REC-17-024

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety and Efficacy of Preoperative N1539 In Colorectal Surgery

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Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

Protocol Number:	**REC-17-024**
Protocol Title:	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Evaluation of the Safety and Efficacy of Preoperative N1539 In Colorectal Surgery**
Date of Original Protocol	**June 01, 2017**
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Date of Protocol Amendment 002	**November 16, 2017**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND PHOURSASES

Abbreviation	Definition
N1539	Injectable NanoCrystal® Colloidal Dispersion (NCD) Meloxicam
AE	Adverse Event
ADC	Actual hospital discharge
ANCOVA	Analysis of Covariance
ATC	The Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
BPI	Brief Pain Inventory
CMH	Cochran-Mantel-Haenszel
CRP	C-Reactive Protein
DBP	Diastolic Blood Pressure
DOW	Hospital Discharge Order Written
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)
FSD	First Dose of Study Drug
FUV-1	Follow-up Visit 1
FUV-2	Follow-up Visit 2
Hour 0	Time of End of Surgery (H0)
ICH	International Conference on Harmonization
IL	Interleukin
ITT	Intent-to-treat
IV	Intravenous
IVMED	IV Morphine Equivalent Dose (mg)
Kg	Kilogram
KM	Kaplan-Meier
LOS	Length of Stay
LSD	Last Dose Date/Time
LSD+1	24 hours after the last dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat

Abbreviation	Definition
mL	Milliliter
NG	Nasogastric
NPRS	Numeric Pain Rating Scale
OBAS	Overall Benefit of Analgesic Score
ODDS	Opioid Distress Dimension Score (a sub domain of OBAS)
PACU	Post-Anesthesia Care Unit
PCSC	Potentially Clinically Significant Change
PDD	Post discharge day (24-hour period starting time of actual hospital discharge)
PGA	Patient Global Assessment
PI	Pain Intensity Score
POD	Postoperative day (determined by calendar date from surgery date)
PSD	Post-Surgery Day (a 24-hour period starting end of surgery)
PT	Preferred term
REM	Relationship with other people, Enjoyment of life, and Mood ((a subdimension of pain inference)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SOC	System Organ Class
SpO2	Peripheral oxygen saturation
TEAE	Treatment emergent adverse event
TNF-α	Tumor Necrosis Factor alpha
Time 0	Time of First Dose (T0)
TTE	Time to Event
TTADC	Time to actual hospital discharge
TTBS	Time to first bowel sound
TTDOW	Time to hospital discharge order written
TTFL	Time to first flatus
TTBM	Time to first bowel movement
µg	Microgram
µL	Microliter

Abbreviation	Definition
WAW	Walk, General Activities, Work (a subdimension of pain inference)
WHODRUG	World Health Organization Drug Dictionary

IN-TEXT TABLES

1. INTRODUCTION AND SCOPE

Protocol REC-17-024 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 or laparoscopic colorectal surgery. The initial study cohort will enroll approximately 50 subjects randomized (1:1) to N1539 30 mg or placebo; additional study cohorts may be enrolled following review of initial study observations.

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-17-024: Amendment 2, November 16, 2017
- REC-17-024 eCRF Completion Guidelines: Version 4, date November 27, 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 evaluate the safety and tolerability of preoperative dosing of N1539 30 mg in subjects undergoing colorectal surgery, including clinical laboratory tests, wound healing evaluation, incidence of anastomotic leaks, and incidence of Adverse Events (AEs) and Serious AEs (SAEs).

Additional objectives include:

- Evaluation of N1539 treatment impact on overall postoperative recovery course, including total opioid consumption, length of hospital stay, pain control, cost of hospital stay, return of bowel function, mobilization, and satisfaction with pain medication.

Each subject is expected to receive at least two doses of study drug during the treatment phase of the study, with the first dose (Dose 1) administered within 30 minutes prior to surgery start and additional doses administered every 24±1 hours from Dose 1 until discharge or until IV analgesia is no longer clinically appropriate, whichever comes first. A final dose of study drug may be administered up to 4 hours early in subjects who are scheduled to be discharged. Subjects who do not receive a dose of study drug for > 28 hours following their previous dose of study drug should be considered off treatment, and not receive further study dosing. Subjects will be asked to return for FUV-1 to complete end of study assessments, with a safety follow-up by phone at FUV-2.

Assessments of efficacy will include total opioid consumption, pain intensity according to an 11-point numeric pain rating scale (NPRS; 0 - 10) on first ambulation, time to first analgesic rescue, time to return of bowel function (including time to first flatus or bowel sounds, and first bowel movement), time to mobilization (including time to first assisted mobilization out of hospital bed and time to first independent mobilization out of hospital bed), patient global assessment of pain control, brief pain inventory, subject satisfaction, time to hospital discharge (including time to hospital discharge order written and time to actual hospital departure), incidence of nasogastric (NG) tube insertion, length of stay, incidence of hospital readmission post initial discharge, and total cost of hospitalization.

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

APPENDIX A: OVERVIEW OF STUDY SCHEDULE

	Screening (Day -21 to Day -1)	Treatment Period Day 1 - Day of Last Study Dose (LSD)			End of Treatment (LSD+1[a])	Hospital Discharge	Follow-Up Visit 1 (5-21 days post-discharge)	Follow-Up Visit 2 (30 ± 4 days post-discharge)
		Prior to Surgery	Surgery (End of Surgery=Hour 0)	Hour 24 & Q24Hr after Hour 0 Until LSD (Including LSD)				
Informed Consent	X							
Eligibility Assessment	X	X						
Demographics and Medical History	X	X						
Physical Examination	X[c]	X			X			
Pregnancy Test (FOCBP only)		X[urine]						
Clinical Laboratory Tests[b]	X[c]	X			X			
Inflammatory Markers		X		X - Once Daily	X			
Vital Signs[d]	X	X			X			
12 Lead ECG	X[c]							
Surgical Procedure			X					
Study Drug Administration			X[e]	Q24 from Dose 1				
PI Assessment				On first ambulation[f]				
Monitoring Bowel Function				X	X			
PGA of Pain Control				X	X			
BPI Assessment	X			X	X			
Subject Satisfaction					X			
Wound Evaluation						X	X	
Incidence of Readmission								X
Prior and Concomitant Medication	←	←	←	←	X	→	→	→
Adverse Event Monitoring		←	←	←	X	→	→	→

a If a subject is prepared for discharge less than 24 hours following the last study dose, LSD+1 procedures should be completed prior to discharge.
b Laboratory tests will be performed locally at screening and centrally at Day 1 prior to surgery and LSD+1.
c Historic results collected within 7 days prior to screening may be utilized for eligibility assessment purposes
d Vital signs (VS) include: resting blood pressure, resting pulse, and SpO2. Tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
e Dose 1 is to be administered approximately 30 minutes prior to first incision. Subsequent doses may be administered every 24±1 hours from Dose 1.
f PI will be assessed within 15 minutes prior to first ambulation, and for the worst pain experienced during first ambulation.

2.1. Study Endpoints

2.1.1. Safety Endpoints

The planned safety endpoints include the following:

1. Incidence of treatment-emergent AEs and SAEs (including AEs of interest and opioid related AEs)
2. Incidence of anastomotic leaks
3. Change from baseline in laboratory tests; incidence of abnormal clinical laboratory tests
4. Change from baseline in vital signs
5. Assessment of surgical wound healing

2.1.2. Efficacy Endpoints

The planned efficacy endpoints include:

1. Total opioid consumption
2. Time to hospital discharge order written
3. Pain intensity on first ambulation
4. Time to actual hospital departure
5. Time to first rescue analgesia use
6. Time to return of bowel function, including time to first bowel sounds or first flatus, and time to first bowel movement
7. Time to mobilization, including time to first assisted mobilization out of hospital bed and time to first independent mobilization out of hospital bed
8. PGA of pain control
9. Brief Pain Inventory
10. Subject assessment of satisfaction with pain medication
11. Hospital length of stay (LOS)
12. Incidence of postoperative NG tube insertion
13. Incidence of hospital readmission.
14. Total cost of hospitalization

2.1.3. Exploratory Endpoints – Change in Inflammatory Markers

Inflammatory markers including, but not limited to: c-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin (IL) 1B, IL-4, IL-6, IL-8, IL-10, and IL-18.

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 3.4.

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. Definitions and Derived Variables

3.4.1. Analysis Center

This is a multicenter study; investigative centers 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.

3.4.2. Baseline

Baseline will be the last measurements taken before the subject receives the study medication. **If an unscheduled visit/assessment occurred before a subject receives the first dose of study drug; the unscheduled visit may be the Baseline if it is the last non-missing value before the first dose.**

3.4.3. Study Period and Analysis Visit

3.4.3.1. Study Periods

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, the **Baseline measurement 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 LSD+1 (ie, 24 hours after the last dose) before being discharged from the hospital.
4. Post discharge period: this period starts after the subject is discharged from the hospital through end of study.

3.4.3.2. End of Treatment and End of Study

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.

End of Treatment (EOT): end of study drug treatment for a subject is when the subject has the LSD+1 Visit or the subject was discharged from hospital, whichever comes first.

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

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

End of Study (EOS): end of study for a subject is when the subject completes the follow up visit 2 (30 ± 4 days post-discharge). All treated subjects who have EOS visits are considered to have completed the study.

3.4.3.3. 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. T0 is used to schedule study drug dosing whereas H0 is used to map efficacy assessments (such as opioid consumptions) in a standardized time window.

3.4.3.4. Analysis Visits

Efficacy data will be mapped to Analysis Visit using the following 2 benchmarks:

1. Relative to the time of end of surgery (Hour 0). A 24-hour period is referred to as a Post-surgery Day (PSD). PSD 1 is the first 24-hour period after end of surgery, PSD 2 is >24 and <=48 hours after end of surgery. Hence, date and time of an assessment will be compared to the end of surgery time in order to determine the PSD of the assessment. An example of this type of visit is the total opioid consumption.
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). A post-operative day is calendar date after surgery. For instance, POD 1 is one calendar day after the surgery date; the time elapsed from end of surgery to the assessment time performed on POD 1 may not be 24-hours. An example of this type of visit is the PGA analysis.

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 day of surgery, therefore, the POD 0 is assigned as Surgery Day (POD 0).
2. In example 2 the assessment time was within 24 hours after the end of surgery, therefore it is assigned to PSD 1 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 >24 and less than 48 hours after the end of surgery, therefore it is assigned to PSD 2 for Post-surgery Day analysis; and the date of the assessment was 1 day after the date of surgery, therefore, the POD 1 is assigned for Post-operative 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	2018-03-13T08:45	PSD 1	POD 1
3	2018-03-12T08:05	2018-03-13T18:05	PSD 2	POD 1

3.4.4. 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 48, this subject will be considered 'Not at risk' for H48-72 hours opioid consumption.
- Another example is the assessment of Brief Pain Inventory. Subjects who responded 'No' to the Question 1 [Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?] will not be 'at risk' for pain intensity and pain interference.

Table 2 provides examples of subjects at risk for 12 periods used in the opioid consumption analysis.

Table 2: Subjects at Risk for 12 Periods Defined for Opioid Consumption

ID	Interval / Period	Subject at Risk
1	Total in Study	mITT subject
2	Pre-operative Period	mITT subject
3	Intra-operative Period	mITT subject
4	T0 - H0 (Perioperative)	mITT subject
5	T0 to T24 (Excluding Dose 2)	mITT subject
6	H0 - H24 (PSD 1)	mITT subject
7	H24 - H48 (PSD 2)	mITT subject with in-patient duration ≥24 hours
8	H48 - H72 (PSD 3)	mITT subject with in-patient duration ≥48 hours
9	H0 - H48 (PSD 1-2)	mITT subject
10	H0 - H72 (PSD 1-3)	mITT subject
11	H0 - EOT (postoperative)	mITT subject
12	H0 – Actual hospital discharge	mITT subject

3.4.5. Opioid Consumption

3.4.5.1. Total Opioid Consumption in IVMED by Period

All concomitant medications will be coded according to WHODrug 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:

- Surgical: This period includes all opioids used pre-surgery as part of the surgery preparation and opioids used during the surgery.

- Pain Management: all opioids used during in-patient period defined as end of surgery to hospital discharge or LSD+1, whichever occurs first. This corresponds to the post-operative period defined in Section 3.4.3.1)
- Prophylaxis: opioid taken in a preventive manner
- 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 expected to be taken before the surgery. Those records will be excluded from the total opioid consumption analysis. Similarly, the opioids with indication of 'OTHER' may be excluded. The opioid records with indication of MEDICAL HISTORY, or OTHER will be reviewed carefully and queried if there are any doubts/questions on records prior to exclusion.

3.4.5.2. 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. Missing Dates
    a. If both the start and the stop dates are unknown, the record will be queried and excluded if confirmed.
    b. If the start date is present but the stop date is missing, the stop date is set to be the start date and vice versa.
2. Missing Time
    a. If the 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 the start and the stop times are missing
            - if the date is the surgery date: missing start and stop start time will be set to 1 minute after end of surgery.
            - If the date is after surgery date: missing start time will be set to 00:01 and missing stop time will be set to 23:59
    b. When the start date is not equal to the stop date
        i. When start time is missing
            - if the start date = surgery date then missing start time will be set to 1 minute after end of surgery
            - if the start date > surgery date the missing start time will be set to 00:01

ii. When stop time is missing

- If stop date = surgery date the missing stop time will be set to 1 minute after end of surgery
- If stop date > surgery date the missing stop time will be set to 23:59

After all the opioid records that have the appropriate start and stop times, the start and the stop relative time (hours) to Hour 0 (end of surgery) or discharge will be determined for each record in order to derive the total opioid consumption within a PSD. **Total dose will be calculated for the following 12 intervals (**Table 4**). Note: if a record indicates that the start and stop time extends beyond one interval, the total dose from this record will be split into appropriate intervals using linear interpolation (hourly dose).**

Table 4: Definition of Opioid Consumption Intervals

ID	Interval	Interval Description	Interval Expression [1]
1	Total in Study	From hospital admission to actual hospital discharge	[ADM, ADC]
2	Pre-operative Period	From hospital admission to surgery start	[ADM, SGST)
3	Intra-operative Period	From surgery start to surgery end	[SGST, SGEN]
4	T0 - H0	From first dose start time to end of surgery	[FSD, SGEN]
5	T0 to T24	From first dose start time to but not include the second dose start time	[FSD, SSD)
6	H0 - H24 (PSD 1)	From surgery stop time to 24 hours after end of surgery	(SGEN, SGEN+24]
7	H24 - H48 (PSD 2)	From 24 hours after end of surgery to 48 hours after surgery	(SGEN+24, SGEN+48]
8	H48 - H72 (PSD 3)	From 48 hours after end of surgery to 72 hours after surgery	(SGEN+48, SGEN+72]
9	H0 - H48 (PSD 1-2)	From end of surgery to 48 hours after surgery	(SGEN, SGEN+48]
10	H0 - H72 (PSD 1-3)	From end of surgery to 72 hours after surgery	(SGEN, SGEN+72]
11	H0 - EOT	From end of surgery to end of treatment	(SGEN, EOT]
12	H0 – Discharge	From end of surgery to actual hospital discharge	(SGEN, ADC]

[1] The square brackets, [ ], means inclusive whereas the parentheses, ( ), means exclusive.
Abbreviations for intervals:
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
LSD+1 is 24 hours after the last dose of study drug, hence, LSD+1 = last dose date/time + 24 hours

3.4.5.3. 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:

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 (i.e., subjects is not at risk). That is, OPFREE=NA when a subject is not At-Risk for an interval. See Table 2 for more information.

3.4.6. Time to First Rescue

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

Time (hours) from end of surgery (H0) to the start time of the first 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 start date and/or time (although those may have imputed date/time, see Section 3.4.5.2) will be excluded in general with one exception, that is, this record will be included if this is the only record for this route of administration. That is, if this is the only record of rescue for this route of administration, the imputed start missing date/time will be used. See Section 3.4.5.2 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 had oral rescue opioid,
   a. Time to first rescue (IV or Oral) will be set to be the same as the time of first oral rescue
   b. 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 had IV rescue opioid,
    c. the time to first rescue (IV or Oral) will be set to the time to first IV rescue opioid (subject is not censored)
    d. 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,
    e. This subject will be censored for all 3 time to rescue endpoints. The censored time will be the time of EOT (see Section 3.4.3.2 for more information).

3.4.7. Time to First Ambulation and Associated Pain Intensity

Two types of ambulation are assessed: assisted ambulation vs unassisted (i.e., independent) ambulation. The eCRF has the following collections for the first assisted ambulation and the first independent ambulation:

1. Start date/time of the ambulation
2. Duration of the ambulation
3. Pain score prior to the ambulation (within 15 minutes prior to the ambulation), including the time of PI assessment.
4. The worst pain score during the ambulation, including the time of PI assessment.

The following rules will apply for partial date/time of an ambulation record when the ambulation occurred and time is unknown

- If the assessment time for pre-ambulation PI score is available: set the start time of ambulation to be 15 minutes after the pre-ambulation PI assessment time
- Otherwise if the worst pain score assessment time is present, the ambulation start time will be set to the time when the worst PI score was assessed.
- Otherwise, subject is excluded from the time to first ambulation analysis.

Time (hours) to first assisted ambulation and time to first independent ambulation will be determined as follows

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

The following rules will apply:

- When a subject did not have any assisted ambulation record, but this subject has a record for independent ambulation, this subject will not be censored for time to first assisted ambulation. The time to first assisted ambulation will be set to the same as time to first independent ambulation for analysis.
- When a subject has the first assisted ambulation record but this subject did not have any record for unassisted ambulation, this subject will be censored for time to first independent ambulation. The censored time will be the time of EOT (see Section 3.4.3.2 for more information).

- When a subject did not have any ambulation event, this subject will be censored at time of EOT for both time to first assisted ambulation and time to first independent ambulation.

Pain Intensity (PI) score prior to ambulation and the worst PI score during ambulation will be recorded on a scale of 0-10 where 0=no pain and 10=the worst imaginable pain. Missing PI score will not be imputed. Subjects with missing PI score will be excluded from the analysis of PI assessment.

3.4.8. Time to Return of Bowel Function

Return of bowel function will include 3 elements: 1) time to first bowel sound, 2) time to first flatus, and 3) time to first bowel movement; numerically, each event will be calculated as

Time (hr) = date/time of event – date/time of End of Surgery (Hour 0)

The following assumption and rules will apply when an event is not captured on the eCRF.

1) When the first bowel sound (BS) is not reported

- If the first flatus is reported: the event of first bowel sound would be considered to have occurred as well; the date/time of first bowel sound is set to be the date/time of first flatus. **The subject will NOT be censored.**
- If the first flatus is not reported but bowel movement is reported: the event of first bowel sound would be considered to have occurred; the date/time of first bowel sound is set to be the date/time of first bowel movement. **The subject will NOT be censored.**
- If the first flatus and first bowel movement are not reported, t**he subject will be censored** for time to first bowel sound analysis. The censored time will be the time of EOT (see Section 3.4.3.2 for more information)**.**

2) First flatus (FL) is not reported:

- If first bowel movement is reported: the event of first flatus would be considered to have occurred as well; the date/time of first flatus is set to be the same as the date/time of first bowel movement. **The subject will NOT be censored.**
- If first bowel movement is not reported: **the subject will be censored** for time to first flatus analysis; censoring time will be the time of EOT (see Section 3.4.3.2 for more information).

3) If first bowel movement (BM) is not reported: **the subject will be censored for** time to first bowel movement analysis; the censoring time will be the time of EOT (see Section 3.4.3.2 for more information).

3.4.9. Length of Hospital Stay Measured by Time to Hospital Discharge

Length of hospital stay is assessed in 2 different forms:

1. Time (hours) to hospital discharge order written (DOW) as follows:

   TTDOW (hours) = Date/Time of DOW – Date/time of End of surgery (Hour 0)

2. Time (hours) to actual hospital discharge (ADC) as follows:

   TTADC (hours) = Date/Time of ADC – Date/time of End of surgery (Hour 0)

The following rules will apply when time of DOW or time of ADC are missing:

1. If time of DOW is unknown but time of ADC is present, the time of DOW will be set to time of ADC and vice versa.
2. If both time of DOW and time of ADC are missing, both times will be set to 23:59.

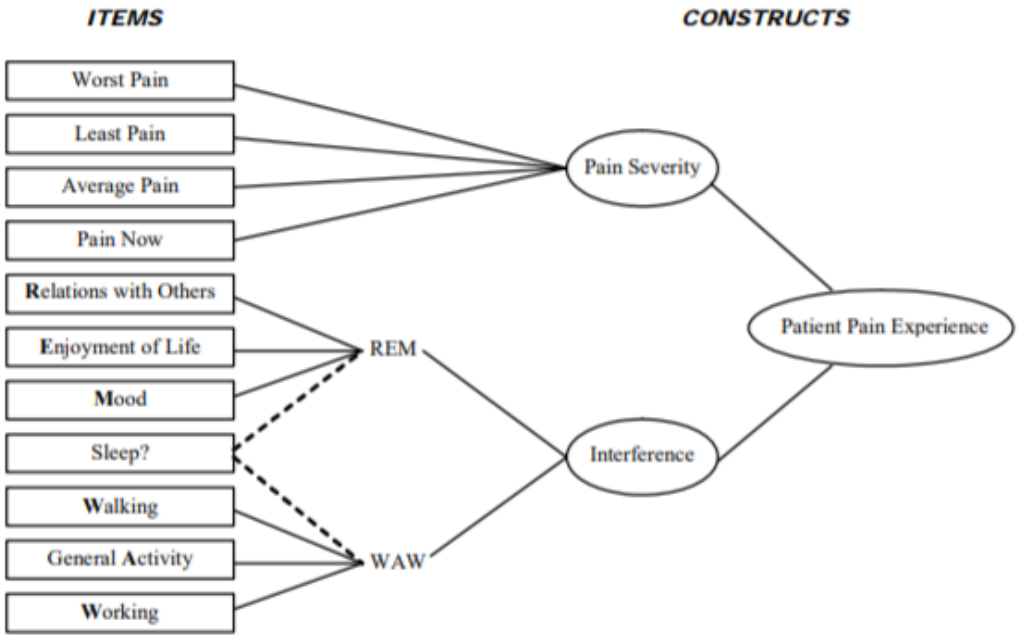
3.4.10. Brief Pain Inventory (BPI)

BPI short form is a questionnaire that assess the "sensory" dimension of pain (intensity, or severity) and the "reactive" dimension of pain (interference with daily function).

1. Four items are used to capture the variability of pain over time: pain at its "worst," "least," "average," and "now" (current pain).
2. Seven items are used to measure how much pain interfered with various daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. The seven items are divided into two subdimensions of pain interference:
   a. an affective subdimension (REM: relations with others, enjoyment of life, and mood, items 9B, 9E, and 9G) and
   b. an activity subdimension (WAW: walking, general activity, and work, items 9A, 9C, and 9D).
      - Please note that he author indicated the appropriate categorization of sleep within these two subdimensions was unclear; hence, the author suggested that item 9F score is included in the dimension of Interference score but excluded from both sub-dimensions REM and WAW.

The items and the dimensions are illustrated graphically as follows. Additional information about can be found in BPI User Guide[1] (2009, Charles S. Cleeland).

[1] The Brief Pain Inventory User Guide. Charles S. Cleeland, PhD. 2009



The BPI scores for each dimension and subdimension will be calculated for each subject as shown in Table 5.

Table 5: Definition of BPI Dimension and Subdimension

Dimension	Composite Score = Average Score of	Interpretation
Pain Severity	Questions 3, 4, 5, 6. All 4 questions must be answered.	The high score indicates the severe average pain
Interference	All 7 scores in Question 9. At least 50% items (or 4 of the 7 scores) must be responded	The high score indicates the greater pain interference
REM	Scores of 9B, 9E, and 9G. At least 2 of the 3 scores must be responded.	The high score indicates the greater pain interference with patient's affection with other people
WAW	Scores of 9A, 9C, and 9D. At least 50%, or 2 of the 3 scores must be responded	The high score indicates the greater pain interference with patient's daily activities
BPI	Average scores of pain severity & pain interference.	The high score indicates the patient had severe pain intensity and a greater pain interference

In addition, the BPI short form has two questions.

Question 1: Throughout our lives, most of us had pain from time to time (such as minor headaches, sprains, and toothaches) Have you had pain other than those everyday kinds of pain today?

Subjects must have a response 'Yes' to be included in the BPI analysis for a given visit. In other words, BPI analysis will be performed based on the concept of 'at Risk'. Subjects who did not have pain will not be at risk for pain severity and pain interference assessments.

Question 8: This question is about pain relief from the pain treatment. Response from this question will be analyzed individually only (i.e., the response will not be included in the composite scores stated above.

BPI scores at screening visit will be the baseline score; change from baseline will be calculated for each Post-Operative Day (POD, see Section 3.4.3.4) for subjects at risk. Missing data will not be imputed for the analysis. In addition, the last observation prior to discharge will also be included as 'Prior to Discharge' time point.

3.4.11. Patient Global Assessment of Pain Control (PGA)

PGA assessments will be mapped to Analysis Visit using the Post-Operative Day benchmark (see Section 3.4.3.4). In addition, the last observation prior to discharge will also be included as 'Prior to Discharge' time point.

A 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 subjects with acceptable pain control for PGA analysis.

3.4.12. Subject Assessment of Satisfaction with Pain Medication

At LSD+1 Visit subjects will report their satisfaction with the pain medication they received to manage their postoperative pain according to a 7-point Likert scale including categories of: completely dissatisfied (1), mostly dissatisfied (2), somewhat dissatisfied (3), neither satisfied to dissatisfied (4), somewhat satisfied (5), mostly satisfied 6), and completely satisfied (7).

Based on the response, subjects will be grouped into 3 groups:

1) Not satisfied if ratings are 1, 2, or 3;

2) Neutral if rating is 4

3) Satisfied if ratings are 5, 6, or 7

3.4.13. Healthcare Utilization Endpoints

The following 3 events endpoints will be assessed for each subject:

1. Incidence (Yes vs No) being re-admitted to hospital, including all cause readmissions
2. Incidence (Yes vs No) of postoperative NG tube insertion
3. Incidence (Yes vs No) of postoperative anastomotic leak

Total cost of hospitalization is also captured on the eCRF.

Missing date related to the endpoints associated with healthcare utilization will not be imputed. Subjects will be excluded for missing data.

4. STUDY POPULATION SUMMARIES

4.1. Disposition

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

- randomized (ITT),
- all treated subjects (Safety),
- mITT Subjects (Efficacy),
- Subjects completed study,
- Subjects prematurely discontinued the study
    - reasons for early termination
- Reasons for subject no longer continuing study drug.

Primary reason for early termination of study includes

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

Primary reason for subject no longer continuing 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 enrollment by site, including ITT analysis set, Safety analysis set, and mITT analysis set for each treatment group and overall. The site with overall highest ITT enrollment will display first.

4.2. Demographics and Baseline Characteristics

The demographic summary will include descriptive statistics for age, age group (age <65, age >=65), sex, race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2) at baseline for overall and by treatment group.

Baseline characteristics and patient population characteristics will include:

1) primary indication for surgery
2) surgery type
3) actual incision type
4) incision length (cm)
5) time (hours) from first dose to surgery start
6) surgery duration (hours)
7) time (minutes) stayed in the PACU

Demographics and baseline characteristics will be tabulated for safety analysis set (**Table 4.1.2.1).** If the mITT set is not the same as the Safety Analysis set, a second table for the mITT analysis set **(Table 14.1.2.2**) will also be provided. No formal inferential tests will be performed.

4.2.1. Other Medical History

All medical history data will be available in SDTM dataset without 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 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. No formal summary of treatment compliance will be produced.

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 could 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 window (23-25 hours or 20-25 if it is the last dose given on the day of discharge) will be considered non-compliance.

Compliance data will be tabulated together with study drug total exposure (see Section 6.1).

4.5. Prior and Concomitant Medications

All prior and concomitant medications will be available in SDTM dataset without formal data summary and data listing.

5. EFFICACY ANALYSIS

5.1. Opioid Consumptions

Opioid consumption will follow at risk approach (see Section Table 2 for Subjects at Risk). The following 12 periods will be included in the summary table.

ID	Interval
1	Total in Study
2	Pre-Operative
3	Intra-Operative
4	T0 - H0
5	T0 to T24
6	H0 - H24 (PSD 1)
7	H24 - H48 (PSD 2)
8	H48 - H72 (PSD 3)
9	H0 - H48 (PSD 1-2)
10	H0 - H72 (PSD 1-3)
11	H0 - EOT
12	H0 - Discharge

The following 3 analyses will be included for each interval **(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 (see Section 3.4.5.3). 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 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 analysis center (CM general association statistic).

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. Subjects with OPFREE=NA at a given interval will be excluded from the analysis for this interval.

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 analysis center. 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 consumptions 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 analysis center. A single set of rank will be produced within each time point across treatment groups using Nplus1 and ties=mean method. P-value from the CMH test will be presented.

5.2. Time to First Rescue

There are 3 time-to-first rescue events in this study associated with opioid analgesic:

- 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

A summary table (**Table 14.2.1.2**) will include the following statistics for each of the event.

- 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)
- 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 analysis center. Hazard ratio (N1539 30 mg / placebo) and 95% CIs and p-value from Wald's chi-square test for treatment and analysis center will be presented.

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

5.3. Length of Hospital Stay Measured by Time to Discharge

Time to DOW and Time to ADC (see Section 3.4.9) will be summarized by treatment group. The summary table (**Table 14.2.2.1**) 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 restricted 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 analysis center. Hazards ratio (N1539 30 mg / placebo) and 95% CIs and p-value from Wald's chi-square test for treatment and analysis center will be presented.

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

5.4. Ambulation Assessments

5.4.1. Time to First Ambulation Events

A summary table (**Table 14.2.3.1**) will include the following statistics for time to first assisted ambulation and time to first independent ambulation.

- 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 restricted 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 analysis center. Hazard ratio (N1539 30 mg / placebo) and 95% CIs and p-value from Wald's chi-square test for treatment and analysis center will be presented.

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

5.4.2. Pain Before and the Worst Pain During Ambulation

PI score will be tabulated by treatment and ambulation type with descriptive statistics (**Table 14.2.3.2.1 – First Assisted Ambulation; Table 14.2.3.2.2 – First Independent Ambulation)**. 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 analysis center.

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

5.5. Time to Return of Bowel Function

There are 3 surrogate events associated with the return of normal bowel function:

- Time from hour 0 to first bowel sound (TTBS)
- time from hour 0 to first flatus (TTFL)
- time from hour 0 to first bowel movement (TTBM)

All 3 parameters will be summarized by treatment group (**Table 14.2.4**); the summary table will include the following statistics for each of the 3 events.

- 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 analysis center. Hazard ratio (N1539 30 mg / placebo) and 95% CIs and p-value from Wald's chi-square test for treatment and analysis center will be presented.

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

5.6. Patient Global Assessment (PGA) of Pain Control

All PGA assessments collected on eCRF will be mapped to POD 1, POD 2, ...etc. for analysis. Hence, the number of subjects at each time point (POD 1, POD 2, POD 3, …., etc.) will expect to decrease as subjects discharged from the hospital. A timepoint of Prior to Discharge (EOT) will be included for all subjects which will be the last PGA assessment during hospital stay.

Number (%) subjects by PGA ratings will be tabulated along with mean (SD) of the rating by treatment and time point (**Table 14.2.5**). Proportion of subjects with acceptable pain control [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 analysis center.

5.7. Brief Pain Inventory Questionnaire

BPI dimension scores and sub-dimension (see Section 3.4.10 for parameter derivation method) and score from each item will be tabulated.

Baseline (screening visit) BPI data for the all subjects at risk at baseline will be tabulated separately (**Table 14.2.6.1**) with descriptive summary; difference between the groups at baseline will be assessed using 1-way ANOVA.

Post baseline BPI data will be tabulated for each POD by treatment. Number of subjects at risk (ie, subjects with pain) at each POD may vary depending on the response to Question No. 1; hence, number (%) of subjects with pain (ie, subjects at risk for pain severity and pain interference) will be tabulated and evaluated using a CMH test (controlling for investigational site) at each time point. Difference between the groups at each POD in domain and sub-domain score will be assessed using ANCOVA model that includes the main effect of treatment, analysis site, and baseline score as covariate. The summary table will present the estimated LSM, difference in LSM and 95% CI for the difference, and p-value for treatment effect, analysis site effect and the baseline effect.

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

The analysis for BPI will be performed for each question individually and at dimension and subdimension level as well (**Tables 14.2.6.2 to 14.2.6.8**).

BPI analysis will be based on POD analysis visit. A timepoint of Prior to Discharge (EOT) will be included for all subjects which will be the last BPI assessment during hospital stay.

5.8. Patient Satisfaction with Postoperative Pain Medication

Number (%) subjects by satisfaction ratings will be tabulated along with mean (SD) and median of the rating by treatment (**Table 14.2.7**). Proportion of subjects who are satisfied or not satisfied or neutral (see Section 3.4.12) will be compared between treatment groups using CMH test (general association) controlling for analysis center.

5.9. Health Care Utilization

Health care utilization related parameters include:

1. Subjects with >=1 all cause hospital readmission
2. Subjects with >=1 postoperative NG Tube insertion
3. Subjects with >=1 incidence of anastomotic leak
4. Total cost of hospitalization

A summary table (**Table 14.2.8.1**) will include descriptive statistics of subjects (%) for first 3 parameters, and another summary table (**Table 14.2.8.2.2**) will provide descriptive summary of total cost of hospitalization, including n mean, standard deviation, median, minimum, maximum.

No inferential statistics will be provided.

5.10. Change in Inflammatory Markers (Exploratory Endpoint)

A summary table (**Table 14.2.9**) will include descriptive statistics of n mean, standard deviation, median, minimum, maximum for each measured inflammatory marker or number (%) of subjects by each category. Results will also be tabulated relative to normal range showing number of subjects (%) in each category (normal, high, low, etc.). Change from baseline will be measured by creating shift (Baseline – Visit) category (Normal – Normal, Normal – High, Normal – Low, etc.).

The table will include only those subjects who agreed to participate this portion of the study. No inferential statistics will be provided.

6. SAFETY AND TOLERABILITY EVALUATIONS

6.1. 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.
2. 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.

6.2. Adverse Events

Adverse events reported post dosing through the final follow-up (30 ± 4 days post-discharge) 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**)

6.3. 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 change (PCSC) in 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)
	Total Bilirubin (TBILI)
	Gamma Glutamyl Transferase (GAMMAGT)
	Serum Creatinine (CREATIN)
Hematology	Hematocrit (HCT)
	Hemoglobin (HGB)
	Platelet (PLT)
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Thromboplastin Time (PT)
	Prothrombin time International Normalized Ratio (PTINR)

A summary table will provide number (%) of 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 in this lab test but all events will be counted in the 'total' events. This analysis will be performed twice: once to include all subjects in the safety analysis set (**Table 14.3.3.1**) and second time to include only the subjects with normal baseline (**Table 14.3.3.2**).

Table 7: Definition of Potentially Clinically Significant Change (PCSC) in Selected Laboratory Tests of Special Interest

Category	Test Code	Category for post baseline result [1]
Hematology tests	HGB, 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
	Bilirubin (Total and Direct)	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.

6.4. Wound Healing

Wound healing progress will be assessed at hospital discharge and at follow-up visit 1 (5-21 days post-discharge). 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 will be assessed using Cochran-Mantel-Haenszel ANOVA (Row Mean Scores) on response controlling for analysis centers.

6.5. Vital Signs

Vital signs will be collected at screening, check-in visit, and LSD+1 Visit. Vital signs at each time point and change from baseline at LSD+1 visit will be summarized by treatment group (**Table 14.3.5**) with descriptive statistics without inferential statistics.