A Phase 2 Multicenter Feasibility Trial to Evaluate Safety and Efficacy in Patients Treated for Hip or Knee Prosthetic Joint Infection with Alternating Irrigation of Vancomycin HCl and Tobramycin Sulfate in Two-Stage Exchange Arthroplasty

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Date:	JUN 28, 2019

Clinical Investigational Plan Approval

A Phase 2 Multicenter Feasibility Trial to Evaluate Safety and Efficacy in Patients Treated for Hip or Knee Prosthetic Joint Infection with Alternating Irrigation of Vancomycin HCl and Tobramycin Sulfate in Two-Stage Exchange Arthroplasty

Sponsor:

Joint Purification Systems, Inc.

215 S. Hwy 101 #200, Solana Beach, CA 92075

_____SIGNATURE ON FILE WITH CRO_____ Date: _____

Jude Paganelli, Chief Executive Officer

Principal Investigator:

_____SIGNATURE ON FILE WITH CRO_____Date: _____

Bryan Springer, MD

Reference: JUN 28, 2019, Version E

Protocol Agreement

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this Protocol, the associated site agreement and in accordance with applicable regulations and conditions required by the trial overseeing authorities. I agree to maintain all study documentation for a minimum of two years after the study has been completed or for longer periods as required by law and regulations. Publication of the results of this study will be governed by the conditions stipulated in the Investigational Site Agreement. I agree to supervise the use of the Investigational Products at my institution and ensure that the informed consent document is obtained prior to subject enrollment.

I have read and understand the information in this Protocol and will ensure that all associates, colleagues and employees assisting in the conduct of the study are informed of the obligations incurred by their participation. I will attest to the delegation of any obligation under this Protocol to my associates, colleagues and employees by signing such delegation in the Study Delegation Log.

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Protocol Date: JUN 28, 2019

Version: E.0

Signature of Site Principal Investigator	Date

Name of Site Principal Investigator

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List of Abbreviations

Abbreviation	**Definition**
AE	Adverse event
AORI	Anderson Orthopaedic Research Institute
BA/BE	Bioavailability/bioequivalence
BUN	Blood urea nitrogen
CBC	Complete blood count
CC	Completed cases
CCI	Charlson Comorbidity Index
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Clinical research organization
CRP	C-reactive protein
eCRF	Electronic case report form
EDC	Electronic data capture
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HgA1C	Glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
I&D	Incision and drainage
ICF	Informed consent form
IDSA	Infectious Diseases Society of America
IMSM	Independent medical safety monitor
IND	Investigational new drug (application)
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-treat
IV	Intravenous
JPS	Joint Purification Systems, Inc.
LE	Leukocyte esterase
MBEC	Minimum biofilm eradication concentration
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MSIS	Musculoskeletal Infection Society
NPWT	Negative pressure wound therapy
NS	Normal saline
OR	Operating room
PEC	Primary engineering control

PI	Principal investigator
PK	Pharmacokinetic
PJI	Prosthetic joint infection
PMN	Polymorphonuclear leukocytes
PP	Per-protocol
PSI	Pounds per square inch
SAE	Serious adverse event
SAL	Sterility assurance level
SAP	Statistical analysis plan
sCr	Serum creatinine
SDV	Source data verification
SOC	Standard of care
SW	Source worksheet
TXA	Tranexamic acid
UADE	Unanticipated adverse device effect
UAE	Unanticipated adverse event
VAC	Vacuum assisted closure
VTE	Venous thromboembolism
WBC	White blood cell

1 Background and Purpose of the Investigation

A prosthetic joint infection (PJI) is a rare complication of joint replacement surgery, also known as arthroplasty. Arthroplasty is done to help relieve pain and restore function in a severely diseased joint, such as a knee, hip or shoulder. Approximately 0.5 to 1 percent of people with replacement joints develop a PJI. Infections can occur early in the course of recovery from joint replacement surgery (within the first two months) or much later. Signs and symptoms of PJI include fever, chills, drainage from the surgical site, and increasing redness, tenderness, swelling and pain of the affected joint. Prosthetic joint infections are often hard to treat because of the development of a structure called a biofilm within the joint. [1].

1.1 Standard of Care Treatment for PJI

The standard of care for treatment of chronic PJI in the US is surgical removal of the infected implant, aggressive debridement and two-stage exchange arthroplasty with administration of systemic antibiotics. Stage 1 of the procedure includes the implantation of a temporary antibiotic impregnated cement spacer and administration of systemic antibiotic therapy as needed, typically for a period of at least 6 weeks. The second Stage of the procedure is performed when patients are considered infection free and includes implantation of a new permanent prosthesis. Cochran et al., in their review of 16,622 Medicare patients treated for PJI from October 2005 through December 2011 reported that 80.3% of reinfections occurred in the first postoperative year, and two-stage revision had the lowest reinfection rate of all first line treatment options for PJI other than amputation as shown in Table 1 [2].

Table 1 Reinfection Rate at 12 Months for Various Treatments for PJI

First Line Treatment for PJI	Reinfection Rate at 12 Months
Incision and Drainage (I&D)	28.2%
I&D with Polyethylene Exchange	25.7%
One-stage Exchange Arthroplasty	24.6%
Two-stage Exchange Arthroplasty	19.0%

1.1.1 Inefficacy of Systemic Route of Administration

The intravenous (IV) administration of systemic antibiotics for PJI does not result in adequate therapeutic concentrations for eradication of biofilm at the site of infection. Bone concentrations of vancomycin hydrochloride (HCl) are typically 10% to 60% of serum and those of tobramycin sulfate range from 9% to 13% of serum concentration [3]. Achievement of locally therapeutic levels is crucial for clinical success; however, this is difficult or impossible due to the fact that most PJI pathogens are biofilm forming. Biofilm-encapsulated bacteria require minimum biofilm eradication concentrations (MBEC) of antibiotics that are several orders of magnitude (100 to 1000X) above the minimum inhibitory concentrations (MIC) sufficient to eradicate planktonic bacteria [4, 5]. Therapeutic target attainment at levels greater than the MBEC is impossible via systemic routes of administration without significant toxicity to other organ systems.

1.1.2 Inconsistent Local Therapy

The multiple variables influencing the release of antimicrobials in cement spacers presents both efficacy limitations and toxicity concerns. For example, antimicrobials contained within the center of the matrix are essentially isolated from the joint environment, with only the surface cement releasing significant amounts of drug. Mixing techniques, antimicrobial concentrations, type of cement, surface area, and movement make for a high degree of variability in elution. The amount of antibiotic released from the cement in one study ranged from 1.3% to 14.8% [6]. Most of the elution from bone cements comes in the first 48 to 72 hours, and by day 5, the concentrations are often sub-therapeutic [7]. The sub-therapeutic antimicrobial concentrations can lead to the formation and colonization of multi-drug resistant (MDR) organisms as evidenced by multiple studies. One study showed the formation of pseudomonas biofilms with increasing slime layers in gentamicin-impregnated cement versus control, while another study isolated coagulase-negative Staphylococci in 88% of cases that used gentamicin loaded cement [8, 9]. The inability to control local elution rate also presents risk of systemic toxicity, and without means of cessation outside of a repeat surgical procedure, this presents risk of a serious adverse event (SAE).

1.1.3 Failure to Complete Treatment

Berend et al. [10] and Gomez et al. [11] authored some of the first retrospective reviews to fundamentally reexamine the definition of successful treatment of PJI from 1989 to 2012. Berend et al. summarized results of two-stage hip exchanges for PJI from 21 publications with an overall reported infection control rate of 88.8%; however, on further examination only 91.5% of patients treated at Stage 1 completed Stage 2. The infection control rate declined to 81.3% when all Intent-to-Treat (ITT) patients are included in the analysis. Because reporting on all patients was not common at the time of these publications, the rate of patients who failed to complete treatment is likely much higher. Gomez et al. reported 81.4% treatment success among 329 knee and hip patients who completed the Stage 2 treatment and had reached 1-year follow-up; however, they reported that of the 504 PJI patients in their review, 60 (11.9%) were re-operated on during the interstage phase to place another spacer (range: one to six additional spacers), and 87 (17.3%) retained their spacer (failed to complete Stage 2). After a minimum 1-year follow-up, just 285/416 (64.4%) of all patients in the retrospective study of the two-stage standard of care (SOC) at the Rothman Institute, a leading joint infection treatment center in the US, were considered a treatment success. The authors recommend that the success of two-stage arthroplasty be considered from the starting point of initial spacer implantation rather than from Stage 2 reimplantation, which is described below.

A summary of the findings from 504 patients in Gomez et al. and from 1,537 hip PJI patients in Berend et al is shown in Table 2. Both publications indicate that the percentage of patients who never complete the Stage 2 revision procedure is comparable to the percentage of patients in whom the Stage 2 procedure is unsuccessful (10% to 20%).

Table 2 Proportion of PJI Patients Who Achieve Reimplantation & Clinical Success

Study	No. of Studies	Stage 2 Reimplantation Rate	Stage 2 Reported Success Rate	Composite Success Rate
Gomez et al. [11]	1	417/504 (82.7%)	268/329 (81.4%)	67.3%

Berend et al. [10]	21	1407/1537 (91.5%)	1250/1407 (88.8%)	81.3%

Of the 87 patients who did not complete the Stage 2 reimplantation in the Gomez study, 15 patients (17.2%) were re-operated on to perform arthrodesis, girdlestone, or amputation procedures, 19 (21.8%) were lost to follow-up, and 36 patients (41.4%) died during the study period without a revision implant, leaving just 17 (19.5%) of patients with retained spacers who were considered treatment successes [11].

1.1.4 Time to Reimplantation

The interstage interval between implantation of the Stage 1 temporary spacer and Stage 2 reimplantation of a revision prosthesis is critical for the patient. During the interstage period, the patient has only limited mobility and partial weight bearing on the affected limb. The risk of significant morbidity and permanent disability is high, as are the risks of systemic antibiotic-related toxicity and development of resistance to antibiotics [12]. Treatment during this period may include inpatient rehabilitation (extended care facility/skilled nursing facility) for part or all of the interstage phase, in-home nursing care for infusion services, extended physical therapy, long-term antibiotic use, extended opioid use, and ongoing monitoring for systemic toxicity. Andersson et al. interviewed 14 PJI patients and reported that patients with deep surgical site infections suffer significantly from pain, isolation and insecurity, and that it changes physical, emotional, social, and economic aspects of life in extremely negative ways, often persistently [13].

Gomez et al. reported an average interstage interval of 4.2 months (range: 0.7 to 131.7 months) and median interval of 2.7 months in 504 patients who received Stage 1 temporary spacers at a single institution. This means that only slightly more than half of all patients completed the critical Stage 2 surgical procedure by the time of the typical 12-week postoperative follow-up. [11].

Berend et al. reported on 19 publications on two-stage exchange arthroplasty of the hip with interstage intervals of 1.5 to 18 months, with a median interval of 4.5 months, and a weighted average interval of 6.5 months in more than 1,000 patients [10]. These intervals are 50% longer than that reported by Gomez et al.

Cancienne et al. reported on 18,533 knee PJI cases and 7,146 hip PJI cases with the ITT as two-stage exchange arthroplasty, of which only 61.6% of knee PJI patients and 60.2% of hip PJI patients completed the Stage 2 revision within 12 months [14, 15].

1.1.5 Interstage Mortality

Gomez et al. and Berend et al. are also among the first to detail the underreported mortality of PJI patients prior to Stage 2 reimplantation. Historically, reports of two-stage exchange arthroplasty reported only the clinical results for patients who completed the Stage 2 revision procedure and they were completely silent on the results of patients who did not complete the procedure. Gomez et al. reported 1.2% mortality (5 of 6 related to infection) in the first 30 days, 2.6% mortality within 90 days, and 6.5% mortality in the first year, compared to a national death rate of 2.0% for the general population of the same age [11]. Berend at al. reported on 202 hip PJI patients, 7% of whom died within 90 days of the Stage 1 procedure, including 4% who died prior to completing Stage 2 revision [10]. Recent evidence demonstrates that patients with PJI have a mortality rate of 25.9% at 5 years, which is 4-fold

higher than the mortality of age- and comorbidity-matched patients undergoing revision arthroplasty for a non-infected cause [16].

1.2 Investigational Products

The investigational products for local irrigation are relabeled commercial product tobramycin injection that contains 40 mg/ml in a 2 ml vial and relabeled commercial product vancomycin in three 1 g vials of vancomycin base as a lyophilized powder that requires reconstitution. Both products are sold by Hospira, Inc. The products are being administered as per Investigational New Drug (IND) application 132585.

1.2.1 Name and Intended Use of Investigational Product

Vancomycin HCl and Tobramycin Sulfate for local irrigation are indicated for the treatment of periprosthetic joint infection in skeletally mature patients undergoing a two-stage revision arthroplasty procedure, where vancomycin HCl and tobramycin sulfate are the most appropriate antibiotics for treatment of the infection. The drugs are administered following removal of the existing prosthetic components and radical debridement by delivering vancomycin HCl and tobramycin sulfate in 0.9% sodium chloride to the affected site. Vancomycin HCl and Tobramycin Sulfate for local irrigation are intended for use for no more than 10 days, at which time a permanent device must be implanted or another appropriate treatment performed.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to vancomycin HCl and tobramycin sulfate.

1.3 Other Products

The V.A.C.® ULTA™ Negative Pressure Wound Therapy (NPWT) system is a commercially available device that is used in this clinical study to deliver the investigational products.

2 Study Objectives

2.1 Study Type

This study is a Phase II prospective, single-arm, open-label, multicenter (3 to 5 sites), interventional trial.

2.2 Study Objective

The primary objective of the study is to determine the safety of local antibiotic irrigation with Vancomycin HCl and Tobramycin Sulfate for the treatment of PJI. The secondary objectives are to collect preliminary efficacy data.

2.3 Outcome Measures

2.3.1 Safety Evaluations

The overall safety profile is characterized by assessing the incidence of adverse events (AEs), serious adverse events (SAEs), suspected adverse reactions, adverse reactions, and unexpected adverse reactions.

2.3.2 Efficacy Evaluations

Composite endpoint of overall success at 12 weeks:

To be considered a success at 12 weeks, subjects must achieve ALL of the following:

- Have a permanent revision prosthesis implanted by 12 weeks post initial surgery;
- Have the same functioning prosthesis at 12 weeks post initial surgery;
- Show no signs of infection, per the Delphi Criteria, between implantation and 12 weeks post initial surgery; AND
- Have no surgical intervention for infection between initial surgery and 12 weeks post initial surgery.

Composite endpoint of overall success at 12 months:

To be considered a success at 12 months, subjects must achieve ALL of the following:

- Have a permanent revision prosthesis implanted by 12 weeks post initial surgery;
- Have the same functioning prosthesis at 12 months post initial surgery;
- Show no signs of infection, per the Delphi Criteria, between implantation and 12 months post initial surgery; AND
- Have no surgical intervention for infection between initial surgery and 12 months post initial surgery.

2.3.3 Exploratory Measures

Changes in erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), serum creatinine (sCr), complete blood count (CBC) with differential, and blood urea nitrogen (BUN) will be measured at each follow-up visit. Tissue viability, bone defects and bone loss will be assessed intraoperatively for the Stage 1 and the Stage 2 surgeries. Serum levels of vancomycin and tobramycin will be measured daily during experimental treatment to monitor for toxic systemic levels, as will the volume of effluent to determine the net fluid volume removed from the joint space. Opioid and other analgesic use will be tracked at each follow-up visit.

3 Follow-up

Subjects will be assessed at the interstage period, stage 2 surgery,, 3 weeks, 6 weeks, 12 weeks, and 12 months from initial surgery.

4 Subject Population and Selection

Skeletally mature patients with chronic PJI of the hip or knee who meet all the following inclusion and none of the exclusion criteria will be recruited for this study.

Enrollment is defined as providing informed consent for study participation and receiving at least one dose of antibiotic via local irrigation. The estimated total number of subjects enrolled is expected to be 15.

Study subjects will be compensated for certain activities required of them during their participation in the clinical study, including travel expenses for each visit.

4.1 Inclusion Criteria

- Signed informed consent;
- Age 18 years or greater;
- Preoperative diagnosis of PJI of the hip or knee per the 2018 Definition of Periprosthetic Hip and Knee Infection [18], which is one of the following two major criteria:
    - The presence of a sinus tract communicating with the prosthesis; OR
    - 2 positive cultures from separate fluid or tissue samples from the affected joint; OR
    - A pre-Stage 1 score ≥ 6 from all minor criteria listed in Table 3, including intraoperative criteria from procedures performed within 8 weeks prior to Stage 1.

Table 3 Criteria for Periprosthetic Hip and Knee Infection

Preoperative Diagnosis: Minor Criteria	**Score**	**Decision**
Serum		≥ 6 Infected 2-5 Possibly infected* 0-1 Not infected
Elevated CRP or D-Dimer	2	
Elevated ESR	1	
Synovial		
Elevated synovial WBC or LE	3	
Positive Alpha-defensin	3	
Elevated synovial PMN (%)	2	
Elevated Synovial CRP	1	
Intraoperative Diagnosis: *Inconclusive Pre-op Score or Dry Tap	**Score**	**Decision**
Preoperative score	-	≥ 6 Infected 4-5 Inconclusive ≤ 3 Not infected
Positive histology	3	
Positive purulence	3	
Single positive culture	2	

Abbreviations: CRP = c-reactive protein; ESR = erythrocyte sedimentation rate; WBC = white blood cell; LE = leukocyte esterase; PMN = polymorphonuclear leukocytes

* Patients with a score ≥ 6 from any preoperative or intraoperative minor criteria obtained within 8 weeks prior to Stage 1 meet the Musculoskeletal Infection Society (MSIS) criteria. Patients with a score of < 6 prior to Stage 1 surgery do not meet the inclusion criteria for this clinical study.

- Chronic PJI (symptoms lasting at least 4 weeks) per Tsukayama et al. [19];
- Medical clearance for surgery;
- Physical and mental ability to comply with the protocol, including the ability to read and complete required forms, and willingness and ability to adhere to the scheduled follow-up visits and requirements of the protocol.

4.2 Exclusion Criteria

- Late acute hematogenous infection per Tsukayama et al. [19];
- Patients for whom a two-stage exchange arthroplasty is not indicated;
- Sepsis;
- Previously failed single- or two-stage revision arthroplasty for PJI (aseptic revision, polyethylene liner exchange, and/or irrigation and debridement with component retention is allowed)
- Patients with PJI of more than one joint;
- Patients on chronic antibiotic therapy (≥ 6 months duration);
- Patients who require therapeutic anticoagulation;
- Patients on antiplatelet therapy for whom withholding antiplatelet therapy for any amount of time is contraindicated;
- Patients with renal insufficiency/failure (sCr ≥ 2.0 mg/dl); [19].
- Patients with uncontrolled diabetes, defined as: hemoglobin A1C levels > 8.0%;
- Patients on immunosuppressive therapy, chemotherapy for malignant disease, or glucocorticoid therapy (e.g. prednisone ≥ 10 mg/day);
- Patients with immunodeficiency (e.g., splenectomy, sickle cell anemia, Stage 3 human immunodeficiency virus (HIV), primary humoral, bone marrow or other transplantation);
- Anticipated or potential patient relocation that may interfere with follow-up examinations;
- Allergy to vancomycin HCl or tobramycin sulfate (Note: prior history of Red Man's syndrome is not considered an allergy);
- Patients who are pregnant or planning to become pregnant;
- Patients in whom negative pressure wound therapy is contraindicated;
- Patients infected with pathogens that are not considered susceptible to vancomycin HCl or tobramycin sulfate, as per the Investigator's opinion.
- Breastfeeding at screening visit;
- Patients who are prisoners;

- Participation in another clinical trial of another Investigational Drug or Investigational Device within the past 30 days

5 Study Treatment Procedures

5.1 Treatment Summary

Subjects considered potential candidates for the study will sign an Institutional Review Board (IRB)-approved Informed Consent Form (ICF) and Health Insurance Portability and Accountability (HIPAA) Authorization Form (if needed) prior to participating in any study activities. The treatment consists of standard of care (SOC) procedures and study procedures. (Table 4.)

Table 4 Treatment Summary

	Pre-operative	**Stage 1 (Day 0)**	**Interstage (Stage 1 to 7-10 Days)**	**Stage 2 (Day 7 -10)**	**Post-op (Stage 2 to 6 weeks post-Stage 1**
Medical treatment per standard of care (SOC)	X	X	X	X	X
Resection arthroplasty & debridement per SOC		X			
Implantation of irrigation line		X			
Application of NPWT			X		per SOC
Local antibiotic irrigation therapy			X		
Revision arthroplasty per SOC				X	
Systemic antibiotic therapy per IDSA guidelines & study protocol			As indicated by positive culture	Start at Stage 2	Stop Day 42*

* Total 6 weeks antibiotic therapy post Stage 1

5.2 Stage 1 Preoperative Treatment

Provide preoperative treatment for all Stage 1 subjects per standard of care. Withholding preoperative antibiotics for 14 days pending intraoperative cultures is recommended. Administer 1 g of commercially available tranexamic acid (TXA) in 100 ml normal saline (NS) intravenously over a period of 10 minutes, prior to the operative procedure per the manufacturer's instructions for use.

5.3 Irrigation, Debridement. and Component Removal

After entering the joint, proceed as follows:

- Collect equal amounts of synovial fluid in two syringes (1 to 3 ml each), one for aerobic and one for anaerobic culture.
- Obtain two synovial tissue samples, each from a different area of the joint, for histological evaluation of neutrophil count.
- Remove all existing implants as per standard of care.
- For knee subjects, obtain two additional samples for tissue culture, one from the femoral

canal and one from the tibial canal or the implant/bone interface.

- For hip subjects, obtain two additional samples for tissue culture, one each from the acetabulum and the femoral canal.
- If no fluid is obtained, obtain one additional sample from the joint for tissue culture.
- As per standard of care, perform a radical debridement and total synovectomy, including debridement of the inner surface of the entire joint capsule including the posterior capsule of knee.
- As per standard of care, debride all bony surfaces, such as gentle reaming of the femur and acetabulum in hips and the femoral and tibial canals in knees, and remove all visibly infected bone from all implant/bone interfaces in the knee.
- Assess and record tissue and muscle viability using the parameters provided in Table 5.
- Assess and record: (i) any bone defects of the knee using the Anderson Orthopaedic Research Institute (AORI) Classification (Table 6), or (ii) any acetabular bone loss (Table 7) and (iii) any femoral bone loss (Table 8) using the Paprosky Classification system.

Table 5 Tissue/Muscle Viability

Muscle contraction upon stimulation with monopolar pencil?	Yes/No
Synovitis?	Yes/No
Purulence?	Yes/No
Necrosis?	Yes/No
Bleeding bone?	Yes/No
Signs of poor tissue perfusion?	Yes/No

Table 6 AORI Bone Defect Types

Type 1 defect	• Intact metaphyseal bone Good cancellous bone at or near a normal joint-line level
Type 2 defect	• Damaged metaphyseal bone Loss of cancellous bone that requires cement fill, augments, or small bone grafts to restore a reasonable joint-line level • 2A-one femoral or tibial condyle • 2B-both femoral or tibial condyles
Type 3 defect • (Deficient metaphyseal bone)	Deficient bone that compromises a major portion of either condyle or plateau; these defects usually require a large structural allograft, a rotating hinged component, or custom component

AORI = Anderson Orthopaedic Research Institute

Table 7 Paprosky Classification of Acetabular Bone Loss

Type I	Minimal deformity, intact rim
Type IIA	Superior bone lysis with intact superior rim

Type IIB	Absent superior rim, superolateral migration
Type IIIC	Localized destruction of medial wall
Type IIIA	Bone loss from 10am-2pm around rim, superolateral cup migration

Table 8 Paprosky Classification of Femoral Bone Loss

Classification	**Description**
Type I	Minimal metaphyseal bone loss
Type 2	Extensive metaphyseal bone loss with intact diaphysis
Type III a	Extensive metadiaphyseal bone loss, minimum of 4 cm of intact cortical bone in the diaphysis
Type III b	Extensive metadiaphyseal bone loss, less than 4 cm of intact cortical bone in the diaphysis
Type IV	Extensive metadiaphyseal bone loss and a non-supportive diaphysis

- After documenting bone defects, irrigate the joint using a short nozzle for surface irrigation and an intramedullary water pic in the canals.
- Per the standard of care, use the following irrigation protocol (lavage pressure not to exceed 15 psi):
    1. Soak the wound in a 50:50 dilution of 3% hydrogen peroxide and NS for 3 minutes. For example, add 250 ml of 3% hydrogen peroxide to 250 ml of NS for a 50% solution.
    2. Irrigate the wound with approximately 3L NS by pulsatile lavage.
    3. Soak the wound in 0.3% dilute povidone-iodine for 3 minutes. For example, povidone-iodine typically comes as a 10% solution. To dilute it to 0.3% bring 15 ml of 10% povidone iodine up to a total volume of 500 ml with NS.
    4. Irrigate the wound with approximately 3L NS by pulsatile lavage.

5.4 Irrigation Line Placement and Closure

- Approximately fifteen minutes prior to release of tourniquet (if used) or wound closure, administer 1 g of commercially available TXA in 100 ml NS intravenously over a period of 10 minutes per manufacturer's instructions for use.
- Use only monofilament suture for wound closure.
- Cut the instillation disk off the end of the negative pressure wound therapy (NPWT) instillation line and place the freshly cut end of the line in the intraarticular space.
- Cut one or more wound vacuum sponges approximately 5 cm wide and slightly longer than the length of the surgical wound, and place the sponge into the wound along the same path as the catheter, leaving approximately 3 cm of sponge extending out of the wound (this provides fluid communication from the joint to the NPWT system and allows bedside removal of the sponge if subject is unable to return to surgery).
- In the knee, partially close the capsule from the distal to the proximal end, leaving approximately 5 cm of the proximal capsule open to maintain fluid communication

with the deep sponge(s). In the hip, no deep fascial closure is necessary.

- Partially close the skin layer with a running subdermal monofilament suture. Leave approximately 5 cm open for communication with the deep sponge(s).

5.5 Wound Dressing and Antibiotic Therapy Start

- Cut the incisional vacuum sponge to cover the entire wound, both closed and open portions, ensuring contact with the deep sponges for fluid communication.
- Place a sterile occlusive wound dressing over the incisional vacuum sponge.
- The infusion line, exiting from the open portion of the wound, requires additional attention to prevent leaking. A "basement layer" of occlusive dressing is applied directly on the skin under the infusion line. A second layer of occlusive dressing is applied over the top of the infusion line, wrapping around it to form a mesentery, which then adheres to the basement layer.
- Create an outflow system by cutting a window approximately 2cm long in the occlusive dressing directly over proximal end of the incisional vacuum sponge and placing the V.A.C.® ULTA™[1] outflow disc with catheter on top of the window cut into the occlusive dressing.
- Place an additional occlusive dressing over the outflow disc and tubing to protect it from being accidentally disconnected.
- Connect the irrigation and vacuum lines to the NPWT cassette and collection cannister, respectively, then load the cassette and cannister on the NPWT system.
- Hang the tobramycin sulfate solution for local irrigation.
- Select V.A.C.® VeraFlo™ Therapy and program the NPWT settings as follows:

  Fill Assist: (Off)
  Start Phase: Instill
  Instill Volume: 50 ml
  Soak Time: 30 min
  VAC (vacuum assisted closure) Therapy Time: ½ hour Target
  Pressure: -125 mmHg
  Intensity: Low

- Select "OK" to confirm the settings on the NPWT system, which will then automatically check for an intact seal.
- Once the seal is confirmed, select "OK" on the NPWT system to proceed to the programmed instillation of tobramycin sulfate. This is the "Operating Room (OR) Therapy Start Time". RECORD the OR Therapy Start Time. This time will be used by nursing to repeat the 24-hour local antibiotic treatment cycles.
- The first dose of tobramycin sulfate will automatically be instilled into the wound in the operating room. Upon completion of the instillation of the tobramycin sulfate solution, CLAMP the VACUUM LINE first, then TURN OFF the NPWT system in order to allow the tobramycin to soak for 2 hours. The NPWT System must be turned off within 30

[1] V.A.C. ULTA is a Trademark of KCI, an Acelity company.

minutes of instillation. DO NOT turn off the NPWT system before clamping. If the NPWT system is not turned off within 30 minutes of instillation, the system will automatically start a vacuum cycle. In this case, immediately turn off the NPWT system. Do not administer additional tobramycin sulfate. Wait 2 hours from the OR Therapy Start Time and proceed with administration of vancomycin HCl per Section 5.5 below.

- Finally, for the knee place a blanket inside an immobilizer. Keep the tubing away from the skin and on top of the blanket within the immobilizer and close the immobilizer while ensuring there are no kinks in the tubing.
- Do not open the wound dressing (hip or knee) until the day of the Stage 2 operation.
- Initiate venous thromboembolism (VTE) prophylaxis with low molecular weight heparin 12 hours post-op, continuing until the last dose is administered the night before Stage 2 surgery

5.6 Interstage Antibiotic Therapy

The total antibiotic dose per 24-hour period reflects current labeling for safe total 24-hour systemic dose of 80 mg/day for tobramycin sulfate and up to 3000 mg/day for vancomycin HCl. Each day, the pharmacy shall reconstitute tobramycin sulfate and vancomycin HCl as specified in Table 9.

Initial Dose

NOTE: The first dose of tobramycin sulfate is administered in the operating room. This is the start of Interstage therapy.

- After the tobramycin sulfate solution has been allowed to soak for 2 hours from the OR Therapy Start Time recorded in the operating room (and no more than 2.5 hours), hang the vancomycin HCl solution, UNCLAMP the vacuum line and TURN ON the NPWT system. RECORD the vancomycin HCl hang time. If the soak time exceeds 2.5 hours, immediately complete this step and proceed to the next step below.
- On the NPWT screen, go to Advanced Settings and change the setting for Start Phase to "VAC" and select "OK". **DO NOT CHANGE ANY OTHER SETTINGS.** Confirm the NPWT Settings as follows:

V.A.C.® VeraFlo™ Therapy
Fill Assist: (Off)
Start Phase: VAC
Instill Volume: 50 ml
Soak Time: 30 min
VAC Therapy Time: 1/2 hour
Target Pressure: -125 mmHg
Intensity: Low

DO NOT CHANGE SETTINGS AGAIN FOR THE DURATION OF THERAPY.

- Select "OK" to confirm the settings, and the NPWT system will automatically check for an intact seal.
- The NPWT system will then automatically begin with a 30-minute vacuum, followed by instillation of vancomycin HCl solution and a 30-minute soak. The

NPWT system will follow this programmed cycle until manually stopped.

- Three to four hours after the OR Therapy Start Time, collect blood for measurement of peak serum tobramycin level. If blood is not collected at the specified time, collect blood as soon as possible thereafter and continue with therapy and blood collection on the schedule described in this protocol.
- Replace the NPWT collection canister approximately every 12 hours as needed, RECORD the total volume of fluid collected in each canister.

Subsequent Interstage Doses

During each subsequent 24-hours of Interstage therapy, perform the following:

- 30 minutes before the OR Therapy Start Time (+/- 30 minutes), press "Stop" on the NPWT screen, hang a new bag of tobramycin sulfate solution, then press "Start". This will perform a final 30-minute vacuum cycle and ensure that the daily antibiotic treatment cycle begins approximately at the OR Therapy Start Time. RECORD the tobramycin sulfate hang time.
- At the same time as hanging the tobramycin sulfate (30 minutes before the OR Therapy Start Time +/- 30 minutes), collect blood for measurement of daily vancomycin serum level, tobramycin trough serum level, sCr, complete blood count (CBC) with differential and BUN. If blood is not collected at the specified time, collect blood as soon as possible thereafter and continue with therapy and blood collection on the schedule described in this protocol.
- Immediately after the tobramycin sulfate solution instillation, CLAMP the VACUUM LINE first, then TURN OFF the NPWT system. The NPWT System must be turned off within 30 minutes of instillation. DO NOT turn off the NPWT system before clamping. If the NPWT system is not turned off within 30 minutes of instillation, the system will automatically start a vacuum cycle. In this case, immediately turn off the NPWT system. Do not administer additional tobramycin sulfate. Wait 2 hours from tobramycin instillation (approximately the OR Therapy Start Time) and proceed to the next step below.
- Two hours after tobramycin sulfate instillation (approximately 2 hours and no more than 2.5 hours after OR Therapy Start Time), hang the vancomycin HCl solution, UNCLAMP the vacuum line and then TURN ON the NPWT system. **DO NOT CHANGE THE NPWT SETTINGS.** RECORD the vancomycin HCl hang time. If the soak time exceeds 2.5 hours, immediately complete this step and proceed to the next step below.
- The NPWT system will then automatically begin with a 30-minute vacuum, followed by instillation of vancomycin HCl solution and a 30-minute soak. The NPWT system will follow this programmed cycle until manually stopped.
- Three hours (and no more than 4 hours) after the OR Therapy Start Time, collect blood for measurement of peak serum tobramycin level. If blood is not collected at the specified time, collect blood as soon as possible thereafter and continue with therapy and blood collection on the schedule described in this protocol.
- Replace the NPWT collection canister every 6 to 8 hours as needed, RECORD the total volume of fluid collected in each canister.

Repeat the 24-hour antibiotic irrigation regimen above until the subject is transferred to surgery for the

Stage 2 procedure. The Stage 2 procedure may be scheduled any time on post-operative day 7. It is acceptable for the Stage 2 procedure to take place earlier in the day than the previous Stage 1 procedure, resulting in less than 24 hours of local antibiotic therapy on day 7.

Always begin each antibiotic therapy cycle as close as possible to 30 minutes before the OR Therapy Start Time. Any deviation in timing of antibiotic therapy or blood collection from a previous day is not carried forward to subsequent days.

During the interstage period, subjects may receive systemic antibiotics as directed by a physician per Infectious Diseases Society of America (IDSA) guidelines. However, systemic vancomycin HCl or tobramycin sulfate administered simultaneously with local vancomycin HCl and tobramycin sulfate should be avoided unless directed by the treating physician, due to the risk of nephrotoxicity or ototoxicity. In the event that intravenous vancomycin or aminoglycoside administration is deemed appropriate in the interstage period, timing of daily laboratory blood collection may be adjusted on the order of the treating physician or pharmacist. See Table 9 for a summary of the local irrigation and monitoring protocol.

Per the standard of care, subjects are non-weight bearing but allowed to stand with toe touch if tolerated. Elevation of the extremity should be continuous when in bed to reduce potential for edema and fluid retention.

For further instruction on programming settings on the V.A.C.® ULTA™ Negative Pressure Wound Therapy System, see the V.A.C.® ULTA™ Quick Reference Guide.

Table 9 Antibiotic Instillation and Monitoring Regimen

Drug	Tobramycin 80mg in 50 ml NS	Vancomycin 3000 mg in 1200 ml NS
Concentration	1.6 mg/ml (1600 µg/ml)	2.5 mg/ml (2500 µg/ml)
Compounding (In ISO Class 7 Clean Room with ISO Class 5 PEC)	Remove 8 ml from 50ml NS infusion bag to yield 48 ml. Add 2 ml of tobramycin 40 mg/ml for total of 80 mg tobramycin in 50 ml NS.	Reconstitute vancomycin powder to concentration of 50 mg/ml. Add 100 ml NS to 1000 ml (1040 ml total volume) NS infusion bag to yield 1140 ml. Add 60 ml of vancomycin (50 mg/ml) to yield vancomycin 3000 mg in 1200 ml NS.
Stability	24 hrs (room temperature) / 48 hrs (refrigerated)	24 hrs (room temperature) / 7 days (refrigerated)
Administration	**Nursing Administration Instructions:** **For Irrigation** **Dispense in Bag** Irrigate with 50 ml tobramycin sulfate solution once every 24 hours via NPWT system with a 2-hour soak time, by UNCLAMPING the irrigation line, starting irrigation, CLAMPING vacuum line during soak, and turning pump OFF to achieve 2-hour soak time (no more than 2.5 hours). NPWT Settings: V.A.C. VeraFlo Therapy Fill Assist: (Off) Start Phase: Vacuum Instill Volume: 50 ml Soak Time: 30 min VAC Therapy Time: 1/2 hour Target Pressure: -125 mmHg Intensity: Low	**Nursing Administration Instructions:** **For Irrigation** **Dispense in Bag** Irrigate with 50 ml vancomycin HCl solution once every hour via NPWT system with a 30-minute soak time and 30 minutes suction @ -125mmHg. Repeat hourly. Stop once daily for administration of tobramycin sulfate. Restart upon completion of tobramycin sulfate soak. NPWT Settings: V.A.C. VeraFlo Therapy Fill Assist: (Off) Start Phase: Vacuum Instill Volume: 50 ml Soak Time: 30 min VAC Therapy Time: 1/2 hour Target Pressure: -125 mmHg Intensity: Low
Monitoring	Collect blood for daily tobramycin serum levels: (i) 3-4 hours after the OR Therapy Start Time (peak level) **(ii)** 30 minutes (+/- 30 minutes) before the OR Therapy Start Time (trough level).	Collect blood for daily CBC with differential, BUN, sCr and vancomycin serum levels 30 minutes (+/- 30 minutes) before the OR Therapy Start Time.
Dose Adjustments	Maintain tobramycin serum trough levels at <1 µg/ml. If serum trough levels are >1 µg/ml or toxicity is a concern, decrease total dose based on serum concentration and PK parameters of the drug. Decrease total drug administered but not total volume. Example: 40 mg tobramycin sulfate in 50 ml NS.	Maintain vancomycin serum levels at <20 µg/ml. If serum levels >20 µg/ml or if toxicity is a concern, decrease total dose based on serum concentration and PK parameters of the drug. Decrease total drug administered but not total volume. Example: 1500 mg vancomycin HCl in 1200 ml NS.

NS = normal saline; ISO = International Organization for Standardization; PEC = primary engineering control; NPWT = negative pressure wound therapy; VAC = vacuum assisted closure; HCl = hydrochloride; OR = operating room; CBC = complete blood count; BUN = blood urea nitrogen; sCr = serum creatinine; PK = pharmacokinetic

5.7 Monitoring for Toxicity

The subject and the surgical site around the NPWT dressing shall be monitored for unexpected increase in:

- edema;
- local tissue redness (erythema) and induration;
- local tissue temperature;
- local itching/pruritus;
- surgical site pain;
- discoloration or worsening appearance of NPWT drainage; and
- frequency of NPWT drainage volume of less than 50 cc per hour.

Moderate increases of the conditions listed above are routinely encountered post-operative to a resection arthroplasty procedure. Should these conditions persist or exceed post-operative clinical expectations, local toxicity should be considered as a possible cause.

Serum levels of each antibiotic are monitored daily during local irrigation therapy. Vancomycin HCl serum levels in this study are not true trough or peak levels, because of the near-continuous irrigation regimen. Serum levels will slowly increase toward a steady state level.

If toxicity is suspected prior to completion of the local antibiotic irrigation therapy, the dose of local antibiotic irrigation may be adjusted, or local antibiotic irrigation may be withheld at the direction of the treating physicians. The subject may also be returned to the operating room for replacement of the NPWT dressing, including all sponges, at which time the local tissue may be examined and debrided if necessary.

All additional treatments, surgical procedures, and deviations from the clinical protocol shall be recorded and reported to the Sponsor as appropriate.

5.8 Stage 2 Revision Arthroplasty

Administer preoperative antibiotics per IDSA guidelines and 1 g of commercially available TXA in 100 ml NS intravenously over a period of 10 minutes, prior to the operative procedure per manufacturer's instructions for use.

Upon entering the joint proceed as follows:

- Collect equal amounts of any available fluid in two syringes (1 to 3 ml each), one for anerobic culture and one for aerobic culture.
- Obtain two synovial tissue samples, each from a different area of the joint, for histopathological evaluation of neutrophil count and complete histological evaluation for toxicity.
- For knee subjects, obtain two additional samples for tissue culture, one from the femoral canal and one from the tibial canal or the implant/bone interface.
- For hip subjects, obtain two additional samples for tissue culture, one each from the acetabulum and the femoral canal.
- If no fluid is obtained, obtain one additional sample for tissue culture from the joint.
- Debride any necrotic tissue, ream the intramedullary canals and lavage at surgeon's discretion to prepare the joint for implant placement.
- Assess and record tissue and muscle viability using the parameters provided in Table 5.
- Assess and record: (i) any bone defects of the knee using the AORI Classification System

(Table 6), or, for hip defects (ii) any acetabular bone loss (Table 7) and (iii) any femoral bone loss (Table 8) using the Paprosky Classification system.

- Repair any bony defects and prepare the bone for implant revision at surgeon's discretion.
- Implant the revision prosthesis using bone cement premixed with 1 gram of vancomycin per package of cement.
- After reimplantation, use the following irrigation protocol (lavage pressure not to exceed 15 psi):
    - Soak the wound in a 50:50 dilution of 3% hydrogen peroxide and NS for 3 minutes. For example, add 250 ml of 3% hydrogen peroxide to 250 ml of NS for a 50% solution.
    - Irrigate the wound with approximately 3L NS by pulsatile lavage.
    - Soak the wound in 0.3% dilute povidone-iodine, while continuing to mechanically debride wound with scrub brushes and sponges for three minutes. For example, povidone-iodine typically comes as a 10% solution. To dilute it to 0.3% bring 15 ml of 10% povidone iodine up to a total volume of 500 ml with NS.
    - Irrigate the wound with approximately 3L NS by pulsatile lavage.
- Approximately fifteen minutes prior to release of tourniquet (if used) or wound closure, administer 1 g of commercially available TXA in 100 ml NS intravenously over a period of 10 minutes per manufacturer's instructions for use.
- Use only monofilament suture for wound closure.
- Apply a commercially available incisional vacuum system at closing and use postoperatively as indicated and directed by the treating physician.

5.9 Stage 2 Postoperative Care

- Per the standard of care, initiate VTE prophylaxis on aspirin 12 hours post-op and continue until the 6-week follow-up visit.
- Per the standard of care, allow weight bearing following Stage 2 at surgeon's discretion.
- Administer postoperative intravenous (IV) antibiotics as follows:
    - Culture-negative subjects receive IV vancomycin and cefepime; and culture-positive subjects receive organism-specific IV or oral antibiotics per IDSA guidelines for approximately 5 weeks, ending 6 weeks after Stage 1 surgery (+/- 3 days).
    - Selection of vancomycin and/or cefepime may be modified for clinical reasons, such as subject allergies, as directed by the treating physicians.
    - Antibiotic therapy is expected to end 6 weeks after Stage 1 surgery unless otherwise directed by the treating physicians. If additional antibiotic therapy is required, RECORD the subject's PJI status per the Delphi criteria and the reason for continued antibiotic therapy.

5.10 Postoperative Physical Therapy

There is no standard physical therapy regimen for subjects undergoing resection arthroplasty.

Numerous factors influence the physical therapy protocol. Thus, physical therapy will be individualized for each subject according to the clinical judgment of the operating surgeon.

6 Schedule of Visits

6.1 Treatment and Data Collection Table

The study treatment and data collection for each scheduled visit are summarized in Table 10.

Table 10 Treatment and Data Collection

Events	**Visit 1 Baseline Screen**	**Visit 2 Stage 1**	**Visit 3 Interstage period Daily**	**Visit 4 Stage 2**	**Visit 5 3-week ± 1 week follow-up**	**Visit 6 6-week ± 1 week follow-up**	**Visit 7 12-week follow-up ± 2 weeks**	**Visit 8 1-year follow-up ± 4 weeks**
Time range permitted for logistical purposes	**Pre-op**	**Day 0**	**Days 1-7 Max. 10**	**Day 7 Max. 10♦**	**Day 14-28**	**Day 35-49**	**Day 70-98**	**Day 337-Day 393**
Inclusion/Exclusion	X							
Informed Consent (& HIPAA)	X	Confirm						
Urine pregnancy test	X							
2 synovial fluid cultures		X		X				
Medical history, vital signs, therapy, CCI score	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Administer 1g IV TXA pre-op and intraop		X		X				
2-3 tissue cultures		X		X				
2 samples for pathology		X		X				
Muscle/bone (AORI) viability assessment		X		X				
Operative time		X		X				
Place irrigation line & NPWT sponges		X						
Program NPWT pump		X		X				
Document implant and local antibiotics/cement				X				
*Administer local tobramycin & vancomycin		Start intra-op Stage 1	ongoing	Stop pre-op Stage 2				
**Administer tailored IV or oral antibiotics per IDSA, if culture +		Start post-op Stage 1	ongoing	ongoing	ongoing	Stop Day 42		
If culture -, administer IV vancomycin & cefepime				Start post-op Stage 2	ongoing	Stop Day 42		
Tobramycin (peak/trough)/ vancomycin serum levels		X	daily	X				
Vancomycin and aminoglycosides serum levels, if administered					X	X		
Transfusion record		X	X	X	X	X		
sCR and BUN	X	X[b]	daily	X	X	X	X	
Complete Blood Count with differential & absolute neutrophils	X	X[b]	daily	daily until discharge	X	X	X	X
ESR, non-Cardiac CRP	X	X[b]	daily	X	X	X	X	X
Concomitant medications, including opioid use	X	X	X	X	X	X	X	X
AE's and complications		X	X	X	X	X	X	X
Wound check /joint assessment/Delphi			No leak. Do not open	X	X	X	X	X

HIPAA = Health Insurance Portability and Accountability Act; CCI = Charlson Comorbidity Index; AEs = adverse events; HgA1C = glycated hemoglobin; AORI = Anderson Orthopaedic Research Institute; NPWT = Negative Pressure Wound Therapy; IV = intravenous; IDSA = Infectious Diseases Society of America; sCr = serum creatinine; BUN = blood urea nitrogen; CBC = complete blood count; ESR = erythrocyte sedimentation rate; CRP = c-reactive protein; AE = adverse event

All study time-points, follow-up visits and time-based outcomes are defined from the day of Stage 1.

* The interstage period shall be completed on the seventh day after Stage 1 whenever possible, and no later than the 10th day, to account for scheduling of Stage 2. The last instillation of antibiotics should be given the day of the Stage 2 surgery. Administer tobramycin first (before vancomycin) so that at least 7 days of both tobramycin and vancomycin are administered. Vancomycin may be administered for less than a full day on the seventh day if needed to accommodate a Stage 2 surgery time that is earlier than the Stage 1 surgery time.

** Subjects may have positive cultures from previous aspirations or early in the interstage period. In either of these cases non-nephrotoxic IV or highly bioavailable oral antibiotics safe for use with vancomycin and tobramycin, are allowed at any time, including during the interstage period for ancillary treatment of specific organisms according to IDSA recommendations. Rifampin is not allowed during the interstage period, due to interaction with anesthetic in Stage 2. Non-nephrotoxic oral companion therapy of rifampin for *Staphylococci* or fluoroquinolones per IDSA recommendations for gram negative infections may be added during post-Stage 2 systemic antibiotic therapy.

[a] Abbreviated medical history, vital signs, change in medical therapy, no CCI score. Vital signs do not need to be collected at Visits 5, 6, 7, and 8.

[b] If baseline blood tests are taken within 48 hours of Stage 1 surgery and new blood tests are not performed day of Stage 1 surgery

The Delphi Criteria as used in this study are defined as: (1) infection eradication, characterized by a healed wound without fistula, drainage, or pain, and no infection recurrence caused by the same organism strain; (2) no subsequent surgical intervention after reimplantation surgery owing to infection; and (3) no occurrence of PJI-related mortality (by causes such as sepsis, necrotizing fasciitis) [17].

Ensure that the subject meets all inclusion/exclusion criteria and document in file. Collect signed informed consent, HIPAA form, screening and baseline data. Subjects found to not meet one or more inclusion/exclusion criteria are documented as screening failures, notified as such and treated outside of the study as directed by the physician. Perform the following activities for all other subjects, starting with Stage 1 surgery and at each subject visit for one year.

6.2 Screening and Baseline Data

- Administer Informed Consent Form
- Confirm that the patient meets all inclusion criteria and none of the exclusion criteria
- Administer pregnancy test (only women of childbearing potential)
- Collect blood for tests in Table 10 and record results
- Record demographics, CCI score, medical history, and current therapy
- Confirm physician's evaluation for chronic PJI diagnostic criteria per MSIS and check all diagnostic criteria on the source worksheet (SW)
- Document infecting organism, if known
- Record dose of all concomitant medications, including opioid use
- Record vital signs: height, weight, heart rate, respiration rate, blood pressure, and temperature

See Section 9.3 for procedures to follow if the subject is unfit for surgery on days 7-10.

6.3 Stage 1 Surgery

- Record date of surgery
- Update medical history, changes in therapy, and preoperative and postoperative vital signs

- Record name and dose of all concomitant medications, including opioid use
- Document type and quantity of NPWT products used
- Collect intraoperative samples for histopathology and cultures and record results
- Record results of blood tests in Table 10 (if time between baseline visit and stage 1 surgery is greater than 48 hours)
- Record use of cell savers, transfusions, and volume transfused
- Record assessment of muscle and bone viability
- Record assessment of AORI bone defect type
- Record assessment of Paprosky Classification of Bone Loss
- Document tourniquet time and surgery time (skin to skin)
- Record blood loss and all clinical laboratory results
- Document all adverse events (AEs)/serious adverse events (SAEs)
- Record time of first tobramycin sulfate instillation (OR Therapy Start Time)

6.4 Interstage Period (Daily Until Stage 2 Surgery)

- Record lot number of all irrigation antibiotics and diluents in the pharmacy.
- Record date and time when tobramycin sulfate and vancomycin HCl is hung.
- Record V.A.C.® ULTA™ settings on Day 1. DO NOT CHANGE after first dose of vancomycin HCl.
- Record fluid volume in effluent (daily total of all cannister volumes)
- Record daily dose of all concomitant medications, including opioid use
- Record changes in therapy, and vital signs
- Collect blood for tests in Table 10 and record results
- Document all AEs/SAEs
- Record transfusion events and volume transfused (including packed cells)

6.5 Stage 2 Surgery (7 to 10 Days After Stage 1)

- Record date and time of surgery
- Record abbreviated medical history, changes in therapy, and preoperative and postoperative vital signs
- Download electronic Therapy Log from NPWT system.
- Record implanted device-identifying data
- Document type and amount of bone cement and antibiotics used for implant fixation
- Record wound assessment
- Collect blood for tests in Table 10 and record results
- Collect intraoperative samples for histopathology and cultures and record results
- Record assessment of muscle and bone viability
- Record assessment of AORI bone defect type
- Record assessment of Paprosky Classification of Bone Loss
- Document tourniquet time and surgery time (skin to skin)

- Record blood loss and all clinical laboratory results
- Document all AEs/SAEs
- Record dose of all concomitant medications, including opioid use
- Record transfusion events and volume transfused (including packed cells)
- Record date of discharge from hospital
- Document results of all cultures

6.6 3 Weeks Post-op (After Stage 1)

- Collect blood for tests in Table 10 and record results
- Record changes in therapy, and vital signs
- Document clinical observations of wound and PJI (per Delphi criteria)
- Record dose of all concomitant medications, including opioid use
- Document all AEs/SAEs
- Record transfusion events and volume transfused (including packed cells)
- Document any change to organism-specific antibiotics based upon positive culture results per study protocol

6.7 6 Weeks Post-op (After Stage 1)

- Collect blood for tests in Table 10 and record results
- Document clinical observations of wound and PJI (per Delphi criteria)
- Record dose of all concomitant medications, including opioid use
- Record changes in therapy and vital signs
- Document all AEs/SAEs
- Record transfusion events and volume transfused (including packed cells)
- Determine and document if the subject is to be taken off systemic antibiotics

If the subject cannot be taken off antibiotic therapy, document reason and schedule additional follow-up as needed.

6.8 12 Weeks Post-op (After Stage 1)

- Collect blood for tests in Table 10 and record results
- Document clinical observations of wound and PJI (per Delphi criteria)
- Record dose of all concomitant medications, including opioid use
- Record changes in therapy, and vital signs
- Document all AEs/SAEs

6.9 12 Months Post-op (After Stage 1)

- Collect blood for tests in Table 10 and record results
- Document clinical observations of wound and PJI (per Delphi criteria)
- Record dose of all concomitant medications, including opioid use
- Record changes in therapy, and vital signs
- Document all AEs/SAEs

6.10 Unscheduled Visits

Visits made to the site's Emergency Department or to the operating surgeon's office for the medical condition related to the index joint surgery are considered Unscheduled Visits, and should be documented on the relevant form provided by the clinical research organization (CRO) and in the electronic data capture (EDC) system.

- Document clinical observations of wound and PJI (per Delphi criteria)
- Record dose of all concomitant medications, including opioid use
- Record changes in therapy
- Document all AEs/SAEs

7 Statistical and Data Considerations

7.1 Overall Statistical Design

This is a single-arm, prospective, multi-center Phase 2 feasibility study. Details of the statistical analysis and handling of missing values will be described in the Statistical Analysis Plan (SAP). This section provides key elements of the statistical approaches.

7.2 Study Endpoints

The study endpoints are:

- Safety endpoints;
- Composite endpoint of overall success at 12 weeks and 12 months;
- Clinical laboratory values;
- Vitals;
- Procedural outcomes (operative time; time between Stage 1 and Stage 2 surgeries)
- Use of pain medications
- Pharmacokinetics of local irrigation route of administration for study drugs

7.3 Analysis Populations

The following analysis populations are defined for the study: Safety, Intent-to-Treat (ITT), Per-Protocol (PP) and Completed Cases (CC). The safety will be evaluated on the Safety population. The primary analysis of the efficacy will be performed on PP population. The ITT and CC populations will be used in a sensitivity analysis of the efficacy endpoints.

- The ITT population includes all enrolled subjects.
- Safety Population includes all ITT subjects who receive at least one dose of investigational medication
- The Per-Protocol population is a subset of the ITT population and includes all subjects who receive the study investigational treatment and do not have major protocol violations.
- The Completed Cases population includes all subjects in the PP population who have the 12-month follow-up visit.

7.4 Type I Error

The alpha level will be set to 0.05 based on the two-sided testing and 0.025 for the one-sided approach, if not explicitly stated otherwise. Unless otherwise indicated, all statistical inferences will be based on two-sided 95% confidence intervals and p-values less than or equal to 0.05 will be considered significant.

7.5 Statistical Approach to Secondary Endpoints

This is a feasibility and safety study. No statistical hypotheses are associated with study endpoints. Endpoints will be described by means and proportions as appropriate. Confidence intervals will be constructed.

7.6 Sample Size and Power

This is a feasibility and safety study and safety. A total of 15 subjects are expected to be enrolled. The sample size for this study was selected based on practical and not on

statistical considerations.

7.7 Statistical Analysis Plan

Data will be summarized by the number, mean, median, standard deviation and range for continuous variables and by number and relative frequency for categorical variables. Summaries will be presented by visit as appropriate. A summary of the subjects combined will be provided for the baseline information only.

7.8 Baseline Descriptive Statistics

The number of subjects in each study population will be summarized. In addition, the number of subjects completing the study and withdrawing from the study will be presented along with reasons for withdrawal.

Descriptive summaries of baseline and demographic characteristics will be presented.

7.9 Safety Analysis

The safety analyses will be performed using the ITT Population. An overall summary of AEs will be provided including the number of events and percent of subjects with any AEs, SAEs, Suspected Adverse Reactions, Adverse Reactions, and Unexpected Adverse Reaction. For each type of event, the number of events and number and percent of subjects with the event will be provided in a table. AEs will be coded using MedDRA medical dictionary.

8 Risk Analysis

Anticipated risks associated with this clinical study are summarized in Table 11, along with potential causes of risk and associated mitigations.

Table 11 Summary Table of Risk Mitigation

Risk to Health	Potential Causes	Current Mitigation
Secondary infection	Device introduces additional pathogens.	Device is sterile packed with a sterility assurance level (SAL) of 10^{-6}
		The concentrations of tobramycin sulfate and vancomycin HCl being delivered to the joint exceed MBEC for the most common PJI pathogens.
	• Additional pathogens migrate down the catheter through the opening in the skin. • The NPWT sponge is left in or on the wound without power and irrigation	Catheter entry and surrounding area is covered and sealed with sterile occlusive dressing that is not removed until stage 2 surgery.
		NPWT is programmed to operate 30 minutes per hour, 22 hours per day until stage 2 surgery.
		The concentrations of tobramycin sulfate and vancomycin HCl being flushed hourly over the catheter and through the sponge during NPWT exceed MBEC for the most common PJI pathogens.
Local adverse tissue reaction	Treatment concentrations of vancomycin cause tissue reaction.	History of use of vancomycin in bone cement and antibiotic impregnated spacers without adverse local tissue reaction
		History of use of vancomycin in allograft and other bone substitutes without adverse local tissue reaction
		History of use of vancomycin in direct intra-articular instillation without adverse local tissue reaction
	Treatment concentrations of tobramycin cause tissue reaction.	History of use of tobramycin in bone cement and antibiotic impregnated spacers without adverse local tissue reaction
		History of use of tobramycin in direct intra-articular instillation without adverse local tissue reaction
		Local irrigation concentrations are below the concentrations reported as toxic to bone in literature.
	Implant materials causes tissue reaction	All materials selected are commonly used in short term implants with a long history of safe clinical use.
		Testing of temporarily implanted devices has been performed by the NPWT manufacturer

	Reaction between antibiotics and implant materials cause tissue reaction.	History of the proposed local antibiotic regimen and identical devices without adverse local tissue reaction
	Reaction between vancomycin and tobramycin cause tissue reaction	History of use of tobramycin and vancomycin combined in bone cement and temporary cement spacers without adverse local tissue reaction
		History of use of tobramycin and vancomycin combined in direct intra-articular instillation at identical dosing and duration without adverse local tissue reaction
Nephrotoxicity and ototoxicity	Systemic levels of tobramycin causing nephrotoxicity	Peak systemic concentrations are <2µg/ml, due to once daily dose and short serum half-life, and history of identical dosing and duration without nephrotoxicity or ototoxicity complications
	Systemic levels of vancomycin causing nephrotoxicity	Average systemic concentration 3-10 µg/ml and history of identical dosing and duration without nephrotoxicity or ototoxicity complications
	The combination of the systemic levels of vancomycin and tobramycin are high enough to cause nephrotoxicity	Studies using the same intra-articular antibiotic protocol showed no signs of nephrotoxicity or ototoxicity
Fracture of bone	Debridement and/or bone removal weakens bone	Amount of debridement and bone removal identical to other standard of care in PJI
Embolism	The pressure created in the medullary canal from the delivery of the antibiotics creates a fat embolism.	The maximum pressure of the irrigation system is 5 psi.
		The NPWT system removes more fluid than delivered to the joint between each irrigation cycle.
		There is no temporary spacer to close the medullary canal, eliminating the risk of locally excessive pressure.
Dissemination of infection	Local irrigation of antibiotics drives infection into surrounding uninfected tissue	The maximum pressure of the irrigation system is 5 psi, which is well below the pulsatile lavage pressure of 15-25 psi.
Bleeding or hemorrhage	NPWT	Subjects are given TXA prior to NPWT therapy. The NPWT dressing is not applied directly over an exposed blood vessel. Subjects with contraindications for NPWT are expressly excluded
Loss of protein/ malnutrition	NPWT	Intra-stage NPWT duration is short (7-10 days). Subjects remain in hospital in proposed feasibility study
Compartment syndrome	Build-up of fluid gets trapped in joint capsule.	Joint capsule is not closed during irrigation treatment. NPWT removes excess fluid hourly, 22 hours per day.

HCl = hydrochloride; MBEC = minimum biofilm eradication concentration; PJI = prosthetic joint infection; NPWT = negative pressure wound therapy; psi = pounds/square inch; TXA = transexamic acid

9 Discontinuation of Study, Study Sites, or Subjects

9.1 Discontinuation of Study Sites

Study site participation may be discontinued if the Sponsor, the investigator, or the IRB judges it necessary for any reason.

9.2 Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations, and good clinical practice or for no reason.

9.3 Discontinuation of Subjects from Study Treatment

The criteria for enrollment must be followed explicitly.

If a subject is medically unfit for surgery for any reason on days 7-10 post-initial surgery, on day 10 local antibiotic irrigation shall be discontinued, the NPWT system shall be removed, and culture-specific or institutional-specific systemic antimicrobial therapy shall be provided as follows:

- Remove the NPWT dressing, using a sterile bedside technique.
- Completely close the wound with dermal layer approximation using suture or staples, followed by incisional VAC over the closed wound.
- Maintain incisional VAC dressing per manufacturer's instructions for use.
- Administer systemic antibiotics per institutional standard of care at the direction of the treating physicians for a period of at least 5 weeks (minimum 6 weeks antibiotic therapy).
- Continue non-weight bearing status until the subject undergoes additional surgery.

In addition to discontinuation of local antibiotic irrigation, a subject who is medically unfit for surgery on days 7-10 post-initial surgery shall be treated for underlying medical conditions, as directed by the treating physicians, until fit for surgery. At the time of subsequent surgery, the subject shall be assessed clinically for signs of PJI. If based on clinical data available at the time of surgery, the treating physician determines that the joint is no longer infected, the subject may undergo stage 2 surgery with a permanent implant. In the event of ongoing clinical signs/symptoms of infection, the subject shall be managed at the direction of the treating physicians as appropriate for the severity of the infection, including any of the following: continuation of systemic antibiotic therapy, repeat debridement with subsequent placement of an antibiotic-impregnated spacer, amputation, arthrodesis, or girdlestone procedure.

All additional treatments, surgical procedures and deviations from the clinical protocol shall be recorded and reported to the Sponsor as appropriate.

In addition, subject will be discontinued from study treatment in the following circumstances:

- The investigator decides that the subject should be withdrawn from study treatment. If this decision is made because of toxicity, an SAE (defined in Section 10), or a clinically significant laboratory value, the study drug(s) are to be discontinued, and appropriate measures are to be taken.
- The subject requests to be discontinued from study treatment.
- The subject becomes pregnant (for subjects who are able to conceive).
- The subject is significantly noncompliant with study procedures, as determined by the investigator.

- The subject meets Safety Stopping Rules as determined by the Investigator in consultation with the Independent Medical Safety Officer (IMSO) and/or Sponsor.

9.4 Subject Completion/Disposition

Every possible effort must be made by the study site personnel to contact the subject, obtain assessments, and determine the reason for discontinuation. Each subject who fails to attend the follow-up visit will first be contacted by phone. Three phone contact attempts will be made during a 2-week period. If phone contact attempts fail, a letter sent via registered mail will be sent to the subject's last known address. If there is no response to the registered letter, the subject will be declared as lost to follow-up.

The measures taken to ensure follow-up must be documented. For each case of premature termination, detailed information will be obtained explaining circumstances leading to the termination. This will be recorded on the Subject Withdrawal Form. Any subject prematurely withdrawn from the study will not be replaced.

If a subject is discontinued from study treatment for any reason, the Sponsor or its designee is to be notified immediately. Subjects discontinued from study treatment will be followed up as required for monitoring of safety events, and they will be included in the ITT population.

10 Adverse Events

10.1 Basis of Adverse Events Management

The definitions, recording, assessment and reporting of AEs required in this protocol is based requirement from 21CFR312.32(Revised as of April 1, 2018), 21CFR821 (Revised as of April 1, 2018), and Guidance for Industry and Investigators: Safety Reporting Requirements for Investigational New Drug (IND) and Bioavailability/Bioequivalence (BA/BE) Studies (FDA, December 2012, Drug Safety).

10.2 Definitions

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

Suspected Adverse Reaction: Any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Adverse Reaction: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event

Unexpected Adverse Reaction: An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For investigational drugs under this study, because they are marketed and approved in the United States, ordinarily FDA-approved prescription drug labeling is used as the basis for determining whether an event is unexpected for reporting purposes.

Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Leads to death
- Is life threatening, or places the participant at immediate risk of death
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization 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.

10.3 Adverse Event Recording

AE information will be collected throughout the study and all AEs will be captured. The Investigator or Research Coordinator will record all AEs on the appropriate Source Worksheet (SW) and entered on an electronic CRF (eCRF). The applicable SW will capture the event term, date of onset, duration, seriousness, severity, actions taken, outcome and causality to the investigational drug, the investigational procedure and the NPWT device. The Investigator is responsible for determination of severity and causality.

The Investigator will assess subjects at each study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked non-leading questions. All AEs reported by the subject or found on examination or laboratory report, must be recorded.

All AEs must be followed until resolution or a stable clinical endpoint is reached. All treatments and outcomes of the AE must be recorded.

All AEs and SAEs must be followed until:

- AE is resolved (i.e. return to normal/baseline values)
- AE is declared clinically insignificant
- AE has stabilized
- Subject is lost to follow-up or withdraws consent
- Subject completes study, including required follow-up visits
- Study closure

The Investigator must, following Good Clinical Practice (GCP) guidelines, continue to treat (or refer subject to an appropriate practitioner for continuing treatment) any AE that remains unresolved after the subject has completed study participation.

10.4 Adverse Event Assessment

The Principal Investigator (PI) is responsible to identify and report all AEs reported from his/her site. The PI is responsible for determination of severity, seriousness and causality for each event reported.

The Sponsor or Sponsor's designee will review promptly all AE information reported by the PI. The Sponsor or Sponsor's designee is responsible to make judgement for serious and causality, and to determine whether the event is "unexpected" for IND safety reporting purposes or to determine whether the event meets the definition of UADE.

In the case of the PI and Sponsor has different assessment in terms of seriousness and life-threatening of an event, for IND safety report purpose, if either the sponsor or investigator believes that the event is serious, the

event must be considered serious and evaluated by the sponsor for possible expedited reporting.

In the case of the PI and Sponsor has different assessment in term of causality of an event, for IND safety report purpose, the Sponsor' judgement will overwrite PI's judgement.

The causality assessment is defined below:

- Unrelated: known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of investigational drug therapy or procedure.
- Reasonable possibility: there is evidence to suggest a causal relationship between the investigational drug, the NPWT device and study procedure to the AE.
- Definitely Related: there is reason to conclude that the investigational drug, NPWT device and/or study procedure caused the event

10.5 Adverse Event Reporting

The investigator is responsible for the collection and submission of AE and SAE data to the Sponsor/CRO. AE data will be collected to Source Worksheet (SW) and entered into the electronic data capture (EDC).

The investigator must report to the Sponsor/CRO ANY SAE within 24 hours of the investigator becoming aware of the SAE, whether or not considered drug or NPWT device related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug or NPWT device caused the event. SAE data will be entered into the EDC and submitted on a Serious Adverse Event Report to the Sponsor/CRO.

The Investigator is responsible for all reporting required as per IRB. The Sponsor/CRO is responsible to advise the Investigator if an AE is an unanticipated problem that needs to be reported to IRB. In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the study. (Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs — Improving Human Subject Protection, FDA, January 2009, Procedural).

11 Drug Accountability

The study site will maintain an inventory of the investigational products. This will include:

- Name of person designated as responsible for the inventory of the investigational products
- Amount received including date, and lot number
- Amount currently in inventory
- Amounts dispensed to each subject, identified by subject initials and a unique subject study number
- Amount destroyed, if applicable – this should not occur without prior notification to Sponsor/CRO
- Non-study disposition (e.g. wasted, broken)
- Amount returned to Sponsor or designee, if applicable

Sponsor, or its designee, will provide forms to facilitate investigational product inventory control. All investigational product accountability forms and treatment logs must be retained in the site's regulatory binder. These records must be available for inspection by the Sponsor, its designees or by regulatory agencies at any time.

Investigational drug shipment to sites will be accompanied by a Drug Shipment Form which must be signed and dated upon receipt and copy sent back to the Sponsor/CRO. This form must be filed in the site regulatory binder.

12 Quality Control and Quality Assurance

12.1 Selection of Study Sites and Investigators

The Sponsor will select Investigators who are qualified by training and experience to perform clinical research in this field and to participate in the clinical investigation. Sites will be selected based upon an assessment of the qualifications of the Primary Investigator and the facilities at each site. All Investigators will be trained on the investigational treatment, the protocol and all study procedures prior to enrolling subjects.

A site initiation visit will be conducted at each study site to assure that the Investigator and the study staff understand the obligations for using and managing the investigational product, following the study protocol, obtaining informed consent, adhering to FDA and IRB regulations, and conducting clinical research.

12.2 Training

12.2.1 Site Training

All Investigators/study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Remote over-the-phone or web-based training will take place as necessary. Training of Investigators/study personnel will include, but is not limited to, the study protocol, enrollment (including review of inclusion and exclusion criteria), subject retention, investigational drug usage, SW/electronic case report form (eCRF) completion, and study personnel responsibilities. All Investigators/study personnel that are trained must sign a training log (or an equivalent) upon completion of the training.

12.3 Monitor Training

The Sponsor or designee will engage monitors that are qualified by appropriate training and experience to review the conduct and quality of the study. Prior to working on the study, monitors will be trained to the investigational plan, SWs/eCRFs, and the drug/procedure knowledge. Such training will be documented.

12.4 Study Monitoring

Sponsor and/or a designee (e.g., a CRO), will monitor the clinical study in a manner consistent with FDA regulations and the Good Clinical Practice (GCP) standards.

The Investigator is required to ensure compliance with all procedures required by the Investigational plan and by study procedures provided by the Sponsor. The Investigator agrees to provide reliable data and all information requested by the Investigational Plan including eCRFs, Data Clarification Forms or other appropriate instrument according to the instructions provided, and to ensure direct access to source documents to Sponsor designees.

A risk-based approach will be used to determine the site monitoring frequency and the data sampling for source verification. Monitoring and data verification may be performed remotely or onsite.

The Investigator and his/her staff will be expected to cooperate with Sponsor’s personnel or designee and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information.

12.5 Source Data Verification (SDV)

Source data verification ensures accuracy and credibility of the data obtained. During SDV, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents.

12.5.1 Definition of Source Data

Source data includes all information in source documents (original records, certified copies of original records, appointment books, original laboratory records, and original data recorded on customized worksheets) and includes all original recordings or copies of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Certain data may be directly entered into SW. In this case, the SW serves as source document.

12.6 Direct Access to Source Data/Documents

The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB and regulatory inspection(s).

Consenting subjects are agreeing to allow the Sponsor or designee access and copying rights to pertinent information in their medical records relevant to study participation. As part of the informed consent, the Investigator or designee will obtain permission for regulatory authorities to review any records identifying subjects in this study. Sponsor will not otherwise release any personal information

12.7 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject. In the event of any deviation from the protocol, a Protocol Deviation Report Form will be completed. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of Investigator compliance to the protocol, Good Clinical Practice (GCP), and regulatory requirements. The Investigator will inform the IRB of protocol deviations according to requirements of each reviewing IRB.

A protocol deviation for this protocol consists of, but is not limited to, the following:

- Failure to obtain subject’s informed consent prior to enrolling subject into the study
- Enrollment of subjects who do not meet all eligibility requirements
- Failure to conduct protocol required clinical follow-ups
- Failure to report SAEs according to protocol requirements

In the event of any deviation from the protocol, the Investigator will be notified of the site’s non-compliance. Corrective actions will be advised if necessary and the methods, plan or other activities put in place to ensure non-recurrence will be documented by the Investigator and forwarded to the sponsor or their designee. Continued protocol deviations despite re-education of study site personnel and/or persistent protocol deviations may result in termination of the site’s study participation. Subjects already enrolled at these sites will continue to be followed per protocol guidelines.

13 Data Handling and Record Keeping

13.1 Subject Coding

The eCRFs and all other documents sent to the Sponsor will not contain identifying study subject information. Each subject will be assigned a unique subject code that reflects the site number and subject number. The subject code will consist of 8 characters in an alphanumeric combination. The site will maintain a log that links the subject code to the name of each subject. An example is shown in Table 12.

Table 12 Example of the Subject Code

Site Code			Connector	Subject Study Number			
A	B	C	-	1	0	0	1

13.2 Data Handling and Record Keeping

For the study duration, the Investigator will maintain complete and accurate regulatory documentation as required per ICH GCP E6 r2 (8). Source Documentation.

The following materials should be included in the subject record:

- Signed Informed Consent Form
- SWs including but not limited to dated and signed notes from each subject's visit (for specific results of procedures and exams and study drug dosing and accountability data)
- Medical records for subject medical history/physical condition prior to study involvement, study progress records, laboratory reports and medication record, device using record.
- AEs reported and their outcome including supporting documents
- Subject's condition upon study completion or withdrawal and information regarding the subject's discontinuation or completion

13.3 Electronic Case Report Form Completion

Accurate primary data collection will be performed by site staff trained on the protocol and eCRF completion. All data fields will be completed where appropriate. However, if data are not available (i.e., missed visit, etc.), the site will receive instruction regarding electronic documentation.

Appropriate error messages will be generated, allowing for the modification and/or verification of the entered data. Queries will generally be sent to the investigational site using an electronic data query system that includes an automated audit trail of the corrections. The Investigator, will certify that the data are complete and accurate by applying an electronic signature to the eCRF. Any subsequent alterations, corrections, or additions will be reviewed and electronically signed by the Investigator prior to the database lock.

The Sponsor or designee will provide clinical monitoring to include eCRF review and parity checks with the source documentation.

13.4 Record Retention

The Investigator/Site will maintain all records pertaining to this study for the later of (a) five years following study completion, or (b) five years after the study has been terminated by the Sponsor, or (c) as

otherwise instructed by the Sponsor. Investigator will be notified by Sponsor of the date of completion or discontinuation of the study.

To comply with these requirements, the Investigator will not dispose of or transfer any records relevant to this study without either (1) written permission from the Sponsor, or (2) providing an opportunity for the Sponsor to archive the records with an external vendor.

14 Ethical Considerations

14.1 Informed Consent

Written informed consent will be obtained from each subject before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits and potential hazards are explained. The subject's willingness to participate in the study will be documented in writing in the ICF, which will be signed by the investigator or designee and the subject with the date of that signature indicated. The Investigator will keep the original consent forms and copies will be given to the subjects. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study will be provided in understandable language to all subjects.

14.2 Institutional Review Boards

IRB approval for the protocol and informed consent form will be obtained prior to study participation by subjects. The approval letter must be obtained prior to beginning this study and a copy must be provided to the Sponsor. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB, the Sponsor and/or the regulatory agencies.

As per responsible IRB requirements, the Investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

14.3 Confidentiality and Protection of Study Files

The identity of subjects enrolled in the study and the information contained in their study records will be kept confidential by Sponsor.

Each subject will be assigned a study identification number to be used on eCRFs and other study records sent to the Sponsor or its designee.

Confidentiality will be protected as much as possible throughout the study. Medical records will be reviewed by designees of Sponsor and/or its designee and will be made available for review as required by the IRB and regulatory authorities. Results of data collected will be reported as statistical information only. The subject's name will not be used or otherwise disclosed unless required by US law or regulation.

15 Sponsor and Investigator Reports

15.1 Investigator Reports

The reports in Table 13 are required of each investigator as described.

Table 13 Investigator Reports

Report	Submit to	Submission Schedule
Screening & Enrollment	CRO	Weekly
All study data	EDC (CRO)	Baseline data: within 48 hours, all others: no later than 14days
Serious adverse events (SAEs)	CRO/IRB	Report to CRO within 24 hours after the Investigator first learns of the event. Reporting to IRB acceding to IRB's reporting roles, or if notified by the Sponsor/CRO that the SAE meets FDA's IND safety report criteria.
Study Deviations and Subject withdrawal	CRO/IRB	Report to CRO and IRB within 48 hours if the deviation affects the subject's safety and wellbeing. Otherwise, report to CRO no later than 14 days; reporting to IRB acceding to IRB's reporting roles.
IRB submission for continued approval	IRB/CRO	Submit to IRB annually or as required during and at the end of the study. Submit IRB's approval document to CRO within 5 working days.

15.2 Sponsor Safety Reports

The Sponsor is responsible for timely reviewing and making determination of safety information submitted from the investigational sites meets the IND safety reporting criteria as defined in 21 CFR 321.32:

- Suspected adverse reaction
- Serious
- Unexpected

The Sponsor is responsible to ensure the serious and unexpected suspected adverse reaction is reported to the FDA in an IND safety reporting format and all participating investigators as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting according to 21 CFR 321.32 (c) (1) (i). For any unexpected fatal or life-threatening suspected adverse reaction, the sponsor must also notify FDA as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. 21 CFR 321.32 (c) (2).

The Sponsor will notify the central IRB and advise all participating investigational sites to notify the local IRBs for the aforementioned IND safety report.

In addition, the sponsors will report the results of an evaluation of an UADE to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect. Per 21 CFR 812.150 (b)(1).

If the sponsor determines that an UADE presents an unreasonable risk to subjects, the sponsor will terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur

not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect as defined in 21 CFR 812.46(b)(2).

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