Official Title: **A POST-MARKET, PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY TO EVALUATE THE IOVERA° DEVICE**

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STATISTICAL ANALYSIS PLAN

Protocol # MYO-1265

A Post-Market, Prospective, Randomized, Controlled Study to Evaluate the iovera° Device in Treating Pain Associated with Total Knee Arthroplasty

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List of Abbreviations

AE	Adverse Event
AFCN	Anterior Femoral Cutaneous Nerve
AUC	Area Under the Curve
ISN	Infrapatellar branch of the Saphenous nerve
ITT	Intent-to-Treat
IV	Intravenous
KOOS JR.	Knee Injury and Osteoarthritis Outcomes Score
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCA	Patient-Controlled Analgesia
[redacted]	[redacted]
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TKA	Total Knee Arthroplasty
TME	Total daily Morphine Equivalent
TUG	Timed Get Up and Go

1.0 INTRODUCTION

This document details the analysis plan for the study entitled "A Post-Market, Prospective, Randomized, Controlled Study to Evaluate the iovera° Device in Treating Pain Associated with Total Knee Arthroplasty". It describes the proposed efficacy and safety analyses, including planned summary tables and by-subject data listings.

Total Knee Arthroplasty (TKA) is a highly effective procedure to relieve symptoms in patients with severe arthritis. Improvements in pain, physical function, and enhanced quality of life in patients who have undergone TKA are well established in the literature[1,2]. However, post-operative pain associated with TKA is severe. Effective pain control following TKA allows for earlier ambulation and initiation of physical therapy, which speeds recovery, reduces hospital length of stay, and decreases the risk of postoperative complications[3]. The Veterans Health Administration/Department of Defense and the American Society of Anesthesiologists have both issued guidelines suggesting that wherever possible, practitioners should use multimodal pain management[4]. Clinical management of post-op TKA pain should include both pharmacologic and non-pharmacologic modalities and minimize preventable postoperative complications[5]. As demand for primary TKAs is projected to grow to 3.48 million procedures per year by 2030 in the United States alone[6], the need for effective and economic multi-modal pain management has never been greater.

Managing pain via multi-modal strategies, including peripheral nerve blocks, in the inpatient postoperative phase has been shown to decrease opioid consumption[7], decrease opioid related side effects, decrease hospital stay, and increase time to ambulation[8,9,10]. Nursing, hospital, and pharmacy utilization in managing PCA, continuous regional nerve blocks, and administration of oral opioid dosing are associated with higher costs of care and introduce sources for staff error[11,12]. Furthermore, the idea of multi-modal pain management extends beyond the in-patient phase of treatment. Decreasing prescription opioid use during outpatient rehabilitation decreases NSAID and opioid related side effects, especially important among the aging population[13,14].

The iovera° device introduces a new mode of pain management delivery in TKA. The iovera° system uses liquid nitrous oxide contained within the device and closed-end needles to create a precise zone of cold at the target nerve sites. This Focused Cold Therapy™ delivery platform causes a temporary peripheral nerve block based on a process called Wallerian degeneration (2nd degree axonotmesis) without disrupting connective nerve tissue. With nerve conduction blocked, pain is relieved in sensory nerves (nerves that pass impulses from receptors toward or to the central nervous system). Degeneration of the nerve axons is followed by a predictable restoration of nerve function involving axon regeneration from the point of treatment to the distal end of the nerve at a rate of 1.0–1.5 mm a day[15,16]. Early clinical study results have demonstrated that the duration of effect of iovera°, when applied to the infrapatellar branch of the saphenous nerve for knee pain, is two to three months; longer than that of other clinically adopted modalities (PCA opioids, single shot regional nerve blocks, continuous regional nerve blocks, extended-release peri-operative local opioids, oral and IV NSAIDs, acetaminophen, and oral opioids). Early clinical data further suggests that iovera°, when applied to the infrapatellar branch of the saphenous nerve (ISN) and anterior femoral cutaneous nerve (AFCN) prior to TKA, reduces the amount of opioids requested by subjects to maintain similar levels of pain relief[17].

This study is designed to investigate whether iovera° treatment prior to TKA decreases cumulative patient opioid use over the course of 6 weeks following TKA while maintaining similar levels of pain relief. The study will also investigate whether there is a relationship between patients treated with iovera° and patient reported pain and function as measured by KOOS JR., Numeric Rating Scale (NRS) for Pain [redacted]

2.0 STUDY OBJECTIVE

The objective of the study is to evaluate the outcomes of patients undergoing iovera° treatment of the ISN and AFCN prior to total knee arthroplasty to provide temporary postoperative pain relief.

3.0 STUDY DESIGN

3.1 Overview

This is a single-site, prospective, randomized trial. The study's schedule of assessments is shown in Table 1.

Table 1. Schedule of Assessments

Assessment	Visit 1 / Screening	Visit 2 / iovera° Treatment	Visit 3 / DAY OF TKA (Day 0)	Visit 4 / 72 Hours Post-op	Visit 5 / 2 Weeks Post-op	Visit 6 / 6 Weeks Post-op	Visit 7 / 12 Weeks Post-op
Informed Consent	X						
Eligibility	X	X					
Medical history	X	X					
Concomitant Medication Assessment	X	X	X	X	X	X	X
Prior/Concurrent Therapy	X	X		X	X	X	X
Randomization*	X						
Study Treatment		X					
Physical Exam	X						
Vital Signs	X	X					
Knee Circumference	X						
KOOS JR. Questionnaire	X			X	X	X	X
NRS for Pain	X			X	X	X	X
[redacted]							
Subject Satisfaction Questions						X	X
Physical Performance Measures	X				X	X	X
Pain Medication Accountability				X	X	X	X
AE/SAE Assessment		X	X	X	X	X	X

* Randomization occurs after the subject has met eligibility criteria

3.2 Method of Assigning Subjects to Treatment

After meeting all of the inclusion and none of the exclusion criteria and prior to study treatment, subjects will be randomized in a 1:1 manner to either:

- **iovera° Treatment:** Subject undergoes treatment with the study device using study supplied Smart Tip.
- **Standard of Care Treatment:** Subject does not undergo iovera° Treatment

The Investigator or designee will record the randomization assignment in the source documentation and CRF.

3.3 Blinding

This is an unblinded study.

3.4 Determination of Sample Size

The sample size was determined based on the primary effectiveness endpoint, the cumulative consumption of opioids from the time of hospital discharge to 6 weeks post-TKA Surgery. Opioid consumption will be converted to morphine equivalents, and subject consumption will be verified by pill count at follow-up visits. The cumulative morphine equivalent will be divided by the number of days to provide the Total Daily Morphine Equivalent (TME) for the subject. Let $\mu_{1,Active}$ and $\mu_{1,SOC}$ denote the true mean TMEs for the active and standard of care treatments, respectively. The required sample size was determined based on providing at least 80% power for the primary effectiveness endpoint using a one-sided, two-independent sample, Satterthwaite t-test to test for superiority of iovera treatment to Standard of Care treatment, with a significance level of 0.025, assuming a 1:1 allocation to treatment, a true treatment effect ($\mu_{1,Active} - \mu_{1,SOC}$) of -12.0 mg, and true standard deviations of 18.2 mg and 26.0 mg, for the iovera and Standard of Care treatments, respectively. Based on these specifications, the required sample size is 57 subjects per treatment group, for a total of 114 subjects. To account for a small number of subjects withdrawing early or not having data available for the analysis of the primary effectiveness endpoint, the required sample size was increased to 120 randomized subjects (approximately 60 Active Treatment subjects and 60 Standard of Care Treatment subjects).

3.5 Changes to the Protocol-Specified Analyses

For the analyses of the primary effectiveness endpoint and the first secondary effectiveness endpoint, missing data will be imputed using multiple imputation methods. The protocol states that t-tests will be performed on the imputed datasets and the results will be summarized using PROC MIANALYZE. Instead, the difference in means between treatments and the corresponding standard error will be obtained for each imputed dataset and PROC MIANALYZE will be used to summarize the results and produce t-tests.

4.0 EFFECTIVENESS AND SAFETY ENDPOINTS

4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the cumulative consumption of opioids from the time of hospital discharge to 6 weeks post-TKA Surgery. Opioid consumption will be converted to morphine equivalents, and subject consumption will be verified by pill count at follow-up visits. The cumulative morphine equivalent will be divided by the number of days to provide the Total Daily Morphine Equivalent (TME) for the subject.

4.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are as follows:

1. AUC/time (see definition of AUC/time below) based on Changes from Baseline in KOOS JR. Scores through 6 weeks post-TKA
2. AUC/time based on Changes from Baseline through 6 weeks post-TKA in NRS for Pain
3. AUC/time based on Changes from Baseline through 6 weeks post-TKA in Timed Get Up and Go (TUG) test

Change in KOOS JR. scores from the Baseline visit to each post-baseline visit will be calculated for each subject as:

Change in KOOS JR. score =
Post-Baseline Visit KOOS JR. score – Baseline Visit KOOS JR. score,

such that a positive value indicates an increase in the KOOS JR. score, which is a positive outcome, while a negative value indicates a decrease, which is a negative outcome. Change in NRS for Pain scores from the Baseline visit to each post-baseline visit will be calculated for each subject as:

Change in NRS for Pain score =
Baseline Visit NRS for Pain score – Post-Baseline Visit NRS for Pain score,

such that a positive value indicates a decrease in the NRS for Pain score, which is a positive outcome, while a negative value indicates an increase, which is a negative outcome. Change from baseline in the TUG test is defined analogously to the change from baseline in NRS for Pain score. The first and key secondary effectiveness endpoint, AUC/time based on Changes from Baseline in KOOS JR. scores through 6 weeks post-TKA, is the area under the curve (AUC) of Change in KOOS JR. scores from the Baseline visit through the 6-week visit divided by the number of days from TKA until the 6-week visit. AUC will be calculated using the trapezoidal rule and the changes in the KOOS JR. score at the following time points: Baseline (change=0), 72 hours, 2 weeks, and 6 weeks post-TKA. The second and third secondary effectiveness endpoints are defined analogously.

[redacted]

- [redacted]
- [redacted]
- [redacted]

4.4 Safety Endpoints

The safety endpoints are as follows:

- All treatment emergent adverse events

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or higher. All statistical tests will be performed at the 0.05 significance level, unless otherwise noted.

The data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages.

Data listings will be sorted by treatment group and subject number, and Study Day (Day of TKA = Day 0), if appropriate. All date fields will be presented in a format of yyyy-mm-dd (e.g., 2018-01-31 for January 31, 2018) in the listings.

5.2 Adjustments for Covariates

No adjustments for covariates will be made.

5.3 Handling of Dropouts and Missing Data

Missing data for the primary effectiveness endpoint and the first secondary effectiveness endpoint will be imputed using multiple imputation methods. First, the relatively uncommon, non-monotone missing data will be imputed using the MCMC option of SAS® PROC MI. For example, for the primary effectiveness endpoint, the imputation model will include a term for treatment and the pill counts at visits 4, 5, and 6. Second, the monotone missing values will be imputed using the chained equation method by SAS® PROC MI option MONOTONE REG. For each subject within each imputed dataset, the value of the endpoint will then be determined. The imputed data sets will each be analyzed as specified in Sections 8.1 and 8.2, and the results will be summarized using PROC MIANALYZE.

5.4 Interim Analysis

The analyses addressed in this SAP will utilize the final, locked database.

5.5 Multicenter Study

This is a single site study.

5.6 Multiple Comparisons / Multiplicity

The fixed sequential testing procedure will be used for the comparison of the two treatments with respect to the first (and key) secondary effectiveness endpoint. Therefore, for this endpoint, the analysis comparing the two treatments will be formally conducted only if the analysis for the primary effectiveness endpoint yields a statistically significant result. For informational purposes, however, the results of the analyses (i.e., p-value) will be presented regardless of the results for the primary effectiveness endpoint.

No adjustments for multiplicity will be made in the analyses.

5.7 Examination of Subgroups

No subgroup analyses are planned.

5.8 Baseline

Baseline will be defined as the value at the Screening visit. If the value for an assessment is missing at Screening and there is an unscheduled assessment prior to treatment, the value from the unscheduled assessment will be used as the baseline value.

5.9 Analysis Windows

All analyses will be based on nominal visits.

6.0 ANALYSIS POPULATIONS

6.1 ITT (Intent-to-Treat) Population

All subjects who are randomized will be included in the ITT Population. In analyses based on the ITT Population, subjects will be analyzed according to the treatment group to which they were randomized. The primary analyses of effectiveness will be conducted based on the ITT Population.

6.2 Per Protocol Population

The Per-Protocol Population is defined as the group of subjects who are randomized, who receive the treatment to which they were randomly assigned, and who complete their 6-week visit without any major protocol deviations. Receipt of an incorrect prescription will be considered as a major deviation; the definition of an incorrect prescription also includes deviations due to patients not taking Tramadol. In analyses based on the Per-Protocol Population, subjects will be analyzed according to the treatment group to which they were randomized. Analyses based on the PP population will be considered secondary analyses of effectiveness.

6.3 Safety Population

All subjects who receive study treatment will be included in the Safety Population. Subjects will be analyzed according to the treatment they actually receive, regardless of their randomized treatment. All safety analyses will be based on the Safety Population.

7.0 DEMOGRAPHICS

Subject demographics collected at the screening visit will be summarized using descriptive statistics for continuous variables (age at informed consent) and frequencies and percentages for categorical variables (gender, ethnicity, and race).

8.0 EFFECTIVENESS ANALYSES

8.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the cumulative consumption of opioids from the time of hospital discharge to 6 weeks post-TKA Surgery. Opioid consumption will be converted to morphine equivalents (see Appendix 2 for conversion factors), and subject consumption will be verified by pill count at follow-up visits. The cumulative morphine equivalent will be divided by the number of days to provide the Total Daily Morphine Equivalent (TME) for the subject.

The difference in the mean TMEs between the two treatment groups will be calculated as Standard of Care TME mean – Active TME mean, such that a positive difference indicates that the Standard of Care Treatment group had a larger mean TME than the Active Treatment group, while a negative difference indicates the opposite. A positive difference between the two treatment groups reflects a positive outcome for the study.

Let $\mu_{1,Active}$ and $\mu_{1,SOC}$ denote the true mean TMEs for the active and standard of care treatments, respectively. Then the null and alternative hypotheses for the primary effectiveness endpoint are as follows:

H_0: $\mu_{1,Active} \geq \mu_{1,SOC}$

H_1: $\mu_{1,Active} < \mu_{1,SOC}$

Missing data for this endpoint will be imputed using multiple imputation methods. First, the relatively uncommon, non-monotone missing data will be imputed using the MCMC option of SAS® PROC MI. For this endpoint, the imputation model will include a term for treatment and the pill counts at visits 4, 5, and 6. Second, the monotone missing values will be imputed using the chained equation method by SAS® PROC MI option MONOTONE REG. For each subject within each imputed dataset, the value of the endpoint will then be determined. The imputed data sets will each be analyzed to obtain the difference in means between treatments and the corresponding standard error, and the results will be summarized using PROC MIANALYZE. A one-sided t-test will be used to test the null hypothesis. The Primary Effectiveness Study Objective will be met if this t-test is statistically significant using a $\alpha = 0.025$ level of statistical significance.

This endpoint will be summarized by treatment group using descriptive statistics, together with 95% confidence intervals for the true mean based on the t-distribution. The estimated difference in mean TMEs between the two treatment groups and a 95% confidence interval based on the t-distribution for the true difference in the mean TMEs between the two treatments will also be provided.

TME data will be summarized in the same manner for other time periods (TKA to 72 hours post-op, 72 hours post-op to 2 weeks post-op, 2 weeks post-op to 6 weeks post-op, 6 weeks post-op to 12 weeks post-op, hospital discharge to 2 weeks post-op, hospital discharge to 6 weeks post-op, and hospital discharge to 12 weeks post-op), but no hypothesis testing will be performed.

These analyses will be performed for the ITT Population and the Per Protocol Population.

For each population, an additional analysis of TME data will be performed excluding subjects that discontinued the study due to adverse events.

8.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are as follows:

1. AUC/time (see definition of AUC/time below) based on Changes from Baseline in KOOS JR. Scores through 6 weeks post-TKA.
   KOOS JR. Scores range from 0 (total knee disability) to 100 (perfect knee health).

2. AUC/time based on Changes from Baseline through 6 weeks post-TKA in NRS for Pain (both pain in the last 7 days and pain right now)
   NRS Pain ratings range from 0 (no pain) to 10 (worst pain imaginable).

3. AUC/time based on Changes from Baseline through 6 weeks post-TKA in Timed Get Up and Go (TUG) test.
   The TUG test measures, in seconds, the time it takes to raise from sitting, walk 10 feet, turn around, walk back and sit back down.

Change in KOOS JR. scores from the Baseline visit to each post-baseline visit will be calculated for each subject as:

Change in KOOS JR. score =
Post-Baseline Visit KOOS JR. score – Baseline Visit KOOS JR. score,

such that a positive value indicates an increase in the KOOS JR. score, while a negative value indicates a decrease. The first and key secondary effectiveness endpoint, AUC/time based on Changes from Baseline in KOOS JR. scores through 6 weeks post-TKA, is the area under the curve (AUC) of Change in KOOS JR. scores from the Baseline visit through the 6-week visit divided by the number of days from TKA until the 6-week visit. AUC will be calculated using the trapezoidal rule and the changes in the KOOS JR. score at the following time points: Baseline (change=0), 72 hours, 2 weeks, and 6 weeks post-TKA. Scoring instructions for the KOOS JR. English Version 1.0 are provided in Appendix 1.

The difference in mean AUC/time between the two treatment groups will be calculated as the mean Active AUC/time – the mean Standard of Care AUC/time, such that a positive difference indicates that the Active Treatment group had a larger mean AUC/time based on Change in KOOS JR. score than the Standard of Care Treatment group, while a negative value indicates the opposite. Because a positive Change in the KOOS JR. score is indicative of pain relief, a positive difference between treatment groups reflects a positive outcome for this endpoint.

Let $\mu_{2,Active}$ and $\mu_{2,SOC}$ denote the true mean AUC/time based on the Change from Baseline in KOOS JR. score from the Baseline visit through the six-week visit for the active and standard of care treatments, respectively. Then the null and alternative hypotheses for the test for non-inferiority for this endpoint are as follows:

H_0: $\mu_{2,SOC} - \mu_{2,Active} \geq \delta$

H_1: $\mu_{2,SOC} - \mu_{2,Active} < \delta$,

where the non-inferiority margin δ=14.

Missing KOOS JR. data will be imputed using multiple imputation methods. First, the relatively uncommon, non-monotone missing data will be imputed using the MCMC option of SAS® PROC MI. The imputation model will include a term for treatment and the KOOS JR. score at visits 1, 4, 5, and 6. Second, the monotone missing values will be imputed using the chained equation method by SAS® PROC MI option MONOTONE REG. For each subject within each imputed dataset, the value of the endpoint will then be determined. The imputed data sets will each be analyzed to obtain the difference in means between treatments and the corresponding standard error, and the results will be summarized using PROC MIANALYZE (with THETA0=14, the non-inferiority margin, in the PROC MIANALYZE statement). The null hypothesis will be tested using a one-sided t-test. One of the secondary objectives of the study is to show that, over the 6-week post-TKA period, the Active Treatment group has similar levels of pain and functioning as compared to the Standard of Care Treatment group. This objective will be met if the t-test for non-inferiority is statistically significant using a 0.025 level of statistical significance.

There is one item in the KOOS JR. scale (Knee Twisting/Pivoting) with a large number of missing responses. Prior to undergoing multiple imputation, missing values for this item will be imputed by performing a linear regression (SAS PROC GLM) on the other 6 KOOS JR. items and imputing the Knee Twisting/Pivoting score for each patient with a missing value based on the estimated linear regression line. At baseline this imputation will be performed across treatment arms; at post-baseline time points the imputation will be performed by treatment arm.

Change in NRS for Pain scores and TUG test scores from the Baseline visit to each post-baseline visit will be calculated for each subject as:

Change score = Baseline Visit score – Post-Baseline Visit score,

such that a positive value indicates a decrease in the score (which is a positive outcome), while a negative value indicates an increase (which is a negative outcome). AUC/time for these endpoints will be calculated in the same way described above for KOOS JR.

Each secondary effectiveness endpoint will be summarized by treatment using descriptive statistics. For each treatment, the null hypothesis that the true mean AUC/time equals zero will be tested using a paired t-test. Ninety-five percent confidence intervals based on the t-distribution for the true mean AUC/time for each treatment and for the true difference in these means between treatments will be provided. For the second and third secondary effectiveness endpoints, a one-sided, two-sample t-test will be used to test the null hypothesis that the iovera mean is less than or equal to the Standard of Care mean versus the alternative hypothesis that the iovera mean is greater than the Standard of Care mean. In addition, for each secondary effectiveness endpoint, the initial result (e.g., KOOS JR. score at 6-weeks post-TKA), as well as the Change from Baseline value, will be summarized by treatment group at each visit at which data for the endpoint are collected using descriptive statistics, together with 95% confidence intervals for the mean based on the t-distribution. The estimated difference in the mean change from baseline between the two treatment groups and a 95% confidence interval based on the t-distribution for the true difference in these means between the two treatments will also be provided.

The fixed sequential testing procedure will be used for the comparison of the two treatments with respect to the first (and key) secondary effectiveness endpoint. Therefore, for this endpoint, the analysis comparing the two treatments will be formally conducted only if the analysis for the primary effectiveness endpoint yields a statistically significant result. For informational purposes, however, the results of the analyses (i.e., p-value) will be presented regardless of the results for the primary effectiveness endpoint.

These analyses will be performed for the ITT Population.

[redacted]

8.4 Other Analyses

AUC/time based on Changes from Baseline in KOOS JR. Scores, NRS for Pain, and TUG test through 72 hours post-TKA (KOOS JR. and NRS for Pain only), 2 weeks post-TKA and 12 weeks post-TKA will be analyzed in the same manner as described in Section 8.2 for the AUC/time endpoints through 6 weeks post-TKA. AUC/time based on Changes from Baseline in ROM through 2 weeks post-TKA, 6 weeks post-TKA, and 12 weeks post-TKA will also be analyzed in this same manner.

[redacted]

Subject satisfaction data will be summarized by treatment group and visit (weeks 6 and 12) using descriptive statistics for both overall knee pain status since the beginning of the study and satisfaction with pain management following surgery and counts and percentages for overall knee pain status since the beginning of the study.

[redacted] last NRS for Pain (both seated and with motion) reported as part of physical therapy will be summarized by treatment group using descriptive statistics.

For each post-baseline visit, p-values will be presented for the test of the null hypothesis that the true mean changes from baseline in NRS for Pain are equal for the two treatments versus the alternative hypothesis that they are not equal. It should be noted that this is an open label study and that these hypothesis tests of superiority are post-hoc and were not pre-planned in the protocol.

These analyses will be performed for the ITT Population.

9.0 SAFETY ANALYSES

All adverse event analyses will be performed on the Safety Population.

The summary of AEs will be limited to treatment emergent AEs, For AEs with a missing start date, the AE will be considered treatment emergent unless there is additional information indicating that the AE started prior to study treatment.

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) are defined as any adverse event with onset on or after study treatment begins or any adverse event already present at baseline that worsens in severity. For AEs with missing start dates, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study treatment. Only treatment emergent AEs will be summarized.

The number and percentage of subjects with at least one TEAE, at least one iovera procedure-related TEAE, at least one iovera device-related TEAE, at least one opioid use related TEAE, at least one serious TEAE, and at least one TEAE leading to study withdrawal will be presented by treatment group. AEs that are definitely, probably, or possibly related, or for which the relationship is missing, will be considered related.

The number and percentage of subjects having a TEAE in each System Organ Class (SOC) and having each individual type of adverse event (Preferred Term) will be presented. TEAEs will also be summarized at the event level by SOC/Preferred Term and severity. This will be done for all TEAEs, iovera procedure related TEAEs, iovera device related TEAEs, and opioid use related TEAEs.

10.0 OTHER ANALYSES

Study exit data consist of the primary reason that the subject is off study and adverse event status at study exit (whether or not there were any unresolved adverse events). End of study data will be summarized by treatment group using counts and percentages.

Protocol deviations will be summarized by type of deviation and overall using counts and percentages.

These analyses will be performed for the ITT Population.

11.0 REFERENCES

[1] Ethgen, O., Bruyere, O., Richy, F., Dardennes, C., Reginster, J. Y. 2004. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *The Journal of Bone & Joint Surgery*,*86*(5), 963-974.

[2] Jones, C. A., Beaupre, L. A., Johnston, D. W. C., Suarez-Almazor, M. E. 2005. Total joint arthroplasties: current concepts of patient outcomes after surgery. *Clinics in Geriatric Medicine*, *21*(3), 527-541.

[3] Paul, J. E., Arya, A., Hurlburt, L., Cheng, J., Thabane, L., Tidy, A., Murthy, Y. 2010. Femoral nerve block improves analgesia outcomes after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Anesthesiology*,*113*(5), 1144-1162.

[4] American Society of Anesthesiologists Task Force on Acute Pain Management. 2004. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*,*100*, 1573-1581.

[5] Veterans Health Administration. VHA/DoD clinical practice guideline for the management of postoperative pain. Washington, DC 2002.

[6] Kurtz, S., Ong, K., Lau, E., Mowat, F., Halpern, M. 2007. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *The Journal of Bone & Joint Surgery*, *89*(4), 780-785.

[7] Allen, H. W., Liu, S. S., Ware, P. D., Nairn, C. S., Owens, B. D. 1998. Peripheral nerve blocks improve analgesia after total knee replacement surgery. *Anesthesia & Analgesia*, *87*(1), 93-97.

[8] [redacted]

[9] Goyal, N., McKenzie, J., Sharkey, P. F., Parvizi, J., Hozack, W. J., Austin, M. S. 2013. The 2012 Chitranjan Ranawat Award: intraarticular analgesia after TKA reduces pain: a randomized, double-blinded, placebo-controlled, prospective study. *Clinical Orthopaedics and Related* 2013, Volume 471, Issue 1, 64-75.

[10] Hebl, J. R., Dilger, J. A., Byer, D. E., Kopp, S. L., Stevens, S. R., Pagnano, M. W., Hanssen, A.D., Horlocker, T. T. 2008. A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. *Regional Anesthesia and Pain Medicine*, *33*(6), 510-517.

[11] Meissner, B., Nelson, W., Hicks, R., Sikirica, V., Gagne, J., Schein, J. 2009. The rate and costs attributable to intravenous patient-controlled analgesia errors. *Hospital Pharmacy*, *44*(4), 312-324.

[12] Strassels, S. A., Chen, C., Carr, D. B. 2002. Postoperative analgesia: economics, resource use, and patient satisfaction in an urban teaching hospital. *Anesthesia & Analgesia*, *94*(1), 130-137.

[13] McCartney, C. J., Nelligan, K. 2014. Postoperative pain management after total knee arthroplasty in elderly patients: treatment options. *Drugs & Aging*, *31*(2), 83-91.

[14] White, P. F. 2002. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. *Anesthesia & Analgesia*, *94*(3), 577-585.

[15] Evans. 1981. Cryoanalgesia: the response to alterations in freeze cycle and temperature. *British Journal of Anesthesiology* **53** (11): 1121–1127.

[16] Tetzlaff, W., Bisby, M.A. 1989. Neurofilament elongation into regenerating facial nerve axons. *Neuroscience 29*, 659-666.

[17] Dasa, V., Lensing, G., Parsons, M., Harris, J., Volaufova, J., Bliss, R. 2016. Percutaneous freezing of sensory nerves prior to total knee arthroplasty. *Knee 23(3)*, 523-528.

Appendix 1:

KOOS, JR SCORING INSTRUCTIONS

The KOOS, JR was developed from the original long version of the Knee injury and Osteoarthritis Outcome Score (KOOS) survey using Rasch analysis. The KOOS, JR contains 7 items from the original KOOS survey. Items are coded from 0 to 4, none to extreme respectively.

KOOS, JR is scored by summing the raw response (range 0-28) and then converting it to an interval score using the table provided below. The interval score ranges from 0 to 100 where 0 represents total knee disability and 100 represents perfect knee health.

Table for converting raw summed scores to interval level scores from 0 (total knee disability) to 100 (perfect knee health)

Raw summed score (0-28)	Interval score (0 to 100 scale)
0	100.000
1	91.975
2	84.600
3	79.914
4	76.332
5	73.342
6	70.704
7	68.284
8	65.994
9	63.776
10	61.583
11	59.381
12	57.140
13	54.840
14	52.465
15	50.012
16	47.487
17	44.905
18	42.281
19	39.625
20	36.931
21	34.174
22	31.307
23	28.251
24	24.875
25	20.941
26	15.939
27	8.291
28	0.000

Appendix 2: Opioid Morphine Equivalent Conversion Factors[1]

Type of Opioid	MME Conversion Factor
Buprenorphine patch[2]	12.6
Buprenorphine tab or film	10
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[3]	0.13
Fentanyl film or oral spray[4]	0.18
Fentanyl nasal spray[5]	0.16
Fentanyl patch[6]	7.2
Hydrocodone	1
Hydromorphone	4
Levorphanol tartrate	11
Meperidine hydrochloride	0.1
Methadone	3
Morphine	1
Nalbuphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4
Tramadol	0.1

1 Centers for Disease Control and Prevention, Atlanta, GA, May 2014. For more information, send an email to Mbohm@cdc.gov.

2 The MME conversion factor for buprenorphine patches is based on the assumption that one milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 5 ug/hr buprenorphine patch * 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day buprenorphine = 9 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8. However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 X 7 = 12.6). In this example, MME/day for four 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 ug/hr buprenorphine patch * (4 patches/28 days)* 12.6 = 9 MME/day.

3 The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given lozenge/troche.

4 The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.

5 The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.

6 The MME conversion factor for fentanyl patches is based on the assumption that one milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 25 ug/hr fentanyl patch * 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent. In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4. However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion

factor by 3 (2.4 X 3 = 7.2). In this example, MME/day for ten 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows: Example: 25 ug/hr fentanyl patch * (10 patches/30 days)* 7.2 = 60 MME/day.

Appendix A: TABLE SHELLS

Appendix B: LISTING SHELLS

Table 1.1

DEMOGRAPHICS
ITT POPULATION

Variable	Statistic	Iovera (N=xx)	Standard of Care (N=xx)	Total (N=xxx)
Age (years) (1)	n	xx	xx	xx
	Mean	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	SD	xx.xx	xx.xx	xx.xx
	Minimum - Maximum	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x
Gender				
Female	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Race (2)				
White	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Black or African American	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Native Hawaiian or Other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xxx (xx.x)
Missing	n	xx	xx	xxx

Program Name: Creation date, time

(1) Age = (Date of informed consent - date of birth)/365.25.

(2) Subjects may check more than one race category, so the percentages may sum to more than 100%.

[Note: This table will be repeated for the Per Protocol Population (Table 1.2).]

Table 2

NUMERIC RATING SCALE (NRS) FOR PAIN
ITT POPULATION

Parameter	Visit	Statistic	Iovera (N=xx) Value	Iovera (N=xx) Change from Baseline	Standard of Care (N=xx) Value	Standard of Care (N=xx) Change from Baseline	Difference in Mean Change from Baseline (Iovera - Standard of Care) and 95% CI (1)
Pain in the past 7 days	Screening (Baseline)	n	xx		xx		
		Mean	x.x		x.x		
		Median	x.x		x.x		
		SD	x.x		x.x		
		Minimum - Maximum	x - x		x - x		
		95% CI for Mean (1)	(x.x, x.x)		(x.x, x.x)		
	72 Hours Post-op	n	xx	xx	xx	xx	
		Mean	x.x	x.x	x.x	x.x	x.x (x.x, x.x)
		Median	x.x	x.x	x.x	x.x	
		SD	x.x	x.x	x.x	x.x	
		Minimum - Maximum	x - x	x - x	x - x	x - x	
		95% CI for Mean (1)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	
		p-value (2)					x.xxxx
	2 Weeks Post-op	...	...	...	...	...	...
	6 Weeks Post-op	...	...	...	...	...	...
	12 Weeks Post-op	...	...	...	...	...	...
AUC/time for Change from Baseline in Pain in the past 7 days	Baseline through 72 Hours Post-op	n	xx		xx		
		Mean	xx.xx		xx.xx		x.x (x.x, x.x)
		Median	xx.xx		xx.xx		
		SD	xx.xx		xx.xx		
		Minimum - Maximum	xx.x - xx.x		xx.x - xx.x		
		95% CI for Mean (1)	(xx.xx, xx.xx)		(xx.xx, xx.xx)		
		p-value (3)	x.xxxx		x.xxxx		
		p-value (4)					x.xxxx
	Baseline through 2 Weeks Post-op	...	...	...	...	...	...
	Baseline through 6 Weeks Post-op	...	...	...	...	...	...
	Baseline through	...	...	...	...	...	...

12 Weeks Post-op

Program Name: Creation date, time

Note: Change from baseline = Baseline value - post-baseline value, so that a positive change value indicates pain relief.
NRS values range from 0 (no pain) to 10 (worst pain imaginable).
(1) Confidence interval based on the t-distribution.
(2) p-value from a two-sided, two-sample t-test, testing the null hypothesis that the iovera and Standard of Care means are equal versus the alternative hypothesis that they are unequal.
(3) p-value from a two-sided, paired t-test, testing the null hypothesis that the true mean equals 0.
(4) p-value from a one-sided, two-sample t-test, testing the null hypothesis that the iovera mean is less than or equal to the Standard of Care mean versus the alternative hypothesis that the iovera mean is greater than the Standard of Care mean.

Table 2 (continued)

NUMERIC RATING SCALE (NRS) FOR PAIN
ITT POPULATION

Parameter	Visit	Statistic	Iovera (N=xx) Value	Iovera (N=xx) Change from Baseline	Standard of Care (N=xx) Value	Standard of Care (N=xx) Change from Baseline	Difference in Mean Change from Baseline (Iovera - Standard of Care) and 95% CI (1)
Pain right now	Screening (Baseline)	n	xx		xx		
		Mean	x.x		x.x		
		Median	x.x		x.x		
		SD	x.x		x.x		
		Minimum - Maximum	x - x		x - x		
		95% CI for Mean (1)	(x.x, x.x)		(x.x, x.x)		
	72 Hours Post-op	n	xx	xx	xx	xx	
		Mean	x.x	x.x	x.x	x.x	x.x (x.x, x.x)
		Median	x.x	x.x	x.x	x.x	
		SD	x.x	x.x	x.x	x.x	
		Minimum - Maximum	x - x	x - x	x - x	x - x	
		95% CI for Mean (1)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	
		p-value (2)					x.xxxx
	2 Weeks Post-op 6 Weeks Post-op 12 Weeks Post-op	...	...	...	...	...	...
AUC/time for Change from Baseline in Pain right now	Baseline through 72 Hours Post-op	n	xx		xx		
		Mean	xx.xx		xx.xx		x.x (x.x, x.x)
		Median	xx.xx		xx.xx		
		SD	xx.xx		xx.xx		
		Minimum - Maximum	xx.x - xx.x		xx.x - xx.x		
		95% CI for Mean (1)	(xx.xx, xx.xx)		(xx.xx, xx.xx)		
		p-value (3)	x.xxxx		x.xxxx		
		p-value (4)					x.xxxx
	Baseline through 2 Weeks Post-op	...	...	...	...	...	...
	Baseline through 6 Weeks Post-op	...	...	...	...	...	...
	Baseline through 12 Weeks Post-op	...	...	...	...	...	...

Program Name: Creation date, time

Note: Change from baseline = Baseline value - post-baseline value, so that a positive change value indicates pain relief.
NRS values range from 0 (no pain) to 10 (worst pain imaginable).

(1) Confidence interval based on the t-distribution.
(2) p-value from a two-sided, two-sample t-test, testing the null hypothesis that the iovera and Standard of Care means are equal versus the alternative hypothesis that they are unequal.
(3) p-value from a two-sided, paired t-test, testing the null hypothesis that the true mean equals 0.
(4) p-value from a one-sided, two-sample t-test, testing the null hypothesis that the iovera mean is less than or equal to the Standard of Care mean versus the alternative hypothesis that the iovera mean is greater than the Standard of Care mean.

Table 3

KOOS JR.
ITT POPULATION

Parameter	Visit	Statistic	Iovera (N=xx) Value	Iovera (N=xx) Change from Baseline	Standard of Care (N=xx) Value	Standard of Care (N=xx) Change from Baseline	Difference in Mean Change from Baseline (Iovera - Standard of Care) and 95% CI (1)
Overall Score	Screening (Baseline)	n	xx		xx		
		Mean	xx.x		xx.x		
		Median	xx.x		xx.x		
		SD	xx.x		xx.x		
		Minimum - Maximum	xx - xx		xx - xx		
		95% CI for Mean (1)	(xx.x, xx.x)		(xx.x, xx.x)		
	72 Hours Post-op	n	xx	xx	xx	xx	
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x, xx.x)
		Median	xx.x	xx.x	xx.x	xx.x	
		SD	xx.x	xx.x	xx.x	xx.x	
		Minimum - Maximum	xx - xx	xx - xx	xx - xx	xx - xx	
		95% CI for Mean (1)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
	2 Weeks Post-op 6 Weeks Post-op 12 Weeks Post-op	...	...	...	...	...	...
AUC/time for Change from Baseline in Overall Score	Baseline through 72 Hours Post-op	n	xx		xx		
		Mean	xx.xx		xx.xx		x.x (x.x, x.x)
		Median	xx.xx		xx.xx		
		SD	xx.xx		xx.xx		
		Minimum - Maximum	xx.x - xx.x		xx.x - xx.x		
		95% CI for Mean (1)	(xx.xx, xx.xx)		(xx.xx, xx.xx)		
		p-value (2)	x.xxxx		x.xxxx		
		p-value (3)					x.xxxx
	Baseline through 2 Weeks Post-op	...	...	...	...	...	...
	Baseline through 6 Weeks Post-op	...	...	...	...	...	...
	Baseline through 12 Weeks Post-op	...	...	...	...	...	...

Program Name: Creation date, time

Note: Change from baseline = Post-baseline value - Baseline value, so that a positive change value indicates a positive outcome. Missing overall scores were imputed using multiple imputation methods.

Koos JR. normalized scores range from 0 (extreme symptoms) to 100 (no symptoms).

(1) Confidence interval based on the t-distribution.

(2) p-value from a two-sided, paired t-test, testing the null hypothesis that the true mean equals 0.

(3) p-value from a one-sided, two-sample t-test, testing the null hypothesis that the Standard of Care mean minus the iovera mean is greater than or equal to the non-inferiority margin of 14 versus the alternative hypothesis that the difference in means is less than 14.

[redacted]

[redacted]

Table 5

TIMED GET UP AND GO (TUG) TEST
ITT POPULATION

Parameter	Visit	Statistic	Iovera (N=xx) Value	Iovera (N=xx) Change from Baseline	Standard of Care (N=xx) Value	Standard of Care (N=xx) Change from Baseline	Difference in Mean Change from Baseline (Iovera - Standard of Care) and 95% CI (1)
TUG Time (seconds)	Screening (Baseline)	n (% of subjects)	xx (xx.x)		xx (xx.x)		
		Mean	xx.x		xx.x		
		Median	xx.x		xx.x		
		SD	xx.x		xx.x		
		Minimum - Maximum	xx - xx		xx - xx		
		95% CI for Mean (1)	(xx.x, xx.x)		(xx.x, xx.x)		
	2 Weeks Post-op	n (% of subjects)	xx (xx.x)	xx	xx (xx.x)	xx	
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x (xx.x, xx.x)
		Median	xx.x	xx.x	xx.x	xx.x	
		SD	xx.x	xx.x	xx.x	xx.x	
		Minimum - Maximum	xx - xx	xx - xx	xx - xx	xx - xx	
		95% CI for Mean (1)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
	6 Weeks Post-op 12 Weeks Post-op	...	...	...	...	...	...
AUC/time for Change from Baseline in TUG time	Baseline through 2 Weeks Post-op	n	xx		xx		
		Mean	xx.xx		xx.xx		x.x (x.x, x.x)
		Median	xx.xx		xx.xx		
		SD	xx.xx		xx.xx		
		Minimum - Maximum	xx.x - xx.x		xx.x - xx.x		
		95% CI for Mean (1)	(xx.xx, xx.xx)		(xx.xx, xx.xx)		
		p-value (2)	x.xxxx		x.xxxx		
		p-value (3)					x.xxxx
	Baseline through 6 Weeks Post-op	...	...	...	...	...	...
	Baseline through 12 Weeks Post-op	...	...	...	...	...	...

Program Name: Creation date, time

Note: Change from baseline = Baseline value - post-baseline value, so that a positive change value indicates a positive outcome.
(1) Confidence interval based on the t-distribution.
(2) p-value from a two-sided, paired t-test, testing the null hypothesis that the true mean equals 0.
(3) p-value from a one-sided, two-sample t-test, testing the null hypothesis that the iovera mean is less than or equal to the Standard of Care mean versus the alternative hypothesis that the iovera mean is greater than the Standard of Care mean.

Table 6.1

OPIOID CONSUMPTION: TOTAL DAILY MORPHINE EQUIVALENT (TME)
ITT POPULATION

Parameter	Time Period	Statistic	Iovera (N=xx)	Standard of Care (N=xx)	Difference between Treatments (Standard of Care - Iovera) and 95% CI (1)
TME	TKA to 72 Hours Post-op	n	xx	xx	
		Mean	xx.x	xx.x	xx.x (xx.x, xx.x)
		Median	xx.x	xx.x	
		SD	xx.x	xx.x	
		Minimum - Maximum	xx - xx	xx - xx	
		95% CI for Mean (1)	(xx.x, xx.x)	(xx.x, xx.x)	
	72 Hours Post-op to 2 Weeks Post-op	n	xx	xx	
		Mean	xx.x	xx.x	xx.x (xx.x, xx.x)
		Median	xx.x	xx.x	
		SD	xx.x	xx.x	
		Minimum - Maximum	xx - xx	xx - xx	
		95% CI for Mean (1)	(xx.x, xx.x)	(xx.x, xx.x)	
	2 Weeks Post-op to 6 Weeks Post-op 6 Weeks Post-op to 12 Weeks Post-op	...	...	...	...
	Hospital Discharge to 2 Weeks Post-op	n	xx	xx	
		Mean	xx.x	xx.x	xx.x (xx.x, xx.x)
		Median	xx.x	xx.x	
		SD	xx.x	xx.x	
		Minimum - Maximum	xx - xx	xx - xx	
		95% CI for Mean (1)	(xx.x, xx.x)	(xx.x, xx.x)	
		p-value (2)			x.xxxx
	Hospital Discharge to 6 Weeks Post-op Hospital Discharge to 12 Weeks Post-op	...	...	...	...

Program Name: Creation date, time
Source: Listing 4
Note: Missing pill count data were imputed using multiple imputation methods.
(1) Confidence interval based on the t-distribution.
(2) p-value from a one-sided, two sample t-test, testing the null hypothesis that the true iovera mean is greater than or equal to the true Standard of Care mean versus the alternative hypothesis that the true iovera mean is less than the true Standard of Care mean.

Table 6.1 will be repeated in the following tables:

Table 6.2

OPIOID CONSUMPTION: TOTAL DAILY MORPHINE EQUIVALENT (TME):
EXCLUDES DISCONTINUATIONS DUE TO ADVERSE EVENTS
ITT POPULATION

Table 7.1

OPIOID CONSUMPTION: TOTAL DAILY MORPHINE EQUIVALENT (TME)
PER PROTOCOL POPULATION

Table 7.2

OPIOID CONSUMPTION: TOTAL DAILY MORPHINE EQUIVALENT (TME):
EXCLUDES DISCONTINUATIONS DUE TO ADVERSE EVENTS
PER PROTOCOL POPULATION

Programming note: for Tables 6.2 and 7.2, please add Listing 2.1 to Source.

Table 8.1

TREATMENT EMERGENT ADVERSE EVENTS (TEAEs): OVERVIEW (SUBJECT LEVEL)
SAFETY POPULATION

Parameter	OCS (N=xx) n (%)	Standard of Care (N=xx) n (%)
At least one TEAE	xx (xx.x)	xx (xx.x)
At least one iovera procedure-related TEAE (1)	xx (xx.x)	-
At least one iovera device-related TEAE (1)	xx (xx.x)	-
At least one opioid use related TEAE (1)	xx (xx.x)	xx (xx.x)
At least one serious TEAE	xx (xx.x)	xx (xx.x)
At least one TEAE leading to study withdrawal	xx (xx.x)	xx (xx.x)

Program Name: Creation date, time:
Source: Listing 2.1
Note: Percentages are calculated based on the number of subjects in the ITT Population.
(1) Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.

Table 8.2

TREATMENT EMERGENT ADVERSE EVENTS: INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
SAFETY POPULATION

System Organ Class/Preferred Term	Iovera (N=xx) n (%)	Standard of Care (N=xx) n (%)
System Organ Class 1	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
...		
System Organ Class 2	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
...		

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of subjects with at least one AE in that system organ class or with that preferred term.

Table 8.3

TREATMENT EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS/PREFERRED TERM AND SEVERITY (EVENT LEVEL)
SAFETY POPULATION

Iovera (N=xx)

System Organ Class/Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Total with Non-Missing Severity n (100%)	Missing n
Any Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
...					

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is the number of AEs with non-missing severity with the given preferred term or in the given system organ class.
[Note: This table will be continued for Standard of Care.]

Table 9.1

IOVERA PROCEDURE RELATED TREATMENT EMERGENT ADVERSE EVENTS: INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
SAFETY POPULATION

System Organ Class/Preferred Term	Iovera (N=xx) n (%)
System Organ Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
...	
System Organ Class 2	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
...	

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of subjects with at least one AE in that system organ class or with that preferred term. Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.

Table 9.2

IOVERA PROCEDURE RELATED TREATMENT EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS/PREFERRED TERM AND SEVERITY (EVENT LEVEL)
SAFETY POPULATION

Iovera (N=xx)

System Organ Class/Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Total with Non-Missing Severity n (100%)	Missing n
Any Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
...					

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is the number of AEs with non-missing severity with the given preferred term or in the given system organ class. Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.

Table 9.3

IOVERA DEVICE RELATED TREATMENT EMERGENT ADVERSE EVENTS: INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
SAFETY POPULATION

System Organ Class/Preferred Term	Iovera (N=xx) n (%)
System Organ Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
...	
System Organ Class 2	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
...	

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of subjects with at least one AE in that system organ class or with that preferred term. Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.

Table 9.4

IOVERA DEVICE RELATED TREATMENT EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS/PREFERRED TERM AND SEVERITY (EVENT LEVEL)
SAFETY POPULATION

Iovera (N=xx)

System Organ Class/Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Total with Non-Missing Severity n (100%)	Missing n
Any Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
...					

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is the number of AEs with non-missing severity with the given preferred term or in the given system organ class. Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.

Table 9.5

OPIOID USE RELATED TREATMENT EMERGENT ADVERSE EVENTS: INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
SAFETY POPULATION

System Organ Class/Preferred Term	Iovera (N=xx) n (%)	Standard of Care (N=xx) n (%)
System Organ Class 1	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
...		
System Organ Class 2	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
...		

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of subjects with at least one AE in that system organ class or with that preferred term. Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.

Table 9.6

OPIOID USE RELATED TREATMENT EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS/PREFERRED TERM AND SEVERITY (EVENT LEVEL)
SAFETY POPULATION

Iovera (N=xx)

System Organ Class/Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Total with Non-Missing Severity n (100%)	Missing n
Any Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (100.0)	xx
...					

Program Name: Creation date, time
Source: Listing 2.1
Note: The denominator for the calculation of the percentage is the number of AEs with non-missing severity with the given preferred term or in the given system organ class. Adverse events that are definitely, probably, or possibly related, or for which the relationship is missing, are considered related.
[Note: This table will be continued for Standard of Care.]

[redacted]

[redacted]

Table 11

SUBJECT SATISFACTION
ITT POPULATION

Visit	Variable	Statistic	Iovera (N=xx)	Standard of Care (N=xx)
Week 6	Overall knee pain status since the beginning of the study			
	Very much worse	n (%)	xx (xx.x)	xx (xx.x)
	Much worse	n (%)	xx (xx.x)	xx (xx.x)
	Minimally worse	n (%)	xx (xx.x)	xx (xx.x)
	No change	n (%)	xx (xx.x)	xx (xx.x)
	Minimally improved	n (%)	xx (xx.x)	xx (xx.x)
	Much improved	n (%)	xx (xx.x)	xx (xx.x)
	Very much improved	n (%)	xx (xx.x)	xx (xx.x)
	Overall knee pain status since the beginning of the study (1)	n	xx	xx
		Mean	x.x	x.x
		Median	x.x	x.x
		SD	x.x	x.x
		Minimum - Maximum	x - x	x - x
	Subject satisfaction with pain management following surgery (2)	n	xx	xx
		Mean	x.x	x.x
		Median	x.x	x.x
		SD	x.x	x.x
		Minimum - Maximum	x - x	x - x
Week 12	...	...	...	...

Program Name: Creation date, time

(1) Very much worse=-3, Much worse=-2, Minimally worse=-1, No change=0, Minimally improved=1, Much improved=2, Very much improved=3.
(2) Measured on a scale of 0 to 10, with 0 being very unsatisfied and 10 being very satisfied.

[redacted]

[redacted]

[redacted]

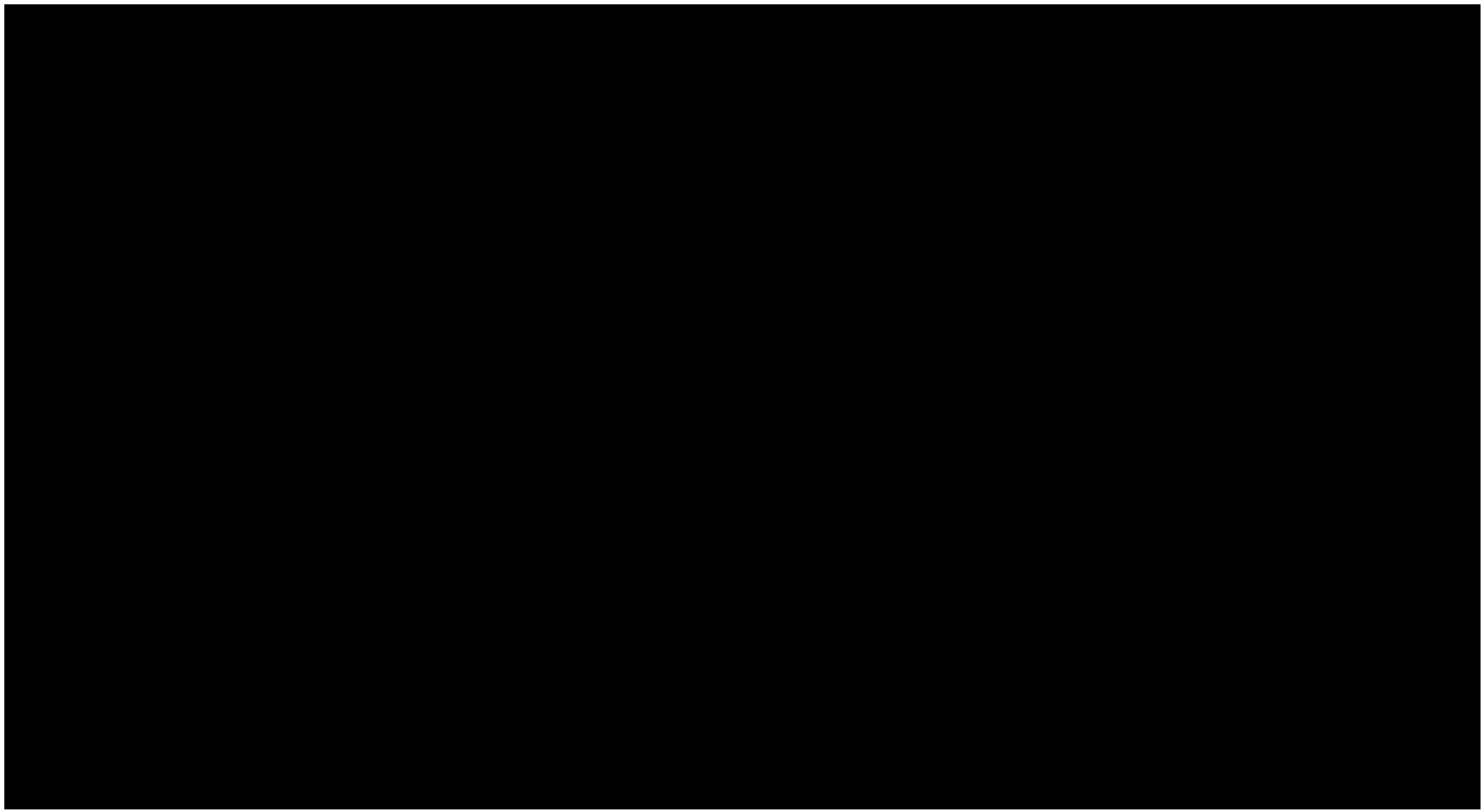

Table 15

STUDY EXIT
ITT POPULATION

Variable	Iovera (N=xx) n (%)	Standard of Care (N=xx) n (%)
Primary Reason Off Study	xx (xx.x)	xx (xx.x)
Completed all visits	xx (xx.x)	xx (xx.x)
AE/SAE	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)
Non-compliant participant	xx (xx.x)	xx (xx.x)
Withdrew consent	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)
Investigator decision	xx (xx.x)	xx (xx.x)
Medical need for prohibited medications or treatment	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)
Did subject exit with unresolved adverse events?		
Yes	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)

Program Name: Creation date, time
Source: Listing 1

Table 16

PROTOCOL DEVIATIONS
ITT POPULATION

Type of Protocol Deviation	Iovera (N=xx) n (%)	Standard of Care (N=xx) n (%)
Any Protocol Deviation	xx (xx.x)	xx (xx.x)
Subject consent not obtained prior to study procedures	xx (xx.x)	xx (xx.x)
Eligibility criteria not met	xx (xx.x)	xx (xx.x)
Pre-treatment assessment not complete	xx (xx.x)	xx (xx.x)
Iovera Treatment not complete	xx (xx.x)	xx (xx.x)
TKA surgery deviation	xx (xx.x)	xx (xx.x)
Anesthesia/analgesia deviation	xx (xx.x)	xx (xx.x)
Post-treatment/follow-up assessment not complete	xx (xx.x)	xx (xx.x)
Follow-up out of window	xx (xx.x)	xx (xx.x)
Follow-up visit not done	xx (xx.x)	xx (xx.x)
Other: Incorrect Prescription (1)		
Other*: reason*	xx (xx.x)	xx (xx.x)

Program Name: Creation date, time
Source: Listing 3
Note: A subject can have more than one type of protocol deviation, so the percentages may sum to more than 100%.
(1) Includes deviations due to patients not taking Tramadol.

Programming note: for 'Other' category, please append specific reason. There will likely be several 'Other' rows.

Listing 1

STUDY EXIT
ITT POPULATION

Treatment Group	Subject Number	Safety Population?	Per-Protocol Population?	Incorrect Opioid Prescription?	Exit Date (Study Day)	Primary Reason Off Study	Did subject exit with unresolved adverse events?	Comments
xxxxxxxx	xxx	xxx	xxx	xxx	yyyy-mm-dd (xx)	xxxxxxxxx	xxx	xxxxxxx
xxxxxxxx	xxx	xxx	xxx	xxx	yyyy-mm-dd (xx)	Other, specify	xxx	xxxxxxxx

Program Name: Creation date, time
Note: Study day is relative to day of TKA (Day 0).

Programming note: footnote any subjects where randomized and actual treatment group differ.

Listing 2.1

ADVERSE EVENTS (AEs)
SAFETY POPULATION
Part 1 of 3

Treatment Group	Subject Number	Event	Event Description	System Organ Class	Preferred Term	Event Start Date (Study Day)	Event Window
xxxxxxxx	xxx	xxxxxxxxx	xxxxxxxxxx	xxxxxxxxxx	xxxxxxxxxx	yyyy-mm-dd (xx)	xxxxxxxxx

Program Name: Creation date, time
Note: Study day is relative to day of TKA (Day 0).

Listing 2.1

ADVERSE EVENTS (AEs)
SAFETY POPULATION
Part 2 of 3

Treatment Group	Subject Number	Event	Severity	Reported as SAE? (#1)	If 'Yes' in #1, Reason	Action(s) Taken	Study Exit due to this AE?
xxxxxxxx	xxx	xxxxxxxxxx	xxxxxxxx	xxx	xxxxxxxxx	xxxx, xxxxxx	xxx

Listing 2.1

ADVERSE EVENTS (AEs)
SAFETY POPULATION
Part 3 of 3

Treatment Group	Subject Number	Event	Relatedness				If 'Possible', 'Probable', or 'Definite' in #1, Pre-Existing Condition
			To Iovera Procedure	To Iovera Device	To Opioid	To Pre-Existing Condition (#1)	
xxxxxxxx	xxx	xxxxxxx	xxxxxxxx	xxxxxxxxx	xxxxxxxx	xxxxxxxxxxx	xxxxxxxx

Listing 2.2

ADVERSE EVENT STATUS
SAFETY POPULATION

Treatment Group	Subject Number	Event	Event Start Date (Study Day)	Visit	Status	Outcome at Completion of Study (#1)	If 'Resolved' in #1, Date Resolved (Study Day)
xxxxxxxx	xxx	xxxxxxx	yyyy-mm-dd (xx)	Treatment Visit Day of TKA 72-Hours Post-op 2 Weeks Post-op 6 weeks Post-op 12 Weeks Post-op Other	xxxxxx	xxxxxxx	yyyy-mm-dd (xx)

Program Name: Creation date, time
Note: Study day is relative to day of TKA (Day 0).

Listing 3

PROTOCOL DEVIATIONS
ITT POPULATION

Treatment Group	Subject Number	Deviation ID	When did deviation occur?	Deviation Type	Reason for Deviation	Clinically Significant?
xxxxxxxx	xxx	xx	xxxxxxxx Other, specify Follow-up Visit, specify	xxxxxxxxxxxxxxx Pre-treatment assessment not complete, specify Iovera° treatment not complete, specify TKA surgery deviation, specify Anesthesia/analgesia deviation, specify Post-treatment/Follow-up assessment not complete, specify Follow-up visit not done, specify Incorrect prescription (1) Other, explain	xxxxxxxx Other, explain	xxx

Program Name: Creation date, time

(1) Incorrect prescription is included in the Other category in the CRF. Includes deviations due to patients not taking Tramadol.

Listing 4

OPIOID ACCOUNTABILITY AND PILL COUNT
ITT POPULATION

Treatment Group	Subject Number	Visit	Medication Name	Strength (Dosage)	Morphine Equivalent	If prescription filled or re-filled, number of new tabs acquired since last visit	Number of tabs re-dispensed at last visit	Number of tabs counted (remaining) at this visit	Total Daily Morphine Equivalent (TME)[1]	Notes/ Discrepancies
xxxxxxxx	xxx	xxxxx	xxxxxxxxxxxxxx	xxxxxxx	xxxx	xx None	xx None	xx	xxx	xxxxxxxxxx

Program Name: Creation date, time

Note: Calculated relative to TKA. The cumulative morphine equivalent will be divided by the number of days to provide the Total Daily Morphine Equivalent (TME) for the subject as of the visit.