A Randomized, Double-Blind, Placebo-Controlled, Multi-center, Parallel-group, Phase 2 Study to Assess the Preventive Effect of ART-123 on Oxaliplatin-Induced Peripheral Neuropathy

Protocol

Asahi Kasei Pharma Corporation

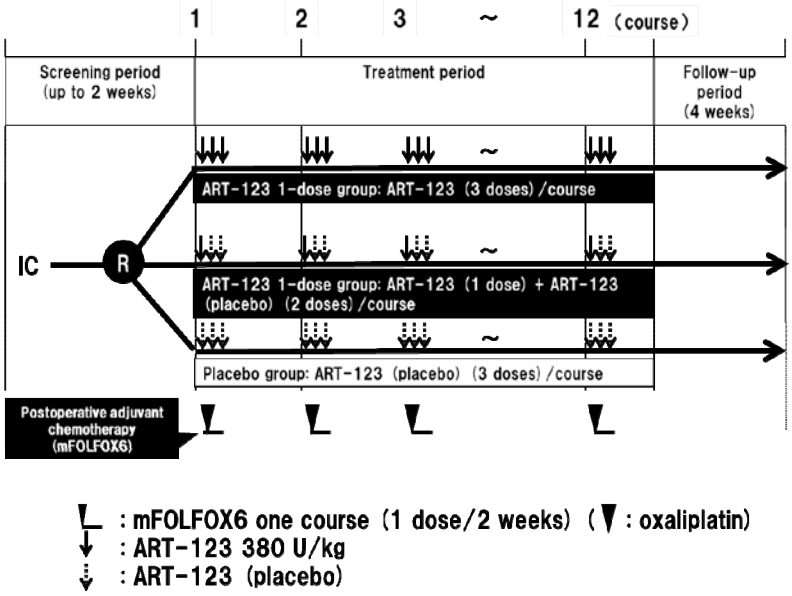
Protocol No. ART-123 (CIPN)–201 Ver.3
Release date: April 22, 2016

This Protocol Contains Confidential Information

The information contained in this protocol is confidential and is intended only for the study center directors, investigators, subinvestigators, clinical research coordinators, investigational product controllers, medical experts, medical advisors, assignment managers, and institutional review boards participating in the study. This protocol must be handled carefully because it may not be disclosed to any third party without the prior written approval of Asahi Kasei Pharma Corporation except when used to obtain informed consent from a subject. The written approval of Asahi Kasei Pharma Corporation is required to externally publish any or all of the study results at a conference, in a journal, or via any other medium.

Version 3, release date: April 22, 2016

Protocol Synopsis

Study title	A randomized, double-blind, placebo-controlled, multi-center, parallel-group, Phase 2 study to assess the preventive effect of ART-123 on oxaliplatin-induced peripheral neuropathy
Protocol number	ART-123 (CIPN) - 201
Study objectives	To assess, under placebo-controlled conditions, the efficacy and safety of ART-123 for preventing the onset of oxaliplatin-induced peripheral neuropathy in postoperative adjuvant chemotherapy that includes oxaliplatin in patients with pStage II or III colon cancer after radical resection (R0 surgery)
Clinical phase	Phase 2
Study design	Multi-center, randomized, double-blind, placebo-controlled, parallel-group comparative study
Study methodology	This study consists of a screening period, a treatment period, and a follow-up period and is of a placebo-controlled, double-blind, intergroup comparative design. After eligibility confirmation in the screening period, subjects will undergo 12 courses of postoperative adjuvant chemotherapy (mFOLFOX6) that includes oxaliplatin in the treatment period. From Days 1 to 3 in each course, subjects will receive ART-123 380 U/kg or placebo once daily by intravenous infusion over 30 minutes and undergo tests and observation (Figure 1). Subjects will be allocated to ART-123 groups: one to receive three doses and the other to receive one dose in each course of postoperative adjuvant chemotherapy (Figure 2). In the follow-up period, subjects will undergo the end-of-study tests and observations. See Appendix Table 1, Summary of study schedule, for details about the tests and observations.  Figure 1 Study design

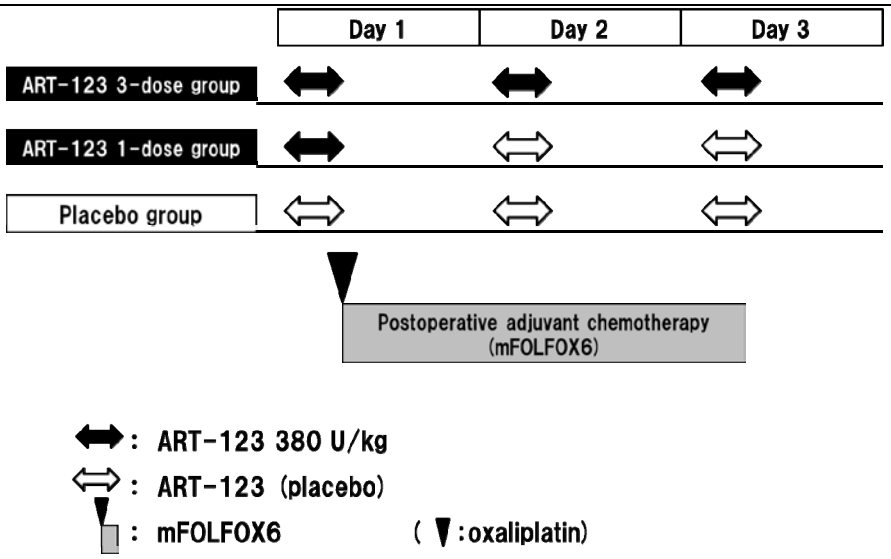
<table>
<tr><td></td><td> 

Figure 2 Investigational product dosing schedule during Days 1 to 3 of each course</td></tr>
<tr><td>Study population</td><td>Patients with pStage II or III colon cancer after radical resection (R0 surgery)

Inclusion criteria
Patients who meet all of the following criteria are eligible:
[1] Age 20 years or older but not older than 79 years at the time of informed consent
[2] Male or female
[3] Inpatient or outpatient
[4] Patients with histologically diagnosed colon cancer (or rectosigmoid cancer) at pStage II, IIIa, or IIIb based on “Japanese Classification of Colorectal Carcinoma (Eighth Edition)”
[5] Deemed to have undergone curative A (Cur A) surgery
[6] ECOG performance status of 0 or 1 on the day of registration
[7] The most recent laboratory findings from 7 days to 1 day before registration meet all of the following criteria:
• White blood cell count >3,500/mm^3 and <100,000/mm^3
• Neutrophil count >1,500/mm^3
• Platelet count >100,000/mm^3
• Haemoglobin >9.0 g/dL
• Total bilirubin <2.0 mg/dL
• Serum creatinine not more than the upper limit of the normal range and not more than 2 mg/dL
• AST (GOT) and ALT (GPT) not more than 2.5-fold the upper limit of the normal range and not more than 100 IU/L
[8] Scheduled as of the time of registration to undergo 12 courses of postoperative adjuvant chemotherapy with mFOLFOX6</td></tr>
</table>

	[9] Able to sufficiently understand the clinical study and give informed consent
	Exclusion criteria The presence of any of the following at the time of registration will exclude the patient from this study: [1] History of hypersensitivity to any of the ingredients in thrombomodulin alfa (recombinant) [2] Peripheral neuropathy or central nervous system (CNS) damage [3] Mental disorder of a severity that would affect the efficacy and safety evaluations in this study [4] Any treatment history of systemic chemotherapy (including any drug in the clinical trial stage) or radiotherapy intended to provide an anti-tumor effect [5] Active double cancer*1 *1 Synchronous double cancer or metachronous double cancer with disease-free period of no more than 5 years; does not include lesions equivalent to carcinoma in situ or intramucosal carcinoma deemed to have resolved with local treatment [6] Yet to recover from an operation or a complication such as a postoperative infection [7] Serious intestinal obstruction, diarrhoea, or pyrexia [8] History of cerebrovascular disorder (e.g., cerebral haemorrhage, cerebral infarction) within 52 weeks (364 days) before informed consent [9] Intracranial haemorrhage, pulmonary haemorrhage, or gastrointestinal haemorrhage (persistent haematemesis/blood in stool or gastrointestinal ulcer-induced haemorrhage) [10] Unconfirmed completion of a haemostasis procedure after central nervous system surgery or after trauma [11] Receiving transfusion, a blood derivative, G-CSF, or another hematopoietic factor within 7 days before the laboratory tests performed to assess registration eligibility [12] Hepatitis B infection and a positive test result for HBs antigen. Patients negative for HBs antigen but positive for HBc or HBs antibody must undergo an HBV-DNA test. A result at or above the normal range will disqualify the patient from enrollment. Test data obtained within 6 months before registration may be used. [13] A positive test result for HIV antigen or antibody [14] Establishment of an artificial anus (even if temporary) in colorectal cancer surgery [15] Administration of another investigational product within 16 weeks (112 days) before informed consent or undergoing observation that is still ongoing a day before informed consent

	[16] Pregnancy or possible pregnancy; wish to become pregnant during the study period; breastfeeding [17] Having participated in this study in the past [18] Prior treatment history with thrombomodulin alfa (recombinant) [19] Is otherwise found unsuited for the study by the investigator or subinvestigator
Investigational products	Investigational medicinal product ➢ Investigational product code: ART-123 ➢ Nonproprietary name: Thrombomodulin alfa (recombinant) (JAN) ➢ A freeze-dried formulation containing 12,800 U thrombomodulin alfa (recombinant) per vial Control drug (placebo) ➢ Investigational product code: ART-123 (placebo) ➢ A freeze-dried formulation free of thrombomodulin alfa (recombinant) that is indistinguishable in appearance from ART-123 (the investigational medicinal product)
Dose and mode of administration and number of doses of the investigational product	Dose and mode of administration Administer the investigational product (ART-123 380 U/kg or placebo) once daily by intravenous infusion over approximately 30 minutes from Days 1 to 3 of each course of postoperative adjuvant chemotherapy (mFOLFOX6). [1] ART-123 3-dose group On Day 1, initiate ART-123 administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of oxaliplatin administration. On Days 2 and 3, administer ART-123 at about the same time as on Day 1 whenever possible. [2] ART-123 1-dose group On Day 1, initiate ART-123 administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of oxaliplatin administration. On Days 2 and 3, administer the placebo at about the same time as on Day 1 whenever possible. [3] Placebo group On Day 1, initiate placebo administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of oxaliplatin administration. On Days 2 and 3, administer the placebo at about the same time as on Day 1 whenever possible. Criteria for suspension/resumption of the investigational product Suspend use of the investigational product when the administration of oxaliplatin, as a part of the postoperative adjuvant chemotherapy, is suspended. Resume investigational product administration concurrently with the resumption

	of oxaliplatin administration. Number of doses 36 (three/course × 12 courses)
Dose and mode of administration of standard concomitant medications	Administer mFOLFOX6 as postoperative adjuvant chemotherapy. See Section 8.3 for the specific doses, administration procedures, and dosing schedule.
Treatments prohibited during the study	Prohibited concomitant medications ➢ The administration of the following medications is prohibited from informed consent until study completion. (1) Other investigational products (2) Thrombomodulin alfa (recombinant) (3) Antineoplastic agents other than those specified for use in the postoperative adjuvant chemotherapy in this study ➢ The administration of the following medications is prohibited from the start of administration of the investigational product until study completion. (1) Thrombolytic drugs (e.g., t-PA preparations, urokinase) Restricted concomitant medications Over-the-counter medications and ready-made transfusion preparations are not considered restricted concomitant medications. ➢ The administration of the following medications is prohibited from informed consent until study completion except in association with use while peripheral motor neuropathy or peripheral sensory neuropathy is found by the investigator or subinvestigator to be Grade 2 or greater based on National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE). (1) Calcium gluconate, magnesium sulfate (2) Glutathione (3) L-glutamine (4) Vitamin B_6, B_{12}, and E preparations (5) Goshajinkigan, shakuyaku-kanzoto (6) Narcotics and similar drugs (including the opioid receptor agonist codeine phosphate) (7) Oral and injected adrenocorticosteroids (except when used to treat nausea/vomiting associated with the administration of an antineoplastic agent or to treat an allergy) (8) Pregabalin, gabapentin

	(9) Nonsteroidal anti-inflammatory drugs (NSAIDs, except when used for a purpose other than chemotherapy-induced peripheral neuropathy [CIPN] treatment) (10) Tricyclic antidepressants (11) Serotonin/noradrenaline reuptake inhibitors ➢ Initiating the administration of or increasing the dose of any of the following medications is prohibited from informed consent until study completion. Subjects may continue to use the medications that they had been using before informed consent provided that no dose changes are made. (Dose reductions are allowed.) (1) Isoniazid, ethambutol, metronidazole, medications for the treatment of HIV infection, HMG-CoA reductase inhibitors, tacrolimus, colchicine, and interferon preparations <u>Prohibited therapies</u> ➢ The following treatments are prohibited from informed consent until study completion. (1) Radiotherapy (2) Operations and other surgical procedures that could affect efficacy evaluation
Endpoints	<u>Efficacy</u> [1] NCI-CTCAE peripheral motor neuropathy, peripheral sensory neuropathy (CIPN only) [2] DEB-NTC [3] FACT/GOG-NTX-12 [4] FACT-G [5] Numerical rating scale (NRS) (pain) [6] Discontinuation, suspension, and dose reduction of oxaliplatin due to CIPN The efficacy endpoints will not be classified as primary or secondary because this is an exploratory study of ART-123 in prevention of the onset of oxaliplatin-induced peripheral neuropathy. <u>Safety</u> [1] Vital signs (body temperature, blood pressure systolic/diastolic, pulse rate) [2] Laboratory tests (routine blood tests, clinical chemistry tests, urine analysis, coagulation tests) [3] Immunogenicity (anti-drug antibodies, neutralising antibodies) [4] Adverse events other than CIPN

	Pharmacokinetics Blood concentration of thrombomodulin alfa (recombinant)
Treatment and observation periods	Screening period: up to 14 days Treatment period: 24 weeks (up to 36 weeks) Follow-up period: 4 weeks (up to 6 weeks)
Target sample size	75 subjects (25 per group)
Study period	July 2016 to January 2018
Primary analysis methods	[1] Analysis set The primary efficacy analysis set is the full analysis set (FAS). [2] Handling of primary efficacy data • Handling of missing data on whether an assessment is NCI-CTCAE Grade 1 or greater Consider subjects for whom these data are missing to have had an NCI-CTCAE Grade 1 or greater event. Perform sensitivity analysis that includes analysis with a missing NCI-CTCAE grade for all such subjects. • Handling of NCI-CTCAE evaluation data in the second and subsequent courses Evaluate the Day 1 (baseline) NCI-CTCAE grades as those from the immediately preceding course. Evaluate the Days 2, 3, 15, and 29 NCI-CTCAE grades as those observed within the course. • Handling of missing efficacy endpoint data (continuous variables) Do not impute missing continuous efficacy endpoint data. Perform sensitivity analyses with imputation using the last-observation-carried-forward (LOCF) approach. [3] General matters pertaining to efficacy analysis This study is conducted to assess and characterize the clinical effect of ART-123 for preventing the onset of oxaliplatin-induced peripheral neuropathy and to explore appropriate efficacy indices. Thus, efficacy analyses will be performed primarily with descriptive statistics obtained by summarizing and graphing data from each evaluation time point. The incidences of NCI-CTCAE Grade 1 or greater events will be evaluated with statistical tests and 95% confidence intervals as necessary in addition to descriptive statistics to allow intergroup comparison. The incidences of NCI-CTCAE Grade 1 or greater events with discontinuations and dropouts factored in will also be estimated. The significance level is set at 5% (two-sided), with a two-sided confidence interval and a confidence coefficient of 95%. Given the exploratory nature of the study, multiplicity will not be adjusted for.

Appendix Table 1 Summary of study schedule

Test/observation schedule		Screening period	Treatment period																							Follow-up period [h]	Unscheduled CIPN evaluation
		-	Course 1								Courses 2 to 11								Course 12							At discontinuation of the treatment [g]	At study completion (d43 of the last course) [i]
			D1 (registration day)			D2	D3			D29	D1 (d15 of the preceding course)			D2 [a]	D3 [a]	D8	D15	D29	D1 (d15 of the preceding course)			D2 [a]	D3 [a]	D8	D15		
			Before	Investigational product administration	After						Before	Investigational product administration	After						Before	Investigational product administration	After							
Permitted window of time from the specified date (days)		d-14 to d-1				-	-	-	+7	+7	By d43 of the preceding course			-	-	-	+7	+7	By d43 of the preceding course			-	-	-	+7	-	+14	-
Written informed consent		●																										
Subject demographic information survey		●	●																									
Patient registration, randomization			●																									
Office visit		●		●		●	●		○	○		●		●	●		○	○		●		●	●		●	●	●	●
Weight measurement			●[k]								●[k]								●[k]									
Investigational product administration				●		●	●					●[a]		●	●					●[a]		●	●					
Investigational product administration status survey				●		●	●		○	○		●		●	●		○	○		●		●	●					
Postoperative adjuvant chemotherapy					←	→	→						←	→	→						←	→	→					
Postoperative adjuvant chemotherapy status survey					●	●[j]	●[j]		○	○			●	●[j]	●[j]		○	○			●	●[j]	●[j]					
Concomitant medications/concomitant therapies survey		←	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	●	●	
Pregnancy test		●									●[d]																●	
Efficacy	NCI-CTCAE		●			●	●		○	○	●			●	●		○	○	●			●	●		●	●	●	●
	DEB-NTC		●						○	○	●						○	○	●						●	●	●	
	FACT/GOG-NTX-12		●					●	○	○	●					●	○	○	●					●	●	●	●	
	FACT-G		●								●[e]								●						●	●	●	

	NRS (pain)		●					●	○	○	●					●	○	○	●					●	●	●	●	
Safety	Laboratory tests	●[c)]									●[k)]								●[k)]						●	●	●	
Safety	Vital signs	●									●								●						●	●	●	
Safety	Adverse events	◄																							►	●	●	
Safety	Immunogenicity		●																								●	
Pharmacokinetics			●		●[f)]	●[f)]	●[f)]							△[f)]	△[f)]							△[f)]	△[f)]					

Time points are expressed as “Day (D),” and numbers of days are expressed as “day (d).”

●: required

○: to be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

△: if no blood samples are available from course 1, perform once in one of the courses from 2 to 12

a) Not required in courses in which oxaliplatin is suspended

b) To be performed before investigational product administration if efficacy and safety evaluations take place on the same day as investigational product administration

c) To be performed between Day −7 and Day −1 (1 day before registration); hepatitis B test data obtained within 6 months before the day of registration may also be used

d) To be performed only in course 2; may be determined on the day before Day 1

e) To be performed only in courses 5 and 9

f) Collect blood samples immediately after and from 30 to 120 minutes after completion of investigational product administration

g) If the evaluation at treatment period discontinuation takes place on or after Day 43 of the last course of postoperative adjuvant chemotherapy, or if the subsequent tests/observations for the study are not possible, perform the end-of-study evaluations instead of the treatment-period discontinuation evaluations. If the course 12 postoperative adjuvant chemotherapy has not commenced within 34 weeks (Day 239 from the day of registration), discontinue the subject from the study, perform the treatment-period discontinuation evaluations, and then perform the end-of-study evaluations on Day 43 of the last course of postoperative adjuvant chemotherapy.

h) If any postoperative adjuvant chemotherapy for the subsequent course has not commenced by Day 43 of a course, discontinue the subject from the study and perform the end-of-study evaluations.

i) If the subject is discontinued from the study in the follow-up period, perform the end-of-study evaluations

j) Determine the status of fluorouracil continuous intravenous infusion use

k) May be determined on the day before Day 1

Table of Contents

Abbreviations and Definitions of Terminology

List of general abbreviations

Abbreviation	Unabbreviated expression
ART-123	Thrombomodulin alfa (recombinant)
Recomodulin	A drug product containing thrombomodulin alfa (recombinant) as the active pharmaceutical ingredient (proprietary name: Recomodulin® Inj. 12800)
CIPN	Chemotherapy-Induced Peripheral Neuropathy
DEB-NTC	Neurotoxicity Criteria of DEBIOPHARM
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
FACT	Functional assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy-General (Version 4)
FACT/GOG-NTX-12	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Version 4)
FAS	Full analysis set
GCP	Good clinical practice
G-CSF	granulocyte-colony stimulating factor
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HMG-CoA	hydroxymethylglutaryl-CoA
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
mFOLFOX6	modified FOLFOX6
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events ver.4.0
NRS	Numerical rating scale
PPS	Per protocol set
pStage	pathological Stage
QOL	Quality of life
TEAE	Treatment-emergent adverse event
TM	thrombomodulin
t-PA	tissue-plasminogen activator

List of laboratory test abbreviations

Abbreviation	Description of abbreviation
AL-P	Alkaline phosphatase
ALT (GPT)	Alanine aminotransferase (glutamic pyruvic transaminase)
AST (GOT)	Aspartate aminotransferase (glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
Cl	Chlorine
HBc	Hepatitis B core
HBs	Hepatitis B surface
K	Potassium
LDH	Lactate dehydrogenase
Na	Sodium
PT-INR	prothrombin time international normalized ratio

1. Background Information and History of Development

1.1 Background Information

1.1.1 Epidemiology and Treatment of Colorectal Cancer

An estimated 136,000 people in Japan were diagnosed with colon cancer in 2015, and the number of afflicted people is growing (2015 estimate of National Cancer Center Japan). Treatment options such as endoscopic treatment, surgery, chemotherapy, and radiotherapy are selected according to how advanced the disease is[1)]. Rapid advances in antineoplastic agents have made chemotherapy an option comparable in benefit to surgery and radiotherapy. Chemotherapy, however, must sometimes be modified or discontinued because of the adverse reactions it causes[2)].

1.1.2 Overview of Chemotherapy-induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is one adverse reaction that can affect whether chemotherapy can be continued. Symptoms of CIPN include numbness, abnormal sensations, and hypoaesthesia of the extremities caused by sensory nerve damage and muscular atrophy and muscular weakness caused by motor nerve damage[3)]. CIPN varies in incidence from drug to drug, occurring most frequently in association with the antineoplastic agent oxaliplatin, which is a platinum compound, followed by the taxane drug paclitaxel[4)].

1.1.3 Oxaliplatin-induced Peripheral Neuropathy

Oxaliplatin-induced peripheral neuropathy takes the forms of acute peripheral neuropathy, which appears just after to several days after oxaliplatin administration, and chronic peripheral neuropathy, which appears later over the course of oxaliplatin treatment. Temporary numbness and abnormal sensations in the limbs and mouth, one manifestation of acute peripheral neuropathy, affect almost everyone (85% to 95%) treated with oxaliplatin. Manifestations of chronic peripheral neuropathy include persistent numbness and abnormal sensations of the limbs, fine-motor impairments such as difficulty buttoning clothing, and movement disorders such as difficulty walking. The risk of these conditions increases as the cumulative dose of oxaliplatin increases. These conditions, moreover, substantially reduce patient quality of life (QOL). The modification and discontinuation of chemotherapy caused by chronic peripheral neuropathy is particularly clinically significant[3)5)6)].

Although the specific mechanism of the onset of oxaliplatin-induced peripheral neuropathy remains uncharacterized, chronic peripheral neuropathy is attributed to axonal degeneration resulting from nerve cell body damage. Because damaged nerves require a long time for repair, symptoms may persist for several months or years after the end of oxaliplatin treatment[7)]. Preventing the onset of oxaliplatin-induced peripheral neuropathy is therefore important.

1.1.4 Status of CIPN Prevention and Treatment

No drug indicated for preventing the onset of or treating CIPN is available in Japan or elsewhere[8)].

In Japan, CIPN is empirically treated with products including calcium-magnesium formulations, carbamazepine, gabapentin, pregabalin, and Chinese herbal medications (goshajinkigan), although

sufficient evidence supporting their use is lacking, and efficacy has not been demonstrated[4)9)]. Oxaliplatin dose reduction or suspension is therefore performed as symptomatic treatment for CIPN[7)].

The American Society of Clinical Oncology published a guideline on the prevention and management of CIPN[8)] in 2014. The guideline recommends only duloxetine for treating CIPN and has no recommended pharmacotherapies for preventing onset.

1.2 History of Development and Characteristics of ART-123

1.2.1 Pharmacological Characteristics of ART-123

Thrombomodulin (TM) is a glycoprotein present on vascular endothelial cells. This physiologic coagulation factor facilitates the regulation of blood coagulation in the body. ART-123 (non-proprietary name: thrombomodulin alfa (recombinant)) is soluble human TM, expressed in animal cells, that consists of only the extracellular domain of poorly soluble natural TM, the extracellular domain containing the active site. ART-123 has a coagulation-regulating effect comparable to natural TM. A drug product containing ART-123 as the active ingredient (proprietary name: Recomodulin® Inj. 12800) was approved in Japan in 2008 for the indication of disseminated intravascular coagulation syndrome. ART-123 appears to have anti-inflammatory actions and protects against vascular endothelial damage[10)].

1.2.2 Characteristics of ART-123 (nonclinical)

One mechanism for the onset of neuropathy is thought to be prolongation of the inflammatory response[11)]. The supposed anti-inflammatory action of ART-123 was investigated in a rat model of CIPN induced with oxaliplatin. Intraperitoneal administration of 0.3 mg/kg (1,900 U/kg) to 10 mg/kg (65,000 U/kg) of ART-123 given for 7 days suppressed escape behavior in response to mechanical hyperalgesia in a dose-dependent manner[12)]. ART-123 did not suppress the growth-inhibiting effect of oxaliplatin on cancer cells in a cultured human cancer cell line[13)]. These findings suggest that ART-123 may prevent the onset of oxaliplatin-induced peripheral neuropathy without affecting the anti-tumor activity of oxaliplatin.

2. Study Objectives

To assess, under placebo-controlled conditions, the efficacy and safety of ART-123 for preventing the onset of oxaliplatin-induced peripheral neuropathy in postoperative adjuvant chemotherapy that includes oxaliplatin in patients with pStage II or III colon cancer after radical resection (R0 surgery)

3. Study Population

Patients with pStage II or III colon cancer after radical resection (R0 surgery)

3.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible:

[1] Age 20 years or older but not older than 79 years at the time of informed consent

[2] Male or female

[3] Inpatient or outpatient

[4] Patients with histologically diagnosed colon cancer (or rectosigmoid cancer) at pStage II, IIIa, or IIIb based on "Japanese Classification of Colorectal Carcinoma (Eighth Edition)"[14)]

[5] Deemed to have undergone curative A (Cur A) surgery

[6] ECOG performance status of 0 or 1 on the day of registration

[7] The most recent laboratory findings from 7 days to 1 day before registration meet all of the following criteria:

- White blood cell count >3,500/mm^3 and <100,000/mm^3
- Neutrophil count >1,500/mm^3
- Platelet count >100,000/mm^3
- Haemoglobin >9.0 g/dL
- Total bilirubin <2.0 mg/dL
- Serum creatinine not more than the upper limit of the normal range and not more than 2 mg/dL
- AST (GOT) and ALT (GPT) not more than 2.5-fold the upper limit of the normal range and not more than 100 IU/L

[8] Scheduled as of the time of registration to undergo 12 courses of postoperative adjuvant chemotherapy with mFOLFOX6

[9] Able to sufficiently understand the clinical study and give informed consent

3.2 Exclusion Criteria

The presence of any of the following at the time of registration will exclude the patient from this study:

[1] History of hypersensitivity to any of the ingredients in thrombomodulin alfa (recombinant)

[2] Peripheral neuropathy or central nervous system (CNS) damage

[3] Mental disorder of a severity that would affect the efficacy and safety evaluations in this study

[4] Any treatment history of systemic chemotherapy (including any drug in the clinical trial stage) or radiotherapy intended to provide an anti-tumor effect

[5] Active double cancer[*1]

*1 Synchronous double cancer or metachronous double cancer with disease-free period of no more than 5 years; does not include lesions equivalent to carcinoma in situ or intramucosal carcinoma deemed to have resolved with local treatment

[6] Yet to recover from an operation or a complication such as a postoperative infection

[7] Serious intestinal obstruction, diarrhoea, or pyrexia

[8] History of cerebrovascular disorder (e.g., cerebral haemorrhage, cerebral infarction) within 52 weeks (364 days) before informed consent
[9] Intracranial haemorrhage, pulmonary haemorrhage, or gastrointestinal haemorrhage (persistent haematemesis/blood in stool or gastrointestinal ulcer-induced haemorrhage)
[10] Unconfirmed completion of a haemostasis procedure after CNS surgery or after trauma
[11] Receiving transfusion, a blood derivative, G-CSF, or another hematopoietic factor within 7 days before the laboratory tests performed to assess registration eligibility
[12] Hepatitis B infection and a positive test result for HBs antigen. Patients negative for HBs antigen but positive for HBc or HBs antibody must undergo an HBV-DNA test. A result at or above the normal range will disqualify the patient from enrollment. Test data obtained within 6 months before registration may be used.
[13] A positive test result for HIV antigen or antibody
[14] Establishment of an artificial anus (even if temporary) in colorectal cancer surgery
[15] Administration of another investigational product within 16 weeks (112 days) before informed consent or undergoing observation that is still ongoing a day before informed consent
[16] Pregnancy or possible pregnancy; wish to become pregnant during the study period; breastfeeding
[17] Having participated in this study in the past
[18] Prior treatment history with thrombomodulin alfa (recombinant)
[19] Is otherwise found unsuited for the study by the investigator or subinvestigator

3.3 Rationale for Inclusion and Exclusion Criteria

3.3.1 Rationale for Inclusion Criteria

[1] Subjects must be at least 20 years old to be sufficiently competent to give consent. An upper age limit of 79 years was set out of concern for subject safety.
[2] The sex of the subjects is not limited because sex is not thought to affect the evaluation of efficacy or safety in the study.
[3] The hospitalization status of the subjects is not limited because this is not thought to affect the evaluation of efficacy or safety in the study.
[4] and [5] The study will be in patients with colorectal cancer following radical resection, who have a better prognosis than patients with unresectable, advanced, or recurrent colorectal cancer. The study will be in patients with pStage II or III colon cancer following resection because the Guidelines for the Treatment of Colorectal Cancer[1)], in the section on chemotherapy eligibility, requires Stage II colorectal cancer with a high risk of recurrence or Stage III colorectal cancer for postoperative adjuvant chemotherapy, and patients with Stage II and III colon cancer are indicated for postoperative adjuvant chemotherapy in the package insert of oxaliplatin.
[6] This criterion was established to select relatively healthy subjects.
[7] This criterion was established out of concern for subject safety.
[8] The efficacy of Recomodulin will be investigated on CIPN induced by oxaliplatin, which frequently causes this condition. The oxaliplatin-containing postoperative adjuvant chemotherapy regimens recommended in the Guidelines for the Treatment of Colorectal Cancer are FOLFOX and CapeOX. FOLFOX compliance is readily determinable because the regimen is administered under the control

of healthcare professionals, which makes the regimen ideal for this first study to evaluate the efficacy of Recomodulin in CIPN. The standard FOLFOX regimen mFOLFOX6 was selected. The standard mFOLFOX6 treatment duration of 6 months (12 courses) was selected to allow evaluation of the efficacy of Recomodulin in oxaliplatin-induced chronic neuropathy.

[9] This criterion was established to ensure that the study is ethically consistent.

3.3.2 Rationale for Exclusion Criteria

[1] This criterion was established out of concern for subject safety.

[2] to [4] These criteria were established because of the possible impact these conditions could have on the efficacy and safety evaluations in the study.

[5] This criterion was established because of the potential impact on the evaluation of safety.

[6] and [7] These criteria were established out of concern for subject safety and in reference to the general indications for postoperative adjuvant chemotherapy in the Guidelines for the Treatment of Colorectal Cancer.

[8] to [10] As these conditions are listed in the Careful Administration and Contraindications sections of the Recomodulin package insert, these criteria were established out of concern for subject safety.

[11] This criterion was established out of concern for subject safety to prevent the registration of patients satisfying the inclusion criteria because of transfusion or the like.

[12] This criterion was established out of concern for subject safety because HBV reactivation during or after postoperative adjuvant chemotherapy could lead to hepatitis B onset[15].

[13] to [16] These criteria were established out of concern for subject safety.

[17] and [18] These criteria were established because of the possible impact these conditions could have on the efficacy and safety evaluations in the study.

[19] This criterion was included to allow exclusion when the evaluation of efficacy and safety in the study could be impacted by another reason and when the investigator or subinvestigator determines that subject safety cannot be guaranteed.

4. Subject Informed Consent

4.1 Authoring of the Informed Consent Form

Based on the reference informed consent form provided by the sponsor, the investigator will author an informed consent form and submit the document to the sponsor. The informed consent form will contain the statements for patients presented below. The investigator will consult with the sponsor to review the completed informed consent form and then obtain the approval of an institutional review board selected by the director of the study site.

Information for patients

[1] That the study involves research.
[2] Purpose of the study.
[3] The name, title, and contact information of the investigator or subinvestigator.
[4] Study methodology.
[5] The expected clinical benefits and risks or inconveniences.
[6] The alternative treatments that may be available for the disease and their important potential risks and benefits.
[7] The scheduled duration of study participation by the subjects.
[8] That participation in the study is voluntary and that the subject may refuse to participate or stop participating in the study at any time. Also that the subject would not be treated disadvantageously for refusing to participate or withdrawing consent and would not lose benefits to which the subject would be otherwise entitled for not participating.
[9] That the monitor(s), the auditor(s), the institutional review board, and the regulatory authority(ies) will be granted direct access to the subject's treatment-related source documents, without violating the confidentiality of the subject, and that, by signing the written informed consent form, the subject is authorizing such access.
[10] The privacy of the subject would be maintained if the study results are published.
[11] The person(s) in the study site to contact for obtaining further information regarding the study and the rights of subjects, and whom to consult or contact in the event of a study-related injury.
[12] Compensation and treatment to which the subject is entitled if the subject is injured in relation to the study.
[13] The number of subjects scheduled to participate in the study.
[14] That the subject will be promptly informed if information becomes available that may be relevant to the subject's willingness to continue participating in the study.
[15] The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
[16] The expenses, if any, required of the subject.
[17] The monetary and other payments, if any, to the subject for participating in the study.
[18] Rules with which the subject is expected to comply.
[19] That any doctor treating the subject will be notified about the participation of the subject in the study.
[20] The type of institutional review board, that the institutional review board will conduct reviews to determine whether the study should be conducted or continued based on its scientific and ethical

merits, and that the opinions of the institutional review board will be relayed to the director of the study site.

[21] The name and address of the person installing the institutional review board and how to obtain information about this person.

[22] That any remaining samples might be used for future research for drug development.

[23] That data may be used not only for approval review of the drug product but also for cross-sectional studies by the regulatory authorities as well as guideline preparation.

[24] That data may be used secondarily.

[25] That data obtained before the subject gives informed consent could be used.

4.2 When and How to Obtain Informed Consent

The investigator or subinvestigator will use the informed consent form to fully inform each patient about the study and his or her rights before the subject begins the study and then obtain voluntary consent from the patient along with the date of consent by having the patient personally sign the informed consent form.

The investigator or subinvestigator will sign or seal the informed consent form and enter the date on which the subject was informed. If a clinical research coordinator provides a supplementary explanation, that clinical research coordinator will also sign or seal the informed consent form and enter the date of the explanation. The investigator or subinvestigator will give the written information for patients and a copy of the informed consent form to the subject. Study-specific tests and treatment changes not performed in routine care and treatment will not be conducted before informed consent is obtained.

4.3 Informing Other Hospitals When Informed Consent Is Obtained

The investigator or subinvestigator will determine if the subject is being treated at another hospital or department. If this is the case, the investigator or subinvestigator will, with the consent of the subject, notify the responsible doctor.

4.4 Information to Consider When Obtaining Informed Consent

The following should be kept in mind when obtaining informed consent:

[1] The investigator or subinvestigator will discuss the study using plain language understandable to the patients.

[2] The investigator or subinvestigator must not force the subjects to participate or continue participating in the study or exert inappropriate influence on their decisions to do so.

[3] After discussing the study, the investigator or subinvestigator will grant the patient an opportunity to ask questions, will address the questions to the patient's satisfaction, and grant adequate time for the patient to decide whether to participate in the study.

[4] The investigator or subinvestigator will specify the visit days for the patients and discuss and obtain permission for the tests and observations.

[5] When informing the subjects, the investigator or subinvestigator must not force the subjects to waive their rights, use language that could be construed as doing so, absolve the investigator, study site or sponsor of their legal obligations, or use language that could be construed as doing so.

[6] Informed consent by a proxy is not allowed in the study.

[7] Patients requiring a witness are not allowed as study subjects.

4.5 Amending the Informed Consent Form

[1] The sponsor will promptly inform the director of the study site and the investigator in writing on obtaining any information that could affect the willingness of the subjects to continue participating in the study.

[2] The investigator or subinvestigator will promptly orally convey this information to the subjects and determine their willingness to continue in the study.

[3] If determining an amendment to be necessary, the investigator will promptly amend the informed consent form based on the information and submit the amended document to the sponsor. The investigator will consult with the sponsor to review the document and then obtain the approval of the institutional review board of the study.

[4] The investigator or subinvestigator will again inform the subjects currently participating in the study using the amended informed consent form and obtain written consent to continue in the study according to Section 4.2 .

5. Study Design and Schedule

5.1 Study Design

Category	Description	Location of detailed description
Study design	Multi-center, randomized, double-blind, placebo-controlled, parallel-group comparative study	-
Clinical phase	Phase 2	-
Group composition	ART-123 3-dose group, ART-123 1-dose group, placebo group	Section 8
Dose and mode of administration	Administer the investigational product (ART-123 380 U/kg or placebo) once daily by intravenous infusion over approximately 30 minutes from Days 1 to 3 of each course of postoperative adjuvant chemotherapy (mFOLFOX6).	Section 8
Target sample size	75 registered subjects (25 per group)	Section 12
Investigational product assignment	The investigational product assignment manager will prepare key codes and assign drug numbers to the investigational products based on these.	Section 6
Assigning subjects to treatment groups	A subject registration center will randomly assign the subjects.	Section 7
Efficacy endpoints	[1] NCI-CTCAE version 4.0 (NCI-CTCAE) peripheral motor neuropathy, peripheral sensory neuropathy (CIPN only) [2] DEB-NTC [3] FACT/GOG-NTX-12 [4] FACT-G [5] NRS (pain) [6] Discontinuation, suspension, and dose reduction of oxaliplatin due to CIPN	Sections 9 and 12
Safety endpoints	[1] Vital signs (body temperature, blood pressure systolic/diastolic, pulse rate) [2] Laboratory tests (routine blood tests, clinical chemistry tests, urine analysis, coagulation tests) [3] Immunogenicity (anti-drug antibodies, neutralizing antibodies) [4] Adverse events other than CIPN	Sections 9 and 12
Others	Pharmacokinetics (blood concentration of thrombomodulin alfa (recombinant))	Sections 9 and 12
Study period	July 2016 to January 2018	Section 5
Interim analysis	Will not be performed.	-

5.2 Rationale for Study Design

5.2.1 Endpoints and Rationale

[1] NCI-CTCAE is widely used throughout the world to evaluate adverse reactions to antineoplastic agents. The NCI-CTCAE events related to peripheral neuropathy are peripheral motor neuropathy and peripheral sensory neuropathy, which are included as endpoints in this study.

[2] DEB-NTC, in addition to NCI-CTCAE, is used for evaluating peripheral neuropathy in Japanese clinical studies of oxaliplatin. Characteristically, DEB-NTC assigns grades according to the duration of the symptoms. DEB-NTC is therefore suited to obtaining information on the duration of CIPN in the study, which is why it was included as an endpoint.

[3] and [4] The FACT subscale FACT/GOG-NTX-12, which is specialized for evaluating oxaliplatin-induced peripheral neuropathy, was selected as a patient reported outcome for assessing peripheral neuropathy severity. Because the significance of CIPN prevention and treatment lies in preventing reductions in patient QOL in addition to facilitating chemotherapy, FACT-G was selected to allow the evaluation of patient-reported QOL.

[5] NRS was selected for evaluating pain, which is highly relevant to patient QOL.

[6] Oxaliplatin compliance was selected as an endpoint because allowing adequate chemotherapy to be initiated and continued for the underlying disease is one reason for this Recomodulin development program.

5.2.2 Control Drug and Rationale

No drug for preventing the onset of CIPN is available. A placebo-controlled design was therefore determined to be appropriate for investigating the absolute effects of the investigational medicinal product on the prevention of CIPN onset.

5.3 Study Methods

As shown in Figure 5.3-1, the study consists of a screening period, treatment period, and follow-up period.

- Screening period (up to 14 days)

  This period for registering subjects lasts for up to 14 days, spanning from the day of informed consent to the day before the first day of investigational product administration.

- Treatment period [24 weeks (up to 36 weeks)]

  This period spans the 24-week period over which 12 courses of biweekly postoperative adjuvant chemotherapy are administered. The treatment period extends from the first day of investigational product administration to Day 15 of the last course or the day of the treatment-period discontinuation evaluations.

- Follow-up period [4 weeks (up to 6 weeks)]

  This period lasts from the day after Day 15 of the last course or the day of the treatment-period discontinuation evaluations to the study completion.

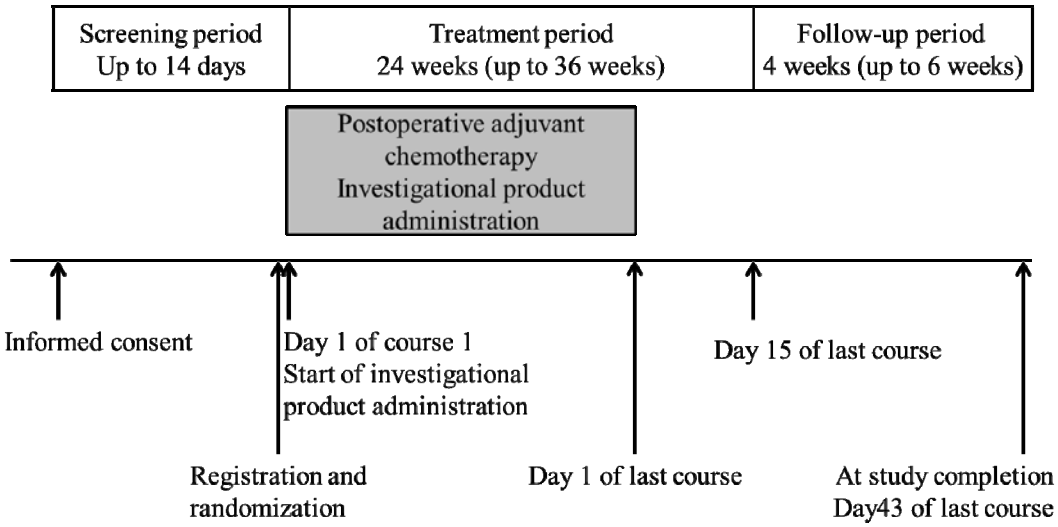


Figure 5.3-1 Screening, treatment, and follow-up periods of the study

5.4 Study Period

July 2016 to January 2018

6. Investigational Products

6.1 Names and Descriptions of Investigational Products

[1] Investigational medicinal product

- Investigational product code: ART-123
- Nonproprietary name: Thrombomodulin alfa (recombinant) (JAN)
- Description: Recomodulin is a glycoprotein consisting of 498 amino acid residues ($C_{2230}H_{3357}N_{633}O_{718}S_{50}$, molecular weight: 52,124.58) produced by Chinese hamster ovary cells designed to express cDNA that encodes amino acid residues 1 to 498 of human thrombomodulin (total molecular weight: approximately 64,000).
- Storage conditions: Store at room temperature and away from light
- Location of manufacture: [redacted].

[2] Control drug (placebo)

- Investigational product code: ART-123 (placebo)
- Storage conditions: Store at room temperature and away from light
- Location of manufacture: [redacted]

6.2 Investigational Product Dosage Form and Strength

[1] Investigational medicinal product

- Injection
- A freeze-dried formulation containing 12,800 U thrombomodulin alfa (recombinant) per vial
- Contains 40 mg L-arginine hydrochloride and a pH adjuster as excipients

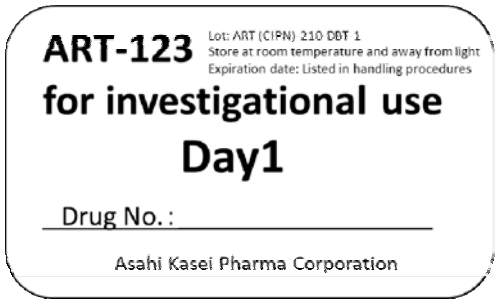
[2] Control drug

- Injection
- A freeze-dried formulation free of thrombomodulin alfa (recombinant) that is indistinguishable in appearance from ART-123 (the investigational medicinal product)
- Contains 29 mg L-arginine hydrochloride, 800.1 mg Polysorbate, 1.5 mg sodium chloride, and a pH adjuster as excipients

6.3 Investigational Product Packaging and Labeling

[1] Vial

Vial label

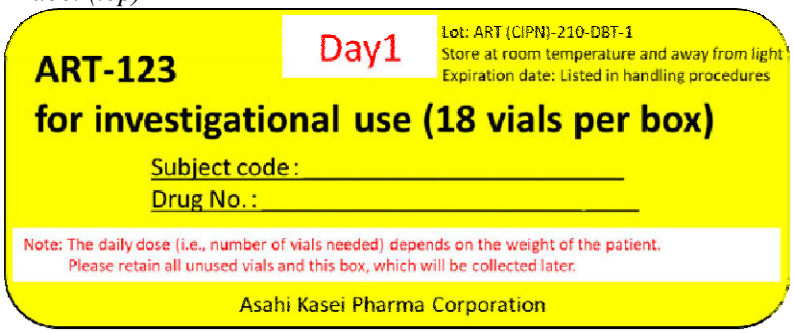


Day 2 and 3 labels are similarly formatted

[2] Inner box

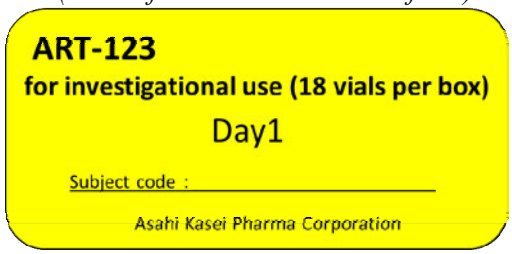
Each Day 1, 2, or 3 inner box contains 18 vials of ART-123 or ART-123 placebo.

Label (top)



Day 2 and 3 labels are similarly formatted

Labels (one on front and one on side of box)



ART-123 for investigational use (18 vials per box)

Day 1

Subject code:

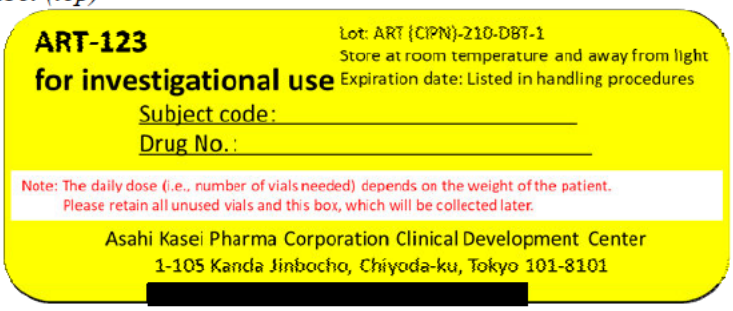
Asahi Kasei Pharma Corporation

Day 2 and 3 labels are similarly formatted

[3] Outer box

Each outer box contains three inner boxes (for Days 1, 2, and 3).

Label (top)



Labels (one on front and one on side of box)

6.4 Shelf Life of Investigational Products

See Appendix 2 of the Investigational Product Handling Procedures.

6.5 Investigational Product Assignment

The investigational product assignment manager will prepare key codes and assign drug numbers to the investigational products based on these.

6.6 Retention of Key Codes and Emergency Keys

Following investigational product assignment, the investigational product assignment manager will retain the key codes until unblinding after the study completion.

Key codes set up in the Interactive Web Response System (IWRS) will be used as emergency key codes.

6.7 Unblinding of Emergency Keys During Study

[1] If a serious adverse event or comparable occurrence requires the identity of an assigned drug to be known to ensure the safety of the affected subject, the investigator or subinvestigator will notify the sponsor and complete the emergency key unblinding request screen of the IWRS to request that the subject registration center unblind the emergency key. The investigator or subinvestigator will discontinue the subject from the investigational product and evaluate safety to the maximum extent possible.

[2] The subject registration center will process the emergency key unblinding request and ask the sponsor for permission to unblind the emergency key.
[3] The sponsor will determine the need to unblind the emergency key and approve the unblinding request of the subject registration center.
[4] After confirming that the sponsor has approved the unblinding request, the subject registration center will issue a passcode for unblinding the emergency key and notify the person who requested unblinding.
[5] The person who requested unblinding will input the passcode from the subject registration center in the emergency key unblinding result screen of the IWRS, submitting this to the subject registration center.
[6] The subject registration center will check the passcode entered and display the result of emergency key unblinding on the emergency key unblinding result screen of the IWRS.
[7] The subject registration center will inform the sponsor that the emergency key has been unblinded.
[8] The sponsor will inform the medical expert of the result of emergency key unblinding.
[9] The investigator or subinvestigator will promptly complete the electronic case report form of the subject in question and submit the document to the sponsor.

6.8 Confirmation of Indistinguishability

At the time of investigational product assignment and after the study completion, the investigational product assignment manager will check some of the investigational products assigned to confirm indistinguishability.

6.9 Dispensing of Investigational Product

The sponsor will confirm that the contract has been executed and then dispense the investigational product to the investigational product controller designated by the study site director.

6.10 Storage and Control of Investigational Product

After receiving the investigational products from the sponsor, the investigational product controller will store and control the investigational products according to Appendix 2 of the investigational product handling procedures provided by the sponsor.

6.11 Collection of Investigational Products

- The study site investigational product controller will determine investigational product usage and document the amount remaining at the time of investigational product replacement or when investigational product administration is discontinued or completed at the study site for the subject in question. All unused investigational product will be returned to the sponsor. At this time, all outer boxes in use (including those that have been opened but not used) will be sealed after the sponsor determines the quantity.

- The investigational product controller will not discard the unused investigational product, inner boxes (empty and in use), or outer boxes (empty and in use), retaining these items until they are collected by the sponsor.

7. From Subject Selection to Start of Treatment

7.1 Subject Registration Flowchart

➢ Procedures from subject selection to the day of subject registration

Subject selection

♦ Interview to determine eligibility as subject (e.g., inclusion and exclusion criteria)
(subject screening)

Informed consent

♦ Explanation with informed consent form, obtaining of written informed consent, and assignment of subject identification code

Confirmation of eligibility

♦ Confirmation of subject eligibility (e.g., inclusion and exclusion criteria)
♦ To be performed during screening period:
- Subject demographic information survey
- Pregnancy test
- Laboratory tests, vital signs

following things on the same day:

Registration

♦ Entry of pertinent information in IWRS followed by submission to subject registration center
♦ Notification of drug number by subject registration center

Blood sampling for pharmacokinetic analysis Immunogenicity

♦ Pharmacokinetics (baseline)
♦ Immunogenicity (baseline)
♦ Efficacy evaluation (baseline)

Start of administration

♦ Weighing of subject to determine investigational product dose (subjects may be weighed on the previous day)
♦ Start of investigational product administration
♦ Start of postoperative adjuvant chemotherapy

Blood sampling for pharmacokinetic analysis

♦ Pharmacokinetics (immediately after and from 30 to 120 minutes after completion of administration)

7.2 Enrolling Subjects in the Study

7.2.1 Information to Enter in IWRS

The investigator or subinvestigator or a clinical research coordinator will enter the following information via the IWRS, based on the source documents, after informed consent for study participation is given and before registration.

[1] Study center and name of investigator or subinvestigator

[2] Subject identification code

[3] Date of informed consent

[4] Confirmation of eligibility in terms of inclusion and exclusion criteria

[5] Background information

Subject background information to determine: Date of birth, age, sex (male, female), race, previous subject identification code (if subject is rescreened)

7.2.2 Creation of Screening Log

The investigator or subinvestigator will create and retain a screening log with the following information for each patient giving informed consent:

- Subject identification code
- Subject name
- Chart number
- Sex
- Date when patient is informed
- Date of informed consent
- Eligibility for registration and date of registration
- Drug number

7.2.3 Assigning Subjects to Treatment Groups

Subjects will be assigned to treatment groups after IWRS entry.

The subject registration center will confirm subject eligibility and then assign each subject to the ART-123 3-dose group, ART-123 1-dose group, or placebo group. Block randomization with the study sites as a stratification factor will be used to achieve an ART-123 3-dose group, ART-123 1-dose group, and placebo group assignment ratio of 1:1:1.

8. Subject Treatment

8.1 Investigational Product Dosage and Administration

8.1.1 Dosage and Administration

Administer the investigational product (ART-123 380 U/kg or placebo) once daily by intravenous infusion over approximately 30 minutes from Days 1 to 3 of each course of postoperative adjuvant chemotherapy (mFOLFOX6).

[1] ART-123 3-dose group

On Day 1, initiate ART-123 administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of oxaliplatin administration. On Days 2 and 3, administer ART-123 at about the same time as on Day 1 whenever possible.

[2] ART-123 1-dose group

On Day 1, initiate ART-123 administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of oxaliplatin administration. On Days 2 and 3, administer the placebo at about the same time as on Day 1 whenever possible.

[3] Placebo group

On Day 1, initiate placebo administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of oxaliplatin administration. On Days 2 and 3, administer the placebo at about the same time as on Day 1 whenever possible.

8.1.2 Number of Doses

36 (three/course × 12 courses)

If the course 12 postoperative adjuvant chemotherapy has not commenced within 34 weeks (Day 239 from the day of registration), discontinue the subject from the study, perform the treatment-period discontinuation evaluations, and then perform the end-of-study evaluations on Day 43 of the last course of postoperative adjuvant chemotherapy.

8.1.3 Instructions for Prescribing the Investigational Product

- Dissolve the contents of one vial (12,800 U) in 2 mL Japanese Pharmacopoeia physiological saline or Japanese Pharmacopoeia glucose injection (5%). Collect the required amount of this solution based on the weight of the subject and dilute with 100 mL of the same diluent to prepare enough infusion for 1 day. Prepare according to the separately provided investigational product handling procedures (Appendix 2) because the number of vials needed and required volume of the dissolved solution depend on the dose and the weight of the subject.
- Determine the investigational product dose by weighing the subject before investigational product administration on Day 1 or on the day before Day 1 of each course. Give the same investigational product dose on Days 1 to 3 of each course.
- If administering an injection concurrently with the investigational product and the injection cannot be combined with other products, follow the procedures that the sponsor will provide to the study site.

8.1.4 Criteria for Suspension/Resumption and Criteria for Discontinuation of the Investigational Product

- Suspend use of the investigational product when the administration of oxaliplatin is suspended. Resume investigational product administration concurrently with the resumption of oxaliplatin administration.
- Discontinue use of the investigational product if the administration of oxaliplatin is discontinued.

8.2 Rationale for Dosage and Administration and Number of Doses of the Investigational Product

8.2.1 Dosage and Administration

A dosage of 380 U/kg once daily, which is already approved and supported by safety data, was selected as the dose for this study. As stated in Section 1.2.2 , moreover, the suppression of hyperalgesia by ART-123 in a rat model of oxaliplatin-induced peripheral neuropathy was correlated with the dose, with greater activity occurring at higher doses, and it is preferable to administer the doses frequently. To make treatment clinically feasible, a 3-dose group that will receive treatment on three consecutive days in each course was established. To make treatment convenient for patients, a 1-dose group was established because administering a single dose in each course is optimal.

8.2.2 Number of Doses

Thirty-six doses (three per course) were selected because the Guidelines for the Treatment of Colorectal Cancer recommend 12 courses of mFOLFOX6, and the investigational product will be administered to match the number of courses of oxaliplatin.

8.3 Dosage and Administration of Standard Concomitant Drugs

8.3.1 Doses, Administration Procedures, and Dosing Schedule

Administer mFOLFOX6 as postoperative adjuvant chemotherapy according to the following administration procedures, doses, and dosing schedule:

One course: Repeat every 2 weeks (14 days)

- Oxaliplatin 85 mg/m^2
  On Day 1 of the course, intravenously infuse over 2 hours[*1]
- Levofolinate 200 mg/m^2
  On Day 1 of the course, intravenously infuse over 2 hours[*1] concurrently with oxaliplatin
- Fluorouracil 400 mg/m^2
  On Day 1 of the course, give as an intravenous bolus after the completion of oxaliplatin administration
- Fluorouracil 2,400 mg/m^2
  On Day 1 of the course, continuously intravenously infuse over 46 hours after the intravenous bolus of fluorouracil

*1 The duration of infusion may be extended to address allergies.

Table 8.3-1 Dosing schedule for investigational product and postoperative adjuvant chemotherapy

	Day 1	Day 2	Day 3
Investigational product	30 min	30 min	30 min
Oxaliplatin infusion	2 h		
Levofolinate infusion	2 h		
Fluorouracil bolus			
Continuous fluorouracil infusion	46 h		

One course: Repeat every 2 weeks (14 days)
On Day 1, initiate investigational product administration from 2 hours to 30 minutes before oxaliplatin administration and complete administration before the start of postoperative adjuvant chemotherapy. On Days 2 and 3, administer the investigational product at about the same time as on Day 1 whenever possible.

8.3.2 Changing the Dosage and Schedule of Postoperative Adjuvant Chemotherapy

This document uses the following terms in relation to changing the dosage and schedule of postoperative adjuvant chemotherapy:

Table 8.3-2 Terms related to changing the dosage and schedule of postoperative adjuvant chemotherapy

	mFOLFOX6	
	All drugs	Some drugs
Postpone	Refers to not starting administration of all drugs in the next mFOLFOX6 course on the Day 15 evaluation day.	-
Suspend	-	Refers to not administering some drugs in a course.
Reduce (the dose)	-	Refers to reducing the dose of some drugs in a course below the specified dose.
Discontinue (discontinue treatment)	Refers to stopping, without resumption, some or all of the mFOLFOX6 drugs beginning in a given course.	

8.3.2.1 Criteria for Changing Postoperative Adjuvant Chemotherapy

[1] Criteria for postponing all postoperative adjuvant chemotherapy drugs

Referring to the criteria in Table 8.3-3 before administration on the day of postoperative adjuvant chemotherapy administration in course 2 and beyond, the investigator or subinvestigator will postpone the administration of all postoperative adjuvant chemotherapy drugs until the subject's condition satisfies the criteria. The administration of all drugs may be postponed if any of the criteria for suspending oxaliplatin in Table 8.3-5 are satisfied on the day scheduled for oxaliplatin administration. If no postoperative adjuvant chemotherapy for the subsequent course is begun within 43 days of the start of the most recent postoperative adjuvant chemotherapy (Day 1), the subject will be discontinued from the study and undergo the end-of-study evaluations.

Table 8.3-3 Criteria for postponing all postoperative adjuvant chemotherapy drugs

Type	Initiation criteria
Neutrophil count	≥1,500/mm^3
Platelet count	≥75,000/mm^3

[2] Criteria for reducing the dose of oxaliplatin and fluorouracil in association with adverse events

If a subject experiences an adverse event, the investigator or subinvestigator will reduce the dose of oxaliplatin and fluorouracil in reference to the following criteria:

Table 8.3-4 Criteria for reducing the dose of oxaliplatin and fluorouracil in association with adverse events

Type	Greatest severity	Next dose
Neutrophil count	<500/mm^3	Reduce oxaliplatin dose to 75 mg/m^2 Reduce fluorouracil dose by 20%
Platelet count	<50,000/mm^3	
Gastrointestinal tract adverse events (occurring despite prophylactic treatment)	≥Grade 3 [a)]	

a) NCI-CTCAE

[3] Criteria for suspending or reducing the dose of oxaliplatin in association with peripheral neuropathy

The investigator or subinvestigator will determine the dose of oxaliplatin according to the criteria in Table 8.3-5 on Day 1 of each course.

- If reducing the oxaliplatin dose, do not increase the dose even if the CTCAE grade improves.
- After suspending oxaliplatin, resume treatment at the dose of 75 mg/m^2.

The investigator or subinvestigator need not comply with these criteria when determining that other criteria are necessary to ensure subject safety.

Table 8.3-5 Criteria for suspending or reducing the dose of oxaliplatin in association with peripheral neuropathy

Greatest NCI-CTCAE[*1] grade after previous oxaliplatin dose	Day 1 NCI-CTCAE grade (day of evaluation)	Action to take for oxaliplatin
≤Grade 1	≤Grade 1	Do not reduce dose or suspend.
≥Grade 2	≤Grade 1	Do not reduce dose or suspend. (The dose may be reduced to 75 mg/m^2.)
Any	Grade 2	Reduce the dose to 75 mg/m^2. (Treatment may be suspended.)
Any	≥Grade 3	Treatment may be suspended.

*1 Assess the NCI-CTCAE grade of the more severe of peripheral motor neuropathy or peripheral sensory neuropathy.

8.4 Prohibited Treatments and Interventions During the Study

8.4.1 Prohibited Concomitant Drugs

- The administration of the following medications is prohibited from informed consent until study completion.
  (1) Other investigational products
  (2) Thrombomodulin alfa (recombinant)
  (3) Antineoplastic agents other than those specified for use in the postoperative adjuvant chemotherapy in this study

  Rationale
  - (1) Out of concern for subject safety.
  - (2) This is the active ingredient of the investigational medicinal product and would not allow proper evaluation of efficacy and safety.
  - (3) The use of these drugs could induce drug-induced peripheral neuropathy, which would prevent proper evaluation of efficacy. Adding other antineoplastic agents, moreover, would affect the safety evaluation of Recomodulin.
- The administration of the following medications is prohibited from the start of administration of the investigational product until study completion.
  (1) Thrombolytic drugs (e.g., t-PA preparations, urokinase)

  Rationale
  - (1) Out of concern for subject safety because the pharmacological action of the investigational medicinal product could increase the risk of bleeding.

8.4.2 Restricted Concomitant Drugs

Over-the-counter medications and ready-made transfusion preparations are not considered restricted concomitant medications.

- The administration of the following medications is prohibited from informed consent until study completion except in association with use while peripheral motor neuropathy or peripheral sensory

neuropathy is found by the investigator or subinvestigator to be Grade 2 or greater based on NCI-CTCAE.

(1) Calcium gluconate, magnesium sulfate
(2) Glutathione
(3) L-glutamine
(4) Vitamin B_6, B_{12}, and E preparations
(5) Goshajinkigan, shakuyaku-kanzoto
(6) Narcotics and similar drugs (including the opioid receptor agonist codeine phosphate)
(7) Oral and injected adrenocorticosteroids (except when used to treat nausea/vomiting associated with the administration of an antineoplastic agent or to treat an allergy)
(8) Pregabalin, gabapentin
(9) Nonsteroidal anti-inflammatory drugs (NSAIDs, except when used for a purpose other than CIPN treatment)
(10) Tricyclic antidepressants
(11) Serotonin/noradrenaline reuptake inhibitors

Rationale

- For ethical reasons, prohibitions of these medications are lifted because NCI-CTCAE Grade 2 or greater peripheral motor neuropathy or peripheral sensory neuropathy is of a severity requiring consideration of oxaliplatin dose reduction/suspension.
- (1) to (5) These drugs are reported to be effective in the prevention or treatment of CIPN, meaning that their use would prevent proper evaluation of efficacy.
- (6) to (11) These drugs may be effective in the treatment of CIPN, meaning that their use would prevent proper evaluation of efficacy.

➢ Initiating the administration of or increasing the dose of any of the following medications is prohibited from informed consent until study completion. Subjects may continue to use the medications that they had been using before informed consent provided that no dose changes are made. (Dose reductions are allowed.)

(1) Isoniazid, ethambutol, metronidazole, medications for the treatment of HIV infection, HMG-CoA reductase inhibitors, tacrolimus, colchicine, and interferon preparations

Rationale

- (1) These drugs could induce drug-induced peripheral neuropathy. Initiation or dose escalation during the study could affect efficacy evaluation.

8.4.3 Prohibited Concomitant Therapies

➢ The following treatments are prohibited from informed consent until study completion.

(1) Radiotherapy
(2) Operations and other surgical procedures that could affect efficacy evaluation

Rationale

- (1) Because of the potential impact on the evaluation of safety.
- (2) Because of the impact on properly evaluating subject efficacy.

9. Investigations/Observations and Evaluations

The investigator or subinvestigator will perform the investigations/observations and evaluations specified in this section. The investigator or subinvestigator or a clinical research coordinator will complete electronic case report forms (eCRFs) based on the source documents.

9.1 Investigation/Observation and Evaluation Schedule

The time points for investigations/observations are shown in Table 9.1-1, Summary of study schedule. Hereafter, time points are indicated with the first day of postoperative adjuvant chemotherapy in each course counted as Day 1 (D1).

Table 9.1-1 Summary of study schedule

Test/observation schedule	Screening period	Treatment period																												Follow-up period[h]	Unscheduled CIPN evaluation
	-	Course 1									Courses 2 to 11										Course 12										At discontinuation of the treatment[e]	At study completion (d43 of the last course)[i]	
		D1 (registration day)			D2	D3			D29		D1 (d15 of the preceding course)			D2[a]	D3[a]	D8	D15	D29		D1 (d15 of the preceding course)			D2[a]	D3[a]	D8	D15					
		Before	Investigational product administration	After						Before	Investigational product administration	After							Before	Investigational product administration	After										
Permitted window of time from the specified date (days)	d-14 to d-1				-	-	-	+7	+7	By d43 of the preceding course			-	-	-	+7	+7	By d43 of the preceding course			-	-	-	+7	-	+14	-				
Written informed consent	●																														
Subject demographic information survey	●	●																													
Patient registration, randomization		●																													
Office visit	●		●		●	●		○	○		●		●	●		○	○		●			●	●		●	●		●			
Weight measurement		●[k]								●[k]									●[k]												
Investigational product administration			●		●	●					●[a]		●	●						●[a]		●	●								
Investigational product administration status survey			●		●	●		○	○		●		●	●		○	○			●		●	●								
Postoperative adjuvant chemotherapy				←	→	→						←	→	→							←	→	→								
Postoperative adjuvant chemotherapy status survey				●	●[j]	●[j]		○	○			●	●[j]	●[j]		○	○				●	●[j]	●[j]								
Concomitant medications/concomitant therapies survey	←	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	●	●	
Pregnancy test	●									●[d]																				●	
Efficacy: NCI-CTCAE		●			●	●		○	○	●			●	●		○	○		●			●	●		●	●		●	●	●	
Efficacy: DEB-NTC		●						○	○	●						○	○		●						●	●		●			
Efficacy: FACT/GOG-NTX-12		●					●	○	○	●					●	○	○		●					●	●	●		●			
Efficacy: FACT-G		●								●[e]															●	●		●			
Efficacy: NRS (pain)		●					●	○	○	●					●	○	○		●					●	●	●		●			

Safety	Laboratory tests	●[c)]									●[k)]									●[k)]						●	●	●	
	Vital signs	●									●									●						●	●	●	
	Adverse events	◀																								▶	●	●	
	Immunogenicity		●																									●	
Pharmacokinetics			●		●[f)]	●[f)]	●[f)]							△[f)]	△[f)]								△[f)]	△[f)]					

Time points are expressed as “Day (D),” and numbers of days are expressed as “day (d).”

●: required

◯: to be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

△: if no blood samples are available from course 1, perform once in one of the courses from 2 to 12

a) Not required in courses in which oxaliplatin is suspended

b) To be performed before investigational product administration if the evaluation takes place on the same day as investigational product administration

c) To be performed between Day −7 and Day −1 (1 day before registration); hepatitis B test data obtained within 6 months before the day of registration may also be used

d) To be performed only in course 2; may be determined on the day before Day 1

e) To be performed only in courses 5 and 9

f) Collect blood samples immediately after and from 30 to 120 minutes after completion of investigational product administration

g) If the evaluation at treatment period discontinuation takes place on or after Day 43 of the last course of postoperative adjuvant chemotherapy, or if the tests/observations for the subsequent clinical study are not possible, perform the end-of-study evaluations instead of the treatment-period discontinuation evaluations. If the course 12 postoperative adjuvant chemotherapy has not commenced within 34 weeks (Day 239 from the day of registration), discontinue the subject from the study, perform the treatment-period discontinuation evaluations, and then perform the end-of-study evaluations on Day 43 of the last course of postoperative adjuvant chemotherapy.

h) If any postoperative adjuvant chemotherapy for the subsequent course has not commenced by Day 43 of a course, discontinue the subject from the study and perform the end-of-study evaluations.

i) If the subject is discontinued from the study in the follow-up period, perform the end-of-study evaluations.

j) Determine the status of fluorouracil continuous intravenous infusion use.

k) May be determined on the day before Day 1

9.2 Investigations/Observations and Evaluations to be Conducted at Each Time Point

9.2.1 Screening Period (Day −14 to Day −1)

- Informed consent
- Subject demographic information survey
- Initiation of a survey on concomitant medications/therapies
- Initiation of a survey on adverse events
- Pregnancy test (only subjects for whom the test is required)
- Vital sign measurement
- Laboratory tests (blood/urine)[*1]

*1 To be performed between Day −7 and Day −1 (1 day before registration)

9.2.2 Treatment Period[*1]

*1 If any postoperative adjuvant chemotherapy for the subsequent course has not commenced by Day 43 of a course, discontinue the subject from the study and perform the study completion evaluations.

9.2.2.1 Day 1 of Course 1

- Before investigational product administration
  - Subject demographic information survey
  - Laboratory test results verification
  - Patient registration
  - Concomitant medications/therapies survey
  - Adverse events survey
  - Efficacy endpoints survey
    - NCI-CTCAE: As of the time of evaluation
    - DEB-NTC
    - FACT/GOG-NTX-12
    - FACT-G
    - NRS (pain)
  - Blood sampling for pharmacokinetic analysis
  - Blood sampling for immunogenicity test
  - Weighing of subject to determine investigational product dose[*1]
- Investigational product administration and administration status survey
- After investigational product administration
  - Postoperative adjuvant chemotherapy administration and administration status survey
  - Blood sampling for pharmacokinetic analysis
  - Adverse events survey

*1 Subjects may be weighed on the previous day

9.2.2.2 Days 2 and 3 of Course 1

- Before investigational product administration
  - Concomitant medications/therapies survey
  - Adverse events survey

- Efficacy endpoint survey
  - NCI-CTCAE: The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation

➢ Investigational product administration and administration status survey

➢ Fluorouracil continuous intravenous infusion status survey

➢ After investigational product administration

- Blood sampling for pharmacokinetic analysis
- Adverse events survey

9.2.2.3 Day 8 of Course 1[*1]

- Efficacy endpoint survey
  - FACT/GOG-NTX-12
  - NRS (pain)

*1 No office visit required. The survey may be performed when the subject is at home or elsewhere.

9.2.2.4 Day 15 (permitted window, +7 days)[*1] and Day 29 (permitted window, +7 days)[*1] of Course 1

- Concomitant medications/therapies survey
- Adverse events survey
- Investigational product administration status survey
- Postoperative adjuvant chemotherapy administration status survey
- Efficacy endpoint survey
  - NCI-CTCAE
    i) The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation
    ii) Condition at the time of evaluation
  - DEB-NTC
  - FACT/GOG-NTX-12
  - NRS (pain)

*1 To be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

9.2.2.5 Day 1 of Courses 2 to 12

➢ Before investigational product administration

- Concomitant medications/therapies survey
- Adverse events survey
- Efficacy endpoints survey
  - NCI-CTCAE
    i) The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation
    ii) Condition at the time of evaluation
  - DEB-NTC

- FACT/GOG-NTX-12
- FACT-G[*1]
- NRS (pain)

• Pregnancy test (only subjects for whom the test is required)[*2]
• Vital sign measurement
• Laboratory tests (blood/urine)[*3]
• Weighing of subject to determine investigational product dose[*3]

➢ Investigational product administration and administration status survey
➢ After investigational product administration
• Postoperative adjuvant chemotherapy administration and administration status survey
• Adverse events survey

*1 To be performed only in Courses 5 and 9
*2 To be performed only in Course 2; may be determined on the day before Day 1
*3 May be determined on the day before Day 1

9.2.2.6 Days 2 and 3 of Courses 2 to 12

➢ Before investigational product administration
• Concomitant medications/therapies survey
• Adverse events survey
• Efficacy endpoint survey
- NCI-CTCAE: The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation

➢ Investigational product administration and administration status survey
➢ Fluorouracil continuous intravenous infusion status survey
➢ After investigational product administration
• Blood sampling for pharmacokinetic analysis[*1]
• Adverse events survey

*1 To be performed once in any of Courses 2 to 12 if blood is not sampled in Course 1

9.2.2.7 Day 8 of Courses 2 to 12[*1]

• Efficacy endpoint survey
- FACT/GOG-NTX-12
- NRS (pain)

*1 No office visit required. The survey may be performed when the subject is at home or elsewhere.

9.2.2.8 Day 15 (permitted window, +7 days)*[1] and Day 29 (permitted window, +7 days)*[1] of Courses 2 to 11

• Concomitant medications/therapies survey
• Investigational product administration status survey
• Postoperative adjuvant chemotherapy administration status survey
• Adverse events survey
• Efficacy endpoints survey

- NCI-CTCAE
  i) The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation
  ii) Condition at the time of evaluation
- DEB-NTC
- FACT/GOG-NTX-12
- NRS (pain)

*1 To be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

9.2.2.9 Day 15 of Course 12 (permitted window, +7 days)

- Concomitant medications/therapies survey
- Adverse events survey
- Efficacy endpoints survey
  - NCI-CTCAE: The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation
  - DEB-NTC
  - FACT/GOG-NTX-12
  - FACT-G
  - NRS (pain)
- Vital sign measurement
- Laboratory tests (blood/urine)

9.2.3 At Discontinuation in the Treatment Period*1

- Concomitant medications/therapies survey
- Adverse events survey
- Efficacy endpoints survey
  - NCI-CTCAE: The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation
  - DEB-NTC
  - FACT/GOG-NTX-12
  - FACT-G
  - NRS (pain)
- Vital sign measurement
- Laboratory tests (blood/urine)

*1 If the evaluation at treatment period discontinuation takes place on or after Day 43 of the last course of postoperative adjuvant chemotherapy, or if the tests/observations for the subsequent clinical study are not possible, perform the end-of-study evaluations instead of the treatment-period discontinuation evaluations.

9.2.4 Follow-up Period*1

*1 If the subject is discontinued from the study in the follow-up period, perform the end-of-study evaluations.

9.2.4.1 At Study Completion (Day 43 of the last course [permitted window, +14 days])

- Concomitant medications/therapies survey
- Adverse events survey
- Efficacy endpoints survey
  - NCI-CTCAE: The worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation
  - DEB-NTC
  - FACT/GOG-NTX-12
  - FACT-G
  - NRS (pain)
- Pregnancy test (only subjects for whom the test is required)
- Vital sign measurement
- Laboratory tests (blood/urine)
- Blood sampling for immunogenicity

9.2.5 At Unscheduled CIPN Evaluations (if a restricted concomitant medication is prescribed by the investigator or subinvestigator for the prevention or treatment of CIPN at any time other than the above-mentioned evaluations)[*1]

- Efficacy endpoint survey
  - NCI-CTCAE: The worst condition noted between the preceding evaluation and the day of evaluation

*1 An office visit is required.

9.3 Subject Demographic Information Survey

The investigator or subinvestigator will determine the following information and enter it in the eCRF.

- Initially assigned drug number
- Day of registration
- Body height and weight (date of measurement and values), smoking status, drinking status and alcohol consumption
- ECOG performance status
- Details of colon cancer (site [cecum/ascending colon/transverse colon/descending colon/sigmoid colon/rectosigmoid], disease stage [I/II/IIIa/IIIb/IV], date of resection)
- Comorbidities: disease(s) present at informed consent
- History: history of peripheral neuropathy (disease name, time of disease), history of CNS neuropathy (disease name, time of disease), history of diabetes mellitus (disease name, time of disease), history of alcohol abuse (time of disease)
- Details of menopause[*1] (premenopausal or <2 years since menopause/≥2 years since menopause)

*1 Female subjects only

9.4 Survey of Investigational Product Administration Status and Postoperative Adjuvant Chemotherapy Administration Status

The investigator or subinvestigator will determine the following information about the investigational product and postoperative adjuvant chemotherapy from after subject registration to study completion (Day 43 of the last course).

[1] Investigational product

- Whether administered, the drug number of the drug actually administered, time and date of the first dose, time and date of the last dose, status of administration (entire amount/other)

[2] Postoperative adjuvant chemotherapy

- Oxaliplatin:
  Whether administered (if not administered, the reason [CIPN/adverse event/other]); any reduction from the planned dose of 85 mg/m^2 (if dose reduction took place, the reason [CIPN/adverse event/other]); time and date of the first dose; time and date of the last dose; the actual dose
- Levofolinate:
  Whether administered (if not administered, the reason [change in fluorouracil dose/adverse event/other]); any reduction from the planned dose of 200 mg/m^2 (if dose reduction took place, the reason [change in fluorouracil dose/adverse event/other]); first day of administration
- Fluorouracil intravenous bolus:
  Whether administered (if not administered, the reason [CIPN/adverse event/other]); any reduction from the planned dose of 400 mg/m^2 (if dose reduction took place, the reason [CIPN/adverse event/other]); first day of administration
- Fluorouracil continuous intravenous infusion:
  Whether administered (if not administered, the reason [CIPN/adverse event/other]); any reduction from the planned dose of 2,400 mg/m^2 (if dose reduction took place, the reason [CIPN/adverse event/other]); first day of administration; last day of administration (if the treatment ended before Day 3, the reason [CIPN/adverse event/other])

9.5 Survey of Concomitant Medications/Therapies

9.5.1 Concomitant Medications

The investigator or subinvestigator will determine the following information about the concomitant medications used from after informed consent to study completion (the day of the Day 43 evaluations in the last course).

9.5.1.1 Concomitant Medications that are Neither Prohibited nor Restricted

- Name of drug, first day of administration, last day of administration

9.5.1.2 Prohibited and Restricted Concomitant Medications

The information listed below will be determined for any prescription drug used that corresponds to the definition of a prohibited or restricted medication, even if the route of administration and the reason for its use are in compliance. Over-the-counter medications and ready-made transfusion preparations are

considered concomitant medications described in "9.5.1.1 Concomitant medications that are neither prohibited nor restricted."

- Name of drug, route of administration, first day of administration, last day of administration, dose, reason for administration (CIPN/adverse event/other)

9.5.2 Concomitant Therapies

The investigator or subinvestigator will determine the following information about all therapies performed concomitantly from after informed consent to study completion.

- Name of therapy, first day of treatment, last day of treatment

9.6 Investigations/Observations Pertaining to Efficacy and Evaluation Methods

9.6.1 Efficacy Endpoints

- Endpoints to be evaluated by the investigator or subinvestigator
  - NCI-CTCAE peripheral motor neuropathy, peripheral sensory neuropathy (CIPN only)
  - DEB-NTC
- Endpoints to be evaluated by the subject
  - FACT/GOG-NTX-12
  - FACT-G
  - NRS (pain)
- Other
  - Discontinuation, suspension, and dose reduction of oxaliplatin due to CIPN

The efficacy endpoints will not be classified as primary or secondary because this is an exploratory study of ART-123 for preventing the onset of oxaliplatin-induced peripheral neuropathy.

9.6.2 Considerations for Efficacy Evaluations

Evaluations performed on a day when the investigational product is administered will be performed before administration.

9.6.3 Evaluation Methods

9.6.3.1 NCI-CTCAE Peripheral Motor Neuropathy, Peripheral Sensory Neuropathy (CIPN only)

The investigator or subinvestigator will evaluate neuropathy as follows:

- Assessment time points
  - Days 1, 2, 3, 15[*1], and 29[*1] of courses 1 to 11
  - Days 1, 2, 3, and 15 of course 12
  - At Study completion
  - At Discontinuation in the Treatment Period
  - At unscheduled CIPN evaluations

*1 To be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

- Information to be determined and evaluated
  - Date and time point of evaluation (before investigational product administration/after investigational product administration/not applicable)
  - Evaluate the grade on a 6-step scale (none, Grade 1 to 5) for each of the evaluation classifications (peripheral motor neuropathy, peripheral sensory neuropathy) based on the NCI-CTCAE grade classification system provided in Appendix 3
  - Assess the condition at the time of evaluation on Day 1 of course 1
  - On Days 15 and 29 of courses 1 to 11 and Day 1 of courses 2 to 12, assess the worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation and the condition at the time of evaluation
  - On days of evaluation other than Day 1 and Days 15 and 29 of courses 1 through 11, assess the worst condition noted between the preceding evaluation (excluding any unscheduled evaluation) and the day of evaluation. At unscheduled CIPN evaluations, assess the worst condition noted between the preceding evaluation and the day of evaluation

9.6.3.2 DEB-NTC

The investigator or subinvestigator will evaluate neuropathy as follows:

- Assessment time points
  - Days 1, 15[*1], and 29[*1] of courses 1 to 11
  - Days 1 and 15 of course 12
  - At Study completion
  - At Discontinuation in the Treatment Period
- Information to be determined and evaluated
  - Date and time point of evaluation (before investigational product administration/after investigational product administration/not applicable)
  - Evaluate each of the following symptoms based on the DEB-NTC grade classification system provided in Appendix 4
    - Peripheral sensory abnormalities or discomfort when touching things (Grade 0 to 2) (If Grade 1 or greater, the site of symptom: hand/foot/lip, tongue and surroundings, face/pharyngolarynx/other)
    - Painless peripheral sensory abnormalities or discomfort under normal conditions (Grade 0 to 2) (If Grade 1 or greater, the site of symptom: hand/foot/lip, tongue and surroundings, face/pharyngolarynx/other)
    - Painful peripheral sensory abnormalities or discomfort under normal conditions (Grade 0 to 2) (If Grade 1 or greater, the site of symptom: hand/foot/lip, tongue and surroundings, face/pharyngolarynx/other)
    - Functional disorders (Grade 0, 3)

*1 To be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

9.6.3.3 FACT/GOG-NTX-12

A clinical research coordinator will have subjects complete the Japanese version of the FACT/GOG-NTX-12 (Version 4, Appendix 5) questionnaire. The clinical research coordinator will collect questionnaires from subjects and enter the date and results of evaluation in the eCRF.

- Assessment time points
  - Days 1, 8, 15[*1], and 29[*1] of courses 1 to 11
  - Days 1, 8, and 15 of course 12
  - At Study completion
  - At Discontinuation in the Treatment Period
- Information to be determined
  - Date and time point of evaluation (before investigational product administration/after investigational product administration/not applicable)
- Considerations for evaluations
  - If the day of an evaluation falls on the day of an office visit, inform the subject to complete the questionnaire before the efficacy evaluation by the investigator or subinvestigator.
  - To allow the evaluation of physician-evaluated severity of peripheral neuropathy independently from subject evaluations, the investigator or subinvestigator and clinical research coordinator present during the physician evaluation of peripheral neuropathy will not review evaluations entered by the subjects.
  - A clinical research coordinator not present during the physician evaluation of peripheral neuropathy will collect the questionnaires from the subjects and enter them in the eCRFs without informing the investigator or subinvestigator and clinical research coordinator present during the physician evaluation of peripheral neuropathy.

*1 To be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

9.6.3.4 FACT-G

The investigator or subinvestigator will have subjects complete the Japanese version of the FACT-G (Version 4, Appendix 6) questionnaire. The clinical research coordinator will collect questionnaires from subjects and enter the date and results of evaluation in the eCRF.

- Assessment time points
  - Day 1 of courses 1, 5, and 9
  - Day 15 of course 12
  - At Study completion
  - At Discontinuation in the Treatment Period
- Information to be determined
  - Date and time point of evaluation (before investigational product administration/after investigational product administration/not applicable)

9.6.3.5 NRS (pain)

The investigator or subinvestigator will have subjects evaluate the severity of pain at the site subject to evaluation based on the NRS. The clinical research coordinator will collect the evaluation forms from subjects and enter the date and results of evaluation in the eCRF.

- Assessment time points
  - Days 1, 8, 15[*1], and 29[*1] of courses 1 to 11
  - Days 1, 8, and 15 of course 12
  - At Study completion
  - At Discontinuation in the Treatment Period
  -
- Sites subject to evaluation
  - Hands
  - Feet
- Date and time point of evaluation (before investigational product administration/after investigational product administration/not applicable)

*1 To be performed only in the event of postponement of the administration of all drugs for postoperative adjuvant chemotherapy

Numerical Rating Scale (NRS)

0: no pain at all; 10: the most severe pain imaginable

9.7 Investigations/Observations Pertaining to Safety and Evaluation Methods

9.7.1 Vital Signs

The investigator or subinvestigator will measure body temperature, blood pressure, and pulse rate. Vital signs will be measured with the subjects at rest.

- Measurement time points
  - Screening period
  - Day 1 of courses 2 to 12
  - Day 15 of course 12
  - At Study completion
  - At Discontinuation in the Treatment Period
  -
- Parameters
  - Axillary temperature
  - Sitting systolic/diastolic blood pressure
  - Sitting pulse rate
- Information to be determined

- Date and time point of measurement (before investigational product administration/after investigational product administration/not applicable)
- Results

9.7.2 Laboratory Tests

The investigator or subinvestigator will collect samples from subjects at the following measurement time points and have the samples analyzed at the study site.

➢ Measurement time points
- Screening period[*1]
- Day 1 of courses 2 to 12[*2]
- Day 15 of course 12
- At Study completion
- At Discontinuation in the Treatment Period

➢ Laboratory test parameters
- Routine blood tests: Red blood cell count, haemoglobin, haematocrit, white blood cell count, white blood cell differential (neut, lympho, mono, eosino, baso), platelet count
- Clinical chemistry tests: AST (GOT), ALT (GPT), ALP, LDH, total bilirubin, total protein, albumin, BUN, creatinine, glucose, uric acid, electrolytes (Na, K, Cl)
- Urine analysis: Protein (qualitative), glucose (qualitative), occult blood (qualitative)
- Immunological assays[*3]: HBs antigen, HBc antibody, HBs antibody, HBV-DNA[*4]
- Coagulation tests: PT-INR, activated partial thromboplastin time, fibrinogen

➢ Information to be determined
- Dates of blood/urine sampling, time points of blood/urine sampling (before investigational product administration/after investigational product administration/not applicable)
- Results (routine blood tests, clinical chemistry tests, urine analysis, coagulations tests)

*1 To be performed between Day −7 and Day −1 (one day before registration)
*2 May be determined on the day before Day 1
*3 To be performed only in the screening period to determine eligibility. Test data obtained within 6 months before registration may be used.
*4 In cases where the test result is positive for HBc antibody or HBs antibody

9.7.3 Immunogenicity (anti-drug antibodies, neutralising antibodies)

The investigator or subinvestigator will collect samples from the subjects at the time points listed below, separate the serum, and temporarily store the serum before submitting the samples to the immunogenicity assay laboratory. Samples will be collected, processed, stored, and shipped as directed in written procedures to be submitted by the sponsor to each study site. The immunogenicity assay laboratory will conduct assays of anti-drug antibodies and neutralising antibodies and submit the results to the sponsor after unblinding. As the sponsor will be electronically notified of the results, the data need not be input into the eCRFs. Only the dates and time points of blood sampling should be entered.

➢ Measurement time points

- Before investigational product administration on Day 1 of course 1
- At study completion

➢ Blood sample volume: 6 mL

➢ Information to be determined
- Date and time point of blood sampling (before investigational product administration/after investigational product administration/not applicable)

9.7.4 Adverse Events

9.7.4.1 Definition of Adverse Events

An adverse event is defined as any untoward or unintended disease or sign (including abnormal laboratory findings and vital signs) that occurs after informed consent. Any adverse event occurring after investigational product administration is considered a treatment-emergent adverse event (TEAE). When a diagnosis can appropriately be assigned for an adverse event, that diagnosis rather than the symptom or sign will be the adverse event name. Abnormal laboratory findings and vital signs are constituted when:

[1] An abnormal laboratory finding or vital sign satisfies the definition of a serious adverse event.

[2] An abnormal laboratory finding or vital sign results in the suspension or discontinuation of the investigational product.

[3] An abnormal laboratory finding or vital sign results in the use of a drug or intervention for treatment.

[4] The physician determines that an abnormal laboratory finding or vital sign is of a medically significant severity (e.g., is an abnormality consistent with [2] or [3] above but there was no opportunity for intervention).

CIPN will not be considered an adverse event in this study.

9.7.4.2 Identification of Adverse Events

The investigator or subinvestigator will identify adverse events spontaneously reported by the subjects and through interview and tests on each observation day.

Information to be determined:

Name of adverse event, date of occurrence, status of investigational product administration (discontinuation/suspension/no change [including completion]), date of outcome, outcome, seriousness classification, rationale for seriousness, severity, causal relationship to the investigational product, whether the subject was discontinued from the study

9.7.4.3 Adverse Event Reporting Period

Adverse events occurring from after informed consent to study completion (Day 43 of the last course) will be reported.

9.7.4.4 Assessing Adverse Events

9.7.4.4.1 Seriousness Classifications

The investigator or subinvestigator will classify each adverse event as a serious adverse event or non-serious adverse event according to the criteria given below. For serious adverse events, the reason will be selected from items 1 to 6 below.

- Serious adverse events:

  1: Results in death (death)

  2: Life threatening (possibility of death)

  3: Requires hospitalization or prolongation of hospitalization for treatment (hospitalization or prolongation of hospitalization)

  4: Persistent or significant disability or incapacity (disability)

  5: Is a congenital anomaly (congenital anomaly)

  6: Other medically significant condition (possibility of disability, seriousness consistent with 1 to 4 above)

- Non-serious adverse events:

  This refers to all adverse events that are not serious adverse events.

9.7.4.4.2 Severity

The investigator or subinvestigator will assess the severity of each adverse event as Grade 1 to 5 based on NCI-CTCAE. The severity of adverse events not corresponding to the events in the glossary will be assessed according to the following criteria:

Table 9.7-1 Adverse event severity assessment criteria

Grade 1	Mild Asymptomatic or mildly symptomatic Clinical findings or laboratory test findings only Treatment not indicated
Grade 2	Moderate Minimal/local/non-invasive treatment indicated Limiting age-appropriate instrumental activities of daily living[a)]
Grade 3	Severe or medically significant but not immediately life-threatening Hospitalization or prolongation of hospitalization indicated Disability/disabling Limiting self-care activities of daily living[b)]
Grade 4	Life-threatening consequences Urgent intervention indicated
Grade 5	Death related to an adverse event

a) Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b) Self-care activities of daily living refer to bathing, dressing and undressing, eating, using the toilet, taking medications, and being not bedridden.

Source: JCOG Japanese translation of the NCI Common Terminology Criteria for Adverse Events Version 4.0.

9.7.4.4.3 Causal Relationships to Investigational Product

The investigator or subinvestigator will assess adverse event causality according to the criteria below. Events classified as item 1 will be handled as adverse reactions.

1. Related

   When there is a reasonable possibility that the investigational product caused the adverse event. The causality will be assessed as "related" when a reasonable possibility that the investigational product caused the adverse event is not evaluable.

2. Not related

   When there is no reasonable possibility that the investigational product caused the adverse event.

9.7.4.5 Follow-up for Adverse Events

All adverse events will be followed until resolution or return to baseline level or until the symptoms/test values are found to have stabilized and are no longer clinically significant. Data obtained during the period specified in Section 9.7.4.3 . will be entered in the eCRFs.

9.8 Other Investigations/Observations and Evaluation Methods

9.8.1 Pharmacokinetics (blood concentration of thrombomodulin alfa (recombinant))

The investigator or subinvestigator will collect samples from the subjects at the time points listed below, separate the plasma, and temporarily store the plasma before submitting the samples to the plasma concentration laboratory. Samples will be collected, processed, stored, and shipped as directed in written procedures to be submitted by the sponsor to each study site. The plasma concentration laboratory will determine plasma drug concentrations and submit the results to the sponsor after unblinding. As the sponsor will be electronically notified of the results, the data need not be input into the eCRFs. Only the times and dates of blood sampling should be entered.

- Assessment time points
  - Day 1 of course 1: Before investigational product administration and just after and 30 to 120 minutes after completion of investigational product administration
  - Days 2 and 3 of course 1[*1]: Just after and 30 to 120 minutes after completion of investigational product administration

    *1 To be performed once in any of courses 2 to 12 if blood is not sampled in course 1
- Blood sample volume: 3 mL
- Information to be determined
  - Time and date of blood sampling

9.8.2 Urine Pregnancy Testing

The investigator or subinvestigator will collect urine samples from subjects at the time points listed below and test for pregnancy in reference to human chorionic gonadotropin test (urine) findings. Only

female subjects will undergo pregnancy testing. Testing is not required for women who have been postmenopausal for at least 2 years at informed consent. Male subjects will be interviewed at these testing times to determine if their partner is pregnant. Data will be entered in the eCRF only if the subject is female.

- Measurement time points: Screening period, Day 1 of course 2[*1], study completion
- Information to be determined: Date of urine sampling, pregnancy status

*2 May be determined on the day before Day 1

9.8.3 Pathology of CIPN and Exploratory Assessments of Efficacy and Safety of the Investigational Product

Collected serum and plasma samples that remain after immunogenicity and pharmacokinetic evaluations will be stored for up to 5 years after study completion in the immunogenicity assay laboratory and plasma concentration laboratory according to separately established sample handling procedures and may be used during this period to elucidate the mechanism of CIPN onset or the mechanism of action of Recomodulin or for research to develop drugs to prevent or treat CIPN. No genetic information will be handled. Any such investigations will be initiated in accordance with procedures established by the sponsor.

10. Ensuring Subject Safety

10.1 Basic Information

The investigator or subinvestigator will determine patient eligibility by conducting observations and examinations at the time of screening and will not enroll a patient in the study when safety cannot be ensured.

The investigator or subinvestigator will investigate the health of the subjects on each observation day during the study and ensure that emergency contact is possible. If a subject-reported or other adverse event occurs, the investigator or subinvestigator will promptly take appropriate actions as necessary for ensuring subject safety.

The sponsor will appropriately collect and relay any safety information relevant to the study.

The investigator or subinvestigator will endeavor to identify adverse reactions early by closely monitoring subject symptoms.

10.2 Particularly Notable Information

10.2.1 Precautions Related to Bleeding

Because Recomodulin has anticoagulant activity and could potentially cause or exacerbate bleeding symptoms, the drug must be administered with bleeding symptoms sufficiently managed. If a bleeding-related serious adverse event occurs, Recomodulin administration will be discontinued as necessary, and appropriate intervention, such as transfusion, will be provided as necessary.

10.2.2 Interventions for Overdoses

There is no drug that is known to neutralise the anticoagulant activity of Recomodulin. In the event of an accidental overdose, discontinue administration of Recomodulin and give intravenous fluids, a transfusion, or other intervention to reduce plasma levels as necessary while closely monitoring for worsening of bleeding tendencies and changes in coagulation activity and the like.

10.2.3 Monitoring for Hypersensitivity

Recomodulin is a protein product and could therefore cause shock, anaphylactoid symptoms, and similar conditions. The investigator or subinvestigator should therefore closely observe the subject during Recomodulin administration. If anaphylaxis is suspected based on skin symptoms such as urticaria, gastrointestinal symptoms, respiratory symptoms such as dyspnea, or disturbance of consciousness and the like, immediately discontinue Recomodulin administration and provide intervention according to “The manual for handling disorders due to adverse drug reactions-focus on the anaphylaxis” (March 2008, Ministry of Health, Labour and Welfare)[16] (Figure 10.2-1).

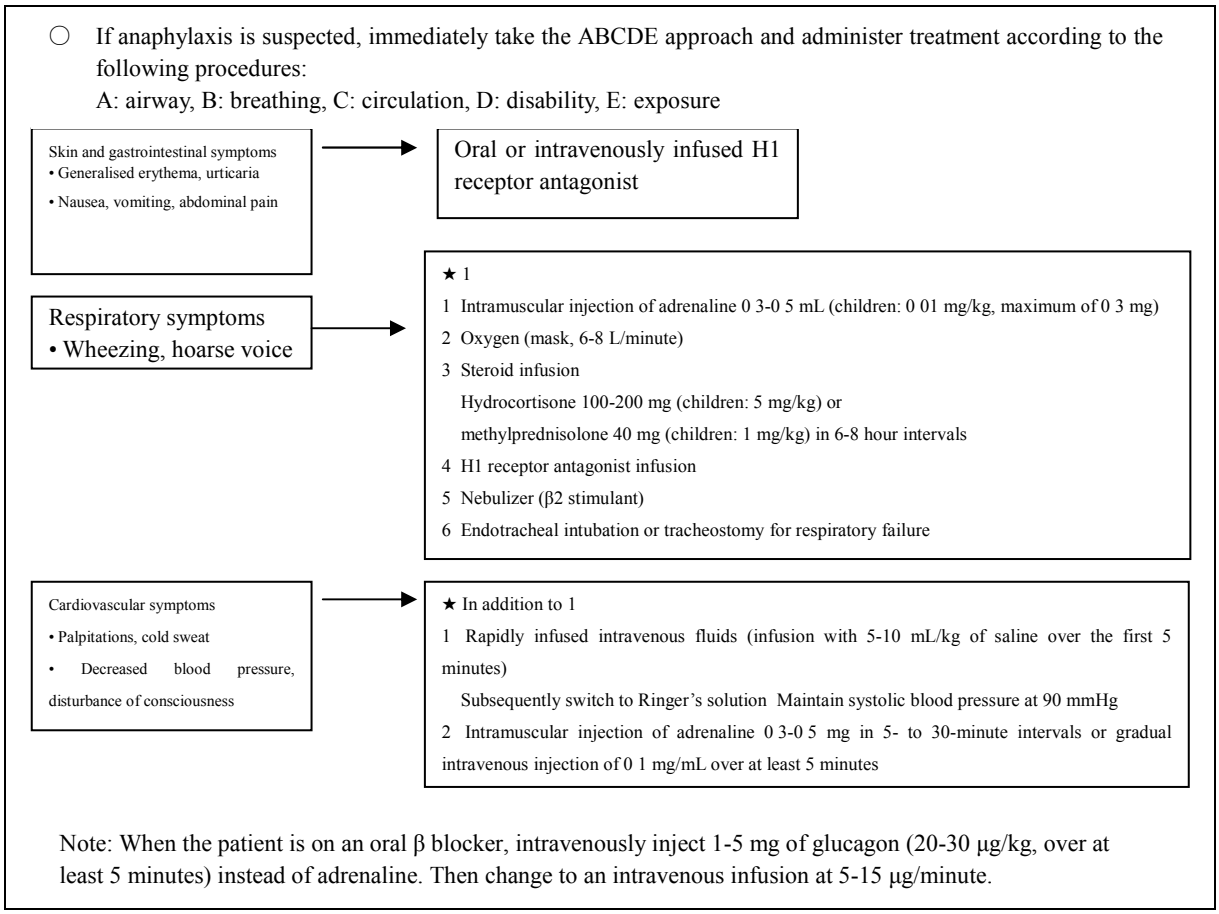


Figure 10.2-1 Procedures for treating anaphylaxis[16)]

10.3 Actions to Take for Serious Adverse Events

10.3.1 Procedures for Investigator or Subinvestigator

When a serious adverse event occurs, the investigator or subinvestigator will promptly notify the sponsor and study site director orally or by telephone, fax, or a similar means regardless of the causal relationship to the investigational product. The sponsor will be notified no later than 24 hours after a serious adverse event is identified.

The investigator will complete a written report about each serious adverse event (using the specified form of the study site or sponsor) for submission to the sponsor and study site director. With the first reporting day as Day 0, the investigator will submit the written report to the sponsor by Day 4 if the event is a death or life threatening or by Day 7 if the event is another serious adverse event.

The investigator or subinvestigator will comply with any instructions of the study site director based on the findings of the institutional review board about whether the study should continue and the instructions of the sponsor about amending the protocol or taking other appropriate actions.

10.3.2 Sponsor Procedures

On receiving a written report of a serious adverse event from the investigator, the sponsor will consult with the medical expert as necessary to deliberate whether the study should be continued or suspended and the need to change the protocol or amend the reference informed consent form.

After this deliberation, the sponsor will notify the regulatory authorities, study site directors, and investigators by the specified deadlines as necessary.

10.3.3 Emergency Protocol Deviations/Modifications and Emergency Key Unblinding

The investigator or subinvestigator may deviate from or modify the protocol without the prior agreement of the sponsor and prior approval of the institutional review board in a medically unavoidable situation such as to avoid exposing a subject to acute risk (Section 13.2). The investigator or subinvestigator may request unblinding of the emergency key when finding this to be necessary to ensure subject safety (Section 6.7).

10.4 Actions to Take for Identified Pregnancies

The investigator or subinvestigator will discontinue any subject found to be pregnant from the investigational product (Section 11).

Pregnancies will not be considered adverse events (unless the investigational product is suspected of having inhibited the effect of a contraceptive drug). The investigator or subinvestigator will conduct follow-up for all pregnancy outcomes (spontaneous abortion, induced abortion, normal delivery, delivery with congenital anomaly) and notify the sponsor. Pregnancies in the partners of male subjects will be similarly handled.

Deliveries, induced abortions, and spontaneous abortions associated with a congenital anomaly and induced abortions and spontaneous abortions because of a maternal abnormality in a female subject will be treated as serious adverse events.

11. Completion and Discontinuation of Treatment and Observations

11.1 Days of Completion and Discontinuation of Individual Subjects

When a subject completes the study, promptly enter the day of completion (i.e., the day when the final tests and observations specified in the protocol are performed) in the eCRF.

When a subject is discontinued from the study, promptly enter the day of discontinuation (i.e., the day when the final tests and observations specified in the protocol are performed) and the reason for discontinuation (select the primary and other reasons from the choices in Section 11.2.1) in the eCRF.

Determine whether oxaliplatin was discontinued and, if so, promptly enter the reason for discontinuation (CIPN/adverse event/other) in the eCRF.

11.2 Discontinuation Criteria for Individual Subjects

11.2.1 Study Discontinuation Criteria

The investigator or subinvestigator will discontinue from the study subjects satisfying any of the following discontinuation criteria:

[1] Adverse event

This refers to when a subject is discontinued for an adverse event. This includes cases when a subject is discontinued by request because of an adverse event and when a subject dies because of an adverse event and cannot continue in the study.

[2] Allowable range for the postoperative adjuvant chemotherapy schedule exceeded

This refers to when a subsequent course of postoperative adjuvant chemotherapy is not started within 43 days of the start of the most recent postoperative adjuvant chemotherapy (Day 1).

[3] Extension of study period

This refers to when the 12th course of postoperative adjuvant chemotherapy has not started as of Week 34 (239 days after the day of registration).

[4] Lack of efficacy

This refers to discontinuations because study procedures are not effective in the targeted disease (CIPN onset). This includes cases when the targeted disease progresses because of lack of efficacy.

[5] Subject lost to follow-up

This refers to when subsequent tests and observations (including follow-up by telephone) are not possible because the subject is unable to visit.

[6] Discontinued by investigator or subinvestigator

This refers to when the physician finds a subject unsuited to study continuation for a reason in another category.

[7] Major protocol deviation

This refers to when the subject is discontinued on the identification of a major protocol deviation (GCP violation, inclusion/exclusion criteria violation, drug number violation, multiple registrations).

[8] Subject ineligible at screening

This refers to discontinuations, taking place before assignment, according to the inclusion/exclusion criteria.

[9] Identification of pregnancy

This refers to when the subject is found to be pregnant during the treatment period.

[10] By subject request

This refers to when a subject is discontinued by request.

[11] Per decision by sponsor

This refers to when a subject is discontinued after the sponsor submits a notification such as to completely or partially terminate or suspend the study or terminate the study at a study site. Termination of the study at a study site includes cases in which an investigator transfer or study site closure complicates study continuation by a subject in the opinion of the sponsor.

11.3 Rationale for Discontinuation Criteria

These criteria were established to respect the wishes of the subjects, ensure safety, avoid influencing evaluations, and honor subject circumstances.

11.4 Discontinuation Procedures

11.4.1 Procedures for Study Discontinuation from Informed Consent to Before Registration

The investigator or subinvestigator will perform discontinuations according to the following procedures if a subject must be discontinued from the study from the time of informed consent to before registration.

[1] Promptly inform the affected subject of discontinuation and state in the medical records that the subject was discontinued on determining that any of the discontinuation criteria in Section 11.2.1 are applicable (criteria 1 and 6 to 11).

[2] Promptly notify the sponsor of the discontinuation. The investigator or subinvestigator will promptly enter the information in Section 7.2.1 and the reason for discontinuation in the IWRS and then send the data to the subject registration center. All complications and adverse events up to the time of discontinuation will be recorded in the eCRF.

11.4.2 Procedures for Post-registration Discontinuations

After deciding to discontinue a subject who has been registered from the study, the investigator or subinvestigator will:

[1] Promptly inform the affected subject and, if the subject is receiving the investigational product, promptly discontinue treatment on determining that any of the above discontinuation criteria in Section 11.2.1 are applicable.

[2] Promptly administer the appropriate treatment to the affected subject when a subject is discontinued for an adverse event, worsening of symptoms, or other incident.

[3] Promptly perform the observations and tests/evaluations scheduled for treatment-period discontinuations if the subject is discontinued during the treatment period. Assess the reason for discontinuation as in Section 11.2 .

- If the evaluation at treatment period discontinuation takes place on or after Day 43 of the last course of postoperative adjuvant chemotherapy, or if the subsequent tests/observations for the

study are not possible, perform the study completion evaluations instead of the treatment-period discontinuation evaluations.

- If the evaluation at treatment-period discontinuation takes place on or before Day 42 of the last course of postoperative adjuvant chemotherapy, have the subject re-visit on Day 43 of the last course of postoperative adjuvant chemotherapy and perform the end-of-study evaluations.

[4] Promptly perform the observations and tests/evaluations scheduled for end of study if the subject is discontinued during the follow-up period. Assess the reason for discontinuation as in Section 11.2.

[5] If a subject is discontinued for not visiting, inquire about the reason and condition after last visit by telephone, written correspondence, or another means whenever possible.

[6] Promptly notify the sponsor of the study discontinuation.

11.5 Procedures for Post-discontinuation Follow-up

All unresolved (including improved) adverse events will be followed as described in Section 9.7.4.5 .

12. Statistical Analysis

12.1 Selection of Sample Size

A precision-based sample size was selected for this exploratory study.

To allow the estimation of the incidence of CIPN in each of the ART-123 1-dose, ART-123 3-dose, and placebo groups at a precision of ±20%, a target sample size of 25 per group for a total of 75 was selected.

12.2 Statistical Analysis Plan

Key elements of the statistical analysis plan are presented here. The detailed aspects of statistical analysis will be stated in a statistical analysis plan to be finalized before unblinding.

12.3 Analysis Populations

12.3.1 Analysis Populations for Assessing Efficacy

The two analysis populations for assessing efficacy are defined as the full analysis set (FAS) and the per-protocol set (PPS). Decisions on whether subjects will be included in the analysis populations and the following details will comply with subject handling criteria to be established later.

- Full analysis set (FAS)

  This population consists of all subjects assigned to the investigational product except:
  - Subjects with a GCP violation
  - Subjects who do not receive oxaliplatin
  - Subjects who do not receive the investigational product
  - Subjects with no available efficacy data following investigational product administration
- Per-protocol set (PPS)

  The PPS consists of all full analysis set subjects except:
  - Subjects with an inclusion/exclusion criterion violation
  - Subjects with another major protocol deviation

12.3.2 Analysis Population for Assessing Safety

This population consists of all subjects assigned to the investigational product except:
- Subjects who do not receive the investigational product

12.3.3 Analysis Populations for Assessing Pharmacokinetics

This population consists of all subjects assigned to the investigational product except:
- Subjects with a GCP violation
- Subjects who do not receive the investigational product

12.4 Handling of Data

Major rules for handling efficacy data are discussed below. Details about the following and other data-handling rules will comply with data-handling criteria to be established later.

- Handling of missing data on whether an assessment is NCI-CTCAE Grade 1 or greater

  Consider subjects for whom these data are missing to have had an NCI-CTCAE Grade 1 or greater event. Perform sensitivity analysis that includes analysis with a missing NCI-CTCAE grade for all such subjects.
- Handling of NCI-CTCAE evaluation data in the second and subsequent courses

  Evaluate the Day 1 (before infusion of investigational product or mFOLFOX6) NCI-CTCAE grades as those from the immediately preceding course. Evaluate the Days 2, 3, 15, and 29 NCI-CTCAE grades as those observed within the course.
- Handling of missing efficacy endpoint data (continuous variables)

  Do not impute missing continuous efficacy endpoint data. Perform sensitivity analyses with imputation using the last-observation-carried-forward (LOCF) approach.

12.5 Analysis of Demographic Variables and Other Baseline Characteristics

Summary statistics will be calculated and categorical tabulations will be performed for demographic variables and other baseline characteristics in the FAS on a by-group basis.

12.6 Analysis of Efficacy

12.6.1 Overall Information

This study is conducted to assess and characterize the clinical effect of ART-123 in preventing the onset of oxaliplatin-induced peripheral neuropathy and to explore appropriate efficacy endpoints. Thus, efficacy analyses will be performed primarily with descriptive statistics obtained by summarizing and graphing data from each evaluation time point.

The incidences of NCI-CTCAE Grade 1 or greater events will be evaluated with statistical tests and 95% confidence intervals as necessary in addition to descriptive statistics to allow intergroup comparison. The incidences of NCI-CTCAE Grade 1 or greater events with discontinuations and dropouts factored in will also be estimated.

The FAS will be used as the primary analysis population for evaluating efficacy. Similar analyses will be conducted as necessary with the PPS as a secondary analysis population to confirm the stability of the analysis results.

The significance level is set at 5% (two-sided), with a two-sided confidence interval and a confidence coefficient of 95%. Given the exploratory nature of the study, multiplicity will not be adjusted for.

12.6.2 Efficacy Endpoints

12.6.2.1 NCI-CTCAE

For subjects found to have had one or more NCI-CTCAE Grade 1 or greater events during the study period, the incidence of NCI-CTCAE Grade 1 or greater events will be calculated by evaluation category, by course, and by treatment group. To provide reference data, differences will be calculated between the ART-123 1-dose and placebo groups and between the ART-123 3-dose and placebo groups. Moreover, survival analysis will be conducted with the occurrence of an NCI-CTCAE Grade 1 or

greater event during the study period considered to be an event, and Kaplan-Meier curves will be plotted with the incidence of events on the vertical axis and items (1) and (2) below on the horizontal axis.

(1) Observation period

(2) Cumulative oxaliplatin dose

The occurrence of NCI-CTCAE Grade 2 and greater events will be analyzed similarly to NCI-CTCAE Grade 1 and greater events.

The number of subjects with events in each NCI-CTCAE grade will be tabulated by evaluation category, evaluation time point, and treatment group. As necessary, shift tables showing Day 1 of course 1 (baseline) and certain evaluation time points will be created for each treatment group.

- Evaluation categories
  - Peripheral motor neuropathy
  - Peripheral sensory neuropathy

12.6.2.2 DEB-NTC

The number of subjects with events in each grade will be tabulated for the symptoms and sites shown below on the basis of the evaluation time point and treatment group. As necessary, shift tables showing Day 1 of course 1 (baseline) and certain evaluation time points will be created for each treatment group.

- Symptoms
  - Peripheral sensory abnormalities or discomfort when touching things
  - Painless peripheral sensory abnormalities or discomfort under normal conditions
  - Painful peripheral sensory abnormalities or discomfort under normal conditions
  - Functional disorders
- Sites
  - Hands, feet, lips/tongue and surroundings, face, pharyngolarynx, other

12.6.2.3 FACT/GOG-NTX-12

Summary statistics will be calculated for FACT/GOG-NTX-12 scores and changes from Day 1 of course 1 (baseline) by evaluation time point and treatment group, and figures showing changes over time in individuals will be plotted.

12.6.2.4 FACT-G

Summary statistics will be calculated for FACT-G scores and changes from Day 1 of course 1 (baseline) by evaluation time point and treatment group. Scores calculated in each of the following evaluation categories will be similarly evaluated.

- Evaluation categories

  Physical, social/family, emotional, and functional well-being

12.6.2.5 NRS (pain)

For each of the sites listed below, summary statistics will be calculated for NRS scores and changes from Day 1 of course 1 (baseline) by evaluation time point and treatment group.

- Sites

  Hands, feet

12.6.2.6 Discontinuation, Suspension, and Dose Reduction of Oxaliplatin due to CIPN

For each treatment group, Kaplan-Meier curves with the observation period and cumulative oxaliplatin dose on the horizontal axis and event incidence on the vertical axis will be plotted, with items [1] and [2] as events.

[1] Discontinuation of oxaliplatin due to CIPN

[2] Discontinuation, suspension, and dose reduction of oxaliplatin due to CIPN

Discontinuations of oxaliplatin other than [1] and [2] is used as censored.

The numbers of subjects who undergo discontinuation, suspension, or dose reduction of oxaliplatin due to CIPN will also be tabulated.

12.6.2.7 Other Analyses

The analyses listed below will be conducted as necessary. The details about statistical analyses will be presented in the statistical analysis plan.

- Analysis adjusted for baseline values and other covariates
- Analysis that factors in the effects of how dropouts or missing data are handled
- Subgroup analyses
- Analysis of the correlation between NCI-CTCAE grades and other efficacy endpoints
- Analysis of postoperative adjuvant chemotherapy administration status

12.7 Safety Analysis

12.7.1 Analysis of Adverse Events

TEAEs evaluated in the study will conform to the definition in Section 9.7.4.1 . All TEAEs identified from the first day of investigational product administration to study completion (Day 43 of the last course) will be included in the tabulations. The numbers of subjects with a TEAE in each treatment group will be tabulated by adverse event name, organ class, severity (per NCI-CTCAE grading), seriousness classification, causality, and the timing of onset. Differences from the placebo group in TEAE incidences will be calculated along with two-sided 95% confidence intervals of these differences.

12.7.2 Analyses of Laboratory Findings

Summary statistics will be calculated according to the evaluation time point and treatment group for each laboratory parameter. Variance in each laboratory parameter will be investigated in each treatment group.

12.7.3 Analyses of Vital Signs

Each vital sign parameter will be analyzed as in Section 12.7.2 .

12.7.4 Analysis of Immunogenicity (anti-drug antibodies, neutralising antibodies)

These data will be categorically tabulated by evaluation time point and treatment group.

12.8 Pharmacokinetic Analysis

Lists and graphs of plasma drug concentrations following investigational product administration will be created for each subject.

12.9 Timing of Analyses

The analyses will be performed after unblinding.

12.10 Reporting of Changes to the Analytical Plan

Any analyses not described in the protocol or statistical analysis plan that are additionally conducted after unblinding will be reported independently of the analyses conducted according to the protocol or statistical analysis plan.

13. Protocol Compliance, Deviations/Modifications, and Amendment

13.1 Protocol Compliance

The investigators and sponsor will conduct the study in compliance with this protocol, to which both parties have agreed. The investigators and sponsor will sign or seal and date an agreement to be decided on elsewhere.

13.2 Protocol Deviations and Modifications

The investigator or subinvestigator will not deviate from or modify the protocol without prior agreement with the sponsor documented in writing and written approval based on prior review by the institutional review board. This is not applicable to protocol deviations for a medically necessary reason, such as to avoid exposing a subject to acute risk, and to clerical modifications.

If deviating from the protocol for a medically necessary reason such as to avoid exposing a subject to acute risk, the investigator will enter the reason and other pertinent information in the "Report of protocol deviation to avoid acute risk," promptly submitting this document to the study site director and sponsor. The investigator or subinvestigator will document all protocol deviations, regardless of the reason.

13.3 Protocol Amendment

The sponsor may amend the protocol as necessary, for example, if obtaining information pertinent to the proper execution of the study, to address a medically unavoidable event, or to correct the protocol as instructed by the study site director based on the findings of the institutional review board.

If the protocol must be amended, the investigators and sponsor will discuss the revisions and sign or seal and date an agreement to be decided on elsewhere. The sponsor or investigators will promptly submit the amended protocol to the study site director. The approval of the institutional review board will be obtained if necessary.

14. Study Completion or Termination

14.1 Study Completion

The sponsor will promptly notify all study sites of the conclusion of registration on confirming that the number of subjects registered has reached the number of subjects targeted in the protocol and deciding that no new patients will be registered.

The investigator will inform the study site director of the completion of the study and submit a summary of the study results in writing after the treatment, examinations, observations, and tests specified in the protocol have concluded for the last patient at that study site.

14.2 Unblinding Following Study Completion

After study completion, the data will be unblinded according to the following procedures:

[1] The sponsor will decide how to handle all subjects registered in the study.

[2] The investigational product assignment manager will confirm that the investigational products are indistinguishable after study completion.

[3] After [1] and [2], the investigational product assignment manager will retrieve the copy of key codes and emergency keys retained by the sponsor and check if they have been opened.

[4] The investigational product assignment manager will seal the documents at data lock.

[5] The investigational product assignment manager will conduct unblinding.

14.3 Termination or Suspension of the Study as a Whole or Partially

The sponsor will resolve to terminate or suspend the study as a whole or partially if determining that the study should not continue due to a serious adverse reaction or similar incident.

Subsequently, the sponsor will promptly submit a written report about study termination and the reason for termination to the investigators and subinvestigators, study site directors, and Pharmaceuticals and Medical Devices Agency (Ministry of Health, Labour and Welfare).

The investigator or subinvestigator will promptly submit written notification to the subjects, and the study site director will promptly submit written notification to the institutional review board.

14.4 Termination at a Study Site

The sponsor may terminate the study at any study site where any of the situations listed below occurs. The sponsor will promptly submit written notification of the reason for termination to the study site director. The study site director will submit written notification to the investigator and the institutional review board. On receiving this notification, the investigator will follow the specified procedures for that study site.

Conditions for terminating the study at a study site

[1] When a study site commits a violation of the Japanese GCP Ministerial Ordinance, the protocol, or the study contract that interferes with the proper execution of the study, the study contract with that study site will be rendered null and void and the study will be terminated. This is not applicable when the violation is committed for a medically necessary reason such as to avoid exposing a subject to acute risk.

[2] When a study site no longer satisfies the conditions required for properly conducting the study.

- There are no patients that satisfy the eligibility criteria.
- Reassignment of the investigator or a similar circumstance is found to make the proper conduct of the study infeasible.

15. Case Report Forms

In the study, an electronic data capture (EDC) system will be used to electronically record the subject data in the eCRFs based on the source documents. The sponsor will provide the system to the study sites. Before using the EDC system, the investigator, subinvestigator, or clinical research coordinator must undergo training and be issued an account. After an account is issued, the user will log in with his or her account and enter data.

The investigator, subinvestigator, or clinical research coordinator will enter patient registration information (e.g., inclusion/exclusion criteria eligibility) in the IWRS and transfer the data to the EDC system.

Anti-drug antibody, neutralising antibody, and pharmacokinetic measurements will not be entered in the system. Anti-drug antibody, neutralising antibody, and pharmacokinetic measurements will be electronically submitted to the sponsor by contract laboratories after unblinding.

15.1 Completion and Reporting of Case Report Forms

The investigator or subinvestigator or a clinical research coordinator will make entries in the eCRFs.

[1] Clinical research coordinators are allowed to enter only information contained in the source documents.

[2] Data are to be entered when required in the EDC system according to the sponsor-provided “Data Entry Handbook.”

[3] EDC system entry based on the source documents will be promptly completed for each subject who has given informed consent after the subject completes the follow-up period. EDC system entry will be promptly completed for any subject discontinued from the study.

[4] The investigator will inspect all entries to confirm that no problems are present before electronically signing the eCRF. The system will be configured so that the investigators and subinvestigators cannot review FACT/GOG-NTX-12 entries, and the investigators will not electronically sign these entries.

[5] After the sponsor locks the database, the investigator will accept electronically viewable electronic reports from the sponsor as the case report forms to be stored at the study site.

15.2 Revising or Adding to a Case Report Form

The investigator or subinvestigator or a clinical research coordinator will revise entries in or add entries to eCRFs. The records of changes made (date, description, and reason of change) will be stored as an audit trail in the EDC system.

The investigator will inspect all revisions made after the investigator has signed the document to confirm that no problems are present before electronically re-signing the eCRF.

16. Direct Access to Source and Other Documents

16.1 Definition of Source Documents

Source documents are all medical records, laboratory test reports, informed consent forms, administration records, investigational product control records, and other documents on which the eCRFs are based.

16.2 Direct Access

The investigators and study sites will make available the source documents and all other study-related records to study-related monitoring, auditing, and institutional review board and regulatory authority inspections.

17. Study Quality Control and Quality Assurance

17.1 Sponsor (and contract research organizations)

The sponsor will conduct quality control and quality assurance according to the “Rules and procedures for conducting clinical studies of pharmaceuticals” (as agreed to by the sponsor and the contract research organization). The sponsor will maintain systems for quality control and quality assurance based on the procedures.

17.2 Study Sites

Study quality control and quality assurance will be conducted according to procedures for study-related duties specified by the study site directors.

18. Retention of Records

18.1 Retention of Records at the Study Sites

[1] The storage manager designated by the study site director will retain all documents and records specified under GCP in the location specified by the study site until the latter of:

- The day of approval of the drug product of the study.
- The day 3 years after the termination or completion of the study.

[2] The approval of the sponsor will be obtained before the documents are destroyed following the retention period.

[3] Appropriate measures will be taken if the location of document retention is moved because of facility relocation or for another reason so that the documents are not lost or destroyed during the retention period. If necessary, records of relocation will be created under the supervision of the study site director or storage manager.

[4] The sponsor will notify the study site when the retention period is over.

18.2 Retention of Records by Sponsor

The GCP management officer designated by the sponsor will retain all documents and records specified under GCP until the latest of:

- The day 5 years after the day of approval of the drug product of the study.
- The day 3 years after the termination or completion of the study.
- The final day of the reexamination period.

18.3 Retention of Records at Other Institutions

The contract research organization, site management organization, testing facility, and subject registration center will retain the contract and all documents for retention specified in the contract until the latter of:

- The day of approval of the drug product of the study.
- The day 3 years after the termination or completion of the study.

19. Compliance with Ethical Principles and Laws

The study will be conducted in compliance with the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, the Ministerial Ordinance on Good Clinical Practice for Drugs, and all other related laws and rules.

20. Monetary and Other Payments and Compensation and Insurance for Injuries

20.1 Monetary Payments

The sponsor will cover the expenses associated with testing and diagnostic imaging performed during the investigational product treatment period and the expenses associated with dispensing and injecting drug products with an indication similar to the investigational product according to the national expenditure system for special healthcare not covered by insurance.

The sponsor will comply with any system put in place by the institutional review board or other body of the study sites for paying an allowance to the subjects to alleviate subject inconvenience and disadvantage. The sponsor will decide on payments and other terms in consultation with the study sites.

20.2 Compensation and Insurance for Injuries

The sponsor will purchase a clinical study insurance plan and take other necessary measures to fulfill its obligations to compensate and pay damages for subject injuries.

The investigator or subinvestigator will appropriately treat any subject who develops a study-related disability, disease, or other injury as a result of participating in the study.

[1] The investigator or subinvestigator will prepare a written request for injury compensation (the form of which will be provided by a monitor when the injury occurs) and submit this document to the sponsor.

[2] The sponsor will pay the medical expenses incurred by the subject for treatment as well as a medical allowance and monetary compensation according to the compensation plan. The sponsor will in general not provide compensation if the injury is a result of the investigational product not providing the expected effect or other benefits.

[3] Compensation for injury will not be paid or the amount paid will be reduced if:

- The injury is the result of an intentional act or gross negligence on the part of the subject.
- The injury is the result of the investigator or subinvestigator substantially deviating from the protocol or another intentional act or gross negligence on the part of the study site.
- The injury is the result of an illegal act or nonperformance by a third party.
- The injury is coincidental (e.g., struck by a speeding car while going to the hospital, food poisoning).
- The injury is caused by postoperative adjuvant chemotherapy.

21. Decisions Regarding Publication

The results of all joint research conducted according to this protocol are the property of the sponsor. If an individual study site wishes to publish the results for its subjects, it must do so after the results of the joint research are published and with the acknowledgment of the sponsor. The privacy of the subjects will be protected when the results are published.

22. Study Administrative Structure

The study administrative structure is presented in Appendix 1.

23. References

1) Japanese Society for Cancer of the Colon and Rectum. JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer. Tokyo: Kanehara & Co., Ltd.; 2014.
2) Kawabata A, Oishi R. Neuropathic Pain Associated with Cancer Chemotherapy: Recent trends in research: Introduction. Folia Pharmacologica Japonica 2013; 141 (2): 61.
3) Nakagawa T, Zhao M, Shirakawa H, Kaneko S. Just what is the true form of "numbness" caused by anticancer drugs!? The role of TRPA1 in acute peripheral neuropathy characteristic of oxaliplatin. Folia Pharmacologica Japonica 2013; 141 (2): 76-80.
4) Oishi R, Egashira N. Peripheral neuropathy caused by anticancer drugs. Fukuoka Acta Med 2013; 104 (5): 171-80.
5) Gamelin E, Gamelin L, Bossi L, Quasthoff S. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol 2002; 29 (5 Suppl 15) : 21-33.
6) Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: A comprehensive survey. Cancer Treat Rev 2014; 40 (7) : 872-82.
7) Arakawa K, Torigoe K, Kuzumaki N, Suzuki T, Narita M. Characteristics of and mechanism of peripheral neuropathy caused by anticancer drugs. Jpn J Pharm Palliat Care Sci 2011; 4: 1-13.
8) Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014; 32 (18) : 1941-67.
9) Egashira N, Kawashiri T, Oishi R. Current state of pharmacotherapy for peripheral neuropathy caused by anticancer drugs. Folia Pharmacologica Japonica 2010; 136: 275-9.
10) Ito T, Kakihana Y, Maruyama I. Thrombomodulin as an intravascular safeguard against inflammatory and thrombotic diseases. Expert Opin Ther Targets 2015; 20 (2) :1-8.
11) Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. Nature Rev Neurosci 2006; 7 (10) : 797-809.
12) [redacted]
13) [redacted]
14) Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma, eighth edition. Tokyo: Kanehara & Co., Ltd.; 2013.
15) Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology. JSH Guidelines for the Management of Hepatitis B Virus Infection. Version 2.1. by Japan Society of Hepatology. 2015.
16) Ministry of Health, Labour and Welfare. The manual for handling disorders due to adverse drug reactions-focus on the anaphylaxis. March 2008. Available from URL:http://www.info.pmda.go.jp/juutoku/file/jfm0803003.pdf