Statistical Analysis Plan

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

SAP Version: Ver. 1.0

Sponsored by:
Asahi Kasei Pharma Corporation

Date Approved: 26 Feb 2018

Approver	Signature	Date
Senior Statistician	[redacted]	26 Feb 2018
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Revision History

Version	Date	Writer	Memo
1.0	26 Feb 2018	[redacted]	

Table of Contents

1. Introduction

The analyses described in this document are for inclusion in a Clinical Study Report (CSR) to support a regulatory submission. This statistical analysis plan (SAP) describes all planned analyses that will be conducted and presented for the ART-123(CIPN)-201 study and is based on protocol version 3 dated April 22, 2016.

2. Study Objectives and Endpoints

2.1 Study Objectives

- To assess whether ART-123 can prevent chemotherapy-induced peripheral neuropathy (CIPN) when administered to subjects with postoperative stage II/III colon cancer who undergo mFOLFOX6 therapy.
- To assess the safety of ART-123 in this population.

2.2 Study Endpoints

➢ Efficacy Endpoints

- NCI-CTCAE ver.4.0 (Peripheral motor neuropathy, Peripheral sensory neuropathy) (Only CIPN)*
- DEB-NTC
- FACT/GOG-NTX-12
- FACT-G
- NRS (Pain)
- Discontinuation/suspension/dose reduction of oxaliplatin (L-OHP) caused by CIPN

* NCI-CTCAE ver.4.0 (Peripheral motor neuropathy, Peripheral sensory neuropathy) (Only CIPN) will be abbreviated to CTCAE (motor, sensory) in this SAP.

➢ Safety Endpoints

- Vital signs
- Clinical laboratory tests
- Presence of antidrug antibodies
- Adverse events

➢ PK endpoint

- Plasma thrombomodulin alfa concentrations

3. Study Design

3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled, multi-center, parallel-group, phase 2 study to assess the preventive effect of ART-123 on CIPN. Following screening, subjects who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned, in a 1 to 1 to 1 ratio, to receive ART-123 3-dose, ART-123 1-dose, or placebo.

- ART-123 3-dose: ART-123 will be administered on day 1 through day 3 in each course of chemotherapy
- ART-123 1-dose: ART-123 will be administered on day 1 and placebo will be administered on day 2 through day 3 in each course of chemotherapy
- Placebo: Placebo will be administered on day 1 through day 3 in each course of chemotherapy

The efficacy-related assessments will include CTCAE (motor, sensory), DEB-NTC, FACT/GOG-NTX-12, FACT-G, NRS (Pain), and discontinuation/suspension/dose reduction of L-OHP caused by CIPN. The safety-related assessments will include vital signs, clinical laboratory tests, presence of antidrug antibodies, and adverse events. PK-related assessments will include plasma thrombomodulin alfa concentrations.

No interim analysis will be conducted.

3.2 Method of assigning subjects to treatment groups

Randomization will use permutated blocks with a 1 to 1 to 1 ratio and will be stratified by study site. Subjects will be randomly assigned to treatment at the baseline visit prior to first dosing.

3.3 Blinding

Study treatment will be assigned and administered in a double-blinded fashion, so that both the subject and the study site will be blinded to subject allocation.

In addition, Asahi Kasei Pharma Corporation and the CROs supporting the study will be blinded with the following exception:

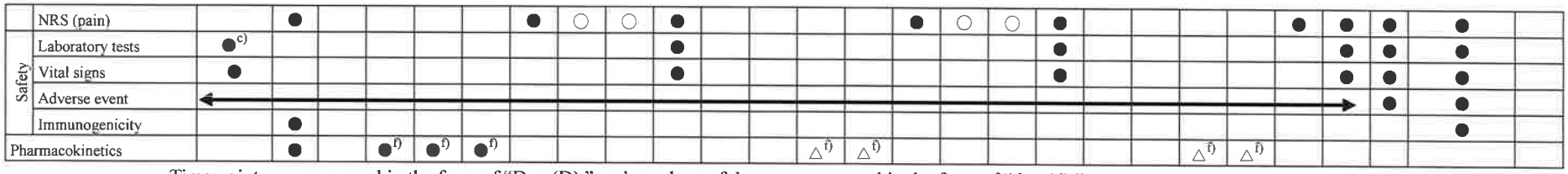
- Central laboratory, who handle pharmacokinetics data, will be unblinded.

3.4 Study schedule

The study schedule is defined in Table 3.1:

Table 3.1 Study schedule outline

Test/observation schedule	Screening Period	Treatment Period																								Follow-up Period[h]	CIPN Evaluation
	-	Course 1									Courses 2 to 11									Course 12								
		D1 (registration day)			D2	D3	D8	D15	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	At discontinuation in the treatment period[g]	At study completion (d43 of the last course)[i]	
		Before	Investigational product administration	After							Before	Investigational product administration	After							Before	Investigational product administration	After							
Permitted window of time from the specified date (day)	d-14 ~ 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		●									●									●									
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[b] NCI-CTCAE		●			●	●		○	○		●			●	●		○	○		●			●	●		●	●	●	●
Efficacy[b] DEB-NTC		●						○	○		●						○	○		●						●	●	●	
Efficacy[b] FACT/GOG-NTX-12		●					●	○	○		●					●	○	○		●					●	●	●	●	
Efficacy[b] FACT-G		●									●[e]															●	●	●	



Time points are expressed in the form of "Day (D)," and numbers of days are expressed in the form of "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 were available in course 1, perform 1 cycle of blood sampling in one of the courses between 2 and 12.

a) Not required in a course in which oxaliplatin washout takes place

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

c) To be performed between Day −7 and Day −1 (a 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

e) To be performed only in courses 5 and 9

f) Collect blood samples at immediately and between 30 and 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 fails to commence in 34 weeks (Day 239 from the day of registration), discontinue 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 of the postoperative adjuvant chemotherapies in the subsequent course fails to commence by Day 43 of the course, discontinue the study, and perform the "end-of-study" evaluations.

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

j) Survey the status of fluorouracil continuous intravenous infusion

4. Sample Size Calculation

Since this study is exploratory, a precision-based sample size calculation has been used. A sample size of 25 subjects per treatment group provides a 95% two-sided confidence interval for the CIPN incidence proportion whose width will be 40%. That is, we would like to be 95% sure that the true CIPN incidence proportion will be within ± 20% of the estimated CIPN incidence proportion.

The sample size calculation was performed with SAS 9.4.

5. Analysis Population

- Full Analysis Set (FAS)

  The Full Analysis Set (FAS) will include all randomized subjects except for the following subjects.
  - Subjects who violate GCP
  - Subjects who do not receive L-OHP
  - Subjects who do not receive study treatment
  - Subjects with no post-baseline efficacy endpoints

- Per Protocol Set (PPS)

  The Per Protocol Set (PPS) will include all FAS subjects except for the following subjects.
  - Subjects who violate eligibility criteria
  - Subjects with any other major protocol deviations

- Safety Population

  The Safety Population will include all randomized subjects except for the following subjects.
  - Subjects who do not receive study treatment

- PK analysis population

  The PK analysis population will include all randomized subjects except for the following subjects.
  - Subjects who violate GCP
  - Subjects who do not receive study treatment

The analysis population will be determined at blind review before blind break.

6. General Considerations for Data Analyses

All statistical tests will be two-sided with a significance level of 0.05. This study is exploratory, and no adjustment for multiplicity will be conducted. Between-treatment comparisons will be conducted between ART-123 3-dose and placebo, and between ART-123 1-dose and placebo.

Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum. All minimum and maximum values will be displayed with the same number of decimal places relative to the raw data. The mean, median, and standard deviation will each have one additional decimal place.

Summary statistics for categorical variables will include the frequency and proportion. The denominator for proportion, unless otherwise specified, will be the number of subjects in each treatment group within the analysis population.

In all populations, subjects will be analyzed based on the treatment group they were randomized to regardless of the study treatment received.

Time-dependent changes in efficacy and safety assessments will be analyzed from the perspective of *between* and *within courses*, as follows

- *Between courses analyses*: measurements will be summarized by each course based on the analysis visit window (Tables 7.1, 7.2, 7.3, 7.5).
- *Within courses analyses*: measurements will be summarized by each course and day based on the analysis visit window (Table 7.4).

Any deviations from the originally planned analysis as specified in the protocol will be detailed in the final clinical study report with an explanation of the alternative methods used.

7. Data Handling Conventions

7.1 Day 1 Definition of each course

According to protocol section 9.1, Day 1 of each course is defined as the start date of mFOLFOX6. If four treatments composed of mFOLFOX6 have different dosing dates or any of the treatments is not administered, the following priority order is used as Day 1:

(1) Date L-OHP administered
(2) Date 5-FU (continuous) administered
(3) Date 5-FU (rapid) administered
(4) Date levofolinate administered

7.2 The Analysis Visit Window for Between- and Within courses Analyses

Efficacy and safety endpoints will be assigned to analysis visit windows described in the definition of the analysis visit window (Tables 7.1-7.5). The analysis visit window depends on the purpose of the analysis. The PK endpoint will be assigned to visits as collected on the CRFs and will disregard the actual date/time of the assessment.

Table 7.1 Definition of the Efficacy Analysis Visit Window for Between courses Analyses <Worst>

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1)
CTCAE, DEB-NTC, FACT/GOG-NTX12, NRS	Baseline	–	From Randomization date to Course 1, Day 1, CT=Predose
	Course 1	–	From Course 1, Day 1, CT=After Dosing to Course 2, Day 1 If a subject discontinues prematurely from the study at course 1, the analysis visit window is set from Course 1, Day 1, CT=After Dosing to Course 1, Day 71
	Course X (2≤X≤11)	–	From Course X, Day 2 to Course X+1, Day 1 If a subject discontinues prematurely from the study at course X, the analysis visit window is set from Course X, Day 2 to Course X, Day 71
	Course 12	–	From Course 12, Day 2 to Course 12, Day 36
	Course 12 Completion	–	From Course 12, Day 37 to Course 12, Day 71
	EOT (End of study Treatment)	–	Measurements assigned to be the last analysis visit during the administration of study treatment
	EOS (End of Study)	–	Measurements assigned to be the last analysis visit

CT: Collection Time Point on EDC

Table 7.1 Definition of the Efficacy Analysis Visit Window for Between courses Analyses <Worst> (Cont.)

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1)
FACT-G	Baseline	–	From Randomization date to Course 1, Day 1, CT=Predose
	Course 5	–	From Course 1, Day 1, CT=After Dosing to Course 7, Day 1 If a subject discontinues prematurely from the study at course X, the analysis visit window is set from Course 1, Day 1, CT=After Dosing to Course X, Day 71 ($1 \leq X \leq 6$)
	Course 9	–	From Course 7, Day 2 to Course 11, Day 1 If a subject discontinues prematurely from the study at course X, the analysis visit window is set from Course 7, Day 2 to Course X, Day 71 ($7 \leq X \leq 10$)
	Course 12	–	From Course 11, Day 2 to Course 12, Day 36 If a subject discontinues prematurely from the study at course 11, the analysis visit window is set from Course 11, Day 2 to Course 11, Day 71
	Course 12 Completion	–	From Course 12, Day 37 to Course 12, Day 71
	EOT (End of study Treatment)	–	Measurements assigned to be the last analysis visit during the administration of study treatment
	EOS (End of Study)	–	Measurements assigned to be the last analysis visit

CT: Collection Time Point on EDC

Table 7.2 Definition of the Efficacy Analysis Visit Window for Between courses Analyses <Worst: excl. Day 2, 3>

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1)
CTCAE	Baseline	–	From Randomization date to Course 1, Day 1, CT=Predose
	Course 1	–	From Course 1, Day 15 to Course 2, Day 1 If a subject discontinues prematurely from the study at course 1, the analysis visit window is set from Course 1, Day 15 to Course 1, Day 71
	Course X (2≤X≤11)	–	From Course X, Day 15 to Course X+1, Day 1 If a subject discontinues prematurely from the study at course X, the analysis visit window is set from Course X, Day 15 to Course X, Day 71
	Course 12	–	From Course 12, Day 15 to Course 12, Day 36
	Course 12 Completion	–	From Course 12, Day 37 to Course 12, Day 71
	EOT (End of study Treatment)	–	Measurements assigned to be the last analysis visit during the administration of study treatment
	EOS (End of Study)	–	Measurements assigned to be the last analysis visit

CT: Collection Time Point on EDC

Table 7.3 Definition of the Efficacy Analysis Visit Window for Between courses Analyses <Day 1>

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1)
CTCAE, FACT/GOG-NTX12,	Course 1 Day 1	–	From Randomization date to Course 1, Day 1, CT=Predose
	Course X Day 1 ($2 \leq X \leq 12$)	–	Course X, Day 1[(1)]
	EOT (End of study Treatment)	–	Measurements assigned to be the last analysis visit during the administration of study treatment
	EOS (End of Study)	–	Measurements assigned to be the last analysis visit

(1) In analyses for CTCAE, CTCAE at the time of evaluation will be used.

Table 7.4 Definition of the Efficacy Analysis Visit Window for Within courses Analyses

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1 if Assessment date ≥ Day 1 date) (Day X: Assessment date minus Day 1 date if Assessment date < Day 1 date)
CTCAE	Course X Day 1[(1)] (1≤X≤12)	–	Course X, Day 1[(2)]
	Course X Day 2 (1≤X≤12)	–	Course X, Day 2
	Course X Day 3 (1≤X≤12)	–	Course X, Day 3
	Course X After Day 15 (1≤X≤11)	–	From Course X, Day 4 to Course X+1, Day 1[(3)] If a subject discontinues prematurely from the study at course X, the analysis visit window is set from Course X, Day 4 to Course X, Day 71
	Course 12 Day 15	–	From Course 12, Day 4 to Course 12, Day 36
	Course 12 Day 43	–	From Course 12, Day 37 to Course 12, Day 71

Table 7.4 Definition of the Efficacy Analysis Visit Window for Within courses Analyses (Cont.)

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1 if Assessment date ≥ Day 1 date) (Day X: Assessment date minus Day 1 date if Assessment date < Day 1 date)
Efficacy (FACT/GOG-NTX-12, NRS)	Course X Day 1 [(1)] (1≤X≤12)	Course X, Day 1	Course X, Day 1
	Course X Day 8 (1≤X≤11)	Course X, Day 8	From Course X, Day 2 to Course X+1, Day -1 If a subject discontinues prematurely from the study at course X, the analysis visit window is set from Course X, Day 2 to Course X, Day 71
	Course 12 Day 8	Course 12, Day 8	From Course 12, Day 2 to Course 12, Day 14
	Course 12 Day 15	Course 12, Day 15	From Course 12, Day 15 to Course 12, Day 36
	Course 12 Day 43	Course 12, Day 43	From Course 12, Day 37 to Course 12, Day 71

(1) In case of X=1: analysis visit window is set from the randomization date to Course 1, Day 1, CT=Predose.

(2) CTCAE at the time of evaluation will be used.

(3) The worst CTCAE grade between the preceding evaluations will be used.

Table 7.5 Definition of the Safety Analysis Visit Window for Between courses Analyses

Endpoints	Analysis Visit	Target Day	Analysis Visit Window (Day X: Assessment date minus Day 1 date plus 1 if Assessment date ≥ Day 1 date) (Day X: Assessment date minus Day 1 date if Assessment date < Day 1 date)
Safety (Vital signs, Lab)	Baseline	Course 1, Day 1	From IC obtained date to Course 1, Day 1, CT=Predose
	Course X Day 1 (2≤X≤12)	Course X, Day 1	From Course X, Day -4 to Course X, Day 1
	Course 12 Day 15	Course 12, Day 15	From Course 12, Day 11 to Course 12, Day 36
	Course 12 Day 43	Course 12, Day 43	From Course 12, Day 37 to Course 12, Day 71
	EOT (End of study Treatment)	–	Measurements assigned to be the last analysis visit during the administration of study treatment
	EOS (End of Study)	–	Measurements assigned to be the last analysis visit
Safety (Presence of antidrug antibodies)	Baseline	Course 1, Day 1	From IC obtained date to Course 1, Day 1, CT=Predose
	EOS (End of Study)	Last Course, Day 43	< For antibody-positive patients > From Course 1, Day 2 to Last Course, Day 71 < For antibody-negative patients > From 14 days after end of study treatment to Last Course, Day 71

※CP03-05 did not collect height data on IC obtain date or later, her/his height collected before IC obtain date will be used in the analyses.

The data of unscheduled visits and CIPN unscheduled visits will be re-assigned to one of the analysis visit windows based on the definition described in Tables 7.1-7.5.

It is possible that a record may not be mapped to one of the above analysis visit windows based on the definition described in Tables 7.1-7.5. In this case, these records will be listed but not included in summary tables when presented by analysis visit.

Time-to-event data analyses will use elapsed days after the randomization date, not these conventions for analysis visit windows, unless otherwise specified.

7.3 Derived Variables and Handling of Missing Data

7.3.1 Demographics and Other Baseline Characteristics

7.3.1.1 Derived baseline variables

- Body Surface Area (m^2)

  Body Surface Area (m^2) will be derived by the Dubois formula:

$$BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725} \times 0.007184$$

  The baseline weight and height will be used to calculate the baseline BSA.

- Diabetes Mellitus

  Subjects with diabetes mellitus will be identified by meeting the following criteria in Standardised MedDRA Queries (SMQ):

  - Hyperglycaemia/new onset diabetes mellitus) (narrow)

7.3.1.2 Handling of Missing Data

All missing demographic and other baseline characteristic data will not be imputed and will be presented as part of a missing category.

7.3.2 CTCAE

7.3.2.1 Endpoint Derivation

- Between courses analyses

  There are three types of between courses analyses, as follows:

  - Between courses analyses <Worst>

    If multiple measurements occur within the same analysis visit window (Table 7.1), the measurement with the worst value will be used.

  - Between courses analyses <Worst: excl. Day 2, 3>

    If multiple measurements occur within the same analysis visit window (Table 7.2), the measurement with the worst value will be used.

  - Between courses analyses <Day 1>

    If multiple measurements occur within the same analysis visit window (Table 7.3), the measurement with the worst value will be used.

  Unless otherwise described in section 9, between courses analyses <Worst> will be conducted.

- Within courses analyses

  If multiple measurements occur within the same analysis visit window (Table 7.4), the measurement with the worst value will be used.

- Time-to-event analyses

  Two types of time-to-event data will be defined in the following.

  - Elapsed time-to-event data

    The elapsed time to event will be defined as follows:

    - If events occur, the elapsed time to the first event will be computed as the date on which the first event is detected minus the randomization date plus 1.
    - If events do not occur, the censoring time will be computed as the last assessment date of CTCAE minus the randomization date plus 1.

  - Cumulative L-OHP dose to event data

    The cumulative L-OHP dose to event will be defined as follows:

    - If events occur, the cumulative L-OHP dose to the first event will be computed as the sum of each administered L-OHP dose until the first event date.
    - If events do not occur, the censoring dose will be computed as the sum of each administered L-OHP dose until the last assessment date of CTCAE.

    The derivation of cumulative L-OHP dose will be defined in section 7.3.7.1.1.

7.3.2.2 Handling of missing data

No imputation will be conducted, unless otherwise specified. In sensitivity analyses, missing post-baseline data will be imputed using last observation carried forward (LOCF) or worst observation carried forward (WOCF). Missing baseline data will not be imputed. LOCF or WOCF will be based on the targeted assessments (i.e. those assigned to be the analyzable assessment based on analysis visits (Tables 7.1-7.4)).

See section 9 for more details.

7.3.3 DEB-NTC

7.3.3.1 Endpoint Derivation

- Between courses analyses

  If multiple measurements occur within the same analysis visit window (Table 7.1), the measurement with the worst value will be used.

7.3.3.2 Handling of missing data

No imputation will be conducted, unless otherwise specified. See section 7.3.2.2 and section 9 for more details.

7.3.4 FACT/GOG-NTX12

7.3.4.1 Endpoint Derivation

The overall score will be derived by NEUROTOXICITY SUBSCALE (NtxS) in Appendix 1. The sensory score will be derived using NTX1, 2, 3, 4, 10 in a similar way to the overall score.

- Between courses analyses

  There are two types of between courses analyses, as follows:

  - Between courses analyses <Worst>

    If multiple measurements occur within the same analysis visit window (Table 7.1), the measurement with the worst value will be used.

  - Between courses analyses <Day 1>

    If multiple measurements occur within the same analysis visit window (Table 7.3), the measurement with the worst value will be used.

  Unless otherwise described in section 9, between courses analyses <Worst> will be conducted.

- Within courses analyses

  If multiple measurements occur within the same analysis visit window (Table 7.4), the measurement closest to the target day will be selected. If there are two measurements equidistant from the target day, the earlier one will be used. If more than one measurement is assessed on the same day, the measurement with the worst value will be used.

- Time-to-event analyses

  Refer to section 7.3.2.1. The last assessment date is set to the last assessment date of FACT/GOG-NTX12.

7.3.4.2 Handling of missing data

No imputation will be conducted, unless otherwise specified. See section 7.3.2.2 and section 9 for more details.

The Duration-Adjusted Average Change (DAAC) will be computed as follows (We refer to lyrica CTD module 2.7.6 (Neuropathic pain)):

- Between courses Analyses <Worst>
  DAAC = (The average post-baseline values on study treatment courses − baseline value) × (The number of study treatment courses received / 12)

- Between courses Analyses <Day 1>
  DAAC = (The average post-baseline values on study treatment courses − baseline value) × (The number of study treatment courses received / 11)

If non-monotone missing data exists, missing data will be imputed by LOCF.

7.3.5 FACT-G

7.3.5.1 Endpoint Derivation

The overall score, physical well-being (PWB) score, social/family well-being (SWB) score, emotional well-being (EWB) score, and functional well-being (FWB) score will be derived by FACT-G in Appendix 1.

- Between courses analyses
  If multiple measurements occur within the same analysis visit window (Table 7.1), the measurement with the worst value will be used.

7.3.5.2 Handling of missing data

No imputation will be conducted, unless otherwise specified. See section 7.3.2.2 and section 9 for more details.

7.3.6 NRS

7.3.6.1 Endpoint Derivation

- Between courses analyses
  If multiple measurements occur within the same analysis visit window (Table 7.1), the measurement with the worst value will be used.

- Within courses analyses
  If multiple measurements occur within the same analysis visit window (Table 7.4), the measurement closest to the target day will be selected. If there are two measurements equidistant from the target day, the earlier one will be used. If more than one measurement is assessed on the same day, the measurement with the worst value will be used.

7.3.6.2 Handling of missing data

No imputation will be conducted, unless otherwise specified. See section 7.3.2.2 and section 9 for more details.

7.3.7 L-OHP-related variables

7.3.7.1 L-OHP dose at each course, Cumulative L-OHP dose

7.3.7.1.1 Endpoint Derivation

The L-OHP dose (mg) at each course will be collected on the CRFs. In L-OHP analysis, L-OHP dose (mg/m^2) will be used. The following conversion from mg to mg/m^2 will be used:

L-OHP dose (mg/m^2) at each course = L-OHP dose (mg) / BSA (m^2)

BSA (m^2) will be derived using weight at each course and height at baseline. Cumulative L-OHP dose (mg/m^2) will be the sum of administered L-OHP doses (mg/m^2).

7.3.7.2 L-OHP Relative Dose Intensity

7.3.7.2.1 Endpoint Derivation

L-OHP Relative Dose Intensity (RDI) (%) will be defined as:
RDI (%) = Cumulative L-OHP dose during the study (mg/m^2) /
(The last course of L-OHP, 5-FU, levofolinate) × 85(mg/m^2)

7.3.7.3 L-OHP suspension, L-OHP dose reduction at each course

7.3.7.3.1 Endpoint Derivation

L-OHP administration (Y, N) and L-OHP dose reduction (Y, N) collected on day 1 and L-OHP discontinuation (Y, N) collected on study completion will be included in the analysis. L-OHP administration or dose reduction on day 15 or day 29 will not be included in the analysis, because these records represent postponement of the administration of all drugs for postoperative adjuvant chemotherapy. If a subject discontinues the study prematurely, such subject will be categorized as L-OHP suspension in subsequent courses.

The reasons for L-OHP dose reduction (CIPN, Non-CIPN) will be derived based on the following:

- If a subject reduces L-OHP caused by CIPN at a course, the reason for L-OHP dose reduction will be CIPN at a corresponding course.
- If a subject does not reduce L-OHP caused by CIPN and reduces L-OHP caused by an AE or other at a course, the reason for L-OHP dose reduction will be categorized as Non-CIPN at the corresponding course.

The reasons for L-OHP suspension (CIPN, Non-CIPN) will be derived based on the following:

- If a subject suspends L-OHP (i.e. L-OHP administration will be N) caused by CIPN at a course, the reason for L-OHP suspension will be CIPN at the corresponding course.
- If a subject does not suspend L-OHP caused by CIPN and suspends L-OHP caused by an AE or other at a course, the reason for L-OHP suspension will be categorized as Non-CIPN at the corresponding course.
- If a subject discontinues the study prematurely, the reason for L-OHP suspension at subsequent courses will retain the reason for discontinuation.

7.3.7.4 L-OHP discontinuation during the study

7.3.7.4.1 Endpoint Derivation

L-OHP discontinuation (Y, N) will be collected on CRFs.

The reasons for L-OHP discontinuation (CIPN, Non-CIPN) will be derived based on the following:

- If a subject discontinues L-OHP caused by CIPN, the reason for L-OHP discontinuation will be CIPN.
- If a subject does not discontinue L-OHP caused by CIPN and discontinues L-OHP caused by an AE or other at a course, the reason for L-OHP discontinuation will be categorized as Non-CIPN.

7.3.7.5 Time-to-event data

7.3.7.5.1 Time to L-OHP discontinuation caused by CIPN

7.3.7.5.1.1 Endpoint Derivation

- The definition of L-OHP discontinuation caused by CIPN
  L-OHP discontinuation (Y, N) collected on study completion will be used in the analysis.

- The definition of time to L-OHP discontinuation caused by CIPN
  - If a subject discontinues L-OHP caused by CIPN, the elapsed time to L-OHP discontinuation caused by CIPN will be computed as follows:
    - The date of the first suspension caused by CIPN following the last L-OHP administration date minus the randomization date plus 1.
    - If this corresponding date does not exist, the elapsed time will be set to the study discontinuation date minus the randomization date plus 1.

  - If a subject does not discontinue L-OHP caused by CIPN, the censoring time will be computed as follows:
    - If L-OHP will be administered at course 12, the date of course 12 day 1 minus the randomization date plus 1.
    - If L-OHP will not be administered at course 12, the date of one course after the last L-OHP administration course day 1 minus randomization date plus 1 (i.e. if last L-OHP administration course is 8, the censoring time will be computed as course 9 day 1 minus the randomization date plus 1).
    - If these corresponding dates do not exist, the censoring time will be set to the study discontinuation date minus the randomization date plus 1.

Cumulative L-OHP dose to L-OHP discontinuation caused by CIPN will be computed as the sum of each administered L-OHP, similar to that described above.

7.3.7.5.2 Time to first L-OHP discontinuation, suspension caused by CIPN

7.3.7.5.2.1 Endpoint Derivation

- The definition of discontinuation/suspension caused by CIPN
  L-OHP administration (Y, N) collected on day 1 and L-OHP discontinuation (Y, N) collected on study completion will be used in the analysis.

- The definition of time to first L-OHP discontinuation/suspension caused by CIPN
  - If a subject discontinues or suspends L-OHP caused by CIPN, the elapsed time to first L-OHP discontinuation/suspension caused by CIPN will be computed as follows:
    - The date of the first suspension caused by CIPN minus the randomization date plus 1
    - If this corresponding date does not exist, the elapsed time will be set to the study discontinuation date minus the randomization date plus 1

  - If a subject does not discontinue or suspends L-OHP caused by CIPN, the censoring time will be computed in a similar way to that described in section 7.3.7.5.1.1.

The cumulative L-OHP dose to first L-OHP discontinuation/suspension caused by CIPN will be computed as the sum of each administered L-OHP, similar to that described above.

7.3.7.5.3 Time to first L-OHP discontinuation, suspension, dose reduction caused by CIPN

7.3.7.5.3.1 Endpoint Derivation

- The definition of discontinuation/suspension/dose reduction caused by CIPN
  L-OHP administration (Y, N) and L-OHP dose reduction (Y, N) collected on day 1 and L-OHP discontinuation (Y, N) collected on study completion will be used in the analysis.

- The definition of time to first L-OHP discontinuation/suspension/dose reduction caused by CIPN
  - If a subject discontinues or suspends or reduces L-OHP caused by CIPN, the elapsed time to first L-OHP discontinuation/suspension/dose reduction caused by CIPN will be computed as follows:
    - The date of the first suspension or dose reduction caused by CIPN, whichever comes first minus the randomization date plus 1
    - If these corresponding dates do not exist, the elapsed time will be set to the study discontinuation date minus the randomization date plus 1

  - If a subject does not discontinue or suspend or reduce L-OHP caused by CIPN, the censoring time will be computed in a similar way to that described in section 7.3.7.5.1.1.

Cumulative L-OHP dose to first L-OHP discontinuation/suspension/dose reduction caused by CIPN will be computed as the sum of each administered L-OHP, similar to that described above.

7.3.8 Vital signs

7.3.8.1 Endpoint Derivation

- Between courses analyses

  If multiple measurements occur within the same analysis visit window (Table 7.5), the measurement closest to the target day will be selected. If there are two measurements equidistant from the target day, the later one will be used. If more than one measurement is assessed on the same day, an average value will be used.

7.3.8.2 Handling of missing data

No imputation will be conducted.

7.3.9 Clinical laboratory tests

7.3.9.1 Endpoint Derivation

The measurements with any information about specimen condition (e.g., hemolyzed, lipemic, clotted) will not be used in the between courses analyses and Individual Clinically Significant Abnormality (ICSA) analyses.

- Between courses analyses

  If multiple measurements occur within the same analysis visit window (Table 7.5), the measurement closest to the target day will be selected. If there are two measurements equidistant from the target day, the later one will be used. If more than one measurement is assessed on the same day, the average value for continuous variables or the worst value for categorical variables will be used.

- ICSA Analyses

  The ICSA analyses will not be conducted by analysis visit. All measurements (except for hemolyzed, etc…) will be included in these analyses (i.e. a record that may not be mapped to analysis visit will be also included in the analyses). An individual clinically significant abnormality will be defined according to ICSA criteria Ver2 (Appendix 2).

7.3.9.2 Handling of BLQ (Below the Limit of Quantitation) values

If a value is reported using a non-numeric qualifier (e.g., less than (<) a certain value), the given numeric value will be used in the summarization ignoring the non-numeric qualifier.

7.3.9.3 Handling of missing data

No imputation will be conducted.

7.3.10 Presence of antidrug antibodies

7.3.10.1 Endpoint Derivation

- Between courses analyses

  If multiple measurements occur within the same analysis visit window (Table 7.5), the measurement closest to the target day will be selected. If there are two measurements equidistant from the target day, the later one will be used. However, if positive measurements occur, positive measurements will be selected regardless of the rules above.

7.3.11 Adverse Events

7.3.11.1 Endpoint Derivation

- Bleeding events

  The subjects with bleeding events will be identified by meeting the following criteria in Standardised MedDRA Queries (SMQ):

  - Haemorrhages

- TEAEs on study treatment

  TEAEs on study treatment courses will be analyzed in section 10.2.4 and defined as follows:

  - TEAEs occurred between Course X Day 1 and Course X+1 day -1 (X: study treatment course)

  In other words, for example, if a subject does not receive study treatment at course 3, her/his TEAEs that occurred between course 3 day 1 and 1 day before course 4 day 1 (i.e. the last day of course 3) will not be included in the analysis (section 10.2.4).

- The relatively common TEAEs

  The relatively common TEAEs will be defined as follows:

  - TEAEs occurring in at least two subjects either in the ART-1 dose group or the ART-3 dose group

7.3.12 Change from Baseline

For the continuous variables, change from baseline will be obtained by subtracting the baseline values from the individual post-baseline values. Change from baseline will not be calculated at baseline. The formula below will be used:

- Change from baseline = Post-baseline values – baseline value

7.3.13 Study Treatment Compliance

7.3.13.1 Endpoint Derivation

A subject's study treatment compliance will be defined as follows:

- Study treatment compliance = The number of total doses administered / (The number of L-OHP administered courses × 3) x 100 (%)

7.3.14 Derived Post-baseline Plasma Thrombomodulin Alfa Concentrations

7.3.14.1 Endpoint Derivation

Derived post-baseline plasma thrombomodulin alfa concentrations will be obtained by subtracting the baseline values from the individual post-baseline values, because thrombomodulin alfa is an intravital substance. The formula below will be used:

- Derived post-baseline plasma thrombomodulin alfa concentrations = Post-baseline values – baseline value

7.3.14.2 Handling of BLQ (Below the Limit of Quantitation) values

If plasma thrombomodulin alfa concentration is reported as <5 ng/ml, the value is set to 0.

If derived post-baseline plasma thrombomodulin alfa concentration is < 0, this value is treated as 0.

7.3.15 Partial Dates

Partial dates will be imputed using the following rules:

- If the year and month are known, but the date is missing, the date will be set to the 15th of that month. (For example, XX-Sep-2016 will be imputed as 15-Sep-2016)

8. Study Population

8.1 Disposition of subjects

The numbers of subjects who are screened, are randomized, start administration of study treatment, complete the treatment period, and complete the follow-up period, as well as subjects who withdraw prematurely from the study, will be displayed by treatment group. The reasons for early discontinuation from this study will be summarized.

The numbers and percentages of the FAS, safety population, and PK population relative to the randomized subjects will be summarized by treatment group. The number of subjects excluded from the randomized subjects will be presented by reason. The number and percentage of the PPS relative to the FAS will be summarized by treatment group. The number of subjects excluded from the FAS will be presented by reason.

8.2 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group in the FAS, PPS, and safety population.

Table 8.1 Demographics and baseline characteristics list

Factor		Category levels summarized	Continuous variables summarized
Sex		Male, Female	
Age at first administration of study treatment		<65, 65≤ <50, 50≤ <60, 60≤ <70, 70≤	Yes
Race		Asian, Others	
Height			Yes
Weight		<50, 50≤ <70, 70≤	Yes
BSA		<1.5, 1.5≤	Yes
Tobacco history		Never, Current, Former	
Alcohol consumption		Never, Current, Former	
Average alcohol consumption per day		≥0 unit/day to <2 unit/day, ≥2 unit/day to <4 unit/day, ≥4 unit/day to <6 unit/day, ≥6 unit/day	
Performance Status Score (ECOG)		0, 1, 2, 3, 4	
Anatomical location of the colon cancer		APPENDIX; COLON, ASCENDING; COLON, TRANSVERSE; COLON, DESCENDING;	

		COLON, SIGMOID; RECTOSIGMOID	
Colon cancer stage		I, II, IIIa, IIIb, IV	
Concomitant diseases			
	Diabetes Mellitus	Yes, No	

8.3 Concomitant Medications

The number and percentage of subjects who take the following concomitant medications will be summarized by treatment group in the FAS.

- Prohibited medications (Y, N)
- Restricted medications (Y, N)

Concomitant medications will be any medications administered to the subject after first study treatment.

The number of subjects by reason for restricted medication use (CIPN, AE and others) will also be presented.

8.4 Study Treatment Compliance

Study treatment compliance will be summarized as a continuous variable in the FAS and also presented in categorical terms according to the following categories: 100, 75-100, 50-100.

9. Efficacy Analyses

9.1 CTCAE

The following two types of CTCAEs will be summarized separately for all analyses.

- Motor
- Sensory

9.1.1 Between courses Analyses

9.1.1.1 CTCAE Grade at Each Course

9.1.1.1.1 Main Analysis for CTCAE Grade at Each Course

The number and proportion of subjects by CTCAE grade at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. Missing data will be presented as a missing category. Also, the number of observed subjects (i.e. observed cases) at each analysis visit will be presented.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.1.2 Sensitivity Analyses

To assess the robustness of the main analysis (section 9.1.1.1.1) to missing data, the following sensitivity analyses will be conducted:

[1] Missing CTCAE grade will be imputed by LOCF (Last Observation Carried Forward), and the main analysis (section 9.1.1.1.1) will be repeated at all analysis visits except for EOT and EOS.

[2] Missing CTCAE grade will be imputed by WOCF (Worst Observation Carried Forward), and the main analysis (section 9.1.1.1.1) will be repeated at all analysis visits except for EOT and EOS.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.1.3 Use of an "Efficacy Subset" of Patient Analyses on the PPS

The following analysis will be performed.

[1] The analysis on the PPS will be performed in a manner as described in section 9.1.1.1.1.

9.1.1.1.4 Subset Analyses

The following analysis will be performed.

[1] The analysis on the subset of subjects with cumulative L-OHP dose $\geq$ 510 mg/m^2 will be performed in a manner as described in section 9.1.1.1.1.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.2 CTCAE Grade Categories at Each Course

9.1.1.2.1 Main Analysis for CTCAE Grade Categories at Each Course

The number and proportion of subjects by the following categories at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. Missing grade will be included in grade 2 or higher.

- None or grade 1
- Grade 2 or higher

The treatment difference in the grade 2 or higher proportion and its 95% two-sided exact confidence interval will be calculated. The treatment difference will be derived by subtracting placebo from ART-123. Also, the between-treatment differences (ART-123 vs placebo) will be assessed using Fisher's exact test.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.2.2 Sensitivity Analyses

To assess the robustness of the main analysis (section 9.1.1.2.1) to missing data, the following sensitivity analyses will be conducted:

[1] The number and proportion of subjects by the following categories will be summarized in a manner as described in section 9.1.1.2.1. Missing grade will be included in none or grade 1.

- None or grade 1
- Grade 2 or higher

[2] Missing CTCAE grade will be imputed by LOCF. The number and proportion of subjects by the following categories will be summarized in a manner as described in section 9.1.1.2.1. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be summarized.

- LOCF-imputed none or grade 1
- LOCF-imputed grade 2 or higher

[3] Missing CTCAE grade will be imputed by WOCF. The number and proportion of subjects by the following categories will be summarized in a manner as described in section 9.1.1.2.1. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be summarized.

- WOCF-imputed none or grade 1
- WOCF-imputed grade 2 or higher

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.2.3 Subset Analyses

The following analysis will be performed.

[1] The analysis on the subset of subjects with cumulative L-OHP dose $\geq$ 510 mg/m^2 will be performed in a manner as described in section 9.1.1.2.1 and 9.1.1.2.2.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.3 Cumulative Incidence of CTCAE Grade 2 or higher over each course

9.1.1.3.1 Main Analysis for Cumulative Incidence of CTCAE Grade 2 or higher over each course

The number and proportion with cumulative incidence of grade 2 or higher over baseline, in each course from course 1 to course 12, course 12 completion, during the study treatment and during the study (i.e.: baseline, and from baseline to each course from course 1 to course 12, baseline - course 12 completion, baseline – end of study treatment and baseline - end of study) based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. Once grade 2 or higher is observed in a certain subject, that subject will be categorized as grade 2 or higher in a subsequent analysis visit even if the grade returns to grade 1 or less.

The treatment difference in cumulative incidence of the grade 2 or higher proportion and its 95% two-sided exact confidence interval will be calculated. The treatment difference will be derived by subtracting placebo from ART-123. Also, the between-treatment differences (ART-123 vs placebo) will be assessed using Fisher's exact test.

Missing grade will be analyzed as incidence of grade 2 or higher.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.3.2 Sensitivity Analyses

To assess the robustness of the main analysis (section 9.1.1.3.1) to missing data, the following sensitivity analysis will be conducted:

[1] Missing grade will be analyzed as no incidence of grade 2 or higher, and the main analysis (section 9.1.1.3.1) will be repeated.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.3.3 Subset Analyses

The following analysis will be performed.

[1] The analysis on the subset of subjects with cumulative L-OHP dose $\geq$ 510 mg/m^2 will be performed in a manner as described in section 9.1.1.3.1 and 9.1.1.3.2.

The three types of between courses analyses described in section 7.3.2.1 will be summarized separately.

9.1.1.4 Cumulative Incidence of CTCAE Grade 1 or higher over each course

9.1.1.4.1 Main Analysis for Cumulative Incidence of CTCAE Grade 1 or higher over each course

The number and proportion with cumulative incidence of grade 1 or higher will be summarized in a manner as described in section 9.1.1.3.1.

Once grade 1 or higher is observed in a certain subject, that subject will be categorized as grade 1 or higher in a subsequent analysis visit even if the grade returns to below grade 1.

Missing grade will be analyzed as incidence of grade 1 or higher.

9.1.2 Within courses Analyses

9.1.2.1 CTCAE Grade at Each Course and Day

9.1.2.1.1 Analysis for CTCAE Grade at Each Course and Day

The number and proportion of subjects by CTCAE grade at course 1 day 1, and each day of each course thereafter to course 12 day 43 based on the definition of analysis visit window (Table 7.4) will be summarized by treatment group in the FAS. Missing data will be presented as a missing category. Also, the number of observed subjects (i.e. observed case) at each analysis visit will be presented.

9.1.3 Time-to-event analyses

The following time-to-event analyses will be conducted with all measurements:

- Elapsed time to first incidence of CTCAE grade 2 or higher
- Cumulative L-OHP dose to first incidence of CTCAE grade 2 or higher
- Elapsed time to first incidence of CTCAE grade 1 or higher
- Cumulative L-OHP dose to first incidence of CTCAE grade 1 or higher

The following time-to-event analyses will be conducted with mapped Day 1 measurements based on the definition of analysis visit (Table 7.3):

- Cumulative L-OHP dose to first incidence of CTCAE grade 2 or higher

The Kaplan-Meier method will be used to estimate at risk, the cumulative incidence rate at the following time points in the FAS. The elapsed time or cumulative L-OHP dose of the 25th, 50th, and 75th percentiles and its 95% confidence interval will also be estimated. Graphical displays of the cumulative incidence curves will be presented. Subjects without events or subjects whose status is unknown will be censored at the last assessment date of CTCAE.

Time points

- Elapsed-time
  - Day 30, Day 60, Day 90, Day 120, Day 150, Day 180, Day 210, Day 240
- Cumulative L-OHP dose (mg/m^2)
  - 200, 400, 600, 800, 1020

9.2 DEB-NTC

9.2.1 Between courses analyses

9.2.1.1 DEB-NTC Grade

9.2.1.1.1 Main Analysis for DEB-NTC Grade

The following DEB-NTC endpoints will be analyzed separately.

- Peripheral sensory abnormalities or discomfort when touching things (Grade 0, 1, 2)
- Painless peripheral sensory abnormalities or discomfort under normal conditions (Grade 0, 1, 2)
- Painful peripheral sensory abnormalities or discomfort, functional disorder under normal conditions (Grade 0, 1, 2)
- Functional disorder (Grade 0, 3)

The number and proportion of subjects by grade at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. Missing data will be presented as a missing category. Also, the number of observed subjects (i.e. observed cases) at each analysis visit will be displayed in this summary.

Except for functional disorder analyses, the counts of subjects by symptom areas at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the subjects with grade 1 or higher.

9.2.1.2 DEB-NTC Grade categories

9.2.1.2.1 Main Analysis for DEB-NTC Grade categories

The number and proportion of subjects by the following categories at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. The treatment difference in the grade 2 proportion or the grade 3 proportion and its 95% two-sided exact confidence interval will be calculated. The treatment difference will be derived by subtracting placebo from ART-123. Also, the between-treatment differences (ART-123 vs placebo) will be assessed using Fisher's exact test. Missing grade will be included in grade 2 or grade 3.

- Peripheral sensory abnormalities or discomfort when touching things
- Painless peripheral sensory abnormalities or discomfort under normal conditions
- Painful peripheral sensory abnormalities or discomfort, functional disorder under normal conditions
  - Grade 0 or grade 1
  - Grade 2

- Functional disorder
  - Grade 0
  - Grade 3

9.2.1.2.2 Sensitivity Analyses

To assess the robustness of the main analysis (section 9.2.1.2.1) to missing data, the following sensitivity analyses will be conducted:

[1] The number and proportion of subjects by the following categories will be summarized in a manner as described in section 9.2.1.2.1. Missing grade will be included in grade 0 or grade 1.
- Grade 0 or grade 1/grade 2
- Grade 0/grade 3

[2] Missing DEB-NTC grade will be imputed by LOCF. The number and proportion of subjects by the following categories will be summarized in a manner as described in section 9.2.1.2.1. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be summarized.
- LOCF-imputed grade 0 or grade 1/grade 2
- LOCF-imputed grade 0/grade 3

[3] Missing DEB-NTC grade will be imputed by WOCF. The number and proportion of subjects by the following categories will be summarized in a manner as described in section 9.2.1.2.1. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be summarized.
- WOCF-imputed grade 0 or grade 1/grade 2
- WOCF-imputed grade 0/grade 3

9.2.1.3 Cumulative Incidence of DEB-NTC Grade 2 or Grade 3 over each course

9.2.1.3.1 Main Analysis for Cumulative Incidence of DEB-NTC Grade 2 or Grade 3 over each course

The number and proportion with cumulative incidence of grade 2 or grade 3 over baseline, in each course from course 1 to course 12, course 12 completion, during the study treatment and during the study (i.e.: baseline, and from baseline to each course from course 1 to course 12, baseline - course 12 completion, baseline – end of study treatment, and baseline - end of study) based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. Once grade 2 or grade 3 is observed in a certain subject, that subject will be categorized as grade 2 or grade 3 in a subsequent analysis visit even if the grade returns to grade 0 or 1.

- Peripheral sensory abnormalities or discomfort when touching things
- Painless peripheral sensory abnormalities or discomfort under normal conditions
- Painful peripheral sensory abnormalities or discomfort, functional disorder under normal conditions
  - Cumulative incidence of grade 2 will be summarized

- Functional disorder
  - Cumulative incidence of grade 3 will be summarized

The treatment difference in the cumulative incidence of the grade 2 or grade 3 proportion and its 95% two-sided exact confidence interval will be calculated. The treatment difference will be derived by subtracting placebo from ART-123. Also, the between-treatment differences (ART-123 vs placebo) will be assessed using Fisher's exact test.

Missing grade will be analyzed as incidence of grade 2 (except for functional disorder) or grade 3 (functional disorder).

9.2.1.3.2 Sensitivity Analyses

To assess the robustness of the main analysis (section 9.2.1.3.1) to missing data, the following sensitivity analysis will be conducted:

[1] Missing grade will be analyzed as no incidence of grade 2 or grade 3, and the main analysis (section 9.2.1.3.1) will be repeated.

9.3 FACT/GOG-NTX-12

9.3.1 Between courses Analyses

9.3.1.1 Observed Case Analysis for FACT/GOG-NTX-12 at each course

[1] Overall scores and change from baseline at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. At each analysis visit, only subjects with baseline and post-baseline measurements will be included in the analysis.

The mean treatment difference of change from baseline and its 95% two-sided confidence interval between ART-123 and placebo in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be calculated. Also, the between-treatment differences (ART-123 vs placebo) will be assessed using t-test.

The median treatment difference of change from baseline between ART-123 and placebo in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be calculated.

The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

[2] The individual overall scores plot based on between courses analyses <Worst> will be provided by treatment group.

[3] The sensory score and its change from baseline at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized in a similar way as above. The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

9.3.1.1.1 Use of an "Efficacy Subset" of Patient Analyses on the PPS

The following analyses will be performed.

[1] The analysis on the PPS will be performed in a manner as described in section 9.3.1.1[1].

9.3.1.1.2 Subset Analyses

[1] The analysis on the subset of subjects with cumulative L-OHP dose $\geq$ 510 mg/m^2 will be performed in a manner as described in section 9.3.1.1[1].

The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

9.3.1.2 LOCF Analysis for FACT/GOG-NTX-12 at each course

Missing overall scores will be imputed by LOCF, and this analysis will be performed in a manner described in section 9.3.1.1[1]. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be summarized.

The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

9.3.1.3 WOCF Analysis for FACT/GOG-NTX-12 at each course

Missing overall scores will be imputed by WOCF, and this analysis will be performed in a manner described in section 9.3.1.1[1]. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be summarized.

The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

9.3.1.4 MMRM Analysis for FACT/GOG-NTX-12 at each course

- Overall scores

  Overall scores will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (MMRM). Analyses will include the fixed, categorical effects of study treatment, analysis visit, and study treatment-by-visit interaction. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If this analysis fails to converge, the compound symmetry structure will be tested. If this analysis fails to converge, we will not conduct MMRM or estimate the least-square mean (LS-mean).

  The LS-mean of the treatment group and LS-mean of the treatment difference between ART-123 and placebo at baseline, in each course from course 1 to course 12, and course 12 completion will be calculated with 95% two-sided confidence interval using this model. Significance tests will be based on LS-means. The values at EOT and EOS based on the definition of analysis visit window (Table 7.1) will not be included in this model.

  The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

- Change from baseline

  Change from baseline will be analyzed using MMRM. Analyses will include the fixed, categorical effects of study treatment, analysis visit, and study treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

LS-means of the treatment group and LS-means of treatment difference will be estimated in a similar way, as above.

The two types of between courses analyses described in section 7.3.4.1 will be summarized separately.

9.3.1.5 Duration-Adjusted Average Change analysis for FACT/GOG-NTX-12

The Duration-Adjusted Average Change (DAAC) as continuous variables will be computed using overall scores based on the definition of analysis visit (Table 7.1 or Table 7.3) and will be summarized by treatment group in the FAS. The treatment difference and its 95% two-sided confidence interval will be calculated. The treatment difference will be derived by subtracting placebo from ART-123 (DAAC in ART-123 – DAAC in placebo).

9.3.2 Within courses Analyses

9.3.2.1 Observed Case Analysis for FACT/GOG-NTX-12 at each course and day

Overall scores and change from baseline at course 1 day 1, and each day of each course thereafter to course 12 day 43 based on the definition of analysis visit window (Table 7.4) will be summarized by treatment group in the FAS. Baseline values will be set to the day 1 value of each course, respectively.

Change from baseline will be calculated using the corresponding course baseline value (i.e.: change from baseline at course 3 = day 8 value at course 3 – day 1 value at course 3).

9.3.3 Time-to-event analyses

The following time-to-event analyses will be conducted with all measurements:

- Elapsed time to first $\Delta \leq -4$
- Cumulative L-OHP dose to first ≤ -4
- Elapsed time to first ≤ -8
- Cumulative L-OHP dose to first ≤ -8
- Elapsed time to first $\Delta \leq -12$
- Cumulative L-OHP dose to first ≤ -12

Δ is change from baseline based on analysis visit (Table 7.1)

The following time-to-event analyses will be conducted with mapped Day 1 measurements based on the definition of analysis visit (Table 7.3):

- Cumulative L-OHP dose to first ≤ -4
- Cumulative L-OHP dose to first ≤ -8
- Cumulative L-OHP dose to first ≤ -12

Δ is change from course 1 day 1 based on analysis visit (Table 7.3)

Kaplan-Meier estimation will be performed in a manner as described in section 9.1.3.

9.4 FACT-G

9.4.1 Between courses Analyses

9.4.1.1 Observed Case analysis for FACT-G at each course

Overall scores and change from baseline at baseline, course 1, course 5, course 9, course 12, course 12 completion, EOT and EOS based on the definitions of the analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. At each analysis visit, only subjects with baseline and post-baseline measurements will be included in the analysis.

Also, PWB score, SWB score, EWB score, and FWB score and their corresponding changes from baseline will be summarized.

9.5 NRS (Pain)

The following endpoints will be analyzed separately.

- Hand
- Foot
- Either worse

9.5.1 Between courses Analyses

9.5.1.1 Analysis for NRS at each course

The number and proportion of subjects by the following categories at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. Missing data will be presented as a missing category. Also, the number of observed subjects (i.e. observed cases) at each analysis visit will be displayed in this summary.

- 0
- 1≤

9.5.1.2 Observed Case analysis for NRS at each course

NRS and change from baseline at baseline, in each course from course 1 to course 12, course 12 completion, EOT, and EOS based on the definition of analysis visit window (Table 7.1) will be summarized by treatment group in the FAS. At each analysis visit, only subjects with baseline and post-baseline measurements will be included in the analysis.

9.5.1.3 MMRM analysis For NRS at each course

NRS will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (MMRM) in a similar way, as described in section 9.3.1.4.

9.5.2 Within courses Analyses

9.5.2.1 Analysis for NRS at each course and day

The number and proportion of subjects by the following categories at course 1 day 1, course 1 day 8, and each day of each course thereafter to course 12 day 43 based on the definition of analysis visit window (Table 7.5) will be summarized by treatment group in the FAS. Missing data will be presented as a missing category. Also, the number of observed subjects (i.e. observed cases) at each analysis visit will be displayed in this summary.

- 0
- 1≤

9.5.2.2 Observed Case Analysis for NRS at each course and day

NRS and change from baseline at course 1 day 1, course 1 day 8, and each day of each thereafter to course 12 day 43 based on the definition of analysis visit window (Table 7.5) will be summarized by treatment group in the FAS. Baseline values will be set to the day 1 value of each course, respectively.

Change from baseline will be calculated using the corresponding course baseline values (i.e.: change from baseline at course 3 = day 8 value at course 3 – day 1 value at course 3).

9.6 L-OHP-related analyses

9.6.1 Cumulative L-OHP dose

Cumulative L-OHP doses (mg/m^2) during the study as continuous variables will be summarized by treatment group in the FAS.

9.6.2 L-OHP RDI

L-OHP RDI during the study as continuous variables will be summarized by treatment group in the FAS.

9.6.3 L-OHP suspension/reduction at each course

The number and proportion of subjects by L-OHP suspension and L-OHP dose reduction at each course will be summarized by treatment group in the FAS.

The number and proportion of subjects by reason for L-OHP suspension (CIPN, Non-CIPN) or L-OHP dose reduction (CIPN, Non-CIPN) will be presented.

9.6.4 L-OHP discontinuation during the study

The number and proportion of subjects by L-OHP discontinuation during the study will be summarized by treatment group in the FAS. Also, the number and proportion of subjects by reason for L-OHP discontinuation (CIPN, Non-CIPN) will also be presented.

9.6.5 Time-to-event analyses

The following time-to-event analyses will be conducted.

- Time to L-OHP discontinuation caused by CIPN
- Cumulative L-OHP dose to L-OHP discontinuation caused by CIPN
- Time to first L-OHP discontinuation/suspension caused by CIPN
- Cumulative L-OHP dose to first L-OHP discontinuation/suspension caused by CIPN
- Time to first L-OHP discontinuation/suspension/dose reduction caused by CIPN
- Cumulative L-OHP dose to first L-OHP discontinuation/suspension/dose reduction caused by CIPN

Kaplan-Meier estimation will be performed in a manner as described in section 9.1.3. The time to first event or censoring time will be as defined in section 7.

9.7 The relationship between CTCAE and FACT/GOG-NTX12

9.7.1 Between courses analyses

9.7.1.1 Observed Case Analysis for FACT/GOG-NTX-12 by CTCAE grade

FACT/GOG-NTX12 overall scores by CTCAE (Sensory) grade at course 3, course 6, course 9, course 12, and course 12 completion based on the definition of analysis visit window (Table 7.1) will be

summarized by overall and treatment group in the FAS. At each analysis visit, only subjects with baseline and post-baseline measurements will be included in the analysis.

10. Safety Analyses

10.1 Extent of Exposure

The number and percentage of subjects by counts of total dose administered of study treatment (1-3, 4-6, …, 34-36) will be summarized by treatment group in the safety population. Also, the counts of total dose administered will be summarized by treatment group in the safety population.

10.2 Adverse Events

Adverse events will be categorized and presented by primary system organ class (SOC), preferred term (PT), causality, and severity in the safety population. The preferred term will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent adverse event (TEAE) is defined as any AE following exposure to study treatment.

All safety summaries will be done by treatment group in the safety population.

10.2.1 Overall summary of safety

An overall summary of TEAEs will be provided to summarize the following information:

- subjects with TEAEs
- subjects with study treatment-related TEAEs
- subjects with serious TEAEs
- subjects with study treatment-related serious TEAEs
- subjects with bleeding TEAEs

The number and percentage of subjects will be summarized by treatment group. The percentage difference, subtracting placebo from ART-123 (ART-123 - Placebo), and the associated 95% two-sided exact confidence interval will be calculated.

Also, the number and percentage of subjects with TEAEs by severity (grade 1, grade 2, grade 3, grade 4, grade 2 or higher, grade 3 or higher) will be summarized by treatment group. Subjects will be classified under the maximum severity experienced. That is to say, if a subject experiences an AE with a grade 1 and grade 2, that subject will be counted in grade 2 only.

10.2.2 Summary of TEAEs and Study treatment-related TEAEs by primary SOC and PT

The number and percentage of subjects with TEAEs and study treatment-related TEAEs by primary SOC and PT will be summarized.

10.2.3 Summary of TEAEs by primary SOC, PT, and Severity

The number and percentage of subjects with TEAEs by primary SOC, PT, and severity will be summarized. Subjects will be classified for each PT under the maximum severity experienced. That is to say, if a subject experiences the same AE with grade 1 and grade 2, that subject will be counted in grade 2 only.

10.2.4 Summary of TEAEs by primary SOC, PT, and time of onset

The TEAEs on study treatment courses will be analyzed.

The number and percentage of subjects with TEAEs by primary SOC, PT, and time of onset will be summarized. Subjects will be classified for each preferred term and each onset time. That is to say, if a subject develops the same AE on Day 1 pre and Day 1 post, that subject will be counted at both onset times.

The count of courses with TEAEs by primary SOC, PT, and time of onset will be summarized. When the same AEs develop on multiple courses, they are counted multiple times. That is to say, if a subject develops the same AE on Day 1 pre at courses 1 and 3, it will be counted twice.

Time of onset

- Day 1 pre
- Day 1 post-Day 3
- Day 4-Day 7
- Day 8-

10.2.5 Summary of Relatively Common TEAEs by primary SOC and PT

The number and percentage of subjects with relatively common TEAEs by primary SOC and PT will be summarized.

10.2.6 Summary of bleeding TEAEs

10.2.6.1 Summary of bleeding TEAEs by primary SOC and PT

The number and percentage of subjects with bleeding TEAEs by primary SOC and PT will be summarized.

10.2.6.2 Summary of bleeding TEAEs by primary SOC, PT, and Severity

The number and percentage of subjects with bleeding TEAEs by primary SOC, PT, and severity will be summarized. Subjects will be classified for each PT under the maximum severity experienced.

10.2.6.3 Summary of bleeding TEAEs by primary SOC, PT, and time of onset

The number and percentage of subjects with bleeding TEAEs by primary SOC, PT, and time of onset will be summarized. This analysis will be conducted in a similar way as section 10.2.4.

10.2.7 Summary of serious TEAEs by primary SOC, PT

The number and percentage of subjects with serious TEAEs by primary SOC and PT will be summarized.

10.3 Clinical laboratory tests

10.3.1 Between courses Analyses

The following clinical laboratory tests at baseline, on day 1 of each course from course 2 to 12, course 12 day 15, course 12 day 43, EOT, and EOS based on the definition of analysis visit window (Table 7.5) will be summarized by treatment group in the safety population.

Clinical laboratory tests

- Erythrocytes, Hemoglobin, Hematocrit, Leukocytes, Leukocytes (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), Platelets
- Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Lactate Dehydrogenase, Bilirubin, Protein, Albumin, Blood Urea Nitrogen, Creatinine, Glucose, Urate, Sodium, Potassium, Chloride
- Urine Protein, Urine Glucose, Urine Occult Blood
- Prothrombin Intl. Normalized Ratio, Activated Partial Thromboplastin Time, Fibrinogen

10.3.2 Individual Clinically Significant Abnormality (ICSA) Analyses

The number and percentage of subjects with clinically significant abnormalities will be summarized by treatment group in the safety population. The ICSA analyses will not be conducted by analysis visit.

10.4 Vital signs

10.4.1 Between courses Analyses

The following vital signs at baseline, on day 1 of each course from course 2 to 12, course 12 day 15, course 12 day 43, EOT, and EOS based on the definition of analysis visit window (Table 7.5) will be summarized by treatment group in the safety population.

Vital Signs

- Body temperature, systolic blood pressure, diastolic blood pressure, pulse rate

10.5 Presence of antidrug antibodies

The number and percentage of subjects with the presence of antidrug antibodies at baseline and EOS based on analysis visit will be summarized by treatment group in the safety population.

11. PK Analysis

Derived plasma thrombomodulin alfa concentrations at course 1 day 1 (Pre dose), course 1 day 1 (immediately after administration), course 1 day 1 (30-120 minutes postdose), day 2 (immediately after administration), day 2 (30-120 minutes postdose), day 3 (immediately after administration), and day 3 (30-120 minutes postdose) will be summarized in the PK population.

Individual derived plasma thrombomodulin alfa concentrations (normal scale) will be provided.