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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLQ	below the limit of quantification
CI	confidence interval
C_{max}	maximum observed plasma concentration
CL/F	apparent total clearance
COVID-19	Coronavirus disease 2019
COWS	clinical opiate withdrawal scale
CV	coefficient of variation
DEC	decrease
DMC	data monitoring committee
ET	early termination
CRF	case report form
INC	increase
INR	international normalized ratio
KM	Kaplan Meier
mITT	Modified Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MME	morphine milligram equivalent
$MR_{M/U}$	metabolic ratio
NPRS	numerical pain rating scale
PK	Pharmacokinetic
PK-C	pharmacokinetic concentration
PK-P	Pharmacokinetic parameter
PPS	Per-protocol Set
PT	preferred term, prothrombin time
RMST	restricted mean survival time
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
STEAE	Serious treatment-emergent adverse event
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
T_{max}	time to maximum plasma concentration

ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handlings to be employed for the analysis of the study protocol 1902G1721, Version 3, dated 18 June 2020. Table, figure, and listing (TFL) mock-ups are provided in the TFL shells prepared separately.

All the analyses described in the SAP will be performed in the Biostatistics Center, Biometrics, Shionogi Inc. Any deviations from the final SAP will be documented in the clinical study report.

2. OVERVIEW

This is a Phase 2, multicenter, randomized, parallel-group, double-blind, placebo-controlled study in patients undergoing partial small or large bowel resection with primary anastomosis or radical cystectomy requiring bowel transection with primary anastomosis.

The study will consist of 3 study periods:

- a Screening/Baseline period (Day –14 to Day 0)
- a Treatment period (study treatment for no more than 11 days, including Day 0 [day of surgery] plus through 10 postoperative days).
- a Follow-up period 30 days after Day 10 or after the day of discharge (whichever is sooner), with a window of + 3 days, but not < 30 days (End-of-study Visit) or an Early Termination (ET) Visit.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the primary endpoint.
  - The primary endpoint is the time from the end of surgery to time to first toleration of solid food and first bowel movement (GI2).

3.2 Secondary Objective

The secondary objective of the study is:

- To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the secondary endpoints.
  - Secondary endpoints are the time from the end of surgery to time when the discharge order is written, proportion of patients requiring postoperative reinsertion of the nasogastric tube, proportion of patients with nausea on Days 1 through 3, proportion of patients with vomiting on Days 1 through 3 and

proportion of patients discharged by Day 10 who are readmitted for any reason within 30 days after discharge from the hospital.

3.3 Other Objectives

- To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the exploratory endpoints
- To characterize the pharmacokinetics (PK) profile of naldemedine 1.25 mg, 2.5 mg, and 5 mg and its metabolite (nor-naldemedine) for the PK endpoints.
- To compare the safety of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the safety endpoints

4. STUDY DESIGN

4.1 Study Blinding and Randomization

Eligible patients will be randomized in a ratio of 1:1:1:1 to one of the following treatment groups: naldemedine 1.25 mg, 2.5 mg, or 5 mg or placebo. Randomization will be stratified by the planned surgical procedure, ie, small bowel resection with primary anastomosis, large bowel resection with primary anastomosis, or radical cystectomy requiring bowel transection with primary anastomosis. All patients will be centrally randomized to study treatment using an Interactive Web Response System (IWRS).

4.2 Sample Size

The sample size of between 44 and 85 per group will be required for the Modified Intention-To-Treat (mITT) Population to provide at least 80% power. The simulation estimated 44 patients per treatment group to see a linear trend in the restricted mean survival time (RMST) up to 240 hours for the time to the event of GI2 in across a 24-hour difference between naldemedine 5 mg and placebo under 80% statistical power at a 2-sided significance level of 0.05. Eighty-five patients per treatment group will be required to see a linear trend in RMST up to 240 hours across an 18-hour difference between naldemedine 5 mg and placebo. The final sample size will be dependent on the enrollment rate during the fixed enrollment period. A minimum of 44 patients per group in the mITT population is desired.

5. ANALYSIS POPULATIONS

5.1 Modified Intention-to-treat Population

The mITT Population will include all randomized patients who received at least 1 dose of study treatment and had at least 1 postbaseline efficacy assessment for the primary efficacy endpoint, which includes all three components (end of surgery time, time when the patient first tolerates solid food, and time of first bowel movement) of the time to event of GI2. Patients will be analyzed according to the treatment to which they were randomized.

This population will be the primary efficacy analysis population.

5.2 Per-protocol Set

The Per-protocol Set (PPS) will include all patients in the mITT Population who did not have a major protocol deviation, as defined in a separate document, Protocol Deviation Plan. Major protocol deviations for the PPS will be determined prior to unblinding of the study data.

This population will be used in a supplementary analysis for the primary endpoint.

5.3 Safety Analysis Population

The Safety Analysis Population will include all randomized patients who received at least 1 dose of the study treatment. The population will be analyzed according to the treatment that patients actually received, rather than the study treatment to which patients were randomized.

This population will be used in all safety analyses.

5.4 Pharmacokinetic Concentration Population

The Pharmacokinetic Concentration (PK-C) Population will include all patients who received at least 1 dose of naldemedine and had at least 1 evaluable concentration of either naldemedine or nor-naldemedine in plasma. This population will be used for the concentration listing.

5.5 Pharmacokinetic Parameter Population

The Pharmacokinetic Parameter (PK-P) Population will include all patients with at least 1 PK parameter estimated appropriately. This population will be used for PK parameter listings and summaries, plotting of the plasma concentration-time data, plasma concentration summaries, and statistical analysis.

6. STATISTICAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1 Statistical Reporting

Unless otherwise noted, continuous variables will be summarized by using the number of nonmissing observations, arithmetic mean, standard deviation (SD), median, and minimum, and maximum values as summary statistics; categorical variables will be summarized by using the frequency count and the percentage of patients in each category.

Patient study data, including data not appearing in tables, will be presented in by-patient data listings. In general, all tables will be presented by treatment group. Individual patient data and any derived data will be presented by treatment and patient.

All analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, NC, USA), or WinNonlin Version 6.2.1 or higher (Certara, St Louis, MO, USA).

6.2 Statistical Testing

All statistical tests will be performed at the 2-sided significance level of 0.05, unless otherwise noted. No multiplicity adjustment will be made in this study.

6.3 Analysis Visit Windows

No analysis visit window will be applied. The data will be collected according to Figure 1-2 and Table 1-2 in the protocol and analyzed according to the time point collected on the case report form (CRF).

6.4 Missing Data

Missing values will not be imputed. All statistical analyses will be based on observed cases unless otherwise noted.

6.5 Definition

6.5.1 Study Day

For programming and analysis purposes, the study days specified in the protocol will be mapped as shown in Table 1. Study day will be presented in this SAP in the same way as presented in the protocol, while TLF shells and TLFs will present "Surgery Day" or "Postop Day X" as shown in parentheses in this mapping table.

Table 1 Mapping Information for Study Days

Protocol Day	Screening Period	Treatment Period								Follow-up Period
	Day −14 to 0	Day 0		Day 1	Day 2	Day 3	Day 4	Days 5 to 10	Day of Discharge	Early Termination	End-of-study Visit
	Baseline	Before Surgery	After Surgery								
Mapped Analysis Day	Day −14 to 1	Day 1 Before Surgery (surgery day)	Day 1 After Surgery (surgery day)	Day 2 (Postop Day 1)	Day 3 (Postop Day 2)	Day 4 (Postop Day 3)	Day 5 (Postop Day 4)	Days 6 to 11 (Postop Days 5 to 10)	Day of Discharge	Early Termination	End-of-study Visit

Postop = postoperative

Study Day 0 will be the day of surgery, and any other study day will be calculated relative to Study Day 0. Therefore, Day 1 will start at midnight after surgery of that calendar day and Day X (X = 1, 2, .., 10) will start at midnight of the X-th day. "Study Day" will simply be represented as "Day" hereafter in this SAP.

6.5.2 Baseline

Baseline except for the Numerical Pain Rating Scale (NPRS) will be defined as the last value obtained before randomization. The baseline value for NPRS will be the value as assessed on the morning of Day 1.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Patient Disposition

The number of patients who failed the Screening Period (ie, screen failure) and its proportion to enrolled patients will be summarized along with the reason for not being randomized to treatment.

A summary table will be produced detailing the number of subjects randomized, the number of patients who completed the study, and the number of patients who prematurely discontinued from the study. In addition, the reason for discontinuation from the study will be summarized.

The number and proportion of patients in each analysis population to the randomized population will be summarized, as well as the reasons for exclusion from the mITT Population, the PPS, the Safety Analysis Population, PK-C and PK-P Populations.

7.2 Demographic and Baseline Characteristics

Demographic data and baseline characteristics shown in **Error! Reference source not found.** will be summarized descriptively as described in Section 6.1 for the mITT Population and the Safety Analysis Population. Prior surgeries can be any abdominal surgery except: gastrectomy, gastric bypass, gastric sleeve, lap banding, pancreatic resection, hepatectomy, intestinal transplant. Prior surgeries will be identified and finalized by the Shionogi Medical Monitor prior to database lock and unblinding. The categories used to summarize these data are shown in Table 7.

Table 2 Demographic and Baseline Characteristics

Continuous variable	• Age
Categorical variables	• Sex • Surgical procedure • Fertility status for females • Race • Ethnicity • Elements of the enhanced recovery protocol • Prior surgery

Medical histories will be summarized by treatment group for the mITT Population. The reported medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

8. STUDY CONDUCT

8.1 Treatment Exposure and Compliance

For the mITT Population and the Safety Analysis Population, the duration of treatment exposure and treatment compliance rate will be summarized descriptively by treatment group. The categories used in the summary of frequency counts (if applicable) are shown in Table 6.

The duration of treatment exposure will be defined as the dosing period during which a patient took the study drug:

(final dose date) – (initial dose date) + 1 [day]

The treatment compliance rate will be defined as:

(total number of tablets that patients actually took during duration of treatment exposure) / (total number of tablets that patients should have taken during duration of treatment exposure) × 100 [%]

A dose will be considered one tablet. Patients will receive the study drug twice daily through Day 10; a total of two tablets per day will be administered. However, depending on the time surgery is done, patients may not take study drug after surgery on Day 0, which means the number of tablets can be one on Day 0.

8.2 Prior and Concomitant Medications and Therapies

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WhoDrugDDEB3 – 201909). Prior medications and therapies will be defined as medication taken prior to Day 0. Concomitant medications and therapies will be defined as medication taken after first dosing.

For the mITT population, the number and proportion of patients who took prior and concomitant medications will be summarized with WHO Drug Dictionary Preferred Term (PT) by category (laxative, opioid, and others) for each treatment group. If a patient has more than 1 drug that codes to the same PT, the patient will be counted only once for that PT.

The number and proportion of patients who took prior and concomitant therapies will be summarized by the preferred term in each treatment group for the mITT population. Patients for whom a particular therapy name was reported more than once will be counted only once for that therapy.

8.3 Protocol Deviation

For all randomized patients, major protocol deviations relating to PPS will be listed. Major protocol deviations, including protocol deviations related to COVID-19, will be specified in the “Protocol deviation plan” separately. A final list of major protocol deviations will be determined based on the data review prior to database lock.

9. EFFICACY

Efficacy analyses will be performed for the mITT population unless otherwise specified.

9.1 Primary Endpoint

The time from the end of surgery (defined as the time the patient leaves the operating room) to time to first toleration of solid food (defined as the time when the patient consumes a meal that requires chewing and has no significant nausea or vomiting, as per the judgment of the investigator, for 4 hours after that solid food) and first bowel movement (GI2) will be the primary endpoint and called "Time to event of GI2". The time to event of GI2 will be the later time at which all of the following criteria are met:

- First toleration of solid food (as defined above)
- First bowel movement after surgery

If one of three time components (end of surgery time, time when the patient first tolerates solid food, and time of first bowel movement) is missing, time to event of GI2 will be considered as missing.

If time to event of GI2 does not occur during the evaluation period of 240 hours, the patient will be censored at the time of his/her last nonmissing postbaseline assessment.

9.1.1 Primary Analysis

The primary objective is to compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the primary endpoint.

Let $\hat{\mu}_{kg}(t)$ be the estimate of RMST at time t for the surgical procedure k (k=1,2,3) and treatment group g (g=1,2,3,4). Let $\hat{\mu}_k(t) = (\hat{\mu}_{k1}(t), \hat{\mu}_{k2}(t), \hat{\mu}_{k3}(t), \hat{\mu}_{k4}(t))^T$ be the vector of estimates of RMST for surgical procedure k. $c = (-3, -1, 1, 3)^T$ is defined as contrast coefficient. The null hypothesis will be

$$H_0: c^T\mu_1(t) = c^T\mu_2(t) = c^T\mu_3(t) = 0$$

and test statistics T will be

$$T = \frac{\sum_{k=1}^{3} c^T\hat{\mu}_k(t)}{\sqrt{\sum_{k=1}^{3}\{Var[c^T\hat{\mu}_k(t)]\}}}$$

, where

$$Var[c^T\hat{\mu}_k(t)] = 9 * Var[\hat{\mu}_{k1}(t)] + 1 * Var[\hat{\mu}_{k2}(t)] + 1 * Var[\hat{\mu}_{k3}(t)] + 9 * Var[\hat{\mu}_{k4}(t)]$$

Therefore p-value will be

$$2\{1 - \Phi(|T^{obs}|)\}$$

, where $\Phi(\cdot)$ will be standard normal distribution and T^{obs} will be the observed test statistics.

For pairwise comparison between treatment groups i and j (i, j =1,2,3,4), the null hypothesis will be

$$H_0: \mu_{1i}(t) - \mu_{1j}(t) = \mu_{2i}(t) - \mu_{2j}(t) = \mu_{3i}(t) - \mu_{3j}(t) = 0$$

and test statistics S will be

$$S = \frac{\sum_{k=1}^{3}\{\hat{\mu}_{ki}(t) - \hat{\mu}_{kj}(t)\}}{\sqrt{\sum_{k=1}^{3}\{Var[\hat{\mu}_{ki}(t)] + Var[\hat{\mu}_{kj}(t)]\}}}$$

1) The mean survival time, which is also referred to as the RMST, of GI2 events within 240 hours will be estimated using the area under the Kaplan-Meier (KM) curve. To demonstrate the linear dose-response relationship between treatment groups (3 naldemedine groups and placebo group) and the RMST, the linear contrast test for trend with contrast coefficients of (-3, -1, 1, 3) will be performed based on the test statistics T described above. Two types of KM curve with 95% confidence bound and point estimate line only will be provided. SAS code will be provided in section 13.2.
2) Pairwise comparisons of all treatments will be undertaken based on the test statistics S described above and the differences of treatment means including their 95% confidence interval (CI) will be calculates as

$$\frac{1}{3}\sum_{k=1}^{3}\{\hat{\mu}_{ki}(t) - \hat{\mu}_{kj}(t)\} \pm z_{\alpha/2} \times \frac{1}{3}\sqrt{\sum_{k=1}^{3}\left\{Var[\hat{\mu}_{ki}(t)] + Var\left[\hat{\mu}_{kj}(t)\right]\right\}}$$

$z_{\alpha/2}$ is the upper 100α % quantile of the standard normal distribution.

9.1.2 Supplementary Analysis

The following supplementary analyses will be undertaken using the mITT population, unless otherwise noted:

- Repeat of the primary endpoint analysis, based on the PPS.
- Repeat of the primary endpoint analysis, excluding all patients who received additional therapies that could impact the primary endpoint at any time until the

day GI2 is achieved or Day 10 or withdrawal or discharge day, whichever comes first. The list of all patients who received additional therapies that could impact the primary endpoint at any time until achievement of the GI2 endpoint or completion of the study will be provided by the Shionogi Medical Monitor prior to database lock and unblinding.

- For each treatment group, a two-way table summarizing the proportion of patients by achievement of GI2 until 240 hours (yes/no) and additional therapies received that could impact the primary endpoint at any time (yes/no) until Day 10 or withdrawal or discharge day, whichever comes first.
- Proportion of patients achieving GI2 by treatment group and cumulative day. As for the definition of cumulative day, if patients achieved GI2 on a certain day, GI2 will be considered as sustained through Day 10 or withdrawal or discharge day, whichever comes first (called "last day"). Pairwise comparison as Cochran Mantel Haenszel test adjusted by surgical procedure will be applied to the proportion at Day 10.
- Proportion of patients achieving GI2 by treatment group, surgical procedure, and cumulative day.

9.1.3 Subgroup Analysis

RMST will be calculated and two types of KM curve with 95% confidence bound and point estimate line only will be provided by following subgroups.

- Surgical procedure (Small bowel resection with primary anastomosis, large bowel resection with primary anastomosis, or radical cystectomy requiring bowel transection with primary anastomosis)
- Prior surgery (No prior surgery, 1 prior surgery, 2 prior surgeries)
- Epidural anesthesia (yes/no)
- Enhanced recovery protocol (all aspects of ERP versus those that had only the 3 that were mandated)

9.2 Secondary Endpoints

9.2.1 Time from the End of Surgery to Time when the Discharge Order is Written

The time from the end of surgery to time when the discharge order is written will be the hours between date and time of surgery and date and time of writing the discharge order. The censoring will be defined in the same manner as defined for the primary endpoint.

9.2.1.1 Analysis

Pairwise comparison will be applied to the time from the end of surgery to time when the discharge order is written in the same way as described in section 9.1.1. A Kaplan-Meier curve will be provided by treatment group.

9.2.2 Proportion of Patients Requiring Postoperative Re-insertion of the Nasogastric Tube

The proportion of patients requiring postoperative re-insertion of the nasogastric tube will be calculated based on the number of patients requiring postoperative re-insertion of the nasogastric tube. Patients in the mITT Population who do not have postoperative re-insertion of the nasogastric tube will be excluded from the denominator.

9.2.2.1 Analysis

Pairwise comparison as Cochran Mantel Haenszel test adjusted by surgical procedure will be applied to the proportion.

9.2.3 Proportion of Patients with Nausea on Days 1 through 3

Nausea will be as reported as an adverse event. The following proportions will be calculated by treatment group.

(1) The proportion of patients who completed the study on Day 1, 2 and 3 with nausea between Day 1 and Day 3
(2) The proportion of patients with nausea between first dosing and Day 1

9.2.3.1 Analysis

Pairwise comparison as Cochran Mantel Haenszel test adjusted by surgical procedure will be applied to the proportion of patients who completed the study on Day 1, 2 and 3 with nausea between Day 1 and Day 3 defined in 1) of section 9.2.3.

9.2.4 Proportion of Patients with Vomiting on Days 1 through 3

Vomiting will be as reported as an adverse event. The proportions described in section 9.2.3 will be calculated for vomiting.

9.2.4.1 Analysis

The proportion will be analyzed in the same way as section 9.2.3.1.

9.2.5 Proportion of Patients Discharged by Day 10 who are Re-admitted for Any Reason Within 30 Days after Discharge from the Hospital

The proportion of patients discharged by Day 10 who are re-admitted to the hospital for any reason will be calculated. Similarly, the proportion of patients discharged by Day 10 who are re-admitted to the hospital for Postoperative GI dysfunction-related causes will be also calculated.

9.2.5.1 Analysis

Each proportion will be analyzed in the same way as described in section 9.2.2.1.

9.3 Exploratory Endpoints

9.3.1 Time from the End of Surgery to Time to Discharge Readiness

The time from the end of surgery to time to discharge readiness will be the hours between the date and time of surgery and the date and time of discharge readiness. The censoring will be defined in the same manner as defined for the primary endpoint.

9.3.1.1 Analysis

Treatment groups will be compared based on the time from the end of surgery to time to discharge readiness in the same way as described in section 9.1.1. A Kaplan-Meier curve will be provided by treatment group to make the comparison.

9.3.2 Time from the End of Surgery to Time to Actual Discharge from the Hospital (Length of Stay)

The time from the end of surgery to time to actual discharge from the hospital will be the hours between the date and time of surgery and the date and time of actual discharge. The censoring will be defined in the same manner as defined for the primary endpoint.

9.3.2.1 Analysis

Treatment groups will be compared based on the time from the end of surgery to time to actual discharge from the hospital in the same way as described in section 9.1.1. A Kaplan-Meier curve will be provided by treatment group to make the comparison.

9.3.3 Proportion of Patients with Prolonged Hospital Stay due to GI Dysfunction

The proportion of patients with prolonged hospital stay due to GI dysfunction for each treatment group will be calculated.

9.3.3.1 Analysis

The proportion will be analyzed in the same way as described in section 9.2.2.1.

9.3.4 Time from Initial Insertion of the Nasogastric Tube to Removal of the Nasogastric Tube

The time from initial insertion of the nasogastric tube to removal will be calculated between these two time points for each patient, expressed in hours with two decimals. It will be summarized by treatment group.

9.3.4.1 Analysis

Summary statistics will be provided by treatment group. A pairwise comparison as ANCOVA adjusted by surgical procedure will be performed. Kaplan-Meier curves by treatment group for time to removal of the nasogastric tube from initial insertion will be provided.

9.3.5 Proportion of Patients with Abdominal Distension on Day 1 through the Day on which GI2 is Achieved

Abdominal distension will be as reported as an adverse event. The following proportions in the mITT Population will be calculated.

(1) The proportion of patients who achieved GI2 after Day 1
   a) And who had abdominal distension on Day 1 through the day on which GI2 is achieved
   b) And who had abdominal distension other than the time window above in a) from first dose to Day 10 or withdrawal or discharge day.
   c) And who did not have abdominal distension

(2) The proportion of patients who did not achieve GI2 after Day 1
   a) And who had abdominal distension from first dose to Day 10 or withdrawal or discharge day
   b) And who did not have abdominal distension

9.3.5.1 Analysis

Pairwise comparison as Cochran Mantel Haenszel test adjusted by surgical procedure will be applied to the proportion of patients who achieved GI2 after Day 1 and had abdominal distension on Day 1 through the day on which GI2 is achieved defined in (1) – a) of section 9.3.5.

9.3.6 Proportion of Patients with Nausea on Day 4 through Day of Discharge

Nausea will be as reported as an adverse event. The following proportions will be calculated.

(1) Proportion of patients who completed the study up to at least Day 4 with nausea occurring at least once between Day 4 and discharge
(2) Proportion of patients who completed the study up to at least Day 4 without nausea occurring at any time between Day 4 and discharge
(3) Proportion of patients who were discharged prior to Day 4

9.3.6.1 Analysis

Pairwise comparison as Cochran Mantel Haenszel test adjusted by surgical procedure will be applied to the proportion of patients who completed the study up to at least Day 4 with nausea occurring at least once between Day 4 and discharge defined in (1) of section 9.3.5.

9.3.7 Proportion of Patients with Vomiting on Day 4 through Day of Discharge

Vomiting will be as reported as an adverse event. The proportions described in section 9.3.6 will be calculated for vomiting.

9.3.7.1 Analysis

The proportion will be analyzed in the same way as described in section 9.3.5.1.

9.3.8 Proportion of Patients who Achieve GI2 in Each Treatment Group by Postoperative Day

The proportion of patients who achieved GI2 by study day will be calculated by treatment group. The denominator will be the number of patients who stayed in the study by each study day.

9.3.8.1 Analysis

The proportion will be analyzed at each postoperative day in the same way as described in section 9.2.2.1.

9.3.9 Proportion of Patients who Receive Concomitant Medication that May Have a Laxative Effect

The proportion of patients who received concomitant medication during study drug exposure that may have a laxative effect will be calculated. Concomitant medication with a laxative effect can be bisacodyl, macrogol and docusate sodium, but is not limited to these. They will be identified and finalized by the Shionogi Medical Monitor prior to database lock and unblinding.

9.3.9.1 Analysis

The proportion will be analyzed in the same way as described in section 9.2.2.1.

9.3.10 Effect of Prior Surgery on the GI2 Endpoint

The proportion of patients who achieved of GI2 until 240 hours (yes/no) by prior surgery (no prior surgery, 1 prior surgery or 2 prior surgery) will be calculated. Prior surgeries can be any abdominal surgery except: gastrectomy, gastric bypass, gastric sleeve, lap banding, pancreatic resection, hepatectomy, intestinal transplant. Prior surgeries will be identified and finalized by the Shionogi Medical Monitor prior to database lock and unblinding.

9.3.10.1 Analysis

Pairwise comparison as Cochran Mantel Haenszel test adjusted by prior surgery will be applied to the proportion.

10. SAFETY

All safety analyses will be performed for the Safety Analysis Population.

10.1 Adverse Events

Adverse events (AEs) will be coded and classified by System Organ Class (SOC) and PT using MedDRA Version 23.0. Unless otherwise specified, analyses will be based on

treatment-emergent adverse events (TEAEs), which is any AE reported after the first dose of the study drug.

The number and proportion of patients who experienced at least 1 TEAE will be summarized by treatment group. The proportions will be presented along with the 95%Cis, calculated with the Clopper-Pearson method. The number of TEAEs reported will also be calculated. TEAEs with an outcome of death, other serious treatment-emergent adverse events (STEAEs), severe TEAEs, TEAEs leading to discontinuation of the study drug, treatment-related TEAEs, treatment-related TEAEs with an outcome of death, other treatment-related STEAEs, severe treatment-related TEAEs, and treatment-related TEAEs leading to discontinuation of the study drug will be summarized in the same manner. The definitions of these events are shown in Table 3.

Table 3 Definition of Adverse Event Terms

Term	Definition
TEAE with an outcome of death	TEAE with "Fatal" in terms of outcome
Other STEAE	TEAE with "Serious" in terms of seriousness excluding TEAE with an outcome of death
TEAE leading to discontinuation of the study drug	TEAE with "Drug withdrawn" in terms of the action taken for study drug
Severe TEAE	TEAE with "Severe" in terms of severity
Treatment-related TEAE	TEAE with "Related" in terms of the causal relationship with study drug
Treatment-related TEAE with an outcome of death	Treatment-related TEAE with "Fatal" in terms of outcome
Other treatment-related STEAE	Treatment-related TEAE with "Serious" in terms of seriousness excluding treatment-related TEAE with an outcome of death
Severe treatment-related TEAE	Treatment-related TEAE with "Severe" in terms of severity
Treatment-related TEAE leading to discontinuation of the study drug	Treatment-related TEAE with "Drug withdrawn" in terms of the action taken for study drug

STEAE = serious treatment-emergent adverse event; TEAE = treatment-emergent adverse event.

The number and proportion of patients who experience TEAEs will be summarized by SOC and PT for each treatment group. For these summaries, patients with multiple TEAEs will be counted only once within an SOC and PT. TEAEs with an outcome of death, other STEAE, TEAEs leading to discontinuation of the study drug, treatment-related TEAEs, treatment-related TEAEs with an outcome of death, and other treatment-related STEAEs will be summarized in the same manner.

TEAEs relating to opioid withdrawal defined in Table 4 will also be summarized.

The proportion of specific TEAEs relating to gastrointestinal disorders and opioid withdrawal defined in Table 4 and all TEAEs by severity will be plotted.

Table 4 Definition of Specific TEAE

Specific TEAE	Definition
Gastrointestinal disorders	All Preferred Terms under Gastrointestinal Disorders (SOC)
Opioid withdrawal	All Preferred Terms (Cholinergic rebound syndrome, Delusion of parasitosis, Drug rehabilitation, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal maintenance therapy, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Rebound effect, Steroid withdrawal syndrome, Withdrawal arrhythmia, Withdrawal catatonia, Withdrawal syndrome) under Drug withdrawal (MedDRA SMQ)

The number and proportion of patients who experience TEAEs in each category of severity will be summarized by SOC and PT for each treatment group. Patients who experience the same TEAE more than once in different categories will be counted only once by the worst severity. Treatment-related TEAEs will be summarized in the same manner.

10.2 Vital Signs

Summary statistics for vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse rate) will be calculated for each time point and for the change from baseline to each time point measured after randomization. Clinical significance will be defined as follows.

- SBP value >= 160 or Increase (INC) >= 20
- SBP value <= 90 or Decrease (DEC) >= 20
- DBP value >= 105 or INC >= 15
- DBP value <= 50 or DEC >= 15
- Pulse rate value >= 120 or INC >= 15
- Pulse rate value <= 50 or DEC >= 15

10.3 Laboratory Evaluations

Summary statistics for laboratory test data will be calculated for each time point and for the change from baseline to each time point measured after randomization. Categorical parameters at each scheduled time point measured at baseline and after randomization will be summarized by using the frequency count and the percentage of patients in each category. Shift tables from baseline to the observed value in each time point will be presented for categorical parameters.

The number and proportion of patients who meet the prespecified criteria shown in Table 5 will be summarized by treatment group for each time point. Patients with laboratory abnormalities at least once throughout the study (including measurements collected outside of the analysis visit window) will be summarized in the same manner.

Table 5 Criteria for Laboratory Tests

Laboratory Test (Unit)	Criteria
ALT (U/L)	Value > 3 × ULN
	Value > 8 × ULN
AST (U/L)	Value > 3 × ULN
	Value > 8 × ULN
AST (U/L) or ALT (U/L)	Value > 3 × ULN
	Value > 5 × ULN
	Value > 8 × ULN
AST (U/L) or ALT (U/L) + total bilirubin (mg/dL) or PT-INR	Meet all of the following criteria: • AST ≥ 3 × ULN or ALT ≥ 3 × ULN • Total bilirubin value ≥ 2 × ULN or PT-INR>1.5
AST (U/L) or ALT (U/L) + other conditions	Meet all of the following criteria: • AST ≥ 3 × ULN or ALT ≥ 3 × ULN • accompanied by fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
Total bilirubin	Value > 2 × ULN
PT-INR	Value > 1.5

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; PT = prothrombin time; ULN = upper limit of normal

10.4 Electrocardiograms

Electrocardiogram findings (normal, abnormal – not clinically significant, abnormal – clinically significant) will be summarized for each time point measured after randomization by treatment group.

10.5 Physical Examinations

Summary of the overall assessment by time point will be presented as categories (normal, abnormal – clinically significant, abnormal - not clinically significant, not done). The same summary by body system (autoimmune, cardiovascular, dermatological, ears/nose/throat, endocrine/metabolic, gastrointestinal, genito-urinary, hematologic/lymphatic, hepatic, immunological, musculoskeletal, neurological, ophthalmological, psychological, respiratory) will be presented.

10.6 Pain Intensity as Assessed on Numerical Pain Rating Scale

Values will be summarized using statistics for continuous variables for all available days. In addition, from Day 2 onwards the change from baseline will be summarized using statistics for continuous variables.

10.7 Clinical Opiate Withdrawal Scale

Total scores across all domains will be summarized using statistics for continuous variables on each day. The proportion of patients in each score category by domain will be calculated.

10.8 Opioid analgesics

Morphine milligram equivalent (MME) (mg) will be calculated as (dose of opioid analgesics) x (conversion factor). The conversion factor by opioid type is shown in Table 6 below; the table will be updated prior to database lock if additional opioid types need to be added.

MMEs will be summarized as continuous variables on each day.

Table 6 Conversion Factor

Opioid Type (Route)	Unit	Conversion Factor
LEVOMETHADONE	mg	8
LEVORPHANOL	mg	7.5
HYDROMORPHONE	mg	4
METHADONE	mg	4
OXYMORPHONE	mg	3
FENTANYL (Topical or Transdermal)	ug/hour	2.4
OXYCODONE	mg	1.5
HYDROCODONE	mg	1
MORPHINE	mg	1
CODEINE	mg	0.15
DIHYDROCODEINE	mg	0.15
FENTANYL (Intravenous, Sublingual or Transmucosal)	ug	0.1
MEPERIDINE	mg	0.1
BUTORPHANOL	mg	0
PENTAZOCINE	mg	0
TAPENTADOL	mg	0
TRAMADOL	mg	0
BUPRENORPHINE	mg	0
SUFENTANIL	mg	0

10.9 Analysis for ClinTrial.gov

This section specifies the safety analyses only for ClinTrial.gov, and the summary will not be included in the clinical study report.

The number and proportion of patients who experience TEAEs excluding treatment-related TEAE with an outcome of death and other STEAEs by SOC and PT will be summarized.

11. Pharmacokinetics

11.1 Plasma Drug Concentrations of Naldemedine and Nor-naldemedine

Plasma drug concentrations of naldemedine and nor-naldemedine will be listed for the PK-C Population and summarized for the PK-P Population by actual treatment group, and nominal sampling time with the number of nonmissing observations (N), arithmetic mean (mean), standard deviation (SD) and coefficient of variation (CV%, calculated by SD/mean × 100), geometric mean and coefficient of variation for geometric mean (Geometric CV%), and median, minimum and maximum values at each sampling time presented. The Geometric CV% will be calculated as follows: Geometric CV% = $[\exp(sd^2)-1]^{1/2} \times 100$, where SD is the standard deviation for natural log (ln)-transformed data. The time course profiles for plasma drug and metabolite concentrations will be presented graphically.

For the summary of plasma drug and metabolite concentrations, concentrations below the limit of quantification (BLQ) will be treated as zero (0) for calculations of the mean, SD, CV%, and median, minimum, maximum values and will be treated as missing for calculation of the geometric mean and geometric CV% values.

Data will be summarized by nominal sampling time, using the following times:

- Day 2 immediately before the morning dose
- Day 3 immediately before the morning dose and 1 hour and 2, 4, 8, and 12 hours after the morning dose before administration of the evening dose
- Day 4 immediately before the morning dose

11.2 PK Parameters for Naldemedine and Nor-naldemedine on Day 3

The PK parameters will be estimated using the PK-P Population. The following PK parameters will be calculated, whenever possible, for naldemedine and nor-naldemedine from plasma concentration data on Day 3 (immediately before the morning dose and 1 hour and 2, 4, 8, and 12 hours after the morning dose before administration of the evening dose) by noncompartmental methods. Other parameters may be computed, as appropriate, upon review of the data. The following estimated PK parameters will be computed for each study patient using the actual sample collection times:

- C_{max} – maximum observed plasma concentration on Day 3
- T_{max} – time to maximum plasma concentration on Day 3. If T_{max} is the actual time for the predose (0 hours) on Day 3, T_{max} will be calculated as 0.
- $AUC_{0-\tau}$ – area under the concentration- time curve over the dosing interval τ (12 hours) on Day 3; calculated by linear up/log down trapezoidal method. $AUC_{0-\tau}$ will

be calculated with observed plasma concentrations from time 0 to τ (actual time) on Day 3 without extrapolation or interpolation. The actual time for the predose (0 hours) on Day 3 will be replaced with 0. If the observed plasma concentration at τ on Day 3 is BLQ, the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$) will be used as $AUC_{0\text{-}\tau}$.

- CL/F – apparent total clearance estimated as CL/F = dose/$AUC_{0\text{-}\tau}$ on Day 3 (for naldemedine only)
- $MR_{M/U,\ Cmax}$ – metabolic ratio of C_{max} of nor-naldemedine to C_{max} of naldemedine, corrected for molecular weight, defined as:
  - $\frac{C_{max} \text{ of nor-naldemedine}}{C_{max} \text{ of naldemedine}} * \frac{570.64}{516.55}$

  (for nor-naldemedine only)
- $MR_{M/U,\ AUC}$ – metabolic ratio of $AUC_{0\text{-}\tau}$ of nor-naldemedine to $AUC_{0\text{-}\tau}$ of naldemedine, corrected for molecular weight, defined as:
  - $\frac{AUC_{0-\tau} \text{ of nor-naldemedine}}{AUC_{0-\tau} \text{ of naldemedine}} * \frac{570.64}{516.55}$

  (for nor-naldemedine only)

The estimated PK parameters except for T_{max} will be summarized by actual treatment group with N, mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum values. The T_{max} will be summarized by analyte and dosing regimen with N, mean, SD, CV%, median, minimum and maximum values. If the number of patients with PK parameter data is < 3, the data will not be summarized.

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the PK study director. Any such exclusion will be disclosed in the study report along with the justification for exclusion.

For the calculations of PK parameters, BLQ before the occurrence of the first quantifiable concentration on Day 3 will be treated as zero, and BLQ after the first occurrence of the quantifiable concentration on Day 3 will be treated as missing.

Pharmacokinetic calculations will be performed by using WinNonlin Version 6.2.1 or higher.

12. INTERIM ANALYSES

A Data Monitoring Committee (DMC) will review all data when assessing the benefit versus risk of the ongoing results. Since such a review may include efficacy data, an alpha spending function will be included in the DMC charter that allows for a small spend of alpha that will not impact on final alpha assessment level (eg, an alpha spend of 0.0001 based on Haybittle–Peto could be used to control alpha for each interim analysis). The DMC charter will specify the spending function to be used.

In addition, depending on the enrollment rate, an interim analysis of efficacy may be feasible. Based on the operational feasibility of such an interim analysis, the interim analysis could include a non-binding futility assessment. For example, should the enrollment project that 85 patients per group is achievable and an interim analysis based on 44 patients per group can be conducted in a timely and worthwhile fashion prior to the last patient enrolled, then the DMC will review the interim analysis results. Details for interim analyses, including futility, will be provided in the DMC Charter, and/or an accompanying DMC Statistical Analysis Plan.

13. PROGRAMMING CONVENTIONS

13.1 Formatting and Programming Rule

Unless otherwise noted, the following conventions should be used when constructing the TFLs:

- Every summary table and figure will clearly specify the analysis population being summarized. Listings will be prepared for all patients randomized.
- Rounding for all variables will occur only as the last step, immediately prior to presentation in TFLs. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Means, SDs, minimums, medians, and maximums will be reported to 1 decimal place beyond the number of decimal places with which the original endpoint is presented.
  - Calculated percentages will be reported to 1 decimal place.
  - Calculated hours will be presented to 2 decimal places.
- All means presented will be arithmetic unless otherwise stated.
- For PK concentrations and PK parameters,
  - Arithmetic mean, geometric mean, median, minimum, and maximum will be presented to the same precision as raw data
  - Standard deviation will be presented to the same precision as the arithmetic mean
  - Coefficient of variation (%) and coefficient of variation (%) for geometric mean will be presented with one decimal place.
  - Individual actual date and time of study treatment dosing, meal prior to dosing, and PK sampling will be reported with the same format as the source data.
  - Individual actual time (i.e., the difference between dosing and PK sampling time) for PK analysis will be reported with two decimal places.

- Individual concentrations will be reported with the same precision as the source data.
- Individual PK parameters C_{max} will be reported with the same precision as the source data.
- Individual PK parameters T_{max} will be reported with two decimal places
- Individual PK parameters $AUC_{0-\tau}$ will be reported with four significant digits.
- Individual PK parameters CL/F will be presented to three significant digits.
- Individual PK parameters $MR_{M/U, Cmax}$ and $MR_{M/U, AUC}$ will be presented with three decimal places.

- Table 7 shows the category displayed in analysis and summary.

Table 7 Category

Data	Category
Age	18<= x < 65, 65 < x < 74, 75<=x<=80
Sex	Male, Female
Surgical procedure	Small bowel resection with primary anastomosis, large bowel resection with primary anastomosis, or radical cystectomy requiring bowel transection with primary anastomosis
Fertility status for females	Surgically sterile, post-menopausal, potentially able to bear children
Race	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not provided
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Unknown, Not provided
Elements of the enhanced recovery protocol	(required) Early removal of the nasogastric tube defined as removal of the nasogastric tube at the end of surgery, early ambulation defined as ambulation on Day 1, early diet advancement on Day 1 (non-required) Antibiotic prophylaxis, preoperative carbohydrate drink, epidural anesthesia in addition to general anesthesia, chewing gum postoperatively
Elements of the enhanced recovery protocol (binary)	All non-required (defined as all of 4 non-mandated ERP elements), not all non-required (defined as otherwise all non-required)
Epidural anesthesia	Yes (defined as Yes in epidural anesthesia in addition to general anesthesia in ERP), No (defined as No in epidural anesthesia in addition to general anesthesia in ERP)
Prior surgery	No prior surgery, 1 prior surgery and 2 prior surgeries
Treatment compliance	x <80%, 80% <= x <=100%, 100% < x

13.2 Sample SAS Code

When dataset A has time of GI2 and censored information, there are mainly 3 steps to calculate RMST.

(1) GI2 after 240 hours should be censored before calculating RMST until 240 hours.

```
DATA B;
 SET A;
        IF (hour > 240) then status=0;
RUN;
```

(2) The program below will provide $\hat{\mu}_{kg}(t)$ in the dataset C0. The number of GI2 (saved in a variable 'Failed') will be given in the dataset C1, where hour is GI2 time, status=0 if censored, 1 if not censored, surgery is surgery procedure, treatment is treatment group.

```
ODS OUTPUT MEANS=C0 CENSOREDSUMMARY=C1;
PROC LIFETEST DATA=B TIMELIM=240;
        BY surgery;
        TIME hour*status (0);
        TEST treatment;
RUN;
```

(3) Standard deviation of each RMST $\sqrt{Var\left[\hat{\mu}_{kg}(t)\right]}$ will be given as 'sd'. The test statistics T and S defined in section 9.1.1 will be calculated by these estimates of RMST and SDs.

```
DATA D;
        MERGE C0(IN = A) C1;
        BY treatment surgery;
         sd = StdErr *SQRT((Failed – 1)/Failed);
        IF A;
RUN;
```

14. REFERENCES

1. Hasegawa, T., et al. (2020) Restricted mean survival time as a summary measure of time-to-event outcome, Pharmaceutical Statistics, 1-18.

SIGNATURE PAGE

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