REC-15-017

# A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety of N1539 Following Major Surgery

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Statistical Analysis Plan

17 February 2017

# Statistical Analysis plan

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| **Protocol Number:** | REC-15-017 |
| **Protocol Title:** | A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety of N1539 Following Major Surgery |
| **Date of Protocol:** | **Amendment 003, 13 July 2016** |

# REVISION HISTORY

| Version No. | Version Date | Author | Description of Modification |
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| Abbreviation | Definition |
|---|---|
| abs | absolute value |
| AE | adverse event |
| AEOI | Adverse event of interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| BPM | Beats per minute |
| CFB | Change from baseline |
| ºC | degrees Centigrade |
| CV | Cardiovascular |
| CS | Clinically Significant |
| eCRF | Electronic case report form |
| eGRF | estimated glomerular filtration rate |
| DBP | Diastolic Blood Pressure |
| ECG | Electrocardiogram |
| EOT | End of Treatment |
| EOS | End of Study |
| ºF | degrees Fahrenheit |
| GFR | Glomerular filtration rate |
| GGT | gamma-glutamyltransferase |
| GI | Gastrointestinal |
| H | Hour |
| HCT | hematocrit |
| Hg | hemoglobin |
| ICH | International Conference on Harmonization |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| IVMED | IV Morphine Equivalent Dose |

| Abbreviation | Definition |
|---|---|
| Kg | Kilogram |
| L | Liter |
| LFT | Liver Function Test |
| LSD | Last Dose Date |
| $m^2$ | square meters |
| MDRD | Modification of Diet in Renal Disease |
| Mg | Milligram |
| mL | Milliliter |
| mm Hg | millimeters of mercury |
| NCS | Not Clinically Significant |
| NRSDV | Normal range standardized value |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| pH | negative log of hydrogen ion concentration |
| PO | by mouth |
| PCFB | Percent change from baseline |
| PCSC | Potentially Clinically Significant Change |
| PLT | Platelet counts |
| PT | prothrombin time |
| PTT | activated partial thromboplastin time |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Standard deviation |
| SJS | Stevens-Johnson Syndrome |
| SOC | System Organ Class |
| SpO2 | Peripheral oxygen saturation |
| TEAE | treatment emergent adverse event |
| TEN | toxic epidermal necrolysis |
| µg | Microgram |
| WBC | white blood cell |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) is prepared to provide a more technical and detailed elaboration of the principal statistical features stated in the protocol. The objective of the SAP is to reasonably assure that the statistical methodologies to be used for analysis are complete and accurate.

In the development of this SAP, the following documents were used:

- Protocol REC-15-017 - Amendment 003, 13 July 2016
- eCRF, version 4, 9 January 2017

The principles in the following guidance documents are followed in preparation of this SAP.

- ICH E3 (1995): Structure and Content of Clinical Study Reports
- ICH E6 (1996): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocols and this document, the description in this document supersedes the descriptions in the statistical section of the protocols.

# 2. STUDY OVERVIEW

## 2.1. Study Design and Objectives

Protocol REC-15-017 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, evaluation of the safety of N1539 in adult subjects undergoing major surgery. The study will enroll approximately 700 subjects.

The primary objective of this study is to evaluate the safety and tolerability of N1539 compared with placebo, as evaluated with physical examination, vital signs, clinical laboratory tests, ECGs, wound evaluation, postoperative opioid consumption, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Adult subjects, age 18 to 80 years inclusive, requiring major surgery that is expected to result in inpatient hospitalization for at least 24-48 hours, will be screened for participation at 30-40 study sites in North America, Australia, and New Zealand. Study enrollment will include a cohort of approximately 30-40 subjects meeting criteria as high risk subjects, defined as age >65 years with a glomerular filtration rate (GFR) of 60-89 mL/min/1.73m$^2$, as calculated using the Modification of Diet in Renal Disease (MDRD) equation. The study has three phases: 1) Pre Treatment Phase, 2) Treatment Phase, and 3) Follow-up. The following describes key activities in each phase in the study.

1. **Pre Treatment Phase:**
    a. Screening Period (Day -28 to Day -1): Subject will be consented and screened for eligibility for the study.
    b. Day of Surgery (Day 1):
        1) Pre surgery: Subject will be admitted to the clinic and reassessed for eligibility for the study. Pre surgery activities will be conducted.
        2) Surgery: Eligible subjects will undergo surgery using an appropriate anesthetic regimen according to the type of surgery (see Protocol Section 5.1)
        3) Postoperative Period: Following surgery, subjects will be evaluated for eligibility for treatment
    c. Randomization Qualification (Day 1): Subjects will be eligible for randomization and study dosing if/when they meet all of the postoperative randomization criteria **within six hours after the end of surgery:**
        1) Be able to achieve hemostasis and surgical incision closure, prior to Operating Room discharge.
        2) The surgical procedure did not require use of > 2 units of packed red blood cells or platelets.
        3) The surgical procedure from incision to closure was not longer than 12 hours.
        4) Subject is expected to have sufficient pain such that parenteral analgesia is clinically appropriate.

5) The subject has had no evidence of respiratory insufficiency, clinically significant hypotension, bradycardia, coagulopathy, or any other abnormality, during or following surgery that, in the investigator's opinion, significantly increases the risks of study participation.

**2. Treatment Phase (Time 0 through Discharge/LSD+1):**

Once the subject meets postoperative randomization eligibility criteria, subjects will be randomly assigned to treatment with N1539 30 mg or placebo in a 3:1 assignment ratio according to the randomization scheme. Randomization will be stratified by risk status (high risk [age > 65 years with GFR 60-89 mL/min/1.73 $m^2$] vs. other, referenced to as Not high risk) and surgery type (orthopedic vs. other surgeries), not high risk subjects will further be stratified by study center.

**The time of first dose of study drug (Dose 1) will be recorded as Hour 0.** Subjects will be administered a study dose according to their randomization every 24 hours so long as IV analgesia is clinically appropriate or until they receive a maximum of 7 study doses. A final study dose may be administered up to 4 hours early in subjects who are scheduled to be discharged. When inpatient care is no longer required, subjects may receive additional study doses under continued supervision of the investigator in an appropriate setting. **Subjects who do not receive a study dose for >28 hours following their previous study dose should be considered off treatment, and should not receive further study dosing.** Subjects may continue to receive standard of care analgesics per the discretion of the investigator, except for medications which may interact with meloxicam or interfere with the objectives of the study, as defined in Protocol Section 5.12.

During the treatment phase, pain symptoms that are not adequately controlled by dosing with study drug, may be treated with opioid analgesics according to the standard practice of the investigator. Once discharged, subjects may utilize oral analgesics according to the standard practice of the investigator. All doses of analgesic medications should be recorded in the subject's eCRF.

Subjects will undergo safety assessments at the earlier of LSD+1 day or at the time of discharge prior to leaving the study center. Study **safety assessments** during treatment period will include monitoring adverse events, vital signs, physical examination, ECG, clinical laboratory test, and wound healing assessment.

**3. Follow-up:**

Subjects will be provided routine standard of care for pain management after discharge from the study center. All subjects will be asked to return to the study center at LSD+7 days to complete end of study assessments. Subjects will complete a final safety assessment by telephone at LSD+28 days.

Safety assessments at the LSD+7 days follow-up visit include AE, clinical Laboratory tests, PE, vital signs, ECG, and wound healing assessments.

## 2.2. Study Assessment Schedule

The following is an overview of study schedule activities (Table 1).

## Table 1: Overview of Study Schedule

| Procedure; Dose/Hour | Screening | Inpatient (Day 1 – Discharge) | | | | | | Follow-Up Visit (LSD+7 days ± 2) | Follow-Up Telephone (LSD+28 days ± 4) |
|---|---|---|---|---|---|---|---|---|---|
| | | Prior to Surgery | Surgery | Dose 1 / Hour 0 | Dose 2 / Hour 24 | Dose 3 / Hour 48 | LSD+1 / Discharge | | |
| Informed Consent | X | | | | | | | | |
| Confinement | | ← | ← | ← | X | → | → | | |
| Eligibility Assessment | X | X | X[d] | | | | | | |
| Demographics and Medical History | X | X | | | | | | | |
| Physical Examination[e] | X | X | | | | | X | X | |
| Pregnancy Test (FOCBP only) | X[serum] | X[urine] | | | | | | | |
| Alcohol Breath Test and UDS | X | X | | | | | | | |
| Clinical Laboratory Tests[a] | X | X[g] | | | | X | X | X | |
| Vital Signs[b] | X | X | | X | X | | X | X | |
| 12 Lead ECG | X | X[c] | | | | | X | X | |
| Surgical Procedure | | | X | | | | | | |
| Study Drug Administration | | | | X | X | X | X[f] | | |
| Wound Evaluation | | | | | | | X | X | |
| Prior and Concomitant Medication | ← | ← | ← | X | → | → | → | → | → |
| Adverse Event Monitoring | | | | ← | ← | ← | X | → | → |

a Laboratory tests will include hematology, chemistry, urinalysis and coagulation tests.
b Vital signs (VS) include: resting blood pressure, resting pulse, and SpO2. Tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
c 12-lead ECG will be done prior to surgery only if screening ECG was done >14 days before Day 1
d Postoperative randomization criteria will be assessed on the day of surgery (Day 1), prior to treatment.
e BMI, height, and weight will be assessed at the screening visit only.
f Doses may be administered every 24±1 hours for up to 7 days while continued use of IV analgesia is clinically appropriate.
g Day 1 clinical laboratory tests will be required if greater than 14 days have elapsed since screening labs were performed or if screening labs were not performed at the central

## 2.3. Study Endpoints

### 2.3.1. Efficacy Endpoints

There is no efficacy endpoint in this safety study.

### 2.3.2. Safety Endpoints

The safety endpoints will include the following:

1. Incidence of AEs and SAEs
2. Change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests, including routine blood chemistry, hematology, coagulation tests, and urinalysis
3. Change from baseline in vital signs; incidence of clinically significant changes in vital signs
4. Incidence of clinically significant abnormal ECG findings
5. Incidence of abnormal wound healing
6. Total opioid consumption during 0-24, 24-48, 48-72, and 0-48, 0-72 hours, and During Treatment post first dose of study drug

## 2.4. Sample Size Consideration

The sample size for this study was selected to support the required total exposure population for N1539. However, for a sample size of 525 subjects to be treated with N1539, this study will have 95% probability to observe at least one event if the event's occurrence rate is 0.57% or higher in the N1539 treatment group.

# 3. GENERAL CONSIDERATIONS

## 3.1. Analysis Population

The following analysis sets will be identified for this study.

**Intent-to-Treat (ITT) Analysis Set:** The ITT set will include all subjects randomized. This dataset could also be referenced as the 'Randomized Set'. The ITT subjects may or may not receive randomized treatment.

**Safety Set:** The safety set will include all treated subjects and will be used for safety and tolerability assessments.

## 3.2. Test Hypothesis and *P* Value Justification

There is no formal null hypothesis to be examined in this safety study. Differences between N1539 30 mg and placebo group will be evaluated primarily using descriptive summary statistics. If appropriate inferential statistics may be provided at the 0.05 level of significance using 2-sided test for null hypothesis of no difference between the two treatment groups. In this case nominal p-values will be reported as is.

## 3.3. Procedures for Handling Missing Data

Unless indicated otherwise, missing data imputation will not be performed for safety parameters. However, AEs with missing severity assessments will be tabulated as "severe," and AEs with missing relationship assessments will be tabulated as "related" for the purpose of analysis; and the missing data will be presented in data listing as is.

## 3.4. Definitions for Analysis Visit

The following analysis visits will be identified based on the date of first dose, date of last dose, and date of (LSD+1/discharge):

**Baseline:** Baseline will be the last non-missing measurement taken before the subject receives the first dose of study medication. Unscheduled visits before the date of first dose could be assigned as the Baseline visit if it is the last non-missing record prior to the First Dose Date.

**Treatment Period:** Treatment period will include all records with date ≥ date of first dose and ≤ date of last dose + 1 (ie, LSD+1). Each record will be identified by their nominal time (hour XX) post Dose 1. Unscheduled visits within this period will also be included and they will be labeled as is.

For example,

1) Hour 24 vital signs will be labeled as **Hour 24**.

2) The first unscheduled record within treatment period will be label as **Unscheduled 1**

**End of Treatment (EOT):** End of treatment record should be the last record post baseline up to and include (LSD+1/Discharge) visit. This record will be taken from the LSD+1/Discharge visit for the majority parameters. However, for clinical laboratory analysis not all subjects will have this LSD+1/Discharge Lab. It is anticipated that

- A Subject will have LSD+1/Discharge lab and not an Hour 48 Lab if the subject has 1 or 2 doses of study drug and is discharged prior to hour 48.
- A subject will not have a LSD+1/Discharge lab but will have an Hour 48 lab if the subject has 3 doses of study drug and the Hour 48 lab is completed.
- A subject will have an Hour 48 Lab and a LSD+1/discharge Lab if the subject has 4 or more doses of the study drug.

Hence, the EOT record will be LSD+1/Discharge record if performed; otherwise (see Scenario 2 above) the Hour 48 lab will be the EOT lab.

- the Hour 48 lab record in Scenario 2 above will have an analysis visit of **End of Treatment** whereas the Hour 48 lab in Scenario 3 will have an analysis visit of **Hour 48** (that is, it is a visit within the treatment period).

**End of Study (EOS):** The expected End of Study record is the measures taken after the date of (LSD+1/Discharge). It is typically taken from the (LSD+7) follow-up visit, however, the **End of Study** record could be an unscheduled visit if this UNSCHEDULED VISIT is after the LSD+7 visit.

## 3.5. Derived Variables for Analysis

### 3.5.1. Subject Group

Four subject groups will be defined based on randomization strata (risk status and surgery type):

1) High Risk Subject Receiving Orthopedic Surgery
2) High Risk Subject Receiving Other Surgery
3) Not High Risk Subject Receiving Orthopedic Surgery
4) Not High Risk Subject Receiving Other Surgery

The following table shows some of the specific surgeries included in each surgery type.

**Table 2: Surgeries Included in Each Surgery Type**

| Surgery Type | Specific Surgery |
|---|---|
| Other Surgery | Hernia Repair |
| | Hysterectomy |
| | Gynecological/Genitourinary |
| Orthopedic Surgery | Ankle Arthroplasty |
| | Bunionectomy |
| | Hip Arthroplasty |
| | Knee Arthroplasty |
| | Shoulder Arthroplasty |
| | Spinal |
| | Total Hip Replacement |
| | Total Knee Replacement |
| | Other |

Risk status is to be determined at the screening visit based on the eGFR and age at Screening Visit. Screening lab for eGFR computation could be performed either at the central lab or at a local lab. eGFR determined at a local lab will be available in the source document at the site and will not be entered to eCRF. The randomization stratus is entered to eCRF.

### 3.5.2. Treatment Group

All subjects will be included in their randomized treatment group for analysis. However if a treatment error (a subject was randomized to N1539 group but received placebo treatment or vice versa), the following rules will apply:

1) All planned analysis will be based on the randomized (planned) treatment group.
2) Sensitivity analysis will be conducted, such as

a. An analysis that includes the subject in the actual treatment group

b. An analysis that excludes the subject from both treatment groups.

Treatment error is a major protocol deviation; hence, this incidence will also be documented in the protocol deviation analysis (see Section 4.3).

### 3.5.3. Analysis Center

This study is planned to enroll subjects from 30-40 investigator sites in North American, Australia, and New Zealand. An analysis center is an investigational site if the site has randomized more than 5 subjects; it could also be a unit of 2 or more small investigational sites. In the event that 2 or more investigator sites are combined to form an analysis center the following rules may apply.

a. Pooled sites are in same geographic area

b. Pooled sites are similar in medical practice / focus

The analysis site will be used as a covariate for total opioids consumption analysis. If data pooling is required to form analysis site, the pooling will be determined and documented prior to database hard lock.

### 3.5.4. Total Opioid Consumption

All concomitant medications will be mapped to WHO Drug (version 2015). Opioid medication will be identified per ATC level 2 and level 3. The dose from each identified opioid record will then be converted to IV Morphine Equivalent Dose (IVMED) in mg. Table 3 shows some examples of IVMED of some commonly used analgesics.

All analgesic medications will be mapped to four time periods: (0-24, 24-48, 48-72, 0-48, 0-72, and During Treatment) hours after Dose 1 based on the start date/time and stop date/time. 'During Treatment' period starts with Dose 1 date/time and ends with the LSD+1; that is, this period will equal to the study drug treatment duration. This period is created to assess potential relationship of total opioid consumption and duration of study drug treatment since the duration of study drug treatment is expected to vary from subject to subject.

**Table 3: IV Morphine Equivalent Dose (mg) For Commonly Used Analgesics**

| Generic Opioid Name | 1 Unit | Route | IV MED (mg) |
|---|---|---|---|
| Morphine | mg | IV | 1 |
| Morphine | mg | PO | 0.333 |
| Methadone | mg | IV | 1 |
| Methadone | mg | PO | 0.333 |
| Nalbuphine | mg | IV | 1 |
| Nalbuphine | mg | PO | 0.333 |
| Buprenorphine | mg | IV | 25 |
| Fentanyl | µg (mcg) | IV | 0.1 |
| Sufentanil | µg (mcg) | IV | 1.00 |
| AlFentanyl | µg (mcg) | IV | 0.02 |
| Hydromorphone | mg | IV | 6.67 |
| Hydromorphone | mg | PO | 1.3 |
| Codeine | mg | PO | 0.05 |
| Meperidine | mg | PO | 0.025 |
| Pentazocine | mg | PO | 0.1 |
| Oxycodone | mg | PO | 0.5 |
| Hydrocodone | mg | PO | 0.3 |

For example, one tablet of 5 mg Oxycodone will equal to 2.5 mg IVMED (5*0.5=2.5).

All opioid medication used for pain management during treatment will be clearly marked as 'Pain Management' when entering the medications in the eCRF. Although all efforts are made to have a date/time entered for all analgesics in the study, the following rules will be used to handle missing date/time if situation is present. The rules should be executed in the same order as follows.

1. All records without start date will be excluded.
2. All records that the start date is before Date 1 or after LSD+1 will be excluded regardless if time is present or missing.
3. If start date is present but stop date is missing, the stop date will be set to be equal to the start date.
4. If the analgesic start date = date of first study dose, the stop time of study drug dose 1 will be assigned to the missing start time.

5. If the start date is after the date of first study dose, the missing start time will be the first minute of the date (i.e., missing time =00:01:00).
6. If stop time is missing, the start time of this analgesic will be used as the stop time as well (ie, start time = stop time) if the medication start date = stop date.
7. If the start date is not equal to end date, and stop time is missing the end time will be set to last minutes of the day (ie, missing time = 00:59:00).
8. If a pain medication started prior to study but the subject was on a stable dose through the treatment period (signaled by ONGOING=Yes) then start and stop date/time will be set to the first dose start date/time and (last dose stop date/time) +1 (ie, LSD+1).
9. If a medication is started prior to Hour 0 but stopped during the treatment period, the duration of the medication will be interpolated for the time period of interest.

The start date/time of first dose of study drug (=Hour 0) and stop date/time of the last dose (=Hour L) will be used to define the period as follows

| Period | Criteria |
|---|---|
| 0-24 Hour | Begin = Hour 0 and End = Hour 0 + 24:00:00 |
| 24-48 Hour | Begin = Hour 0+24:01:00 and End = Hour 0+ 48:00:00 |
| 48-72 Hour | Begin = Hour 0+48:01:00 and End = Hour 0+ 72:00:00 |
| During Treatment | Begin = Hour 0 and End = Hour L + 24:00:00 |
| | Hour 0 = Start time of first dose<br>Hour L = Stop time of last dose |

After IVMED is determined for each record, the total opioid consumption will be determined for each subject per time interval by sum of all records within a period. If the duration of a record covered 2 periods (e.g., started during 0-24 period but stopped after Hour 24), linear interpolation method will be used to split the IVMED into 2 intervals based on the start and stop time**.**

Opioids consumption during treatment is an 'At-risk' analysis. The following rules will be used to derive this parameter.

1. If a subject did not use any opioids for pain management during a period and this subject is in the study during this period a zero ('0') will be assigned to this subject for this period.
2. If a subject discontinues from the study drug treatment during 0-24 hours, this subject will be included in the analysis for period 0-24 and period 0-48 hours (rule No.1 above will apply to this subject for periods of 0-24 and 0-48 hours if this subject did not use any opioids for pain management prior to discontinuation); but this subject will be excluded from the analysis of 24-48 hours, 48-72 hours (opioids consumption is set to missing in those periods).

3. If a subject discontinues study drug treatment from the study during 24-48 hours, this subject will be included in the analysis of 0-24, 24-48, and 0-48 hours; rule No. 1 above will apply to this subject for a period if this subject did not use any rescue medications during this period.

Since the study drug treatment is once daily regimen the following table summarizes the At-Risk period based on number of study drug treatment received.

| Number of Doses | At Risk Period |
|---|---|
| Subjects with 1 dose of study drug | 0-24, 0-48, 0-72, During Treatment |
| Subjects with 2 doses of study drug | 0-24, 24-48, 0-48, 0-72, During Treatment |
| Subjects with 3+ doses of study drug | 0-24, 24-48, 48-72, 0-48, 0-72, During Treatment |

### 3.5.5. Potentially Clinically Significant Changes in Vital Signs

Vital signs will be taken at Screening, Day 1 (prior to surgery), Hour 0 on Day 1 (prior to first dose), Hour 24 (prior to Dose #2), LSD+1, and LSD+7. Baseline vital signs will be the last non-missing value prior to Dose 1; this typically would be the Hour 0 vital signs. Change from baseline (CFB) and percent change from baseline (PCFB) in vital signs will be calculated for each post dosing vital signs.

CFB = Post Baseline - Baseline

PCFB = 100*(CFB/Baseline)

Blood pressure results and change from baseline will be grouped into the following categories (Table 4).

**Table 4: Blood Pressure Results and Change from Baseline Category**

| Parameter | Observation | Change from Baseline (Post baseline – Baseline) |
|---|---|---|
| SBP (mmHg) | ≤90<br>91-120<br>121-150<br>151-179<br>≥180 | ≥ +20 (increased 20 or more mmHg)<br>+19 to -19 (changed within 19 mmHg)<br>≤ -20 (decreased 20 or more mmHg) |
| DBP (mmHg) | ≤50<br>51-80<br>81-90<br>91-104<br>≥105 | ≥ +15 (Increased 15 or more mmHg)<br>+14 to -14 (changed within 14 mmHg)<br>≤ -15 (decreased 14 or more mmHg) |

Subjects are considered having a potentially clinically significant change (PCSC) in blood pressure if SBP change is 20 or more mmHg or DBP change is 15 or more mmHg, or Percent change is 25% or more. Mathematically, the PCSC could be expressed as

- PCSC=Y if abs(CFB_SBP) ≥20 mmHg or
- PCSC=Y if abs(CFB_DBP) ≥15 mmHg or
- PCSC=Y if abs(PCFB) ≥25%

Where abs = absolute value

Vital sign analysis will focus on blood pressure; other vital signs (heart rate and SpO2) will be available in data listings

# 4. STUDY POPULATION SUMMARIES

## 4.1. Disposition

A summary table (Table 14.1.1.1) will provide frequency counts for subject disposition, including

- Number (%) subjects randomized
- Number (%) subjects treated with >=1 dose of study drug
- Number (%) subjects completed study drug treatment
    - Number (%) subjects by reason for discontinuation of study drug treatment
- Number (%) subjects completed study
    - Number (%) subjects by reason for discontinuation of study

Subjects who did not complete study will include all subjects who discontinued from the study before the second follow-up (LSD+28) visit.

Disposition information will be provided by treatment group for overall, and by surgery type and risk status

A table (Table 14.1.1.2) will provide enrollment summary by site, including number of subjects screened, number of subjects randomized, number of subjects treated, number of subjects completed treatment, and number of subjects completed study.

## 4.2. Demographics and Baseline Characteristics

The demographic summary will include descriptive statistics for age, age group (<65, ≥65, ≥75), sex, race, ethnicity, weight, height, BMI, and BMI group (BMI < 35, BMI ≥ 35) overall and by treatment group.

Baseline characteristics will include

1. Child bearing potential among females
2. Surgery duration (hr), surgery type, incision type, surgery site, and risk status. Based on the detail information provided on the surgery page, specific surgeries will be grouped for the purpose of summary.
3. Time (hr) from end of surgery to first dose of study drug

Demographics and baseline characteristics will be tabulated for safety population by treatment group for overall, by risk status, and by surgery type (Tables 14.1.2.1.1). Demographics table will also be provided by randomization strata and subgroups (Tables 14.1.2.2 - 14.1.2.2.5).

Medical and surgical (Table 14.1.3) history will be tabulated by treatment group for the overall, by surgery type, and by risk status in safety analysis set. No formal inferential tests will be performed.

## 4.3. Protocol Deviations

All protocol deviations will be identified and will be classified as either an "Important Protocol Deviation" or "Protocol Deviation".

Important Protocol Deviation: An Important Protocol Deviation is a protocol deviation that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Examples may include:

- Failure to meet all entry criteria;
- Non-compliant with study drug treatment regimen;
- Did not receive randomized treatment;
- Did not receive correct randomization treatment;
- Use of prohibited concomitant medications;

Protocol Deviation: Any alteration/modification, divergence or departure from the IRB-approved protocol. A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of an approved study that is not consistent with the current research protocol, consent document or study agenda.

All protocol deviations will be tabulated by protocol category, type, and treatment group for the overall and by surgery type and risk status in safety analysis set (Table 14.1.4).

**Table 5: Protocol Deviation Category**

| Protocol Deviation Category |
|---|
| Informed Consent |
| Eligibility Criteria not met |
| Study procedure |
| Exclusionary medication taken |
| Other |

## 4.4. Treatment Compliance

Doses of study medication will be administered to the study subjects by study personnel. The exact start and stop time of administration of study medication will be documented within each subject's eCRF. No formal summary of treatment compliance will be produced.

## 4.5. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population and by treatment group (Table 14.1.5.1). Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version 2015. The table will also provide number of subjects in each medication grouped by ATC class (defined as ATC Level 2 or Level 3 if Level 2 is not defined).

### 4.5.1. Total Opioid Consumption for Pain Management During Treatment

Total opioid consumptions in IV morphine equivalent dose (mg) per subject will be determined for each period. A summary table will be prepared to provide group descriptive statistics, including sample size, mean, standard deviation, minimum, median, and maximum. Difference between treatment groups will be evaluated using an ANCOVA model that will include main effect of treatment and investigational site; sites with less than 5 subjects in total will be pooled to form an analysis site for this purpose (See Section 3.5.3). Nominal p-values will be reported as is. This analysis will be prepared for treatment groups overall, and by surgery type, risk status, randomization strata and subgroups (Tables 14.1.5.2.1 - 14.1.5.2.5).

# 5. EFFICACY ANALYSIS

Not applicable.

# 6. SAFETY AND TOLERABILITY EVALUATIONS

## 6.1. Extent of Exposure

The extent of exposure will be assessed by number of doses of study drug taken. The summary will provide number of subjects (%) who had 1, 2, 3… or 7 doses of study drug in the study by treatment overall, by surgery type, risk status and randomization strata. Percentage will be calculated based on total number of treated subjects in the group (Tables 14.3.1.1 and 14.3.1.2). The table will also provide cumulative statistics for each group.

## 6.2. Adverse Events

### 6.2.1. Adverse Event Summary

Adverse events reported after Dose 1through the final follow-up (LSD+28) will be considered as treatment emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities **(Version 18.1)** will be used to classify all AEs with respect to system organ class (SOC) and preferred term.

The following 7 summaries will be prepared for the TEAEs. All data summaries will provide event rate (number (%) subjects) as well as total number of events in each category. A subject who had same event more than once will be counted only once in the event rate [n (%)] but all events will be included in the total 'Events' column. TEAE summaries are planned for all subjects, by risk status, and by surgery category. If data warrants additional summary by subgroup (combination of risk status and surgery type) may be produced.

1. a topline summary of TEAEs for overall, by risk status, and surgery type, and subgroups (Tables 14.3.2.1.1 – 14.3.2.1.5).
2. a summary table by preferred term displayed in descending order of total events across treatment group in the study for overall, by risk status, and surgery type, randomization strata, and subgroups (Tables 14.3.2.2.1 – 14.3.2.2.5).
3. a summary table by SOC and preferred term in the study for overall, by risk status, surgery type, randomization strata, and subgroups (Tables 14.3.2.3.1 – 14.3.2.3.5).
4. a detailed summary table by system organ class, preferred term and intensity level for overall, by risk status, surgery type, randomization strata and subgroups (Tables 14.3.2.4.1 – 14.3.2.4.5).
5. a detailed summary table by system organ class, preferred term and relationship to study drug for overall, by risk status, surgery type, randomization strata, and subgroups (Tables 14.3.2.5.1 – 14.3.2.5.5).
6. a table of serious TEAEs by system organ class and preferred term for overall, by risk status, and surgery type and randomization strata (Tables 14.3.2.6.1 – 14.3.2.6.2).

7. a table of TEAEs leading to discontinuation of study drug treatment / study by system organ class and preferred term for overall, by risk status, and surgery type (Tables 14.3.2.7).

### 6.2.2. Adverse Event Analysis

#### 6.2.2.1. Adverse Event of Special Interest

A subset of TEAEs will be marked as Adverse Event of Special Interest (AEOSI) for adverse event analysis. The AEOSI may include but are not limited to the following categories:

1) Cardiovascular events
2) Thrombotic events
3) Bleeding-related events
4) Renal events
5) Hepatobiliary events
6) Infusion site related events
7) Wound healing related events

AEOSI will be tabulated by category and AE preferred term for treatment overall, by risk status, surgery type, randomization strata, and subgroup (Tables 14.3.2.8.1 - 14.3.2.8.5).

#### 6.2.2.2. Acute Reactions

Acute Reactions will include all AEs that occurred within 60 minutes (inclusive) of study drug administration. This analysis will require complete onset data/time for AE. Hence, if an AE's onset time is absent this AE will be excluded from this analysis.

To identify these events all TEAEs will be mapped to associated infusion number based on the onset date and time; the elapsed time (minutes) will be calculated between the onset date/time and the corresponding infusion end date/time. If the elapsed time is within 0-60 minutes (inclusive), the event would be flagged as an Acute Reaction. Acute reactions will be identified in the TEAEs from all studies.

Acute Reactions will be tabulated by treatment group for overall, by risk status, surgery type, randomization strata, and subgroups (Tables 14.3.2.9.1 - 14.3.2.9.5).

## 6.3. Clinical Laboratory Tests

Laboratory values, including chemistry, hematology, urinalysis, and coagulation tests, will be collected at screening, 24 hours, Day 1 prior to surgery, at Hour 48 , LSD+1/discharge (if prior to Hour 48, or to be repeated in subjects who receive ≥ 4 doses), and LSD+7.

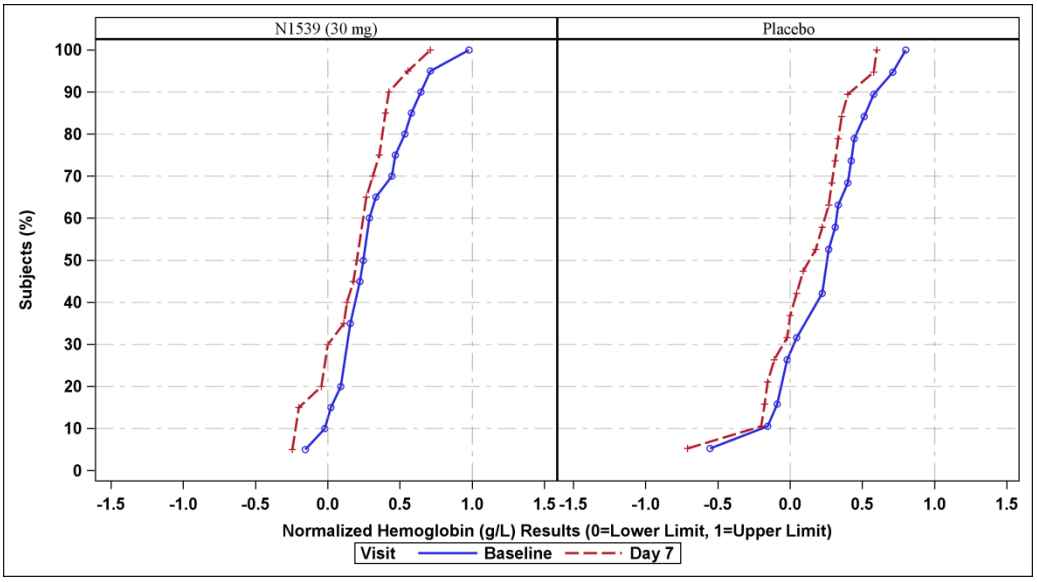
A central lab will be used for this study. To evaluate change in lab test results, the observed value at each time point will be compared to the normal range, expressed as normal range standardized value (NRSDV).

NRSDV = (Observed – NRLO)/(NRHI – NRLO)

Where NRLO = normal range lower limit, NRHI = normal range upper limit, when NRSDV is less than 0, the lab result is lower than the lower limit, whereas when NRSDV is greater than 1 the lab result is greater than the upper limit.

Each lab test result at each time point will be displayed using a cumulative distribution curve. Figure 1 is an example showing the cumulative distribution curves of hemoglobin at baseline and Day 7.

**Figure 1: Example of Hemoglobin Distribution Population Shift Analysis**




When a post baseline NRSDV cumulative distribution curve is on the left of the baseline curve, one concludes that the lab test result is shifted downward in the population. On another hand, if the post baseline curve is on the right of the baseline curve, one concludes that the lab test result is shifted upward in the population.

The significance of the shift will be evaluated based on the degree of shift comparing to the baseline and shift pattern observed in the placebo group. This approach is referred to as the population shift analysis. The population shift curves will be produced for Baseline, End of Treatment and End of Study. Subjects who have 4 or more doses will also have an Hour 48 lab during treatment (see Section 3.4); this time point may be excluded from the analysis if there is not sufficient number of subjects with this data point (Figures 14.3.3.1 to 14.3.3.4).

Unless an unscheduled Lab is served as the Baseline or End of Treatment or End of Study record (see Section3.4) the unscheduled laboratory tests will not be included in the shift analysis, but all lab results will be included in data listing.

### 6.3.1. Analysis of Laboratory Tests of Special Interest

Proportion of subjects with clinically significant abnormal laboratory tests will be identified. The selected laboratory tests and the criteria for clinically significant abnormal results are provided in Table 6. All lab tests, scheduled and un-scheduled will be included for this assessments. This analysis will be an at risk analysis (Tables 14.3.3.5.1 - 14.3.3.5.4).

**Table 6: Abnormal Results in Selected Laboratory Tests of Special Interest**

| Category | Test Name (s) | Category for post baseline result [1] |
|---|---|---|
| Hematology tests | HGB, WBC, PLT, HCT | 1) Shift from Normal to Abnormal, Low<br>2) Shift from Normal to Abnormal, High |
| Renal function tests [2] | BUN,<br>Serum creatinine | 1) >1 to <1.5 times of ULN<br>2) >=1.5 to 3 times of ULN<br>3) ≥ 3 times of ULN |
| Liver function tests [2] | ALT, AST, GGT, ALP | 1) >1 to <3 times of ULN<br>2) >=3 to 10 times of ULN<br>3) ≥ 10 times of ULN |
| | Albumin | 1) Shift from Normal to Abnormal, Low |
| | Total Bilirubin | >1 to <1.5 times of ULN<br>1.5 to <2 times of ULN<br>2 to <2.5 times of ULN<br>2.5 to <3 times of ULN<br>≥ 3 times of ULN |
| Coagulation tests | PTT, PT, INR | 1) Shift from Normal to Abnormal, Low<br>2) Shift from Normal to Abnormal, High |

[1] ULN = Upper limit of normal range; LLN = Lower limit of normal range; ACM Global Central Laboratory was used in Phase 3 studies.

[2] Subjects who had abnormal baseline will be tabulated separately if those subjects had post baseline lab tests that met the criteria in the renal and liver function tests.

## 6.4. Vital Sign Measurements

A vital sign listing will be prepared to display all vital signs measurements (blood pressure, heart rate, and $SpO_2$). Blood pressure will be analyzed visually (Figure 14.3.4.1) by showing the proportion of subjects in each result category and in each change from baseline category as demonstrated in example Figure 2 to Figure 5. In addition, a cumulative distribution plot (Figure 14.3.4.2.1 - 14.3.4.2.2) showing blood pressure percent change from baseline will be produced for each post baseline time point as demonstrated in example Figure 6.

If data warrant, a summary table may be produced to examine number of subjects meeting the PCSC criteria (SBP abs(CFB) ≥ 20 mmHg or DBP abs(CFB) ≥ 15 mmHg or abs(PCFB) ≥25%) at any time, during treatment and during follow-up (ie, post discharge) for treatment group overall, by risk status, and surgery type (Table 14.3.4.3).

**Figure 2: Example of SBP Results Distribution Analysis**

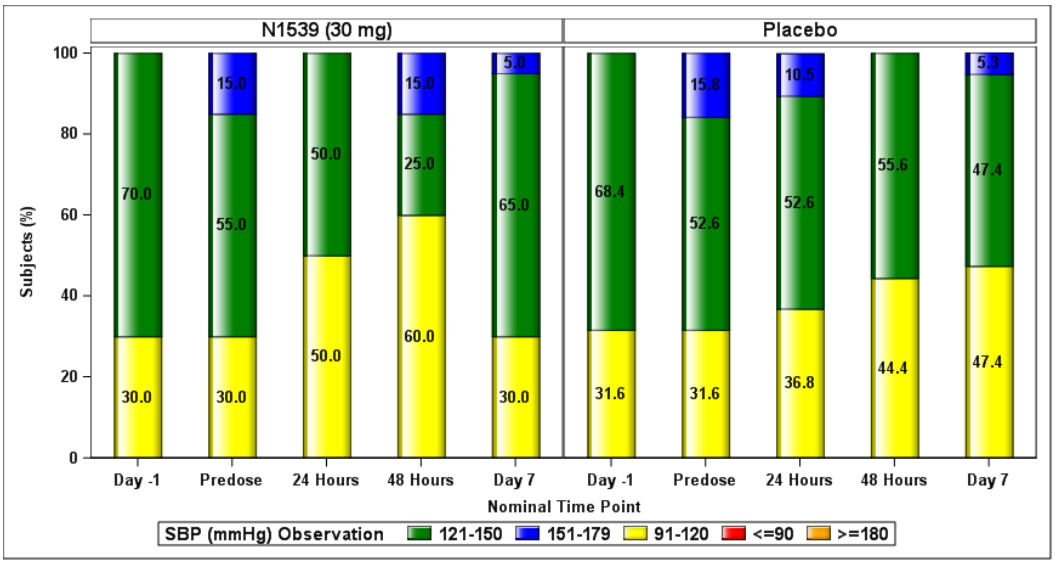



**Figure 3: Example of SBP Change from Baseline Distribution Analysis**

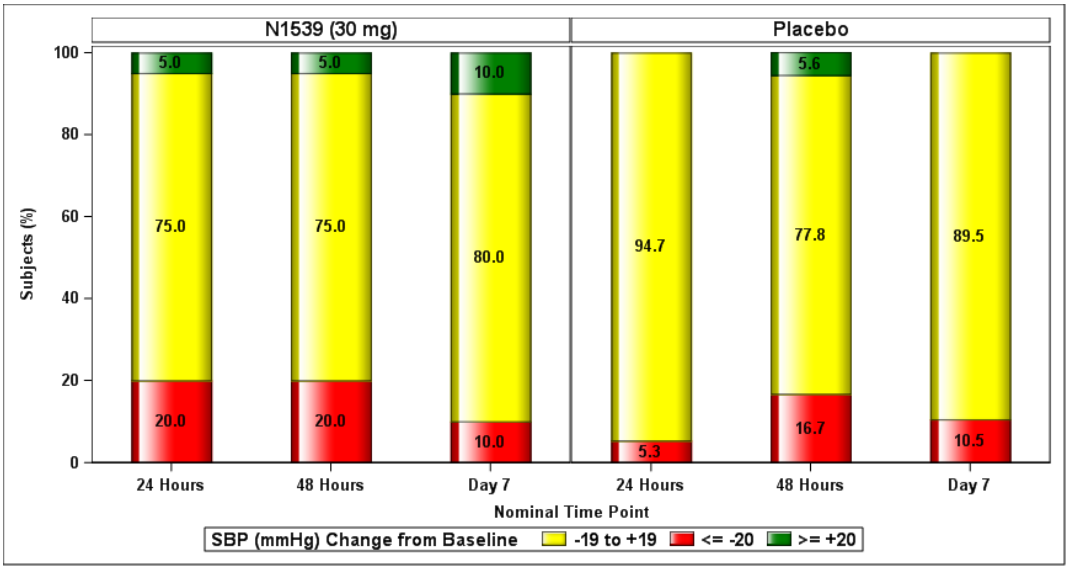


**Figure 4: Example of DBP Results Distribution Analysis**

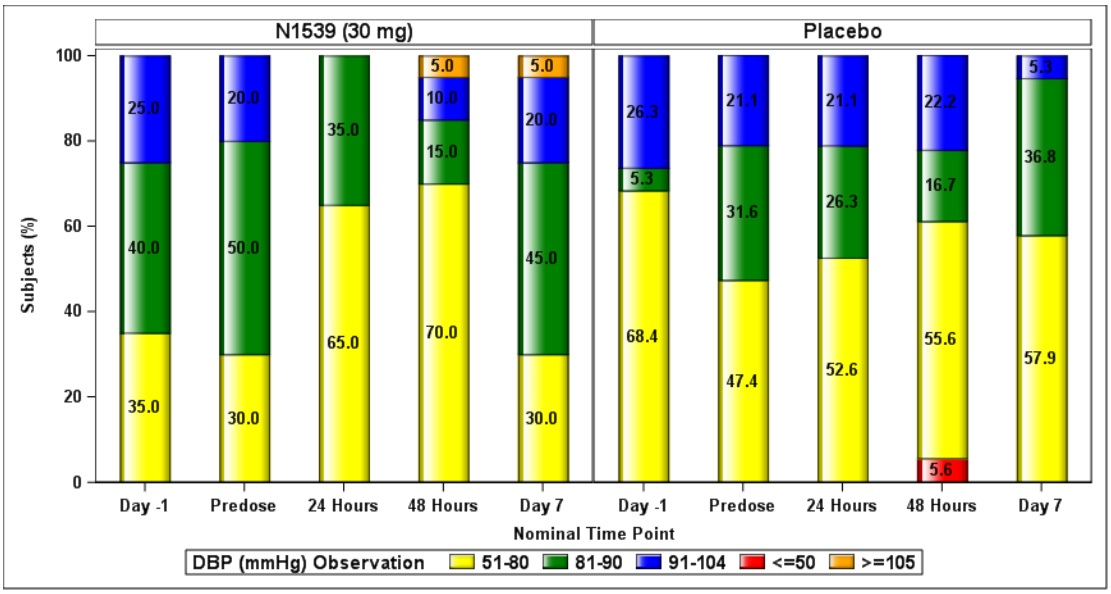



**Figure 5: Example of DBP Change from Baseline Distribution Analysis**

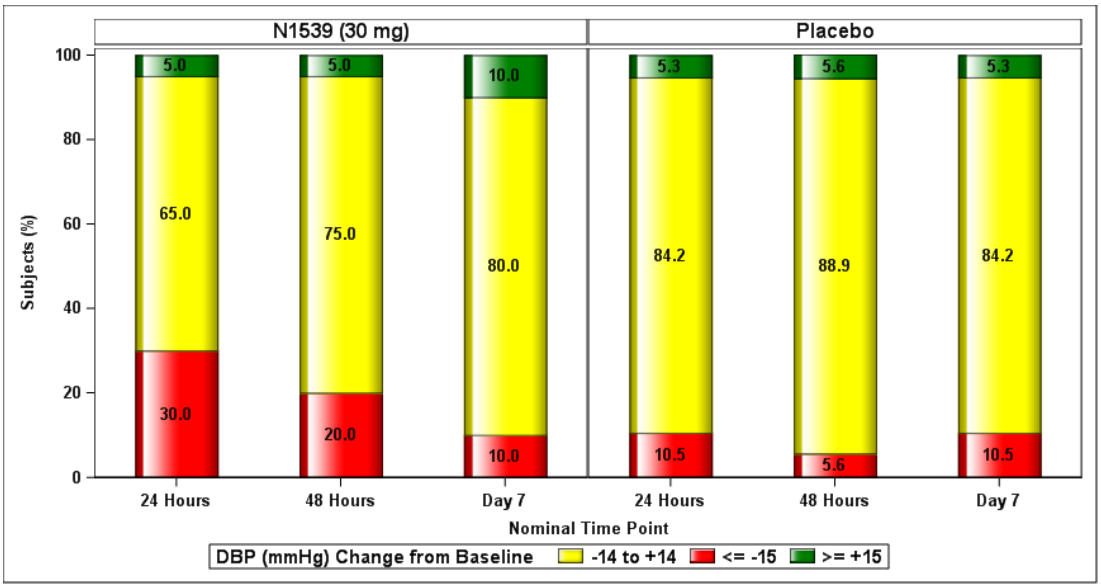
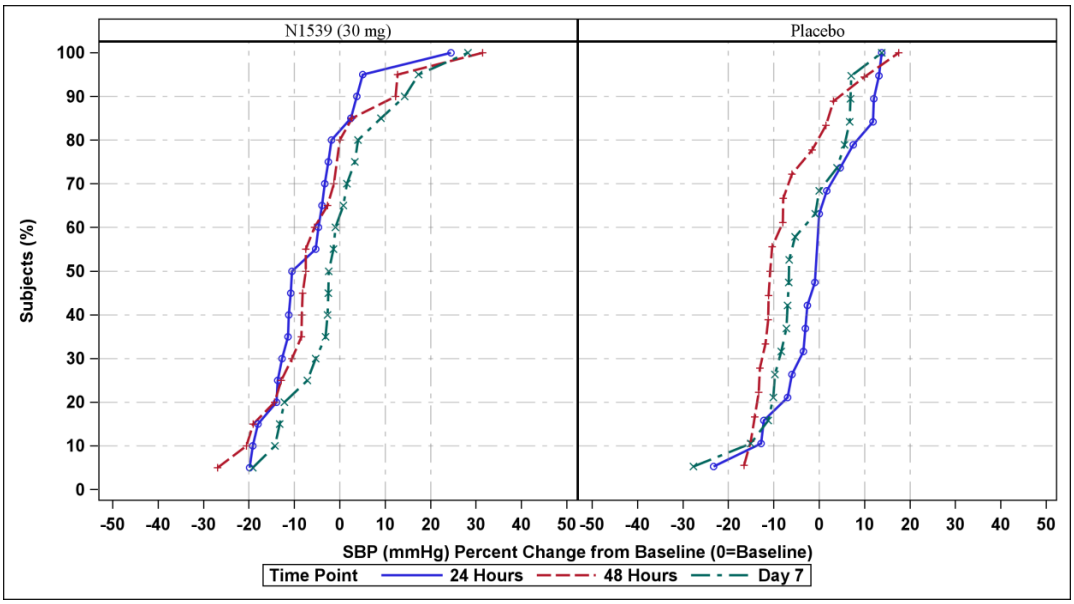


**Figure 6: Example of SBP Percent Change from Baseline Distribution Curves**



## 6.5. Electrocardiograms

12-Lead ECG will be taken at screening, at Check-in, LSD+1 /discharge, LSD+7 and at time of early discontinuation. Clinical interpretation of ECG results will be recorded as normal, abnormal and not clinically significant (NCS), or abnormal and clinically significant (CS). ECG findings at each time point collected will be tabulated by treatment group at analysis visits of Baseline, End of Treatment, and End of Study for overall, by risk status, and by surgery type (Table 14.3.5).

An ECG listing will be prepared and time point where the abnormal ECG is observed will be flagged.

## 6.6. Wound Healing

Wound healing progress will be assessed on LSD+1/ discharge, LSD+7 days, and at time of discontinuation. Wound evaluation assessments will include investigator satisfaction score (0=completely unsatisfied and 10=completely satisfied) performed on LSD+1/discharge, and LSD+7days or discontinuation and surgical wound healing status performed on LSD+7 days or discontinuation only (see Table 7).

Wound healing investigator satisfaction score will be tabulated with descriptive statistics of sample size, mean, standard deviation, minimum, median, and maximum. Grading of erythema, drainage, edema, induration, and hematoma, severity of each symptom, and investigator's judgement of clinical significance will be tabulated by treatment group with n (%) in each grade/category without inferential statistics. A summary will be provided for overall, by risk status, and surgery type (Tables 14.3.6.1 – 14.3.6.6).

A listing will be prepared for wound healing assessments.

**Table 7: Surgical Wound Status Assessment**

| Parameter | Grade | Description |
|---|---|---|
| Erythema | 0 | None |
| | 1 | Very slight (barely perceptible) |
| | 2 | Slight (well defined) |
| | 3 | Moderate |
| | 4 | Severe (beet redness) to slight eschar formation (injuries in depth) |
| Drainage | 0 | None |
| | 1 | Serous |
| | 2 | Serosanguinous |
| | 3 | Bloody |
| | 4 | Purulent |
| Edema | 0 | None |
| | 1 | Very slight (barely perceptible) |
| | 2 | Slight (edges well defined) |
| | 3 | Moderate (raised approximately 1 mm) |
| | 4 | Severe (raised >1 mm and beyond area of exposure) |
| Induration | 0 | None |
| | 1 | Minimal |
| | 2 | Mild (spongy tissue) |
| | 3 | Moderate (firm, warm) |
| | 4 | Severe (hard, red, hot, crepitus) |
| Hematoma | 0 | None |
| | 1 | Minimal |
| | 2 | Mild |
| | 3 | Moderate |
| | 4 | Severe |

## 6.7. Subgroup Analyses for Safety Endpoints

This study employs a stratified randomization based on surgery type and risk status. Hence, study subjects are grouped into 4 subgroups based on their randomization strata.

1) High Risk + Orthopedic Surgery
2) Not High Risk + Orthopedic Surgery
3) High Risk + Other Surgery
4) Not High Risk + Other Surgery

The following subgroups are planned in this study:

A. Subgroup by surgery type (Orthopedic vs Other)
B. Subgroup by risk status (High Risk vs Not High Risk)
C. Subgroup by randomization strata (see above)
D. Subgroup by age (age <65 vs age ≥65 at baseline)
E. Subgroup by sex (male vs female)
F. Subgroup by race (white vs non-white)

Subgroup analyses are already planned for risk status, surgery type and randomization strata for all key safety parameters in this study. The following parameters will also have a table for subgroups of (D) to (F):

- Demographics and baseline characteristics
- Total opioid consumption for pain management
- TEAE, AEOSI, and Acute Reactions

# 7. REFERENCES

None