Shionogi Study Title:	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study of Naldemedine in Patients Undergoing Surgeries That Include a Bowel Resection or Bowel Transection
Shionogi Study Number:	1902G1721
ClinicalTrials.gov Registration No.	NCT04355169
Study Document	Protocol Version 3 June 18, 2020

History of Protocol Amendments

Original	November 21, 2019
• Wording and description changed for clarification • Medical monitor's information changed	
Version 2	February 14, 2020
• Range of differences across treatment groups, in time to GI2, was revised to be 24 hours instead of 18 hours • Section added to support addition of endpoint	
Version 3	June 18, 2020

TITLE PAGE

Protocol Title:

A phase 2, multicenter, randomized, double-blind, placebo-controlled study of naldemedine in patients undergoing surgeries that include a bowel resection or bowel transection

Protocol Number: 1902G1721

Version: 3

Compound Name (Number):

Naldemedine (S-297995)

Short Title:

Naldemedine for patients undergoing surgeries that include a bowel resection or bowel transection

Sponsor Name:

Shionogi Inc.

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Regulatory Agency Identifying Number: Investigational New Drug (IND) [redacted]

Issue Date: 18 Jun 2020

Sponsor Signatory:

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Shionogi & Co., Ltd.

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Date

Medical Monitor Name and Contact Information:

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Shionogi Inc.
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PROTOCOL SUMMARY OF CHANGES: VERSION 3

DOCUMENT HISTORY	
Document	**Date**
Version 3	18 Jun 2020
Version 2	14 Feb 2020
Original Protocol	21 Nov 2019

Version 3: 18 Jun 2020

Section # and Name	Description of Change (Deleted text shown with strikethroughs; added text shown with underlines)	Brief Rationale
Section 1.1, Synopsis, Section 9.4.5.3, Exploratory Efficacy Endpoints	• Effect of prior surgery (yes/no) on the GI2 endpoint	Added since Inclusion Criterion 5 was revised to allow 2 prior surgeries
Section 1.1, Synopsis, Table 1-1; Section 1.3, Schedule of Activities, Table 1-2; Section 3, Objectives and Endpoints, Table 3-1	Day 0, 0.5-hour, postdose, presurgery pharmacokinetic blood sample removed	To reduce the burden of venipuncture
Section 1.1, Synopsis, Number of Patients; Section 4.1, Overall Design; Section 9.2, Sample Size Determination	Patients to be screened changed from approximately 425 to between 250 and 425, patients to be randomized changed from approximately 340 to between 200 and 340, and patients to be in each treatment group changed from approximately 85 to between 50 and 85	The expectation of the range of differences across treatment groups, in time to GI2, was revised to be 24 hours instead of 18 hours, requiring less patients to achieve the desired 80% power for the primary objective

Section 1.3, Schedule of Activities, Figure 1-2	Medical history row revised to include prior postoperative ileus and postoperative gastrointestinal dysfunction, prior and current therapy row revised to include preoperative bowel preparation and volume of intravenous fluids administered during surgery	Recording these data may provide information for future study design
	Enhanced recovery protocol elements added	To ensure all 7 elements of the enhanced recovery protocol (planned and actual) are recorded
	Baseline physical examination and electrocardiogram revised to allow preoperative physical examination and electrocardiogram without clinically significant abnormal findings within 2 weeks of the patient signing the informed consent form, and a urine pregnancy test was added from Day -14 to 0	To reduce unnecessary duplicate preoperative physical examinations and electrocardiograms, and to identify pregnant patients earlier and exclude them from the study
Section 5.2, Exclusion Criteria	1. Scheduled to undergo a total colectomy or any procedure that results in a colostomy or ileostomy.	To clarify that any procedure resulting in an ileostomy or colostomy is excluded.
	~~3. Emergency surgery~~	There was no reason to exclude patients who needed emergency surgery if the protocol criteria could be met
	5~~6~~. ~~Previous~~More than 2 prior major abdominal ~~surgery~~surgeries (eg, gastrectomy, gastric bypass, gastric sleeve, lap banding, ~~Whipple,~~ pancreatic resection, ~~total/subtotal colectomy, hemicolectomy, extensive bowel resection).~~hepatectomy, intestinal transplant).	To allow patients with prior surgeries to enroll in the study

	7~~8~~. Chemotherapy within 4 weeks prior to surgery; otherwise, patients with cancer are eligible.	Clarification
	8~~9~~. Scheduled to receive chemotherapy, immunotherapy, or radiation therapy intraoperatively or within 14 days after surgery; otherwise patients with cancer are eligible.	Clarification
Section 6.5, Medical History and Prior and Concomitant Therapy	Title revised to include Medical History	Updated to match section content
	Any prior history of postoperative ileus and postoperative gastrointestinal dysfunction must be recorded on the eCRF as part of the patient's medical history. The preoperative bowel preparation, if any, must be recorded in the eCRF. Additionally, the total volume of intravenous fluids administered during the surgery must be recorded in the eCRF.	To ensure histories of postoperative ileus and gastrointestinal function, preoperative bowel preparation, and total volume of intravenous fluids administered are recorded
	The following elements of the enhanced recovery protocol at the study site must be recorded as yes or no in the eCRF at Baseline (planned) and at the day of discharge or early termination (actual): • Three elements required by the protocol: o Early removal of the nasogastric tube, defined as removal of the nasogastric tube at the end of surgery o Early ambulation, defined as ambulation on Day 1	To ensure the 3 elements of the enhanced recovery protocol required by the protocol and the 4 other elements at the study site (planned and actual) are recorded

	○ Early diet advancement on Day 1 • Four other elements that may be used at the study site: ○ Antibiotic prophylaxis ○ Preoperative carbohydrate drink ○ Epidural anesthesia in addition to general anesthesia ○ Chewing gum postoperatively	
Section 7.1, Discontinuation of Study Treatment	The patient has an unplanned ileostomy or colostomy during the surgical procedure.	Clarification
Section 8, Study Assessments and Procedures	Procedures conducted as part of the patient's routine clinical management (eg, physical examination, blood count, electrocardiogram [ECG]) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SoA.	Clarification
Section 8.1.3.6, Effect of Prior Surgery on G12 Endpoint	The effect of prior surgery (yes/no) on the GI2 endpoint will be assessed.	Section added to support addition of endpoint
Section 8.2.1, Physical Examinations	Revised to match wording in Figure 1-2 and allow preoperative physical examination (within 2 weeks prior to the study patient signing the informed consent form)	Clarification
Section 8.2.3, Electrocardiograms	Revised to match wording in Figure 1-2 and allow electrocardiogram 2 weeks prior to the patient signing the informed consent form	Clarification

Section 9.2, Sample Size Determination	The restricted mean survival time up to 240 hours for the time to event of GI2 was revised to between 44 and 85 patients per treatment group to see a linear trend in RMST up to 240 hours across a 24-hour difference between naldemedine 5 mg and placebo, following the Weibull distribution by referring to the survival curve for the time to the event of GI2 shown in the alvimopan package insert	The target 18-hour difference was changed to a 24-hour difference
Section 9.4.3, Medical History and Prior and Concomitant Therapies	Title revised to include Medical History	Updated to match section content
	Medical histories will be listed and summarized for the mITT Population.	Inadvertently omitted previously
Section 9.5, Interim Analyses	A possible interim efficacy analysis was added, depending on the enrollment rate, that will be reviewed by the Data Monitoring Committee	To provide flexibility to the study
Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	• Any ~~clinically significant~~ abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.	Correction since "clinically significant" necessary
	• Hospitalization for preplanned and elective procedures between discharge and follow-up to treat a pre-existing condition that did not worsen after start of study will not be considered an AE and therefore will not be considered an SAE	Correction since prolonged hospitalization is considered an SAE

	despite requiring hospitalization ~~or prolonged hospitalization~~.	
Section 10.3.1, Definition of Serious Adverse Event	If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met ~~(eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease)~~.	Correction since hospitalization and death are considered SAEs
Section 10.10, Appendix 10: Protocol Version History	Strong cytochrome P450 3A (CYP3A) and P glycoprotein (P-gp) inhibitors (eg, clarithromycin, diltiazem, grapefruit juice, indinavir, ketoconazole, ritonavir) added as prohibited prior and concomitant therapy	Correction

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A phase 2, multicenter, randomized, double-blind, placebo-controlled study of naldemedine in patients undergoing surgeries that include a bowel resection or bowel transection

Protocol Number:

1902G1721

Compound Name (Number):

Naldemedine (S-297995)

Short Title:

Naldemedine for patients undergoing surgeries that include a bowel resection or bowel transection

Rationale:

Gastrointestinal (GI) dysfunction is a common finding in the postoperative setting, with a delay in the return of GI function extending the length of hospitalization. Naldemedine is an orally administered, peripherally acting mu-opioid receptor antagonist (PAMORA). Its use is currently being studied in the perioperative setting to assess its effect on the time to GI recovery following surgeries that include bowel resection and bowel transection.

Objectives and Endpoints

Table 1-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the primary endpoint	• Time from the end of surgery to time to first toleration of solid food and first bowel movement (GI2)
Secondary	
• To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the secondary endpoints	• 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 • Proportion of patients discharged by Day 10 who are readmitted for any reason

	within 30 days after discharge from the hospital
Exploratory	
• To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the exploratory endpoints	• Time from the end of surgery to time to discharge readiness • Time from the end of surgery to time of actual discharge (departure) from the hospital • Proportion of patients with prolonged hospital stay due to gastrointestinal dysfunction • Time from initial insertion of the nasogastric tube to removal of the nasogastric tube • Proportion of patients with abdominal distention on Day 1 through the day on which GI2 is achieved • Proportion of patients with nausea on Day 4 through day of discharge • Proportion of patients with vomiting on Day 4 through day of discharge • Proportion of patients who achieve GI2 in each treatment group by postoperative day • Proportion of patients who receive concomitant medication that may have a laxative effect • Effect of prior surgery (yes/no) on the GI2 endpoint
Pharmacokinetics	

• 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	• Plasma drug concentrations of naldemedine and nor-naldemedine on:
	  • 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
	• PK parameters of naldemedine and nor-naldemedine (C_{max}, T_{max}, AUC, CL/F, $MR_{M/U,\ Cmax}$, and $MR_{M/U,\ AUC}$)

Safety	
• To compare the safety of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the safety endpoints	• Incidence of treatment-emergent adverse events, including those that are serious and those that result in discontinuation of study treatment

	• Proportion of patients with clinically significant changes in clinical laboratory tests, vital signs, and ECGs • Change from baseline in pain intensity, as assessed on a Numerical Pain Rating Scale (NPRS) • Total dose of intra- and postoperative opioid analgesics in morphine milligram equivalents (MMEs)

AUC = area under the plasma concentration-time curve; CL/F = apparent total clearance estimated according to: CL/F = Dose/$AUC_{0-\tau}$ on Day 3 (for naldemedine only); C_{max} = maximum observed plasma concentration on Day 3; ECGs = electrocardiograms; $MR_{M/U, AUC}$ = metabolic ratio of AUC_{0-last} of nor-naldemedine to AUC_{0-last} of naldemedine, corrected for molecular weight, defined as (nor-naldemedine AUC_{0-last})/(naldemedine AUC_{0-last}) × (naldemedine molecular weight [570.64])/(nor-naldemedine molecular weight [516.55]) (for nor-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 (nor-naldemedine C_{max})/(naldemedine C_{max}) × (naldemedine molecular weight [570.64])/(nor-naldemedine molecular weight [516.55]) (for nor-naldemedine only); T_{max} = time to maximum plasma concentration on Day 3

Overall Design:

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. 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.

Number of Patients:

Between 250 to 425 patients will be screened to achieve between 200 and 340 randomly assigned patients, with between 50 and 85 patients in each of 4 treatment groups. The planned sample size of approximately 50 patients per group was determined by a simulation study with 10,000 iterations to see a linear trend across doses of 24 hours for a difference in the primary endpoint between naldemedine 5 mg and placebo. The maximum of 85 patients per group will detect an 18-hour difference under 80% power at a 2-sided significance level of 0.05. The final sample size between 50 and 85 patients per group will be determined by the number of patients enrolled during the fixed enrollment period.

Treatment Groups and Duration:

Throughout this protocol, study treatment refers to naldemedine 1.25 mg, naldemedine 2.5 mg, naldemedine 5 mg, and matching placebo, unless otherwise noted.

Test Drug and Dose: Naldemedine orally disintegrating tablet (ODT) will be administered as a dose of 1.25 mg, 2.5 mg, or 5 mg twice daily (BID).

Control Drug and Dose: Matching placebo ODT will be administered BID.

Mode of Administration of Test and Control Drugs: The first dose of study treatment will be administered 30 minutes to 6 hours prior to the scheduled start of surgery on the operative day (Day 0), and the second dose will be administered postoperatively the evening of the operative day. Beginning on Day 1, patients will receive study treatment BID for up to 10 days postoperatively (ie, Day 10). Every effort will be made to give the Day 1 morning dose approximately 12 hours after the Day 0 evening dose and to give all morning and evening doses from Day 1 to Day 10 at approximately 12-hour intervals.

The patient will be instructed to place the ODT on the tongue and to let it dissolve. Administration with water is not required, but water is allowed if the patient prefers.

Duration of Administration of Test and Control Drugs: Duration of administration will be determined by the date on which the primary endpoint, GI2, is met or the date on which the discharge order is written, whichever occurs sooner, and will not exceed 10 postoperative days (excluding the postoperative dose on Day 0). Note: Study treatment may be administered on the day of discharge.

Study Duration for Individual Study Patients (Includes Screening, Treatment and Follow-up Periods):

Study duration for individual patients is approximately 8 weeks. This includes the Screening Period (no more than 14 days), the Treatment Period (no more than 11 days), and the Follow-up Period (no more than 30 days after Day 10 or after the day of discharge [whichever is sooner]).

Prior and Concomitant Therapy:

Prohibited Prior and Concomitant Therapy:

- Strong cytochrome P450 3A (CYP3A) inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort)
- Strong CYP3A and P-glycoprotein (P-gp) inhibitors (eg, clarithromycin, diltiazem, grapefruit juice, indinavir, ketoconazole, ritonavir)
- Other opioid antagonists
- Prophylactic use of laxatives (eg, magnesium citrate, magnesium hydroxide, magnesium sulfate, castor oil, sodium phosphate, sodium biphosphate, polyethylene glycol enemas, and stimulant laxatives, including bisacodyl); however, if needed, laxatives may be used for rescue therapy

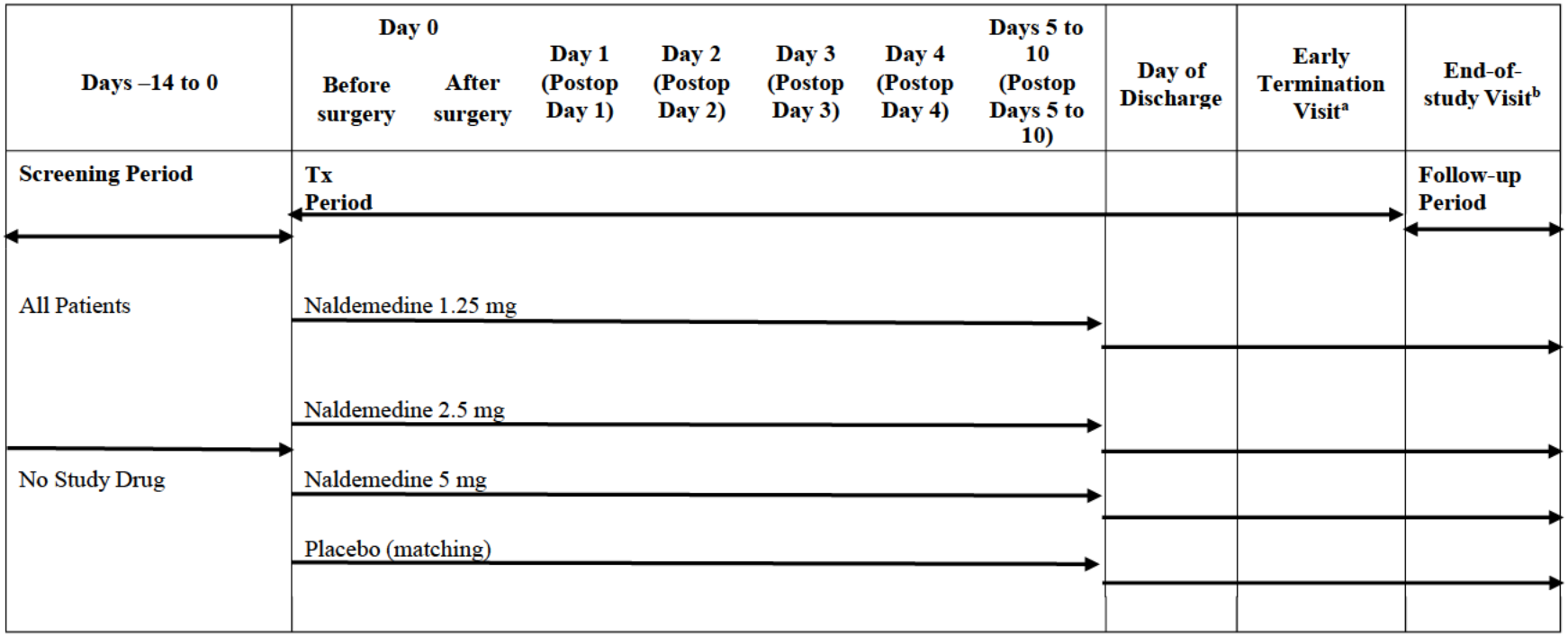
Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will be instituted for this study. The functions of the DMC are detailed in the DMC Charter.

1.2 Schema

The study schema is provided in Figure 1-1.

Figure 1-1 Study Schematic



Postop = postoperative; Tx = treatment

a These assessments will be performed for patients who discontinue study treatment early (ie, before postoperative Day 10) and for those who are withdrawn from the study.

b The End-of-study Visit will occur 30 days after Day 10 or after the day of discharge (whichever is sooner), with a window of + 3 days, but not < 30 days. A patient will be considered lost to follow-up if he or she fails to return for the End-of-study Visit and is unable to be contacted by the hospital or doctor's office staff (ie, does not respond to at least 2 telephone calls, 1 e-mail, and a registered letter).

1.3 Schedule of Activities (SoA)

The Schedule of Activities (SoA) is provided in Figure 1-2, and the schedule for pharmacokinetic sample collection is provided in Table 1-2.

Figure 1-2 Schedule of Activities

	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[a]	Early Termination[b]	End-of-study Visit[c]
Procedure/Assessment	**Baseline**	**Before Surgery**	**After Surgery**								
Administrative assessments											
Informed consent	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history, including prior postoperative ileus and postoperative gastrointestinal dysfunction	X[d]										
Prior and current therapies, including preoperative bowel preparation, volume of IV fluids administered during surgery, and intra-operative and postoperative opioid analgesics[e]	X	X	X	X	X	X	X	X	X	X	X
Time of beginning of surgery		X[f]									
Time of end of surgery		X[f]									
Enhanced recovery protocol elements[g]	X								X	X	
Clinical assessments											
Physical examination	X[h]	X[i]		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	
Vital signs and blood pressure[j]	X	X	X	X	X	X	X	X	X	X	
12-lead electrocardiogram	X[k]								X	X	
Pain assessment on NPRS[l]				X	X	X	X	X	X	X	X
COWS assessment		X		X	X	X	X	X	X	X	
Adverse event assessment	←										→

Procedure/Assessment	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[a]	Early Termination[b]	End-of-study Visit[c]
	Baseline	Before Surgery	After Surgery								
Laboratory assessments											
Routine laboratory tests[m]	X				X					X	
Urine pregnancy test[n]	X	X									
Blood sampling to determine plasma drug concentration and to characterize PK		See Table 1-2									
Study treatment (naldemedine or placebo) procedures											
Randomization and study treatment assignment by IWRS		X									
Study treatment administration[o]		X[p]	X[q]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]		
Study treatment: overdose or medication error[s]		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]		
Efficacy assessments											
Re-insertion of nasogastric tube				X	X	X	X	X			
First toleration of solid food and first bowel movement (GI2)				X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	
Time to discharge readiness[u]			X	X	X	X	X	X	X		
Time discharge order written									X		
Time of actual discharge (departure) from hospital									X		
Re-admission to hospital within 30 days after discharge											X

BID = twice daily; COWS = Clinical Opiate Withdrawal Scale; eCRF = electronic case report form; EDC = electronic data capture; IV = intravenous; IWRS = Interactive Web Response System; NPRS = Numerical Pain Rating Scale; PK = pharmacokinetics

a To be recorded in the eCRF through the End-of-study Visit, which will occur 30 days after Day 10 or after the day of discharge (whichever is sooner), with a window of + 3 days, but not < 30 days. Patients will receive no more than a total of 11 days of study treatment (Day 0 [day of surgery] plus up to 10 days beginning on Day 1).

b These assessments will be performed for patients who discontinue study treatment and for those who are withdrawn from the study.

c The End-of-study Visit will occur 30 days after Day 10 or after the day of discharge (whichever is sooner), with a window of + 3 days, but not < 30 days (preferably in person, but by phone if necessary).

d Includes prior and current conditions and all past surgeries; to be recorded on eCRF.

e Includes (as applicable to the study period) a review of prior and current therapies. The preoperative bowel preparation, if any, as well as the total volume of IV fluids administered during surgery, must be recorded in the eCRF. Intra-operative and postoperative opioid analgesics administered to patients will be recorded in the eCRF.

f Time of the beginning of surgery is defined as the time when the first incision is made. Time of end of surgery is defined as the time the patient leaves the operating room.

g The 3 enhanced recovery protocol elements required by the protocol (early removal of the nasogastric tube [defined as removal of the nasogastric tube at end of surgery], early ambulation [defined as ambulation on Day 1], early diet advancement on Day 1) and 4 other elements at the study site (antibiotic prophylaxis, preoperative carbohydrate drink, epidural anesthesia in addition to general anesthesia, and chewing gum postoperatively) must be recorded as yes or no in the eCRF at Baseline (planned) and at the day of discharge or early termination (actual).

h A preoperative physical examination within 2 weeks prior to the patient signing the informed consent form may be used, as long as the eCRF is completed.

i As per standard of care at the hospital or, for End-of-study Visit, at the hospital or doctor's office.

j To be measured once daily as close as possible after waking; vital signs include systolic/diastolic blood pressure (assessed after approximately 3 to 5 minutes of rest), and pulse rate.

k To be performed any time from 14 days to day of surgery (Day –14 to Day 0, respectively). An electrocardiogram obtained within 2 weeks prior to the patient signing the informed consent form that shows no clinically significant abnormal finding may be used.

l To be assessed once daily in the morning at approximately the same time of day; baseline is defined as the pain assessment on the morning of Day 1.

m Hematology (platelet count, erythrocytes [red blood cell count], hemoglobin, hematocrit, leukocytes [white blood cell count with differential: neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count]), clinical chemistry (blood urea nitrogen, creatinine, chloride, potassium, sodium, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, international normalized ratio, total protein, and albumin).

n Required for female patients of childbearing potential (that is, not surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation with appropriate documentation of such surgery *OR* not postmenopausal [defined as at least 12 months of spontaneous amenorrhea in a woman > 45 years of age]). If the urine pregnancy test is obtained prior to Day –1 and is negative, the test must be repeated on Day –1 or Day 0. Additional pregnancy testing is not required during the treatment period unless clinically indicated.

o The actual date and time (24-hour clock) of all study treatment dosing and each meal prior to dosing will be recorded in the eCRF.

p First dose is to be administered 30 minutes to 6 hours prior to the scheduled start of surgery on the operative day (Day 0).

q A second dose will be administered postoperatively the evening of the operative day (Day 0).

r Beginning on Day 1, patients will receive study treatment BID for up to 10 days postoperatively (ie, Day 10). Every effort will be made to give all morning and evening doses at approximately 12-hour intervals. The duration of study treatment will be determined by the date on which the primary endpoint, GI2 (patient tolerates solid food and has a bowel movement), is met or the date on which the discharge order is written, whichever occurs first, and will not exceed 10 postoperative days. Study treatment may be administered on the day of discharge.

s Any overdose or medication error of the study treatment must be reported to the contract research organization's medical monitor via eCRF (or paper form if EDC is not available) by the investigator or qualified designee using a Special Situations Report Form as soon as becoming aware.

t To be assessed until both 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 occur and to be recorded in the eCRF. If a patient is discharged from the hospital prior to having a first bowel movement, he/she is to be instructed to inform the investigator or qualified designee by phone within 24 hours of having a first bowel movement up to and including Day 10. Additionally, the investigator or qualified designee will communicate (phone, text, or e-mail) with the patient daily up to and including Day 10 to record when the first bowel movement occurred.

u Discharge readiness is defined as gastrointestinal recovery based on the clinical judgment of the investigator (yes or no).

Table 1-2 Schedule for Pharmacokinetic Sample Collection

Day	Time					
	Predose	Postdose (hour)				
	0	1	2	4	8	12
2	X[a, b]					
3	X[a, b]	X[b, c]	X[b, c]	X[b, c]	X[b, c]	X[b, c]
4	X[a, b]					

a Immediately before the morning dose.

b Required only if the patient remains hospitalized.

c Performed after the morning dose but before administration of the evening dose.

2. INTRODUCTION

2.1 Study Rationale

Gastrointestinal (GI) dysfunction is a common finding in the postoperative setting, with a delay in the return of GI function extending the length of hospitalization. Naldemedine is an orally administered, peripherally acting mu-opioid receptor antagonist (PAMORA). Its use is currently being studied in the perioperative setting to assess its effect on the time to GI recovery following surgeries that include bowel resection and bowel transection.

2.2 Background

In the surgical setting, a temporary reduction or cessation of intestinal motility is common postoperatively. The pathophysiology of this condition is multifactorial and complex. Overall, intestinal equilibrium is altered, resulting in a loss of coordinated propulsive action and an accumulation of gas and fluids. Hospitalization may thus be prolonged, increasing patient exposure to such risks as hospital-acquired infection and deep vein thrombosis, as well as increasing healthcare costs.

Naldemedine (also referred to as S-297995) is a PAMORA developed by Shionogi & Co. Ltd. Naldemedine as a 0.2-mg tablet for once-daily oral administration was approved in the US on 23 Mar 2017 for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dose escalation (see NDA 208854). A detailed description of the chemistry, pharmacology, efficacy, and safety of naldemedine is provided in the current edition of the Investigator's Brochure and in the package insert for naldemedine 0.2-mg tablets (SYMPROIC® [naldemedine tablets for oral use]).

Shionogi has developed an orally disintegrating tablet (ODT) formulation of naldemedine for short-term perioperative use in patients undergoing surgeries that include bowel resection and bowel transection. This Phase 2 controlled study will be conducted to evaluate the naldemedine ODT in patients undergoing partial small or large bowel resection with primary anastomosis or radical cystectomy requiring bowel transection with primary anastomosis.

2.3 Benefit/Risk Assessment

Naldemedine has not previously been studied for short-term perioperative use in patients undergoing surgeries that include bowel resection and bowel transection. Therefore, the expected benefits and risks of naldemedine for this patient population are not known.

Detailed information about naldemedine is provided in the current edition of the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the primary endpoint	• Time from the end of surgery to time to first toleration of solid food and first bowel movement (GI2)
Secondary	
• To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the secondary endpoints	• 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 • Proportion of patients discharged by Day 10 who are readmitted for any reason within 30 days after discharge from the hospital
Exploratory	
• To compare the efficacy of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the exploratory endpoints	• Time from the end of surgery to time to discharge readiness • Time from the end of surgery to time of actual discharge (departure) from the hospital • Proportion of patients with prolonged hospital stay due to GI dysfunction • Time from initial insertion of the nasogastric tube to removal of the nasogastric tube • Proportion of patients with abdominal distention on Day 1 through the day on which GI2 is achieved • Proportion of patients with nausea on Day 4 through day of discharge • Proportion of patients with vomiting on Day 4 through day of discharge • Proportion of patients who achieve GI2 in each treatment group by postoperative day • Proportion of patients who receive concomitant medication that may have a laxative effect • Effect of prior surgery (yes/no) on the GI2 endpoint

Pharmacokinetics	

• 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	• Plasma drug concentrations of naldemedine and nor-naldemedine on:
	  • 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
	• PK parameters of naldemedine and nor-naldemedine (C_{max}, T_{max}, AUC, CL/F, $MR_{M/U,\ Cmax}$, and $MR_{M/U,\ AUC}$)

Safety	
• To compare the safety of naldemedine 1.25 mg, 2.5 mg, and 5 mg and placebo for the safety endpoints	• Incidence of treatment-emergent adverse events, including those that are serious and those that result in discontinuation of study treatment • Proportion of patients with clinically significant changes in clinical laboratory tests, vital signs, and ECGs • Change from baseline in pain intensity, as assessed on a Numerical Pain Rating Scale (NPRS) • Total dose of intra- and postoperative opioid analgesics in morphine milligram equivalents (MMEs)

AUC = area under the plasma concentration-time curve; CL/F = apparent total clearance estimated according to: CL/F = Dose/$AUC_{0-\tau}$ on Day 3 (for naldemedine only); C_{max} = maximum observed plasma concentration on Day 3; ECGs = electrocardiograms; $MR_{M/U,\ AUC}$ = metabolic ratio of AUC_{0-last} of nor-naldemedine to AUC_{0-last} of naldemedine, corrected for molecular weight, defined as (nor-naldemedine AUC_{0-last})/(naldemedine AUC_{0-last}) × (naldemedine molecular weight [570.64])/(nor-naldemedine molecular weight [516.55]) (for nor-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 (nor-naldemedine C_{max})/(naldemedine C_{max}) × (naldemedine molecular weight [570.64])/(nor-naldemedine molecular weight [516.55]) (for nor-naldemedine only); T_{max} = time to maximum plasma concentration on Day 3

4. STUDY DESIGN

4.1 Overall Design

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. 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.

This study consists of:

- 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 up to 10 postoperative days). Duration of study treatment will be determined by the date on which the primary endpoint, GI2, is met or the date on which the discharge order is written, whichever occurs first, and will not exceed 10 postoperative days (excluding the postoperative dose on Day 0)
- 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 (see Figure 1-1)

Between 250 and 425 patients will be screened to determine eligibility to participate in the study. It is planned that between 200 and 340 patients will be randomly assigned in a ratio of 1:1:1:1 to study treatment, with approximately 50 patients assigned to each of 4 treatment groups (see also Section 9.2).

Enrolled patients will be managed preoperatively according to standard of care. On Day 0, before surgery, patients will be randomly assigned to 1 of 4 treatment groups to receive study treatment, as follows:

- Naldemedine 1.25 mg: One 1.25 mg ODT twice daily (BID), identical in shape, size, and color to the 2.5- and 5-mg ODT
- Naldemedine 2.5 mg: One 2.5 mg ODT BID, identical in shape, size, and color to the 1.25- and 5-mg ODT
- Naldemedine 5 mg: One 5 mg ODT BID, identical in shape, size, and color to the 1.25- and 2.5-mg ODT
- Matching placebo: One ODT BID, identical in shape, size, and color to the naldemedine ODT

Throughout this protocol, study treatment refers to naldemedine 1.25 mg, naldemedine 2.5 mg, naldemedine 5 mg, and matching placebo, unless otherwise noted.

The first dose of study treatment will be administered 30 minutes to 6 hours prior to the scheduled start of surgery on the operative day (Day 0), and the second dose will be administered postoperatively the evening of the operative day. Beginning on Day 1, patients will receive study treatment BID for up to 10 days postoperatively (ie, Day 10). Every effort will be made to give the Day 1 morning dose approximately 12 hours after the Day 0 evening dose and to give all morning and evening doses from Days 1 to 10 at approximately 12-hour intervals. Note that duration of administration will be determined by the date on which the primary endpoint, GI2, is met or the date on which the discharge order is written, whichever occurs first, and will not exceed 10 postoperative days (excluding the postoperative dose on Day 0). Study treatment may be administered on the day of discharge. Details regarding study treatment administration are provided in Section 6.1.

During the treatment period, procedures and assessments will be performed as specified in the Schedule of Activities (SoA) in Section 1.3.

Patients will be discharged based on the clinical judgment of the investigator and standard of care at the study hospital. Patients who are discharged by Day 10 will have an End-of-study Visit 30 days after Day 10 or after the day of discharge (whichever is sooner), with a window of + 3 days, but not < 30 days.

Patients who discontinue study treatment prior to meeting the primary endpoint, GI2, will have an ET Visit and will be followed until 30 days after the day of discharge for safety. Patients who are withdrawn from the study will have an ET and an End-of-study Visit.

4.2 Scientific Rationale for Study Design

Prolonged hospitalization due to delay in return of GI function after bowel surgery may increase patient exposure to such risks as hospital-acquired infection and deep vein thrombosis, as well as increase healthcare costs. As described in Section 2.2, there is a need for a pharmacologic agent with an improved benefit/risk profile that can be administered to patients who are undergoing bowel resection and bowel transection.

The current study (Study 1902G1721) with naldemedine (which is approved in the US for the treatment of OIC in adult patients with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent [eg, weekly] opioid dosage escalation), will be conducted to determine whether naldemedine can accelerate the time to upper and lower GI recovery following surgeries that include partial bowel resection with primary anastomosis and radical cystectomy with bowel transection and primary anastomosis.

This study employs a standard interventional clinical study design and will be conducted at multiple hospitals. The design of this study allows assessment of the efficacy, safety, and tolerability of naldemedine administered orally by ODT at 3 different doses compared with placebo in patients undergoing partial small or large bowel resection with primary anastomosis or radical cystectomy requiring bowel transection with primary anastomosis.

The randomization and stratification for this study (Section 6.3) allows for a well-balanced distribution of patients across treatment groups and will help determine whether there is a dose response to allow the choice of the most effective dose. The double-blind, placebo-controlled design was chosen because blinding of patients and investigators/study personnel helps to prevent bias and the inclusion of placebo is appropriate for use in this patient population.

4.3 Justification for Dose

Opioids exert their analgesic effects primarily through the central mu-opioid receptors and are commonly used to manage postoperative pain. In the postoperative setting, surgery on the GI tract is commonly associated with GI dysfunction, which may be caused by both endogenous and exogenous opioids, as well as other factors [1]. The GI dysfunction may delay a patient's recovery after surgery and prolong hospitalization [2].

In the postoperative period, severe postoperative pain therapy may ideally be managed with an opioid analgesic, with maintenance of efficacious plasma opioid concentrations as the goal of therapy [3, 4]. In this setting, functional blockage of intestinal transit may be caused by binding of opioids at mu-opioid receptors in the enteric nervous system. Blockage of this binding is important and, for this purpose, the trough plasma concentration of naldemedine should be kept above the effective opioid concentration.

Naldemedine 0.2 mg once daily improved the frequency of spontaneous bowel movements in Phase 3 trials (NCT01993940 and NCT01965158; data on file). In addition, naldemedine suppressed morphine-induced inhibition of small intestinal transit in rats; the amount of drug that produced the desired effect in 50% (ED_{50}) was 0.03 mg/kg. The maximum observed plasma concentration value with a naldemedine 0.2-mg dose in humans and the plasma drug concentration 1 hour after oral administration of naldemedine 0.03 mg/kg (ED_{50}) to rats (at the end of efficacy assessment) were 3.07 ng/mL (data on file) and 2.51 ng/mL (data on file), respectively. Because these values for efficacious anti-OIC plasma concentrations in humans and the anticonstipation effect in rats were close, a trough plasma naldemedine concentration of 3.07 ng/mL in the clinical setting may be appropriate in managing postoperative GI motility. Based on the plasma concentration profile in humans after multiple-dose administration of naldemedine 3 mg on Day 1 (C_{12hr} [the concentration 12 hours after administration], 9.47 ng/mL) (NCT01443403; data on file), it is estimated that administration of naldemedine 1.25 mg will provide a plasma drug concentration close to 3.07 ng/mL 12 hours after administration. Therefore, the doses of naldemedine chosen in this study are 1.25 mg, 2.5 mg, and 5 mg administered BID.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study. A patient is considered to have completed the study if he/she has completed all periods of the study through the End-of-study Visit, even if he or she completes study treatment prior to Day 10 because of meeting the primary endpoint, GI2 (see SoA in Section 1.3).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. Patient must be 18 to 80 years of age, inclusive, at the time of signing the informed consent form (ICF).

Type of Patient and Disease Characteristics

2. Scheduled to undergo 1 of the following procedures via open (nonlaparoscopic) surgery under general anesthesia:
   - partial small or large bowel resection with primary anastomosis
   - radical cystectomy requiring bowel transection with primary anastomosis
3. Planned to be managed postoperatively with an enhanced recovery protocol, which, at a minimum, includes all of the following elements:
   - early removal of the nasogastric tube, which is defined as removal of the nasogastric tube at the end of surgery
   - early ambulation, which is defined as ambulation on Day 1
   - early diet advancement on Day 1
4. Planned to receive primary postoperative pain management with opioid analgesia administered by any route.
5. American Society of Anesthesiologists (ASA) Physical Status Score of I, II, or III (a normal healthy patient, a patient with mild systemic disease, or a patient with systemic disease, respectively).

Sex

6. Male or female

   Male patients:

   - There are no specific requirements for contraceptive measures for male patients.

   Female patients:

   - A female patient is eligible to participate if she is not pregnant (negative urine pregnancy test at Screening for a woman of childbearing potential [WOCBP]; see also Appendix 4), not breastfeeding, and at least 1 of the following conditions applies:
     i. Postmenopausal (defined as at least 12 months of spontaneous amenorrhea in a woman > 45 years)

ii. Surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation

iii. Agree to use an acceptable effective form of birth control (with failure rates > 1% per year) from the start of Screening through 14 days after the last dose of study treatment, such as:

(a) Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)

(b) Male or female condom with or without spermicide

(c) Cap, diaphragm, or sponge with spermicide

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Scheduled to undergo a total colectomy or any procedure that results in a colostomy or ileostomy.
2. Scheduled for endoscopic or laparoscopic surgery.
3. Complete bowel obstruction.
4. Complicated inflammatory bowel disease (such as ulcerative colitis or Crohn's disease).
5. More than 2 prior major abdominal surgeries (eg, gastrectomy, gastric bypass, gastric sleeve, lap banding, pancreatic resection, hepatectomy, intestinal transplant).

Prior and Concomitant Therapy

6. More than 3 doses of an opioid (regardless of the route of administration) during the 7 days prior to surgery.
7. Chemotherapy within 4 weeks prior to surgery; otherwise, patients with cancer are eligible.
8. Scheduled to receive chemotherapy, immunotherapy, or radiation therapy intraoperatively or within 14 days after surgery; otherwise, patients with cancer are eligible.
9. Any prohibited medication within 14 days prior to the first dose of study treatment as specified in Section 6.5.

Prior and Concurrent Clinical Study Experience

10. Exposure to an investigational drug within 90 days prior to the start of Screening.
11. Prior exposure to naldemedine.

Diagnostic Assessments

12. Severe hepatic impairment.

Other Exclusions

13. Pregnancy or lactation.
14. Presence of peritoneal catheter (eg, for dialysis or chemotherapy).
15. Any other reason considered by the investigator or qualified designee to make the patient ineligible to take part in the study.

5.3 Lifestyle Considerations

No meal, dietary, caffeine, alcohol, tobacco, or other lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study.

Rescreening of patients who meet all entry criteria but who are not entered in the study because the date of surgery is rescheduled (by study site staff or by the patient) to a date more than 14 days after signing the ICF is permitted. Rescreened patients must resign the ICF if the surgery is rescheduled more than 14 days after the originally-scheduled surgery, and the medical monitor should be contacted to see if any screening tests will need to be repeated. Patients who are screen failures for any other reasons are not to be rescreened.

6. STUDY TREATMENT

Study treatment is defined as naldemedine 1.25 mg, naldemedine 2.5 mg, naldemedine 5 mg, and matching placebo.

6.1 Study Treatments Administered

Study treatment is described in Table 6-1.

Table 6-1 Study Treatments

Study Treatment Name:	Naldemedine	Naldemedine	Naldemedine	Matching Placebo
Dosage formulation:	ODT	ODT	ODT	ODT
Unit dose strength(s)/Dosage level(s):	1.25 mg	2.5 mg	5 mg	Not applicable
Physical Description	White to light yellow, round shaped plain tablets	White to light yellow, round shaped plain tablets	White to light yellow, round shaped plain tablets	White to light yellow, round shaped plain tablets
Route of Administration:	Oral	Oral	Oral	Oral
Dosing Instructions:	One 1.25-mg tablet BID Specific dosing instructions are provided in Table 6-2	One 2.5-mg tablet BID Specific dosing instructions are provided in Table 6-2	One 5-mg tablet BID Specific dosing instructions are provided in Table 6-2	One placebo tablet BID Specific dosing instructions are provided in Table 6-2
Packaging and Labeling:	Study treatment for each patient will be provided in a wallet containing 24 tablets for the entire study. Each wallet will be labeled as necessary per country requirement.	Study treatment for each patient will be provided in a wallet containing 24 tablets for the entire study. Each wallet will be labeled as necessary per country requirement.	Study treatment for each patient will be provided in a wallet containing 24 tablets for the entire study. Each wallet will be labeled as necessary per country requirement.	Study treatment for each patient will be provided in a wallet containing 24 tablets for the entire study. Each wallet will be labeled as necessary per country requirement.
Manufacturer:	Shionogi Pharma Co., Ltd.	Shionogi Pharma Co., Ltd.	Shionogi Pharma Co., Ltd.	Shionogi Pharma Co., Ltd.

BID = twice daily; ODT = orally disintegrating tablet

Dosing instructions are provided in Table 6-2. Investigators are encouraged to consider the time of the surgery in order to ensure that the evening dose on Day 0 can be administered.

Table 6-2 Dosing Instructions During the Treatment Period

Study Treatment	Dose	Dosing Instructions
Naldemedine	1.25 mg	**Day 0 (Operative Day)** Before surgery: Administer first dose 30 minutes to 6 hours prior to the scheduled start of surgery. The patient will be instructed to place the orally disintegrating tablet (ODT) on the tongue and to let it dissolve. Administration with water is not required, but water is allowed if the patient prefers. After surgery: Administer second dose postoperatively on the evening of the day of surgery. **Day 1 to Day 10** Patients will receive study treatment twice daily (BID) for up to 10 days (ie, Day 10). Every effort will be made to give the Day 1 morning dose approximately 12 hours after the Day 0 evening dose and to give all morning and evening doses from Day 1 to Day 10 at approximately 12-hour intervals. Duration of administration will be determined by the date on which the primary endpoint, GI2 (time from end of surgery to time to first toleration of solid food and first bowel movement), is met or the date on which the discharge order is written, whichever occurs first, and will not exceed 10 postoperative days. Study treatment may be administered on the day of discharge.
	2.5 mg	
	5 mg	
Matching Placebo	Not applicable	

6.2 Preparation/Handling/Storage/Accountability of Study Treatment

1. Wallets containing naldemedine and matching placebo must be stored according to the study treatment label at 59°F to 86°F (15°C to 30°C). The investigator or qualified designee must confirm that appropriate temperature conditions have been maintained during transit for all study treatment received and that any discrepancies are reported and resolved before use of the study treatment.
2. Only study patients enrolled in the study may receive study treatment and the investigator or qualified study personnel may administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator or the head of the hospital (as applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

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). Before each site is initiated, the login information and directions for the IWRS will be provided.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the contract research organization (CRO) prior to unblinding unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the CRO must be notified within 24 hours after breaking the blind, and the treatment assignment should not be disclosed to the CRO. The date and reason that the blind was broken must be recorded in the source documentation and the IWRS.

6.4 Study Treatment Compliance

The investigator or qualified study personnel will administer study treatment to each patient and will observe the patient for compliance with taking the study treatment. Study treatment administration will be recorded in the electronic case report form (eCRF). In addition, if the patient refuses study treatment or if he or she vomits within 1 hour of dosing, this information will also be recorded in the eCRF.

6.5 Medical History and Prior and Concomitant Therapy

Any prior history of postoperative ileus and postoperative gastrointestinal dysfunction must be recorded on the eCRF as part of the patient's medical history.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with the following information:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, route of administration, and frequency

The preoperative bowel preparation, if any, must be recorded in the eCRF. Additionally, the total volume of intravenous fluids administered during the surgery must be recorded in the eCRF.

The CRO's medical monitor should be contacted if there are any questions regarding permissible prior or concomitant therapy.

In addition to the prior and concomitant therapy exclusions in Section 5.2, the following medications are prohibited for 14 days before the first dose of study treatment and through the end of study treatment:

- Strong cytochrome P450 3A (CYP3A) inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) (see Appendix 6)
- Strong CYP3A and P-glycoprotein (P-gp) inhibitors (eg, clarithromycin, diltiazem, grapefruit juice, indinavir, ketoconazole, ritonavir) (see Appendix 7)
- Other opioid antagonists
- Prophylactic use of laxatives (eg, magnesium citrate, magnesium hydroxide, magnesium sulfate, castor oil, sodium phosphate, sodium biphosphate, polyethylene glycol enemas, and stimulant laxatives, including bisacodyl); however, if needed, laxatives may be used for rescue therapy

Re-insertion of the nasogastric tube is permitted if needed (see Section 8.1.2.2).

The following elements of the enhanced recovery protocol at the study site must be recorded as yes or no in the eCRF at Baseline (planned) and at the day of discharge or early termination (actual):

- Three elements required by the protocol:
  - 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
- Four other elements that may be used at the study site:
  - Antibiotic prophylaxis
  - Preoperative carbohydrate drink
  - Epidural anesthesia in addition to general anesthesia
  - Chewing gum postoperatively

The investigator must determine appropriate management and treatment of the patient, as clinically indicated, in the event of signs or symptoms of any of the following:

- Opioid withdrawal; if opioid withdrawal is suspected, the patient should be monitored
- Severe hypersensitivity thought to be related to study treatment
- Gastrointestinal perforation

6.6 Dose Modification of Study Treatment

Dose modification of study treatment is not permitted in the study.

6.7 Treatment after the End of the Study

Study treatment will not be administered after the end of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

A patient may discontinue study treatment prior to Day 10 if he or she meets the primary endpoint, GI2, or on the date on which the discharge order is written, whichever occurs first. Discontinuation of study treatment for any other reason will be determined by the investigator if he or she believes that it is in best interest of the patient. Female patients who become pregnant during the study will be followed as described in Section 7.2, Section 8.3.5, and Appendix 4. The investigator will withdraw a patient from study treatment based on the management and discontinuation criteria for abnormal liver function tests (Appendix 5). The investigator should consider discontinuation of study treatment if opioid withdrawal is suspected on any assessment day. In addition, discontinuation of study treatment is required if:

- The patient has an unplanned ileostomy or colostomy during the surgical procedure.
- A patient has a score > 36 on the Clinical Opiate Withdrawal Scale (COWS) on any assessment day
- Hypersensitivity thought to be related to study treatment occurs and is considered severe in intensity, as assessed by the investigator
- There is any sign or symptom suggestive of gastrointestinal perforation, as assessed by the investigator

See the SoA for data to be collected at the time of treatment discontinuation (eg, at the Early Termination Visit).

7.2 Patient Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. However, unless there is a safety reason, the patient should remain in the study until the End-of-study Visit, even when off study treatment, to protect the integrity of the study and the patient's well-being.
- If the patient withdraws consent, the CRO may retain and continue to use any data collected before the withdrawal of consent.
- If a patient withdraws consent, he/she may request destruction of any samples taken and not tested, and the investigator or qualified designee must document this in the site study records.
- See the SoA for data to be collected at the time of patient discontinuation/withdrawal from the study. The reason for the patient's withdrawal from the study and the withdrawal date should be recorded in the eCRF.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she fails to return for the End-of-study Visit and is unable to be contacted by the hospital or doctor's office staff (ie, does not respond to at least 2 telephone calls, 1 e-mail, and a registered letter).

The following actions must be taken if a patient fails to return to the hospital or doctor's office for the End-of-study Visit:

- Before a patient is deemed lost to follow-up, the investigator, or qualified designee must make every effort to contact the patient and reschedule the missed End-of-study Visit as soon as possible. Contact will include at least 2 telephone calls, at least 1 e-mail, and a registered letter. The contact attempts should be within 30 days of the missed End-of-study visit and be documented in the patient's medical record.
- Should the patient continue to be unreachable by the above methods, he/she will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator or qualified designee must maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screen failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, physical examination, blood count, electrocardiogram [ECG]) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SoA.
- Safety concerns should be discussed with the CRO immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

8.1 Efficacy Assessments

8.1.1 Primary Efficacy Assessments

8.1.1.1 Time from End of Surgery to Time to First Toleration of Solid Food and First Bowel Movement

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 recorded in the eCRF. First toleration of solid food and first bowel movement will be recorded until the patient meets the primary endpoint described above. If the patient discontinues study treatment, the patient still needs to be followed for GI2 until the achievement of this endpoint or until he/she completes the study. If the patient is withdrawn from the study, first toleration of solid food and first bowel movement, as applicable, will be recorded at the ET Visit (see also Section 9.4.5.1). If a patient is discharged from the hospital prior to having a first bowel movement, the reason for discharge prior to having the first bowel movement will be recorded in the eCRF. Additionally, the patient will be instructed to inform the investigator or qualified designee by phone, text, or e-mail within 24 hours of having a first bowel movement up to and including Day 10. The investigator or qualified designee will communicate (phone, text, or e-mail) with the patient daily up to and including Day 10 to record when the first bowel movement occurred.

8.1.2 Secondary Efficacy Assessments

8.1.2.1 Time from End of Surgery to Time When the Discharge Order is Written

The time from the end of surgery (as defined for the primary endpoint) to the time when the discharge order is written will be recorded in the eCRF (see also Section 9.4.5.2).

8.1.2.2 Reinsertion of the Nasogastric Tube

Whether a patient requires reinsertion of the nasogastric tube at any time during the postoperative treatment period will be recorded in the eCRF as yes or no along with the duration of the reinsertion (if applicable).

8.1.2.3 Readmission within 30 Day After Hospital Discharge

Whether a patient is discharged by Day 10 and then readmitted for any reason within 30 days after discharge will be recorded in the eCRF as yes or no, along with the reason why the patient is readmitted (if applicable).

8.1.3 Exploratory Efficacy Assessments

8.1.3.1 Time from End of Surgery to Discharge Readiness

The time from the end of surgery (as defined for the primary endpoint) to the time to discharge readiness (defined as GI recovery based on the clinical judgment of the investigator) will be evaluated and recorded in the eCRF.

8.1.3.2 Time from End of Surgery to Time of Actual Discharge

The time from the end of surgery (as defined for the primary endpoint) to time of actual discharge (departure) from the hospital will be recorded in the eCRF.

8.1.3.3 Prolonged Hospital Stay Due to Gastrointestinal Dysfunction

Prolonged hospital stay (defined as hospitalization for ≥ 7 days postoperatively) due to GI dysfunction will be recorded in the eCRF.

8.1.3.4 Patients Who Achieve GI2 in Each Treatment Group By Postoperative Day

The postoperative day for achievement of GI2 will be recorded in the eCRF.

8.1.3.5 Patients Who Receive Concomitant Medication That May Have a Laxative Effect

Any concomitant medication that may have a laxative effect will be recorded in the eCRF.

8.1.3.6 Effect of Prior Surgery on G12 Endpoint

The effect of prior surgery (yes/no) on the GI2 endpoint will be assessed.

8.2 Safety Assessments

Safety assessments will include recording of adverse events (AEs), including those that are serious and those that result in discontinuation of study treatment; clinical laboratory test results; vital signs measurements; 12-lead ECG findings; physical examination findings; postoperative pain, as assessed on the Numerical Pain Rating Scale (NPRS); and the administration of intra-operative and postoperative opioid analgesics.

Planned time points for all safety assessments are provided in the SoA.

For any abnormal laboratory test results (defined as hematology or blood chemistry values outside the reference range) or other safety assessments (eg, physical examination, vital signs, ECGs) that worsen from baseline following exposure to study treatment, the investigator will consider whether those results are clinically significant. For test results that are abnormal at baseline and significantly worsen (as per the judgment of the investigator) following the initiation of the study, the investigator must also consider whether those results are clinically significant. Any test result that is considered by the investigator or qualified designee to be clinically significant is to be recorded in the eCRF as an AE. If an abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as an AE.

The investigator will consider test results to be clinically significant in the following circumstances:

- Test results lead to any of the outcomes included in the definition of a serious adverse event (SAE) (see Section 8.3).
- Test results lead to a change in study treatment administration or discontinuation from the study.
- Test results lead to a concomitant drug treatment or other therapy.
- Test results require additional diagnostic testing (except for a confirmatory test) or other medical intervention.
- Test results meet the management and stopping criteria for abnormal liver function tests identified in Section 7.1 and Appendix 5. When any test result meets the management and stopping criteria for liver function abnormalities (Section 7.1 and Appendix 5), the results of further assessments and required follow-up should be recorded in the Liver Event Form.

In addition, the investigator should use his or her judgment in assessing the clinical significance of test results.

8.2.1 Physical Examinations

- A physical examination will be performed as per standard of care at the hospital or, for the End-of-study Visit, at the hospital or doctor's office. A preoperative physical examination (within 2 weeks prior to the patient signing the ICF) may be used, as long as the eCRF is completed. As per

8.2.2 Vital Signs

- Systolic/diastolic blood pressure and pulse rate will be measured once daily as close as possible after waking and recorded in the eCRF. Blood pressure will be assessed after approximately 3 to 5 minutes of rest.
- Blood pressure and pulse measurements will be measured with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Clinically significant changes in vital signs from baseline (as per the judgment of the investigator or qualified designee) will be recorded in the eCRF as AEs.

8.2.3 Electrocardiograms

- A 12-lead ECG will be obtained at specified time points as outlined in the SoA (see Section 1.3). A 12-lead ECG obtained within 2 weeks prior to the patient signing the ICF that shows no clinically significant abnormal finding may be used for Screening or Baseline purposes. The ECG results will be recorded in the eCRF as normal, abnormal – not clinically significant, or abnormal – clinically significant.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA in Section 1.3 for the timing and frequency. All protocol-required laboratory assessments must be conducted in accordance with the local laboratory manual and the SoA.
- The investigator or qualified designee must review the laboratory test results and record any clinically significant changes occurring during the study in the AE section of the eCRF. Clinically significantly abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition (see Appendix 3). The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal should be repeated until the values return to normal or baseline or are no longer considered by the investigator to be clinically significant.
    - If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, every effort should be made to determine the etiology and record it in the eCRF.
- If laboratory values from unscheduled laboratory tests require a change in patient management or are considered by the investigator to be clinically significantly abnormal (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Numerical Pain Rating Scale

The NPRS is an 11-point numerical scale on which patients will rate their pain on a scale of 0 (no pain at all) to 10 (worst possible pain) over the past 24 hours (see Appendix 8).

The scale is a reliable instrument for assessing pain intensity [6]. Pain will be assessed once daily in the morning at approximately the same time of day at the time points specified in the SoA, and the rating will be recorded in the eCRF (Section 1.3).

8.2.6 Clinical Opiate Withdrawal Scale

The COWS is a clinician-administered scale that rates 11 common opiate withdrawal signs and symptoms on a scale of 0 to a maximum of 4 or 5, depending on the sign or symptom (see Appendix 9). The scale is a reliable instrument for assessing a patient's level of opioid withdrawal [7]. Opioid withdrawal will be assessed using this instrument at the time points specified in the SoA, and the rating will be recorded in the eCRF (Section 1.3).

8.2.7 Intra-operative and Postoperative Opioid Analgesics

Intra-operative and postoperative opioid analgesics administered to patients will be recorded in the eCRF (see also Section 9.4.6). Doses of these medications will be recorded as specified in the SoA (Section 1.3).

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

Adverse events reported by the patient (or, when applicable, by a caregiver, surrogate, or the patient's legally authorized representative) must be captured in source documents. Abnormal laboratory test results, blood pressure, pulse rate, and ECG findings after the first dose that are considered to demonstrate a clinically significant change from baseline will be recorded in the eCRF as treatment-emergent adverse events (TEAEs).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or caused the patient to discontinue study treatment or withdraw from the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs/SAEs will be collected from the date of signing of the ICF until the End-of-study Visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded in the eCRF and reported to the CRO within 24 hours of awareness, as indicated in Appendix 3. The investigator or qualified designee will submit any updated SAE information to the CRO within 24 hours of awareness.

The investigators or qualified designees are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator or qualified designee learns of any SAE, including a death, at any time after a patient is no longer in the study, and the investigator or qualified designee considers the event to be reasonably

related to the study treatment or study participation, the investigator or qualified designee must promptly notify the CRO via phone, e-mail, or fax (see Appendix 3). Investigator assessment of causality must be included with all SAEs reported to the CRO. Serious adverse events with missing investigator causality will be followed up urgently until provided to the CRO.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading questioning of the patient is the preferred method to identify AEs.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator or qualified designee is required to proactively follow each patient at subsequent visits/phone contacts. All AEs/SAEs will be followed until resolution, stabilization, the event becomes chronic, or the event is otherwise explained or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator or qualified designee to the CRO of an SAE is essential so that legal obligations and ethical responsibilities for the safety of patients and the safety of an investigational study treatment are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs; ie, those not listed as expected in the Investigator's Brochure under Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the CRO will review it and then file it with the Investigator's Brochure and will notify the IRB, if appropriate, according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female patients and female partners of male patients who receive naldemedine will be collected from the start of Screening through 14 days after the last dose of study treatment.

- If a pregnancy is reported, the investigator or qualified designee should inform the CRO within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Special Situations - Overdose and Medication Error

Overdose and medication error of the study treatment (as defined below) must be reported to the CRO's medical monitor via eCRF (or paper form if EDC is not available) by the investigator or qualified designee using a Special Situations Report Form as soon as possible. If there are associated SAEs, the investigator or qualified designee must also complete and submit an SAE submission in EDC as well. A missed dose (or doses) of an investigational product is not to be reported as a medication error.

- Overdose - intentional or unintentional intake of study treatment 1 tablet more than the dose required in the protocol.
- Medication Error - any unintended error in the prescribing, dispensing, or administration of study treatment. Cases of patients missing doses of study treatment are not considered reportable as medication errors.

8.4 Treatment of Overdose

In the event of an overdose, the investigator/treating physician will treat the patient according to standard of care. The treatment will depend on the adverse reactions that occur as a result of the overdose. Any event of overdose should be recorded in the eCRF (or paper form if EDC is unavailable) and reported as a special situation to the CRO's medical monitor as soon as possible.

8.5 Pharmacokinetics

- The actual date and time (24-hour clock) of all study treatment dosing and each meal prior to dosing will be recorded in the eCRF.
- Blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of naldemedine and nor-naldemedine at the time points specified in the SoA (Figure 1-2) and in Table 1-2. Instructions for the collection and handling of biological samples will be provided by the CRO in the PK laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF.
- Samples will be used to analyze the plasma drug and metabolite concentrations of naldemedine and nor-naldemedine. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up).
- Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.
- Pharmacokinetic parameters and definitions are provided in Section 9.4.7.1.2. Further details will be provided separately in the statistical analysis plan (SAP).

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics/Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The study design and primary objective are based on the hypothesis that naldemedine 1.25 mg, 2.5 mg, and/or 5 mg are superior to placebo for patients undergoing surgeries that include a bowel resection or bowel transection.

9.2 Sample Size Determination

The planned sample size of between 44 and 85 patients per treatment in the mITT Population was determined by a simulation study with 10,000 iterations to provide 80% power to demonstrate the linear dose-response relationship between treatment groups (3 naldemedine groups and placebo group) in the primary endpoint at a 2-sided significance level of 0.05. In total, approximately 200 to 340 patients in the study will be required.

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 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. In addition, the time to the event of GI2 in each group follows the Weibull distribution by referring to the survival curve for the time to the event of GI2 shown in the alvimopan package insert. It was assumed that an independent censoring followed an exponential distribution with a rate such that approximately 20% of patients were censored within 240 hours.

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.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All patients who signed the ICF.
Randomized patients	All patients randomly assigned to naldemedine 1.25 mg, 2.5 mg, 5 mg, or placebo.
Modified Intention–to–Treat (mITT)	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.
Per Protocol Set	All patients in mITT who did not have a major protocol deviation, as defined in a separate document.
Safety	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.

Population	Description
Pharmacokinetic (PK) concentration	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.
Pharmacokinetic (PK) parameter	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.

9.4 Statistical Analyses

The detailed statistical analysis methods will be specified in the separate SAP. Changes from analyses outlined in the protocol will be detailed and justified in the SAP. The initial SAP will have a version 1.0 available by first patient randomized and will be finalized before unblinding/database lock. The SAP will be finalized before scheduled database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

For programming and analysis purposes, the protocol study days will be mapped as shown in Table 9-1.

Table 9-1 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

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

Patient study data, including data not appearing in tables, will be presented in by-patient data listings. In general, all tables and graphs will be presented by treatment group. Pharmacokinetic data and any derived data will be listed. All analyses and tabulations will be performed by using SAS Version 9.2 or higher, and Phoenix WinNonlin Version 6.2.1 or higher.

If statistical tests are performed, they will be performed at the 0.05 significance level using 2-sided tests, except where otherwise noted. No multiplicity adjustment of statistical tests will be applied in this study. Missing data will not be replaced.

9.4.1 Patient Disposition

Among the randomized patients in the Safety Population, and the mITT Population, the numbers and percentages of patients who complete the study and who withdraw from the study will be summarized. In addition, reasons leading to discontinuation from the study will be summarized for each treatment group. The number and percentage of patients for the randomized patients included in each analysis population will also be presented.

9.4.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the mITT Population.

9.4.3 Medical History and Prior and Concomitant Therapies

Medical histories will be listed and summarized for the mITT Population.

Prior therapies for drugs will be coded using the World Health Organization Drug Dictionary (WHO-DD). Patients who received prior therapy will be listed and summarized for the Safety Population. Concomitant therapies for drugs will be coded using WHO-DD. Patients who receive concomitant therapy, including intra-operative and postoperative opioid analgesics, will be listed and summarized for the Safety Population.

The 3 elements of the enhanced recovery protocol required by the protocol and the 4 other elements at the study site will be listed for each patient and summarized for the mITT Population.

9.4.4 Extent of Exposure and Treatment Compliance

Summary statistics for treatment duration will be presented by treatment group for the Safety Population.

Summary statistics for compliance with study drug administration will be presented by treatment group for the mITT Population.

9.4.5 Efficacy Analyses

The mITT Population will be the primary population for efficacy analyses.

9.4.5.1 Primary Efficacy Endpoint

The primary endpoint will be 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).

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. If a dose-response relationship is detected, then pairwise comparisons of the RMST between each dose group of naldemedine and the placebo group will be conducted, and the treatment differences (with its 95% confidence interval [CI]) will be provided. If an event 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. The same analysis will be performed in the Per Protocol set. In addition, the reason for discharge prior to having the first bowel movement will be listed.

Patients will continue to be evaluated for efficacy regardless of treatment adherence. The use of additional therapies or interventions that could treat any component of the primary endpoint (eg, motility agents, anti-emetics, laxatives, etc), may confound the results of the primary efficacy analysis. This list of therapies will be finalized before database lock. To examine this issue, the following exploratory analyses of the GI2 endpoint will be performed or provided:

- Repeat of the primary analysis, excluding all patients who received additional therapies at any time postrandomization that could treat any of the components of the GI2 endpoint. It is recognized that this subset is selected based on postrandomization decisions, may be confounded with the treatment group, and may not represent a randomized subgroup of the primary endpoint.
- Table of proportion of patients in each treatment group who received additional therapies that could treat any of the GI2 components.
- Two-way table summarizing each patient's status at the end of the trial regarding receipt of an additional therapy that could treat any of the GI2 components and whether the GI2 endpoint was achieved. For example, the rows can be yes/no for GI2 endpoint achieved, and the columns can be receipt of additional therapy. This

table will be done during the evaluation period of 240 hours for patients and by treatment group.

- Proportion of patients in each group that achieve the GI2 endpoint, regardless of use of additional therapies that could treat any of the GI2 components. This will be tabulated cumulatively by day. The cumulative proportions achieving the GI2 endpoint will be compared at Day 10 with the difference in proportions and an associated 95% CI will be provided.
- Proportion of patients in each group that achieve the GI2 endpoint, where the use of additional therapies that could treat any of the GI2 components included in the analysis as a patient failure to achieve the GI2 endpoint, beginning with the day the patient first receives the additional therapy. This will be tabulated cumulatively by day. The cumulative proportions achieving the GI2 endpoint will be compared at Day 10, with the difference in proportions and an associated 95% CI provided.

9.4.5.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be as follows:

- Time from the end of surgery (as defined for the primary endpoint) 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
- Proportion of patients discharged by Day 10 who are readmitted for any reason within 30 days after discharge from the hospital

For time from the end of surgery to time when the discharge order is written, the same KM approach as used for the primary efficacy analysis will be performed. The proportion of patients for each of the other parameters will be summarized by treatment group.

9.4.5.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be as follows:

- Time from the end of surgery (as defined for the primary endpoint) to time to discharge readiness (defined as GI recovery based on the clinical judgment of the investigator)
- Time from the end of surgery (as defined for the primary endpoint) to time of actual discharge (departure) from the hospital
- Proportion of patients with prolonged hospital stay (defined as hospitalization for ≥ 7 days postoperatively) due to GI dysfunction
- Time from initial insertion of the nasogastric tube to removal of the nasogastric tube

- Proportion of patients with abdominal distention on Day 1 through the day on which GI2 is achieved
- Proportion of patients with nausea on Day 4 through day of discharge
- Proportion of patients with vomiting on Day 4 through day of discharge
- Proportion of patients who achieve GI2 in each treatment group by postoperative day
- Proportion of patients who receive concomitant medication that may have a laxative effect
- Effect of prior surgery (yes/no) on the GI2 endpoint

For time from the end of surgery to time to discharge readiness and to time of actual discharge from the hospital, the same KM approach as used for the primary efficacy analysis will be performed. The proportion of patients for each of the other parameters will be summarized by treatment group.

9.4.6 Safety Analyses

All safety analyses will be performed on the Safety Population.

Adverse events will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events reported after the initial dose of study drug will be considered TEAEs and will be analyzed.

The number and the percentage of patients who experienced TEAEs will be summarized by treatment group. Treatment-emergent SAEs, AEs related to study treatment, and TEAEs leading to discontinuation of study drug will also be summarized by treatment group. The number of occurrences of TEAEs, which are counted among patients reporting those TEAEs, will also be presented in the categories above in an overall summary.

For the summary of TEAEs by system organ class and preferred term, the number and percentage of patients who experienced TEAEs will be presented for each treatment group. A summary of TEAEs by severity and by relationship to study treatment will be presented by system organ class, preferred term, and treatment group.

All AEs, including AEs that have occurred before and after the first dose of the study treatment, will be listed.

Summary statistics for laboratory tests and vital signs will be presented for all time points. The change from baseline to each time point in laboratory tests and vital signs will be summarized. In addition, the proportion of patients with clinically significant changes from baseline in laboratory tests, vital signs, and ECG data will be presented. Criteria for clinically significant changes in laboratory tests, vital signs, and ECG data will be defined in the SAP.

Summary statistics for NPRS, COWS, and intraoperative and postoperative MME opioid dose will be presented for all time points. The COWS score in each domain will be summarized categorically. The opioid dose recorded in the eCRF will be converted to the MME opioid dose using conversion factors. The details will be defined in the SAP.

9.4.7 Other Analyses

9.4.7.1 Pharmacokinetic Analyses

All PK analyses will be performed on the PK Populations.

9.4.7.1.1 Plasma Concentration

Plasma concentrations of naldemedine and nor-naldemedine will be listed and summarized by treatment and nominal sampling time with the number of non-missing 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. 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 lower 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.

9.4.7.1.2 Pharmacokinetic Parameters

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 non-compartmental methods. Other parameters may be computed, as appropriate, upon review of the data. The estimated PK parameters will be computed for each study patient using the actual sample collection times recorded in the eCRF during the study.

PK parameters:

C_{max} (ng/mL)	Maximum observed plasma concentration on Day 3
T_{max} (hr)	Time to maximum plasma concentration on Day 3
$AUC_{0-\tau}$ (ng·hr/mL)	Area under the concentration-time curve over the dosing interval τ (12 hours) on Day 3, calculated by Linear Up/Log Down Trapezoidal Method
CL/F (L/hr)	Apparent total clearance estimated according to: CL/F = Dose/$AUC_{0-\tau}$ 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 (nor-naldemedine C_{max}) / (naldemedine C_{max}) × (naldemedine molecular weight [570.64]) / (nor-naldemedine molecular weight [516.55]) (for nor-naldemedine only)
$MR_{M/U, AUC}$	Metabolic ratio of $AUC_{0-\tau}$ of nor-naldemedine to $AUC_{0-\tau}$ of naldemedine, corrected for molecular weight, defined as (nor-naldemedine $AUC_{0-\tau}$) / (naldemedine $AUC_{0-\tau}$) × (naldemedine molecular weight [570.64]) / (nor-naldemedine molecular weight [516.55]) (for nor-naldemedine only)

The estimated PK parameters except for T_{max} will be summarized by treatment 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 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.

$AUC_{0-\tau}$ 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 observed plasma concentration at τ on Day 3 is BLQ, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing (AUC_{0-last}) will be used as $AUC_{0-\tau}$.

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

9.4.7.1.3 Exposure-response Analysis

An exploratory exposure-response analysis will be conducted for efficacy and safety and will be reported in a separate pharmacokinetic report.

9.5 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 the 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 efficacy analysis may be feasible. Based on the operational feasibility of such an interim analysis, the interim analysis could include a nonbinding 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 SAP.

9.6 Data Monitoring Committee

A DMC will review the study data periodically as specified in a separate DMC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The investigator will be responsible for the following:

- Submitting the protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) to an IRB for review and approval by the IRB before the study is initiated at the study site. Competent authority notification, review, and approval may be required as appropriate according to local country requirements.
- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

Any amendments to the protocol will require competent authority and/or IRB approval (as appropriate) before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

10.1.2 Financial Disclosure

Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The information on financial disclosure for investigators will be addressed in a separate agreement between the sponsor and the investigator.

10.1.3 Informed Consent Process

- The investigator or his/her representative must explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time that written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF during their participation in the study.
- A copy of the signed ICF must be provided to the patient or the patient's legally authorized representative.

10.1.4 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient directly identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

All information regarding naldemedine supplied by the sponsor to the investigator is confidential information. The investigator agrees to use this information to conduct the study and will not use it for other purposes without the written consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of naldemedine and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

The sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the sponsor's approval requirements.

10.1.6 Data Quality Assurance

- All patient data required for the study will be recorded in an eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source documents.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
    - Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. Records will be retained for the longest of the following periods:
        - At least 2 years after approval of the last marketing application
        - Three years after formal discontinuation of the clinical development of the investigational product or after discontinuation of the study
        - For a minimum of 15 years after the end of the clinical study or longer if required by local regulations and EU Directive 2003/63/EC Article 5.2
        - Other period in accordance with applicable local laws, regulations, and other regulatory requirements, whichever is latest

10.1.7 Source Documents

- Source documents provide evidence of the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- Source documents are defined as original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after

verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial).

10.1.8 Study and Site Closure

The sponsor/designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

A study site will be closed upon study completion at the site. A study site is considered closed when all required documents and study supplies have been collected, data have been collected, and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patients and should assure appropriate patient therapy and/or follow-up.

10.1.9 Publication Policy

- All information regarding study treatment/naldemedine supplied by the sponsor to the investigator is confidential. The investigator agrees to use this information to accomplish the study and must not use it for other purposes without consent from the sponsor.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined to be necessary by the investigator or required by local regulations.

Table 10-1 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet count Erythrocytes (RBC count) Hemoglobin Hematocrit Leukocytes (WBC count with differential: neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count)
Clinical chemistry[a]	Blood urea nitrogen Creatinine Chloride Potassium Sodium Calcium Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Total bilirubin INR Total protein Albumin
Other screening tests	Urine pregnancy test (as specified and clinically needed for a woman of childbearing potential)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. All events of ALT or AST > 3 × ULN **AND** total bilirubin > 2 × ULN or INR > 1.5; also report as an SAE, which may indicate severe liver injury, must be reported as a serious adverse event.

Investigators must document their review of each laboratory report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE (unless fatal). Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- An elective procedure not reflecting a worsening of a known underlying medical condition is not considered an AE, and therefore will not be considered an SAE despite requiring hospitalization. However, complications of a procedure will be considered an AE and may be considered an SAE if hospitalization is prolonged (or any other SAE criterion is met).
- Hospitalization for preplanned and elective procedures between discharge and follow-up to treat a pre-existing condition that did not worsen after start of study will not be considered an AE and therefore will not be considered an SAE despite requiring hospitalization. The exception is when the patient experiences another event that is fatal, is life-threatening, results in disability, leads to prolonged hospitalization, or is considered to be medically significant during/following the procedure.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.1 Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.2 Recording and Follow-up of Adverse Events and Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records/discharge summary to the CRO in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the CRO. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the CRO.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grades (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50):

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- An event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as Grades 3, 4, or 5.
- The highest severity during the period in which the AE occurred will be recorded in the eCRF.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- The relationship of an event to the study treatment will be determined by the investigator or subinvestigator according to the following criteria:
  - Related: An AE that can be reasonably explained as having been caused by the study treatment. For example, the occurrence of the AE can be explained by any of the following: a pharmacological effect of the study treatment (eg, a similar event had been reported previously); an increase/decrease of the dose affects the occurrence or seriousness of the AE; or all other causative factors (eg, medical history, concomitant medication, etc) have been ruled out after careful analysis of sufficient information.

- Not related: An AE that cannot be reasonably explained as having been caused by the study treatment.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- The investigator should provide a rationale for the causality assessment in the Medical Comment field on the eCRF or if reporting via paper, the rationale for causality should be provided in the narrative section of the paper SAE form.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the CRO. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment and update the eCRF.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the CRO with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the eCRF.
- The investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information.

10.3.3 Reporting of Serious Adverse Events

All SAEs must be reported to the CRO in detail via EDC within 24 hours from the time point when the investigator or qualified designee first becomes aware of the SAE. If EDC is not available, complete the paper SAE case report form (CRF) and fax or e-mail it to:

[redacted]
Fax: [redacted]
E-mail: [redacted]

SAE Reporting to Shionogi via EDC

- The primary mechanism for reporting an SAE to the CRO will be EDC.
- If EDC is unavailable, then the site will use the paper SAE data collection (see next section).
- The site will enter the SAE data into EDC as soon as it becomes available.
- After the study is completed at a given site, EDC will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after EDC has been taken off-line, then the site should report this information on a paper SAE form (see next section) to the CRO or to the CRO's medical monitor by telephone/fax.

SAE Reporting to Shionogi via Paper CRF (if EDC is unavailable)

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the CRO's medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A female patient is considered a WOCBP following menarche if she meets 1 of the following criteria:

1. Not surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation with appropriate documentation of such surgery. Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

OR

2. Not postmenopausal (defined as at least 12 months of spontaneous amenorrhea in a woman > 45 years of age)

Contraception Guidance:

Male patients

There are no specific requirements for contraceptive measures for male patients.

Female patients

Female patients of childbearing potential are eligible to participate if they are not pregnant (negative urine pregnancy test at Screening for WOCBP; see also below), not breastfeeding, and at least 1 of the following conditions applies:

i. Postmenopausal (defined as at least 12 months of spontaneous amenorrhea in a woman > 45 years)
ii. Surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation

iii. Agree to use an acceptable effective form of birth control (with failure rates > 1% per year) from the start of Screening through 14 days after the last dose of study treatment, such as:
   a. Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)
   b. Male or female condom with or without spermicide
   c. Cap, diaphragm, or sponge with spermicide

Pregnancy Testing:

- WOCBP should only be eligible after a verbally confirmed menstrual period and a negative urine pregnancy test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Details of this procedure are described in Section 8.3.5.

Male patients with partners who become pregnant

- The investigator or qualified designee will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive naldemedine.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator or qualified designee will record pregnancy information on the paper Pregnancy Form and submit it to the CRO within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the CRO. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female patients who become pregnant

- The investigator or qualified designee will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the CRO within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The investigator or qualified designee will collect follow-up information on the patient and the child and the information will be forwarded to the CRO. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination of a pregnancy will be reported as an AE or SAE on the Pregnancy form. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator or qualified designee will be reported to the CRO as described in Section 8.3.4. While the investigator or qualified designee is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study treatment and will be followed as described in this appendix (see also Section 7.2 and Section 8.3.5).

All pregnancies must be reported to the CRO within 24 hours of becoming aware of the pregnancy. Complete the Pregnancy paper Form and fax or e-mail it to:

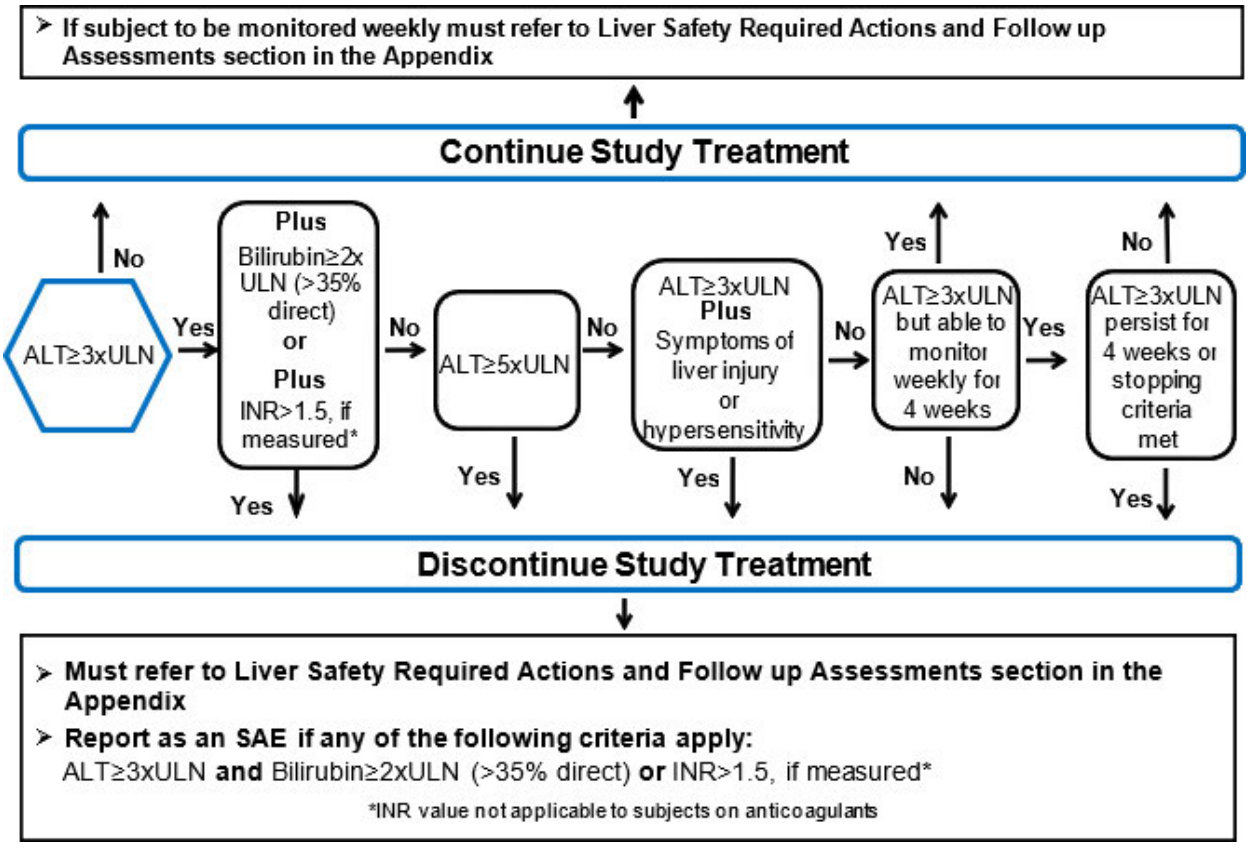
[redacted]
Fax: [redacted]
E-mail: [redacted]

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) - absolute</td><td colspan="2">ALT or AST > 8 × upper limit of normal (ULN)[1]
See additional actions and follow-up assessments listed below.</td></tr>
<tr><td>Increased bilirubin and international normalized ratio (INR)</td><td colspan="2">ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN or INR > 1.5; also report as a serious adverse event (SAE).[2]</td></tr>
<tr><td>Symptomatic</td><td colspan="2">ALT or AST > 3 × ULN accompanied by fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%); also, report as an SAE.</td></tr>
<tr><th colspan="3">Suggested Actions and Follow-up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow-up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study intervention.
• Report the event to the contract research organization (CRO) within 24 hours
• Complete the liver event electronic case report form (eCRF), and complete an SAE data collection tool if the event also met the criteria for an SAE.[2]
• Perform liver chemistry follow-up assessments.
• Monitor the patient until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see MONITORING).
• Do not restart/rechallenge patient with study intervention unless allowed per protocol and CRO approval is granted.
• If restart/rechallenge is either not allowed per protocol or not granted, permanently discontinue study intervention. The patient may continue in the study for any protocol-specified follow-up assessments</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis immediately after the event occurs[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 × ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) eCRF</td></tr>
</table>

MONITORING: **If ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN or INR > 1.5:** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase [ALP], bilirubin, and INR) and perform liver event follow-up assessments within 24 hours. • Monitor patient twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT or AST > 3 × ULN AND total bilirubin < 2 × ULN or INR ≤ 1.5:** • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor patients weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	• Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF. **If ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN or INR > 1.5:** • Anti-nuclear antibody, anti–smooth muscle antibody,Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week [5]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy in eCRFs.

1. All events of ALT or AST > 3 × ULN **AND** total bilirubin > 2 × ULN or INR > 1.5 may indicate severe liver injury **and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to patients receiving anticoagulants.
2. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT or AST > 3 × ULN **and** total bilirubin > 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
3. hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
4. Pharmacokinetic sample may not be required for patients known to be receiving placebo or noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the patient's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the PK laboratory manual.



ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event;
ULN = upper limit of normal

10.6 Appendix 6: List of Examples of Strong Cytochrome P450 3A Inducers

Strong CYP3A inducers include, but are not limited to, the following:

- St John's Wort extract
- apalutamide
- avasimibe
- carbamazepine
- enzalutamide
- ivosidenib
- lumacaftor
- mitotane
- phenobarbital
- phenytoin
- rifabutin
- rifampin
- rifapentine

10.7 Appendix 7: List of Examples of Strong Cytochrome P450 3A and P-glycoprotein Inhibitors

Strong CYP3A and P-gp inhibitors include, but are not limited to, the following:

- grapefruit juice
- atazanavir/ritonavir
- boceprevir
- clarithromycin
- cobicistat
- conivaptan
- cyclosporine
- danoprevir/ritonavir
- diltiazem
- erythromycin
- elvitegravir/ritonavir
- faldaprevir
- gemfibrozil/itraconazle
- glecaprevir
- idelalisib
- indinavir
- indinavir/ritonavir
- itraconazole
- ketoconazole
- lopinavir/ritonavir
- mibefradil
- mifepristone
- nefazodone
- nelfinavir
- paritaprevir/ritonavir/ombitasvir
- paritaprevir/ritonavir/ombitasvir/dasabuvir
- posaconazole
- ribociclib
- ritonavir
- saquinavir
- saquinavir/ritonavir
- simeprevir/odalasvir

- telaprevir
- telithromycin
- tipranavir/ritonavir
- troleandomycin
- voriconazole

10.8 Appendix 8: Numerical Pain Rating Scale

To be completed by the subject:

Numerical Pain Rating Scale

Please select the number that best describes your pain where you had your operation in the past 24 hours.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Subject Signature Date (ddMmmyyyy) Time

To be completed by site staff:

Please circle the visit day that this assessment was completed.

Day 1	Day 2	Day 3	Day 4
Day 5	Day 6	Day 7	Day 8
Day 9	Day 10	Early Termination	End-of-study

10.9 Appendix 9: Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

10.10 Appendix 10: Protocol Version History

The Summary of Changes Table for Version 3 of the protocol is located directly before the Table of Contents.

Version 2: 14 Feb 2020

Section # and Name	Description of Change	Brief Rationale
Sponsor Signatory Page	Medical monitor's name and contact information changed	Administrative change
Section 1.1, Synopsis, Table 1-1 Section 1.3, Schedule of Activities, Figure 1-2 Section 3, Objectives and Endpoints, Table 3-1 Section 8.1.1.1, Time from End of Surgery to Time to Toleration of Solid Food and First Bowel Movement Section 9.4.5.1, Primary Efficacy Endpoint	"First" added before toleration of food in primary endpoint	Clarification
Section 1.1, Synopsis, Overall Design Section 4.1, Overall Design Section 6.3, Measures to Minimize Bias: Randomization and Blinding	"Primary" added before anastomosis after small and large bowel resection in randomization statement	Clarification
Section 1.1, Synopsis, Number of Patients Section 4.1, Overall Design	Number of screened patients changed from 680 to 425	Correction
Section 1.1, Synopsis, Concomitant Therapy Section 6.5, Prior Therapy and Concomitant Therapy	Strong cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp) inhibitors (eg, clarithromycin, diltiazem, grapefruit juice, indinavir, ketoconazole, ritonavir) added as prohibited prior and concomitant therapy	Request from regulatory agency
Section 1.1, Synopsis, Treatment Groups and Duration Section 1.2, Schema, Figure 1-1 Section 1.3, Schedule of Activities, Figure 1-2 Section 4.1, Overall Design	Description of when the End-of-study Visit will occur revised from 30 days after Day 10 to 30 days after Day 10 or after the day of discharge (whichever is sooner)	Clarification

Section 1.3, SOA, Figure 1-2 Section 8.2.6, Clinical Opiate Withdrawal Scale Section 9.4.6, Safety Analyses Section 10.9, Appendix 9, Clinical Opioid Withdrawal Scale	Clinical Opiate Withdrawal Scale (COWS) assessment added along with a description that the score in each domain will be summarized categorically	Request from regulatory agency to monitor patients for signs/symptoms of opioid withdrawal
Section 5.4, Screen Failures	Sentences added allowing rescreening of patients who met all entry criteria but whose surgery was rescheduled more than 14 days after signing the informed consent form (ICF) and stating that these patients must resign the ICF if the rescheduled surgery is more than 14 days after the originally-scheduled surgery and the medical monitor should be contacted to see if any screening tests will need to be repeated	Administrative change to allow patients who met the entry criteria to participate in the study even though their surgeries were rescheduled
Section 6.5, Prior Therapy and Concomitant Therapy	Wording for prohibited medications revised from up to end of treatment to through the end of study treatment	Clarification
Section 6.5, Prior Therapy and Concomitant Therapy Section 9.4.3, Prior and Concomitant Therapies	Sentences added citing the 4 enhanced recovery protocol elements that must be captured in the electronic case report form (eCRF) and that the investigator should determine the appropriate management of patients with signs/symptoms of opioid withdrawal, severe hypersensitivity to study treatment, and gastrointestinal perforation; statistical analyses modified to state that elements of the enhanced recovery protocol will be listed for each patient and summarized	Request from regulatory agency
Section 7.1, Discontinuation of Study Treatment	Sentence added that the investigator should consider	Request from regulatory agency to add specific

	discontinuation of study treatment if opioid withdrawal is suspected, and that study treatment must be discontinued if patients have a COWS score > 36, severe hypersensitivity thought to be related to study treatment, or signs/symptoms of gastrointestinal perforation	guidance regarding discontinuation in specific situations
Section 8.1.1.1, Time from End of Surgery to Time to Toleration of Solid Food and First Bowel Movement Section 9.4.3, Prior and Concomitant Therapies Section 9.4.5.1, Primary Efficacy Endpoint	Sentence added to record the reason for discharge prior to having the first bowel movement in the eCRF and text and e-mail added as ways to contact the investigator within 24 hours of the first bowel movement after discharge; statistical analyses modified to state that the reason for discharge prior to having the first bowel movement will be listed	Request from regulatory agency (reason for discharge); administrative change (provision for text and e-mail communication contact)
Section 8.1.2.2, Reinsertion of the Nasogastric Tube	"Postoperative" added to define when to capture reinsertion of the nasogastric tube	Clarification
Section 8.2.5, Numerical Pain Rating Scale	Phrase specifying pain to be assessed once daily in the morning at approximately the same time of day added	Clarification
Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information Section 8.3.2, Method of Detecting Adverse Events and Serious Adverse Events	Sentence referencing Appendix 3 for information about recording, evaluating, and assessing causality of adverse events and serious adverse events moved from Section 8.3.1 to 8.3.2	Clarification
Section 9.4, Statistical Analyses	Table 9-1 added to show how protocol study days will be mapped to analysis study days	For programming and analysis purposes to ensure compliance with CDISC requirements
Section 9.4.7.1.3, Exposure-response Analysis	Section added that an exploratory exposure-response analysis will be conducted for	Clarification

	efficacy and safety and reported in a separate pharmacokinetic report	
Section 10.2, Appendix 2: Clinical Laboratory Tests	International normalized ration (INR) added to clinical chemistry	Addition to ensure consistency with revised liver safety criteria in Section 10.5
Section 10.3.3, Reporting of Serious Adverse Events	Fax added as a way to report a new serious adverse event or update data on a serious adverse event after electronic data capture is taken offline	Administrative change
Section 10.5, Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments	Alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) was revised to ALT or aspartate aminotransferase (AST) > 8 × ULN for the liver chemistry study treatment stopping criteria; bilirubin was revised to total bilirubin, ALT or AST ≥ 3 × ULN AND bilirubin ≥ 2 × ULN (> 35% direct bilirubin) OR international normalized ratio (INR) > 1.5 was revised to ALT or AST > 3 × ULN AND total bilirubin < 2 × ULN or INR ≤ 1.5, and ALT ≥ 3 × ULN AND bilirubin ≥ 2 × ULN or INR > 1.5 was revised to ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN or INR > 1.5 under the monitoring actions; and a flowchart was added	Requested by regulatory agency
Section 10.7, Appendix 7: List of Examples of Strong Cytochrome P450 3A and P-glycoprotein Inhibitors	List of strong CYP3A and P-gp inhibitors added	Requested by regulatory agency
Section 10.8, Appendix 8: Numerical Pain Rating Scale	Numerical Pain Rating Scale added	Clarification

10.11 Appendix 11: Investigator Signature Page

Study Title:	A phase 2, multicenter, randomized, double-blind, placebo-controlled study of naldemedine in patients undergoing surgeries that include a bowel resection or bowel transection
Study Number:	1902G1721
Date of Original:	21 Nov 2019
Date of Latest Version:	18 Jun 2020 (Version 3)

I have read the protocol described above. I agree to comply with all local and country regulatory requirements and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>

10.12 Appendix 12: Abbreviations and Acronyms

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration after dosing
$AUC_{0\text{-}\tau}$	area under the concentration-time curve over the dosing interval τ (12 hours) on Day 3, calculated by Linear Up/Log Down Trapezoidal Method
BID	twice daily
BLQ	below the lower limit of quantification
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
CL/F	apparent total clearance estimated according to: $CL/F = Dose/AUC_{0\text{-}\tau}$ on Day 3 (for naldemedine only)
C_{max}	maximum observed plasma concentration on Day 3
COWS	Clinical Opiate Withdrawal Scale
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	amount of drug that produced the desired effect in 50%
EDC	electronic data capture
ET	early termination
GCP	Good Clinical Practice
GI	gastrointestinal
GI2	time from end of surgery to time to first toleration of solid food and first bowel movement
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIPAA	Health Information Portability and Accountability Act
HPLC	high performance liquid chromatography
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LDH	lactate dehydrogenase
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention–to-Treat
MME	morphine milligram equivalent
$MR_{M/U, AUC}$	metabolic ratio of $AUC_{0\text{-last}}$ of nor-naldemedine to $AUC_{0\text{-last}}$ of naldemedine, corrected for molecular weight, defined as (nor-naldemedine $AUC_{0\text{-last}}$)/(naldemedine $AUC_{0\text{-last}}$) × (naldemedine molecular weight [570.64])/(nor-naldemedine molecular weight [516.55]) (for nor-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 (nor-naldemedine C_{max})/(naldemedine C_{max}) × (naldemedine molecular weight [570.64])/(nor-naldemedine molecular weight [516.55]) (for nor-naldemedine only)
N	number of non-missing observations
NPRS	Numerical Pain Rating Scale
ODT	orally disintegrating tablet
OIC	opioid-induced constipation
PAMORA	peripherally acting mu-opioid receptor antagonist
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
postop	postoperative
RBC	red blood cell
RMST	restricted mean survival time
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration on Day 3
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential

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Electronic Signature Page for [redacted]

Approval	[redacted] 18-Jun-2020 23:38:01 GMT+0000

Final Approval	[redacted] 18-Jun-2020 23:39:56 GMT+0000

Electronic Signature Page for [redacted]

SHIONOGI INC.

Erratum

Date: **22 July 2020**

Study Number: **Protocol 1902G1721 Version 3**

Section 8.2.1 (Physical Examinations) of Protocol 1902G1721 Version 3, issued 18 June 2020, includes the extraneous words, "As per," which should be disregarded:

8.2.1 Physical Examinations

- A physical examination will be performed as per standard of care at the hospital or, for the End-of-study Visit, at the hospital or doctor's office. A preoperative physical examination (within 2 weeks prior to the patient signing the ICF) may be used, as long as the eCRF is completed. As per

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Approval	[redacted] 22-Jul-2020 14:01:11 GMT+0000

Final Approval	[redacted] 22-Jul-2020 14:02:00 GMT+0000

Electronic Signature Page for [redacted]