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STATISTICAL ANALYSIS PLAN

A single-center, randomized, pilot study to assess iovera° lumbar medial branch cryoneurolysis vs lumbar radiofrequency ablation for facet mediated chronic low back pain

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1. SIGNATURE PAGE

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3. LIST OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
ASA	American Society of Anesthesiologists
ATC	anatomical therapeutic class
AUC	area under the curve
BMI	body mass index
CI	confidence interval
CLBP	chronic low back pain
CRF	case report form
d	day
EMA	European Medicines Agency
FDA	Food and Drug Administration
hr, h	hour
ICF	informed consent form
ICH	International Conference on Harmonisation
IRC	Independent Review Committee
LOCF	last observation carried forward
LSM	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
MPADSS	Modified Post Anesthesia Discharge Scoring System
NRS	Numerical Rating Scale
n	number of subjects
PO	oral
RCT	randomized controlled trial
RFA	radiofrequency ablation
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	standard of care
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	table, listings and figures
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary
WOCF	worst-observation-carried-forward

4. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned final analysis and reporting of the clinical study CRS-107 titled "A single-center, randomized, pilot study to assess iovera®° lumbar medial branch cryoneurolysis vs lumbar radiofrequency ablation (RFA) for facet mediated chronic low back pain".

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (1999) and the Royal Statistical Society (1993), for statistical practice.

The purposes of this SAP are to:

- Outline the types of analyses and presentations of data that will form the basis for drawing conclusions to the study objectives and hypotheses as outlined in the protocol.
- Explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices for Good Statistical Practice.

The following documents related to clinical study Protocol CRS-107 were reviewed in preparation of this SAP:

- Protocol v1.0, issued 11 APR 2022.
- Amendment-1, issued 06 FEB 2023.
- AICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical protocol and other identified documents for details on the planned conduct of this study. Operational aspects related to the collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this study is to assess the safety and feasibility of iovera° lumbar medial branch cryoneurolysis vs. radiofrequency ablation (RFA) for facet-mediated chronic low back pain (CLBP).

5.2. Secondary Objectives

The secondary objectives of this study are to:

1. Evaluate safety outcomes (i.e., adverse device effects, serious adverse device effects, adverse events [AEs]) related to iovera° treatment vs. RFA;
2. Evaluate clinical outcomes related to iovera° vs. RFA treatment including pain, functional disability, and concomitant medication use (including opioids and analgesics);
3. Evaluate the treatment success and failure rate of iovera° medial branch cryoneurolysis vs. RFA;
4. Evaluate subject satisfaction with pain management;
5. Identify subgroups of patients who are most and least likely to benefit from iovera° medial branch cryoneurolysis for facet-mediated CLBP.

6. STUDY OVERVIEW

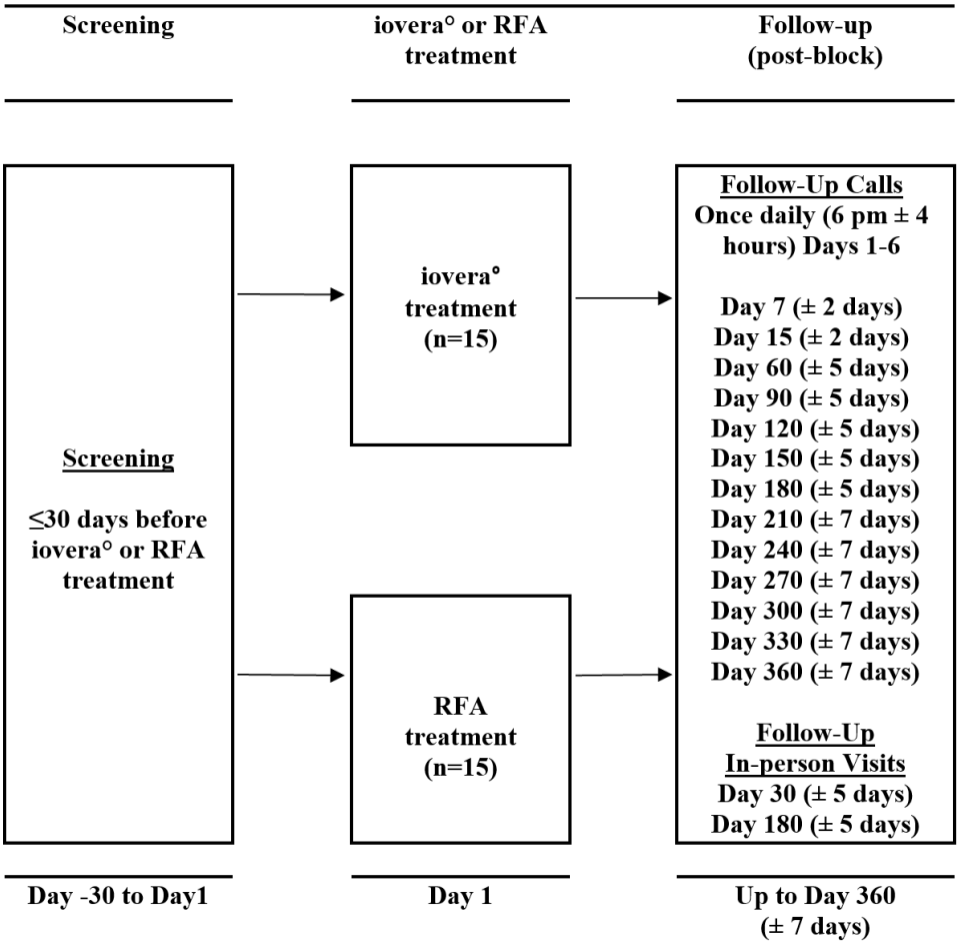
This is a single-center, randomized, pilot study in adult subjects with facet-mediated CLBP. Thirty (30) subjects are planned for initial enrollment and will be randomized 1:1 to receive iovera° medial branch cryoneurolysis or radiofrequency ablation.

This study is designed to determine if a full efficacy RCT can be successfully conducted using the procedures and protocols described in the current pilot study protocol, or if protocol modifications are necessary before moving forward with a full efficacy RCT. Furthermore, the study will assess the feasibility of the outcome measurements employed, construct a foundation for sample size calculation, and the acceptability/practicality of conducting the full efficacy RCT.

Randomization to treatment groups according to the randomization assignment will be performed on the day of treatment. The treatment groups are:

- **Group 1:** subjects will receive iovera° cryoneurolysis of the medial branch nerves
- **Group 2:** subjects will receive RFA of the medial branch nerves

Figure 1 Study Schema



7. DEFINITIONS

Diagnostic Medial Branch Block (MBB)

As part of the eligibility criteria, subjects must have undergone two successful diagnostic medial branch blocks consisting of two positive blocks with local anesthetic only (i.e., no steroids) under fluoroscopic guidance that results in at least 50% relief of primary (index) pain for the duration of the local anesthetic used.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are adverse events started on/after the start of iovera° treatment.

Baseline

Baseline is defined as the last available measurement or assessment prior to the start of study treatment.

8. ANALYSIS SETS

The safety analysis set includes all randomized subjects who receive treatment with the study treatment (iovera° or RFA). All analyses based on the safety set will be by actual treatment received.

The efficacy analysis set will include all randomized subjects who receive treatment with the study device. All analyses based on the efficacy analysis set will be by randomized treatment regardless of the actual treatment received.

The per-protocol analysis set will include all subjects in the efficacy analysis set who do not have any key protocol deviations. All efficacy analyses based on the per-protocol analysis set will be by randomized treatment regardless of the actual treatment received. All analyses based on the per-protocol analysis set will be by randomized treatment regardless of the actual treatment received.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). All analyses and tabulations will be performed using SAS Version 9.4 or later. Continuous variables will be summarized using descriptive statistics [sample size (n), mean, standard deviation (SD), minimum, median, and maximum]. Categorical variables will be tabulated with the number and percentage of unique subjects. Unless otherwise noted, percentages will be calculated using the number of subjects in the respective treatment group and analysis set as the denominator and presented with only those categories appearing in the data.

Individual subject data will be provided in listings. All listings will be sorted by treatment, site, subject, and, if applicable, collection date and time.

9.1.1. Handling Missing Values

9.1.1.1. NRS Pain Intensity Scores from Day of iovera°/RFA treatment from 24hr after treatment to Day X (7, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, and 360)

For subjects who drop out of the study early because of a related AE or lack of efficacy, their later missing timepoints will be imputed using worst-observation-carried-forward (WOCF) method, in which their worst observation since the first daily pain assessment will be carried to Day 15 (or subsequent days), For subjects dropping out early for any other reason, last-observation-carried-forward (LOCF) imputation will be used.

9.1.1.2. Adverse Event (AE) and Prior/Concomitant Medications

It is expected that the dates and times for AEs will be complete. For AEs with missing or partially missing start date/time, the following imputation rules will be applied for the determination of treatment-emergent status:

For partial start date/time:

- If the year is unknown, then the date will be assigned the date and time of study treatment.
- If the year is known to be different from the year of the first dose, then missing month and day will be imputed as the first month and first day of the month.
- If the year is known to be the year of the first dose,
    a) If the month is unknown or is the same as the month of the first dose, then the missing month and day will be imputed by the month and day of the first dose.
    b) If the month is known to be different from the month of the first dose, then the missing day is imputed as 01 (first day of the month).

The same missing data handling techniques will be used for prior/concomitant medications.

9.1.1.3. Adverse Event Severity or Relationship to Study Drug

If the severity of an AE is not reported, then for tables of AEs by severity, the event will be classified as 'Severe' and will be footnoted for the table to indicate this imputation. If the relationship to study treatment is not reported for an AE, then for tables of study-drug related AEs, the event will be assigned the relationship of 'definite'. Tables presenting related AEs will include all AEs with relationships of 'possible', 'probable' or 'definite' as assessed by the investigator.

9.2. Subject Disposition

Subject disposition summaries will include the number of subjects

- Randomized
- Completed Study, with reason for termination

The safety analysis set and enrollment data will be presented as treated. All other data will be presented as randomized.

The disposition summary will present the data for each treatment group.

9.3. Protocol Deviations

A blinded review before database lock will be conducted to determine important protocol deviations. Protocol deviations are considered important if, based on Sponsor assessment, they can impact the study integrity or interpretability of study results.

Important protocol deviations will also be evaluated if they impact efficacy data. Important protocol deviations with potential impact on efficacy will be used to exclude subjects from the Per-Protocol analysis set.

All protocol deviations will be reviewed and categorized before database lock. All important protocol deviations will be summarized by deviation category (including Inclusion Criteria, Exclusion Criteria, ICF, Concomitant Medication, and other if applicable). The protocol deviation data will also be presented as a by-subject data listing using the safety analysis set.

9.4. Description of Demographics and Baseline Characteristics

9.4.1. Demographic Data

The summary of demographic data will present:

- Age (years) – descriptive statistics
- Sex – n (%)
- Ethnicity – n (%)
- Race – n (%)

The demographic summary will present the data for each treatment group. Demographic data will be summarized overall.

9.4.2. Baseline Characteristics

The summary of baseline characteristic data will present:

- Body Mass Index (BMI) (kg/m^2)
- Tabaco use status
- NRS current pain intensity score (pain “average”)
- Duration of having diagnosed with low back pain (years)
- Oswestry Disability Index

Baseline characteristics summaries will present the data for each treatment group. Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided for continuous variables. The number and percent of subjects will be tabulated for the categorical variables.

Baseline characteristic data will be summarized and listed using the safety analysis set.

9.5. Medical and Surgical History

Medical and surgical history will be summarized by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA v 26.1) or more recent version.

All medical and surgical history will be included in the data listings.

9.6. Safety Analyses

Safety data will be summarized descriptively by treatment groups and overall. No statistical testing for comparison of treatment groups will be performed for safety variables.

9.6.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 26.1) or more recent version.

A treatment related adverse event will be considered a TEAE if it starts on/after the time of study (iovera° or RFA) treatment. If an AE has a partial onset date and time, the imputed start dates will be used to determine treatment-emergence (**Section 9.1.1.2**).

All summaries of AEs will include AEs that occur after the start of iovera° treatment. Events that start prior to iovera° treatment will be identified in listings only.

AEs will be summarized using subject incidence table. An overview of AEs will be presented. This table will include n (%) of subjects with:

- Any TEAE
  - Maximum severity: Mild
  - Maximum severity: Moderate
  - Maximum severity: Severe
- At least one related TEAE
- At least one serious TEAE
- Subjects discontinued due to a TEAE
- Serious treatment-emergent adverse events (TESAEs)
- Died on study.

Additionally, n (%) are calculated based on the number of unique subjects within each MedDRA category (e.g., preferred term) by treatment group. A subject reporting multiple events of the same category will be counted only once for that category. For summary purposes, AE relationship to the iovera° or RFA will be grouped into “Unrelated” for “unrelated” or “unlikely related” and “Related” for “possible”, “probably”, or “definite”. For subjects with more than one event coded to the same PT, the subjects will be counted for the categories with the strongest relationship and the greatest severity. The following subject incidence tables will be presented:

- TEAEs by PT (Preferred Term) sorted by the decreasing order of subject incidence in the combined group
- TEAEs by SOC (System Organ Class) and PT sorted alphabetically
- TEAEs treatment-related by SOC and PT
- TEAEs by severity and by SOC and PT

- TESAEs by SOC and PT.

A data listing will be provided for all AEs. Included in the listing are the reported term, PT, SOC, TEAE and TESAE flag, study day when AE starts, duration, relationship to treatment(s), severity, action taken, outcome, and seriousness category.

Separate data listings will be provided for subjects who experience SAEs and die on study.

9.6.2. Adverse Device Effects

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) associated with the use of a device in subjects, whether or not considered related to the device. This also includes adverse device effects related to the use of a device resulting from failure, insufficient or inadequate instructions for use, improper or inadequate design, deployment, implantation, installation, or operation, or any malfunction of the device, as well as any event resulting from user error (or use error) or from intentional misuse of the device.

Serious adverse device effects are categorized by any of the following which results in any of the consequences characteristic of a serious adverse event:

- Results in death
- Is immediately life-threatening (i.e., an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect
- Is an important medical event where medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate, such as events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in above definition. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The incidences of death, serious injury, or malfunction resulting from the device will be summarized for each treatment group.

9.6.3. Study Stopping Rules

The study may be terminated if the Investigator, or officials from regulatory authorities, identify conditions during the study that indicate so.

The Investigator will review all serious adverse device effects and serious adverse events (SAEs) reported from the clinical study on an ongoing basis and in real time (i.e., as the events are reported). The Investigator will be responsible for temporarily halting the study if the type, frequency, or seriousness/severity of such events suggests a potential threat to the safety of the study participants. If such action is taken, a thorough review of all available data will be conducted. Based on the results of this review and discussions with the investigator and/or regulatory authorities as warranted, the study may be restarted or permanently terminated.

The following adverse event study stopping rules will be applied:

[redacted]

In addition, any death will be thoroughly reviewed, and appropriate action taken.

9.6.4. Determination Study Success

[redacted]

9.7. Efficacy Analysis

For efficacy analyses, descriptive statistics that are appropriate for the efficacy variable will also be shown by treatment.

9.7.1. Efficacy Endpoints

9.7.1.1. Primary Endpoint

NRS “average pain over past 24 hours” intensity scores from first pain assessment post-treatment (24 hr) to Day 360

9.7.1.2. Secondary Endpoints

The following endpoints are secondary efficacy endpoints:

- NRS "average pain over past 24 hours" intensity scores from first pain assessment post-treatment (Day 1) to Day 30, Day 180, and Day 360
- Changes in NRS pain intensity scores ("average pain over 24 hours") from pre-treatment to Day 360
- Oswestry Disability Index scores (ODI) from Day 30 to Day 360
- Change in Oswestry Disability Index (ODI) scores from pre-treatment to Day 360
- Patient's Global Impression of Change (PGIC) scores from Day 30 to Day 360
- Patient satisfaction with pain management from Day 30 to Day 360
- Percentage of subjects who are in "no disability" determined by ODI scores at Day 360
- Concomitant medication use

9.7.2. Methods of Analysis

For Primary and Secondary Efficacy Analyses, descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be provided for continuous data. Tabulations (number and percentage of subjects) by category will be provided for categorical data. All efficacy analyses will be performed on the efficacy analysis set.

9.7.2.1. Primary Efficacy Analysis

9.7.2.1.1. NRS "average pain over past 24 hours" Intensity Score scores from first pain assessment post-treatment (Day 1) to Day 360

The primary analysis of the primary efficacy endpoint will compare the iovera° and RFA group. The superiority of iovera° to RFA will be evaluated based on the following null hypothesis and alternative hypothesis:

> H_0: iovera° is not superior to RFA with respect to mean of NRS pain intensity scores at Day 360
>
> H_a: iovera° is superior to RFA with respect to mean of NRS pain intensity scores at Day 360

A two-sided hypothesis test will be performed at α=0.05 level of significance comparing EXPAREL and bupivacaine HCl as follows:

- If the two-sided p-value for the least squares mean treatment difference in NRS at Day 360 (iovera°- RFA) is >0.05, then the superiority of iovera° to RFA is not achieved.
- If the p-value for the least squares mean treatment difference in NRS at Day 360 (iovera°- RFA) is ≤0.05, then the superiority of iovera° to RFA is achieved.

Least Squares Means (LSM) of “average pain over 24 hours” at Day 360 will be calculated for each subject. LSM for “average pain over 24 hours” at Day 360 will be summarized by treatment group, and overall.

To test for significant differences between iovera° and RFA group, a Linear Regression Model with adjustment of baseline NRS, sex, and tobacco status was used. The LS means for each treatment group, two-sided 95% CI for the LS mean difference, and p-value will be presented.

9.7.2.2. Secondary Efficacy Analyses

9.7.2.2.1. NRS "average pain over past 24 hours" intensity scores from first pain assessment post-treatment (Day 1) to Day 30, Day 180, and Day 360

Analysis and presentation will be the same as that of the primary analysis for the primary efficacy endpoint as outlined in **Section 9.7.2.1.1**.

9.7.2.2.2. Changes in NRS pain intensity scores (“average pain over 24 hours) from pre-treatment until Day 360

The percent changes will be calculated for each subject as follows:

$$\% \text{ Change} = \{NRS_{\text{current}} - NRS_{\text{screening}}\}/NRS_{\text{screening}} \times 100\%.$$

The current pain will be used at each post-treatment visit, and the change of NRS current pain will be defined as post iovera°/RFA - pre iovera°/RFA. Analysis and presentation will be the same using percent changes as an outcome as that of the primary analysis for the primary efficacy endpoint as outlined in **Section 9.7.2.1.1**. However, the regression model will not incorporate adjustments for covariates.

9.7.2.2.3. Oswestry Disability Index scores from Day 30 to Day 360

Analysis and presentation will be the same as that of the primary analysis for the primary efficacy endpoint as outlined in **Section 9.7.2.1.1**.

9.7.2.2.4. Change in Oswestry Disability Index (ODI) scores from pre-treatment to Day 360

Analysis and presentation will be the same as that of the primary analysis for the primary efficacy endpoint as outlined in Section **9.7.2.1.1.**

9.7.2.2.5. Patient’s Global Impression of Change (PGIC) from Day 30 to Day 360

Analysis and presentation will be the same as that of the primary analysis for the primary efficacy endpoint as outlined in **Section 9.7.2.1.1**.

10. SAMPLE SIZE CALCULATIONS

As the aim of this pilot study is not to assess effectiveness or efficacy, formal hypothesis testing will not be determined, and sample size will not be calculated based on desired statistical power to detect a treatment effect. A total of 30 subjects are planned for this pilot study, with 15 randomized to each of the 2 study groups.

11. REFERENCES

Birkenmaier C., Veihelmann A., Trouillier H., et al. “Percutaneous cryodenervation of lumbar facet joints: a prospective clinical trial, *International orthopedics*. Vol 31, p 525-530.