Abbreviated Protocol for Two-Stage Exchange

A Randomized Controlled Trial of Alternating Irrigation of Vancomycin HCl and Tobramycin Sulfate in Patients Undergoing Two-Stage Exchange Arthroplasty for Periprosthetic Joint Infection of the Hip or Knee

Protocol Number:	JPS-0301
IND Number:	132585
Study Phase:	2b
Sponsor:	Osteal Therapeutics, Inc.
Address:	750 N. Saint Paul St., Suite 250, PMB 72129 Dallas, Texas 75201-3206
Date:	October 17, 2022

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 authorities overseeing this trial. I agree to maintain all study documentation for a minimum of two years after the study has been completed or for a longer period as required by law and regulations. Publication of the results of this study will be governed by the conditions stipulated in the Study Site Agreement. I agree to supervise the use of the Investigational Products at my institution and ensure that the informed consent form is obtained prior to subject enrollment.

I have read and understand the information in this Protocol and will ensure that all associates, colleagues, and personnel 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 personnel by signing such delegation in the Study Delegation Log.

Protocol Number: JPS-0301

Protocol Title:	A Randomized Controlled Trial of Alternating Irrigation of Vancomycin HCl and Tobramycin Sulfate in Patients Undergoing Two-Stage Exchange Arthroplasty for Periprosthetic Joint Infection of the Hip or Knee
Protocol Date:	OCT 17, 2022
Version:	F.0

Signature of Site Principal Investigator at Each Study Site	Date
Printed Name of Site Principal Investigator	

Contents

List of Abbreviations

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
API	Application programming interface
BA/BE	Bioavailability/bioequivalence
BMI	Body mass index
BUN	Blood urea nitrogen
CAPA	Corrective and preventive action
CBC	Complete blood count
CC	Completed case
CCI	Charlson Comorbidity Index
CFR	Code of Federal Regulations
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
CRA	Clinical research associate
CRO	Contract research organization
CRP	C-reactive protein
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic data capture
EMC	Electromagnetic compatibility
EMR	Electronic medical record
EPS	Extracellular polymeric substances
EQ-5D-3L	EQ-5D 3-level version
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HOOS	Hip Disability and Osteoarthritis Outcome Score
I&D	Incision and drainage
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMMI	International Consensus Meeting of Musculoskeletal Infection
IDSA	Infectious Diseases Society of America

IFU	Instructions for use
IMSM	Independent medical safety monitor
IND	Investigational new drug
IRB	Institutional review board
ISO	International Organization for Standardization
ITT	Intent-to-treat
IV	Intravenous
KOOS	Knee Injury and Osteoarthritis Outcome Score
LAL	Limulus amoebocyte lysate
LE	Leukocyte esterase
MBEC	Minimum biofilm eradication concentration
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
µg/mL	Micrograms per milliliter
mg/dL	Milligrams per deciliter
mg/mL	Milligrams per milliliter
MMRM	Mixed models for repeated measures
MSIS	Musculoskeletal Infection Society
ng/mL	Nanograms per milliliter
NPWT	Negative pressure wound therapy
PI	Principal investigator at each study site
PJI	Periprosthetic joint infection
PMN	Polymorphonuclear leukocytes
PP	Per-protocol
PSI	Pounds per square inch
Q48	Every 48 hours
QoL	Quality of life
RCT	Randomized controlled trial
SADE	Serious adverse device effect
SAE	Serious adverse event
SAL	Sterility assurance level
SAP	Statistical analysis plan
sCr	Serum creatinine
SDV	Source data verification
SIV	Site initiation visit
SNF	Skilled nursing facility
SOC	Standard of care
SW	Source worksheet
TTWB	Toe touch weight bearing
TXA	Tranexamic acid
UADE	Unanticipated adverse device effect
UAE	Unanticipated adverse event
USADE	Unanticipated serious device effect

USP	U.S. Pharmacopeia
WBC	White blood cells

1 Summary

Official Title:	A Randomized Controlled Trial of Alternating Irrigation of Vancomycin HCl and Tobramycin Sulfate in Patients Undergoing Two-Stage Exchange Arthroplasty for Periprosthetic Joint Infection of the Hip or Knee
Short Title:	APEX (**A**bbreviated **P**rotocol for Two-stage **Ex**change)
Protocol Number:	JPS-0301
Sponsor:	Osteal Therapeutics, Inc. 750 N. Saint Paul St., Suite 250, PMB 72129 Dallas, Texas 75201-3206
IND:	132585
Investigational Product:	VT-X7, a drug-device combination product consisting of 2 antibiotics, vancomycin hydrochloride (HCl) and tobramycin sulfate, which are locally delivered via a short-term implantable delivery device.
Proposed Indication:	[redacted]
Study Design:	A multi-site, parallel group, randomized trial.
Patient Population:	Up to 76 patients with PJI of the hip or knee undergoing two-stage exchange arthroplasty.
Study Conduct:	Patients will be randomly assigned in a 1:1 ratio to the Experimental Arm and Control Arm. A minimum of 24 hip and 24 knee subjects will be enrolled. Experimental Arm: Two-stage exchange arthroplasty consisting of Stage 1 resection arthroplasty and debridement per standard of care (SOC), [redacted] with 7-day local antibiotic irrigation [redacted]

	Control Arm: Two-stage exchange arthroplasty per SOC, consisting of Stage 1 resection arthroplasty and debridement, insertion of a temporary antibiotic-impregnated cement spacer and administration of 6 weeks systemic antibiotics followed by 2 weeks antibiotic holiday, and Stage 2 revision arthroplasty at a time deemed clinically appropriate by the investigator. Both Arms: All subjects receive 12 weeks of systemic antibiotics post-Stage 2.
Objectives:	The objective is to evaluate safety and determine preliminary efficacy of VT-X7. Efficacy is evaluated as superiority of the Experimental Arm in a composite endpoint of Overall Success at 90 days, consisting of a revision prosthesis implanted at Stage 2, patient survival, absence of reoperation and absence of PJI. Secondary objectives are to evaluate superiority at 180 days and 365 days in a composite endpoint of Overall Success, and in separate secondary endpoints for quality of life (QoL), rate of successful reimplantation and patient survival. The exploratory objective is to compare Experimental and Control Arms in exploratory endpoints.
Study Endpoints(s):	**Primary Endpoint** Composite endpoint of Overall Success at 90 days consisting of: • Stage 2 revision prosthesis implanted; • Absence of PJI* post-Stage 2; • Absence of reoperation*** of the affected joint pre- or post- Stage 2; and • Absence of mortality. * If clinical evidence of infection is present post-Stage 2 surgery, use ICMMI 2018 for definitive PJI confirmation. *** Reoperation includes only procedures to irrigate, debride, remove or replace the Stage 1 spacer or any Stage 2 implant component. **Secondary Outcome Endpoints** 1. Composite endpoint of Overall Success at 180 days consisting of: • Stage 2 revision prosthesis implanted; • Absence of PJI* post-Stage 2; • Absence of continued antibiotic therapy for treatment or prophylaxis of PJI **; • Absence of reoperation*** of the affected joint pre- and post-Stage 2; and • Absence of mortality. * If clinical evidence of infection is present post-Stage 2 surgery, use ICMMI 2018 for definitive PJI confirmation. ** Continued antibiotic therapy includes antibiotic therapy at 180 days or beyond 12 weeks post-Stage 2 surgery, excluding antibiotics for documented pre-procedural prophylaxis or infection other than PJI. *** Reoperation includes only procedures to irrigate, debride, remove or replace the Stage 1 spacer or any Stage 2 implant component.

2. Composite endpoint of Overall Success at 365 days consisting of:

- Stage 2 revision prosthesis implanted;
- Absence of PJI* post-Stage 2;
- Absence of continued antibiotic therapy for treatment or prophylaxis of PJI **;
- Absence of reoperation*** of the affected joint pre- and post-Stage 2; and
- Absence of mortality.

* If clinical evidence of infection is present post-Stage 2 surgery, use ICMMI 2018 for definitive PJI confirmation.

** Continued antibiotic therapy includes antibiotic therapy at 365 days or beyond 12 weeks post-Stage 2 surgery, excluding antibiotics for documented pre-procedural prophylaxis or infection other than PJI.

*** Reoperation includes only procedures to irrigate, debride, remove or replace the Stage 1 spacer or any Stage 2 implant component.

3. Cumulative proportion of subjects with a revision prosthesis implanted at Stage 2 by time to implantation.
4. Comparison of Quality Adjusted Life Years (QALY) at 365-day follow-up between the treatment arms.
5. Survival at 365 days post-Stage 1 surgery.

Exploratory Endpoints:

- Cumulative number of surgeries on the affected joint per subject;
- Change in Knee Injury and Osteoarthritis Outcome Total Score (KOOS) (for patients with knee joint treatment) at 90-, 180-, and 365-day follow-up compared to baseline;
- Change in Hip Disability and Osteoarthritis Outcome Total Score (HOOS) (for patients with hip joint treatment) at 90-, 180-, and 365-day follow-up compared to baseline;
- Clinical lab data;
- Bacterial culture data;
- Serum levels of vancomycin HCl and tobramycin sulfate during the irrigation therapy to monitor for toxic systemic levels (Experimental Arm only);
- Duration and cumulative Morphine Milligram Equivalents of prescribed opioids;
- Duration of antibiotic administration;
- Number of units of blood transfused in 1 week after Stage 1 and Stage 2 surgery.

<table>
<tr><td></td><td>Cost Outcome
Overall treatment cost determined from Medicare Claims Data using BlueButtonPro™, a Centers for Medicare and Medicaid Services (CMS)-approved Blue Button® 2.0 Application Programming Interface (API).</td></tr>
<tr><td>Safety:</td><td>The safety profile will be characterized by assessing the incidence of adverse events (AEs), serious adverse events (SAEs), suspected adverse reactions, adverse reactions, unexpected adverse reactions, serious adverse device effects (SADEs), and unanticipated adverse device effects (UADEs).</td></tr>
<tr><td>Inclusion Criteria:</td><td>1. Scheduled two-stage exchange arthroplasty due to hip or knee PJI[1];
2. Signed informed consent;
3. 22 to 84 years of age (inclusive);
4. Medical clearance for surgery;
5. Preoperative diagnosis of PJI of the hip or knee per the International Consensus Meeting of Musculoskeletal Infection (ICMMI) 2018 definition of Periprosthetic Hip and Knee Infection, which is one of the following 2 major criteria:
a. The presence of a sinus tract communicating with the prosthesis;
b. Two positive growths of the same organism from at least 2 separate fluid or tissue samples from different areas of the affected joint using standard culture methods;
OR
- A pre-Stage 1 score ≥6 from all minor criteria for Periprosthetic Hip and Knee Infection listed in the table below, including intraoperative criteria from procedures performed prior to Stage 1. [2]
<table><tr><th>Preoperative Diagnosis: Minor Criteria</th><th>Score</th></tr><tr><td>Serum</td><td></td></tr><tr><td>Elevated CRP (>1 mg/dL) or D-dimer (>860 ng/mL)</td><td>2</td></tr><tr><td>Elevated ESR (>30 mm/h)</td><td>1</td></tr><tr><td>Synovial</td><td></td></tr><tr><td>Elevated synovial WBC (>3000 cells/µL) or LE (++)</td><td>3</td></tr></table></td></tr>
</table>

[1] For this study, a scheduled two-stage exchange arthroplasty consists of two planned surgical procedures for treatment of PJI in which the first stage includes surgical removal of an implant from the infected joint, and the second stage includes implantation of a permanent replacement prosthesis. The implant removed in the first stage may be either i) a permanent implant or, ii) a temporary spacer implanted during the first stage of a prior two-stage exchange arthroplasty that has failed.

	Positive alpha-defensin (signal-to-cutoff ratio >1) — 3 Elevated synovial PMN (>80%) — 2 Elevated synovial CRP (>6.9 mg/L) — 1

Intraoperative Diagnosis: Inconclusive Pre-op Score or Dry Tap*	**Score**
Preoperative score	-
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 prior to Stage 1 meet the ICMMI criteria. Patients with a score of <6 prior to Stage 1 surgery do not meet the inclusion criteria for this clinical study.

** More than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 400X magnification.

Exclusion Criteria:

1. Patients with 2 or more prior one-stage or two-stage exchange arthroplasties of the infected joint;
2. Patients who have been diagnosed with an acute PJI as a result of a total joint arthroplasty which took place within the last 4 weeks;
3. Patients with bacteremia or positive bacterial blood culture in the last 30 days;
4. Patients with concurrent PJI of more than one joint;
5. Patients with ongoing active infection of an intravenous (IV) site;
6. Patients who require long-term anticoagulation or antiplatelet therapy, and for whom bridging or withholding therapy is not recommended based on the individual's clinical condition;
7. Patients with advanced renal insufficiency (chronic kidney disease (CKD) Stage 4 or greater or glomerular filtration rate (GFR) <30 mL/min);
8. Patients on chemotherapy for malignant disease;
9. Patients on systemic glucocorticoid therapy (prednisone >10 mg/day

	or equivalent); 10. Patients with immunodeficiency (e.g., splenectomy, sickle cell anemia, Stage 3 human immunodeficiency virus (HIV) infection, primary immunodeficiency disease), except immunodeficiency due to immunosuppressive therapy; 11. Patients who have an allergy to vancomycin HCl or tobramycin sulfate (Note: prior history of red man syndrome is not considered an allergy); 12. Patients who have an allergy to titanium, titanium alloys, polymethylmethacrylate or polyurethane. 13. Patients who are pregnant or planning to become pregnant in the next 12 months; 14. Patients in whom NPWT is contraindicated; 15. Patients with a fungal PJI as determined by one or more positive fluid and/or tissue cultures; 16. Patients who have a skeletal defect greater than 150 mm in length in the tibia or femur of the infected joint; 17. Patients who have a planned surgical procedure within 6 months of enrollment that can impact the conduct of the study; 18. Patients who are breastfeeding at the screening visit; 19. Patients who are incarcerated or are facing impending incarceration; 20. Patients who have been in treatment or referred to treatment for substance abuse within the past year; 21. Patients with any medical condition, including schizophrenia or another psychiatric disorder with hallucinations and/or delusions, that would interfere with the interpretation of the study results, the conduct of the study, or patient participation would not be in the best interest of the patient in the opinion of the Study Site PI; 22. Patients who will participate in another clinical study of an investigational drug or investigational device or have participated in another clinical study of an investigational drug or investigational device within the past 30 days that would interfere with the interpretation of the study results or the conduct of the study; 23. Patients who are judged by the Investigator to be unsuitable for the study. 24. Patients receiving immunosuppressive drug therapy for bone marrow or another transplant. 25. Patients currently or previously enrolled in this study. 26. Patients who receive therapy including any of the following biologic agents, which will not be withheld for a period beginning at least one dosing cycle (minimum 7 days) prior to planned surgery and

	ending at least 14 days following planned surgery: Adalimumab (Humira) Tocilizumab (Actemra) Etenercept (Enbrel) Anakinra (Kineret) Golimumab (Simponi) Secukinimab (Cosentyx) Infliximab (Remicade) Ustekinumab (Stelara) Abatacept (Orencia) Rituximab (Rituxan) Certolizumab (Cimzia) Tofacitinib (Xeljanz) Belimumab (Benlysta)
Follow-up Schedule:	Patients will be evaluated at 90-, 180-, and 365-day follow-up visits.
Safety Monitoring:	Safety will be monitored throughout the study. The Investigators will assess the occurrence of AEs at each follow-up visit. The Independent Medical Safety Monitor (IMSM) will evaluate all SAEs, Suspected Adverse Reactions, Adverse Drug Reactions, Unexpected Adverse Reactions, and UADEs. The DSMB will monitor and evaluate the safety data throughout the study. [redacted]
Phase:	Phase 2b.
Number of Sites Enrolling Participants:	Up to 20 Study Sites will enroll 76 Randomized subjects.
Participant Duration:	Subjects will be followed up from the time when they sign the informed consent form (ICF) to 365 days after the Stage 1 surgery.
Statistical Planning:	The efficacy will be confirmed by establishing superiority of Overall Success at 90 days (Primary Endpoint) in the Experimental Arm as compared to the Control Arm. A sample size of 76 subjects in a ratio of 1:1 will have 90% power to reject the superiority constructed statistical null hypothesis of no difference between the groups under the assumption of an Overall Success proportion of 80% in the Experimental Arm and 45% in the Control Arm, and a one-sided alpha of 0.025. A pre-planned analysis of the secondary endpoints will be performed testing the superiority of the Experimental Arm compared to the Control Arm. The multiplicity and Type 1 Error within the secondary endpoints family will be controlled using the fixed sequence approach and one-sided alpha value of 0.025. Exploratory endpoints will be analyzed using t-test, McNemar's test, chi-square test, and Fisher's exact test, as appropriate. Longitudinal changes will be analyzed using mixed models for repeated measures (MMRM). AEs will be tabulated by body system, preferred term, severity, relationship to the investigational product, relationship to the procedure, and time to occurrence. [redacted]

2 Background and Purpose of the Investigation

A periprosthetic joint infection (PJI) is a rare complication of joint replacement surgery, also known as arthroplasty. Arthroplasty is done to relieve pain and restore function in a severely diseased joint. Approximately 0.5% to 1% of people with replacement joints develop a PJI. [3] Infections can occur early in the course of recovery from joint replacement surgery or much later. Signs and symptoms of PJI include fever, chills, drainage from the surgical site, and increasing redness, tenderness, swelling, and pain in the affected joint [4]. PJIs are often hard to treat because of the development of a structure called a biofilm within the joint [5, 6, 7]. Biofilms are multicellular aggregates of microbes encased in extracellular polymeric substances (EPS), which form a physical barrier against antibiotics and acts as a shield between the microbes and the patient's immune system. [5, 7].

2.1 Standard of Care Treatment for PJI

A number of surgical interventions are used to treat PJI. The SOC for treatment of chronic PJI in the U.S. is a two-stage exchange arthroplasty. Stage 1 of the procedure includes removal of the infected implant, radical debridement and insertion of a temporary antibiotic-impregnated cement spacer followed by administration of systemic antibiotic therapy as needed, typically for a period of 6 weeks. Stage 2 of the procedure is performed when patients are considered infection-free and includes removal of the temporary spacer and 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. Looking at both acute and chronic cases in their review, two-stage revision had the lowest reinfection rate (19%) of all first-line treatment options for PJI other than amputation, as shown in Table 1 [8].

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%

2.1.1 Inefficacy of Systemic Route of Administration

The 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 HCl range from 10% to 60% of serum and those of tobramycin sulfate range from 9% to 13% [9]. Achievement of locally therapeutic levels is crucial for clinical success; however, this is difficult or impossible because 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 [10, 11]. Therapeutic target attainment at levels greater than the MBEC is impossible via systemic routes of administration without significant risk of toxicity to other organ systems.

2.1.2 Inconsistent Local Therapy

The multiple variables influencing the release of antimicrobials in cement spacers and other carriers present both efficacy limitations and toxicity concerns. For example, antimicrobials contained within the center of the spacer 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% [12]. Most of the elution from bone cements occurs in the first 48 to 72 hours, and, by day 5, the concentrations are often sub-therapeutic even for MIC targets for planktonic bacteria [13]. 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 [14, 15]. The inability to control local elution rate also presents risk of systemic toxicity, without means of cessation outside of a repeat surgical procedure.

2.1.3 Failure to Complete Treatment

Gomez et al. [16] authored one of the first retrospective reviews to fundamentally reexamine the definition of successful treatment of PJI. They reported 81.4% treatment success among 329 knee and hip patients who completed the Stage 2 treatment and had reached one-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 at least one more spacer (range of one to 6 additional spacers), and 87 (17.3%) retained their spacer (failed to complete Stage 2). After a minimum one-year follow-up, just 285/416 (68.5%) of all patients in the retrospective study of the two-stage SOC were considered a treatment success. The authors recommended that the success of two-stage arthroplasty be considered from the starting point of initial spacer insertion rather than from Stage 2 reimplantation.

Of those 87 cases in the Gomez study who did not undergo second-stage reimplantation, 15 underwent amputation, arthrodesis, or Girdlestone procedures, and there were 72 (82.8%) cases of retained spacers. Of the 72 cases of retained spacers, 19 (26.4%) were lost to follow-up. When excluding these cases, treatment success was 32.1% (17 cases). In 36 (50.0%) of the 72 cases, the patients died before the second stage. [16].

In 2019, the Workgroup of the MSIS published guidelines for reporting of outcomes after surgical treatment of PJI. The need for reoperation, including: septic or aseptic revision, amputation, resection arthroplasty or arthrodesis, as well as a retained temporary spacer are all

reported as Tier 3 failure of the intended treatment [56]. Based upon this guidance, all patients who have failed a prior attempt at two-stage exchange arthroplasty due to the need for septic or aseptic revision of the stage 1 spacer or retention of such spacer beyond 12 weeks of concomitant systemic antibiotic therapy may be considered for a new two-stage exchange arthroplasty.

2.1.4 Time to Reimplantation

The interstage interval between Stage 1 insertion of the temporary spacer and Stage 2 implantation 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 [17]. Treatment during this period may include inpatient rehabilitation (extended care facility/SNF) 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 those 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 [18].

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. Only slightly more than half of all patients completed the critical Stage 2 surgical procedure by the typical 12-week postoperative follow-up [16].

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 [19, 20].

2.1.5 Interstage Mortality

Gomez et al. were 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 mortality rate of 2.0% for the general population of the same age [16]. 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 [21].

2.1.6 Cost-effectiveness

The burden of PJI for patients and society is substantial [22]. As described in Section 2.1.4, treatment burden, limited weight-bearing and mobility, pain management, and antibiotic-related complications are some of the challenges that patients face, resulting in critical negative impacts on physical, emotional, social, and financial aspects of life. Risk of amputation and death are

higher for patients with PJI. From hospital, insurer, and societal perspectives, in-hospital and direct costs for patients with PJI are high. Recent studies estimated that costs were 3 to 5 times higher than for those without infection [23-27]. The combination of morbidity and mortality and personal financial costs for patients, and costs for providers and society, necessitates that research into solutions for this devastating problem include estimates of health effects and costs.

2.2 Investigational Product

2.3.5 Prior Clinical Experience

2.3.5.1 Retrospective Clinical Study (JPS-R01)

A matched retrospective cohort study was conducted to determine whether two-stage arthroplasty treatment of hip or knee PJI with local irrigation using vancomycin HCl and tobramycin sulfate by a single PI safely reduced the risk of delay or failure to implant a permanent hip or knee joint with effective infection control relative to SOC two-stage exchange arthroplasty. After matching for various covariates (age-adjusted Charlson Comorbidity Index

(CCI), body mass index (BMI), operative joint, and gender), a larger proportion of patients who received the experimental local irrigation therapy had a permanent prosthesis implanted by 84 days post-Stage 1 surgery and retained the same functioning prosthesis 365 days post-Stage 1 surgery with no signs of infection and no additional surgery for infection compared to the matched SOC group (control arm), 91.7% vs 55.6%.[46]

The median interstage period between Stage 1 resection arthroplasty and Stage 2 reimplantation was 7 days in the experimental arm and 74 days in the control arm, a difference of 67 days (95% confidence interval [CI], 61 to 74 days). In the experimental arm, 36 of 36 patients (100%) received the Stage 2 implant within 9 days. In the control arm, 22 of 36 patients (61.1%) received the Stage 2 implant within 84 days.

2.3.5.2 Feasibility Clinical Study (JPS-001)

The Phase 2 Feasibility Study to determine the safety profile of local antibiotic irrigation for the treatment of PJI ("Safety and Efficacy in Patients Treated for Hip or Knee PJI with Vancomycin and Tobramycin Joint Irrigation", ClinicalTrials.gov Identifier: NCT03721328) was completed in August 2020 as per IND 132585. The study was a prospective, single-arm, open-label, multicenter (4 sites), interventional trial that enrolled 15 patients (14 with knee PJI and 1 with hip PJI). The study employed the same 7-day local antibiotic irrigation protocol to be used in VT-X7 but without the use of the VT-X7 Spacer. Instead, the instillation line from the NPWT system manufacturer was placed in the joint space to irrigate the joint during the interstage period.

Fourteen (14) of 15 Feasibility Study subjects had no clinically significant changes in CRE and blood urea nitrogen (BUN) measurements or SAEs due to renal impairment during the interstage or post-Stage 2. One of 15 subjects had an SAE of renal impairment in the post-Stage 2 period and had a higher-than-expected BUN value at screening; thus, this subject may have had some renal impairment prior to study enrollment [47]. A clinically significant BUN value at screening was not an exclusion criterion of this study.

The serum antibiotic levels from JPS-001 show that with a high antibiotic concentration applied locally, subjects maintain serum levels within safe therapeutic ranges and less than that of similar doses given via the IV route, thus reducing the risks of nephrotoxicity.

There were no observations of purulence at Stage 2, compared to 12/15 such cases at Stage 1 ($p < 0.0015$). Eradication of infection at 84 days was achieved in all 15 subjects.

Using a composite efficacy endpoint, 12 out of 15 subjects (80%) were classified as Overall Success at their 12-month follow-up visit. One subject was a failure due to a trauma-related fracture of both the tibia and fibula which resulted in exchange of the permanent tibial prosthesis component. One subject was a failure due to subsequent surgery for aseptic loosening which resulted in replacement of the permanent femoral component. One subject did not satisfy eradication of infection during the 12-month follow-up.

3 Study Objectives

The objective is to evaluate safety and determine preliminary efficacy of VT-X7. Specific objectives are to:

1. Evaluate superiority of the investigational product (Experimental Arm) compared to SOC (Control Arm) in a composite endpoint of overall success at 90 days consisting of successful Stage 2 surgery by 90 days post-Stage 1, patient survival, absence of reoperation, and absence of PJI.
2. Evaluate superiority of the investigational product (Experimental Arm) compared to SOC (Control Arm) in a composite endpoint of overall success at 180 days consisting of successful Stage 2 surgery, patient survival, absence of reoperation, absence of PJI, and absence of continued antibiotics.
3. Evaluate superiority of the investigational product (Experimental Arm) compared to SOC (Control Arm) in a composite endpoint of overall success at 365 days consisting of successful Stage 2 surgery, patient survival, absence of reoperation, absence of PJI, and absence of continued antibiotics.
4. Evaluate superiority of the investigational product (Experimental Arm) compared to SOC (Control Arm) in cumulative proportion of subjects with a revision prosthesis implanted at Stage 2 by time to implantation.
5. Evaluate superiority of the investigational product (Experimental Arm) compared to SOC (Control Arm) in Quality Adjusted Life Years outcomes as estimated by EQ-5D-3L.
6. Evaluate superiority of the investigational product (Experimental Arm) compared to SOC (Control Arm) in patient survival.
7. Compare the investigational product (Experimental Arm) and SOC (Control Arm) in exploratory endpoints.
8. Perform a cost-effectiveness analysis of the investigational product.

4 Study Design

4.1 Study Design

This study is a multi-site, parallel group randomized trial. A total of up to 76 subjects will be randomized in a 1:1 allocation to the Experimental Arm or the Control Arm with a minimum enrollment of 24 knee and 24 hip subjects.

The Experimental Arm subjects will receive the investigational product [redacted]

The Control Arm subjects will receive a two-stage exchange procedure per SOC, consisting of Stage 1 resection arthroplasty and debridement, insertion of a temporary antibiotic-impregnated cement spacer and administration of six (6) weeks systemic antibiotics followed by 2 weeks antibiotic holiday, and Stage 2 revision arthroplasty at a time deemed clinically appropriate by the treating physician.

Subjects in Both Arms will receive twelve (12) weeks administration of systemic antibiotics post-Stage 2.

All subjects will receive postoperative rehabilitation per SOC at the participating Study Sites.

Subjects will be followed up from when they sign the ICF to their 365-day follow-up visit after Stage 1 surgery, with follow-up visits scheduled at regular time intervals beginning with the Stage 1 surgery. Depending on the timing of the Stage 2 surgery, one or more study follow-up visits for subjects in the Control Arm may occur prior to the Stage 2 surgery.

4.2 Subject Recruitment and Enrollment

Subjects will be recruited by Investigators at each Study Site. Candidates who are potentially eligible for the study will be scheduled for a screening visit. After giving written informed consent, subjects will undergo screening assessments. Screening data will be reviewed to determine subjects' eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be enrolled into the study.

A subject is considered enrolled in the study when the subject has given written informed consent and the Stage 1 surgery has been initiated.

4.2.1 Randomization and Blinding

Subjects will be randomized to either the Experimental Arm receiving the investigational product or the Control Arm in a 1:1 ratio stratified according to the affected joint (hip or knee). The exact approach will be described in the Randomization Plan.

Randomization occurs upon successful completion of subject screening.

Subjects will be blinded to their Randomized Arm assignment until the completion of Stage 1 surgery. Blinding of subjects after Stage 1 surgery, and blinding of Investigators during the entire study, is not possible.

Microbiology labs at each investigational site will be blinded to the therapy received by each subject.

4.2.2 Early Study Termination

The Sponsor reserves the right to discontinue the study at any stage for any reason at any time. Possible reasons for early termination may include, but are not limited to, unexpected adverse reactions or UADEs that may present unreasonable subject risk.

If the study is terminated early, the sponsor will provide a written explanation describing why premature termination has occurred, and notify the PI, the Institutional Review Board (IRB), and the regulatory authority. All applicable clinical study documents will be subject to the same retention policy as detailed in the applicable section of this Protocol.

4.2.3 Measures Taken to Avoid/Minimize Bias

Measures to avoid or minimize bias include the use of a randomized controlled study design. Randomization minimizes the effect of confounding. Subjects will be blinded to the randomization of treatment until they complete the Stage 1 surgery to further minimize bias. Subjects in both Arms will receive the same minimum duration of post-Stage 2 systemic antibiotics and will receive the same post-Stage 2 surgery rehabilitation per SOC at the Study Site.

5 Study Endpoints

5.1 Efficacy Evaluations

5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is a composite endpoint of Overall Success at 90 days consisting of:

- Stage 2 revision prosthesis implanted;
- Absence of PJI* post-Stage 2;
- Absence of reoperation** of the affected joint pre- and post-Stage 2; and
- Absence of mortality.

* If clinical evidence of infection is present post-Stage 2 surgery, use ICMMI 2018 for definitive PJI confirmation.

** Reoperation includes only procedures to debride, remove, or replace the Stage 1 spacer or any Stage 2 implant component.

5.1.2 Secondary Efficacy Endpoints

5.1.2.1 Composite Endpoint of Overall Success at 180 days Consisting of:

- Stage 2 revision prosthesis implanted;
- Absence of PJI* post-Stage 2;
- Absence of continued antibiotic therapy for treatment or prophylaxis of PJI **;

- Absence of reoperation*** of the affected joint pre- and post-Stage 2; and
- Absence of mortality.

* If clinical evidence of infection is present post-Stage 2 surgery, use ICMMI 2018 for definitive PJI confirmation.

** Continued antibiotic therapy at 180 days or beyond 12 weeks post-Stage 2 surgery, excluding antibiotics for documented pre-procedural prophylaxis or infection other than PJI.

*** Reoperation includes only procedures to debride, remove, or replace the Stage 1 spacer or any Stage 2 implant component.

This endpoint of Overall Success at 180 days is a Key Secondary Endpoint.

5.1.2.2 Composite Endpoint of Overall Success at 365 days Consisting of:

- Stage 2 revision prosthesis implanted;
- Absence of PJI* post-Stage 2;
- Absence of continued antibiotic therapy for treatment or prophylaxis of PJI **;
- Absence of reoperation*** of the affected joint pre- and post-Stage 2; and
- Absence of mortality.

* If clinical evidence of infection is present post-Stage 2 surgery, use ICMMI 2018 for definitive PJI confirmation.

** Continued antibiotic therapy at 365 days or beyond 12 weeks post-Stage 2 surgery, excluding antibiotics for documented pre-procedural prophylaxis or infection other than PJI.

*** Reoperation includes only procedures to debride, remove, or replace the Stage 1 spacer or any Stage 2 implant component.

This endpoint of Overall Success at 365 days is a Key Secondary Endpoint.

5.1.2.3 Cumulative Proportion of Reimplantation of a Permanent Prosthesis at Stage 2

Completion of the Stage 2 surgery including implantation of a permanent prosthesis will be recorded, and the cumulative proportion of subjects with a revision prothesis implanted at Stage 2 from time of Stage 1 surgery to 365 days post-Stage 1 surgery will be calculated, by time to implantation.

5.1.2.4 Quality Adjusted Life Years by 365-day follow-up visit.

Quality Adjusted Life Years (QUALY) will be estimated utilizing EQ-5D-3L. The EQ-5D-3L is a widely used health status and health utility measure that consists of 5 questions representing 5 dimensions of health status including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The measure provides a health status profile and a single index/utility value that can be used for health economic evaluation and cost-effectiveness analysis [48-51]. A utility is a measure of preference for a health state that is anchored at 0 = death and 1 = perfect health. Individual EQ-5D profiles (responses to each of the 5 questions) are transformed into a utility using an algorithm based on U.S utilities. U.S. norm EQ-5D utilities were estimated from a U.S.

sample, eliciting time trade off preferences for a wide range of health states.

5.1.2.5 Survival at 365 Days Post-Stage 1 Surgery

Mortality for any cause will be recorded through safety monitoring, and the survival from Stage 1 surgery to 365 days post-Stage 1 surgery will be calculated.

5.1.3 Exploratory Endpoints

5.1.3.1 Number of Surgeries of the Affected Joint

The total number of surgical procedures per subject performed on the joint treated for PJI for any reason will be reported.

5.1.3.2 The HOOS and KOOS

The HOOS is a self-reported measure consisting of a 40-item questionnaire that assesses pain, symptoms, function in activities of daily living (ADLs), function in sport and recreation (Sport/Rec), and QoL over the previous week. Dimensions are scored separately on a scale of 0 to 100 (higher score is better). The instrument is valid and responsive in total hip replacement patients [52].

The KOOS is a self-reported measure consisting of a 42-item questionnaire that assesses the knee through dimensions of pain, function in ADLs, function in sport and recreation (Sport/Rec), other symptoms, and knee-related QoL. Dimensions are scored separately on a scale of 0 to 100 (higher is score better). The instrument is valid and responsive in total knee replacement patients [53].

5.1.3.3 Clinical Lab Data

Clinical lab data will be obtained at scheduled follow-up visits, including serum creatinine (sCr), complete blood count (CBC) with differential, and BUN.

5.1.3.4 Bacterial Culture Data

Results of cultures from intraoperative samples of tissue and synovial fluid during Stage 1 and Stage 2 surgeries will be collected.

5.1.3.5 Serum Levels of Experimental Antibiotics

In the Experimental Arm only, serum levels of vancomycin HCl and tobramycin sulfate will be measured during irrigation therapy to monitor for toxic systemic levels.

5.1.3.6 Opioid Prescriptions

Duration and cumulative Morphine Milligram Equivalents of prescribed opioids will be collected in both Arms as part of the concomitant medications log.

5.1.3.7 Duration of Antibiotic Therapy

Duration and dose of antibiotic prescriptions will be collected in both Arms as part of the concomitant medications log.

5.1.3.8 Transfusions

The number of units of blood transfusions administered in the perioperative period (within 1 week post-operative to Stage 1 and Stage 2 surgeries) will be collected.

5.1.4 Healthcare Service Costs

Healthcare service utilization for inpatient, outpatient, physician, SNF, home healthcare, physical therapy, hospice services, and medical equipment will be obtained from claims data for subjects enrolled in Medicare. The healthcare service utilization will be calculated from the time of Stage 1 surgery (inclusive) to the 365-day follow-up visit (inclusive). At the time of the 365-day follow-up visit, all subjects who are enrolled in Medicare will be asked to provide consent for the Sponsor to gain access to claims data using Blue Button® 2.0. Blue Button® 2.0 is Medicare's data service which allows patients to access and share their claims data with healthcare providers and researchers. Subjects who do not grant access to their claims data will complete all other final follow-up visit tasks as detailed in this Protocol. There will be no penalty or loss of benefit for subjects who are eligible for, but do not participate in, the healthcare service utilization data effort. Data collected as part of this study effort will be collected independently of the electronic case report forms (eCRFs).

5.2 Safety

Safety will be monitored throughout the study. The Investigators will assess the occurrence of AEs at each follow-up visit. The IMSM will evaluate all SAEs to determine the event's causality to the investigational drugs, device, and procedures, and to determine whether the event meets the definition of a Serious Unexpected Adverse Reaction or Unanticipated Serious Adverse Device Effect.

The DSMB will periodically monitor and evaluate the safety data throughout the study.

6 Subject Population and Selection

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

6.1 Inclusion Criteria

1. Scheduled for two-stage exchange arthroplasty due to hip or knee PJI[2];
2. Signed informed consent;

[2] For this study, a scheduled two-stage exchange arthroplasty consists of two planned surgical procedures for treatment of PJI in which the first stage includes surgical removal of an implant from the infected joint, and the second stage includes implantation of a permanent replacement prosthesis. The implant removed in the first stage may be either i) a permanent implant or, ii) a temporary spacer implanted during the first stage of a prior two-stage exchange arthroplasty that has failed.

3. 22 to 84 years of age (inclusive);
4. Medical clearance for surgery;
5. Preoperative diagnosis of PJI of the hip or knee per the ICMMI 2018 definition of Periprosthetic Hip and Knee Infection, which is **one of the following 2** major criteria:
    a. The presence of a sinus tract communicating with the prosthesis;
    b. Two positive growths of the same organism from at least 2 separate fluid or tissue samples from different areas of the affected joint using standard culture methods;

OR

- A pre-Stage 1 score ≥6 from all minor criteria for Periprosthetic Hip and Knee Infection listed in the table below, including intraoperative criteria from procedures performed prior to Stage 1 [2].

Preoperative Diagnosis: Minor Criteria	**Score**
Serum	
Elevated CRP (>1 mg/dL) or D-dimer (>860 ng/mL)	2
Elevated ESR (>30 mm/h)	1
Synovial	
Elevated synovial WBC (>3000 cells/µL) or LE (++)	3
Positive alpha-defensin (signal-to-cutoff ratio >1)	3
Elevated synovial PMN (>80%)	2
Elevated synovial CRP (>6.9 mg/L)	1
Intraoperative Diagnosis: *Inconclusive Pre-op Score or Dry Tap	**Score**
Preoperative score	-
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 prior to Stage 1 surgery meet the ICMMI criteria. Patients with a score of <6 prior to Stage 1 surgery do not meet the inclusion criteria for this clinical study.

** More than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 400X magnification.

6.2 Exclusion Criteria

1. Patients with 2 or more prior one-stage or two-stage exchange arthroplasties of the infected joint;
2. Patients with acute PJI, defined as total joint arthroplasty surgery within 4 weeks prior to enrollment (Stage 1) in this study;
3. Patients with bacteremia or positive bacterial blood culture in the last 30 days;
4. Patients with concurrent PJI of more than one joint;
5. Patients with ongoing active infection of an IV site;
6. Patients who require long-term anticoagulation or antiplatelet therapy, and for whom bridging or withholding therapy is not recommended based on the individual's clinical condition;
7. Patients with advanced renal insufficiency (CKD Stage 4 or greater or GFR <30 mL/min);
8. Patients on chemotherapy for malignant disease;
9. Patients on systemic glucocorticoid therapy (prednisone >10 mg/day or equivalent);
10. Patients with immunodeficiency (e.g., splenectomy, sickle cell anemia, Stage 3 HIV infection, primary immunodeficiency disease), except immunodeficiency due to immunosuppressive therapy;
11. Patients who have an allergy to vancomycin HCl or tobramycin sulfate (Note: prior history of red man syndrome is not considered an allergy);
12. Patients who have an allergy to titanium, titanium alloys, polymethylmethacrylate, polyethylene, or polyurethane;
13. Patients who are pregnant or planning to become pregnant in the next 12 months;
14. Patients in whom NPWT is contraindicated;
15. Patients with a fungal PJI as determined by fluid and/or tissue culture;
16. Patients who have a skeletal defect of greater than 150 mm in length in the tibia or femur of the infected joint;
17. Patients who have a planned surgical procedure within 6 months of enrollment that can impact the conduct of the study;
18. Patients who are breastfeeding at the screening visit;
19. Patients who are incarcerated or are facing impending incarceration;
20. Patients who have been in treatment or referred to treatment for substance abuse within the past year;
21. Patients who have any medical condition including schizophrenia or another psychiatric disorder with hallucinations and/or delusions that would interfere with the interpretation of the study results, the conduct of the study, or study participation

would not be in the best interest of the patient in the opinion of the Site PI;

22. Patients who will participate in another clinical study of an investigational drug or investigational device or have participated in another clinical study of an investigational drug or investigational device within the past 30 days that would interfere with the interpretation of the study results or the conduct of the study;
23. Patients who are judged by the Investigator to be unsuitable for the study.
24. Patients receiving immunosuppressive therapy for bone marrow or another transplant;
25. Patients currently or previously enrolled in this study.
26. Patients who receive therapy including any of the following drugs, which will not be withheld for a period beginning at least one dosing cycle (minimum 7 days) prior to planned surgery and ending at least 14 days following planned surgery:

Adalimumab (Humira)	Tocilizumab (Actemra)
Etenercept (Enbrel)	Anakinra (Kineret)
Golimumab (Simponi)	Secukinimab (Cosentyx)
Infliximab (Remicade)	Ustekinumab (Stelara)
Abatacept (Orencia)	Rituximab (Rituxan)
Certolizumab (Cimzia)	Tofacitinib (Xeljanz)
Belimumab (Benlysta)	

6.3 Subject Completion

A subject will be considered to have completed the study if he/she has completed the 365-day follow-up visit.

6.4 Subject Discontinuation

Once enrolled, every effort will be made to keep the subject in the study until the required follow-up period is complete. The subject has the right to withdraw from the study at any time without penalty or loss of benefit. The following events will result in terminating the subject's follow-up:

- Subject voluntarily withdraws;
- Subject is lost to follow-up;
- Subject dies; or
- Study is terminated.

The Sponsor must be notified of the reason for subject withdrawal. The Study Site will document this information on the Subject Withdrawal Form and make every effort to give a full description of the reason for withdrawal. Investigators must also report this information to the local IRB as defined by their institution's procedure.

Withdrawn subjects will not be replaced by enrolling additional subjects. Investigational drugs assigned to the withdrawn subject shall not be assigned to another subject. The remaining investigational drugs for the subject will be kept at the Study Site to be processed according to

the Sponsor's disposal or return instructions.

A subject who withdraws from the study for any reason, will be assessed for safety evaluation purposes. For investigational subjects, this assessment shall occur within 24 hours of the last dose of the investigational drugs if at all possible.

7 Study Treatment Procedures

7.1 Summary of Study Treatment

Experimental Arm: Stage 1 surgery consists of surgical removal of an implant (permanent prosthesis or temporary spacer) from the infected joint, debridement per SOC, and [redacted]

Administration of 7-days local antibiotic irrigation [redacted]

The daily investigational drug regimen is repeated on consecutive days until the time of the Stage 2 surgery and is not discontinued before the 7th day of investigational drug therapy. The Stage 2 surgery may occur at any time during the 7th day of investigational drug therapy, such that the 7th day of investigational therapy may be less than a complete 24-hour period. [redacted]

Stage 2 surgery is performed at the completion of the local antibiotic therapy and consists of removal of the VT-X7 Spacer, debridement, and replacement with a permanent prosthesis, unless reimplantation is contraindicated by an intraoperative clinical finding during the Stage 2 procedure. Note: Because of the short duration of the Interstage period in the Experimental Arm, common inflammatory markers such as ESR and CRP are typically still elevated at time of Stage 2 surgery and therefore should not influence the decision to proceed with Stage 2.

All subjects in the Experimental Arm receive 12 weeks of systemic antibiotics post-Stage 2 (typically 6 weeks IV therapy and 6 weeks culture-specific, highly bioavailable oral therapy). Specific post-Stage 2 antibiotic selection, dose, and route of administration are determined by the treating physician supported by the local infectious disease and pharmacy teams.

[redacted]

Control Arm: Stage 1 surgery consists of surgical removal of an implant (permanent prosthesis or temporary spacer) from the infected joint, debridement, and insertion of an antibiotic-impregnated cement spacer per SOC of the Study Site.

Stage 1 surgery is immediately followed by systemic antibiotic administration for 6 weeks followed by a minimum 2-week antibiotic holiday. Post-Stage 1 antibiotics in the Control Arm are typically administered by IV, but culture-specific, highly bioavailable oral antibiotics may be used if appropriate. Specific post-Stage 1 antibiotic selection, dose, and route of administration is determined by the treating physicians.

Stage 2 surgery consists of removal of the cement spacer, debridement, and replacement with a permanent prosthesis. Stage 2 surgery is scheduled following the 2-week antibiotic holiday and performed when deemed clinically appropriate by the Investigator. It is recommended that the Stage 2 surgery be preliminarily scheduled at the time of Stage 1 surgery to avoid unnecessary delay due to schedules of operating staff or facilities.

All subjects in the Control Arm receive 12 weeks of systemic antibiotics post-Stage 2 (typically 12 weeks culture-specific, highly bioavailable oral therapy). Specific post-Stage 2 antibiotic selection, dose, and route of administration are determined by the treating physicians.

Both Arms: Complications associated with the temporary spacer, such as dislocation, loosening, or mechanical failure may occur between Stage 1 and Stage 2. Such complications may or may not have clinical implications or relevance and therefore may or may not require an unplanned surgical intervention prior to the Stage 2 surgery. The decision to perform surgery to address such complications is made by the Investigator based upon available clinical information and the Investigator's best clinical judgment. Perioperative blood transfusions may be required for some subjects. It is recommended that 1 unit of blood be administered based upon the clinical judgment of the treating physician when hemoglobin levels are confirmed at less than 7 grams/deciliter.

8 Schedule of Visits

8.1 Treatment and Data Collection Table

The study treatment and data collection for each scheduled visit in the Experimental Arm are summarized in Table 2 and in the Control Arm in Table 3.

Table 2 Treatment and Data Collection in the Experimental Arm

Events	**Screening and Baseline Visit**	**Stage 1 Surgery**	**Interstage Period**	**Stage 2 Surgery**	**90-Day Follow-up Visit**	**180 Day Follow-up Visit**	**365-Day Follow-up Visit**
Visit window		**Day 0**	**Days 0-7**	**Day 7**	**Days 90-104**	**Days 180-210**	**Days 365-395**
Obtain informed consent (and HIPAA)	X						
Verify Inclusion/Exclusion	X						
Administer pregnancy test[3]	X						
Obtain medical history and CCI score	X						
Perform Randomization[4]	X						
Administer 1g IV TXA pre-op and intra-op		X		X			
Obtain 2 synovial fluid cultures[5]		X		X			
Obtain 2-3 tissue cultures[5]		X		X			
Record Operative time		X		X			
Implant VT-X7 Spacer		X					
Place irrigation line and NPWT sponges		X					
Document implant and local antibiotics/cement				X			
Administer local tobramycin sulfate and vancomycin HCl;[6] record date and time		Start intra-op Stage 1	X				
Administer tailored IV antibiotics per IDSA, if culture + [7]		Start post-op Stage 1	X				

[3] Applicable only if subject is female of child-bearing age.
[4] Subject is to be blinded to randomization until completion of Stage 1 procedure.
[5] Samples to be cultured for fungal and bacterial pathogens.
[6] The interstage period shall be completed on the 7th day after Stage 1 whenever possible. The last irrigation cycle of antibiotics should be given the day of the Stage 2 surgery. Vancomycin HCl may be administered for less than a full day on the 7th day to accommodate a Stage 2 surgery time that is earlier in the day than the Stage 1 surgery time.
[7] If subjects have positive cultures from previous aspirations, non-nephrotoxic IV or highly bioavailable oral antibiotics safe for use with vancomycin HCl and tobramycin sulfate 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.

Events	Screening and Baseline Visit	Stage 1 Surgery	Interstage Period	Stage 2 Surgery	90-Day Follow-up Visit	180 Day Follow-up Visit	365-Day Follow-up Visit
Administer post-op Stage 2 systemic antibiotics per treating physician and Study Treatment Guide				12 weeks[8]			
Obtain tobramycin sulfate peak serum level (taken 2 hours after the local tobramycin irrigation treatment on the specified Interstage days)		X	Q48 (days 1, 3, 5, 7)				
Obtain tobramycin sulfate trough serum level (taken prior to the local tobramycin irrigation treatment on the specified Interstage days)		X (at any time prior to the local irrigation treatment)	Q48 (days 1, 3, 5, 7)				
Obtain vancomycin HCl serum level (taken at any time daily during the Interstage period)		X (at any time prior to the local irrigation treatment)	Daily				
Obtain transfusion record		For 1 week post-Stage 1		For 1 week post-Stage 2			
Obtain sCr, BUN and CBC with differential (taken at any time on the specified days)	X	X[9]	Day 1, day 2, then Q48 until discharge	Post op day 1, day 2, then Q48 until discharge	X		
Obtain GFR	X						
Document concomitant medications, including opioid use	X	X	X	X	X	X	X
Document AEs and complications		X	X	X	X	X	X
Perform PJI assessment[10]					X	X	X
Obtain EQ-5D-3L	X				X	X	X
Obtain HOOS/KOOS	X				X	X	X
Obtain Blue Button® consent for claims data							X

HIPAA = Health Insurance Portability and Accountability Act; CCI = Charlson Comorbidity Index; AEs = adverse events; NPWT = negative pressure wound therapy; IV = intravenous; IDSA = Infectious Diseases Society of America; sCr = serum creatinine; BUN = blood urea nitrogen; CBC = complete blood count; Q48 = every 48 hours; TXA = tranexamic acid

[8] Total of 12 weeks (inclusive) of systemic antibiotic therapy post-Stage 2: typically, 6 weeks culture-specific, IV therapy per IDSA guidelines followed by 6 weeks culture-specific highly bioactive oral therapy.
[9] If baseline blood tests are taken within 48 hours of Stage 1 surgery, new blood tests are not required the day of Stage 1 surgery.
[10] If clinical evidence of infection is present, use ICMMI 2018 for definitive PJI diagnosis.

Table 3 Treatment and Data Collection in the Control Arm

Events	Screening and Baseline Visit	Stage 1 Surgery	Interstage Period	Stage 2 Surgery	90-Day Follow-up Visit	180-Day Follow-up Visit	365-Day Follow-up Visit
Time range permitted for logistical purposes		**Day 0**	**Day 0 - Stage 2**	**Day 57 or later[11]**	**Days 90-104**	**Days 180-210**	**Days 365-395**
Obtain informed consent (and HIPAA)	X						
Verify Inclusion/ Exclusion	X						
Obtain medical history and CCI score	X						
Administer pregnancy test[12]	X						
Perform treatment for PJI per SOC		X	X	X	X		
Perform randomization	X[13]						
Administer 1g IV TXA pre-op and intra-op		X		X			
Obtain 2 synovial fluid cultures[14]		X		X			
Obtain 2-3 tissue cultures[14]		X		X			
Record Operative time		X		X			
Administer IV antibiotics per IDSA per SOC			6 weeks[15]				
Administer 12 weeks post-op Stage 2 systemic antibiotics per treating physician and Study Treatment Guide				X[16]			
Document implant and local antibiotics/cement				X			
Obtain transfusion record		For 1 week post-Stage 1		For 1 week post-Stage 2			
Obtain sCr, BUN and CBC with differential	X	X[17]	Day 1, 2, then Q48 until discharge	Day 1, 2, then Q48 until discharge	X		
Obtain GFR	X						

[11] Stage 2 procedure may occur later than one or more follow-up visits. Maintain schedule of follow-up visits on days specified, independent of Stage 2 procedure date.
[12] Applicable only if subject is female of child-bearing age.
[13] Subject is to be blinded to randomization until completion of Stage 1 procedure.
[14] Samples to be cultured for fungal and bacterial pathogens.
[15] Systemic antibiotic therapy using culture-specific, IV antimicrobial therapy for 6 weeks per IDSA guidelines and SOC, followed by antibiotic holiday for minimum of 2 weeks. Use of biofilm active companion drugs is encouraged when isolate is known to be susceptible.
[16] Total of 12 weeks (inclusive) of culture-specific, highly bioactive oral antibiotic therapy post-Stage 2.
[17] If baseline blood tests are taken within 48 hours of Stage 1 surgery, new blood tests are not required the day of Stage 1 surgery.

Events	Screening and Baseline Visit	Stage 1 Surgery	Interstage Period	Stage 2 Surgery	90-Day Follow-up Visit	180-Day Follow-up Visit	365-Day Follow-up Visit
Document concomitant medications, including opioid use	X	X	X	X	X	X	X
Document AEs		X	X	X	X	X	X
Perform wound check and PJI assessment[18]					X	X	X
Obtain EQ-5D-3L	X				X	X	X
Obtain HOOS/KOOS	X				X	X	X
Obtain Blue Button® consent for claims data							X

HIPAA = Health Insurance Portability and Accountability Act of 1996; CCI = Charlson Comorbidity Index; AEs = adverse events; NPWT = negative pressure wound therapy; IV = intravenous; IDSA = Infectious Diseases Society of America; sCr = serum creatinine; BUN = blood urea nitrogen; CBC = complete blood count; TXA = tranexamic acid; Q48 = every 48 hours

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

8.2 Unscheduled Visits

Visits made to the Study Site's Emergency Department or to the operating surgeon's office for a medical condition related to the index joint surgery, including SOC post-operative follow-up visits, are considered Unscheduled Visits, and the following should be documented in the relevant eCRF:

- Reason for visit;
- Result of wound check;
- Concomitant medications; and
- AEs/SAEs/UADEs.

9 Data and Safety Monitoring Board

The DSMB is composed of independent physicians and a biostatistician who will not participate in the study and who are not affiliated with the Sponsor, the Investigators, or any of the Study Sites. The DSMB will have access to study data, will review the study on a periodic basis, will be responsible for making recommendations regarding any safety or compliance issues throughout the course of the study, and may recommend to the Sponsor to modify or stop the study. Final decisions regarding study modifications or study termination rest with the Sponsor.

Cumulative safety data will be reported to the DSMB and reviewed by the DSMB on periodic basis periods to ensure subject safety. Every effort will be made to allow the DSMB to conduct

[18] If clinical evidence of infection is present, use ICMMI 2018 for definitive PJI confirmation.

an unbiased review of subject safety information.

The DSMB will meet according to the schedule specified in the DSMB Charter.

10 Statistical and Data Considerations

10.1 Overall Statistical Design

This study is a multi-center, prospective, parallel, concurrent RCT. Details of the statistical analysis, including the handling of missing values will be described in the Statistical Analysis Plan (SAP). This section provides key elements of the statistical approaches.

10.2 Efficacy Endpoints

10.2.1 Primary Efficacy Endpoint

The primary endpoint is a composite of Overall Success at the 90-day follow-up visit, as described in Section 5. The study hypothesis is that the Investigational treatment will have superior outcomes compared to the Control treatment in terms of Overall Success at 90 days.

The statistical null and alternative hypotheses are:

$$H_0: \Pi_I - \Pi_C \leq 0$$

vs.

$$H_A: \Pi_I - \Pi_C > 0,$$

Where,

Π_I is the proportion of subjects who meet criteria for Overall Success at 90 days in the Experimental Arm, and

Π_C is the proportion of subjects who meet criteria for Overall Success at 90 days in the Control Arm.

The hypotheses will be tested using a one-sided z-score test for independent samples for proportions at the 1-sided alpha level of 0.025. If the test value exceeds the nominal critical point, the H_0 will be rejected. The 2-sided 95% CI for the difference in Overall Success between the Experimental and Control Arms will be calculated.

10.2.2 Secondary Endpoints

A pre-planned analysis of the secondary endpoints will be performed testing the superiority of Experimental Arm compared to Control Arm conditioned by success in testing of the primary efficacy endpoint. The multiplicity and Type 1 Error within the secondary endpoints' family will be controlled using the fixed sequence approach and one-sided alpha value of 0.025. Refer to the SAP for details on the analysis of the secondary endpoints.

10.2.3 Exploratory endpoints

Exploratory endpoints will be analyzed using t-test, McNemar's test, chi-square test, and Fisher's exact test, as appropriate. Longitudinal changes will be analyzed using mixed models for repeated measures (MMRM).

10.3 Analysis Populations

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

- The ITT population includes all Randomized subjects, regardless of whether the subject received the treatment to which the subject has been randomly assigned.
- The mITT population includes all Randomized subjects where the randomly assigned treatment has been attempted.
- The PP population is a subset of the ITT population and includes all subjects who receive the assigned treatment and do not have any major protocol violations.
- The CC population includes all subjects in the ITT population who have the 365-day follow-up visit.
- The Safety population includes all ITT subjects.

10.4 Type I Error

The alpha level will be set to 0.05 based on the 2-sided testing and 0.025 for the one-sided approach, if not explicitly stated otherwise. Control for multiplicity in testing of secondary endpoints is based on fixed sequence approach. Unless otherwise indicated, all statistical inferences will be based on 2-sided 95% CIs.

10.5 Sample Size and Power

A sample size of 76 subjects will have 90% power to detect .35 (35%) difference in the proportion of subjects who are classified as Overall Success at 90-day follow-up, under the assumption that the proportion of subjects in the Control Arm who are classified as Overall Success is 50%.

10.6 Missing Value Imputations

Details concerning missing value imputations will be described in the SAP.

10.7 Sub-group Analyses

Pre-planned sub-group analyses will include analyzing the primary and secondary endpoints by joint and by drug resistance (none versus one or more multi-drug resistant pathogens at Stage 1).

10.8 Additional Analyses

10.8.1 Interim Analysis of Stage 2 Success

An interim analysis of percent success of Stage 2 implantation in the Experimental Arm will be initiated 10 days after the Stage 1 surgery of the 15th subject in the Experimental Arm. The analysis will describe proportion of subjects who were not implanted with the permanent prosthesis, describe any unplanned surgical interventions, list the reasons for failure to perform the second stage surgery, and describe approaches to the management of these subjects

10.8.2 Interim Safety Analysis

An interim safety analysis will be performed when the 15th subject in the Experimental Arm reaches 90 days post-Stage 1 surgery. The analysis will include, but not be limited, to the number of subjects retaining the prosthesis implanted at the second stage and describing any unplanned post-stage 2 interventions for all subjects.

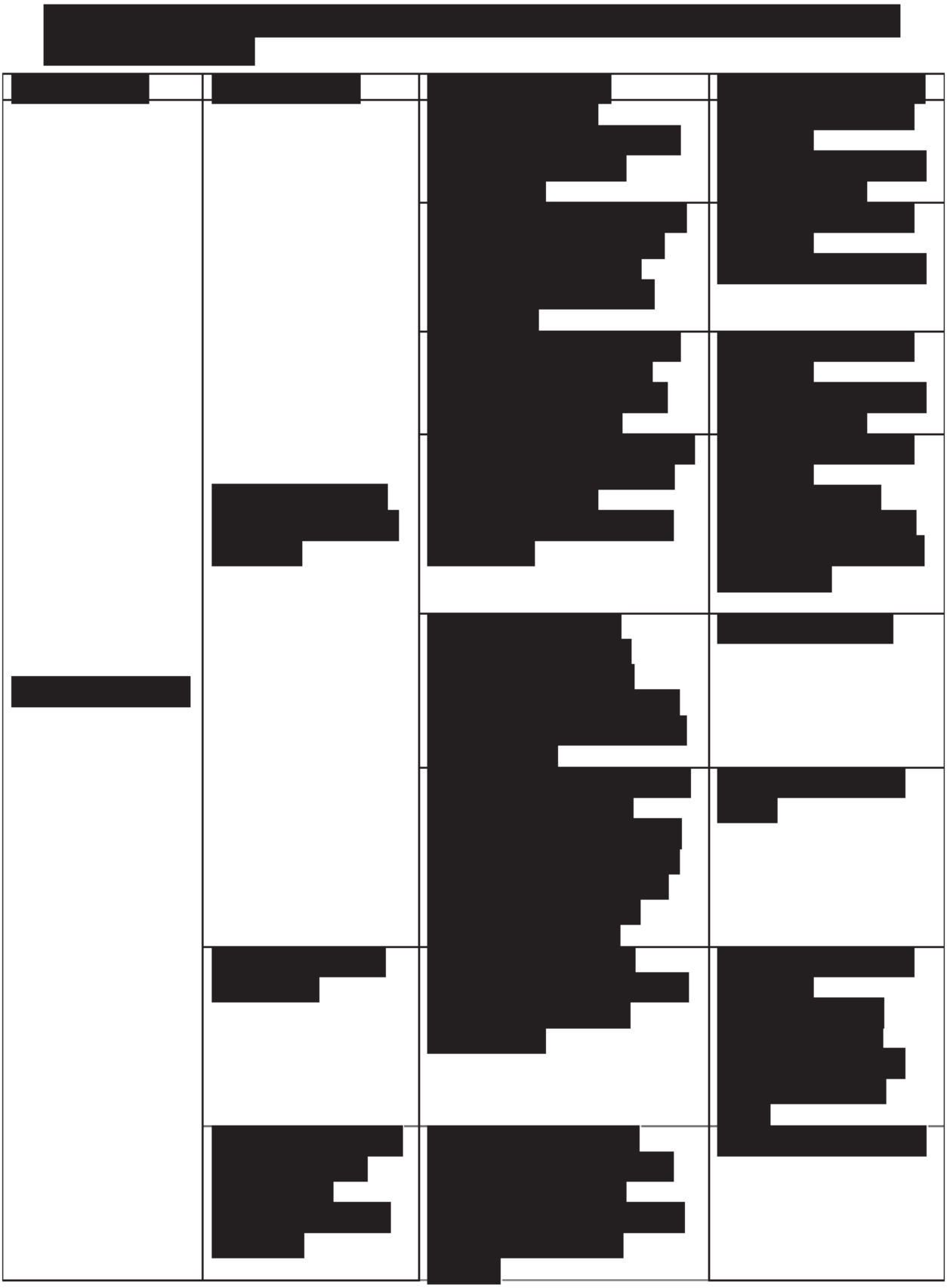
11 Risk-Benefit Analysis

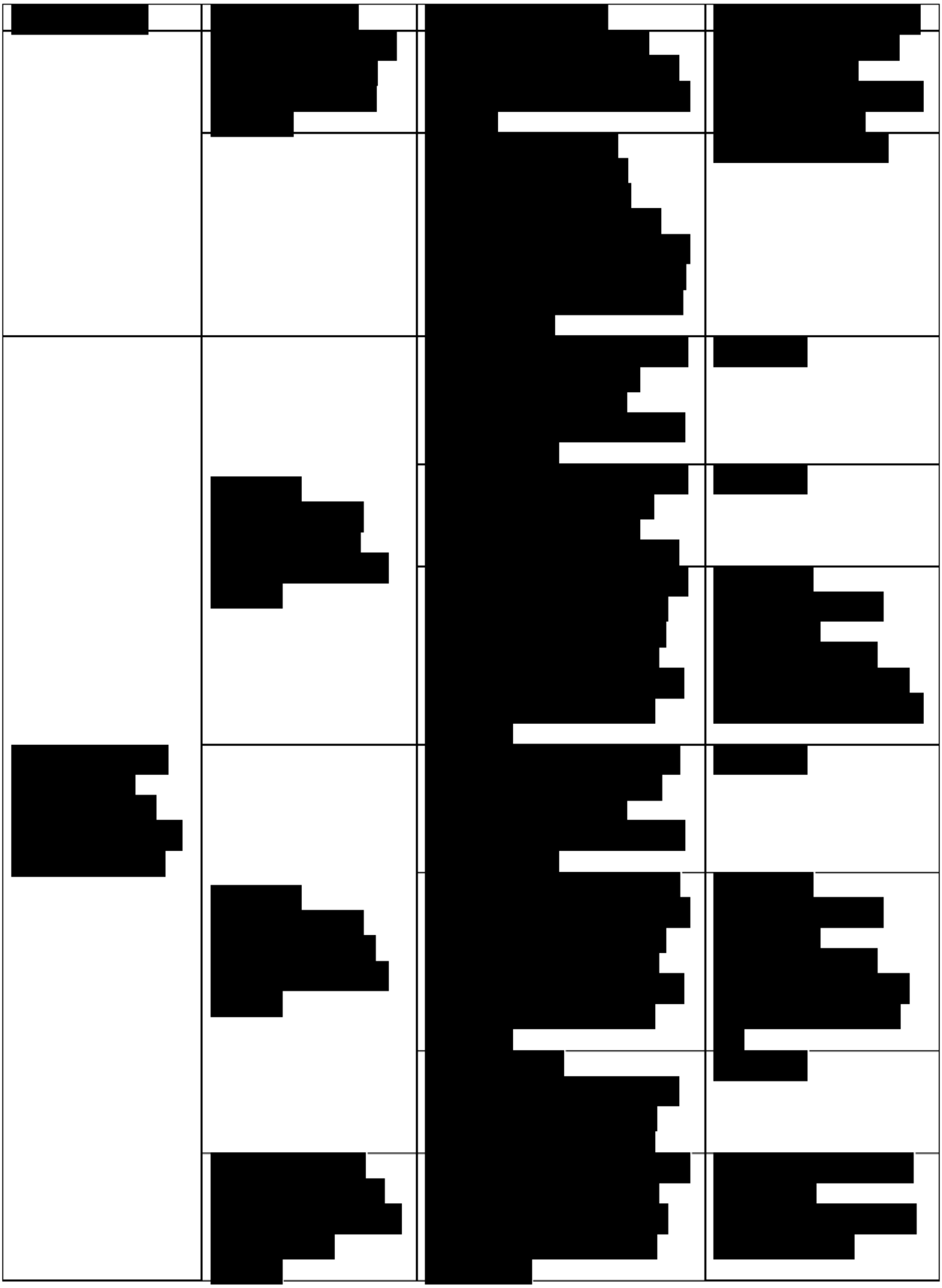
11.1 Potential Benefits

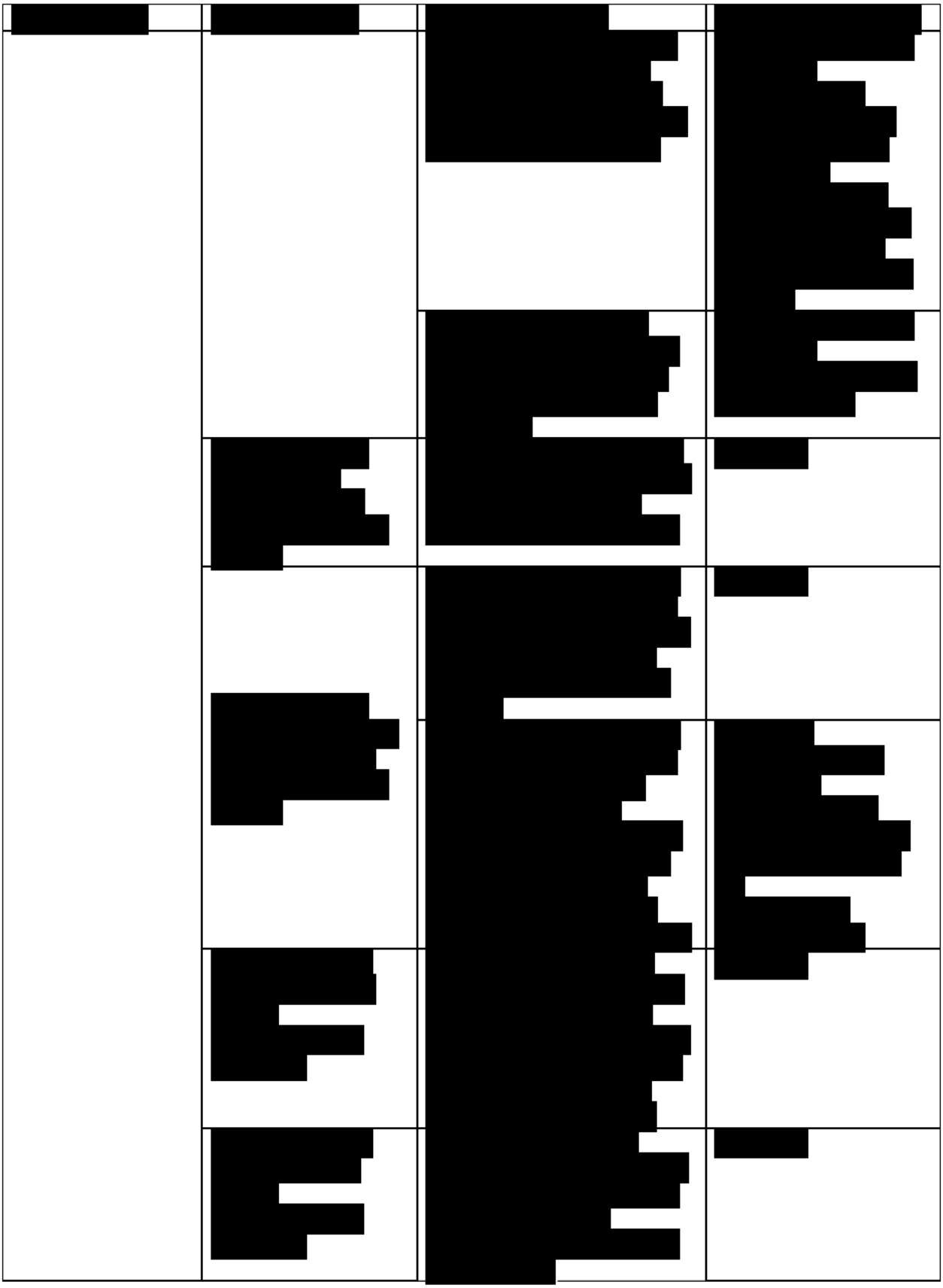
There are significant potential benefits for Experimental subjects who participate in this clinical study. Subjects to be included in the present study have a serious and potentially life-threatening clinical condition. The investigational product, if effective as anticipated, will provide better outcomes compared to current SOC treatment. Subjects who are randomized into the Control Arm will receive SOC treatment and will not be worse off than if they did not participate in the study. Data from the Phase 2 study (JPS-001) showed an acceptable safety profile for the intervention. The efficacy findings from the Phase 2 study were also acceptable and are expected to be translated to this study, thus justifying the assumed benefit-to-risk ratio.

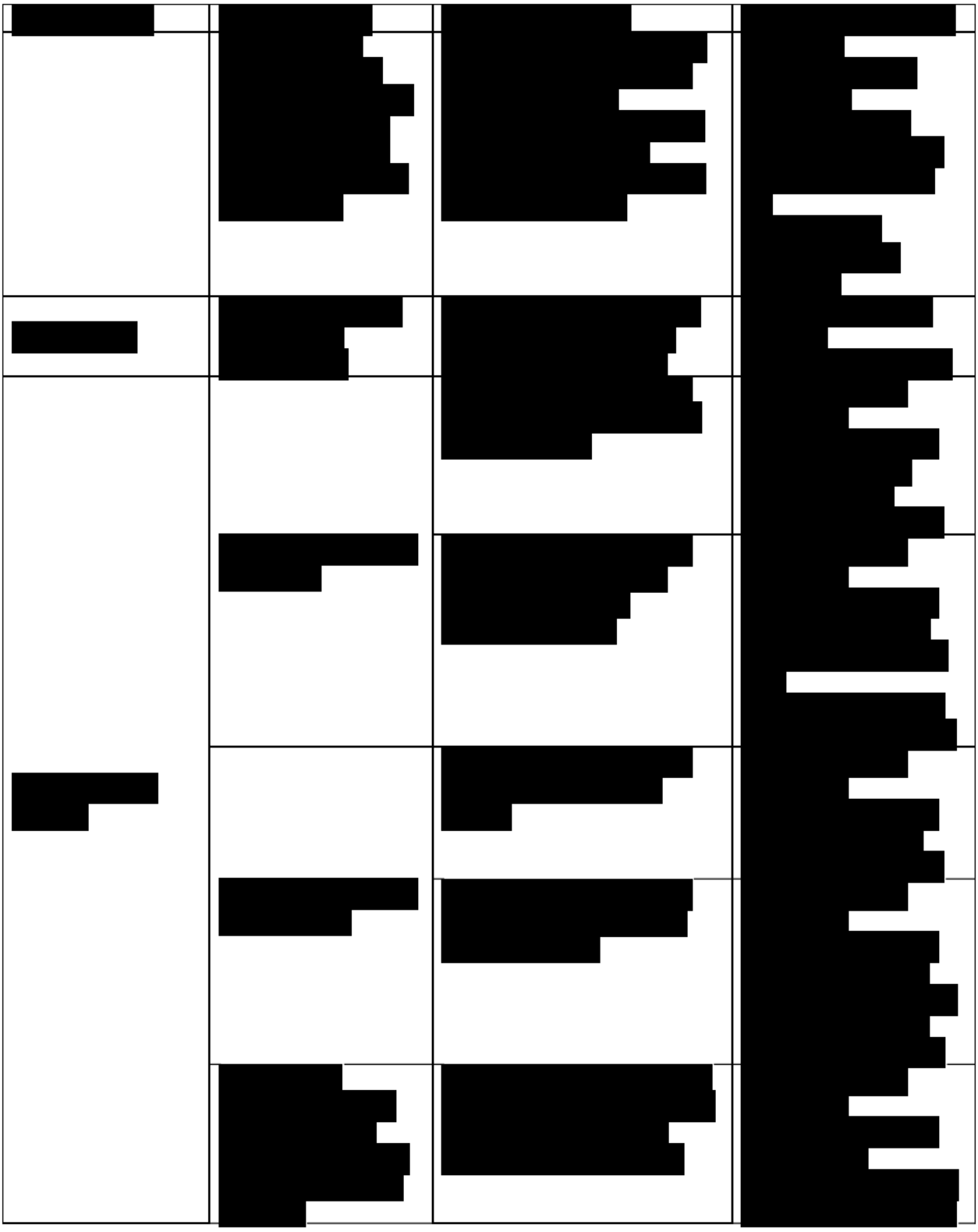
There are potential societal benefits to a novel antimicrobial therapy application with the possibility of shortening treatment durations thus minimizing antimicrobial resistance and toxicity. PJI and its associated comorbidities are serious medical events that consume a large amount of health care resources. If the treatment is shown to be more effective and/or safer than the current SOC treatment, the investigational product will provide a therapeutic option that fills the treatment gap and thus contributes to overall management of PJI while advancing antimicrobial stewardship. Additionally, the shortened intervention duration has the potential to reduce opioid usage and misuse, a serious national crisis that affects public health as well as social and economic welfare.

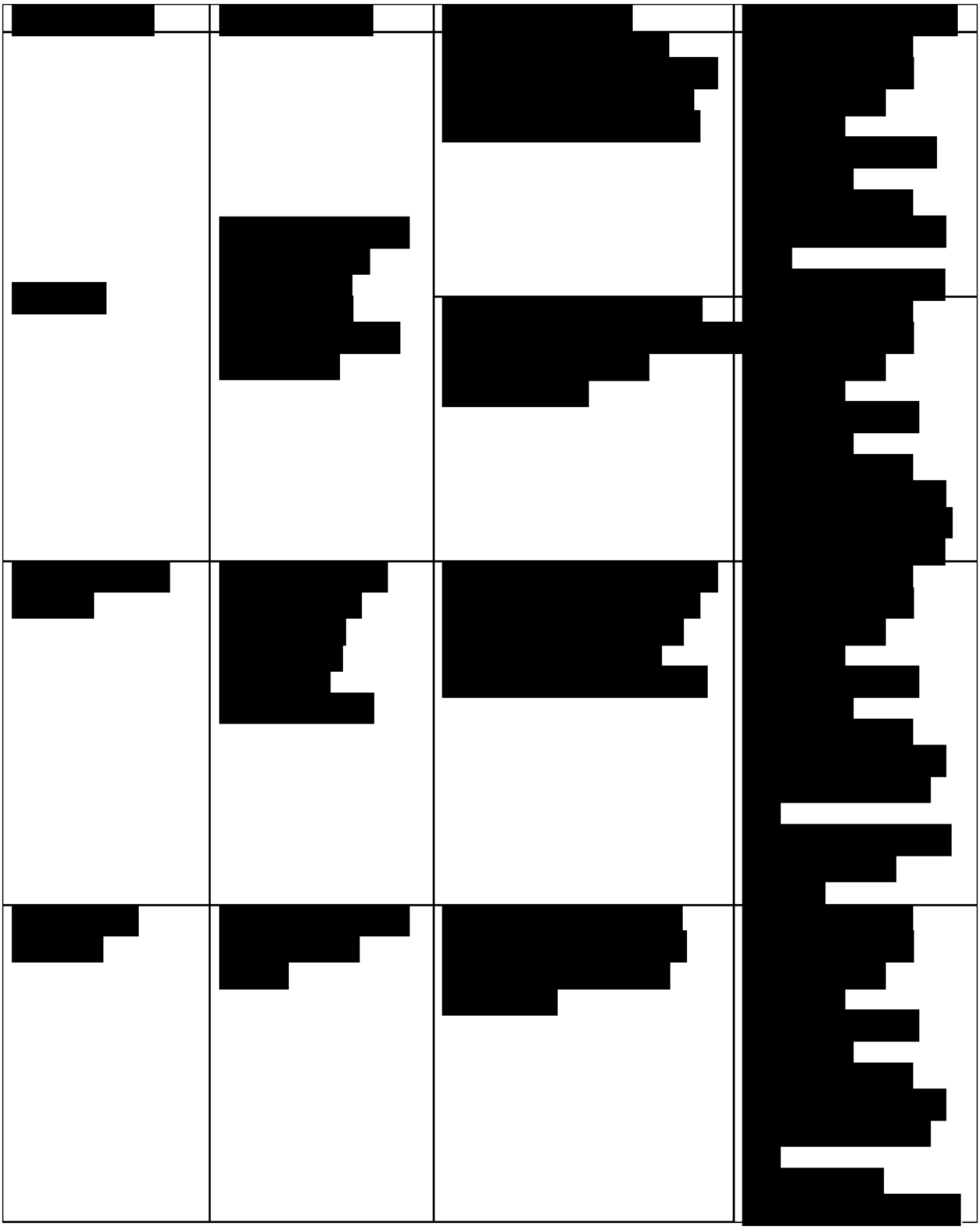
[redacted]

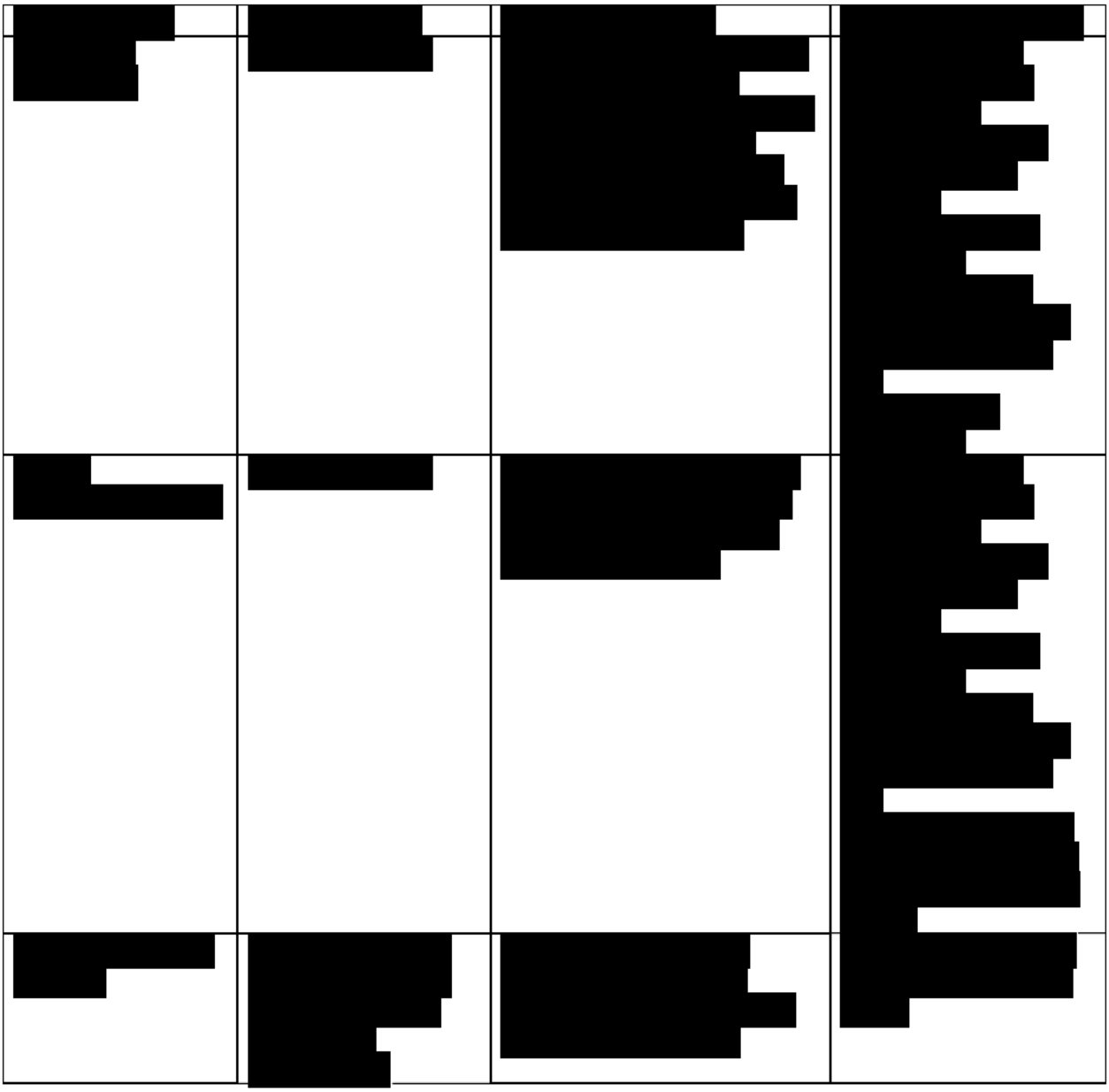












11.3 Risks Associated with Participation in the Clinical Investigation

There are risks associated with participation in a clinical investigation. There is only limited clinical experience with the investigational drugs and no experience with the VT-X7 Spacer to date, and there may be unanticipated adverse events (UAEs). There are protocol-defined tests that require blood draws that may carry additional risk to the subjects.

11.4 Minimization of Risks

The following steps have been taken to further minimize the risks of the study:

- The study Protocol has built-in measures to control potential adverse effects, including study inclusion/exclusion criteria, clinical surveillance, and laboratory surveillance;
- Training and technical support will be provided for device placement/removal procedures;
- A DSMB is set up to monitor the safety of the subjects in the study;
- An interim safety analysis has been implemented to compare safety outcomes early in the study.
- Non-clinical studies of the investigational product components were performed to minimize or eliminate risks (see Table 5 Summary Table of Risks and Risk Mitigation Associated with the Investigational Product or Treatment);
- The Phase 2 study (JPS-001) has not indicated any major risks associated with the investigational drugs; and
- Clinical study results from the Phase 2 study (JPS-001) show that there were no investigational treatment-related AEs in any of the 15 enrolled subjects.

In summary, subjects included in the present study have a clinical indication for two-stage arthroplasty. Prior clinical experience shows that the investigational product, VT-X7, can be used successfully, that subjects may achieve favorable outcomes, and that the complications are acceptable and can be managed clinically. The risks associated with the investigational product including the VT-X7 Spacer have been mitigated as much as possible. The current study design includes additional measures to further minimize risks.

12 Discontinuation of Study, Study Sites, or Subjects

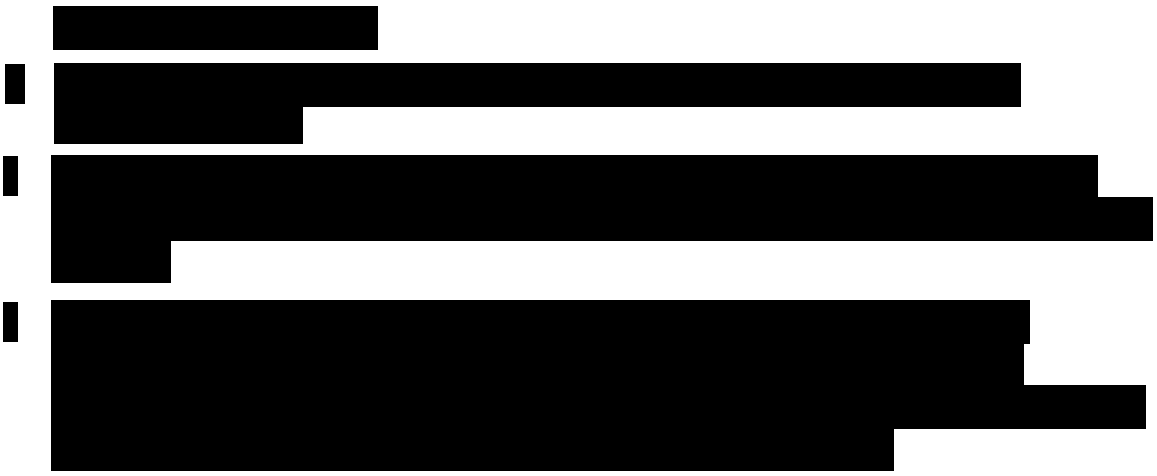
12.1 Discontinuation of Study Sites

Study Site participation may be discontinued if the Sponsor, the PI, or the IRB judges it necessary for any or no reason. Subjects at discontinued Study Sites will be followed up in accordance with Section 6.4.

12.2 Treatment Discontinuation in the Experimental Arm

If a subject is unable to continue the investigational treatment for any reason which requires premature removal of the investigational device, antibiotic irrigation shall be discontinued, the device shall be removed, and appropriate medical treatment shall be administered at the direction of the treating physicians.

[redacted]



12.3 Treatment Discontinuation in the Control Arm

If a subject is unable to continue treatment for any reason which requires premature removal of the cement spacer or discontinuation of antibiotic therapy in the Control Arm, appropriate medical treatment shall be administered at the direction of the treating physicians.

12.4 Subject Lost to Follow-Up

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit and study personnel are unable to contact the subject. Study personnel must make a reasonable effort to contact the subject and document the following contact attempts prior to declaring a subject to be lost to follow-up: 3 phone calls with at least 2 days in between each call followed by a certified letter. The first phone call must occur no more than 3 business days after the subject has failed to show up for a visit.

When possible, study personnel will aim to determine the reason for the subject being lost to follow-up and record any information obtained.

12.5 Study Discontinuation

The study will be discontinued if the Sponsor decides it necessary for medical, safety, regulatory, no reason, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

13 Adverse Events

13.1 Basis of Adverse Event Management

The definitions, recording, assessment, and reporting of AEs required in this Protocol are based on requirements from FDA 21 Code of Federal Regulations (CFR) 312.32 (Revised as of April 1, 2018), FDA 21 CFR 812 (Revised as of April 1, 2018), ISO 14155:2020, and Guidance for Industry and Investigators: Safety Reporting Requirements for IND and Bioavailability/Bioequivalence (BA/BE) Studies (FDA, December 2012, Drug Safety) [54].

13.2 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. Or,

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

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's Brochure (IB) or is not listed at the specificity or severity that has been observed. For the investigational drugs in this study, because they are marketed and approved in the U.S., ordinarily FDA-approved prescription drug labeling is used as the basis for determining whether an event is unexpected for reporting purposes.

Adverse Device Effect (ADE): An AE related to the use of an investigational medical device includes AEs resulting from insufficient or inadequate instructions for use (IFU), deployment, implantation, installation, or operation, or any malfunction or any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE): An ADE that has resulted in any of the consequences characteristic of an SAE.

Unanticipated Adverse Device Effect or Unanticipated Serious Adverse Device Effect (UADE or USADE): Any serious adverse effect on the health or safety of a subject, 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 Protocol 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:

- Leads to death;
- Is life threatening, or places the participant at immediate risk of death;
- Requires inpatient hospitalization or prolongation of existing hospitalization; or

- Results in 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.

13.3 Adverse Event Recording

AE information will be collected throughout the study. The Investigator or his/her designee will record all AEs on the appropriate Source Worksheet (SW) and enter this data on an eCRF. The applicable SW will capture the event term, date of onset, duration, seriousness, severity, actions taken, outcome, and causality to the investigational product (drug, implanted spacer, or the investigational procedure) or NPWT. The Investigator is responsible for determination of seriousness, 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 in a laboratory report must be recorded.

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

All AEs and SAEs must be followed until one of the following occurs:

- 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 the study, including required follow-up visits; or
- Study is closed.

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

13.4 Adverse Event Assessment

The Investigator is responsible for identifying and reporting all AEs from his/her site. The Investigator is responsible for the determination of severity, seriousness, and causality for each event reported.

The Sponsor or Sponsor’s designee will routinely review AE information as reported by the Investigators. The Sponsor or Sponsor’s designee will also review and assess SAEs for seriousness and causality. Further, he/she will determine whether the event is “unexpected” for

IND safety reporting purposes and whether the event meets the definition of a UADE.

If the Investigator and Sponsor/Sponsor's designee have different assessments of the seriousness or life-threatening nature of an event, the more serious assessment will prevail and be evaluated by the Sponsor for possible expedited reporting for IND safety report purposes.

If the Investigator and Sponsor have different assessments of event causality, for IND safety report purposes, the Sponsor' judgement will override the Investigator's assessment.

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 product or procedure;
- Reasonable possibility: there is evidence to suggest a causal relationship between the investigational product and/or study procedure to the AE;
- Definitely related: there is reason to conclude that the investigational product and/or study procedure caused the event.

13.5 Adverse Event Reporting

The Investigator is responsible for the collection and submission of AE and SAE data to the Sponsor/Contract Research Organization (CRO).

AE data will be entered into the electronic data capture (EDC) system.

The Investigator must report to the Sponsor/CRO any SAE within 24 hours of the Investigator becoming aware of the SAE, whether or not it is considered investigational product-related, including those listed in the Protocol or IB. The Investigator must include an assessment of whether there is a reasonable possibility that the investigational product and/or study procedure caused the event. SAE data will be entered into the EDC system 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 for advising the Investigator if an AE is an unanticipated problem that needs to be reported to the 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 was 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).

13.6 Device Deficiency

13.6.1 Definition of Device Deficiency

A device deficiency is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This may include malfunctions, use errors, and

inadequacy in the information supplied by the manufacturer including labelling. For the purposes of this study, this definition includes device deficiencies related to the investigational medical device (i.e., the VT-X7 Spacer) and medical devices used as part of therapy (i.e., the NPWT system) or in the Control Arm in the clinical investigation.

13.6.2 Device Deficiency Report

The Investigator is responsible for documenting all device deficiencies related to both the investigational device (i.e., the VT-X7 Spacer) and the medical device used as part of therapy (i.e., the NPWT system), or the medical devices used in the Control Arm throughout the clinical investigation. The reporting shall be done using the Device Deficiency Report form provided by the Sponsor or designee, and via entry into the EDC system.

The data from the Device Deficiency Report will be periodically reviewed by the DSMB. When applicable, appropriate corrective and preventive actions (CAPAs) will be taken to protect the safety of subjects, users, and other persons. The sponsor or designee will arrange for the safe return of the investigational device that is subject to a device deficiency.

13.6.3 Timing for Reportable Event

The Investigator is responsible for assessing the reportability of each event, and submitting the Device Deficiency Report when the deficiency meets the following criteria:

- For any device deficiency that led to a SAE, the Investigator must submit **both** an SAE report and the associated Device Deficiency Report to the Sponsor/designee following the timeline as described in Section 13.5.
- For any device deficiency that might have led to an SAE if either:
    - suitable action had not been taken,
    - intervention had not been made, or
    - circumstances had been less fortunate,

The Investigator must submit the Device Deficiency Report to the Sponsor/CRO as soon as possible, but not later than 5 business days following the date of awareness of the event.

The Investigator is responsible for reporting the device deficiency to the IRB, if required per IRB regulations.

The Sponsor will promptly evaluate the report to determine further actions.

The Investigator is reminded that mandatory reporting to the FDA, as per 21 CFR Part 803, is required for the NPWT pumps throughout the course of the study.

14 Investigational Product Accountability

14.1 Investigational Drug

The Study Site will maintain an inventory of the investigational drugs. This inventory will include:

- Name of person designated as responsible for the inventory of the investigational products;
- Amount received including date and lot number(s);
- Amount currently in inventory;
- Amounts dispensed to each subject, identified by the subject identification 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.

Investigational drugs must be stored in a secure space with double lock and limited access. Neither the Investigator nor any member of the study staff will distribute any of the investigational drug to any person not participating in this study. The drugs should be stored at a controlled room temperature of 20° to 25°C (68° to 77°F).

The Sponsor or designee will provide forms to facilitate investigational drug product inventory control. All completed investigational drug accountability forms and treatment logs must be retained in the Study Site's pharmacy binder or equivalent information retained in the electronic medical record. These records must be available for inspection by the Sponsor, its designees, and/or by regulatory agencies at any time.

14.2 Investigational Device and Instruments

The VT-X7 Spacer will be provided by the Sponsor to the Study Site at the time of Stage 1 surgery. The VT-X7 Spacer will be available in multiple sizes because the choice of size of spacer components is determined during the Stage 1 surgery. The required surgical instruments for insertion and removal of the VT-X7 Spacer will be provided non-sterile in a surgical tray. The surgical instruments tray will be provided to the Study Site ahead of the planned Stage 1 and Stage 2 surgeries to allow time for the cleaning and sterilization of the tray.

The VT-X7 Spacer removed during Stage 2 surgery should be discarded per the Study Site's biohazardous material handling procedures unless it appears broken or the irrigation line is detached from the Spacer, in which case the device is to be shipped for evaluation per the Sponsor's instructions.

Documentation of the investigational device and instrument accountability will be maintained on logs provided by the Sponsor.

15 Selection of Study Sites and Principal Investigators

The Sponsor will select PIs who are qualified by training and experience to perform clinical research in this field and to participate in the clinical investigation. Study Sites will be selected based upon an assessment of the qualifications of the PI and the facilities at each Study Site. All PIs will be trained on the investigational product, the Protocol, and all study procedures prior to enrolling subjects.

A Site Initiation Visit (SIV) will be conducted at each Study Site to ensure the Investigators and study personnel 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.

15.1 Training

15.1.1 Site Training

All Investigators/study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, an SIV, 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 product usage, investigational product accountability, source documentation and eCRF completion, and study personnel responsibilities. All Investigators and relevant site personnel must sign a training log (or equivalent) upon completion of the training.

15.1.2 Monitor Training

The Sponsor or designee will engage Clinical Research Associates (CRAs) who are qualified by appropriate training and experience to review the conduct and quality of the study. Prior to working on the study, CRAs will be trained on the Protocol, SWs/eCRFs, and the drug/device/procedure. Such training will be documented.

15.2 Study Monitoring

The Sponsor and/or a designee (e.g., a CRO) will monitor the clinical study in a manner consistent with FDA regulations and GCP standards. A Monitoring Plan will be generated to document the monitoring process to ensure compliance with all procedures required by the Protocol and to verify data quality.

A risk-based approach will be used to determine the site monitoring frequency. Monitoring and Source Data Verification (SDV) may be performed remotely or on-site.

The Investigator and his/her personnel 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.

15.3 Source Data Verification

SDV ensures accuracy and credibility of the data obtained. During SDV, reported data are

reviewed for accuracy, completeness, attributability, and verifiability.

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 necessary for the reconstruction and evaluation of the study.

15.4 Direct Access to Source Data/Documents

The PI(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, and IRB and regulatory inspection(s). The process for direct access to source documents in the electronic medical record (EMR) will be determined during site qualification as this process varies by Study Site procedure.

Consenting subjects agree 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. The Sponsor will not otherwise release any personal information.

15.5 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 will be completed. The occurrence of protocol deviations will be assessed by the Sponsor for evaluation of Investigator compliance to the Protocol and to GCP and regulatory requirements. Protocol deviations will be designated as significant or minor. The Investigator will inform his/her IRB of protocol deviations according to the requirements of each reviewing IRB.

Significant protocol deviations for this Protocol consist of, but are not limited to, the following:

- Failure to obtain subject's informed consent prior to enrolling into the study;
- Enrollment of subjects who do not meet all eligibility requirements;
- Failure to conduct Protocol-required procedures and clinical follow-ups;
- Failure to report SAEs according to Protocol requirements.

In the event of any deviation from the Protocol, the Sponsor will be notified of the Study Site's non-compliance. Corrective actions will be recommended if indicated, and the methods, plan, or other activities implemented to ensure non-recurrence will be documented by the Investigator and forwarded to the Sponsor or designee. Repeated protocol deviations despite re-education of Study Site personnel and/or significant protocol deviations may result in termination of the Study Site's study participation. Subjects already enrolled at these Study Sites will continue to be followed for safety per Protocol guidelines.

16 Data Handling and Record Keeping

16.1 Subject Coding

The eCRFs and all other documents/data sent to the Sponsor will not contain identifying study subject information. Each subject will be assigned a unique subject identification number that reflects the Study Site number and subject number. The subject identification number will consist of 8 characters in an alphanumeric combination. Each Study Site will be assigned a 3-digit alphabetic code.

The Study Site will maintain a log that links the subject identification number to the name of each subject. An example is shown in Table 5.

Table 5 Example of the Subject Identification Number

Site Code			Connector	Sequential Number			
A	B	C	-	0	0	0	1

16.2 Data Handling and Record Keeping

For the study duration, the Investigator will maintain complete and accurate documentation as required per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP E6(R2).

The following materials should be included in the subject record:

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

16.3 Electronic Case Report Form Completion

Accurate data recording will be performed by Study Site personnel trained on the Protocol and electronic case report form (eCRF) completion. All data fields will be completed. However, if data are not available (i.e., missed visit, etc.), the Study Site will receive instructions regarding how to properly document these facts.

Error messages will be generated for the modification and/or verification of the entered data.

Queries will be generated 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.

16.4 Record Retention

The Investigator/Site will maintain all records pertaining to this study for the later of: (a) 2 years following study completion; (b) 2 years after the study has been terminated by the Sponsor; (c) as otherwise instructed by the Sponsor; or (d) as required by local laws or regulations. The 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.

17 Ethical Considerations

17.1 Subject Compensation

Study subjects may be compensated for certain activities required of them during their participation in the clinical study.

17.2 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 on the ICF, which will be signed by the subject with the date of that signature indicated, as well as the dated signature of the study personnel who obtained the consent. The Investigator will keep the original ICF and a copy will be given to the subject. As part of the informed consent process, study personnel will explain to the subject that he/she is 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.

17.3 Institutional Review Boards

IRB approval for the Protocol and ICF will be obtained prior to subjects' study participation. 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 ICF without appropriate approval from the

IRB, the Sponsor, and/or the regulatory agencies.

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

17.4 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 the Sponsor.

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

Confidentiality will be protected as much as possible throughout the study. 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 U.S. law or regulation.

18 Sponsor and Principal Investigator Reports

18.1 Principal Investigator Reports

The reports in Table 6 are required of each PI as described.

Table 6 Investigator Reports

Report	Submit to	Submission Schedule
Screening and Enrollment	CRO	Weekly
All study data	EDC (CRO)	Baseline data: within 48 hours; all others: no later than 7 days
Serious Adverse Events (SAEs)	CRO/IRB	Report to CRO within 24 hours after the PI first learns of the event. Report to IRB according to IRB's reporting roles, or if notified by the Sponsor/CRO that the SAE meets FDA's IND safety report criteria.
Device Deficiency Report	CRO/IRB	If associated with an SAE, use the same schedule for SAE reporting. Otherwise, within 5 days after the PI first learns of the event. Report to IRB according to IRB's reporting roles, or if instructed by the Sponsor/CRO.
Study protocol deviations	CRO/IRB	Report to CRO and IRB within 48 hours if the deviation affects the subject's safety and well-being. Otherwise, report to CRO no later than 7 days; report to IRB according to IRB's reporting roles.
Subject withdrawal	CRO/IRB	Report to CRO and IRB within 48 hours if the deviation affects the subject's safety and well-being. Otherwise, report to CRO no later than 7 days; report to IRB according 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 of receipt.
IRB suspensions or terminations of approvals	CRO	Report to the Sponsor/CRO within 48 hours of receiving any IRB communications of suspensions or termination of approvals. Sponsor/CRO will report to the FDA.

18.2 Sponsor Safety Reports

The Sponsor is responsible for timely review of safety information and determining whether the safety information submitted from the Study Sites meets the IND safety reporting criteria as defined in FDA 21 CFR 321.32:

- Suspected adverse reaction;
- Serious;
- Unexpected.

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

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

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

If the Sponsor determines that a 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 no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first received notice of the effect as defined in FDA 21 CFR 812.46(b)(2).

19 Reporting and Publication of Results

All unpublished information provided to the Investigators by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The publication of results in academic journals and any patent application(s) based on the results of the trial submitted by the Investigator will be guided by the Investigational Site Agreements

between the Sponsor and the Investigator.

The Sponsor or its designee will prepare a Clinical Study Report that will comprehensively describe the trial findings. When the Sponsor generates reports from the data collected in this trial for presentation to regulatory authorities, drafts may be circulated to the Investigator for comments and suggestions.

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