Title: A Phase 1, Open-label Study of Niraparib as Single Agent in Patients With Advanced Solid Tumors

NCT Number: NCT03497429

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Niraparib-1001

A Phase 1, Open-label Study of Niraparib as Single Agent in Patients With Advanced Solid Tumors

PHASE 1

Version: 2nd

Date: 03 April 2019

Prepared by:

PPD

Based on:

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloblastic leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC24	area under the plasma concentration-time curve
BRCA	breast cancer (gene)
C24	plasma concentration at 24 hrs after last dose
Cmax	maximum observed concentration
Cmin	minimum observed concentration at multiple dose
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	(United States) Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HRD	homologous recombination deficiency
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall response rate
R(AUC24)	accumulation ratio based on AUC24
R(Cmax)	accumulation ratio based on C_{max}
Tmax	time of first occurrence of C_{max}
TEAE	treatment-emergent adverse event

4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the safety and tolerability of niraparib administered orally QD to Japanese patients with advanced solid tumors.

4.2 Secondary Objectives

To evaluate the pharmacokinetics of niraparib administered orally QD to Japanese patients with advanced solid tumors.

4.3 Additional Objectives

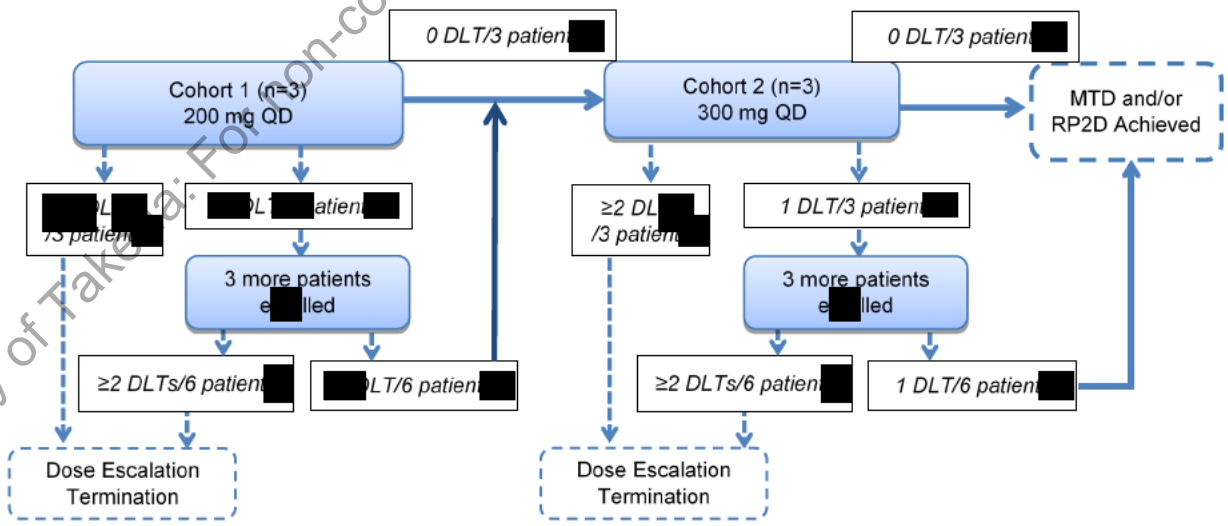
To evaluate the anti-tumor activity of niraparib administered orally QD to Japanese patients with advanced solid tumors

4.4 Study Design

This study is a phase 1, open-label, non-randomized, cohort-based, dose-escalation study to establish the safety and tolerability of niraparib in Japanese patients with advanced solid tumors. A total of 6 to 12 patients are treated with 200 mg QD (Cohort 1) or 300 mg QD (Cohort 2).

Niraparib will be administered QD, continuously for 21 days in Cycle 1. There will be no drug holiday. Niraparib will be administered QD, continuously in 21-day cycles from Cycle 2 onward. Episodes of DLT within the first 21 days of Cycle 1 are used to decide whether to escalate the dose. Subjects will receive niraparib under inpatient hospitalization (hospitalization from Cycle 1 Day 1 to Cycle 1 Day 8 will be mandatory) and monitored for DLTs. Escalation to the next dose level does not occur until the results of safety measurements from Cycle 1 have been obtained and reviewed. The overview of study design is shown in Figure 4.a.

Figure 4.a Schematic of Study Design



5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

- The number and percentage of subjects with DLTs during Cycle 1.
- The number and percentage of subjects with TEAEs.
- The number and percentage of subjects with Grade 3 or higher TEAEs.
- The number and percentage of subjects with serious TEAEs.
- The number and percentage of subjects who discontinued the study drug because of TEAEs.

5.1.2 Secondary Endpoints

- PK parameters of niraparib on Cycle 1 Day 1 and Day 21: C_{max}, T_{max} and AUC_{24}.

5.1.3 Additional Endpoints

- Overall response rate (ORR) (complete response [CR] + partial response [PR]) as measured by the RECIST guidelines.
- Laboratory safety assessments, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms (ECGs) and vital signs.
- PK parameters of a metabolite, M1, on Cycle 1 Day 1 and Day 21: C_{max}, T_{max} and AUC_{24}.

6.0 DETERMINATION OF SAMPLE SIZE

Expected number of subjects: 6 to 12 patients (3 to 6 patients per Cohort).

This study will use a 3+3 design. In the study, 2 ascending dose cohorts (3 to 6 patients per Cohort) are planned and approximately 6 to 12 DLT evaluable patients will be enrolled.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): Adverse events that occur after administration of the first dose of study drug and through 28 days after the last dose of study drug.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug.
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Dose: Initial dose level of 200 mg for Niraparib, Initial dose level of 300 mg for Niraparib.
- Group: Initial dose level of 200 mg for Niraparib, Initial dose level of 300 mg for Niraparib.
- Coefficient of variation (CV) (%): Standard deviation / mean * 100.

7.1.2 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (ie, date of first dose [Day 1]), if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

All evaluable data (ie, non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

Table 7.a Visit Window of Clinical Laboratory Test

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Cycle 1, Day 1(Predose)	Study Day:	1	-7 to 1
Cycle 1, Day 8	Study Day:	8	5 to 11
Cycle 1, Day 15	Study Day:	15	12 to 18
Cycle 2, Day 1	Study Day:	22	19 to 25
Cycle 2, Day 8	Study Day:	29	26 to 32
Cycle 2, Day 15	Study Day:	36	33 to 39
Cycle (n) (Cycle 3 and thereafter), Day 1	Study Day:	21(n - 1) + 1	21(n - 1) - 2 to 21(n - 1) + 4
Cycle (n) (Cycle 3 and thereafter), Day 8	Study Day:	21(n - 1) + 8	21(n - 1) + 5 to 21(n - 1) + 11

7.1.3 Conventions for Missing Adverse Event Dates

Not applicable.

7.1.4 Conventions for Missing Concomitant Medication Dates

Not applicable.

7.2 Analysis Sets

- Safety analysis set:
  Patients who receive at least 1 dose of study drug.
- Pharmacokinetic analysis set:
  Patients with sufficient dosing and PK measurement data to reliably estimate 1 or more PK parameters.
- DLT-evaluable set:
  Patients who have received at least 80% of planned doses of niraparib in Cycle 1 (for at least 17 days out of 21 days) unless interrupted by study drug-related toxicities and have sufficient follow-up data considered by sponsor and investigator to determine whether DLT occurred.
- Response-evaluable set:
  Patients who receive at least 1 dose of study drug, have sites of measurable disease at baseline, and have at least 1 postbaseline disease assessment.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Date First Subject Signed Informed Consent Form

Date of Data Cutoff

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Method(s):

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variable(s):

Age (years)

Gender [Male, Female]

Analytical Method(s):

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Eligibility Status

[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible

[Death, Adverse Event, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Lost to Follow-up, Screen Failure, Other]

Analytical Method(s):

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Disposition of Subjects

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Study Drug Administration Status

[Ongoing, Discontinued]

Reason for Discontinuation of Study Drug Administration

[Death, Adverse Event, Protocol Deviation, Progressive Disease, Study Terminated by Sponsor, Pregnancy, Withdrawal by Subject, Lost to Follow-up, Other]

Analytical Method(s):

(1) Disposition of Subjects

Frequency distributions will be provided by dose and overall. When calculating percentages for the reasons for discontinuation, the total number of subjects who discontinued treatment will be used as the denominator.

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s):

(1) Protocol Deviations

Frequency distribution will be provided by dose and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.5.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Safety Analysis Set	[Included]
Pharmacokinetic Analysis Set	[Included]
DLT-evaluable Set	[Included]
Response-evaluable Set	[Included]

Analytical Method(s):

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided by dose for (1), and by dose and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Age (years)

Gender [Male, Female]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

ECOG performance status [0, 1, 2, 3, 4]

Diagnosis [Adrenal cancer, Breast cancer, Cervical cancer, Colorectal cancer, Endometrial cancer, Gastric cancer, Head and neck cancer, Liver cancer, Malignant melanoma, Non small cell lung cancer, Ovarian cancer, Pancreatic cancer, Prostatic cancer, Small cell lung cancer, Other]

Prior Surgery/Procedure [Yes, No]

Prior Radiation Therapy [Yes, No]

BRCA1 Mutant [Yes, No, Unknown]

BRCA2 Mutant [Yes, No, Unknown]

Analytical Method(s):

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by dose and overall.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided by dose and overall. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Prior Anticancer Drug Therapy

Concomitant Medications

Analytical Methods:

(1) Prior Anticancer Therapy by Preferred Medication Name.

(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name.

(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name.

Frequency distributions will be provided by dose and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set:

DLT-evaluable Set

Safety Analysis Set

Analysis Variable(s):

Treatment Compliance at Cycle1 (%) [Min<= - <80, 80<= - <=Max]

Days on Treatment

Number of Cycles

Analytical Method(s):

(1) Study Drug Exposure and Compliance

Frequency distributions and descriptive statistics for continuous variables will be provided by dose and overall.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Analysis Set:

Response-Evaluable Analysis Set

Analysis Variables:

ORR

Overall Response [CR, PR, SD, PD, NE]

Analytical Methods:

(1) Primary Analysis

For ORR, point estimate and the 2-sided 95% exact CI will be provided by dose.

(2) Summary of Overall Response

For overall response, frequency distributions will be provided by dose.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results will not be used for estimations.

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Plasma Concentrations of Niraparib and M1

Visit:

Cycle 1 Day 1/Day 21: Predose, 1, 1.5, 2, 3, 4, 6, 8, 10, 24* hours postdose

Cycle 1 Day 1/Day 3/Day 5/Day 8/Day 15 and Day 21: Predose

* Corresponding to predose at Cycle 1 Day 2 and Cycle 2 Day 1 for Cycle 1 Day 1 and Cycle 1 Day 21, respectively.

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics will be provided by visit.

(2) Mean and Standard Deviation Plot of Plasma Concentrations on Cycle 1 Day 1 and Cycle 1 Day 21

Mean and standard deviation will be plotted. Relative nominal time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 1 Day 21, separately. The vertical axis will be a normal scale.

(3) Mean Plot of Plasma Concentrations on Cycle 1 Day 1 and Cycle 1 Day 21

Mean will be plotted. Relative nominal time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 1 Day 21, separately. The vertical axis will be a common logarithmic scale.

(4) Plot of Individual Plasma Concentrations on Cycle 1 Day 1 and Cycle 1 Day 21

Individual plasma concentrations will be plotted. Relative actual time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 1 Day 21, separately. The vertical axis will be normal scale.

7.9.1.2 Pharmacokinetic Parameters

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variable(s):

Pharmacokinetic parameters of Niraparib and M1

Cycle 1 Day 1

Cmax, Tmax, AUC24

Cycle 1 Day 21

Cmax, Tmax, AUC24, Cmin, R(AUC24), R(Cmax)

Visit:

Cycle 1 Day 1 and Cycle 1 Day 21

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Pharmacokinetic Parameters by Visit

For Tmax, descriptive statistics will be provided. For other parameters, descriptive statistics, geometric mean, and CV will be provided.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

In this study, safety will be evaluated as the primary endpoint.

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

TEAE

Categories:

Relationship to Study Drug [Related, Not Related]

Analytical Method(s):

The following summaries will be provided by dose.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects).
3) Grade 3 or higher Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
4) Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
5) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects).
6) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
7) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects).
8) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects).
9) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects).

TEAEs will be counted according to the rules below. Percentages will be based on the number of subjects in the safety analysis set.

Number of subjects

- Summaries for 2) and 7)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summaries other than 2) and 7)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.11.1.2 Frequency of Subjects with DLTs during Cycle 1

Analysis Set:

DLT-evaluable Set

Analysis Variable(s):

DLTs during Cycle 1

Analytical Method(s):

The number and percentage of Subjects with DLTs will be provided by dose.

7.11.1.3 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

TEAE

Categories:

Toxicity Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Method(s):

The following summaries will be provided using frequency distribution by dose.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(2) Treatment-Emergent Adverse Events by System Organ Class.

(3) Treatment-Emergent Adverse Events by Preferred Term.

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(5) Toxicity Grade of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(6) Toxicity Grade of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term.

(7) Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term (number of events, number and percentage of subjects).

(8) Treatment-Emergent Adverse Events Leading to Study Drug Dose Interruption by System Organ Class and Preferred Term (number of events, number and percentage of subjects).

(9) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (number of events, number and percentage of subjects).

(10) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

The frequency distribution will be provided according to the rules below. Percentages will be based on the number of subjects in the safety analysis set.

Number of subjects

- Summary tables other than (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum toxicity grade.

7.11.1.4 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

PTE

Analytical Method(s):

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Hematology

Erythrocytes, Hemoglobin, Hematocrit, Platelet Count, Leukocytes with Differentials (ANC, Eosinophils Count, Basophils Count, Absolute Lymphocytes Count, Monocyte Count), MCV

Serum Chemistry

Amylase, Protein (Total Protein), Albumin, ALP, Urea Nitrogen, Creatinine, Magnesium, Total Bilirubin, Sodium, Potassium, Chloride, Calcium, Bicarbonate, Inorganic Phosphate, AST, ALT, LDH, GGT, Glucose (fasted)

Categories:

Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit:

Cycle 1: Day 1(Predose), Day 8, Day 15

Cycle 2: Day 1, Day 8, Day 15

Cycle 3 and Thereafter: Day 1, Day 8

Analytical Method(s):

For each variables other than Platelets Count, The following summary (3) will be provided by dose.

For Platelets Count, The following summaries (1) ~ (3) will be provided by dose.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade for laboratory abnormalities will be provided.

Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

For each laboratory test, the laboratory values will be classified as “Low”, “Normal” or “High” relative to the normal reference range. The shift tables will be based on these classifications.

7.11.2.2 Urinalysis

Not applicable.

7.11.3 Vital Signs and Weight

Not applicable.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

From the SAP version 1.0, the following parts were updated. In section 7.1.2, the visit window of clinical laboratory test was modified as below.

Before the change

Section 7.1.2 Definition of Study Visit Windows

Table 7.a Visit Window of Clinical Laboratory Test

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Cycle 1, Day 1(Predose)	Study Day:	1	-3 to 1
Cycle 1, Day 8	Study Day:	8	5 to 11
Cycle 1, Day 15	Study Day:	15	12 to 18
Cycle 2, Day 1	Study Day:	22	19 to 25
Cycle 2, Day 8	Study Day:	29	26 to 32
Cycle 2, Day 15	Study Day:	36	33 to 39
Cycle (n) (Cycle 3 and thereafter), Day 1	Study Day:	21(n - 1) + 1	21(n - 1) - 2 to 21(n - 1) + 4
Cycle (n) (Cycle 3 and thereafter), Day 8	Study Day:	21(n - 1) + 8	21(n - 1) + 5 to 21(n - 1) + 11

After the change

Section 7.1.2 Definition of Study Visit Windows

Table 7.a Visit Window of Clinical Laboratory Test

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day
Cycle 1, Day 1(Predose)	Study Day:	1	-7 to 1
Cycle 1, Day 8	Study Day:	8	5 to 11
Cycle 1, Day 15	Study Day:	15	12 to 18
Cycle 2, Day 1	Study Day:	22	19 to 25
Cycle 2, Day 8	Study Day:	29	26 to 32
Cycle 2, Day 15	Study Day:	36	33 to 39
Cycle (n) (Cycle 3 and thereafter), Day 1	Study Day:	21(n - 1) + 1	21(n - 1) - 2 to 21(n - 1) + 4
Cycle (n) (Cycle 3 and thereafter), Day 8	Study Day:	21(n - 1) + 8	21(n - 1) + 5 to 21(n - 1) + 11

Reason for the change

Cycle 1 Day 1 (Predose) Time Interval was modified to include the results of pre-treatment test of Cycle 1 Day 1 in accord with the protocol.

8.0 REFERENCES

Not applicable.