peripheral vascular disease
  - the presence of lymphedema in the operative limb
  - insulin-dependent diabetes mellitus
  - current tobacco use or previous history of smoking and quitting within the past 30 days
  - a history of prior infection of the operative site
  - current use of immunomodulators or steroids
  - current or history of cancer or hematological malignancy (excluding localized skin cancer)
  - rheumatoid arthritis
  - current renal failure or dialysis

- malnutrition as determined by the investigator
- liver disease as determined by the investigator
- status post solid organ transplant
- HIV

- is willing and able to return for all scheduled study visits
- if female, has a negative urine or serum pregnancy test at screening and day of revision surgery. Women who have had surgical sterilization by a medically accepted method such as tubal ligation, hysterectomy, or oophorectomy or are post-menopausal, defined as not having menstruation for ≥ 12 months will be excluded from requiring this test.

4.2.2. Pre-Operative Exclusion Criteria

The subject:

- is pregnant or lactating
- will undergo a bilateral TKA within the same operative visit
- will undergo a bilateral TKA in which the first TKA surgery is on the knee selected for study
- will undergo a staged bilateral TKA in which the TKA revision surgery for the knee under study occurs within 30 days of the first TKA procedure
- was previously randomized in this protocol
- has a systemic active infection at the time of revision not including chronic viral infections such as HIV or hepatitis
- has a remote-site skin infection at the time of revision
- was tattooed on the area of the incision within 30 days prior to randomization
- 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 currently enrolled in another investigational trial that requires additional interventions
- is planned to be enrolled in another investigational trial that requires additional interventions at any time during the study
- has localized skin cancer around the incision site

4.2.3. Intra-Operative Inclusion Criteria

The subject:

- continues to meet all pre-operative inclusion criteria
- has undergone a TKA revision resulting in a closed surgical incision

4.2.4. Intra-Operative Exclusion Criteria

The subject:

- is found to meet any of the pre-operative exclusion criteria
- has a surgical incision that precludes placement of dressing
- has a TKA revision resulting in a muscle flap
- has a TKA revision resulting in the placement of a spacer
- has an incision drainage and debridement procedure only
- has a surgical incision closed with skin glue

4.3. Premature Study Termination

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

4.3.1. By Sponsor

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

- The study is not conducted in accordance with the approved protocol.

- 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.

KCI 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 to the study protocol and/or with applicable regulatory or IRB 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.

4.3.2. By IRB

The IRB may choose to discontinue the study at the site for which they granted approval. If the IRB discontinues the study, the Investigator will report a withdrawal of IRB approval to KCI 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 participation of the 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.

An Investigator must terminate participation of a subject from the study for any of the reasons indicated in section 4.15.

4.4.2. Handling of Withdrawal or Termination

Every effort should be made to assess SSCs and adverse events prior to the subject withdrawal. If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

For subjects who are lost to follow-up, the Investigator will make attempts to collect at least the vital status (e.g., 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, 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 KCI.

4.5. Demographics and Subject Characteristics

The following demographic data and subject characteristics will be collected and documented after the subject signs the informed consent and before the TKA revision:

- Date of birth
- Sex
- Race
- Ethnicity
- Co-morbidities
- Primary TKA characteristics
- Date of surgery
- Diagnosis (osteoarthritis, rheumatoid arthritis, other)
- Unilateral or bilateral
- Primary reason for failure
- Aseptic loosening
- Infection
- Wear
- Mechanical causes

- Instability
- TKA revision septic/aseptic

4.6. Vital Signs

The subject's height and weight will be collected and documented at the screening visit. If the screening visit and the TKA revision occur on different days, only weight will be taken and documented on Day 0, prior to the revision procedure.

4.7. Medical/Surgical History

As part of screening procedures, the Investigator, or medically licensed sub-investigator, will collect a complete medical and surgical history for each subject. If the screening visit and the TKA revision occur on different days, the medical and surgical history will be updated on Day 0, prior to the revision procedure.

4.8. Laboratory Assessment for Pregnancy

Serum or urine hCG assessment to determine pregnancy status in female subjects of child-bearing potential will be conducted during screening and prior to surgery, if the screening visit and the TKA revision occur on different days. If the subject's pregnancy test is positive, she will not be eligible for randomization, will discontinue from the study, and will be considered a screen failure.

4.9. Randomization and Subject Numbering

Subjects who sign an informed consent will be assigned a unique subject identifier. The identifier will be unique to the subject. 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 in the operating room after the TKA revision procedure has been completed and the surgical incision has been closed. Randomization to study treatment will be centralized, electronic, and web-based. Subjects will be randomized in a 1:1 ratio (ciNPT vs. SOC) stratified by type of revision (septic vs. aseptic). For details, see section 8.4.3.

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

4.10. Surgical Procedures and Assessments

4.10.1. TKA Revision Procedure

The surgical procedure will be performed in accordance with the Investigator's standard practice and the resultant surgical incision will be closed with sutures (resorbable or permanent) or staples. Incisional skin glue (e.g., Dermabond) must not be used.

The following information regarding the TKA revision will be documented after the surgery:

- Material used (polyethylene, cross-linked polyethylene, antioxidant polyethylene)
- Location (left or right knee)
- Length of the incision
- Method of closure (sutures or staples)
- Start and stop time of the surgical procedure

4.10.2. Application of Study Treatments

4.10.2.1. ciNPT

Subjects randomized to ciNPT will receive treatment for a duration consistent with the IFU document included with the selected Prevena™ Dressing but no shorter than five days post-surgery. Depending on the length of the incision, an appropriate Prevena™ Dressing will be used to cover the closed surgical incision, according to the instructions for use included with the product. Total treatment time should not exceed the maximum number days indicated in the IFU document included with the Prevena™ Dressing applied immediately following surgery.

For the delivery of negative pressure, an ActiV.A.C.® or Prevena Plus™ 125 Therapy Unit will be attached to the dressing tubing and ciNPT will be initiated in the operating room. The ActiV.A.C.® Unit must be set to 125mmHg of continuous negative pressure. If the dressing leaks and a seal cannot be maintained, replacement of the initial ciNPT dressing is acceptable and will be documented.

In the event that the Therapy Unit malfunctions, a replacement unit may be used. A dressing may also be replaced during the treatment period.

4.10.2.2. Standard of Care (SOC)

Subjects randomized to standard of care will have their closed surgical incision covered with the silver-impregnated dressing, Aquacel® Ag Surgical or other equivalent, up to the maximum number of days specified in the IFU but no shorter than five days post-surgery. Total treatment time should not exceed the maximum number days indicated in the IFU document included with the dressing applied immediately following surgery.

4.10.2.3. Documentation

The following information regarding the application of study treatments will be documented after the surgery:

- SOC
- Type of dressing applied
- ciNPT
  - Type of dressing applied (eg, Prevena Plus™ Customizable™ Dressing, Prevena™ Peel & Place™ Dressing)
- Type of therapy unit
  - ActiV.A.C.®
  - Prevena Plus™ 125
- Replacement of the initial dressing to maintain the seal

4.10.3. Removal of Study Treatments

4.10.3.1. ciNPT

All subjects must receive ciNPT for a duration consistent with the IFU document included with the selected Prevena™ Dressing but no shorter than five days post-surgery. A maximum duration indicated in the IFU document of the Prevena™ Dressing applied immediately following surgery is encouraged. The dressing should not be lifted or removed for reasons other than those related to the device such as initial malfunction or leak alarm.

At the end of the ciNPT treatment period, the dressing and unit are to be removed; re-application of the Prevena™ dressing is prohibited after the treatment period. If continued drainage is determined by the Investigator's visual inspection of the incision at the time of dressing removal, an SSC event should be documented.

4.10.3.2. Standard of Care Dressing

The Aquacel® Ag Surgical or other equivalent dressing may be replaced as needed for the duration of the treatment period. Total treatment time should be no shorter than five days post-surgery and should not exceed the maximum number days indicated in the IFU document included with the dressing applied immediately following surgery.

4.10.3.3. Documentation

The following information regarding the application of study treatments will be documented after the surgery:

- Date of removal
- SOC only
- The number of dressing replacements
- Type of dressing (if any) applied after removal of study treatment
- ciNPT only
- Replacement of therapy unit
- Number and dates of dressing replacements (Prevena™ Peel & Place™ or Prevena Plus™ Customizable™)
- Type of dressing (if any) applied after removal of ciNPT

4.11. Post-Operative Assessments

4.11.1. Investigator-Assessed Surgical Site Complication (SSC)

The Investigator will examine the subject and the surgical incision at the scheduled assessment visits – Weekly, Midterm Follow-up, and Long Term Follow-up – as well as any unscheduled visits initiated by the subject or the Investigator. The Investigator will evaluate the subject for all complications at each visit, regardless if the subject has a documented SSC event.

For all SSC events, the date of onset will be recorded. Not all reported adverse events that are surgical complications will meet the criteria for an SSC event.

Subjects with a documented SSC event will continue to be assessed through the Long Term Follow-up visit or study withdrawal and all newly occurring complications will be recorded.

4.11.1.1. SSC Components

1. Superficial Incisional Surgical Site Infection (SSI) involves only skin and subcutaneous tissue of the incision and meets at least one of the following criteria:
    - purulent drainage from superficial incision;
    - organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing [ASC/AST]);
    - both of the following:
        - superficial incision that is deliberately opened by Investigator and culture or non-culture based testing is not performed, and
        - at least one of the following signs or symptoms:
            - pain or tenderness;
            - localized swelling;
            - erythema; or
            - heat.
    - diagnosis of superficial SSI by the Investigator.
2. Deep Incisional SSI which involves deep soft tissue of the surgical incision, occurs within 90 days after the revision, and has at least one of the following:
    - purulent drainage from the deep surgical incision;
    - both of the following:
        - a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by the Investigator and organism is identified by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing (ASC/AST) or culture or non-culture based microbiologic testing method is not performed:
        - at least one of the following signs or symptoms:

- fever(>38°C);
- localized pain, or
- tenderness.

Note: A culture or non-culture based test that has a negative finding does not meet this criterion.

- an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

3. Full thickness skin dehiscence, defined as a separation of the closed incision at least through the subcutaneous tissue or deeper and at least one mm wide.
4. Seroma or hematoma requiring drainage or surgery. The fluid accumulation will be classified as hematoma (bloody fluid) or seroma (clear or serous fluid) after drainage. The drainage may be percutaneous, an open technique at the bedside, or open surgical drainage.
5. Skin necrosis is defined as the presence of necrotic tissue/skin eschar at the incision site that requires intervention with antibiotics, excision, and/or re-operation.
6. 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.

4.11.1.2. Special Reporting Instructions for Superficial SSI

Assessments of SSI will follow the CDC classification of superficial infections.[17] Specifically, the following do not qualify as criteria for meeting the National Healthcare Safety Network (NHSN) definition:

- Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet the last criterion for superficial incisional SSI. Conversely, an incision that is draining or that has organisms identified by culture or non-culture based testing is not considered a cellulitis.
- A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration).

4.11.1.3. Special Reporting Instructions for Continued Drainage

It is typical for a closed incision to drain up to 72 hours after surgery. However, if the closed incision continues to drain at the time of dressing removal (> 5 days) as determined by the Investigator to require significant medical intervention, then the occurrence will be

documented as an SSC. Investigators will assess any signs of infection, including purulent discharge or pus, for an SSI and document accordingly.

4.11.2. Intervention Assessment

Information related to all interventions that are performed for an SSC will be documented at all post-surgery visits including unscheduled visits. Information collected will include but is not limited to:

- Date of intervention
- Type of interventions
- Types of interventions may include open surgical or percutaneous drainage, debridement, excision, or re-operation.

4.11.3. Healthcare Utilization Assessment

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

- Relatedness to the TKA revision
- Duration of stay for TKA revision
- Length of hospital stay (days)
- Days in ICU
- Re-admission after TKA revision (yes/no)
- Length of hospital stay (days)
- Days in ICU
- Number of home health visits after hospital discharge
- Number of clinic visits after hospital discharge
- Number of rehab/physical therapy visits

4.12. Pain Assessment

Subjects will answer two questions asking them, on a scale from 0 (no pain) to 10 (pain as bad as you can imagine), to recall and rate their worst and average pain in the last 24

hours. Subjects will answer these questions prior to the TKA revision, at the earlier of discharge or 24 hours (± 2 hours) after the TKA revision, and at the weekly study treatment visits. Subjects will document whether they completed the assessment before or after consultation with the Investigator. At the weekly study treatment visits, the subject will record whether the pain assessment was performed before or after the dressing removal.

4.13. Patient Reported Outcomes (PRO) Assessments

4.13.1. Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is a 42-item disease-specific patient reported outcome (PRO) measure designed to assess short-term and long-term symptoms and function in subjects with knee injury and osteoarthritis. The KOOS has been validated for several orthopaedic interventions including total knee replacement.[18-21] The KOOS consists of five subscales:

- Knee-related Quality of Life,
- Function in Sport and Recreation,
- Function in Daily Living,
- Pain, and
- Other Symptoms.

Intended for use over short-term or long-term intervals to assess changes from visit to visit, subjects will be asked to complete the KOOS questionnaire on their own at the Screening, weekly study treatment visits, Midterm Follow-up, and the Long Term Follow-up visits.

Subjects will record whether they completed the assessment at a particular visit before or after consultation with the Investigator.

4.13.2. Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 Assessment

The PROMIS Global-10 is a generic health assessment that measures the physical, social, and emotional health of individuals and is often used for those living with chronic conditions.

Subjects will be asked to complete the PROMIS Global-10 questionnaire on their own at the Screening, weekly study treatment visits, Midterm Follow-up, and Long Term Follow-up visit.

Subjects will record whether they completed the assessment at a particular visit before or after consultation with the Investigator.

4.14. Concomitant Medications

Concomitant medications will be collected from the time of informed consent through the Long Term Follow-up visit. The medication name, start date, end date, and indication will be reported.

Special consideration should be given to report medications given to treat SSCs or that may affect the healing process such as:

- all antimicrobial medications taken by the subject from time of informed consent throughout the duration of the study especially IV, which may be given to the subject for pre-op prophylaxis within 24 hours of surgery followed by a course of oral antibiotics post-TKA revision
- opioid medications (e.g., morphine) taken by the subject within 14 consecutive days after randomization
- immunosuppressants
- corticosteroids
- non-steroidal anti-inflammatory drugs (NSAID)
- anti-coagulants (e.g., Lovenox, aspirin, Coumadin)
- all medications with a prophylactic indication
- all medications the subject is given to treat an AE during the study

4.15. Prohibited Procedures and Treatments

Subjects who undergo a subsequent surgery involving the initial TKA incision within 90 days must withdraw from the study.

Subjects who receive a subsequent TKA revision on the same knee within 90 days of the study revision must withdraw from the study prior to the procedure. Sites will record any SSCs that occur prior to the subsequent TKA revision and document the revision as the reason for the withdrawal from the study.

In the absence of an SSC, subjects receiving cross-over therapy after completing the original study treatment (ie, therapy from the arm in which the subject was not initially treated) must withdraw from the study.

4.16. 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. Subjects who consent to participate in the study but do not satisfy the inclusion and exclusion criteria will be considered screen failures.

The following information will be documented:

- Date of study termination
- Completion of the study (yes/no)
- Primary reason for discontinuation

5. VISIT SCHEDULE AND DESCRIPTION OF STUDY VISITS

5.1. Schedule of Visits

	Screening	TKA Revision		End of Treatment	Midterm Follow-up	Long Term Follow-up	Unscheduled
		Pre	Post				
	Day -30 to 0	Day 0	Day 0	Per Dressing IFU	Day 30-45	Day 90 (+14 days)	
Informed Consent	X						
Pre-Operative Inclusion & Exclusion Criteria	X						
Demographics & Subject Characteristics	X						
Vital Signs	X	X[2]					
Medical & Surgical History	X	X[3]					
Laboratory Assessment for Pregnancy[1]	X	X					
Intra-operative Inclusion & Exclusion Criteria			X				
TKA Revision Procedure			X				
Randomization			X				
Application of Study Treatment			X				
Removal of Study Treatment				X			
SSC Assessment				X	X	X	X
Intervention Assessment				X	X	X	X
Pain Assessment		X	X[4]	X			
Patient-Reported Outcomes Assessments (KOOS and PROMIS Global-10)	X			X	X	X	
Healthcare Utilization Assessment				X	X	X	X
End of Study						X	X[5]
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Assessment and SAE Reporting			X	X	X	X	X

1 - Assessed on women of child-bearing potential

2 - Weight only

3 - Updates to medical and surgical history to be documented.

4 - Pain will be assessed at the earlier of discharge or 24 hours (± 2 hours) after the TKA Revision.

5 - End of Study assessed at an unscheduled visit only when a subject discontinues prior to the 90-day visit.

5.2. Description of Study Visits

5.2.1. Screening/ Day -30 to 0

The following procedures and assessments will be performed and documented.

- Informed Consent
- Pre-Operative Inclusion and Exclusion Criteria
- Demographics and Subject Characteristics
- Vital Signs
- Medical and Surgical History
- Laboratory Assessment for Pregnancy
- PRO Assessments (KOOS and PROMIS Global-10)
- Concomitant Medications

5.2.2. TKA Revision – Pre-Surgery/ Day 0

The following procedures and assessments will be performed and documented.

If Screening Visit occurs prior to Day 0:

- Vital Signs
- Medical and Surgical History
- Laboratory Assessment for Pregnancy
- Concomitant Medications

For all subjects regardless of timing of Screening Visit:

- Pain Assessment

5.2.3. TKA Revision – Post-Surgery/ Day 0

- Intra-Operative Inclusion and Exclusion Criteria Evaluation
- TKA Revision Procedure

- Randomization to either the ciNPT arm or the SOC arm (in operating room [OR])
- Application of Study Treatment
- Pain Assessment – assessed at the earlier of discharge or 24 hours (± 2 hours) after the TKA revision
- Concomitant Medications
- AE Assessment and SAE Reporting

5.2.4. Weekly Visit (Study Treatment Visits)

The following procedures and assessments will be performed and documented.

- Removal of Study Treatment
- SSC Assessment
- Intervention Assessment
- Pain Assessment
- PRO assessments (KOOS and PROMIS Global-10)
- Healthcare Utilization Assessment
- Concomitant Medications
- AE Assessment and SAE Reporting

5.2.5. Midterm Follow-up/Day 30 to 45

The following procedures and assessments will be performed and documented.

- SSC Assessment
- Intervention Assessment
- PRO assessments (KOOS and PROMIS Global-10)
- Healthcare Utilization Assessment
- Concomitant Medications

- AE Assessment and SAE Reporting

5.2.6. Long Term Follow-up/ Day 90 (+ 14 days)

The following procedures and assessments will be performed and documented.

- SSC Assessment
- Intervention Assessment
- PRO assessments (KOOS and PROMIS Global-10)
- Healthcare Utilization Assessment
- Concomitant Medications
- AE Assessment and SAE Reporting
- End of Study

5.2.7. Unscheduled Visits

Outside of scheduled study visits, if the subject needs to be assessed by the Investigator for any reason, the following procedures and assessments will be performed and documented.

- SSC Assessment
- Intervention Assessment
- Healthcare Utilization Assessment
- Concomitant Medications
- AE Assessment and SAE Reporting
- End of Study (only when a subject discontinues prior to the 90-day visit)

6. RISKS ASSOCIATED WITH STUDY PARTICIPATION

The following are the risks associated with the devices and dressings used in this study, specifically, ActiV.A.C.® Therapy Unit, Prevena Plus™ 125 Therapy Unit, and Prevena™ Dressings.

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

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.

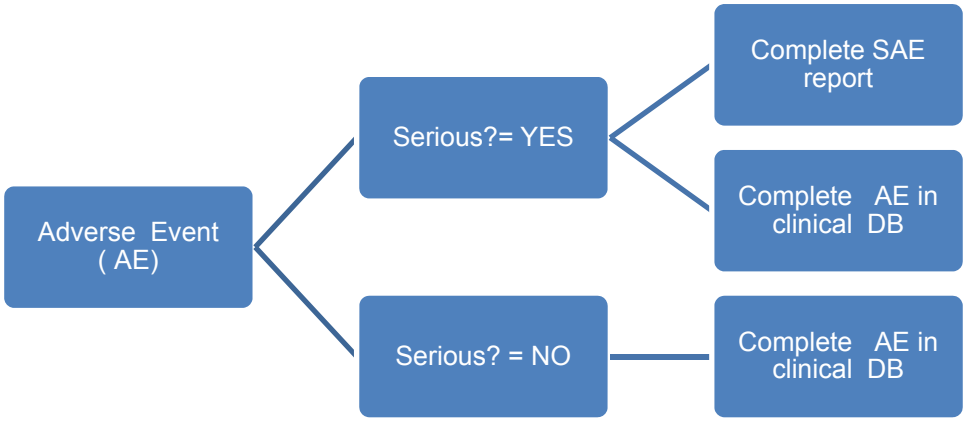
7.1.2. Serious Adverse Event (SAE)

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



7.3. Relationship to Study Treatment

The Investigator will assess the relationship of the AE as:

- **Related** to the study product: any adverse event for which there is a reasonable possibility that the study product caused the adverse event.
- **Not Related** to the study product: when is determined that there is no relationship between the adverse event and the use of the study product.

7.4. Severity

The study investigator will assign severity as follows:

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

7.5. Expectedness

All SAEs will be classified for expectedness by the Sponsor based on the following definitions:

- **Expected, Anticipated**: the effect, problem, or death has been previously identified in the study or product documentation.

- **Unexpected, Unanticipated**: if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study or product documentation.

The Sponsor will provide the Investigator with the classification of the event based on the information reported by clinical sites.

7.6. 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.

7.7. 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 recorded on the appropriate CRFs 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 reporting of all AEs is to continue for the duration of the study or until the patient receives an alternative therapy, whichever occurs first. Any SAE that occurs after treatment with alternative therapy is to be reported only if the Investigator or treating physician assesses the SAE as related to the study treatment.

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. Indicate if the AE caused the subject to be discontinued from the study.

7.8. SAE Reporting to KCI

SAEs will be reported via the KCI SAE Report Form. This form should be completed by the Investigator, or designee, and submitted (fax or email) to KCI within 24 hours of the Investigator becoming aware of the event. The KCI SAE line is available for SAE reporting 24 hours per day and is monitored during normal business hours.

7.9. 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. (21 CFR 812.3)

The Sponsor (KCI) 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 an UADE, KCI will report the results of the evaluation to FDA, and participating Investigators.

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

7.10. Follow-up Period for Ongoing AEs

Treatment-related AEs (serious and non-serious) which are ongoing at the final study visit will be followed until resolution or stabilization. All other adverse events will be considered closed (outcome = “ongoing”) at the time the subject completes participation in the study.

8. STATISTICAL CONSIDERATIONS

8.1. Endpoint Definitions for Analysis

8.1.1. Primary Endpoint – Subject Incidence SSC

The primary endpoint is the incidence of surgical site complications (SSCs) within 90 days of TKA revision in subjects treated with ciNPT as compared to standard of care surgical dressing. The SSC endpoint includes any occurrence of superficial SSI, deep SSI, dehiscence, seroma, hematoma, skin necrosis, or continued drainage as outlined in section 4.11.1. For this endpoint there are three possible outcomes:

- "Occurred", which is assigned if the subject had one or more occurrences of any complication and the onset date of the complication was between the time of the TKA revision and not later than 90 days after;
- "No occurrences", which is assigned if the subject had no known occurrences of a complication within 90 days of the TKA revision and was assessed at least once on or after the 90th day following the TKA revision;
- "Incomplete follow-up", which is assigned if the subject had no occurrences of the complication within 90 days of the TKA revision and did not have an assessment at least 90 days after the date of the revision surgery.

If a subject experiences one occurrence of any of the six complications, the primary outcome will be considered "Occurred".

For each component of the SSC, the start date of the complication will be recorded in order to calculate the number of days from the revision surgery until occurrence of the event. If the complication did not occur, the number of days will be calculated using the last assessment which confirmed the subject to be complication-free.

8.1.2. Secondary Endpoints

8.1.2.1. Subject Incidence SSI

This secondary endpoint is the incidence of any SSI (superficial or deep) within 90 days of TKA revision in subjects treated with ciNPT as compared to SOC dressing. Superficial SSI is a component of the primary endpoint and specific instructions for ascertainment are described in sections 4.11.1. Subjects will be categorized using methods similar to those described in section 8.1.1.

8.1.2.2. Subject Incidence Deep SSI

This secondary endpoint is the incidence of deep SSI within 90 days of TKA revision in subjects treated with ciNPT as compared to SOC dressing. Deep SSI is a component of the primary endpoint and specific instructions for ascertainment are described in section 4.11.1. Subjects will be categorized using methods similar to those described in section 8.1.1.

8.1.3. Exploratory Endpoints

8.1.3.1. Pain Assessment

The pain assessment consists of two self-administered questions used to evaluate the severity of a subject's pain in the past 24 hours. Both questions are measured from 0 (no pain) to 10 (pain as bad as you can imagine).

Subjects will respond using the integer value. Subjects who have withdrawn prior to the scheduled assessments will be categorized as "Discontinued study prior to assessment"; otherwise subjects who do not have an assessment recorded at a particular visit will be summarized as "Assessment not done".

8.1.3.2. Knee Injury and Osteoarthritis Outcome Subscale Score (KOOS)

The KOOS instrument is a patient-reported questionnaire to assess short-term and long-term symptoms and functions.

The KOOS consists of 42 items asked on a 5-point Likert scale. The items will be converted to numeric values and summarized into five domain scores: Knee-Related Quality of Life, Function in Sport and Recreation, Function in Daily Living, Pain, and Other Symptoms. The subscales are scored separately and interpreted separately. Each subscale score will be normalized from 0 (extreme symptoms) to 100 (no symptoms).

All efforts will be made to ensure the subjects complete the entire assessment at each scheduled visit. Each subscale will be scored using the most recent KOOS Users Guide and Scoring Instruction manuals which outline methods for imputing missing data.[18;19]

For the subscale scores, four possible outcomes will be summarized and listed:

- Normalized numeric subscale score;
- Assessment done but incomplete (sufficient number of items not complete);
- Discontinued study prior to assessment;
- Assessment not done

8.1.3.3. Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10

The PROMIS Global-10 is a generic health assessment that measures the physical, social, and emotional health of individuals and is often used for those living with chronic conditions. All efforts will be made to ensure the subject completes the entire assessment, which consists of 10 questions, at each scheduled visit.

Two domains will be scored separately and each will be interpreted separately: Global Physical Health and Global Mental Health. For each subscale, there are three possible outcomes:

- Raw numeric subscale score and converted t-score;
- Assessment done but incomplete (sufficient number of items not complete);
- Discontinued study prior to assessment;
- Assessment not done.

8.1.3.4. 30-Day Subject Incidence of SSC

This endpoint is the incidence of the SSC within 30 Days post TKA revision in subjects treated with ciNPT as compared to SOC dressing. Section 4.11.1 describes the methods for ascertaining surgical site complications. Subject outcomes will be categorized using methods similar to those described in section 8.1.1.

8.1.3.5. 45-Day Subject Incidence of SSC

This endpoint is the incidence of the SSC within 45 Days post TKA revision in subjects treated with ciNPT as compared to SOC dressing. Section 4.11.1 describes the methods for ascertaining surgical site complications. Subject outcomes will be categorized using methods similar to those described in section 8.1.1.

8.1.3.6. Safety Endpoint

Adverse events will be coded using the MedDRA dictionary. Treatment-emergent adverse events (TEAE) are those which first appear or worsen after the application of the study treatment. Subject incidence of TEAEs will be summarized by system organ class and preferred term by treatment group.

All adverse events occurring during the study will be listed by subject in data listings.

8.2. Analysis Sets

The following analysis sets will be used:

- ITT Analysis Set – The ITT (intention-to-treat) Analysis Set will consist of all randomized subjects. Subjects will be analyzed according to the treatment allocated at randomization.

- Safety Analysis Set – The Safety Analysis Set will consist of all randomized subjects who received any study-related treatment procedures. It is expected that all randomized subjects will be treated. All safety results will be presented based on the Safety Analysis Set. Subjects will be analyzed according to the study treatment they received immediately following the TKA revision.

- Modified ITT (mITT) Analysis Set – This set will include subjects in the ITT Analysis Set with the following: 1) an SSC on or before 90 days post-TKA revision or 2) no known occurrence of an SSC within 90 days of the TKA revision and was assessed at least once on or after the 90^{th} day following the TKA revision. Subjects will be analyzed according to their randomized treatment assignment.

- Per-Protocol Analysis Set – This will include subjects in the mITT Analysis Set and had 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 in a blinded fashion prior to the final database lock by the Protocol Deviation Review Committee. Subjects will be analyzed according to their randomized treatment assignment.

- Modified Per-Protocol (mPP) Analysis Set – This will include subjects in the Per-Protocol Analysis Set excluding any subjects that received prohibited therapy as described in section 4.15 or any subjects that received alternative therapy following the study treatment period.

8.3. Planned Analysis and Data Summaries

8.3.1. General Analysis Techniques

In general, continuous variables will be summarized by providing the number of subjects with available data (n), the mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percentage of subjects that are in each category will be provided. Unless otherwise specified, the denominator for percentages will be all relevant subjects in a particular analysis, including those for whom data are not available, i.e., “not reported” or “not available” will generally be considered a separate

category and included in the displays of data, with the denominator for percentages including these subjects. Subjects will be summarized by their assigned and actual treatment group (e.g., ciNPT and SOC).

8.3.2. Subject Disposition

Summaries of disposition will be tabulated by treatment group. The number and percentage of subjects in each analysis set will be described, as will the number (and percentage, if relevant) of subjects who:

- provided informed consent;
- failed screening, and reason for failing screening;
- were randomized;
- were randomized and treated;
- discontinued early from the study for any reason, along with the reason for discontinuation (if the reason is adverse event, the system organ class and preferred term); and
- completed the study as planned.

Subject disposition also will be described in a flowchart (CONSORT diagram[22]).

8.3.3. Demographic and Baseline Characteristics

Demographic characteristics (age, sex, race, and ethnicity), baseline characteristics, and other disease characteristics, will be summarized according to the general techniques in section 8.3.1. Subjects in the Safety, ITT, mITT, Per-Protocol, and/or mPP Analysis Sets will be summarized within each treatment group and overall.

8.3.4. Analysis of Primary Endpoint

The analyses described in this section will be performed for the overall primary endpoint, “Any Surgical Site Complication (SSC)”, within 90 days of TKA revision, and repeated for each type of complication.

The proportion of subjects with each possible result – “Occurred”, “No occurrences”, or “Incomplete follow-up” will be reported, using the mITT Analysis Set as the denominator. See section 8.1.1 for definitions of these outcomes.

The comparative analysis of the primary endpoint will only consider subjects in the mITT Analysis Set, i.e., subjects with “Incomplete Follow-up” will be excluded. The proportions

of subjects with “Occurred” will be calculated within each treatment group and compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) p-value stratified for type of revision (aseptic vs. septic). The difference between the proportions (ciNPT – SOC) and asymptotic 95% confidence interval will be computed. At the final analysis, a two-sided significance level adjusted for the interim efficacy analyses and potential sample size recalculation (e.g., $\alpha = 0.048$ if interim look is at $t=0.50$ and no sample size adjustment is made) will be used to compare the SSC proportions between the two treatment arms.

Supportive/exploratory analyses of the primary efficacy endpoint, SSC, may include:

- analyses comparing the treatment groups for the septic and aseptic revisions;
- analyses comparing the treatment groups for age, BMI, race/ethnicity, material used in the revision, and sex subgroups;
- analyses comparing the heterogeneity of the treatment groups across clinical sites;
- multivariable analyses comparing the treatment groups with covariate adjustment where possible covariates might include (but not limited to) age, BMI, sex, type of revision (aseptic or septic), and subject co-morbidities;
- Fisher’s exact test presenting the unstratified p-value;
- A repeat of any analysis above using the Per-Protocol and/or mPP Analysis Sets;

and other exploratory analyses as deemed appropriate.

8.3.5. Analysis of Secondary Endpoints

Any SSI (superficial or deep) and Deep SSI will be analyzed in a similar fashion as the primary endpoint described in section 8.3.4. Superficial and Deep SSI will be analyzed separately and jointly; individual infection components will be summarized descriptively.

8.3.6. Exploratory Endpoints

In general, analyses will be performed on subjects in the ITT and/or mPP Analysis Sets using methods outlined in section 8.3.1. The number of subjects in each treatment arm at each scheduled visit with adequate assessments will be summarized for each visit. Assessments performed outside the scheduled visit windows may not be included in the models but will be listed separately. The patterns of missing data will be presented using

descriptive analyses. Other statistical analyses exploring the effects of imputation methods for non-response may be generated as appropriate.

Because the analyses are exploratory, no adjustment will be made for multiple comparisons. Confidence intervals may not be created for subsets with less than ten subjects, although standard errors or deviations will be presented to provide a measure of variability. Complete details for all endpoints will be outlined in the Statistical Analysis Plan.

8.3.7. Analysis of Safety Endpoint

Treatment-emergent adverse events (TEAEs) will be summarized by treatment arm. 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) leading to treatment/study discontinuation; or
- serious adverse event(s) leading to treatment/study discontinuation

will be reported. Subject incidence of TEAEs by severity (mild, moderate, severe) will also be presented. Events will be reported by MedDRA system organ class and preferred term. A listing of death(s), subjects who died of any cause during study, will be presented.

8.4. Additional Statistical Details

8.4.1. Hypothesis

This study will assess whether closed incision negative pressure therapy (ciNPT) reduces the surgical site complications (SSCs) compared to standard of care (SOC) among subjects who undergo a total knee arthroplasty (TKA) revision. The primary endpoint is measured by the proportion of subjects with SSC within 90 days of TKA revision among subjects in the mITT Analysis Set; the corresponding null and alternative hypotheses are:

Null: $\Delta_{ciNPT\text{-}SOC} = 0$ Alternative: $\Delta_{ciNPT\text{-}SOC} \neq 0$

where $\Delta_{ciNPT-SOC}$ is the difference in the proportion of subjects in the ciNPT group population with at least one SSC – proportion of subjects in the SOC dressing group with at least one SSC.

8.4.2. Sample Size Determination

The primary endpoint of this study is the subject incidence of SSC as defined in section 4.11.1. The incidence rates of SSC are different for septic and aseptic revisions; the assumed SSC rate is 33% for septic and 6.9% for aseptic. This study plans to enroll at least 50% septic revisions overall. These enrollment rates lead to an assumed pooled SSC rate of 20% in the SOC dressing arm.

Assuming an overall type 1 error rate of 0.05, with a two-sided hypothesis test, the study will have at least 80% power to detect a difference of 10% (50% reduction) in SSCs in the ciNPT arm with 199 subjects in each treatment arm, with one interim analysis at about 50% of the evaluable subjects for a total of 398 subjects using the likelihood ratio test. With an estimated 5%-10% loss, a non-binding interim analysis for superiority at approximately 50% of the evaluable subjects using O'Brien-Fleming method for monitoring boundaries, the planned sample size will be inflated for potential loss of follow-up for a total of 440 subjects.

8.4.3. Randomization

Subjects who meet all inclusion criteria and no exclusion criteria will be randomized in a 1:1 ratio to either the ciNPT or SOC dressing treatment arm. The randomization will be stratified by status at revision (septic versus aseptic).

For each stratum, 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.

8.4.4. Open-Label Study Reporting Results

In order to reduce operational bias that can be introduced during the analysis, while the study is ongoing summary statistics by treatment groups across all sites will be limited to a small analytical group at the Sponsor not involved in the daily operations of the study. Treatment groups will be masked in the summary outputs (tables, listings, and figures) in order to reduce the inference should results be inadvertently accessed. The limited results of the interim analysis will be shared with Investigators and IRBs as necessary to conduct the study.

Upon study completion, the full results will be shared with all investigators and clinical sites.

8.4.5. Interim Analysis

An interim analysis may be conducted at information-time *t*=0.5, i.e., when approximately half the planned study subjects [n=200] have had their primary endpoint assessed. The interim analysis will be performed at the α=0.0052 level; if the p-value for the primary endpoint is < 0.0052, the study will be stopped and null hypothesis rejected. Otherwise, the final analysis will be conducted at α=0.048 (i.e., by constructing a 95.2% confidence interval) to preserve overall Type I error rate at 5%. These α values were chosen using an O'Brien-Fleming α-spending function assuming *t* = 0.5. The alpha levels that will be used at the interim and final will be calculated according the precise information time at the interim analysis.

If warranted, based on the unblinded interim results, the final sample size may be increased using appropriate statistical methodology as described in Chen.[23] The increase to the final sample size would only occur if the interim results had conditional power of success ≥ 50%, would be subject to the restrictions in Chen, and would not be considered statistically binding.

At the interim analysis, the rate of SSC for septic and aseptic revisions will be examined to confirm assumptions of the sample size calculations.[24] In addition, the rate of SSC will be independently assessed for septic and aseptic revisions at the interim analysis to determine if a modification of enrollment from a 1:1 ratio of septic:aseptic revisions to focus on enrollment for either revision type is needed. This type of adaptive enrichment design will be further detailed in the interim statistical analysis plan.[25]

8.4.6. Study Sites

This is a multi-center study following the same protocol and procedures. It is anticipated that approximately 15 study sites in North America will participate, and each site will randomize and treat subjects in both treatment groups. The data and the results of the study will be pooled across clinical sites and centers.

8.4.7. Statistical Analysis Plans and Changes in Analyses

Statistical Analysis Plans (SAPs) containing full details of the statistical analyses and execution will be prepared for both the interim analysis and the final analysis. The interim SAP (iSAP) will be finalized prior to conducting interim analysis. The final SAP (fSAP) will be finalized prior to locking the study database and the final analysis. Any changes from the planned analyses in this protocol, the iSAP, and/or the fSAP 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 KCI if study product or other study supplies are missing. The KCI 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 KCI.

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. KCI will provide support to site staff for any questions or concerns related to study products and procedures. KCI will not have 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 Investigator will allow access to his/her clinical study records for periodic on-site monitoring visits by a designated KCI representative, with the understanding that the representative is bound by professional secrecy and will not disclose a subject's personal 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. The data will be entered into the clinical study database and verified for accuracy.

10.4. Data Handling

KCI 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 clinical study report.

10.5. Records Retention

The study site will maintain all study documentation and institute measures to prevent 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 KCI 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 US and international standards of good clinical practice (FDA Title 21 part 812 and International Conference on Harmonization guidelines), applicable government regulations 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 IRBs will be provided all relevant study documentation in order to safeguard the rights, safety, and well-being of subjects as mandated. Participating Investigators will obtain IRB approval of the study prior to initiation at their sites. The protocol, Instructions for use, informed consent, written information given to subjects, safety updates, and any revisions to these documents will be provided to the IRB 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 and other applicable regulatory requirements (21 CFR part 50). The Investigator is responsible for continuing an open conversation with the subject in regard to their continued participation in the study. KCI will conduct periodic monitoring to ensure informed consent is obtained from 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 and Health Insurance Portability and Accountability Act of 1996 (HIPAA).

In the event that a subject revokes 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. Clinicaltrials.gov Registration

A description of this study will be available on http://www.ClinicalTrials.gov as required by U.S. law. This website 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.

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 (e.g., source documents, regulatory documents, data collection instruments, study data) by the IRB/IEC, KCI, and government regulatory bodies.

12. PUBLICATION POLICY

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

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14. APPENDICES

14.1. KOOS Questionnaire

14.2. PROMIS 10 Questionnaire