Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER

KCI.PREVENA.2017.01

PRODUCT/PROJECT

ActiV.A.C.® Therapy Unit or **Prevena Plus™ 125 Therapy Unit**
in combination with **Prevena™ Incision Dressing**

TITLE

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

(PROMISES)

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
BMI	Body Mass Index
ciNPT	closed incision Negative Pressure Therapy
CMH	Cochran-Mantel-Haenszel test
CSR	Clinical Study Report
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
ICH	International Conference on Harmonization
IFU	Instructions for Use
ITT	Intention-To-Treat
mITT	Modified Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mPP	Modified Per-Protocol
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SSC	Surgical Site Complication
SSI	Surgical Site Infection
TEAE	Treatment-emergent Adverse Event
TKA	Total Knee Arthroplasty
WHODrug	WHO Drug Dictionary for Regulatory Activities

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1 PURPOSE

The purpose of this Statistical Analysis Plan (SAP) for the KCI.PREVENA.2017.01 study is to outline the analyses planned to support the generation and completion of the Clinical Study Report (CSR). This SAP has been written to be in accordance with the clinical protocol (**Post-market, Randomized, Open-Label, Multicenter, Study to Evaluate the Effectiveness of Closed Incision Negative Pressure Therapy versus Standard of Care Dressings in Reducing Surgical Site Complications in Subjects with Revision of a Failed Total Knee Arthroplasty Version 3.0 dated October 6th, 2018**) and relevant data collection documents. This SAP adheres to the requirements and guidelines identified by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1998][1].

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Post-hoc exploratory analyses not identified in this SAP may be performed to examine study data further. Any post-hoc or unplanned exploratory analysis will be identified as such. This document will be endorsed prior to database lock. Changes made to the SAP prior to the final database lock will be described in the document history. The SAP will not be amended after the final database lock. Deviations from planned analyses, including additional exploratory analyses after database lock will be noted in the CSR.

2 OVERVIEW OF STUDY DESIGN

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

Each potential study participant will complete the procedures and assessments listed in Protocol Sections 4.1 and 4.2 by the Investigator or designee within 30 days prior to study start. Only subjects who meet all pre-operative and intra-operative eligibility criteria will be randomized in the study. Each enrolled subject will be randomized in a 1:1 ratio to receive either ciNPT or SOC after a revision TKA. The anticipated maximum participation for each subject from screening initiation to the last visit is up to 134 days.

2.1 Sample Size and Power

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

Assuming an overall type 1 error rate of 0.05, with a two-sided hypothesis test, the study will have at least 80% power to detect a difference of 10% (50% reduction) in SSCs in the ciNPT arm with 199 subjects in each treatment arm, with one interim analysis at about 50% of the evaluable subjects for a total of 398

subjects using the likelihood ratio test. With an estimated 5%-10% loss, a non-binding interim analysis for superiority at approximately 50% of the evaluable subjects using O'Brien-Fleming method for monitoring boundaries, the planned sample size will be inflated for a potential loss of follow-up for a total of 440 subjects.

2.2 Study Population and Subpopulations

The study population will consist of subjects undergoing a revision of a failed total knee arthroplasty (TKA). Per Section 8.4.2 and Section 8.4.3 of the study protocol, the overall study population can be further partitioned into two predefined subpopulations (Septic versus Aseptic) based on the TKA revision type.

2.3 Treatments

ciNPT: Subjects randomized to ciNPT will receive treatment for a duration consistent with the Instructions for Use (IFU) document included with the selected Prevena™ Dressing but no shorter than five days post-surgery. Depending on the length of the incision, an appropriate Prevena™ Dressing will be used to cover the closed surgical incision, according to the instructions for use included with the product. Total treatment time should not exceed the maximum number of days indicated in the IFU document included with the Prevena™ Dressing applied immediately following surgery. For the delivery of negative pressure, an ActiV.A.C.® (The ActiV.A.C.® Unit is set to 125mmHg of continuous negative pressure) or Prevena Plus™ 125 Therapy Unit will be attached to the dressing tubing, and ciNPT will be initiated in the operating room.

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

2.4 Randomization

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

For each stratum, a randomization schedule including randomization numbers and treatment assignments will be generated and maintained centrally in the web-based clinical database management system. Once randomized, a subject's assignment cannot be altered or changed; a subject should not be randomized twice.

2.5 Schedule of Events and Visits

A detailed schedule of events and visits for the study is provided in Table 1.

Table 1: Schedule of Events

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

1 - Assessed on w omen of child-bearing potential

2 - Weight only

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

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

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

3 STUDY OBJECTIVE

The objective of this study is to evaluate surgical site complications (SSC) in subjects undergoing a revision of a failed total knee arthroplasty (TKA) when closed incision negative pressure therapy (ciNPT) is used to manage the closed incision, as compared to standard of care (SOC) surgical dressing.

4 STUDY ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the subject incidence of Investigator-assessed surgical site complications (SSCs) within 90 days of TKA revision in subjects treated with ciNPT as compared to standard of care (SOC) surgical dressing. SSCs include any occurrence of superficial surgical site infection (SSI), deep SSI, dehiscence, seroma, hematoma, skin necrosis, or continued drainage as outlined in Section 4.11.1 of the study protocol. Three possible values for the primary endpoint are:

- "Occurred": If the subject had one or more occurrences of SSC on or before 90 days post TKA revision;
- "No occurrences": If the subject had an assessment of SSC on or after 90 days post TKA revision and had no known occurrence of any SSC within 90 days of the TKA revision.
- "Incomplete follow-up": If the subject had no known occurrences of SSC and did not have any SSC assessment at least 90 days post TKA revision.

The start date of the complication will be recorded in order to calculate the number of days from the revision surgery until occurrence of the event.

4.2 Secondary Endpoints

4.2.1 Subject Incidence SSI

This secondary endpoint is the subject incidence of any Investigator-assessed SSI (superficial or deep) within 90 days of TKA revision in subjects treated with ciNPT as compared to SOC dressing. Superficial SSI and deep SSI are components of the primary endpoint. Subjects will be categorized using methods similar to those described in section 4.1 of this document.

4.2.2 Subject Incidence Deep SSI

This secondary endpoint is the subject incidence of any Investigator-assessed deep SSI within 90 days of TKA revision in subjects treated with ciNPT as compared to SOC dressing. Deep SSI is a component of the primary endpoint. Subjects will be categorized using methods similar to those described in section 4.1 of this document.

4.3 Exploratory Endpoints

Exploratory endpoints for this study include:

4.3.1 Pain Assessment

- Worst pain last 24 hours
- Average pain in last 24 hours

The pain assessment consists of two self-administered questions used to evaluate the severity of a subject's pain in the past 24 hours post TKA revision.
Subjects will respond using the integer value. All efforts will be made to ensure the subject completes both pain assessments at each scheduled visit: Day 0 pre-TKA revision, Day 0 post-TKA revision and End of Treatment.

4.3.2 Knee Injury and Osteoarthritis Outcome Subscale Score (KOOS)

The KOOS instrument is a patient-reported questionnaire to assess short-term and long-term symptoms and functions. KOOS consists of 5 subscales:

- KOOS: Knee-Related Quality of Life (QOL)
- KOOS: Sport and Recreation Function (Sport/Rec)
- KOOS: Activities of Daily Living (ADL)
- KOOS: Pain
- KOOS: Other Symptoms

The scoring details are in Section 8.7.2. All efforts will be made to ensure the subjects complete the entire assessment at each scheduled visit: Baseline (Screening or Day 0), End of Treatment, Midterm Follow-up, and Long-Term Follow-up.

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

- Mental health – as assessed by PROMIS Global 10 t-score
- Physical health – as assessed by PROMIS Global 10 t-score

The PROMIS Global-10 is a generic health assessment that measures the physical, social, and emotional health of individuals and is often used for those living with chronic conditions. The scoring methods can be found in Section 8.7.3. All efforts will be made to ensure the subject completes the entire assessment, which consists of 10 questions, at each scheduled visit: Baseline (Screening or Day 0), End of Treatment, Midterm Follow-up, and Long-Term Follow-up.

4.3.4 30-Day Subject Incidence of SSC

This endpoint is the subject incidence of any Investigator-assessed SSC within 30 days post TKA revision in subjects treated with ciNPT as compared to SOC dressing. Subjects will be categorized using methods similar to those described in section 4.1 of this document.

4.3.5 45-Day Subject Incidence of SSC

This endpoint is the subject incidence of any Investigator-assessed SSC within 45 days post TKA revision in subjects treated with ciNPT as compared to SOC dressing. Subjects will be categorized using methods similar to those described in section 4.1 of this document.

4.4 Safety Endpoint

The safety endpoint is the subject incidence of adverse events (AEs). All captured AEs will be coded using the MedDRA coding dictionary version 20.1 or higher.

5 ANALYSIS SETS

The following analysis sets are planned for this study:

- *Safety Analysis Set:* The Safety Analysis Set consists of all randomized subjects who received any study-related treatment procedures. Subjects will be analyzed according to the study treatment they received immediately following the TKA revision.
- *ITT Analysis Set:* The ITT (intention-to-treat) Analysis Set consists of all randomized subjects. Subjects will be analyzed according to their randomized treatment assignment.
- *mITT Analysis Set:* The modified ITT Analysis Set will include subjects in the ITT analysis set with the following: 1) who had any SSC on or before 90 days post TKA revision, or 2) had an assessment of SSC on or after 90 days post TKA revision and had no known occurrence of any SSC within 90 days post the TKA revision. Subjects will be analyzed according to their randomized treatment assignment.
- *Per-Protocol Analysis Set:* This will include subjects in the mITT analysis set who had no disqualifying protocol deviation(s) that would impact the interpretation of the primary endpoint. The disqualifying protocol deviation(s) for exclusion from this set will be defined and documented in a treatment-blinded fashion prior to the final database lock by the Protocol Deviation Review Committee. Subjects will be analyzed according to their randomized treatment assignment.
- *Modified Per-Protocol (mPP) Analysis Set:* This will include subjects in the Per-Protocol analysis set excluding any subjects who received prohibited therapy as described in Section 4.15 of the study protocol or any subjects that received alternative therapy following the study treatment period.

6 INTERIM ANALYSIS

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

If warranted, based on the unblinded interim results, the final sample size may be increased using the appropriate statistical methodology as described in Chen et al. [2004][2]. Per Section 8.4.5 of the study protocol, it stated the increase to the final sample size would only occur if the interim results had a conditional power of success ≥ 50%, would be subject to the restrictions in Chen et al. [2004][2], and

would not be considered statistically binding. However, the interim SAP further clarified that an increase to the final sample size could occur if the conditional power is below 50%. If the sample size is increased when conditional power is ≥ 50%, a type I error rate would not be inflated as mentioned in Chen et al. [2004][2]. If the sample size is increased when conditional power is < 50%, an adjustment will be needed to control the Type I error. The adjustment was outlined in Section 7.3 of the interim SAP.

At the interim analysis, the rate of SSC for septic and aseptic revisions will be examined to confirm assumptions of the sample size calculations. In addition, the rate of SSC will be independently assessed for septic and aseptic revisions at the interim analysis to determine if a modification of enrollment from a 1:1 ratio of septic or aseptic revisions to focus on enrollment for either revision type is needed.

In the final analysis, the type 1 error rate (α=0.048) for statistical significance will be used for the primary and secondary analyses using the O'Brien-Fleming method per study protocol.

Both, the interim SAP and the interim analysis results, will be included in the final clinical study report for this study.

Decisions and/or results from the interim analysis may affect the planned final data analysis. Therefore, this SAP may be amended after the interim analysis and before the final study database lock if necessary. Any changes will be documented appropriately in the corresponding Sections like "DOCUMENT HISTORY" and Section 10 "Changes from Planned Analysis".

7 GENERAL STATISTICAL CONSIDERATIONS

7.1 General Considerations

- Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical report will detail software deployed along with their reasons for use.
- Summaries of continuous variables will show the number of non-missing values [n], along with the mean, median, standard deviation, minimum and maximum. In general, the maximum and minimum values will be presented to the same precision as the raw data; the mean and median will be presented to one decimal place more than the raw data. The standard deviation and confidence interval limits will be presented to two decimal places more than the raw data.
- P-values will be presented to four decimal places. A p-value less than 0.0001 will be presented as < 0.0001 or < .0001.
- The most recent assessment prior to TKA revision procedure will be used as the baseline reference for all analyses which incorporate a baseline value.
- Change from baseline will be calculated using the relevant post initial dressing application of either ciNPT or SOC value minus baseline value. Percent change from baseline will be calculated using change from baseline value divided by baseline value and multiplied by 100.

- Summaries of categorical (qualitative) variables will include the frequency and percentage of subjects. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population, unless otherwise specified. Percentages will be presented to 1 decimal place unless otherwise specified.
- Other ad hoc data analyses to characterize the activity of the treatment may be conducted. These additional ad hoc analyses will be decided at the time of analysis. Ad hoc analyses will be identified in the output and the CSR and labeled as such.
- All collected data will be listed for all subjects who provided inform consent.
- For all exploratory endpoints, assessments performed outside the scheduled visit windows may not be included in the analysis but will be listed separately.

7.2 Conventions/Imputations for Adverse Events

For determination of treatment emergent adverse events only, the following analysis date conventions will be applied:

If the adverse event (AE) start date is partially missing [e.g. the month of the start date is missing, or the day of the date is missing], the following conventions will be applied:

- If only the day is missing then the imputed day will be: The day of the initial dressing/treatment application if the month is the same, or the first day of the month will be used if the month differs or the imputed day results in a start date after the end date.
- If only the month is missing then the imputed month will be: the month of the initial dressing/treatment application if the year is the same, or 'January' if the year differs.
- If both month and day are missing, then the month is imputed as the month and day of the initial dressing/treatment application. If the imputed day results in a start date after the end date, then the first day of the month will be used.

If the AE start date is completely missing and the end date is complete

- If the end date is on or after the date of the initial dressing application/treatment, the start date will be imputed as the date of the initial dressing application/treatment start.
- If the start date is completely missing and the end date is completely missing then the AE will assume to be "on-study", then the start date will be set to the date of the initial dressing application/treatment.
- If the start date is completely missing and end date is prior to the initial dressing application/treatment, the AE will assume to be 'prior to study' and not be included in any summaries.

7.3 Handling of Missing data/Dropouts

In general, missing data will not be imputed except for the followings:

- the date of AEs as described in Section 7.2 of this document

- the data imputation for sensitivity analyses for exploratory endpoints Pain, KOOS scores and PROMIS Global 10 as described in Sections 8.7.1, 8.7.2 and 8.7.3 respectively

8 STATISTICAL ANALYSES OF EFFICACY MEASURES

8.1 Subject Enrollment and Disposition

Summaries in this section, section 8.1, will be based on all subjects who provided informed consent. The summary of enrollment and subject disposition will include:

- All screened subjects who provided informed consent
- All randomized subjects – ITT analysis set (overall and by revision type)
- In ITT analysis set: All subjects who completed and discontinued from the study along with their reasons for discontinuation
- All randomized and treated subjects – Safety analysis set
- All subjects in mITT, PP, mPP and Safety analysis sets (overall and by revision type)

Additionally, figure(s) may be generated to display the enrollment and disposition summary graphically.

Summaries for all screen failure subjects or subjects excluded from any analysis sets will be provided as well. The summaries will include:

- All screen failure subjects along with the reason for failing screening
- All subjects excluded from mITT analysis set along with the reason for exclusion
- All subjects excluded from PP analysis set along with the reason for exclusion
- All subjects excluded from mPP analysis set along with the reason for exclusion
- All subjects excluded from Safety analysis set along with the reason for exclusion

8.2 Demographics and Baseline Characteristics

The summary statistics for demographics and baseline characteristics will be presented by treatment arm and overall. The summary tables will include:

1. Baseline demographics and other characteristics (e.g. age, race, sex, ethnicity, height, weight, body mass index (BMI)) will be summarized. Additionally, Age and BMI will be compared between the treatment arms using a 2-sample t-test. Race/ethnicity and sex will be compared between the treatment arms using Fisher's exact test or Chi-Square test as appropriate. This analysis will be based on the ITT analysis set.
2. Baseline comorbidities will be summarized based on both ITT and mITT analysis sets.
3. Characteristics for TKA revision procedure on Day 0 (e.g., type of TKA revision, TKA location, duration of TKA procedure derived by taking the difference of TKA procedure stop time and TKA procedure start time, material used, location, length of incision, method of closure) will be summarized based on the ITT analysis set.
4. All captured medical and surgical history will be coded using the MedDRA coding dictionary version 20.1 or higher and will be summarized based on the ITT analysis set. The following summaries will be presented:
    - Incidence of all medical and surgical history by System Organ Class and Preferred Term

- Incidence of medical and surgical history that can impact wound healing including immune suppressive disease or therapy, impaired nutritional status, Diabetes Mellitus I & II, active tabacco use, chronic obstructive pulmonary disease, peripheral vascular disease, lymphedema, malnutrition, congestive heart failure, and previous infections in operative site, iron or vitamin deficiency by System Organ Class and Preferred Term

8.3 Concomitant Medication Analysis

Concomitant medications/therapies are defined as medications taken during the study (during the 30 days preceding the Day 0 TKA revision through the final visit). The WHO Drug Dictionary released MAR2017 or later will be used for the coding of medications.

Listings for concomitant medications will be presented by subject. The number of subjects using concomitant medications will be summarized using the pharmacological subgroup name (ATC3) and preferred drug name based on the WHODrug medical coding dictionary. In any given category (e.g., ATC3 or preferred drug name) a subject will be counted only once. All subjects in the Safety analysis set will be accounted for in the summation. The following summaries will be presented by treatment arm:

- Incidence of all concomitant medications / therapies by pharmacological subgroup name (ATC3) and preferred drug name
- Incidence of pain killers/narcotics medications by pharmacological subgroup name (ATC3) and preferred drug name

8.4 Protocol Deviations

Protocol deviations will be defined as departures from the study protocol that could potentially affect clinical results or safety conclusions. All protocol deviations will be identified, recorded and presented in subject data listings. Following applicable KCI standard operating procedures, the Protocol Deviation Review Committee evaluates the protocol deviation data and identifies all important disqualifying protocol deviations prior to the final database lock. The results from the review will be imported and incorporated in the corresponding analysis.

All protocol deviations will be presented in subject data listings. Additionally, disqualifying protocol deviations for Per-Protocol analysis set will be subsequently presented in listings and will be summarized by coded term/description.

8.5 Primary Endpoint Analysis

The proportion of subjects with each value of “Occurred” or “No occurrences” or “Incomplete-Follow-up” will be summarized, as applicable, by treatment arm based on the ITT, mITT, Per Protocol and Modified Per Protocol analysis sets.

Superiority Testing

The following hypothesis will be tested for superiority:

Null H_0: $\Delta_{ciNPT\text{-}SOC} = 0$ Alternative H_a: $\Delta_{ciNPT\text{-}SOC} \neq 0$

where $\Delta_{ciNPT\text{-}SOC}$ is the difference in the proportion of subjects in the ciNPT arm with at least one SSC and the proportion of subjects in the SOC dressing arm with at least one SSC.

There are three populations including subpopulations: septic, aseptic and combined (septic + aseptic).

i) For the combined population, a Cochran-Mantel-Haenszel (CMH) test stratified by randomized type of revision (Septic, Aseptic) will be used to compare the SSC incidence rates between two treatment arms based on the mITT analysis set. The odds ratio and its asymptotic 95% confidence interval will be computed. This test is equivalent to the test of difference for the proportions. ii) For the septic and aseptic subpopulations, a Chi-square or Fisher's test, as appropriate will be performed within each randomized revision type for SSC incidence rates between treatment groups based on the corresponding mITT analysis set.

At the final analysis, a two-sided significance level of $\alpha = 0.048$ will be used to compare the SSC proportions between the two treatment arms after adjustment for the interim analysis.

Based on the interim analysis results, we will be considering three possible cases:

- Case 1: population was not enriched at interim analysis;
- Case 2: population was enriched by septic at interim analysis;
- Case 3: population was enriched by aseptic at interim analysis.

If the population is not enriched, then analyses described in Case 1 will be carried out. If the population is enriched, then analyses described in Case 2 or Case 3 will be carried out. If the population is enriched by increasing enrollment of one of the subpopulations based on statistical information, a closed testing strategy to ensure a strong control of type-1 error for the primary endpoint will be carried out based on two tests for the primary analysis.

The first test will utilize all subjects from the mITT combined population included in the interim and subjects post-interim. The second test will utilize only the post-interim mITT subjects from either the septic or aseptic population depending on the results and/or decision from the interim analysis. The second test will be performed only if the test 1 is statistically significant at the 0.048 level.

Case 1 Did Not Enrich	Case 2 Enriched with Septic	Case 3 Enriched with Aseptic
• Test 1: Adaptive test of H_0 (Combined population)	• Test 1: Adaptive test of H_0 (Combined population) • Test 2: standard test of H_0 (post-interim population only)	• Test 1: Adaptive test of H_0 (Combined population) • Test 2: standard test of H_0 (post-interim population only)

For Case 1, if the 2-sided p-value from the test 1 is =<0.048 and the SSC rate of the ciNPT arm is lower than the SSC rate of SOC arm, then the null hypothesis is rejected; superiority in effectiveness of the ciNPT arm compared with the SOC arm will be established. However, for Case 2 or Case 3, both test 1 and test 2 must reject the null hypothesis at the 0.048 level in order to claim statistical significance.

Additionally, figure(s) may be generated to display the results from the analyses of the primary endpoint graphically.

Supportive/exploratory analyses of the primary efficacy endpoint described below in Section 8.5.1 will be performed on the mITT analysis set unless otherwise specified.

8.5.1 Additional Analyses of Primary Endpoint

The below additional analyses (identified as sensitivity analyses in tables) described below may be performed for the primary efficacy endpoint, SSC:

- The primary analysis will be repeated using the actual revision type.
- A CMH test for SSCs stratified by randomized and actual revision type for the ITT, PP, and mPP will be included. Odds ratios and 95% confidence intervals will be presented.
- Summary of SSC events by type which include superficial SSI, deep SSI, dehiscence, seroma, hematoma, skin necrosis, or continued drainage based on the ITT, mITT, PP, and mPP analysis sets. Additionally, we will include SSC events of continued drainage that developed into SSIs.
- Summarize SSC events required intervention by type which include superficial SSI, deep SSI, dehiscence, seroma, hematoma, skin necrosis, and continued drainage based on the ITT, mITT, PP, and mPP analysis sets.
- For the septic and aseptic subpopulations, a Chi-square or Fisher's test as appropriate, will be performed within each actual revision type for SSC incidence rates between treatment groups based on the corresponding septic and aseptic mITT analysis sets.
- Perform a Fisher's exact test or Chi-square to compare the SSC incidence rates between two treatment arms without revision type stratification based on the mITT analysis.
- Multivariable analyses comparing the treatment groups with covariate adjustment where possible covariates might include (but not limited to) site, age, BMI, sex, type of revision (aseptic or septic), and subject comorbidities using logistic regression based on the mITT.

- Analyses comparing the heterogeneity of the treatment groups across clinical sites using logistic regression. (CMH) test stratified by clinical site based on the mITT.

8.6 Secondary Endpoint Analyses

Any SSI (superficial or deep) and Deep SSI will be analyzed.

8.6.1 Analysis of Subject Incidence SSI

The proportion of subjects with each value of "Occurred" or "No occurrences" or "Incomplete-Follow-up" for SSI will be summarized, as applicable, by treatment arm based on the ITT, mITT, Per Protocol and Modified Per Protocol analysis sets.

Superiority Testing

The following hypothesis will be tested for superiority:

Null H_0: $\Delta_{ciNPT\text{-}SOC} = 0$ Alternative H_a: $\Delta_{ciNPT\text{-}SOC} \neq 0$

where $\Delta_{ciNPT\text{-}SOC}$ is the difference in the proportion of subjects in the ciNPT arm with at least one SSI and the proportion of subjects in the SOC dressing arm with at least one SSI.

For the combined population, a Cochran-Mantel-Haenszel (CMH) test stratified by randomized and actual type of revision (Septic, Aseptic) will be used to compare the SSI incidence rates between two treatment arms based on the mITT analysis set. The odds ratio and its asymptotic 95% confidence interval will be computed. This test is equivalent to the test of difference for the proportions.

For the septic and aseptic subpopulations, a Chi-square or Fisher's test, as appropriate will be performed within each actual revision type for SSI incidence rates between treatment arms based on the corresponding mITT analysis set.

Additionally, figure(s) may be generated to display the results from the analyses of this endpoint graphically.

8.6.2 Analysis of Subject Incidence Deep SSI

The proportion of subjects with each value of "Occurred" or "No occurrences" or "Incomplete-Follow-up" for deep SSI will be summarized, as applicable, by treatment arm based on the ITT, mITT, Per Protocol and Modified Per Protocol analysis sets.

The deep SSI subject incidence rates between two treatment arms based on the mITT analysis set will be compared in a similar fashion as the other endpoint described in section 8.6.1 of this document.

Additionally, figure(s) may be generated to display the results from the analyses of this endpoint graphically.

8.7 Exploratory Endpoint Analyses

In general, analyses listed below will be performed on subjects in the ITT analysis set unless otherwise specified. Analyses including revision type will be based on per actual revision type.

8.7.1 Pain Analysis

Both worst pain and average pain are measured from 0 (no pain) to 10 (pain as bad as you can imagine). A positive value of change from baseline indicates increased pain post-baseline as compared with baseline; a negative value indicates reduced pain post-baseline as compared with baseline. Both worst pain score and average pain score along with change from baseline will be summarized separately by treatment arm and by visit. Change from baseline for both worst pain score and average pain score will be analyzed separately using a mixed model, which includes ("Treatment Arm" and "Visit") plus the interaction term ("Treatment Arm by Visit"), revision type, clinical site, and with subject as a random effect. Least squares (LS) means along with 95% confidence intervals and p-values at each post-baseline timepoint will be presented.

If an overall missing data rate for worst or average pain scores is 10% or greater, then an approach of multiple imputation based on Rubin's [1976, 1987][3,4] for missing data will be used by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. A basic description of the multiple imputation includes:

1. Using SAS procedures including Proc MI and Proc MIANALYZE;
2. Using the fully conditional specification (FCS) method / algorithm [Brand 1999 and van Buuren 2007][5,6] which is a linear regression for continuous variables;
3. Including treatment arm, age (≥65 or <65 years), sex, BMI (≥35 kg/m^2 or <35 kg/m^2), race/ethnicity, material used in the TKA revision, and co-morbidities in the imputation model;
4. Creating five imputed datasets [Rubin 1996][7];
5. Combining completed-data estimates from five imputed datasets.

The mixed model analysis described above will be repeated based on the imputed data.

8.7.2 KOOS Score Analysis

As described in Section 4.3.2 of this document, the KOOS has 5 subscales: Quality of Life (QOL), Sports and Recreation Function (Sport/Rec), Activities of Daily Living (ADL), Pain, and other Symptoms. For calculation purpose, the 2012 User's Guide to: Knee injury and Osteoarthritis Outcome Score KOOS and KOOS Scoring 2012 will be followed and used for this study.

The KOOS consists of 42 items. Each item will be asked on a 5-point Likert scale and then will be converted to a numeric value as listed below:

SCALE	None	Mild	Moderate	Severe	Extreme
VALUE	0	1	2	3	4

All 5 subscales are scored separately and interpreted separately. According to the KOOS Scoring 2012, at least 50% of the items should be responded by each patient in order to calculate the subscale for the subject based on the minimum required non-missing items listed in the table below. For each subscale, if more than 50% of the subscale items for a subject are omitted, then the calculated score for the subject will be considered missing in the subscale since there will be no imputation for any omitted/non-responded item.

SUBSCALES	QOL	Sport/Rec	ADL	Pain	Symptoms
# of Non-missing Items	2	3	9	5	4
Total Number of Items	Q1 – Q4	SP1 – SP5	A1 – A17	P1 – P9	S1 – S7

Each subscale score will be normalized by applying the mean of the observed items within the subscale, divided by 4, and multiplying by 100, and then subtracted from 100. i.e.

1. KOOS QOL = 100 – Mean score (Observed Q1 to Q4) * 100 / 4
2. KOOS Sport/Rec = 100 – Mean score (Observed SP1 to SP5) * 100 / 4
3. KOOS ADL = 100 – Mean score (Observed A1 to A17) * 100 / 4
4. KOOS Pain = 100 – Mean score (Observed P1 to P9) * 100 / 4
5. KOOS Symptoms = 100 – Mean score (Observed S1 to S7) * 100 / 4

For each subscale, the range of a normalized score will be from 0 (0 indicating extreme symptoms / problems) to 100 (100 indicating no symptoms / problems). For change from baseline, a positive value indicates fewer symptoms / problems post-baseline as compared with baseline; a negative value indicates more symptoms / problems post-baseline as compared with baseline.

The normalized scores and change from baseline for each subscale will be summarized by treatment arm and by visit. Change from baseline for normalized scores for each subscale will be analyzed using a mixed model, which includes fixed effects ("Treatment Arm" and "Visit") plus the interaction term ("Treatment Arm by Visit"), revision type, clinical site, and with subject as a random effect. LS means along with 95% confidence intervals and p-values at each post-baseline timepoint will be presented.

If a missing data rate for any subscale is 10% or greater, then an approach of multiple imputation based on Rubin's [1976, 1987][3,4] for missing data for all subscales will be used by creating several different plausible imputed data sets and appropriately combining results obtained from each of them.

A basic description of the multiple imputation includes:

1. Using SAS procedures including Proc MI and Proc MIANALYZE;
2. Using the fully conditional specification (FCS) method / algorithm [Brand 1999 and van Buuren 2007][5,6] which is a linear regression for continuous variables;
3. Including treatment arm, age (≥65 or <65 years), sex, BMI (≥35 kg/m^2 or <35 kg/m^2), race/ethnicity, material used in the TKA revision, and co-morbidities in the imputation model;
4. Creating five imputed datasets [Rubin 1996][7];
5. Combining completed-data estimates from five imputed datasets.

The mixed model analysis for each subscale described above will be repeated based on the imputed data.

8.7.3 PROMIS Global 10 t-score Analysis

For calculation purpose, the PROMIS Adult Global Scale v1.2 will be followed and used for this study.

Global07 has a scale of 0 (0 indicating no pain) to 10 (indicating worst pain imaginable) response scores. Global01, Global10, Global08, Global06, Global02-05, and Global09 will be asked on a 5-point Likert scale and their numeric values as listed below:

Value	5	4	3	2	1
Global01	Excellent	Very Good	Good	Fair	Poor
Global10	Never	Rarely	Sometimes	Often	Always
Global08	None	Mild	Moderate	Severe	Very Severe
Global06	Completely	Mostly	Moderately	A Little	Not At All
Global09, 05, 04, 03, 02	Excellent	Very Good	Good	Fair	Poor
Global07	0	1-3	4-6	7-9	10

The 10-question PROMIS Global-10 has 2 subscales:

Global Physical Health raw score = (Gloabl03+ Global06 + Global07 + Global08)

Global Mental Health raw score = (Global02 + Global04 + Global05 +Global10)

All four questions in each subscale must be answered in order to produce a valid raw score. The raw score will be converted into T-Score according to the conversion table below.

Global Physical Health Conversion Table				**Global Mental Health Conversion Table**		
Raw Score	**T Score**	**Standard Error**		**Raw Score**	**T Score**	**Standard Error**
4	16.2	4.8		4	21.2	4.6
5	19.9	4.7		5	25.1	4.1
6	23.5	4.5		6	28.4	3.9
7	26.7	4.3		7	31.3	3.7
8	29.6	4.2		8	33.8	3.7
9	32.4	4.2		9	36.3	3.7
10	34.9	4.1		10	38.8	3.6
11	37.4	4.1		11	41.1	3.6
12	39.8	4.1		12	43.5	3.6
13	42.3	4.2		13	45.8	3.6
14	44.9	4.3		14	48.3	3.7
15	47.7	4.4		15	50.8	3.7
16	50.8	4.6		16	53.3	3.7

17	54.1	4.7		17	56.0	3.8
18	57.7	4.9		18	59.0	3.9
19	61.9	5.2		19	62.5	4.2
20	67.7	5.9		20	67.6	5.3

The range of a T-Score for Global Physical Health will be from 16.2 to 67.7 with higher scores reflecting better health. The range of a T-Score for Global Mental Health will be from 21.2 to 67.6 with higher scores reflecting better health. For both Global Physical Health and Global Mental Health, a positive value of change from baseline indicates improved health post-baseline as compared with baseline; a negative value indicates declined health post-baseline as compared with baseline.

Both Global Physical Health and Global Mental Health T-Scores and their corresponding changes from baseline will be summarized separately by treatment arm and by visit. Changes from baseline for both Global Physical Health and Global Mental Health T-Scores will be analyzed separately using a mixed model, which includes ("Treatment Arm" and "Visit") plus the interaction term ("Treatment Arm by Visit"), revision type, clinical site, and with subject as a random effect. LS means along with 95% confidence intervals and p-values at each post-baseline timepoint will be presented.

If a missing data rate for Global Physical Health or Global Mental Health is 10% or greater, then an approach of multiple imputation based on Rubin's [1976, 1987][3,4] for missing data for both Global Physical Health and Global Mental Health will be used by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. A basic description of the multiple imputation includes:

1. Using SAS procedures including Proc MI and Proc MIANALYZE;
2. Using the fully conditional specification (FCS) method / algorithm [Brand 1999 and van Buuren 2007][5,6] which is a linear regression for continuous variables;
3. Including treatment arm, age (≥65 or <65 years), sex, BMI (≥35 kg/m^2 or <35 kg/m^2), race/ethnicity, material used in the TKA revision, and co-morbidities in the imputation model;
4. Creating five imputed datasets [Rubin 1996][7];
5. Combining completed-data estimates from five imputed datasets.

The mixed model analysis for both Global Physical Health and Global Mental Health described above will be repeated based on the imputed data.

8.7.4 30-Day Subject Incidence of SSC Analysis

The proportion of subjects with each value of "Occurred" or "No occurrences" or "Incomplete-Follow-up" for 30-Day SSC will be summarized, as applicable, by treatment arm based on the ITT, mITT analysis sets. Additionally, 30-Day SSC events by type: superficial SSI, deep SSI, dehiscence, seroma, hematoma, skin necrosis, or continued drainage will be summarized based on the mITT analysis set.

Superiority Testing

The following hypothesis will be tested for superiority:

Null H_0: $\Delta_{ciNPT\text{-}SOC} = 0$ Alternative H_a: $\Delta_{ciNPT\text{-}SOC} \neq 0$

where $\Delta_{ciNPT\text{-}SOC}$ is the difference in the proportion of subjects in the ciNPT arm with at least one SSC and the proportion of subjects in the SOC dressing arm with at least one SSC.

For the combined population, a Cochran-Mantel-Haenszel (CMH) test stratified by type of revision (Septic, Aseptic) will be used to compare the SSC incidence rates between two treatment arms based on the mITT analysis set. The odds ratio and its asymptotic 95% confidence interval will be computed. This test is equivalent to the test of difference for the proportions.

For the septic and aseptic subpopulations, a Chi-square or Fisher's test, as appropriate will be performed within each revision type for SSC incidence rates between treatment arms based on the corresponding mITT analysis set.

Additionally, figure(s) may be generated to display the results from the analyses of this endpoint graphically.

8.7.5 45-Day Subject Incidence of SSC Analysis

Any 45-Day subject incidence of SSC will be analyzed in a similar fashion as the 30-Day subject incidence of SSC endpoint described in section 8.7.4 of this document.

8.7.6 Time to SSC Analysis

Time to SSC: defined as the time in day(s) from the date of TKA revision to the first SSC event and is calculated as:

TTSSC= (Start Date of the first SSC – Date of the TKA revision) + 1

Censoring will occur for the following:

1.) Subjects who experience their first SSC on the day of TKA revision after initial dressing application will be considered to have a time to SSC of 1 day.
2.) Subjects, who do not have any SSC assessment after initial dressing application and they withdraw before the first scheduled SSC assessment at the end of treatment, will be censored at the date of TKA revision.
3.) Subjects who do not have any SSC assessment at Day 90 will be censored at Day 90 or end of study date, whichever comes first.

A Kaplan-Meier curve will be generated for each treatment arm and the quartile estimates will be generated as well. A log-rank test will be used to compare the time-to-SSC between treatment arms. These analyses may be repeated utilizing data calculated from the additional way of calculation described above.

8.7.7 Duration of Treatment and Number of Dressing Changes Analysis

Duration of Treatment: defined as the time in day(s) from the date of TKA revision to the end of treatment and is calculated as:

DOT= (Date of end of treatment – Date of the TKA revision)

Subjects who have their end of treatment on the same day of TKA revision after receiving initial dressing application will be considered to have a duration of treatment of 0.5 days. If subjects did not receive the initial dressing application, then the duration of treatment will be 0 days.

Treatment duration and number of dressing changes will be calculated and summarized by treatment arm, and then will be compared using a 2-sample t-test or Wilcoxon Rank-Sum test as appropriate.

8.7.8 Healthcare Utilization Analysis

The TKA revision related readmission (Yes/No) to hospital after discharge will be summarized by treatment arm and will be compared using a Fisher's exact test or Chi-Square test as appropriate.

All healthcare utilization parameters that related to the TKA revision including:

- number of home health visit(s)
- number of clinic visit(s)
- number of rehab or physical therapy visit(s)
- number of all healthcare visit(s) (number of home health visit(s) + number of clinic visit(s) + number of rehab or physical therapy visit(s))
- total length of hospital stay (days) after readmission
- number of day(s) spent in the ICU after readmission

Each healthcare utilization parameters will be accessed at visits of End of Treatment, Midterm Follow-up, and Long-Term Follow-up and unscheduled. These parameters will be summarized by treatment arm and compared using a 2-sample t-test.

8.7.9 ciNPT Device Replacement Analysis

The number of replacements of ciNPT therapy unit and Prevena dressing and reasons for replacements will be listed and summarized using frequencies and percentages.

8.7.10 Laboratory Test Analysis

Pregnancy tests results will be presented in listings only.

9 STATISTICAL ANALYSES OF SAFETY MEASURES

In general, the summary results of safety parameters will be based on descriptive statistics. If desired, statistical tests of selected safety parameters may be performed for exploratory purposes, and descriptive p-values comparing the two treatment groups will be provided. All Safety analysis set subjects will be evaluated for safety and will be accounted for in the summation.

9.1 Adverse Events

All treatment-emergent adverse events (TEAEs), which are defined as adverse events with onset or worsening of pre-existing condition on or after the initial dressing application through the course of the study, will be summarized. Number and percentage of treated subjects who experienced at least one adverse event in each system organ class by preferred term will be summarized. In any given category (e.g., system organ class or preferred term) a subject will be counted only once. The denominator for the calculation of percentages will be the number of subjects in the Safety analysis set.

The following summary tables and listings will be presented by treatment arm:

- Overview of all treatment-emergent adverse events (TEAEs)
- Incidence of all treatment-emergent adverse events (TEAEs) by system organ class and preferred term
- Incidence of all treatment-emergent adverse events (TEAEs) by system organ class, preferred term, and maximum severity
- Incidence of all serious adverse events (SAEs) by system organ class and preferred term
- Incidence of treatment-related TEAEs by system organ class and preferred term
- Incidence of treatment-related TEAEs by system organ class, preferred term, and maximum severity
- Incidence of treatment-related serious adverse events (SAEs) by system organ class and preferred term
- Listing of all treatment-related adverse events
- Listing of all treatment-related serious adverse events (SAEs)
- Listing of discontinuations: Subjects who discontinued from the study due to any adverse event
- Listing of deaths: Subjects who died of any cause during the study

10 CHANGES FROM PLANNED ANALYSIS

All changes made from planned analyses in the study protocol are listed below.

- For the interim analysis, per Section 8.4.5 of the study protocol, it was stated the increase to the final sample size would only occur if the interim results had conditional power of success ≥ 50%, would be subject to the restrictions in Chen et al. [2004][2], and would not be considered statistically binding. To further clarify, an increase to the final sample size can occur if the conditional power is below 50%. If the sample size is increased when conditional power is ≥ 50%, a type I error rate would not be inflated as mentioned in Chen et al. [2004][2]. If the sample size is increased when conditional power is < 50%, an adjustment will be needed to control the Type I error. The adjustment is outlined in Section 7.3 of the interim SAP.
- Per Section 8.1.3.2 of the study protocol, it was stated: For the subscale scores, four possible outcomes will be summarized and listed: i) Normalized numeric subscale score; ii) Assessment done but incomplete; iii) Discontinued study prior to assessment; iv) Assessment not done. Section 8.7.2 of this final SAP only have two possible outcomes: i) Normalized numeric subscale score calculated based on KOOS Scoring 2012; ii) Missing assessment score for any reason.
- Per Section 8.1.3.3 of the study protocol, it was stated: For each subscale, there are four possible outcomes: i) Raw numeric subscale score and converted t-score; ii) Assessment done but

incomplete; iii) Discontinued study prior to assessment; iv) Assessment not done. Section 8.7.3 of this final SAP will have two possible outcomes: i) Raw numeric subscale score and converted t-score; ii) Missing assessment score by any reason.

- Per Section 8.3.4 of the study protocol, it was stated: The difference between the proportions (ciNPT – SOC) and their corresponding asymptotic 95% confidence intervals will be computed. Section 8.5 of this final SAP made a clarification as: For the combined population, a Cochran-Mantel-Haenszel (CMH) test stratified by type of revision (Septic, Aseptic) will be used to compare the SSC incidence rates between two treatment arms based on the mITT analysis set. The odds ratio and its asymptotic 95% confidence interval will be computed. This test is equivalent to the test of difference for the proportions. ii) For the septic and aseptic subpopulations, a Chi-square or Fisher's test, as appropriate will be performed within each revision type for SSC incidence rates between treatment groups based on the corresponding mITT analysis set.

All changes made in the SAP version 2.0 comparing with planned analyses in the SAP version 1.0 are listed below.

- Section 8.5 and 8.6 were updated to specify whether actual or randomized revision type will be utilized. Additional analyses to include actual revision stratification for primary and secondary endpoint were added.
- Section 8.7.6 of the SAP version 2.0, it is updated to: Censoring will occur for the following: 1) Subjects who experience their first SSC on the day of TKA revision after initial dressing application will be considered to have a time to SSC of 1 day. 2) Subjects, who do not have any SSC assessment after initial dressing application and they withdraw before the first scheduled SSC assessment at the end of treatment, will be censored at the date of TKA revision. 3) Subjects who do not have any SSC assessment at Day 90 will be censored at Day 90 or end of study date, whichever comes first.
- MedDRA coding dictionary version was updated to be version 20.1 or higher.

11 REFERENCE

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4. Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons.
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12 APPENDIX: TABLES, FIGURES, AND LISTINGS

The tables, listings and figures will be provided in a separate appendix document.