REC-17-025

A Phase 3b, Randomized, Double-Blind, Placebo-Control, Multicenter, Evaluation of the Safety and Efficacy of N1539 Administered Preoperatively in Open Unilateral Total Knee Arthroplasty

NCT03434275

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

Protocol Number:	**REC-17-025**
Protocol Title:	**A Phase 3b, Randomized, Double-Blind, Placebo-Control, Multicenter, Evaluation of the Safety and Efficacy of N1539 Administered Preoperatively in Open Unilateral Total Knee Arthroplasty**
Date of Original Protocol	**September 29, 2017**
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Date of Protocol Amendment 002	**January 24, 2018**

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LIST OF ABBREVIATIONS AND PHRASES

Abbreviation	Definition
N1539	Injectable NanoCrystal® Colloidal Dispersion (NCD) Meloxicam
AE	adverse event
ANCOVA	Analysis of Covariance
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
EOS	End of Study (POD 30 ± 4 days)
EOT	End of Treatment Period (Discharge or LSD+1, whichever comes first)
Hour 0	Time of End of Surgery (H0)
ICH	International Conference on Harmonization
ITT	Intent-to-treat
IV	Intravenous
IVMED	IV Morphine Equivalent Dose (mg)
Kg	Kilogram
mITT	Modified Intent-to-treat
OBAS	Overall Benefit of Analgesic Score
ODDS	Opioid Distress Dimension Score (a sub domain of OBAS)
PDD	Post discharge day (24-hour period starting time of actual hospital discharge)
PGA	Patient Global Assessment
PI	Pain Intensity Score
POD	Post-operative day (number of calendar day(s) after surgery date)
PSD	Post-surgery day (a 24-hour period starting end of surgery)
LSD	Last Study Drug Dose
LSD+1	24 hours after the last dose
mL	Milliliter
NPRS	Numeric Pain Rating Scale
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SPI	Summed of time weighted pain intensity

Abbreviation	Definition
SPI_{AA}	Summed of time weighted pain intensity from Time 0 to first assisted ambulation
SPI_{IA}	Summed of time weighted pain intensity from Time 0 to first independent ambulation
SPI_{DC}	Summed of time weighted pain intensity from Time 0 to hospital discharge
TEAE	Treatment emergent adverse event
Time 0	Time of First Dose (T0)
TTE	Time to Event
µg	Microgram
µL	Microliter

IN-TEXT TABLES

1. INTRODUCTION AND SCOPE

Protocol REC-17-025 is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of preoperative dosing with N1539 30 mg in adult subjects undergoing open unilateral total knee arthroplasty surgery. The study will enroll approximately 200 subjects randomized (1:1) to N1539 30 mg or placebo.

This Statistical Analysis Plan (SAP) is intended to provide a more technical and detailed elaboration of the principal statistical features stated in the protocols. 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-17-025: Amendment 2, January 24, 2018
- REC-17-025 eCRF Completion Guidelines Version 3.0 dated October 22, 2018
- REC-17-025 eCRF Version 3.0 dated June 7, 2018

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 protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol.

2. OVERVIEW OF STUDY OBJECTIVES AND ASSESSMENTS

The primary objective of this study is to assess the effect of preoperative administration of N1539 on opioid consumption in subjects undergoing open unilateral total knee arthroplasty compared to placebo.

Secondary objectives are to assess:

- The safety and tolerability of preoperative administration of N1539 compared to placebo
- The effect of preoperative administration of N1539 on postoperative pain compared to placebo
- The effect of preoperative administration of N1539 on healthcare utilization costs compared to placebo.

Each subject is expected to receive at least two doses of study drug, with the first dose (**T0**) to be administered following the administration of spinal anesthesia and before the start of surgery (ie, time of first incision) according to randomization. Additional doses of study drug will be administered every 24 hours (±1 hour) after the first dose. Dosing will continue until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically appropriate.

After first dose of study drug, all subjects will then undergo the surgical procedure according to the investigator's clinical practice and in accordance with institutional standards. At the end of the surgical procedure (**Hour 0,** defined as the time of last suture, staple, or steri-strip placement) and through hospital discharge, postoperative pain management will be according to the protocol; other standard of care procedures associated with the surgical procedure will be carried out according to the investigator's clinical practice and in accordance with institutional standards.

Subjects will remain as inpatients for at least 24 hours or until inpatient care is no longer clinically indicated. Upon discharge, subjects will be provided a standard of care regimen for pain management and for physical therapy as determined by the investigator.

Twenty-four hours and 48 hours after hospital discharge qualified study staff will conduct telephone interviews to assess opioid medication use, pain intensity, physical therapy visits, and utilization of healthcare resources (ie, hospital readmission, use of skilled nursing facilities, unscheduled phone calls and/or office visits related to pain, and emergency room [ER] visits related to pain and/or other medical issues). An office follow-up visit is to be scheduled on Post-operative day (POD) 10-14 days and a final telephone interview will be conducted onPOD 30 to assess for AEs, opioid use, and utilization of healthcare resources. After the POD 30 telephone interview, subjects will be discharged from the study.

Assessments of efficacy will include total opioid consumption, pain intensity according to an 11-point numeric pain rating scale (NPRS; 0 - 10) at a set of predefined time points, before and during ambulation, before use of any rescue analgesic, and at time discharge, Patient Global

Assessment (PGA) of pain control, Overall Benefit of Analgesia Score Questionnaire (OBAS), and a panel of healthcare utilization assessments.

Study safety assessments will monitor adverse events, change in clinical laboratory tests, and wound healing assessments. Study procedure schedule (Protocol Appendix A) is included here for the convenience of review

APPENDIX A: STUDY ASSESSMENTS: PROTOCOL REC-17-025

	Screening	Surgery (Day 1) Through Hospital Discharge or LSD+1, whichever occurs first			Hospital Discharge	Telephone Interview	Follow-up Visit	Telephone Interview
	Day 28 to Day -1	Preoperative	Intraoperative (End of Surgery= Hour 0)	Postoperative Hour 0 Through Hospital Discharge or LSD +1		24 Hours and 48 Hours Post-Discharge	POD 10 to Day 14	POD 30 ± 4 days
Informed consent	X							
Eligibility assessment	X	X						
Demographics and medical history	X	X (update)						
Prior/concomitant medications/procedures	X	X	X	X[c]	X	X	X	X
Physical examination	X	X					X	
12-Lead electrocardiogram	X							
Vital signs	X[b]	X[b]						
Clinical laboratory testing	X (local lab)	X			X		X, if indicated	
Urine pregnancy testing	X	X						
Randomization		X						
Perioperative medications		X[c]	X[c]					
Intrathecal anesthesia (spinal)		X[f]						
Study drug administration		X[f]		Q24H from Dose 1[f,g]	X[g]			
PI assessment				X[h]	X	X	X	X
Opioid pain medication				X[h]	X	X	X	X
Physical therapy				X[h]		X	X	X
Ambulation				X[h]				
PGA of pain control				Each postop day starting with POD 1[i]				
OBAS				Each postop day starting with POD 1[i]				
Wound healing assessment					X		X	
Serious adverse events only	X							
Adverse events		X	X	X[c]	X	X	X	X
Healthcare utilization[j]						X	X	X

IV=intravenous; OBAS=Overall Benefit of Analgesia Score Questionnaire; PGA=Patient Global Assessment; PI=pain intensity; PO=by mouth; POD=postoperative day

a Through hospital discharge.
b Vital signs after the subject has rested (seated/supine) for ≥5 minutes. Results will be used to determine subject eligibility.
c Acetaminophen 650 PO, gabapentin 600 mg PO, tranexamic acid 1 g IV, and prophylactic IV antibiotic 30 to 90 minutes before start of surgical procedure. Subjects will continue to receive acetaminophen 650 mg PO Q8H through LSD+1. Venous thromboembolism prophylaxis before and after surgery according to standard practice, based on the subject's individual needs, at the discretion of the investigator and surgeon, and taking into consideration the ACCP and AAOS guidelines for orthopedic surgery.
d Local infiltrate prior to wound closure.
e Prior to start of surgical procedure.
f Dose 1 is to be administered after spinal anesthesia and before the start of the surgical procedure. Subsequent doses may be administered Q24±1 hours from Dose 1.
g At the discretion of the investigator.
h PI will be assessed upon arrival at the PACU, at various scheduled timepoints relative to first dose of study drug, before each administration of opioid medication (Time 0 through hospital discharge or LSD+1, whichever first), before and during each ambulation (Time 0 through hospital discharge or LSD+1, whichever first), before hospital discharge, 24 hours and 48 hours after discharge, POD 10 to 14, and POD 30 (Section 6.2.6).
i Through hospital discharge or LSD+1, whichever occurs first.
j Hospital readmission, use of skilled nursing facilities, unscheduled phone calls or office visits related to pain, and ER visits related to pain.

2.1. Study Endpoints

2.1.1. Efficacy Endpoints

The primary efficacy endpoint is total use of opioid analgesia from Hour 0 through 24 hours.

Secondary endpoints include:

1. Sum of pain intensity from the time of first dose of study drug through 24 hours (SPI_{24})
2. Percentage of subjects who are opioid free from Hour 0 through 24 hours
3. Time to first use of IV or oral opioid analgesia

Other efficacy endpoints include:

1. Total use of opioid analgesia from first dose of study drug through 24 hours (before 2nd dose of study drug)
2. Total use of opioid analgesia from Hour 0 through 48 hours
3. Total use of opioid analgesia from Hour 0 through hospital discharge
4. Total use of opioid analgesia from hospital discharge through 24-hour telephone interview
5. Total use of opioid analgesia from the 24-hour telephone interview through the 48-hour telephone interview
6. Percentage of subjects that are opioid free from Hour 0 through 48 hours
7. Percentage of subjects that are opioid free from Hour 0 through hospital discharge
8. Percentage of subjects who used any opioid medication after hospital discharge through POD 30.
9. Time to first IV opioid medication defined as the time from Hour 0 until time of first use of IV opioid medication
10. Time to first oral opioid rescue medication defined as the time from Hour 0 until time of first use of oral opioid medication
11. Pain intensity during first assisted ambulation
12. Pain intensity during first unassisted ambulation
13. SPI from time of first dose of study drug through first assisted ambulation
14. SPI from time of first dose of study drug through first unassisted ambulation
15. SPI from time of first dose of study drug through 48 hours
16. SPI from time of first dose of study drug through hospital discharge or LSD+1, whichever comes first

17. Time to first assisted ambulation defined as the time from Hour 0 until time when first assisted ambulation occurs
18. Time to first unassisted ambulation defined as the time from Hour 0 until time when first unassisted ambulation occurs
19. Patient Global Assessment (PGA) of pain control on 5-point categorical scale on each postoperative day, starting on POD 1 and continuing through hospital discharge or LSD+1, whichever occurs first.
20. The OBAS total score and opioid distress dimension subscore on each postoperative day, starting on POD 1 and continuing through hospital discharge or LSD+1, whichever occurs first
21. Pain intensity at the following follow-up time points: 24 hours and 48 hours post discharge, and POD 10-14, and POD 30

2.1.2. Healthcare Utilization Endpoints

Healthcare utilization endpoints include:

1. Length of hospital stay defined as days from hospital admission until the hospital discharge order is written.
2. Total cost of hospitalization (taken from the UB-04/hospital claims form)
3. Duration of time in the PACU (time in through time out of PACU)
4. Percentage of subjects with hospital readmission through POD 30
5. Total number of postsurgical physical therapy visits through POD 30
6. Percentage of subjects who required a skilled nursing facility from hospital discharge through POD 30
7. Total time spent in skilled nursing facility from hospital discharge through POD 30
8. Percentage of subjects who made a phone call related to postsurgical pain from hospital discharge through POD 30
9. Total number of phone calls per subject related to postsurgical pain from hospital discharge through POD 30
10. Percentage of subjects who had an unscheduled visit related to postsurgical pain from hospital discharge through POD 30
11. Total number of unscheduled visits per subject related to postsurgical pain from hospital discharge through POD 30
12. Percentage of subjects who had an emergency room visit for postsurgical pain from hospital discharge through POD 30
13. Total number of visits to the emergency room per subject for postsurgical pain from hospital discharge through POD 30

Note: tabulation for the Health Utilization endpoints will be covered by this SAP; a separate analysis pertaining to the cost elements of the Health Care Utilization endpoints will be covered by a separate analysis plan.

2.1.3. Safety Endpoints

The safety endpoints include

1. Incidence of treatment-emergent adverse events (TEAEs)
2. Incidence of potentially clinically significant abnormal clinical laboratory values
3. Investigator satisfaction with wound healing before hospital discharge and during the follow-up visit (POD 10 to 14).

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 randomized subjects. This dataset may 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.

Efficacy Set: The efficacy population will consist of all subjects who receive at least one injection of study drug and have the scheduled surgery. This is also referenced as the modified intent-to-treat (mITT) Analysis Set. All efficacy evaluations will be based on the mITT population.

3.2. Test Hypothesis and *P* Value Justification

The null hypothesis is that there is no difference between N1539 30 mg and placebo groups. The alternative hypothesis is that the treatment groups are different.

Differences between N1539 30 mg dose and placebo group will be evaluated via a 2-sided 2-sample t-test at the 0.05 level of significance. Nominal p-values will be reported as is.

3.3. Procedures for Handling Missing Data

Missing data imputation rules for pain intensity will be discussed extensively in Section 3.5.

No missing data imputation will 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. Analysis Center

This is a multicenter study; investigative center will be included in the analysis model as a covariate. Centers with small enrollment may be pooled to form an analysis center. The final decision on pooling will be made prior to database hard lock.

3.5. Definitions and Derived Variables

3.5.1. Definitions

To facilitate the opioid consumption data summary, the following phrases and definitions are introduced.

3.5.1.1. Study Period

The study duration for each subject is divided into 4 periods

1. Screening Period: The duration from signing informed consent until before receiving the first dose of study drug will be described as the screening period. **The last measurement taken prior to receiving the first dose of study drug is the Baseline measurement.** Hence, **Baseline measure could be either a scheduled assessment or an unscheduled assessment.**
2. Peri-operative period: this period starts when the subject receives the first dose of study drug and ends at time of end of surgery (T0 to H0).
3. Post-operative period: postoperative period starts at the end of surgery and ends when the subject is discharged from the hospital or when the subject has reached 1 day after the last dose of study drug (LSD+1) timepoint before being discharge from the hospital.
    a. Post-Surgery Day (PSD): A post-operative day is a 24-hour period from the time of end of surgery. Hence, a PSD start time and stop time varies from subject to subject, depending on the time of surgery stop time.
    b. In-patient period: This period starts at the end of surgery to actual hospital discharge. This period is used to determine if a subject is at risk for opioid consumption analysis.
4. Post discharge period: this period starts after the subject is discharged from the hospital through end of study.
5. End of Study period (EOS): end of study for a subject is the last follow up visit (POD 30 ± 4 days)

3.5.1.2. Treatment Period and Time of End of Treatment

The treatment period covers the duration from the date/time of the first dose of study drug (**T0**) through 24 hours after the last dose of study drug (**LSD+1**). However, it is expected that, for the majority of subjects, the treatment period ends when the subject is discharged from the hospital. Hence, the treatment period would be described as the time period from the first dose (T0) through hospital discharge or LSD+1, whichever comes first.

Time of End of Treatment Period (EOT) for a subject could be mathematically expressed as

Time of EOT =min (date/time of discharge, data/time of LSD+1), where min is the function of minimal.

3.5.1.3. Time 0 and Hour 0

Time 0 (T0) is referred to the date/time of first dose of study drug, whereas **Hour 0** (H0) is referred to the date/time of End of Surgery. **Hour 0** is typically used as the starting point for postoperative measurements, for example, opioid consumption (see Section 3.5.4 for details) and time to rescue and time to ambulation; **T0** is used to schedule pain intensity assessments at scheduled time points (see Section 3.5.10).

3.5.2. Analysis Visit

Efficacy data will be mapped to Analysis Visit using the following benchmarks:

1. Relative to the time of end of surgery. A 24-hour period is referred to as a Post-surgery Day (PSD). This analysis will be based on the assessment date and time and the reference point is end of surgery (H0).
2. Relative to the surgery date. This analysis will be based on the assessment date only and will be referred to as the Post-operative Day (POD) where the date of surgery is POD 0.

Analysis visit (POD vs PSD) will be clearly spelled out for each efficacy endpoint. The difference between POD and PSD can be illustrated in the following 3 examples.

1. In example 1 the assessment time was within 24 hours after the end of surgery, therefore it is assigned to PSD 1 for Post-surgery Day analysis; and the date of the assessment was the same date of surgery, therefore, the POD=0 is assigned.
2. In example 2 the assessment time was > 24 and <48 hours after the end of surgery, therefore it is assigned to PSD 2 for Post-surgery Day analysis; but the date of the assessment was 1 day after the date of surgery, therefore, the POD 1 is assigned for Post-operative Day Analysis.
3. In example 3 the assessment time was >48 and less than 72 hours after the end of surgery, therefore it is assigned to PSD 3 for Post-operative Day analysis; and the date of the assessment was 2 days after the date of surgery, therefore, the POD 2 is assigned for Post-surgery Day Analysis.

Table 1: Analysis Visit Using Post-operative Day and Post-surgery Day

Example	End of Surgery Time	Assessment Time	Post-Surgery Day	Post-Operative Day
1	2018-03-12T11:01	2018-03-12T16:45	PSD 1	Surgery Day (POD 0)
2	2018-03-12T11:01	2018-03-13T18:45	PSD 2	POD 1
3	2018-03-12T08:05	2018-03-14T12:05	PSD 3	POD 2

3.5.3. Subjects at Risk

A subject is at risk if the subject is still available for assessment. This concept is used for several analyses that pertain to a period. For example, for analysis of opioid consumption from Hour 48 to Hour 72 after end of surgery, if a subject has been discharged before Hour 24, this subject will be considered 'Not At Risk' for H48-72 hour opioid consumption. Table 2 provides examples of subjects at risk for 13 periods used in the opioid consumption analysis.

Table 2: Subjects at Risk for 16 Periods Defined for Opioid Summary

ID	Interval / Period	Subject at Risk
1	Pre-operative Period	mITT subject
2	Intra-operative Period	mITT subject
3	T0 - H0 (Perioperative)	mITT subject
4	T0 to T24 (Excluding Dose 2)	mITT subject
5	H0 - H24 (PSD 1)	mITT subject
6	H24 - H48 (PSD 2)	mITT subject with in-patient duration ≥24 hours
7	H48 - H72 (PSD 3)	mITT subject with in-patient duration ≥48 hours
8	H0 - H48 (PSD 1-2)	mITT subject
9	H0 - H72 (PSD 1-3)	mITT subject
10	H0 - EOT (postoperative)	mITT subject
11	0-24 hours post discharge	mITT subject who was discharged
12	24-48 hours post discharge	mITT subject who was discharged
13	0-48 hours post discharge	mITT subject who was discharged
14	24 hours before POD 10-14 visit	mITT subject who was discharged
15	EOT - EOS (post discharge to EOS)	mITT subject who was discharged
16	Total in Study	mITT subject

3.5.4. Total Opioid Consumption in IVMED (mg)

All concomitant medications will be coded according to WHO Drug library. Opioid medications 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; examples of IVMED of some commonly used analgesics are provided in Table 3.

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
Alfentanil	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

The eCRF page for opioid medications uses the following indications to identify study periods:

- Intraoperative: All opioids used before and during the surgery, the opioid used before surgery includes all opioids used after the first dose of study drug; this corresponds to the peri-operative period defined in Section 3.5.1.
- Rescue: all opioids used during the in-patient period defined as end of surgery to hospital discharge or LSD+1. This corresponds to the post-operative period defined in Section 3.5.1.

- Pain management: opioids used post hospital discharge or post LSD+1 until end of study. This corresponds to the post-discharge period defined in Section 3.5.1.
- Medical history: opioids taken for medical history events
- Other: opioids that do not fall under any of the above 4 categories

Opioids for medical history events are excluded from the total opioid consumption analysis. The opioids with indication of 'OTHER' may be excluded depending on the specification. Those records (MEDICAL HISTORY + OTHER) will be reviewed carefully and queried if there are any doubts/questions on records prior to exclusion.

3.5.5. Missing Date/time Imputation for Opioid Records

After all efforts to clean up the database, if date or time is missing for opioid medications, the following rules will apply during programming to create the analysis dataset.

1. **If start and stop dates are unknown, the record will be queried and excluded if confirmed**.
2. If a partial date/time is entered and the indication is not 'Medical History' the following imputation rules will be applied:

- If start date is present and stop date is missing, the stop date is set to be the start date and vice versa.
- When the start date and stop date are present:
    1. If start date is equal to the stop date
        i. If the start time is missing but the stop time is present, the start time is set to be the stop time and vice versa.
        ii. When both start and stop times are missing:
            1) If indication is **Intraoperative**: missing start time is set 1 minute after surgery start time and missing stop time is set to 1 minute before surgery stop time.
            2) If indication is **Rescue**: If date=surgery date: missing start and stop start time will be set to 1 minute after end of surgery. If date > surgery date: missing start time will be set to 00:01 and missing stop time will be set to 23:59.
            3) If indication is **Pain Management:** If date=discharge date: missing start and stop start time will be set to 1 minute after discharge time. If date > discharge date: missing start time will be set to 00:01 and missing stop time will be set to 23:59.

2. When start date is not equal to stop date:
    i. If start time is missing:
        1) If indication is **Rescue** and start date=surgery date then missing start time will be set to 1 minute after end of surgery
        2) If indication is **Rescue** start date > surgery date the missing start time will be set to 00:01.
        3) If indication is **Pain Management** and start date=discharge date: missing start time will be set to 1 minute after discharge time.
        4) If indication is **Pain Management** and start date >discharge date: missing start time will be set to "00:01".
    ii. If stop time is missing:
        1) If indication is **Rescue** and stop date = surgery date the missing stop time will be set to 1 minute after end of surgery.
        2) If indication is **Rescue** and stop date > surgery date the missing stop time will be set to 23:59.
        3) If indication is **Pain Management** and stop date=discharge date: missing stop time will be set to 1 minute after discharge time.
        4) If indication is **Pain Management** and stop date >discharge date: missing stop time will be set to 23:59.

After all the opioid records that have the appropriate start and stop time, the start and stop time relative time (hours) to Hour 0 (end of surgery) or discharge will be determined for each record. **Total dose will be calculated for the following time points. Note: if a record indicates that the start and stop time extends beyond one period, the total dose from this record will be split into appropriate period using linear interpolation of hourly dose.**

Table 4: Definition of Opioid Consumption Period

ID	Time Interval	Interval Description	Interval Expression [1]
1	Pre-operative Period	From hospital admission to surgery start	[ADM, SGST)
2	Intra-operative Period	From surgery start to surgery end	[SGST, SGEN]
3	T0 - H0	From first dose start time to end of surgery	[FSD, SGEN]
4	T0 to T24 (Excluding Dose 2)	From first dose start time to but not include the second dose start time	[FSD, SSD)
5	H0 - H24 (PSD 1)	From surgery stop time to 24 hours after end of surgery	(SGEN, SGEN+24]
6	H24 - H48 (PSD 2)	From 24 hours after end of surgery to 48 hours after surgery	(SGEN+24, SGEN+48]
7	H48 - H72 (PSD 3)	From 48 hours after end of surgery to 72 hours after surgery	(SGEN+48, SGEN+72]
8	H0 - H48 (PSD 1-2)	From end of surgery to 48 hours after surgery	(SGEN, SGEN+48]
9	H0 - H72 (PSD 1-3)	From end of surgery to 72 hours after surgery	(SGEN, SGEN+72]
10	H0 - EOT	From end of surgery to end of treatment	(SGEN, EOT]
11	0-24 hours post discharge	From discharge to 24 hours after discharge	(ADC, ADC+24]
12	24-48 hours post discharge	From 24 hours post discharge to 48 hours post discharge	(ADC+24, ADC+48]
13	0-48 hours post discharge	From discharge to 48 hours after discharge	(ADC, ADC+48]
14	24 hours before POD 10-14 visit	24 hours before POD 10-14 telephone interview	[POD10-24, POD10]
15	EOT - EOS	From end of treatment to end of study	(EOT, EOS]
16	Total in Study	From hospital admission to end of study	[ADM, EOS]

[1] Abbreviations for intervals in (hours):
ADM: hospital admission date/time;
SGST=surgery start date/time;

SGEN=surgery stop date/time;
FSD=study drug first dose start date/time;
SSD=study drug second dose start date/time;
ADC=actual hospital discharge date/time;
EOT=end of treatment date /time, defined as hospital discharge date/time or LSD+1, whichever comes first) and LSD+1 is 24 hours after the last dose of study drug, hence, LSD+1 = last dose date/time + 24 hours
POD10= POD 10-14 telephone interview date. **Because the time of interview is not captured, the analysis will be based on the calendar date. Any records with date of the interview and the date before the interview will be included.**
EOS=end of study date/time; where the end of study visit date is the POD 30 telephone interview date and the time is set to 23:59
The square brackets, [ ], means inclusive whereas the parentheses, ( ), means exclusive

3.5.6. Opioid Free Subjects

A subject who did not use any opioids is classified as an opioid free subject. The status of opioid free (OPFREE = Yes/No/NA) will be determined for each period based on the following rules:

In-Patient Phase (Intervals 1 to 10):

1. If any opioid records are found in the opioid concomitant medication page for corresponding period regardless if the total dose was known or unknown, the subject is assigned OPFREE=No; otherwise, OPFREE=Yes.
2. If a subject is discharged from hospital (based on actual discharge date/time) prior to the start of a period (e.g., H48-H72 period), the subject is assigned to OPFREE=NA for this period (Not at risk).

Post-Discharge Phase (Intervals 11 to 14):

1. Post discharge telephone interviews are to be done at 24 hours and 48-hours post discharge, an in-person office visit on POD10-14, and a final telephone interview on POD 30. Subject is asked if any of the opioid medication prescription given to the subject at discharge for pain related to surgery since discharge (at 24 hour post discharge call) or since last study contact (at other 3 follow-up call or visit) The response to this question will be used to determine the opioid free status for post discharge time point regardless if the total dose was or was not captured on the eCRF.
2. If any opioid records found on the opioid page that corresponds to the defined interval for a subject: the subject is considered Not opioid free for that interval regardless if the total dose is known or unknown.

3.5.7. Time to First Rescue

Rescue opioid (IV opioid or oral opioid analgesic) will be those opioid records with 'Rescue' as the indication in the database.

Time (hours) from first dose to the start time of the rescue opioid will be calculated for each opioid record.

Time (hours) = start date/time of analgesics – date/time of end of surgery (Hour 0)

A rescue opioid record without a start date and/or start time (although those records may have imputed date/time) will be excluded from the time to rescue analysis in general with one exception, that is, if this is the only record for this route of administration then this record will be included. In this case, the imputed missing date/time will be used. See Section 3.5.5 for missing date/time imputation rules.

Following the determination of the time from end of surgery (Hour 0) to the rescue start time for each rescue record the following data derivations will be performed:

1. when a subject has both IV and oral rescue opioid records, the time to first rescue (IV or Oral) will be the first rescue record based on the start time, mathematically, it can be expressed as

   Time to first rescue = min (time to first IV rescue, time to first oral rescue) if both events have occurred.

2. When a subject did not have any IV rescue opioid but have oral rescue opioid:
   - This subject will not be censored for the time to first rescue (IV or Oral) analysis; time to first rescue will be set to be the same as the time of first oral rescue
   - This subject will be censored for time to first IV rescue. The censored time will be date/time of first oral rescue.
3. When a subject did not have any Oral rescue opioid but have IV rescue opioid:
   - the time to first rescue (IV or Oral) will be set to the time to first IV rescue opioid (subject is not censored)
   - this subject will be censored to EOT for the time to first oral rescue analysis.
4. When a subject does not have any rescue opioid records:
   - this subject will be censored for all 3 time to rescue endpoints. The censored time will be EOT.

3.5.8. Missing Date/time Imputation for Ambulation Records

Each time a subject ambulates, the eCRF will record the following information

1. ambulation type [assisted vs unassisted (ie, independent)]
2. pre-ambulation PI score and assessment date/time.
3. the worst pain score during walk and assessment date/time

The assessment date/time of the pain score prior to ambulation is used as the proxy for this ambulation start date/time. Time to First Ambulation will be derived from this field. When an ambulation occurs but the PI assessment was not performed, the date/time of ambulation will be captured in the comments field; hence, programming effort will be used to extract this information from the comments for this analysis.

The following rules will apply for partial date/time of an ambulation record:

- If assessment time for pain score prior to ambulation is unknown but the assessment time for 'The worst PI score during the ambulation' is known, the missing time for prior to ambulation PI score will be set to 15 minutes BEFORE the time for the worst PI score. For example, if the worst pain assessment time is 11:00, the imputed time pain score prior to ambulation will be 10:45.
- If assessment time for the worst pain score during an ambulation is unknown, the assessment time for prior to ambulation is known, the missing time for the worst pain score will be set to 15 minutes AFTER the assessment time for the pain score prior to this ambulation. For example, if the pain prior to ambulation assessment time is 11:00, the imputed assessment time for the worst pain during ambulation will be 11:15.
- If both assessments have unknown times (time of pain prior to ambulation and time of the worst pain during the ambulation), the ambulation record will be EXCLUDED from the time to first ambulation analysis (see Section 3.5.9). This record will also be EXCLUDED from the Sum of Pain Intensity analysis (See Section 3.5.10). But the ambulation record will be INCLUDED in the total number of ambulation analysis (see Section 5.3.3).

3.5.9. Time to First Ambulation

Ambulation records with partial time will be imputed using the rules specified in Section 3.5.8**.** Time (hours) from first dose to each ambulation record will be determined as follows:

Time (hours) = date/time of ambulation – date/time of end of surgery (Hour 0)

The first assisted ambulation record and the first independent ambulation record will be identified for each subject. The following rules will be applied when:

- a subject did not have any assisted ambulation records, but this subject has records for independent ambulation, this subject will not be censored for time to assisted ambulation. The time of assisted ambulation will be set to the same as time to first independent ambulation for analysis.
- a subject has assisted ambulation records, but this subject did not have records for unassisted ambulation, this subject will be censored for time to first independent ambulation. The censored time will be the time of EOT.
- a subject does not have any ambulation event (response on eCRF for ambulation was 'None'), this subject will be censored at EOT for both time to assisted ambulation and time to independent ambulation.

3.5.10. Sum of Pain Intensity (SPI)

A total of 14 pain intensity scores are scheduled: 13 PI scores are to be collected within the first 48 hours after end of surgery plus a PI score at the time of hospital discharge. The time points for scheduled PI scores include

- Upon arrival at the PACU
- Time points relative to first dose of study drug (Time 0): 4 hours ± 15 minutes, 6 hours ±15 minutes, 8 hours ± 30 minutes, 10 hours ± 1 hour, 12 hours ± 1 hour, 16 ± 1 hour, 20 hours ± 1 hour, 24 hours ± 1 hour (before study drug administration, if indicated), 30 hours ± 2 hours, 36 hours ± 2 hours, 42 hours ± 2 hours, and 48 hours ± 2 hours (before study drug administration, if indicated), when the subject is awake
- Before hospital discharge

In addition, unscheduled PI assessments will be performed prior to use of rescue analgesic; PI will also be assessed prior to each ambulation attempt, and the worst pain intensity during an ambulation will also be collected; however, the worst pain score during ambulation will not be included in the SPI analysis.

In order to calculate the weight for SPI, the assessment time from each pain score is required. When the assessment time for a non-missing pain score is unknown, the following rules will apply:

- If it is one of the scheduled pain assessments the nominal time will be used. For example, Hour 8 pain score nominal time is 8 hours after the first dose of study drug.
- If it is a PI score prior to use of rescue opioids, and the opioid medication start time is non-missing, the medication start time will be used as the assessment time of this PI score. If the medication start time is also missing, and the missing time was imputed for opioid consumption, the imputed medication start time will be used. If the missing time was not imputed, then the pain score will be EXCLUDED from the analysis.

- If the pain score prior to ambulation has unknown assessment time the imputed ambulation start date/time will be used (see Section 3.5.8). If both assessments had missing time (time of pain prior to ambulation and time of the worst pain during the ambulation), the ambulation record will be EXCLUDED from the Sum of Pain Intensity analysis.

Sum of PI score (SPI) is time-weighed cumulative pain intensity from first dose. The weight factor at each time point is the time elapsed since the previous observation. SPI for this study will be derived for the following intervals

- Time 0 to time of first assisted ambulation (inclusive), this will be referred to as SPI_{AA}. The last PI score for this parameter will be the PI score prior to the first assisted ambulation. Subjects who do not have any assisted ambulation but who have independent ambulation will be based on time to first independent ambulation. Subjects who do not have any ambulation attempts will be excluded.
- Time 0 to first independent (unassisted) ambulation (inclusive); this will be referred to as $SPI_{IA.}$ The last PI score for this parameter will be the PI score prior to first independent ambulation. Subjects who did not have any independent ambulation attempts will be excluded.
- Time 0 to hospital discharge. This will be referred to as SPI_{DC}. SPI_{DC} will include all PI scores collected from this subject prior to hospital discharge.

SPI is mathematically expressed as

$SPI_p = \sum (PI_t \bullet W_t)$, where PI_t is the pain intensity at time point t, and W_t = time in minutes elapsed since the previous observation ($date/time_t - date/time_{t-1}$).

SPI will include all non-missing PI scores (scheduled plus the unscheduled PI scores). Weight will be the elapsed time between 2 consecutive PI assessments regardless the type of PI scores.

Therefore, the magnitude of SPI is affected by not only the pain intensity score but also the duration of assessment and the number of pain scores collected in this duration. That is, the totality from the following factors is contributed to the size of the SPI for a subject:

1) Pain intensity score
2) Duration of pain intensity assessments, for example, a subject who is discharged about 30 hours after end of surgery would have a fewer pain assessments than another subject who is not discharged until 60 hours after the end of surgery.
3) Number of PI scores prior to use of rescue opioids
4) Number of PI scores prior to assisted ambulation
5) Number of PI scores prior to independent ambulation

The impact of those factors will be identified for each subject and treated as a covariate during the analysis (see Section 5.2.1.1 for details). In addition, an hourly pain score will be derived for each subject as follows:

Hourly Pain Score = SPI / Duration of Pain Assessment.

where the duration of pain assessment (hours) = date/time of last PI score – date/time of end of surgery; and the duration of PI assessments for each SPI may or may not be the same for a subject.

3.5.11. Overall Benefit of Analgesia Score (OBAS)

All OBAS assessments will be mapped to Analysis Visit using the Post-operative Day benchmark (see Section 3.5.2). In addition, the last observation prior to discharge will also be included as 'Prior to Discharge' time point.

OBAS (ie, domain score) at each time point is the sum of scores in items 1–6 and add (4 - score in item 7). For example, a subject with minimal pain (Item 1=0), severe vomiting (Item 2=4), no itching (Item 3=0), no sweating (Item 4=0), no freezing (Item 5=0), slightly dizzy (Item 6=1), and is not very satisfied with his postoperative pain treatment (Item 7=1) has an OBAS of 8 (OBAS = [0+4+0+0+0+1]+ [4-1]). Hence, a lower OBAS score indicates a higher analgesia benefit.

Opioid Distress Dimension Score (ODDS, sub-domain score): ODDS is the sum of scores in items 2–6. The ODDS for the example above would be 5 [severe vomiting (Item 2=4) and no itching (Item 3=0), sweating (Item 4=0), and freezing (Item 5=0) and is slightly dizzy (Item 6=1)]. Hence, a lower ODDS score indicates a lower opioid distress.

Table 5: Overall Benefit of Analgesia Questionnaire and Rating

1. Please rate your current pain at rest on a scale between 0=minimal pain and 4=maximum imaginable pain
2. Please grade any distress and bother from vomiting in the past 24 hours (0=not at all to 4=very much)
3. Please grade any distress and bother from itching in the past 24 hours (0=not at all to 4=very much)
4. Please grade any distress and bother from sweating in the past 24 hours (0=not at all to 4=very much)
5. Please grade any distress and bother from freezing in the past 24 hours (0=not at all to 4=very much)
6. Please grade any distress and bother from dizziness in the past 24 hours (0=not at all to 4=very much)
7. How satisfied are you with your pain treatment during the past 24 hours (0=not at all to 4=very much)
OBAS = [sum of scores in items 1-6] + [4 - score in item7] **ODDS = sum of scores in item 2-6**

Item Score: The scores in items 1 to 7 will be analyzed as is. That is, the directional transformation for item 7 score for OBAS computation will not be done when item 7 score is analyzed separately. Hence, in item 7, a high score indicates a higher degree of satisfactory with the pain management treatment.

Missing Data: The following rules will be following to handle missing data:

1. For OBAS and ODDS: if only 1 item is missing, the missing data will be imputed to the worst score (4 for items 1 to 6, and 0 for item 7).
2. If there is more than 1 item with missing data, the total score will not be calculated. Hence, the OBAS and ODDS will be set to missing.
3. Missing data will not be imputed for summary and analysis of the individual item.

Additional imputation method may be explored if data warrants.

3.5.12. Patient Global Assessment of Pain Control (PGA)

All PGA assessments will be mapped to Analysis Visit using the Post-operative Day benchmark (see Section 3.5.2). In addition, the last observation prior to discharge will also be included as 'Prior to Discharge' time point.

Study staff will ask subjects to respond to the following question:

"Overall, please rate how well your pain has been controlled during the last 24 hours?"

Poor (0)
Fair (1)
Good (2)
Very Good (3)
Excellent (4)

Subjects with ratings of 2 (good), 3 (very good) or 4 (excellent) will be grouped as responders (ie, subjects satisfied with pain control) for PGA analysis.

3.5.13. Physical Therapy

Physical therapy (PT) assessments will be mapped to Analysis Visit using the Post-surgery Day benchmark (see Section 3.5.2). Number of sessions within a PSD will be derived for each subject, including

1. Number of PT sessions performed
2. Number of PT sessions not performed due to pain
3. Number of PT sessions completed
4. Number of PT sessions not completed due to pain
5. Number of PT sessions that the subject hit the target functional range of motion
6. Number of PT sessions that the subject did not hit the target functional range of motion due to pain

3.5.14. Additional Health Care Utilization Endpoints

Each of the following events will be mapped using the PSD Analysis Visit benchmark (see Section 3.5.2). The following endpoints will be derived for each subject from discharge to end of study (post-operative day 30 (POD 30)).

1. Number of times admitted to a Skilled Nursing Facility
2. Number of times a phone call made to the doctor due to post surgery pain
3. Number of times had unscheduled doctor visits due to post surgery pain
4. Number of times visited Emergency Room (ER) due to post surgery pain
5. Number of all-cause Hospital Readmissions
6. Total cost of hospital Stay

4. STUDY POPULATION SUMMARIES

4.1. Disposition

A summary table (**Table 14.1.1.1**) will provide frequency counts for subject disposition (randomized (ITT), all treated subjects (Safety), subjects who completed study). After the POD 30 telephone interview, subjects will be discharged from the study. Hence, Completed Study will be defined based on completion of POD 30 following up visit. Subjects (%) by reasons for end of study drug treatment will also be included.

Primary reason for early termination of study includes

1) Adverse Event
2) Study Non-compliance
3) Lost to Follow-Up
4) Physician Decision
5) Sponsor Decision
6) Subject Decision
7) Other

Primary reason for subject no longer requiring study drug treatment includes:

1) IV access removed
2) Subject discharged
3) Adverse event
4) Physician decision
5) Subject decision
6) Other

A summary table (**Table 14.1.1.2**) will provide number of subjects in each analysis population by site. The table will display the site with the highest enrollment (ITT analysis set) first.

4.2. Demographics and Baseline Characteristics

The demographic summary (**Table 14.1.2**) will include descriptive statistics for age, age group (age <65, age >=65), sex, race, ethnicity, weight, height, and BMI at baseline for overall and by treatment group.

Baseline characteristics and patient population characteristics will include:

1) Surgery site (left or right knee), was a transfusion required (Yes/No), was the quadriceps tendon spared during the surgery (Yes/No), time (hours) stayed in the PACU, disposition post PACU.
2) Time (hours) from first dose to surgery start; time (hours) from first dose to surgery stop; surgery duration (hours)
3) Time (hours) from end of surgery to end of treatment (EOT)

Demographics and baseline characteristics will be tabulated for the safety analysis set with no formal inferential tests. If the mITT set and safety set are different, a second table will be prepared for the mITT analysis set.

4.2.1. Other Medical History

All medical history data will be available in the SDTM dataset without a formal data summary and data listing.

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, or consent document.

All protocol deviations will be tabulated by protocol type, protocol deviation category for each treatment group and study overall (**Table 14.1.4**).

4.4. Treatment Compliance

Doses of study medication (N1539 30 mg or Placebo) will be administered to the study subjects under the observation of study personnel while confined to the study site. The exact time of administration of study medication will be documented within each subject's eCRF.

A subject is expected to receive at least 2 doses of study drug. All doses after dose 1 are to be given every 24 hours (± 1 hour, i.e., window=23-25 hours from previous dose). The last dose may be given up to 4 hours earlier from previous dose (i.e., window=20-25 hours from previous dose) if the last dose is given on the day of discharge.

Compliance relative to dosing window will be checked based on dosing interval (hours). Mathematically dosing interval will be derived as (date/time of $dose_{(n+1)}$ – date/time of $dose_n$).

Dosing interval will be calculated for each dose starting dose #2. Dosing intervals outside the dosing widow (23-25 hours or 20-25 if it is the last dose given on the day of discharge) will be considered non-compliance.

In addition, all subjects will receive 650 mg of acetaminophen Q8H PO as tolerated until LSD+1. Compliance associated with concomitant acetaminophen usages will also be checked.

Compliance data will be tabulated with study drug total exposure (see Section 7.1).

4.5. Prior and Concomitant Medications

All prior and concomitant medications will be available in a SDTM dataset without formal data summaries and data listings.

5. EFFICACY ANALYSIS

5.1. Opioid Consumptions

Opioid consumption will follow an risk approach (see 3.5.1 Subjects at Risk). The following 16 periods will be included in the summary table.

ID	Time Interval	Note
1	Pre-operative Period	
2	Intra-operative Period	
3	T0 - H0	
4	T0 to T24 (Excluding Dose 2)	
5	H0 - H24 (PSD 1)	This is the primary efficacy endpoint for the study
6	H24 - H48 (PSD 2)	
7	H48 - H72 (PSD 3)	
8	H0 - H48 (PSD 1-2)	
9	H0 - H72 (PSD 1-3)	
10	H0 - EOT	
11	0-24 hours post discharge	
12	24-48 hours post discharge	
13	0-48 hours post discharge	
14	24 hours before POD 10-14 visit	
15	EOT - EOS	
16	Total in Study	

The following 3 analyses will be included for each period **(Table 14.2.1.1)**.

5.1.1. Number (%) Subjects Opioid Free

A subject is opioid free if this subject did not use any opioid (IV or Oral) analgesic in this period. Number (%) subjects opioid free (Yes/No) will be tabulated by treatment group. The denominator for each period should include all subjects at risk (see Table 2: Subjects at Risk):

Treatment group difference in proportion of subjects who used rescue and 95% confidence intervals for the difference will be provided. The difference will be evaluated using Cochran-Mantel-Haenszel (CMH) test controlling for investigator center (CM general association statistic). If positive treatment effect is observed the difference in proportion subjects rescued will also be expressed as number needed to treat (NNT=1/difference in proportion).

5.1.2. ANCOVA Analysis of Total Opioid Consumption

Total opioid consumptions in IVMED (mg) per subject will be determined for each interval. Subjects who did not use any rescue medication in a period (ie, opioid free =Yes in Section 5.1.1) will be set to zero '0' for total opioid consumption analysis. **Total opioid from Hour 0 to Hour 24 post first dose is the primary efficacy endpoint for this study.**

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. LS means from each group and difference in LS means and corresponding 95% CI for the difference and nominal p-values will be reported in the summary table.

5.1.3. Rank Analysis of Total Opioid Consumption

Total opioid consumption may not be normally distributed, hence, the statistical assumption for parametric analysis using ANCOVA specified in Section 5.1.2 above may not be held. A confirmatory analysis using CMH ANOVA (Row Mean Scores Differ) on rank (a nonparametric approach) will also be performed for total opioid consumption. The test will control for investigational site. The rank will be produced within a time point using Nplus1 and ties=mean method. P-value from the CMH test will be presented.

5.1.4. Time to First Rescue

There are 3 time-to-first rescue events in this study associated with opioid analgesic (**Table 14.2.1.2**):

- time from hour 0 to first use of IV or Oral rescue analgesic
- time from hour 0 to first use of IV rescue analgesic
- time from hour 0 to first use of Oral rescue analgesic

Summary tables will include

- number (%) subjects with and without (censored) event,
- Kaplan-Meier product limit estimates of quartiles of time to first event (25%, 50%, and 75% tiles and 95% CIs) and
- KM means (SE) of time to first event
- the log rank test for homogeneity between the treatment groups.
- Differences between the groups in time to event will be further analyzed using Cox proportional hazards analysis model that include the main effects of treatment and investigational sites. Hazard ratio (N1539 30 mg / placebo) and 95% CIs and p-value from Wald's chi-square test for treatment and investigational site will be presented.

Kaplan-Meier survival curves will be presented for each treatment group.

5.1.5. Number of Times Used Rescue Analgesia

Opioid records with indication of **Rescue** will be used for this analysis. Total number of doses of rescue opioids will be derived for each subject from end of surgery (H0) to hospital discharge or LSD+1 (ie, end of treatment), H0-H24, H24-H48, and H48-H72. A table (**Table 14.2.1.3**) will tabulate total doses by treatment group for each period without inferential statistics.

5.2. Scheduled Pain Intensity (PI) Assessment

5.2.1. Sum of Pain Intensity by Intervals

SPI_{AA}, SPI_{IA}, SPI_{DC} and the Hourly PI Score for each subject will be derived (see Section 3.5.10). Difference between the treatment groups will be evaluated using ANOVA model that includes treatment and investigator center. LS mean for each treatment group, difference between treatment groups in LS mean (LSM) and 95% CI for the difference in LSM will be provided.

A sensitivity analysis using CMH ANOVA (Row Mean Scores Differ) on rank controlling for investigator center will also be provided.

Normal p-value at each time point will be reported as is without controlling for multiple comparisons.

5.2.1.1. Evaluation of SPI Potential Covariates

A sensitivity analysis will provide assessment of interactions between treatment and investigational site (**Table 14.2.2.2.1**) in SPIs parameters.

The effect of the following potential covariates of SPI will also be formally assessed in the sensitivity analyses (Table 14.2.2.2.2):

1. Number of times Used Rescue. This value is the number of PI scores prior to rescue that are included in each specific SPI calculation. Hence, it is period dependent. For Example, number of times rescued prior to the time to first assistant ambulation (period corresponding to SPI_{AA}) may or may not the same as the number of times rescued for the period of time to first independent ambulation (period corresponding to SPI_{IA}).
2. Number of times with assisted ambulation. This value is the number of PI scores prior to assisted ambulation that are included in each specific SPI calculation. This covariate is irrelevant for SPI_{AA}.
3. Number of times with independent ambulation. This value is the number of PI scores prior to independent ambulation that are included in each specific SPI calculation. This covariate is irrelevant for SPI_{AA} and SPI_{IA}.
4. Duration of PI assessment. This value is the elapsed hours from the end of surgery to the last PI score used in a specific SPI calculation. This covariate is irrelevant for Hourly PI score.

5.2.2. Scheduled Pain Intensity by Time Points

Pain intensity at each scheduled time point (14 data time points, **Table 14.2.2.3;** pain intensity after discharge, **Table 14.2.2.4**) will be tabulated with descriptive statistics; difference between the treatment groups will be evaluated using ANOVA model that includes treatment and investigator center. LS mean for each treatment group, difference between treatment groups in LS mean (LSM) and 95% CI for the difference in LSM will be provided. **Missing PI score at a scheduled time point will not be imputed with one exception: if a subject is discharged before 48 hours, the last scheduled PI assessment prior to discharge will also be used as the PI score prior to discharge.**

A sensitivity analysis using CMH ANOVA (Row Mean Scores Differ) on rank controlling for investigator center will also be provided.

Normal p-value at each time point will be reported as is without controlling for multiple comparisons.

5.3. Ambulation Assessments

5.3.1. Time to First Ambulation Events

There are 2 time-to-event parameters related to ambulation in this study; they are

- time from hour 0 to first assisted ambulation
- time from hour 0 to first independent ambulation

Summary table (**Table 14.2.3.1**) will include

- number (%) subjects with and without (censored) event,
- Kaplan-Meier product limit estimates of quartiles of time to first event (25%, 50%, and 75% tiles and 95% CIs) and
- KM means (SE) of time to first event
- the log rank test for homogeneity between the treatment groups.
- Differences between the groups in time to event will be further analyzed using Cox proportional hazards analysis model that include the main effects of treatment and investigational sites. Hazard ratio (N1539 30 mg / placebo) and 95% CIs and p-value from Wald's chi-square test for treatment and investigational site will be presented.

Kaplan-Meier survival curves will be presented for each treatment group.

5.3.2. Pain Before and the Worst Pain During Ambulation

Pain intensity (0-10) prior to each ambulation and the worst pain intensity (0-10) during an ambulation will be collected. Each ambulation will be assigned a sequential number (referred to

as ambulation attempt identification number according to the date/time within an ambulation type (assisted vs not assisted).

PI score will be tabulated by treatment and ambulation ID with descriptive statistics (**Table 14.2.3.2** - assisted ambulation; **Table 14.2.3.3** - independent ambulation). POD will be assigned based on the calendar date, with the date of surgery being POD 1. Difference between the groups will be evaluated using an ANOVA model that include treatment and investigator center. Difference between the treatment groups in LSM and 95% CI for the difference will be provided along with p-value for the effect of treatment and investigational site.

A sensitivity analysis using CMH ANOVA (Row Mean Scores Differ) on rank controlling for investigator center will also be provided.

Normal p-value at each time point will be reported as is without controlling for multiple comparisons. Pain intensity analysis will include only the subjects with PI assessment prior to and during ambulation. That is, subjects without ambulation assessments and subjects without PI assessment prior to and/or during ambulation will be excluded.

5.3.3. Number of Times of Ambulation

Total number of times a subject ambulated before hospital discharge will be tabulated by treatment group and ambulation type (assisted vs not assisted, **Table 14.2.3.4**). Differences between the treatment groups will be evaluated via ANCOVA. Ambulation records with a date but with unknown time (see Section 3.5.9) will be included in this analysis.

5.4. Patient Global Assessment (PGA) of Pain Control

PGA records will be tabulated using POD benchmarked. In addition, the last observation prior to discharge will also be included as 'Prior to Discharge' time point.

Number (%) subjects by PGA ratings will be tabulated along with mean (SD) of the rating by treatment and time point (**Table 14.2.4**). Proportion of subjects with positive response [including ratings of 2 (good), 3 (very good) or 4 (excellent)] vs proportion of subjects with non-positive response [including ratings of 0 (poor) or 1 (fair)] will be compared between treatment groups using CMH test (general association) controlling for investigational site.

5.5. Overall Benefit of Analgesic Questionnaire

OBAS, ODDS, and score from each item will be tabulated for each POD by treatment (see Section 3.5.11 for parameter derivation method). In addition, the last observation prior to discharge will also be included as 'Prior to Discharge' time point.

ANCOVA models with main effects of treatment and investigational sites will be used to compare LSM between treatment groups at each time point. Summary table **(Table 14.2.5)** will provide descriptive for observed score, the estimated LSM, difference in LSM and 95% CI for the difference, and p-value for treatment effect and investigational site effect.

6. HEALTHCARE RESOURCE UTILIZATION

The following healthcare resource utilizations endpoints will be tabulated by Treatment groups without inferential statistics.

6.1. Total Cost of Hospital Stay

Total cost of hospitalization will be tabulated by treatment group. The summary will provide descriptive summary, including n mean, standard deviation, median, minimum, maximum (**Table 14.2.6**).

6.2. Hospital Readmission, ER Visits, Doctor Visits, and Phone Calls

A summary table (**Table 14.2.7**) will include the following events from discharge to POD 30 (ie, EOS)

1. Subjects with >=1 all cause hospital readmission
2. Total number of all-cause readmissions by subjects
3. Subjects with >=1 ER visit due to pain
4. Total number of ER visits due to pain by subjects
5. Subjects with >=1 unscheduled doctor visit due to pain
6. Total number of unscheduled doctor visits due to pain by subjects
7. Subjects with >=1 phone calls due to pain
8. Total number of phone calls due to pain by subjects

6.3. Physical Therapy Sessions from Post Surgery to POD 30

A summary table (**Table 14.2.8**) will include the following data from physical therapy (PT) from end of surgery to POD 30 (ie, EOS)

1. Total number of PT sessions performed per subject
    a. Total number of PT sessions that were scheduled but not performed due to pain per subject
2. Total number of PT sessions completed per subject
    a. Number of PT sessions that were not completed due to pain
3. Total number of PT sessions performed and target function range of motion that was met per subject
    a. Total number of PT sessions that did not meet the target function range of motion due to pain (while subject is in hospital)

The summary table will include group summary of mean, SD, median, minimum and maximum as well as number (%) subjects in the following range categories (note: the range

categories identified here may be modified as appropriate based on the data, each parameter may have a different set of range categories appropriate for that parameter).

- 0 session
- 1-5 sessions
- 6-10 sessions
- 11-15 session
- 16 or more sessions

6.4. Requiring a Skilled Nursing Facility from Post Discharge to POD 30

A summary table (**Table 14.2.9**) will provide

1. Number (%) of subjects who required a skilled nursing facility at least once from hospital discharge through POD 30
2. Total time (days spent in skilled nursing facility from hospital discharge through POD 30)
3. Total number of times admitted to a skilled nursing facility per subject

Time (days) spent in skilled nursing facility will be calculated for each admission as follows

Time (days) = Date of Discharge – Date of Admission +1

Total time (days) per subject is calculated as the sum of days across all admissions from discharge to POD 30 for each subject.

7. SAFETY AND TOLERABILITY EVALUATIONS

7.1. Extent of Exposure

The extent of exposure will be assessed by number of doses taken. The summary will provide number of subjects (%) who had 1, 2, 3, …. etc. doses of study drug in the study. Percentage will be calculated based on total number of treated subjects in each treatment group (**Table 14.3.1.1**).

The exposure table will also include dosing compliance (see Section 4.4) information based on based on a subset of subjects who had ≥ doses of study drug. The compliance data will include number of subjects (%) with all doses taken within dose interval and number subjects (%) with >=1 dose that was dosed outside the dosing interval will be tabulated by treatment group.

In addition, number of subjects and total number of doses that are dosed <23 hours, <22 hours, <21 hours, and <20 hours from the previous dose will also be identified.

Subjects compliance with concomitant acetaminophen usages will also be tabulated by treatment group (Table 14.3.1.2)

7.2. Adverse Events

Adverse events reported post dosing through the final follow-up (POD 30 ± 4 days) will be considered as treatment emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities **(Version 20.1)** will be used to classify all AEs with respect to system organ class and preferred term.

The following summary tables will be produced for the TEAEs. All data summaries will provide number (%) subjects as well as total number of events in each category.

1. a topline summary of TEAEs (**Table 14.3.2.1**)
2. a summary table by preferred term in descending order of total incidence (Table **14.3.2.2**)
3. a detailed summary table by system organ class, preferred term and severity (**Table 14.3.2.3.1**)
4. a detailed summary table by system organ class, preferred term and relationship (**Table 14.3.2.3.2**)
5. a table of serious TEAEs by system organ class and preferred term (**Table 14.3.2.4**)

7.3. Change in Laboratory Tests

Safety laboratory tests are scheduled to be performed at check-in and at hospital discharge. Additional unscheduled laboratory tests would be performed as clinical indicates. Central lab will be provided by PPD Global Central Labs.

Incidence of potentially clinically significant abnormal clinical laboratory values will be identified for selected laboratory tests of special interest.

Table 6: Selected Laboratory Tests of Special Interest

Lab Category	Description (Code)
Chemistry	Alkaline Phosphatase (ALP)
	Alanine Aminotransferase (ALT)
	Aspartate Aminotransferase (AST)
	Blood Urea Nitrogen (BUN)
	Direct Bilirubin (DBILI)
	Gamma Glutamyl Transferase (GAMMAGT)
	Serum Creatinine (CREATIN)
	Total Bilirubin (TBILI)
Hematology	Hematocrit (HCT)
	Hemoglobin (HGB)
	Platelet (PLT)
	White Blood Cell (WBC)
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Thromboplastin Time (PT)
	Prothrombin time International Normalized Ratio (PTINR)

A summary table (**Table 14.3.3**) will provide number (%) subjects with abnormal results that meet the criteria in Table 7 post baseline. All post baseline lab tests (scheduled plus unscheduled) will be included in the analysis. If a subject had more than 1 lab draw and all results are abnormal, this subject is counted only for this lab test but all events will be counted in the 'total' events.

Table 7: Definition of Potentially Clinically Significant Abnormal Results in Selected Laboratory Tests of Special Interest

Category	Test Code	Category for post baseline result [1]
Hematology tests	HGB, WBC, PLT, HCT	1) Shift from Normal to Abnormal, Low 2) Shift from Normal to Abnormal, High
Renal function tests [2]	BUN, Serum creatinine	1) > 1 to < 1.5 times of ULN 2) ≥ 1.5 to < 3 times of ULN 3) ≥ 3 times of ULN
Liver function tests [2]	ALT, AST, GGT, ALP	1) > 1 to < 3 times of ULN 2) ≥ 3 to < 10 times of ULN 3) ≥ 10 times of ULN
	Total Bilirubin	1) 1 to < 1.5 times of ULN 2) ≥ 1.5 to <2 times of ULN 3) ≥ 2 to < 2.5 times of ULN 4) ≥ 2.5 to < 3 times of ULN 5) ≥ 3 times of ULN
Coagulation tests	PTT, PT, INR	1) Shift from Normal to Abnormal, Low 2) Shift from Normal to Abnormal, High

[1] ULN = Upper limit of normal range; LLN = Lower limit of normal range.

7.4. Wound Healing

Wound healing progress will be assessed at hospital discharge and at the follow-up visit (POD 10-14). Wound evaluation assessments will include investigator satisfaction score (0=completely unsatisfied and 10=completely satisfied).

The summary table (**Table 14.3.4**) will include number (percent) subjects in each response category; Group mean, median, and standard deviation will also be provided. Differences between the groups be assessed using Cochran-Mantel-Haenszel ANOVA (Row Mean Scores Differ) on response controlling for investigational sites.