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

NCT Number: NCT03497429

Protocol Approve Date: 18-JAN-2018

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PROTOCOL

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

Sponsor:	Takeda Pharmaceutical Company Limited. 4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645		
Study Number:	Niraparib-1001		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Niraparib (MK-4827)		
Date:	18 January 2018 (English translation: 16 March 2018)	**Version/Amendment Number:**	Initial version

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	See Section 10.0.
Medical Monitor (medical advice on protocol and compound)	See Protocol Annex

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

Date

Program Clinical Lead (or designee)
Study Clinical Science Lead (or designee)

PPD

Date

Statistician
Biostatistics Lead

PPD

Date

Clinical Pharmacology Lead

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Pharmaceutical Company, Ltd.</td><td colspan="2">Compound:
Niraparib (MK-4827)</td></tr>
<tr><td colspan="2">Title of Protocol: A Phase 1, Open-label Study of Niraparib as Single Agent in Patients With Advanced Solid Tumors</td><td>IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td colspan="2">Study Number: Niraparib-1001</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="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 once daily (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 dose-limiting toxicity (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.
Dose-escalation will proceed according to a 3+3 design. The initial niraparib dose will be 200 mg QD (Cohort 1) and will be escalated to 300 mg QD (Cohort 2), provided that the safety and tolerability of the 200 mg dose have been demonstrated.</td></tr>
<tr><td colspan="4">Primary Objective:
To evaluate the safety and tolerability of niraparib administered orally QD to Japanese patients with advanced solid tumors.</td></tr>
<tr><td colspan="4">Secondary Objective:
To evaluate the pharmacokinetics of niraparib administered orally QD to Japanese patients with advanced solid tumors.</td></tr>
<tr><td colspan="4">Subject Population:
Japanese patients with locally advanced and/or metastatic solid tumors who have failed standard therapy or for whom no standard therapy exists.</td></tr>
<tr><td colspan="2">Number of Subjects:
6 to 12 patients (3 to 6 patients per Cohort)</td><td colspan="2">Number of Sites:
1 site in Japan</td></tr>
<tr><td colspan="2">Dose Level(s):
Niraparib will be administered QD, given continuously in 21-day cycles.
The initial niraparib dose will be 200 mg QD (Cohort 1) and will escalate to 300 mg QD (Cohort 2), provided that the safety and tolerability of the 200 mg dose has been demonstrated.</td><td colspan="2">Route of Administration:
Oral</td></tr>
<tr><td colspan="2">Duration of Treatment:
Treatment will continue until disease progression (PD), unacceptable toxicities, or withdrawal due to other reasons.</td><td colspan="2">Period of Evaluation:
It is anticipated that this study will last for approximately 16 months [from first patient in (FPI) to last patient last visit (LPLV)].
Subjects will be followed for 28 days after the last dose of</td></tr>
</table>

	niraparib.

Main Criteria for Inclusion:

1. Japanese male or female patients aged 20 years or older on the day of signing informed consent.
2. Patients must have a cytologically- or histologically-confirmed metastatic or locally advanced solid tumor and have failed or progressed after standard therapy, or for which standard therapy does not exist in the opinion of the investigator.
3. Patients must have Performance Status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.
4. Patients must have adequate organ function as indicated by the following laboratory values:
   a. Hematology
      – Absolute neutrophil count: ≥1500/μL
      – Platelet count: ≥100,000/μL
      – Hemoglobin: ≥9 g/dL
   b. Kidney
      – Serum creatinine: ≤1.5 × institutional upper limit of normal (ULN), OR creatinine clearance of ≥50 mL/min (as calculated using the Cockcroft Gault equation or measured using 24-hour urine creatinine clearance) for patients with creatinine levels ≥1.5 × institutional ULN.
   c. Liver
      – Total bilirubin in serum: ≤1.5 × ULN (except in patients with Gilbert's syndrome). Patients with Gilbert's syndrome may be enrolled if the patient's direct bilirubin is ≤1.5 ×ULN of the direct bilirubin.
      – AST and ALT: ≤2.5 × ULN OR ≤5 × ULN if patients have liver metastases.
   d. Coagulation (does not pertain to patients receiving anticoagulants)
      – Prothrombin time (PT): ≤1.2 × ULN
      – Activated partial thromboplastin time (aPTT): ≤1.2 × ULN
5. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

   Male patients, even if surgically sterilized (ie, vasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug. If the female partner of a male subject is of child bearing potential, it should also be advised to use a highly effective method of contraception, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
6. Voluntary written consent must be given before performance of any study related procedure not part of

standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Main Criteria for Exclusion:

1. Patient who have received chemotherapy, radiotherapy, hormonal or biological therapy within 14 days (within 28 days for anticancer monoclonal antibody, within 42 days for nitrosoureas or mitomycin C) prior to Cycle 1 Day 1. If the patient has residual toxicity from prior chemotherapy treatment, such toxicity must be ≤Grade 1 (NOTE: patients with Grade 2 alopecia may qualify for this study). If bevacizumab had been used in the past, all bevacizumab-related toxicities must have resolved. Patients with prostate cancer may have been treated with luteinizing hormone-releasing hormone (LH-RH) analogs.
2. Patients who received a known or putative poly (ADP-ribose) polymerase (PARP) inhibitor or other drugs that may inhibit the PARP, either as part of a clinical trial or as standard of care.
3. Patients who initiated bisphosphonate therapy or are adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1. Patients on a stable bisphosphonate regimen are eligible and may continue the treatment.
4. Treatment with any investigational products within 28 days or 5 half-lives (whichever was longer) before Cycle 1 Day 1.
5. Patients who have symptomatic ascites or a symptomatic pleural effusion. A patient who is treated and clinically stable for these conditions is eligible.
6. Patients with a known primary central nervous system (CNS) tumor.
7. Patients with known CNS metastases and/or carcinomatous meningitis are excluded. However, patients with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for 30 days prior to Cycle 1 Day 1 defined as: (1) no evidence of new or enlarging CNS metastases, (2) off steroids, or (3) on a stable dose and administration of steroids.
8. Patients who have a hypersensitivity to the components of the study drugs or their analogs.
9. Patients who are considered to be at high medical risk due to a serious, uncontrolled disease, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days prior to Cycle 1 Day 1) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, or any psychiatric disorder that prohibits obtaining informed consent.
10. Patients who have a history or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient's participation throughout the study period, or study participation is not in the best interest of the patient.
11. Known gastrointestinal (GI) disease or GI surgery that could interfere with the GI absorption of study drug, such as difficulty swallowing capsules and total gastrectomy.
12. Patients who have a psychiatric disorder that may interfere with the conduct of the trial.
13. Patient is, at the time of signing informed consent, a regular user (including “recreational use”) of any illicit drugs or had a recent history (within the past year) of drug or alcohol abuse.
14. Patients who are pregnant or breast-feeding, or expecting to conceive or be a father of children within the planned duration of the study.
    NOTE: If a breast-feeding woman discontinue breast-feeding, she may be enrolled in the study.
15. Known HIV positive.
16. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.
    NOTE: Patients who are positive for hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- The number and percentage of subjects with DLTs during Cycle 1.
- The number and percentage of subjects with treatment-emergent adverse events (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.

Secondary Endpoints:

- Pharmacokinetic (PK) parameters of niraparib on Cycle 1 Day 1 and Day 21: maximum observed concentration (C_{max}), time of first occurrence of C_{max} (T_{max}) and area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24})

Additional Endpoints:

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

Statistical Considerations:

The number of cases and incidence of DLTs during Cycle 1 will be tabulated using DLT-evaluable set.

Adverse events (AEs) will be tabulated by dose level using the safety analysis set for TEAEs, drug-related TEAEs, Grade 3 or higher TEAEs, Grade 3 or higher drug-related TEAEs, serious TEAEs and TEAEs leading to drug discontinuation.

Summary statistics will be provided by dose levels using the PK analysis set for pharmacokinetic parameters including AUC, C_{max}, and T_{max} on niraparib and metabolite M1.

Sample Size Justification:

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.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the protocol annex. The identified vendors in the protocol annex for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Clinical Study Report Signatory Investigator's Responsibilities

Takeda will select a signatory for the clinical study report (CSR) from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory investigator will be required to review and sign the CSR and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
AML	acute myeloblastic leukemia
aPTT	activated partial thromboplastin time
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
BRCA	breast cancer gene
C_{max}	maximum observed concentration
CBC	complete blood cell count
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	(United States) Food and Drug Administration
FPI	first patient in
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
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
HRD	homologous recombination deficiency
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	institutional review board
ITT	intent-to-treat
LPLV	last patient last visit
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate

PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PBMC	peripheral blood mononuclear cells
PD	progressive disease (disease progression)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PR	partial response
PT	prothrombin time
QD	once daily
RP2D	recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time of first occurrence of C_{max}
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal disposition phase half-life
ULN	upper limit of normal

4.0 INTRODUCTION

4.1 Background

Niraparib is an orally available, potent, and highly selective poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) -1 and -2 inhibitor. The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway, as a sensitizing agent in combination with cytotoxic agents and radiotherapy, and in combination with immune-oncology biologics.

PARP-1 and -2 are zinc-finger DNA-binding enzymes that detect damaged DNA and promote DNA repair. PARP detects DNA damage and converts it into intracellular signals that activate the base excision repair (BER) pathway. This pathway is particularly important in cells that are deficient in a second cellular mechanism for high-fidelity DNA repair, homologous recombination. Homologous recombination deficiency (HRD) is generally induced by inactivation of genes such as breast cancer gene 1 (BRCA1), BRCA2, ataxia telangiectasia mutated (ATM) and others. Therefore, tumors with a deficiency in the homologous recombination DNA repair pathway are particularly sensitive to PARP inhibitors [1], a situation known as synthetic lethality.

Clinical studies have shown that PARP inhibitors have antitumor activity in patients with certain types of cancer, including but not limited to those with defined BRCA mutations[2]-[5]. BRCA1 and BRCA2 mutations are found in the majority of patients with inherited breast or ovarian cancer[6][7], and inactivation of BRCA1 and BRCA2 and other genes in the homologous recombination repair pathway by somatic mutations or gene silencing due to promoter hypermethylation occurs in a significant portion of sporadic tumors[8][9]. In particular, germline BRCA1 or BRCA2 mutations are found in 10% to 15% of all newly diagnosed epithelial ovarian carcinomas, and strongly reduced expression of BRCA1 has been observed in a significant portion of sporadic ovarian cancers[8][10]. Collectively, over half of newly diagnosed ovarian cancers have defects in the homologous recombination pathway and may be sensitive to PARP inhibitors[11]-[13].

Niraparib has been approved in the US in March 2017 and in the EU in November 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Currently, niraparib is being evaluated for the treatment of several types of solid tumors including breast cancer and prostate cancer.

Nonclinical and clinical study result summaries are shown below.

4.1.1 Nonclincal Studies

In preclinical animal models, maximal in vivo efficacy was achieved in mutant breast cancer-1 (BRCA1mut) ovarian tumor models with once daily oral administration of niraparib at a dose sufficient to suppress 90% of the PARP enzymatic activity in the tumor at 8 hours postdose. Administration of the same dose translated to a >50% inhibition of PARP activity in peripheral blood mononuclear cells (PBMCs) at 8 hours postdose. Clinical development data from the

niraparib Phase 1 study demonstrated 50% inhibition of PARP activity in PBMCs at dose levels of ≥80 mg.

Nonclinical tests found that tumors containing BRCA mutations or otherwise positive by the myChoice® homologous recombination deficiency (HRD) test regressed in response to niraparib treatment. Moreover, tumor growth inhibition was observed in a subset of HRD negative models, suggesting there is a gradient of response to niraparib that is observed on a population basis by use of different biomarkers.

4.1.2 Clinical Studies

In overseas, TESARO-sponsored clinical studies are ongoing in patients with advanced solid tumors.

4.1.2.1 Study PN001 (Overseas Phase 1 Monotherapy)

The primary objective of the open-label study PN001 was to establish the safety, tolerability, pharmacokinetic (PK), pharmacodynamics, and recommended phase 2 dose (RP2D) of niraparib in patients with advanced solid tumors.

The first part of the study (Part A) was a dose escalation and confirmation scheme to determine the maximum tolerated dose (MTD) and RP2D of niraparib in patients with advanced solid tumors. The second part of the study (Part B) was a cohort expansion in patients with platinum-resistant, recurrent, high-grade serous ovarian cancer or prostate cancer at the MTD established in Part A. Part D included patients with colorectal cancer, endometrial cancer, partially platinum-sensitive high-grade serous ovarian cancer, or breast cancer. Due to non-clinical reasons, Part C of the study did not enroll patients (T-cell prolymphocytic leukemia or chronic lymphocytic leukemia).

<u>MTD and RP2D</u>

A total of 60 patients were treated in Part A once daily (QD) at 10 dose levels of niraparib ranging from 30 to 400 mg. A total of 40 patients were treated in Part B at the MTD of niraparib 300 mg QD as determined in Part A.

Based upon information obtained in Part A, an MTD of 300 mg QD was determined for niraparib. During dose escalation, 1 dose-limiting toxicity (DLT) of Grade 3 fatigue was reported out of 6 patients treated at 30 mg. One DLT of Grade 3 pneumonitis was reported out of 7 patients treated at 60 mg. The DLT of Grade 4 thrombocytopenia was observed in 2 of 6 patients treated at 400 mg, establishing that level as having exceeded MTD, per study design. During dose escalation and dose confirmation, none of the patients treated at either 290 or 300 mg had a DLT, confirming 300 mg as the MTD.

The RP2D determined on the basis of cumulative data from Part A and Part B was 300 mg QD.

<u>PK</u>

PK exposures had moderate to high variability, with coefficient of variance values generally less than 75%. An exploratory analysis of dose proportionality indicated no dose-dependent trends in

dose-normalized area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) and maximum observed concentration (C_{max}) values, suggesting dose-proportional increases in exposure across the range of doses studied. Following multiple days of dosing, accumulation levels were consistent across all doses. Time of first occurrence of C_{max} (T_{max}) and terminal disposition phase half-life ($t_{1/2}$) did not display dose-dependent trends, suggesting the lack of any nonlinearities in absorption or elimination pathways.

Following multiple oral doses of 30 to 400 mg niraparib per day for 21 days (Parts A and B), niraparib was rapidly absorbed, with a median T_{max} ranging from 3.0 to 3.6 hours on Day 1 and 1.5 to 4.0 hours on Day 21 (last day of administration). By inspection, the average plasma concentration profiles following multiple doses fall from peak levels in an approximately biphasic manner. Trough concentrations generally approach steady-state by Day 12 across all dose levels. For the 30 to 400 mg dose range studied, the AUC_{24} and C_{max} geometric mean accumulation ratios (Day 21/Day 1) after 21 days of dosing ranged from 1.99 to 4.22 and 1.55 to 3.62, respectively. Mean terminal $t_{1/2}$ ranged from 32.8 to 46.0 hours over the 60 to 400 mg dose range.

The maximum steady-state exposures observed on Day 21 following multiple 400 mg doses of niraparib were 79,055 nmol/L·hr and 4,448 nmol/L for AUC_{24} and C_{max}, respectively.

4.1.2.2 Study PR-30-5011-C (NOVA main) (Overseas Phase 3)

The main study of PR-30-5011-C is a double-blind, 2:1 randomized, placebo-controlled study in platinum-sensitive ovarian cancer patients who have either gBRCAmut or a tumor with high-grade serous histology, but without a gBRCA mutation (non-gBRCAmut) who were in response to their last platinum-based therapy. Enrollment into the cohorts was determined prospectively by the results of Myriad's Integrated BRACAnalysis® testing.

A total of 203 patients were enrolled in the gBRCAmut cohort and 350 patients were enrolled in the non-gBRCAmut cohort. Overall, 553 patients were randomized, 372 patients to niraparib and 181 patients to placebo. Preliminary efficacy data (as of the data cut date of 30 May 2016) are available for the 553 patients who comprised the intent-to-treat (ITT) population and the 546 patients who comprised the safety population. 266 patients remain on-treatment.

<u>Efficacy</u>

The primary endpoint, progression-free survival (PFS), was determined by central independent assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 [14] or clinical signs and symptoms and increased cancer antigen 125 (CA-125). PFS was measured from the time of randomization to disease progression (PD) or death.

In this study, niraparib met the primary endpoint of prolonging PFS versus placebo in all 3 prospectively defined primary patient populations (g*BRCA*mut cohort, HRDpos group of the non-g*BRCA*mut cohort, and the overall non g*BRCA*mut cohort) as displayed in Table 4.a.

Table 4.a Progression-Free Survival in the Primary Efficacy Cohorts (ITT Population, N=553)

Treatment	Median PFS (a) (95% CI) (Months)	Hazard Ratio (b) (95% CI) p-value (c)	% of Patients without Progression or Death at (d):		
			6 Months	12 Months	18 Months
g*BRCA*mut Cohort					
Niraparib (n = 138)	21.0 (12.9, NE)	0.27 (0.173, 0.410) p<0.0001	80%	62%	50%
Placebo (n = 65)	5.5 (3.8, 7.2)		43%	16%	16%
HRDpos Group					
Niraparib (n = 106)	12.9 (8.1, 15.9)	0.38 (0.243, 0.586) p<0.0001	69%	51%	37%
Placebo (n = 56)	3.8 (3.5, 5.7)		35%	13%	9%
Non-g*BRCA*mut Cohort					
Niraparib (n = 234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607) p<0.0001	61%	41%	30%
Placebo (n = 116)	3.9 (3.7, 5.5)		36%	14%	12%

Source: PR-30-5011-C (NOVA main) CSR
Abbreviations: gBRCA, breast cancer susceptibility gene; CI, confidence interval; g*BRCA*mut, germline BRCA mutation; HRDpos, homologous recombination deficiency positive; ITT, intent-to-treat; NE, not estimated; non-g*BRCA*mut, without a germline BRCA mutation; PFS, progression-free survival.
(a) Progression-free survival is defined as the time in months from the date of randomization to progression or death.
(b) Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.
(c) Based on stratified log-rank test using randomization stratification factors.
(d) Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

Safety

The most commonly observed non-hematologic treatment-emergent adverse events (TEAEs) (all grades) of niraparib were nausea, fatigue, constipation, and vomiting. The majority of the non-hematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of niraparib were anemia (48.5%), thrombocytopenia (66.2%), and neutropenia (31.4%).

TEAEs that led to dose interruption, dose reduction or discontinuation of treatment were 68.9%, 66.5% and 14.7%, respectively. Approximately 50% of patients required dose interruption during the first month of niraparib therapy, and 47% required dose reduction during the first 2 months of therapy. Most patients achieved their individual MTD by the third month. The average dose of niraparib during the study was 206 mg. After 3 to 4 months of treatment, new incidents of thrombocytopenia were reported in <1% of patients. Although Grade 3 or 4 hematologic laboratory events were common at the beginning of treatment, no severe clinical sequelae were observed, and relatively few patients discontinued due to these adverse events (AEs) (discontinuation rate was 3.3% for thrombocytopenia and 1.9% for neutropenia). Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these events beyond Cycle 3. Furthermore, PFS for patients whose dose were reduced to either 200 mg or 100 mg was consistent with that for patients whose dose remained at

300 mg, indicating that patients who required dose reduction do not appear to have decreased efficacy relative to those whose dose remain at the starting dose of 300 mg.

4.1.2.3 Study MK-4827/005 (Japanese Phase 1 study)

Study PN005, sponsored by Banyu Pharmaceutical Company Limited (current Merck Sharp and Dohme [MSD] K.K), was designed to evaluate the recommended clinical dose, the safety, tolerability, PK, and efficacy of niraparib in Japanese patients with solid tumors. The study was terminated after 3 patients received the study drug in the first cohort (150 mg QD).

4.1.2.4 Population Pharmacokinetic and Pharmacodynamic Analysis

A population PK/pharmacodynamics analysis was performed using the data collected in overseas Phase 1 study (PN001) and Phase 3 (Study PR-30-5011-C) datasets. The concentration-time data for niraparib were modeled using a compartmental approach and the effects of study variables were examined to determine if they influenced drug exposure. In addition, the relationship between measures of exposure at steady-state of niraparib and measures of efficacy and safety were explored.

A two-compartment model was selected for the population PK analysis. None of the covariates investigated (age, race, baseline body weight, serum chemistry, etc.) had a statistically significant impact on the PK of niraparib. Population PK/pharmacodynamics analysis suggested that there is a relationship between the exposure to niraparib and the PFS in g*BRCA*mut, non-g*BRCA*mut, and HRDpos populations. For TEAEs of interest (thrombocytopenia, vomiting, neutropenia, and fatigue) explored for potential relationship with niraparib exposure, no statistically significant relationship was observed. Possible relationships between body weight, platelet count, absolute neutrophil count, etc. and incidence of thrombocytopenia were further explored, and correlation were seen between the baseline platelet count and thrombocytopenia. For further details, refer to the current Investigator's Brochure and package inserts in regions/countries where niraparib is approved.

4.2 Rationale for the Proposed Study

In overseas Phase 1 study (PN001), investigating the safety, tolerability and AE profile of niraparib in patients with locally advanced or metastatic solid tumors who have failed standard therapy or for whom no standard therapy exists, niraparib at doses of 30 to 400 mg QD has been administered to 104 patients. The MTD determined in Part A was 300 mg QD in continuous 21-day treatment cycles. During dose escalation (Part A), 1 DLT of Grade 3 fatigue was reported out of 6 patients treated at 30 mg. One DLT of Grade 3 pneumonitis was reported out of 7 patients treated at 60 mg. The DLT of Grade 4 thrombocytopenia was observed in 2 of 6 patients treated at 400 mg, establishing that level as having exceeded MTD, per study design. During dose escalation and dose confirmation, 0 of 5 patients treated at 290 mg and 0 of 10 patients treated at 300 mg had a DLT, confirming 300 mg as the MTD. The safety data indicated that a niraparib dose of 300 mg QD is generally well tolerated, with an AE profile that is acceptable and predictable.

Based on preclinical and clinical safety and/or efficacy data, it is anticipated that the administration of niraparib can be reasonably well tolerated and effective as monotherapy in Japanese patients with advanced and/or metastatic solid tumors. Current population PK analyses of niraparib indicated that race had no significant impact on the PK of niraparib. The starting dose in this study is 200 mg QD, which is two thirds of the recommended dose of niraparib as monotherapy (300 mg) determined based on results of previous clinical studies.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

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

5.1.2 Secondary Objectives

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

5.1.3 Additional Objectives

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

5.2 Endpoints

5.2.1 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.

5.2.2 Secondary Endpoints

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

5.2.3 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 STUDY DESIGN

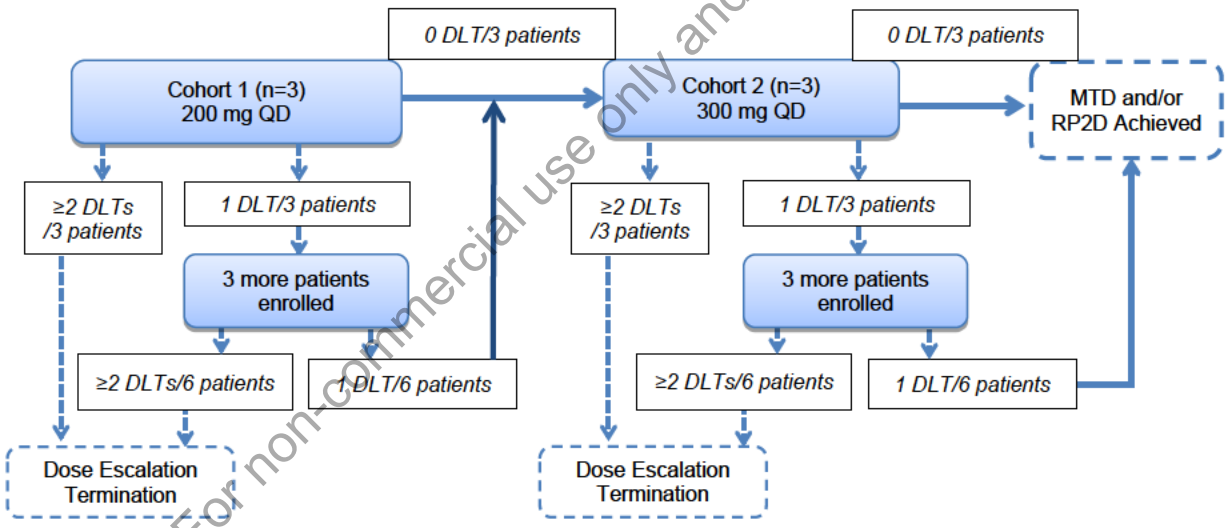
6.1 Overview of Study Design

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 6.a.

Figure 6.a Overview of Study Design



Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Dose-escalation will proceed according to a 3+3 design. The initial niraparib dose will be 200 mg QD (Cohort 1) and will be escalated to 300 mg QD (Cohort 2), provided that the safety and tolerability of the 200 mg dose have been demonstrated. The details of dose-escalation will be shown in Section 8.3.

Frequent blood sampling will be performed during Cycle 1 to assess the pharmacokinetic profile of niraparib in plasma.

Subjects who do not have PD or unacceptable toxicity during Cycle 1, and who do not withdraw their consents may continue to receive niraparib at the same dose as the one that they were assigned at enrollment (200 mg QD or 300 mg QD). Dose modification (ie, dose reduction at a

minimum of 100 mg) will be permitted only in case of DLTs during Cycle 1 and any toxicity from Cycle 2 onward. Individual subjects who experienced DLTs may also resume the treatment with niraparib and continue treatment from Cycle 2 onward if they meet the criteria for restarting the study drug after onset of DLTs. The dose modification guidelines are shown in Section 8.4.

6.2 Number of Patients

Approximately 6 to 12 patients will be enrolled in this study from 1 study center in Japan. Enrollment is defined as the time when the sponsor sends an enrollment sheet back to the investigational site.

Patients who did not receive ≥80% of the study medication in Cycle 1 for reasons other than related toxicities must be replaced.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive study drug until they experience PD, unacceptable toxicity, withdrawal of consent, or for any of the other reasons outlined in Section 9.9.

Patients will be followed for 28 days after the last dose of niraparib or the start of subsequent alternative anticancer therapy to permit the detection of any delayed treatment-related AEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the primary endpoint and authoring of a CSR will be conducted after all patients enrolled in the study have completed the study treatment with niraparib and the 28-day safety follow-up. It is anticipated that this study will last for approximately 16 months (from first patient in [FPI] to last patient last visit [LPLV]).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame (a)
Primary:		
• The number and percentage of subjects with DLTs during Cycle 1.	The number and percentage of patients with DLTs during Cycle 1 in the DLT-evaluable set.	Prior to administration on Cycle 2 Day 1
• The number and percentage of subjects with TEAEs. (b)	The number and percentage of patients with TEAEs in the safety analysis set.	Approximately 13 months.
• The number and percentage of subjects with Grade 3 or higher TEAEs. (b)	The number and percentage of patients with Grade 3 or higher TEAEs in the safety analysis set.	Approximately 13 months.
• The number and percentage of subjects with serious TEAEs. (b)	The number and percentage of patients with serious TEAEs in the safety analysis set.	Approximately 13 months.
• The number and percentage of subjects who discontinued the study drug because of TEAEs. (b)	The number and percentage of patients with TEAEs leading to study drug discontinuation in the safety analysis set.	Approximately 13 months.
Secondary:		
• PK parameters of niraparib on Cycle 1 Day 1 and Day 21: C_{max}, T_{max} and AUC_{24}	Descriptive statistics for PK parameters of niraparib on Cycle 1 Day 1 and Day 21 in the PK-evaluable set.	Up to Cycle 1 Day 2 and Cycle 2 Day 1

Abbreviations: AUC_{24}, area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}, maximum observed concentration; DLT, dose-limiting toxicity; T_{max}, time of first occurrence of C_{max}; TEAE, treatment-emergent adverse event.
(a) Time to last assessment for that endpoint for an individual patient.
(b) TEAEs are defined as AEs that occur after the first dose of study drug until 30 days after the last dose of study drug.

6.3.4 Total Study Duration

It is anticipated that patient enrollment into both cohorts will be completed approximately 4 months from the enrollment of the first patient into Cohort 1. This estimation is based on the condition that no DLTs occur and only 3 patients per cohort are enrolled.

It is anticipated that this study will last for approximately 16 months (from FPI to LPLV).

7.0 STUDY POPULATION

The study will be conducted in Japanese patients with locally advanced and/or metastatic solid tumors for which standard therapy does not exist or is not available.

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Japanese male or female patients aged 20 years or older on the day of signing informed consent.
2. Patients must have a cytologically- or histologically-confirmed metastatic or locally advanced solid tumor and have failed or progressed after standard therapy, or for which standard therapy does not exist in the opinion of the investigator.
3. Patients must have Performance Status of ≤1 on the ECOG Performance Status Scale.
4. Patients must have adequate organ function as indicated by the following laboratory values:
   a. Hematology
      – Absolute neutrophil count: ≥1500/μL
      – Platelet count: ≥100,000/μL
      – Hemoglobin: ≥9 g/dL
   b. Kidney
      – Serum creatinine: ≤1.5 × institutional upper limit of normal (ULN), OR creatinine clearance of ≥50 mL/min (as calculated using the Cockcroft Gault equation or measured using 24-hour urine creatinine clearance) for patients with creatinine levels ≥1.5 × institutional ULN.
   c. Liver
      – Total bilirubin in serum: ≤1.5 × ULN (except in patients with Gilbert's syndrome). Patients with Gilbert's syndrome may be enrolled if the patient's direct bilirubin is ≤1.5 ×ULN of the direct bilirubin.
      – AST and ALT: ≤2.5 × ULN OR ≤5 × ULN if patients have liver metastases.
   d. Coagulation (does not pertain to patients receiving anticoagulants)
      – Prothrombin time (PT): ≤1.2 × ULN
      – Activated partial thromboplastin time (aPTT): ≤1.2 × ULN
5. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR

- If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, vasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug. If the female partner of a male subject is of child bearing potential, it should also be advised to use a highly effective method of contraception, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

6. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

Patients who meet any of the following criteria will not be enrolled in the study:

1. Patient who have received chemotherapy, radiotherapy, hormonal or biological therapy within 14 days (within 28 days for anticancer monoclonal antibody, within 42 days for nitrosoureas or mitomycin C) prior to Cycle 1 Day 1. If the patient has residual toxicity from prior chemotherapy treatment, such toxicity must be ≤Grade 1 (NOTE: patients with Grade 2 alopecia may qualify for this study). If bevacizumab had been used in the past, all bevacizumab-related toxicities must have resolved. Patients with prostate cancer may have been treated with luteinizing hormone-releasing hormone (LH-RH) analogs.
2. Patients who received a known or putative PARP inhibitor or other drugs that may inhibit the PARP, either as part of a clinical trial or as standard of care.
3. Patients who initiated bisphosphonate therapy or are adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1. Patients on a stable bisphosphonate regimen are eligible and may continue the treatment.
4. Treatment with any investigational products within 28 days or 5 half-lives (whichever was longer) before Cycle 1 Day 1.

5. Patients who have symptomatic ascites or a symptomatic pleural effusion. A patient who is treated and clinically stable for these conditions is eligible.
6. Patients with a known primary central nervous system (CNS) tumor.
7. Patients with known CNS metastases and/or carcinomatous meningitis are excluded. However, patients with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for 30 days prior to Cycle 1 Day 1 defined as: (1) no evidence of new or enlarging CNS metastases, (2) off steroids, or (3) on a stable dose and administration of steroids.
8. Patients who have a hypersensitivity to the components of the study drugs or their analogs.
9. Patients who are considered to be at high medical risk due to a serious, uncontrolled disease, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days prior to Cycle 1 Day 1) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, or any psychiatric disorder that prohibits obtaining informed consent.
10. Patients who have a history or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient's participation throughout the study period, or study participation is not in the best interest of the patient.
11. Known gastrointestinal (GI) disease or GI surgery that could interfere with the GI absorption of study drug, such as difficulty swallowing capsules and total gastrectomy.
12. Patients who have a psychiatric disorder that may interfere with the conduct of the trial.
13. Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the past year) of drug or alcohol abuse.
14. Patients who are pregnant or breast-feeding, or expecting to conceive or be a father of children within the planned duration of the study.
    NOTE: If a breast-feeding woman discontinue breast-feeding, she may be enrolled in the study.
15. Known HIV positive.
16. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.
    NOTE: Patients who are positive for hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.

8.0 STUDY DRUG

8.1 Study Drug Administration

Niraparib will be administered QD orally, given continuously in 21-day cycles.

Dose escalation will follow a 3+3 escalation scheme. Starting dose is 200 mg QD (Cohort 1), which is a two thirds (2/3) of the recommended dose of niraparib as monotherapy in previous clinical studies. If 200 mg QD is safe and tolerable, then the dose will proceed to 300 mg QD (Cohort 2). This is the recommended dose of niraparib as monotherapy in previous clinical studies.

Subjects may receive study drug until they experience objective PD, experience unacceptable toxicity or until study discontinuation due to any other reasons.

The study drug should be administered at approximately the same time every day. In the event of missed doses or vomited doses, the dose will not be re-administered. The study drug should not be chewed before swallowing. The study drug may be taken with water.

Subjects are required to fast for 2 hours before and after administration of niraparib when PK samples are to be drawn.

8.2 Definitions of DLT

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective 14 June 2010 [15].

DLT will be defined as any of the following events that are considered by the investigator or subinvestigator to be related to treatment with niraparib (note that AEs for which the relationship to study drug cannot be ruled out should be considered related to study drug).

Hematologic DLTs:

- Any Grade 5 hematologic toxicity.
- Any Grade 4 hematologic toxicity, except Grade 4 neutropenia <7 days in duration.
- Grade 3 or Grade 4 neutropenia with fever >38.5°C and/or infection requiring antibiotic or anti-fungal treatment.

Non-hematologic DLTs:

Any Grade 3, 4, or 5 non-hematologic toxicity with the exception of:

- Grade 3 nausea, vomiting, diarrhea, or dehydration occurring in the setting of inadequate compliance with supportive care and lasting less than 48 hours.
- Inadequately treated hypersensitivity reactions.
- Grade 3 acidosis or alkalosis that responds to intervention by improving to ≤Grade 2 within 48 hours.

- Isolated, asymptomatic Grade 3 amylase elevation.
- Grade 3 hypercholesterolemia.
- Grade 3 hypertriglyceridemia.

Additional DLTs:

- Any treatment-related AE, regardless of NCI CTCAE grade, leading to an interruption of niraparib for greater than 14 days.

For determination of MTD, only DLTs occurring between Cycle 1 Day 1 and Cycle 2 Day 1 (predose) will be considered. In Cycle 1, treatment may be interrupted at any time for any grade of toxicity if the investigator or subinvestigator deems that the toxicity will interfere with safe continuation of the study treatment. If dose interruption was required in Cycle 1, the patient should be continuously monitored during Cycle 2 Day 1 onwards to determine whether or not the toxicity is a DLT, and confirm the required duration of dose interruption. If any DLT is observed, the dose may be reduced at any time, but dose reduction for reasons other than DLT will not be allowed.

Patients who did not receive ≥80% of the study medication in Cycle 1 for reasons other than related toxicities will not be taken into account for dose escalation purposes and must be replaced for DLT counting purposes and for full assessment of the safety of that dose level.

8.3 Dose Escalation Rules

Dose-escalation will proceed according to a 3+3 design. The initial niraparib dose will be 200 mg QD in Cohort 1 and will be escalated to 300 mg QD (Cohort 2), provided that the safety and tolerability of the 200 mg dose have been demonstrated.

If 0 of 3 subjects experience a DLT in Cohort 1, the cohort is proceeded to the next dose level (Cohort 2). If 2 of 3 or all subjects experience a DLT in Cohort 1, this dose is considered exceeded MTD, and the dose-escalation of the trial will be terminated. If 1 of 3 subjects experience a DLT, 3 more subjects will be enrolled at this dose level. If 1 of 6 patients in the combined dose-group experience a DLT, the cohort is proceeded to the next dose level (Cohort 2). If ≥2 of 6 subjects experience a DLT, this dose is considered exceeded MTD, and the dose-escalation of the trial will be terminated.

If 0 of 3 subjects experience a DLT in Cohort 2, MTD is considered 300 mg or higher, and the dose-escalation of the trial will be completed. If 2 of 3 or all subjects experience a DLT in Cohort 2, this dose is considered exceeded MTD. If 1 of 3 subjects experience a DLT in Cohort 2, 3 more subjects will be enrolled at this dose level. If 1 of 6 subjects experience a DLT, MTD is considered 300 mg or higher, and the dose-escalation of the trial will be completed. If ≥2 of 6 subjects experience a DLT, this dose is considered exceeded MTD. Further dose-escalation beyond Cohort 2 (300 mg QD) is not anticipated in this study.

These rules are shown in Table 8.a.

Table 8.a Dose Escalation Rules

DLT occurred in	Decision	
0/3 subjects (a)	Go to next cohort	
1/3 subjects	Reevaluation with 3 more subjects	
	1/6 subjects (a)	Go to next cohort
	≥2/6 subjects (b)	Exceeded MTD
≥2/3 subjects (b)	Exceeded MTD	

(a) If 0 of 3 or 1 of 6 subject experiences a DLT, proceed to the next dose level (Cohort 2) in Cohort 1 or and dose-escalation is completed in Cohort 2 (no further dose-escalation).
(b) If ≥2/3 or ≥2/6 subjects experience a DLT in Cohort 1 (200 mg QD), this dose is considered exceeded MTD, and not escalate to the next dose level (Cohort 2). Subjects who are considered safe at this dose of niraparib by the investigator or subinvestigator may continue to receive the study drug at the same dose.

8.4 Dose Modification Guidelines

8.4.1 Criteria for Dose Reduction, Interruption, and Discontinuation

In Cycle 1, treatment may be interrupted at any time for any grade of toxicity if the investigator or subinvestigator deems that the toxicity will interfere with safe continuation of the study treatment. If dose interruption was required in Cycle 1, the patient should be continuously monitored during Cycle 2 Day 1 onwards to determine whether or not the toxicity is a DLT, and confirm the required duration of dose interruption. If any DLT is observed, the dose may be reduced at any time, but dose reduction for reasons other than DLT will not be allowed.

In Cycle 2 onwards, treatment may be interrupted and/or dose reduced at any time for any grade of toxicity if the investigator or subinvestigator deems that the toxicity will interfere with safe continuation of the study treatment.

Treatment must be interrupted for any NCI CTCAE (v.4.03) Grade 3 or 4 non-hematologic toxicity which the investigator or subinvestigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days, the patient may restart treatment with niraparib at the same dose level. However, if prophylaxis with medication or blood transfusion is not considered feasible, treatment with niraparib should be restarted with a dose level reduction according to Table 8.b. If the event recurs at the same or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted.

Table 8.b Dose Reductions for Non-Hematologic Toxicities (Cycle 2 and Onwards)

Event	Dose(a)	
	Cohort 1	Cohort 2
Initial dose	200 mg QD	300 mg QD
1st dose reduction for NCI CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis with medication or blood transfusion is not considered feasible	100 mg QD	200 mg QD
2nd dose reduction for NCI CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis with medication or blood transfusion is not considered feasible	Discontinue study medication	100 mg QD
Continued NCI CTCAE Grade 3 or 4 treatment-related SAE/AE ≥28 days	Discontinue study medication	Discontinue study medication

Abbreviations: AE, adverse events; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QD, once daily; SAE, serious adverse events.
(a) Dose not to be decreased below 100 mg QD.

If the toxicity requiring dose interruption has not resolved completely or to NCI CTCAE Grade 1 during the maximum 4 week (28 day) dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

The dose interruption/modification criteria for hematologic parameters will be based on blood counts and are outlined in Table 8.c.

Table 8.c Dose Interruption/Modification for Hematologic Toxicities (Cycle 2 and Onwards)

Finding	Modification
Platelet count: 75,000-99,999/μL	Study medications must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at same dose or reduced dose based on clinical judgment.
2nd occurrence of platelet count: 75,000-99,999/μL	Study medications must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.
Platelet count: <75,000/μL*	Study medications must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.
Neutrophil: <1,000/μL	Study medications must be interrupted until neutrophil counts are ≥1,500/μL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.
Hemoglobin: <8 g/dL	Study medications must be interrupted until hemoglobin is ≥9 g/dL, with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at a reduced dose.

Abbreviation: CBC, complete blood cell count.
*For patients with platelet count ≤10,000/μL prophylactic platelet transfusion per guidelines may be considered[16][17].
For patients taking anticoagulation or antiplatelet drugs consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤20,000/μL.

If dose interruption or modification is required at any point on study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for complete blood cell count (CBC) will be required for an additional 4 weeks after the AE has been resolved to the specified levels. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a dose reduction upon recovery if study treatment is resumed.

The patient must be referred to a hematologist for further evaluation (1) if transfusions are required on 1 or more occasions or (2) if the treatment-related hematologic toxicities have not recovered to NCI CTCAE Grade 1 or less after 4 weeks. If a diagnosis of myelodysplastic syndrome (MDS)/acute myeloblastic leukemia (AML) is confirmed by a hematologist, the patient must permanently discontinue study treatment.

For major surgery while on treatment, up to 28 days of drug interruption is allowed.

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the electronic case report from (eCRF).

8.4.2 Re-Escalation After Dose Reduction

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the medical monitor.

8.4.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Niraparib will be administered in continuous cycles; therefore, study drug should be administered continuously unless TEAEs occur that meet the dose modification criteria outlined in Section 8.4.1 (Criteria for Dose Reduction, Interruption and Discontinuation).

If dose interruption was required due to TEAE at the beginning of a Cycle, the Cycle should not be postponed. Once the patient recovers from the TEAE, the study treatment will be resumed in the middle of the cycle, without waiting for the first day of the next Cycle.

However, the timing of efficacy and safety evaluations will not be affected by the dose interruption or dose reduction.

8.5 Excluded Concomitant Medications and Procedures

The following medications, procedures and foods are prohibited during the study:

- Other anticancer therapies other than study treatment, with the exception as follows:
  - Patients with prostate cancer may have been treated with LH-RH analogs (Section 7.2, exclusion criterion 1).
  - Patients who initiated bisphosphonate therapy ≥30 days prior to Cycle 1 Day 1 may continue the treatment (Section 7.2, exclusion criterion 3).
  - Patients with a stable dose and administration of steroids ≥30 days prior to Cycle 1 Day 1 may continue the administration (Section 7.2, exclusion criterion 7).
  - Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of PD is present.
- Medications that prolong QTc.
- Conventional chemotherapy drugs, live virus and bacterial vaccines (an increased risk of infection have been observed with concomitant administration of these medications).
- Prophylactic cytokine (granulocyte colony-stimulating factor [GCSF]) administration should not be given in Cycle 1; however, if the patient experiences a DLT, prophylactic cytokine can be given thereafter. Prophylactic cytokine may be administered in Cycle 2 onwards according to local guidelines, etc.

The following medications, procedures, and foods should be used with caution during the study.

- Drugs that are substrates for cytochrome P450 (CYP) 1A2 (Appendix G) (niraparib is a CYP1A2 inducer).

- Drugs that are inhibitors or substrates for P-glycoprotein (P-gp) (niraparib is a substrate for P-gp).
- Anticoagulation and antiplatelet drugs (niraparib potential risk includes thrombocytopenia).

8.6 Permitted Concomitant Medications and Procedures

For patients with platelet count ≤10,000/μL prophylactic platelet transfusion per guidelines may be considered (except Cycle 1).

8.7 Precautions and Restrictions

8.7.1 Pregnancy and Contraception

It is not known what effects niraparib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit (natural amenorrhea, not due to other medical reasons), or
- Surgically sterile, or
- If they are of childbearing potential*, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception** at the same time, from the time of signing of the informed consent form (ICF) through 180 days after the last dose of study drug.
- Agree to practice true abstinence from the time of signing of the informed consent form through 180 days after the last dose of study drug, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, vasectomy) must agree to 1 of the following:

- Agree to practice 1 highly effective method and 1 additional effective barrier contraception** from the time of signing of the informed consent form through 120 days after the last dose of study drug. If the female partner of a male subject is of child bearing potential, it should also be advised to use a highly effective method of contraception**.
- Agree to practice true abstinence from the time of signing of the informed consent form through 120 days after the last dose of study drug, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods of the female partner], condoms only, withdrawal, spermicides only,

and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

*Women of childbearing potential is defined as any sexually active female subjects who meet both of the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy.
- Those who have not had natural menopause for 12 consecutive months or longer.

Note: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Examples of highly effective contraception methods are listed below:

- Hormonal birth control pills.
- Intrauterine device.
- Intrauterine hormone-releasing system.

8.7.2 Other Precautions and Restrictions

- Patients who are blood donors should not donate blood during the study and for 90 days after the last dose of study treatment.

8.8 Management of Clinical Events

Detailed niraparib dose modification and prevention/prophylaxis guidelines for specific clinical events are provided in the following sections. General guidelines for niraparib interruption, dose reduction and discontinuation are provided in Section 8.4.1.

8.8.1 Hematologic Toxicities

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia), including clinical diagnoses and/or laboratory findings, have been reported in patients treated with niraparib. In patients who have experienced hematologic toxicities after niraparib administration, study medication must be interrupted until platelet, hemoglobin and neutrophil levels have returned to the levels specified in Table 8.c (Section 8.4.1).

If deemed clinically necessary, supportive therapy with platelet or RBC transfusion and supportive therapy with hematopoietic growth factors (G-CSFs) may be considered for these hematologic toxicities. Generally, G-CSFs should not be administered in the first cycle of the study; however if the patient experiences a DLT, G-CSFs can be administered thereafter.

After the toxicity has resolved, CBCs should be tested weekly for the first month, followed by testing as a part of clinical laboratory evaluation on study visits to monitor for clinically significant changes in any hematologic parameter during treatment.

If a patient develops severe persistent hematologic toxicity that does not resolve within 28 days following interruption, niraparib should be discontinued (Section 8.4.1).

Due to the risk of thrombocytopenia, anticoagulant and antiplatelet drugs should be used with caution (Section 8.5)

8.8.2 Myelodysplastic Syndrome/Acute Myeloid Leukemia

MDS/AML, including cases with fatal outcome, have been reported in a small number of patients who received niraparib or placebo. If MDS and/or AML are confirmed while on treatment with niraparib, then niraparib should be permanently discontinued (See Section 8.4.1).

8.8.3 Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Blood pressure should be monitored periodically on study visits during treatment with niraparib. Hypertension should be medically managed with antihypertensive medications as well as adjustment of the niraparib dose, if necessary.

8.8.4 Diarrhea

Diarrhea should be treated promptly with appropriate supportive care, including administration of an anti-diarrheal agent according to standard practice guidelines. Anti-diarrheal agents should not be taken prophylactically. Subjects should be instructed to begin taking anti-diarrheal medication at the first sign of:

1. Poorly formed or loose stool.
2. Occurrence of more bowel movements than usual in one day.
3. Unusually high volume of stool.

Anti-diarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Subjects should also be advised to have sufficient oral fluid intake to prevent dehydration.

8.8.5 Nausea and/or Vomiting

Nausea and vomiting should be treated proactively, according to standard institutional practice, including administration of prophylactic antiemetic therapy. Subjects should be strongly encouraged to maintain sufficient oral fluid intake.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

Niraparib capsule contains 100 mg of niraparib (free form). The hard capsules have a white body with a printed black bar, and a purple cap with a printed white bar.

8.11 Preparation, Reconstitution, and Dispensation

Detailed instructions for dispensing niraparib tablets are provided in the Pharmacy Manual. Niraparib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling niraparib.

8.12 Packaging and Labeling

Niraparib capsules are packaged in a high-density polyethylene (HDPE) white bottle with a two-piece, pulp-backed, heat-induction-foil inner seal, tamper-proof cap. Each bottle contains 93 capsules. The label text of the study drug will comply with the national legislation to meet all requirements in Japan.

8.13 Storage, Handling, and Accountability

Investigational study drug must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed to the patients and returned to the sponsor or its designated disposal vendor, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

All investigational study drug supplies in the US must be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature) and investigation study drug supplies in the EU must be stored below 30°C. Refer to the Pharmacy Manual for further details.

8.14 Other Protocol-Specified Materials

Not applicable.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the sponsor's medical monitor for this study, other third-party vendors, and the list of investigators may be found in the protocol annex or the Study Manual.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator or subinvestigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB).

9.3 Treatment Group Assignments

This phase 1 study includes 2 cohorts, consisting of Cohort 1 (200 mg QD) and Cohort 2 (300 mg QD), and each subject will be assigned to either one of the cohorts based on the Dose Escalation Rules described in Section 8.3.

A subject identification code will be assigned to each patient after he/she signed the ICF.

Patient eligibility will be confirmed by the sponsor's Medical Monitor (or designee) before enrollment by the investigator or subinvestigator into the study. If a subject discontinues the study, the subject identification code will not be reused.

9.4 Study Procedures

Refer to the Schedule of Events (Appendix A) for the timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.4.2 Patient Demographics

The date of birth, race and sex of each subject are to be recorded during the Screening period. If available, the data on whether individual subjects have BRCA mutations will also be collected.

9.4.3 Medical History

During the Screening period, all concurrent conditions will be collected for each subject. Also, medical history that are considered to be clinically useful by the investigator will be collected.

As the information about the underlying disease, the following data will be collected and recorded specifically: the date of initial diagnosis, the type of tumor, the stage of disease at the initial diagnosis, the results of histology at diagnosis, grade and recent biopsy results (if performed).

During screening, the following medications are to be recorded as prior medications based on hearing from the subjects:

- All non-chemotherapeutic medications given to subjects within 14 days before Cycle 1 Day 1.
- All chemotherapeutic agents and treatment given to subjects after the initial diagnosis: drug used in the first treatment and its start and end dates, drugs used in subsequent treatments and their start and end dates, and the best response to each treatment.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events (Appendix A).

9.4.5 Patient Height and Weight

Height will be measured at Screening only. Weight will be measured at the times specified in the Schedule of Events (Appendix A).

9.4.6 Vital Signs

Vital signs include diastolic and systolic blood pressure, pulse rate and body temperature (axillary) measured at the times specified in the Schedule of Events (Appendix A). Subjects must be resting in a sitting position for 10 minutes prior to obtaining vital signs. This measurement method will be used throughout the study. To determine the effects of niraparib on the cardiovascular system, blood pressure will be measured prior to obtaining blood samples.

If blood pressure exceeds 150/100 mmHg or diastolic blood pressure exceeds 20 mmHg from baseline despite the subject has no history of hypertension, blood pressure must be re-measured within 10 minutes for confirmation.

If there was a change in blood pressure from prior to study drug administration, which was judged by the investigator as an AE, such change will be recorded in the eCRF.

9.4.7 ECOG

ECOG performance status will be assessed and recorded according to Appendix E at the times specified in the Schedule of Events (Appendix A).

The investigator will evaluate the performance status.

9.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential (defined in Section 8.7.1) within 7 days before Cycle 1 Day 1, and negative results must be obtained. Subsequently, urine pregnancy tests will be performed predose on Day 1 of Cycle 2 and thereafter, and negative results must be obtained before the study drug administration.

9.4.9 Concomitant Medications and Procedures

Medications used by the subject and therapeutic procedures completed by the subject will be recorded in the eCRF from the time of signing the informed consent through 28 days after the last dose of study drug. See Section 8.5 and Section 8.6 for medications and therapies that are prohibited or allowed during the study.

All medications other than the study drug (including Chinese herbal medicine and other non-traditional remedies) used by subjects as concomitant drugs during the study period should be investigated and recorded by hearing from the subjects. For each medication, the nonproprietary name, the start and end date and the purpose of use will be recorded.

9.4.10 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and serious AEs (SAEs).

9.4.11 Enrollment

A subject is considered to be enrolled in the study when the sponsor sends an enrollment sheet back to the investigational site. Procedures for completion of the enrollment information are described in the Study Manual.

9.4.12 Electrocardiogram

A 12-lead ECG will be performed at time points specified in the Schedule of Events (Appendix A) and Detailed Schedule of PK Sample Collection and 12-lead ECG in Cycle 1 (Appendix B) , and the results of 12-lead ECG will be evaluated at each study site. The heart rate, RR, PR, QRS, QT, and corrected QT (QTcF) intervals will be recorded in the eCRF.

An additional ECG measurement may be performed as clinically indicated.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally before administration of the study drug.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained

on the same day, before administration of the study drug, as specified in the Schedule of Events (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	**Serum Chemistry**	
• Erythrocyte • Hematocrit • Hemoglobin • Leukocytes with differential (ANC, basophil count, eosinophil count, absolute lymphocyte count, monocyte count) • Platelet count • MCV	• Albumin • ALP • ALT • Amylase • AST • Total bilirubin • Urea nitrogen • Calcium • Bicarbonate • Creatinine	• Chloride • GGT • Glucose (fasted) • LDH • Magnesium • Inorganic phosphate • Potassium • Sodium • Protein (total protein)
Blood coagulation test	**Pregnancy test (serum, urine)**	
• aPTT • PT • INR	• hCG	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; hCG, human chorionic gonadotropin; INR, international normalized ratio; LDH, lactate dehydrogenase; MCV, mean cell volume; PT, prothrombin time.

Table 9.b Clinical Urinalysis Tests

Urinalysis	
• Bilirubin • Glucose • Ketone body • Nitrite • Occult blood	• Protein • Specific gravity • Urobilinogen • Leukocyte esterase

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed as follows:

$$Estimated\ creatinine\ clearance = [(140 - Age) * Weight(kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

For female subjects, the result of the formula above should be multiplied by 0.85.

9.4.13.2 HIV and Hepatitis Testing

HIV and hepatitis testing will be performed during the screening period.

HBsAg, HBsAb and HBcAb will be tested to screen HBV. For patients who are HBsAg negative but HBsAb and/or HBcAb positive, hepatitis B viral load (HBV-DNA) will also be assessed at Screening. Patients who are HBsAg-negative but HBsAb and/or HBcAb-positive may be eligible if they have an undetectable HBV-DNA.

HCVAb will also be tested for hepatitis C at Screening. Patients who are positive for HCVAb will also be tested for hepatitis C viral load (HCV-RNA) at Screening. Patients who are positive for HCVAb may be eligible if they have an undetectable HCV-RNA.

Patients who were positive for serum virus tests and had an undetectable HBV-DNA or HCV-RNA may be enrolled in this study, but they should be measured for viral load (HBV-DNA or HCV-RNA) and monitored at Day 1 of each cycle, at the end of the treatment (EOT) and at the Follow-up visit 28 days after the last dose. If HBV-DNA or HCV-RNA is detected, the patient would be withdrawn from the study and treated according to the institutional guidelines. In this case, a consultation with a hepatologist should be considered.

9.4.14 Disease Assessment

Subjects will undergo computed tomography (CT) with contrast as appropriate to monitor and assess PD, using modified RECIST criteria (Version 1.1) (Appendix F) [14]. Specific disease sites that cannot be adequately imaged by CT with contrast may be documented by magnetic resonance imaging (MRI). Bone scans may be performed on subjects with bone metastases rather than contrast enhanced CT or MRI.

During the study, anatomical measurements will be collected for each target lesion using an imaging modality consistent with that used at Screening. The same method (CT with contrast, MRI or bone scan) must be consistently used on a subject throughout the study.

Objective assessments will be performed at each time point as described in the Schedule of Events (Appendix A) as long as there is no evidence of early PD. When possible, the same qualified physician will interpret the results to reduce variability.

Diagnostic imaging/tumor assessment performed within 42 days before the first dose of the study drug may be used as screening assessment. Appropriate imaging evaluation at screening should include a CT/MRI of the chest, abdomen and pelvis. Imaging evaluations of other body parts are not necessary unless clinically indicated.

The sizes of visible lesions will be recorded using a ruler. The sizes of palpable lesions will be recorded in the subject's source documents at the physical examination. The tumor status will be compared with that at screening, using physical findings, imaging results and ECOG performance status.

Radiographic images will be maintained at each site, and test results and physicians' findings will be filed in subject's source documents. The sponsor may request electronic images for those subjects who demonstrate tumor reduction.

9.4.15 Pharmacokinetic Measurements

Blood samples for PK analysis of niraparib will be serially collected at the time points specified in the Pharmacokinetic Sample Breakdown table (Appendix A) and Detailed Schedule of PK Sample Collection and 12-lead ECG in Cycle 1 (Appendix B). The exact dates and times of administration of niraparib before collection of the blood sample for PK analysis and the exact dates and times of collection of the blood sample for PK analysis will be recorded on the eCRF.

9.4.16 Hospitalization

Subjects will receive niraparib under inpatient hospitalization (from Cycle 1 Day 1 to Cycle 1 Day 8 will be mandatory) during Cycle 1. If a subject wishes to return home temporarily and the investigator or subinvestigator confirms that the subject's symptoms are stable based on the available data, then the subject may return home temporarily, except from Cycle 1 Day 1 to Cycle 1 Day 8, provided this does not interfere with the study assessments. The investigator or subinvestigator must document the confirmation record that there is no problem in the subject's safety in the medical records before the patient's temporary leave.

9.4.17 Dosing Compliance (Patient Diary)

Subjects will be provided a patient diary to confirm their dosing compliance with niraparib treatment, and record each dose they take in their diary every day. The investigator will check the patient diary on their visits.

9.5 Documentation of Screen Failure

Investigators must account for all subjects who sign the ICF.

Even if the subject is found to be not eligible prior to the first dose of the study drug, the investigator or subinvestigator should complete the applicable eCRF.

The primary reason for subject failure is recorded in the eCRF using the following categories:

- Death
- Adverse event
- Screen failure (failed inclusion criteria or did meet exclusion criteria)
- Protocol deviation
- Lost to Follow-up
- Withdrawal by subject
- Study terminated by sponsor

Subject identification codes assigned to subjects who fail screening should not be reused.

9.6 Completion of Investigational Product Administration / Study Treatment (for Individual Patients)

Patients will be considered to have completed treatment if they discontinue treatment with study drug for any of the reasons outlined in Section 9.8.

Treatment will continue until PD, unacceptable toxicities, or withdrawal due to other reasons.

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they discontinue the treatment and complete the 28-day safety follow-up.

9.8 Discontinuation of Treatment With Study Drug

Treatment with study drug may be discontinued for any of the following reasons:

- Adverse event
- Protocol deviation
- PD
- Study terminated by sponsor
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Other

The sponsor should be notified of all discontinuations of study drug as soon as possible. The primary reason for study drug discontinuation will be recorded in the eCRF.

Once the study drug has been discontinued, all study procedures outlined for the Early Termination will be completed as specified in the Schedule of Events (Appendix A). All subjects will be followed until 28 days after the last dose of study drug, unless the subject withdraws consent to participate in the study.

If a subject did not receive at least 80% of planned doses of study drug in Cycle 1 due to reasons other than study drug-related toxicity, the subject may be replaced.

9.9 Withdrawal of Subjects From Study

A subject may be withdrawn from the study for any of the following reasons. However, subjects may withdraw their consent to participate in the study at any time without prejudice.

- Lost to follow-up

- Study terminated by sponsor
- Withdrawal by subject
- Death
- Other

The sponsor should be notified of all subject withdrawals from the study as soon as possible. If a subject withdraws consent to participate in the study, no study data will be collected or data added to the database for this subject thereafter. However, every effort will be made to follow all subjects for safety.

9.10 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Subjects will receive a sufficient quantity of study drugs for each treatment cycle and provided a diary where the date of study drug administration will be recorded. The study site staff will check the patient diary versus the subject's supply of remaining niraparib at each study visit to ensure proper compliance with dosing. Subjects who are not compliant with the dosing schedule may be withdrawn from the study.

Tests and procedures should be performed on schedule. However, except Cycle 1 Day 1, Cycle 2 Day 1, Early Termination and follow-up 28 days after the last dose, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a subject from beginning treatment or completing a planned procedure or assessment within 3 days of the scheduled time, the subject may continue the study at the discretion of the investigator and after consultation with the sponsor's medical monitor or designee. However, the timing of PK assessment as specified in the Schedule of Events (Appendix A) and Detailed Schedule of PK Sample Collection and 12-lead ECG in Cycle 1 (Appendix B) is not flexible.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

AE means any untoward medical occurrence in a subject or subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment (including an investigational product). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator or subinvestigator to be a clinically significant change from baseline.

10.1.2 Serious Adverse Event Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe).
- Requires **inpatient hospitalization or prolongation of an existing hospitalization** (see Section 10.2 for planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important** event. It may be considered serious when, an AE may not result in death or immediately life threatening or require hospitalization, but may jeopardize the subject, or require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent, based on appropriate medical judgment. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disorders or convulsions that do not result in hospitalization, or the development of drug dependence or drug abuse; any microorganism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity of each AE including any lab abnormality will be determined using the NCI CTCAE, Version 4.03 (effective date: 14 June 2010) [15]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache), so that this is NOT the same as serious. "Serious" is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe), but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator or subinvestigator to the Takeda Global Pharmacovigilance Department or designee (contact information provided below). This should be done by faxing, calling or e-mailing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to the clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

BI Medical, Inc.

PPD

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator or subinvestigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective on 14 June 2010 [15].

A **relationship** of the event to study drug administration (ie, its causality) will be determined by the investigator or subinvestigator responding "Yes" (related) or "No" (unrelated) to the following question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 28 days after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 28 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator or subinvestigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail address provided below, or immediately contact the study monitor.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and

underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail address provided below, contact the study monitor, and record the event in the Overdose page of the eCRF.

Product	Call center	Phone number	E-mail	Fax
All other molecules	DLSS	PPD	PPD	PPD

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to BI Medical, Inc. (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, IRBs, and the head of the institution, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization (CRO) partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator, subinvestigator, or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore,

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

In this study, statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed.

13.1.1 Analysis Sets

Analysis sets will include the following:

- Safety analysis set: patients who receive at least 1 dose of study drug.
- PK analysis set: patients with sufficient dosing and PK 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.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by dose cohort using the safety analysis set.

13.1.3 Efficacy Analysis

ORR and its two-sided 95% confidence interval based on binominal distribution will be provided by dose cohort using the response-evaluable set. The two-sided 95% confidence interval will be calculated based on binominal distribution.

13.1.4 Pharmacokinetic Analysis

All PK analyses will be performed using the PK analysis set.

Plasma niraparib concentrations obtained from Cycle 1 will be summarized by descriptive statistics according to nominal (scheduled) time postdose and day for each cohort. Mean and individual plasma niraparib concentration data from Cycle 1 will be plotted over time for each day (Days 1 and 21) for each cohort. All plasma concentration data will be listed by cohort. The same analyses will be applied for the major metabolite M1 obtained from Cycle 1.

PK parameters will be calculated on Cycle 1 Days 1 and 21 for niraparib by noncompartmental analysis as permitted by the data. These parameters will include, but will not be limited to, C_{max}, T_{max}, and AUC. PK parameters will be summarized using descriptive statistics for each cohort and day. Individual PK parameters will be listed by cohort. The same analyses will be applied for the major metabolite M1.

13.1.5 Safety Analysis

The number of cases and incidence of DLTs during Cycle 1 will be tabulated using DLT-evaluable set.

Safety analyses for TEAE will be performed by dose levels using the safety analysis set. TEAE is defined as adverse events that occur after administration of the first dose of study drug and through 28 days after the last dose of study drug. TEAEs will be coded using the MedDRA dictionary, and will be tabulated by system organ class and preferred terms.

- TEAEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation

Shift tables based on changes in NCI CTCAE grade from baseline to the worst postbaseline value for laboratory parameters will be generated using the safety analysis set. Of the laboratory parameters, platelet count at each time point and changes from baseline will be summarized using descriptive statistics by dose level.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of niraparib QD.

13.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned.

13.3 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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, subinvestigator, and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or subinvestigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The ICF describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF, must be approved by both the IRB and the sponsor prior to use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or subinvestigator to explain the detailed elements of the ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the ICF must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator and subinvestigator must also sign and date the ICF at the time of consent and prior to subject entering into the study.

Once signed, the original ICF will be stored in the investigator's site file. The investigator or subinvestigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor or designee requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA and PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires

the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators, subinvestigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, the sponsor will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. The sponsor's contact information, along with facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

The sponsor will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or

sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator or subinvestigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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