Official Title of Study : Embrace TDD: Prospective, Multi-Center, Post-Market Study to Evaluate Intrathecal (IT) Morphine as an Alternative to Systemic Opioids for the Treatment of Chronic, Intractable, Non-Malignant Primary Back Pain with or without Leg Pain

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Embrace TDD: Prospective, Multi-Center, Post Market Study to Evaluate Intrathecal (IT) Morphine as an Alternative to Systemic Opioids for the Treatment of Chronic, Intractable, Non-Malignant Primary Back Pain with or without Leg Pain
Clinical Investigation Plan Identifier	MDT18026
Clinical Investigation Plan Version	Version 3.0
Sponsor/Local Sponsor	Medtronic, Inc. Medtronic Neuromodulation 7000 Central Avenue NE Minneapolis, MN 55432 USA 1-763-514-4000

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted] Principal Statistician

2.0	• Transferred content to new template (vB)
	• Updated non-inferiority margin for Secondary Objective #1 to 10 from 1
	• Added considerations due to COVID-19, including:
	  ○ Exits and deviations
	  ○ Data handling of remote visits
	• [redacted]
	• Updated primary analysis for primary objective
	• Added explanation of differing follow-up duration for CIP v3
	• Added analysis clarifications and minor edits throughout
		[redacted] Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
CI	Confidence Interval
CIP	Clinical Investigational Plan
COVID-19	Coronavirus Disease 2019
DD	Device Deficiency
[redacted]	[redacted]
FCS	Fully Conditional Specification
IDDS	Intrathecal Drug Delivery System
IT	Intrathecal
MedDRA	Medical Dictionary for Regulatory Affairs
MI	Multiple Imputation
MME	Morphine Milligram Equivalents
NOSE	Numerical Opioid Side Effect
[redacted]	[redacted]
PFMS	Preservative-Free Morphine Sulfate
[redacted]	[redacted]

Abbreviation	Definition
AE	Adverse Event
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
[redacted]	[redacted]
TDD	Target Drug Delivery
VAS	Visual Analog Scale
WHO	World Health Organization

3. Introduction

This statistical analysis plan (SAP) is based on Version 3 of the Embrace TDD Study Clinical Investigational Plan (CIP). CIP v3.0 changed the last study visit from the 12-Month Visit to the 6-Month Visit. Some subjects will have follow-up in the study past the 6-Month Visit, and other subjects will not have follow-up through the 12-Month Visit due to being consented and exited under CIP v3.0. The SAP presents the details of the methods to be used to analyze and report the study results of the Embrace TDD study, protocol number MDT18026.

4. Study Objectives

4.1 Primary Objective

To characterize the proportion of subjects with Clinical Success at the 6-Month Visit based on changes in pain intensity using the Visual Analog Scale (VAS) and changes in opioid-related side effects using the Numerical Opioid Side Effect (NOSE) Assessment Tool.

Clinical Success is defined as any of the following *(refer to grid below with matching numbers)*:

1) Reduced opioid-related side effects with equal pain
2) Reduced pain with equal opioid-related side effects
3) Reduced pain and reduced opioid-related side effects

Criteria for Clinical Success

Change from Baseline to the 6-Month Visit			Opioid-Related Side Effects (NOSE)		
			≥20% Increase	< ±20% Change	≥20% Reduction
			Worse	Equal	Better
Pain Intensity (VAS)	≥20% Increase	Worse			
	< ±20% Change	Equal			**1**
	≥20% Reduction	Better		**2**	**3**

4.2 Secondary Objectives

1. To demonstrate pain intensity scores (VAS) at the 6-Month Visit is non-inferior to VAS at Baseline
2. To characterize the change in opioid-related side effect scores (NOSE) from Baseline to the 6-Month Visit
3. To characterize the proportion of subjects who eliminate systemic opioids through the 6-Month Visit

[redacted]

4.4 Safety Assessment

To characterize all systemic opioid weaning-related, device-related, IT drug-related, and procedure-related adverse events (AEs), all serious adverse events (SAEs) (regardless of relatedness), and device deficiencies (DD) for all subjects from enrollment until the subject exits.

5. Investigation Plan

5.1 Study Design

The purpose of the study is to assess pain control and opioid-related side effects following a route of delivery change from systemic opioid therapy to IT morphine therapy.

This is a prospective, multi-center, post market study with commercially available products to evaluate the pain control and opioid-related side effects following a route of delivery change from systemic opioid therapy to IT morphine therapy in subjects with chronic, intractable, non-malignant primary back pain with or without leg pain. The study will be conducted at approximately 15 study sites in the United States.

5.2 Study Measures

5.2.1 Efficacy Measures

5.2.1.1 Visual Analog Scale (VAS)

Pain will be assessed using VAS. The VAS is a 100 mm line, with “No pain” on the left side of the line and “Worst pain imaginable” on the right side of the line. Subjects will be asked to mark a line perpendicular to the VAS line that best describes their average pain in the last 24 hours.

5.2.1.2 Numerical Opioid Side Effect Assessment Tool (NOSE)

The Numerical Opioid Side Effect (NOSE) Assessment Tool is a tool to evaluate 10 opioid-related side effects using a 11-point numeric scale.[4] Subjects are asked to evaluate each of the 10 opioid-related side effects on a scale of 0-10 with 0 being not present and 10 being as bad as you can imagine. A total sum score can range from 0-100. The opioid side effects included: 1) Nausea, vomiting, and/or lack of appetite; 2) Fatigue, sleepiness, trouble concentrating, hallucinations, and/or drowsiness/somnolence; 3) Constipation; 4) Itching; 5) Decreased sexual desire/function and/or diminished libido; 6) Dry mouth; 7) Abdominal pain or discomfort/cramping or bloating; 8) Sweating; 9) Headache and/or dizziness; 10) Urinary retention. The score from each side effect as well as the total sum score from all side effects may be reported.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2.2 Safety Measures

Subjects will be assessed from enrollment through the end of the study for AEs related to the following:

- Systemic opioid weaning
- Device
- IT drug
- Procedure

In addition, all SAEs (regardless of relatedness) and device deficiencies reported during the study will be collected. All subject deaths (regardless of relatedness) must be reported to Medtronic.

5.2.3 Schedule of Events by Visit and Visit Windows

Study procedures and data collection requirements for the study are summarized in Table 5-1. The study visit windows for all the required study visits are provided in Table 5-2. The 9- and 12-Month Visits were required under CIP v1.0 and v2.0; they are not scheduled study visits under CIP v3.0.

Table 5-1 Schedule of Events by Visit

Study Procedures, Tasks, and Data Collection (row) by Visit (column)	Baseline Visit (Enrollment)	Intrathecal Trial Visit	Implant Visit	Post-Op Visit	IT Therapy Initiation	1-Month Visit	3-Month Visit	6-Month Visit	9-Month Visit [1]	12-Month Visit [1]	Unscheduled Visits
Informed Consent Process	√										
Demographics	√										
Inclusion/Exclusion Criteria	√	√									
Urine Pregnancy Test	√	√	√[2]		√	√	√	√	√	√	
Drug Test	√	√			√	√	√	√	√	√	
Adjunctive pain management therapies	√	√	√		√						
Back and Leg Pain/Surgical History	√										
VAS	√	√			√	√	√	√	√	√	√
NOSE Assessment	√	√			√	√	√	√	√	√	√
IT PFMS Dose					√	√	√	√	√	√	√
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
Fluoroscopy/x-ray			√								
Device information (model, serial/lot #)			√								
Drug information (name, lot #/identifier, dose & concentration)		√			√	√	√	√	√	√	√
Initial and final device interrogation reports			√	√	√	√	√	√	√	√	√
Collect AEs/DDs	√[3]	√	√[3]	√	√	√	√	√	√	√	√
Pain Medications	√	√	√	√	√	√	√	√	√	√	√

[1]Required visits under CIP v1.0 and v2.0, not required under CIP v3.0.

[2]Confirm pregnancy test completed within 2 weeks prior to implant visit

[3]Device Deficiencies will be collected and reported from the Implant Visit through the 12-Month Visit/Study Exit

Table 5-2 Visit Windows

	Study Visits	Visit Windows
	Baseline Visit	Date of Enrollment (Date ICF/HIPAA signed and dated)
	Intrathecal Trial Visit	After Baseline and prior to Implant
IT Therapy Initiation **(Day 0)** Implant to Post-Op Visit	Implant Visit	≤150 days after the Baseline Visit
	Post-Op Visit	14 ± 4 days after the Implant Visit
	1-Month Visit	30 days ± 5 days after **Day 0**
	3-Month Visit	90 days ± 10 days after **Day 0**
	6-Month Visit[1]	180 days ± 10 days after **Day 0**
	9-Month Visit[2]	270 days ± 15 days after **Day 0**
	12-Month Visit (Study Exit)[2]	360 days ± 15 days after **Day 0**

[1] Study Exit Visit under CIP v3.0

[2] Required Visits under CIP v1.0 and 2.0

6. Determination of Sample Size

Approximately 100 subjects will be enrolled into the study to get a minimum of 67 implanted subjects and at least 50 evaluable subjects at the 6-Month Visit. The sample size of 50 evaluable subjects was chosen to assure acceptable levels of precision for estimation of the primary objective of Clinical Success and provide adequate power to test the secondary objective related to pain score.

There were no available data in the target population on the primary objective of Clinical Success, nor on the secondary objective of opioid-related side effects score. The secondary objective of pain intensity score is used for sample size calculation. It is hypothesized that the pain intensity score of VAS at the 6-Month Visit is non-inferior to those at Baseline using a non-inferiority approach.

The PASS 11 Non-Inferiority Tests for One Mean was used to calculate the power for pain intensity of VAS with the following assumptions: Sample size = 50, Alpha = 0.025, Non-Inferiority Margin = 1, True Difference = 0, Standard Deviation = 1.9, with Higher Means are Worse (one-sided) t-test. A sample size of 50 would achieve 95% power with the above assumptions. This power calculation was performed using a pain scale of 0-10; however, the power calculation is identical to one with a non-inferiority margin of 10 and assuming a standard deviation of 19 on a VAS pain scale of 0-100.

The non-inferiority margin of 10 points was chosen based on a review of pain study literature. Non-inferiority margins between 1 and 1.5 were reported for pain scales of 0-10, including one study in a similar population of chronic non-malignant pain subjects comparing 2 oral opioids that utilized a margin of 1.[1] The estimated actual difference was assumed to be 0 because the goal is to achieve same or better pain control as compared to Baseline. [redacted] The non-inferiority margin of 1 on a pain scale of 0-10 is equivalent to a non-inferiority margin of 10 on a VAS pain scale of 0-100.

A 33% attrition between enrollment and subject implant is assumed and a 25% attrition between Implant and the 6-Month Visit is assumed. To achieve at least 50 evaluable subjects at the 6-Month Visit, a minimum of 67 subjects are required to be implanted and approximately 100 subjects to be enrolled.

The 33% attrition between enrollment and subject implant accounts for the subjects who don't meet inclusion and/or exclusion criteria, those who can't follow the weaning process to eliminate systemic opioids, those who don't have a successful IT trial, those who have adverse events that can no longer be followed in the study, withdrawals, and lost-to-follow-up, etc. The attrition between implant and the 6-Month Visit is conservatively set at 25% to potentially account for the subjects who have adverse events that can no longer be followed in the study, withdrawals, are lost-to-follow-up, or subjects who can't be effectively managed on morphine monotherapy.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized using a flow diagram. Reasons for subject discontinuations, including those due to COVID-19 and/or the pump supply shortage, will be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All CIP deviations will be summarized by type of deviation. Details of CIP deviations that affect scientific integrity or patient safety will be presented. Additionally, separate summaries of study deviations due to COVID-19 and due to the pump supply shortage with their respective impact on the study data will be provided.

7.1.3 Analysis Sets

Full Analysis Set

All enrolled subjects will be included in the Full Analysis Set. This data set is also used for safety analysis, as well as for the analysis of systemic opioids weaning and holiday process.

IT Trial Analysis Set

All subjects who experience the IT trial will be included in the IT Trial Analysis Set.

Implanted Analysis Set

All subjects who are implanted with the Intrathecal Drug Delivery System (IDDS) will be included in the Implanted Analysis Set. This data set is used for supporting analysis for the primary and secondary objectives, as well as the analysis of adverse events that are related to device, IT drug, and procedure, and device deficiencies.

Completers Analysis Set

The implanted subjects who provide data at both the Baseline and the 6-Month Visit will be included in the Completers Analysis Set. This data set is used for supporting analysis for the primary and secondary objectives, as well as some additional measures at the 6-Month Visit. Completers Analysis Set may vary for different measures based on the subjects who provide data.

Per-protocol Analysis Set

The implanted subjects who maintain morphine monotherapy and provide data at both the Baseline and the 6-Month Visit will be included in the Per Protocol Analysis Set. This data set is used for a supporting analysis for the primary objective and the primary analyses for the secondary objectives, as well as some additional measures at the 6-Month Visit. Per-protocol Analysis Set may vary for different measures based on the subjects who provide data.

Primary Objective Analysis Set

The implanted subjects who maintain morphine monotherapy and provide data at both the Baseline and the 6-Month Visit through the date of the snapshot that will be conducted in November 2021 will be included in the Primary Objective Analysis Set. This data set is used for primary analysis for the primary objective. This analysis set may be a subset of subjects in the Per-Protocol and Completers Analysis Sets, as additional subjects may complete their 6-Month Visit following the November 2021 snapshot.

Long-term Analysis Sets

The implanted subjects who provide data at both the Baseline and the 12-Month Visit will be included in the Long-term Analysis Sets. These analysis sets include both per-protocol population (who maintain morphine monotherapy throughout the 12-Month Visit) and completers population.

7.2 General Methodology

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package will be used for the analyses of the study results (e.g., SAS).

This SAP is developed prior to data analysis and will include a comprehensive description of the statistical methods to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

7.3 Center Pooling

The investigators of this study will conduct the study according to a common protocol and use the same CRFs to collect study data. The site study personnel will be trained prior to the study initiation at each site. Periodic study monitoring by Medtronic will ensure compliance with protocol requirements.

There is not a priori provision to exclude any sites from the analysis. The data from all sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 15 subjects will be enrolled at each site, unless the site gets pre-approval from Medtronic for additional enrollments.

Due to the relatively small number of subjects expected at each center, there is no plan to use statistical methods to test for a difference among centers. Primary objective results will be summarized by center to verify there is not a site that unduly influences the results, and will be included in reports if there are concerns about the center effect.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring.

The primary analysis of the primary and secondary objectives will include subjects who maintain morphine monotherapy and provide data (per-protocol population). Sensitivity analyses will be performed for the primary and secondary objectives for VAS and NOSE using the Multiple Imputation (MI) methodology for missing data in VAS and NOSE scores for all implanted subjects. Details of the imputation method are described in Sections 7.9.2.3 and 7.9.3.3.

7.4.1 Data collected via remote visits due to COVID-19

With the onset of the COVID-19 pandemic in 2020, some study visits will be conducted remotely with the patient reported outcome data collected via telephone. Data captured via remote visit will be included in the main analyses of the primary, secondary, and additional objectives, where applicable. If more than 10% of the 6-Month Visits are completed remotely, sensitivity analyses of the Primary Objective and Secondary Objectives #1 and #2 will be conducted separately for subjects whose responses were collected exclusively during in-clinic visits and for subjects whose 6-Month data were collected remotely.

7.5 Adjustments for Multiple Comparisons

As there is only one hypothesis testing for one secondary objective, adjustment for multiple endpoints is not required.

7.6 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized in the report for enrolled subjects, implanted subjects, and per-protocol subjects who complete the 6-Month Visit.

7.7 Treatment Characteristics

The implanted pump and catheter models as well as catheter tips and locations will be summarized. The exposure to the IT therapy is defined as duration from the date of IT Therapy Initiation to the date of last study follow-up.

Subjects' pain medications will be collected and summarized. All pain medications will be coded using the appropriate version of the World Health Organization (WHO) Drug Dictionary at the appropriate Anatomical Therapeutic Chemical (ATC) level.

7.8 Interim Analyses

There is no planned interim analysis for the primary and secondary objective #1 for VAS in this study. The primary objective analysis will include all subjects in the Per-protocol Analysis Set who have completed their 6-Month Visit by the snapshot date in November 2021 (Primary Objective Analysis Set). Supporting analyses for the primary objective will include all subjects who complete the 6-Month Visit. Additional details are provided in Section 7.9.1.

7.9 Evaluation of Objectives

7.9.1 Primary Objective - Clinical Success at the 6-Month Visit

To characterize the proportion of subjects with Clinical Success at the 6-Month Visit based on changes in pain intensity using the Visual Analog Scale (VAS) and changes in opioid-related side effects using the Numerical Opioid Side Effect (NOSE) Assessment Tool.

7.9.1.1 Hypothesis

There is no formal hypothesis. The objective is to estimate the proportion of Clinical Success at the 6-Month Visit.

7.9.1.2 Experimental Design

The Clinical Success comprises 2 separate measures, pain intensity and opioid-related side effects. The measurements of pain intensity using VAS and opioid-related side effects using NOSE are described in Sections 5.2.1.1 and 5.2.1.2. Both pain intensity and opioid-related side effects are measured as a percent change from Baseline to the 6-Month Visit to calculate the Clinical Success.

Pain Intensity:

Percent change in pain intensity will be calculated as VAS at the 6-Month Visit minus VAS at Baseline, then divided by VAS at Baseline, expressed as a percentage. Individual subject percent change in pain intensity is categorized into three responder groups at the 6-Month Visit:

- Worse than Baseline: percent of change in VAS $\geqslant$20% (increased equal to or more than 20%) if Baseline VAS is $\geqslant$10, or change in VAS is $\geqslant$2 if Baseline VAS is <10
- Equal to Baseline: percent of change in VAS <20% and > -20% (increased less than 20% or decreased less than 20%) if Baseline VAS is $\geqslant$10, or change in VAS is between -2 and 2 if Baseline VAS is <10
- Better than Baseline: percent of change in VAS $\leqslant$ -20% (decreased equal to or more than 20%) if Baseline VAS is $\geqslant$10, or change in VAS is $\leqslant$ -2 if Baseline VAS is <10

Opioid-Related Side Effects:

Percent change in NOSE will be calculated as NOSE at the 6-Month Visit minus NOSE at Baseline, then divided by NOSE at Baseline, expressed as a percentage. Individual subject percent change in NOSE is categorized into three responder groups at the 6-Month Visit:

- Worse than Baseline: percent of change in NOSE ⩾20% (increased equal to or more than 20%) if Baseline NOSE is ⩾10, or change in NOSE is ⩾2 if Baseline NOSE is <10
- Equal to Baseline: percent of change in NOSE <20% and > -20% (increased less than 20% or decreased less than 20%) if Baseline NOSE is ⩾10, or change in NOSE is between -2 and 2 if Baseline NOSE is <10
- Better than Baseline: percent of change in NOSE ⩽ -20% (decreased equal to or more than 20%) if Baseline NOSE is ⩾10, or change in NOSE is ⩽ -2 if Baseline NOSE is <10

Clinical Success:

A subject's Clinical Success is defined as any of the following and displayed in Figure 7-1:

1. Reduced opioid-related side effects with equal pain
2. Reduced pain with equal opioid-related side effects
3. Reduced pain and reduced opioid-related side effects

Figure 7-1 Clinical Success

Change from Baseline to the 6-Month Visit			Opioid-Related Side Effects (NOSE)		
			≥20% Increase	< ±20% Change	≥20% Reduction
			Worse	Equal	Better
Pain Intensity (VAS)	≥20% Increase	Worse			
	< ±20% Change	Equal			1
	≥20% Reduction	Better		2	3

7.9.1.3 Analysis Methods

The proportion of subjects with Clinical Success and its exact binomial two-sided 95% confidence interval will be reported. The primary analysis method will use all the implanted subjects who maintain morphine monotherapy and provide data at both Baseline and the 6-Month Visits through the snapshot date in November 2021 (Primary Objective Analysis Set). Assuming the estimated proportion of Clinical

Success is 70%, with a sample size of 50 subjects, the exact two-sided 95% confidence interval (CI) would be 55.4-82.1%, with a confidence width of 26.7%. The widest 95% CI would be at 28.9% for an estimated proportion of Clinical Success of 50% (95% CI 35.5-64.5%).

Three sensitivity analyses will be performed: (1) the proportion of subjects with Clinical Success and its 95% CI will be reported in subjects who maintain morphine monotherapy and provide data at the Baseline and the 6-Month Visits (Per-protocol Analysis Set), (2) the proportion of subjects with Clinical Success and its 95% CI will be reported in subjects who provide data at the Baseline and the 6-Month Visits (completers), (3) the proportion of subject with Clinical Success and its 95% CI will be reported in all implanted subjects with imputation method of MI for those who have missing VAS or NOSE at the Baseline or the 6-Month Visit. Details of the imputation method are described in Sections 7.9.2.3 and 7.9.3.3.

If more than 10% of the 6-Month Visits within the Per-protocol Analysis Set are conducted remotely, an additional sensitivity analysis of the Per-protocol Analysis Set will be performed as described in Section 7.4.1.

7.9.2 Secondary Objective #1 – VAS at the 6-Month Visit

To demonstrate pain intensity scores (VAS) at the 6-Month Visit is non-inferior to VAS at Baseline.

7.9.2.1 Hypothesis

The mean change in pain intensity using VAS from Baseline to the 6-Month Visit is not worse than 0 by more than 10 points.

H0: $\mu \geq 0 + |M|$

HA: $\mu < 0 + |M|$

Where μ is the mean change in VAS from Baseline to the 6-Month Visit and $|M|$ is the absolute value of non-inferiority margin of 10.

7.9.2.2 Experimental Design

The measurement of pain intensity using VAS is described in Section 5.2.1.1. The change in VAS is calculated using VAS at the 6-Month Visit minus VAS at the Baseline Visit. A negative change is an improvement.

7.9.2.3 Analysis Methods

The change in VAS as well as VAS at both Baseline and the 6-Month Visit will be summarized using descriptive statistics, (e.g., mean, standard deviations, etc.). The non-inferiority null hypothesis will be tested using a one-sided 0.025 alpha level one sample t-test. The upper bound of the 95% CI of the mean change must be less than 10. If non-inferiority is met, a two-sided 0.05 alpha level t-test for superiority (vs. 0 change from Baseline) will be performed. If the distribution of the change in VAS doesn't meet normality assumption (Shapiro-Wilk test), an appropriate non-parametric analysis such as Wilcoxon signed rank test will be performed. The primary analysis will use all the implanted subjects who maintain morphine monotherapy and provide data at both Baseline and 6-Month Visits.

Two sensitivity analyses will be performed, one will include subjects who provide data (completers) and one will include all implanted subjects. The sensitivity analysis of all implanted subjects will be performed using MI method for missing data at the Baseline and the 6-Month Visits. For missing VAS at

the scheduled 6-Month Visit, if an Unscheduled Visit occurred within the 6-Month Visit window, and the VAS is collected at the Unscheduled Visit, the VAS from the Unscheduled Visit will be used in the analysis of the 6-Month Visit. Otherwise, the missing VAS will be imputed using MI. Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and the need for transformation if they are not normally distributed. The model variables in MI may include the following when deemed appropriate: study site, subject age, gender, primary diagnosis, VAS at Baseline, 1-Month Visit, 3-Month Visit. The fully conditional specification (FCS) method with 10 burn-in iterations within SAS and 10 repetitions (M = 10) will be used for imputation. Constraints will be set so that the imputed VAS are restricted to values ranging from 0-100. If the MI procedure is unable to successfully impute values within that range, the constraints will be applied after imputation, such that any values less than 0 will be set to 0, and any values greater than 100 will be set to 100. Following imputation, the objective will be evaluated using MI analysis method in SAS.

In addition, percentage of change in VAS will be calculated using change in VAS divided by VAS at Baseline. A negative percentage of change in VAS is a percentage of reduction in VAS, thus an improvement. The percentage of change in VAS will be summarized using descriptive statistics, (e.g., median and inter-quartile range, etc.). If a subject has VAS equal to 0 at both the Baseline and the 6-Month Visit, the percentage of change will be 0%. If a subject has VAS equal to 0 at the Baseline visit, and non-zero at the 6-Month Visit, this subject will be excluded from summary of percentage of change in VAS.

If more than 10% of the 6-Month Visits within the Per-protocol Analysis Set are conducted remotely, an additional sensitivity analysis of the Per-protocol Analysis Set will be performed as described in Section 7.4.1. Changes in VAS will be characterized without statistical testing for this analysis.

7.9.3 Secondary Objective #2 – NOSE at the 6-Month Visit

To characterize the change in opioid-related side effects scores (NOSE) from Baseline to the 6-Month Visit.

7.9.3.1 Hypothesis

There is no formal hypothesis. The objective is to estimate the change in NOSE from Baseline to the 6-Month Visit.

7.9.3.2 Experimental Design

The measurement of opioid-related side effect using NOSE is described in Section 5.2.1.2. The total NOSE score is the sum of each score from the 10 opioid-related side effects normalized by the number of scores provided. The change in NOSE is calculated using total NOSE score at the 6-Month Visit minus the total NOSE score at Baseline. A negative change is an improvement.

7.9.3.3 Analysis Methods

The change in NOSE as well as the total NOSE score at Baseline and the 6-Month Visit will be summarized using descriptive statistics (e.g., mean, standard deviations, etc.). The analysis will use all the implanted subjects who maintain morphine monotherapy and provide data at both Baseline and the 6-Month Visits.

Two sensitivity analyses will be performed, one will include subjects who provide data (completers) and one will include all implanted subjects. The sensitivity analysis of all implanted subjects will be

performed using MI method for missing data at the Baseline and the 6-Month Visits. For missing NOSE at the scheduled 6-Month Visit, if an Unscheduled Visit occurred within the 6-Month Visit window, and NOSE is collected at the Unscheduled Visit, the NOSE from the Unscheduled Visit will be used in the analysis of the 6-Month Visit. Otherwise, the missing NOSE will be imputed using MI. Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and the need for transformation if they are not normally distributed. The model variables in MI may include the following when deemed appropriate: study site, subject age, gender, primary diagnosis, NOSE at Baseline, 1-Month Visit, 3-Month Visit. The fully conditional specification method with 10 burn-in iterations within SAS and 10 repetitions (M = 10) will be used for imputation. Constraints will be set so that the imputed NOSE are restricted to values ranging from 0-100. If the MI procedure is unable to successfully impute values within that range, the constraints will be applied after imputation, such that any values less than 0 will be set to 0, and any values greater than 100 will be set to 100. Following imputation, the objective will be evaluated using MI analysis method.

In addition, percentage of change in NOSE will be calculated using change in NOSE divided by the total NOSE score at Baseline. A negative percentage of change in NOSE is a percentage of reduction in NOSE, thus an improvement. The percentage of change in NOSE will be summarized using descriptive statistics, (e.g., median and inter-quartile range, etc.). If a subject has NOSE equal to 0 at both the Baseline and the 6-Month Visit, the percentage of change will be 0%. If a subject has NOSE equal to 0 at the Baseline visit, and non-zero at the 6-Month Visit, this subject will be excluded from summary of percentage of change in NOSE.

NOSE score for each individual opioid-related side effect at Baseline and 6-Month Visit will be summarized using descriptive statistics (e.g., mean, standard deviations, etc.).

If more than 10% of the 6-Month Visits within the Per-protocol Analysis Set are conducted remotely, an additional sensitivity analysis of the Per-protocol Analysis Set will be performed as described in Section 7.4.1.

7.9.4 Secondary Objective #3 – Systemic Opioids Elimination through the 6-Month Visit

To characterize the proportion of subjects who eliminate systemic opioids through the 6-Month Visit.

7.9.4.1 Hypothesis

There is no formal hypothesis. The objective is to estimate the proportion of subjects who eliminate systemic opioids through the 6-Month Visit.

7.9.4.2 Experimental Design

The test for systemic opioids and illicit drug use will be collected at all scheduled study visits except for the Implant Visit and Post-op Visit. If a subject has a negative test for systemic opioid use, this subject will be considered as having eliminated systemic opioids at the scheduled study visit.

7.9.4.3 Analysis Methods

The proportion of subjects who eliminate systemic opioids and its exact binomial two-sided 95% CI will be reported at the 6-Month Visit as well as for those having eliminated systemic opioids from therapy initiation through the 6-Month Visit. The primary analysis method will use all the implanted subjects who maintain morphine monotherapy and provide data at the 6-Month Visit for the analysis at the 6-

Month Visit. The implanted subjects who maintain morphine monotherapy and have no more than one missing test through the 6-Month Visit (out of the IT Therapy Initiation, 1-Month, and 3-Month Visits) will be included in the analysis of eliminate systemic opioids through the 6-Month Visit. Assume the estimated proportion is 80%, with a sample size of 50 subjects, the exact two-sided 95% CI would be 66.3-90.0%, with a confidence width of 23.7%. The widest 95% CI would be at 28.9% for an estimated proportion of 50% (95% CI 35.5-64.5%).

Two sensitivity analyses for both at and through 6-Month Visit will be performed, one will include subjects who provide data (completers) and one will include all implanted subjects. The sensitivity analysis in all implanted subjects' analysis will display the full range on the potential impact of missing data by running an analysis assuming all missing values had eliminated systemic opioids to none of the missing values having eliminated systemic opioids.

In addition, an analysis following the primary analysis methods but excluding subjects who were not taking systemic opioids at baseline will be performed. The subjects who were not taking systemic opioids at baseline is defined as reporting MME = 0 at baseline.

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[redacted]

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7.10 Safety Evaluation

The safety evaluation will characterize all systemic opioid weaning-related, device-related, IT drug-related, and procedure-related adverse events (AEs), all serious adverse events (SAEs) (regardless of relatedness), and device deficiencies (DD) for all subjects from enrollment until the subject exits.

Adverse events and device deficiencies will be coded and summarized using the most recent version of Medical Dictionary for Regulatory Affairs (MedDRA).

The adverse events will also be categorized by relationship to systemic opioid weaning-related, device-related, IT drug-related, and procedure-related adverse events. The CEC adjudicated relatedness will be used for summary tables in the final report. Any differences between CEC adjudication and investigator reporting will be noted in the final report.

Adverse events will be presented in summary tables displaying the number of serious events, the number of events, and the number and percentage of subjects with one or more events. A summary of all adverse events by System Organ Class (SOC) and Preferred Term (PT) will also be provided.

Device deficiencies will be presented in summary tables displaying the number of deficiencies, and the number and percentage of subjects with device deficiencies.

7.11 Changes to Planned Analysis

The main analysis for the primary objective was originally planned to be evaluated after all subjects had reached the 6-Month Visit. The primary analysis was changed to analyze all per-protocol subjects with a 6-Month Visit through the snapshot date in November 2021 (Primary Objective Analysis Set, which will be a subset of the Per-Protocol Analysis Set). The primary objective is a characterization of the clinical success rate; it is a descriptive analysis with no hypothesis testing. Therefore, this change will affect the precision around the estimated clinical success rate for the main analysis but will otherwise minimally impact the objective. Additionally, all subjects within the Per-Protocol Analysis Set who eventually complete the 6-Month Visit will be evaluated as a sensitivity analysis for the primary objective to assess the robustness of the results.

8. Validation Requirements

Statistical programming code that affects the result of the main analysis for the primary objective shall be validated using Level I validation, which is defined as the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

Statistical programming code that affects the result of the main analysis for the secondary objectives shall be validated using at least Level II validation, which is defined as the peer reviewer reviews the code, and where appropriate, performs manual calculations or simple programming checks to verify the output. The CIP deviation summary shall be validated using at least Level III validation and the high-level adverse event summary shall be validated using at least Level II validation.

In addition, the main statistical analyses that are planned for publication and have not been previously validated should be validated with at least Level II validation.

9. References

1. Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS® hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain, Pain Pract. 2010;10(5):404–415.

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4. NOSE: Smith HS, Kirsh KL. Documentation and potential tools in long-term opioid therapy for pain. Anesthesiol Clin. 2007 Dec;25(4):809-23, vii.

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