NIRAPARIB (ZEJULA®)

3000-01-003

An Open-Label, Non-Randomized, Multicenter Study to Determine the Pharmacokinetics and Safety of Niraparib Following A Single Oral Dose in Patients with Advanced Solid Tumors and Either Normal Hepatic Function or Moderate Hepatic Impairment

Sponsor:	TESARO 1000 Winter Street Suite 3300 Waltham, MA 02451 PPD
Sponsor's Responsible Representative:	PPD, MD Medical Director PPD
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Sponsor Protocol No.:	3000-01-003
IND No.:	100,996
EudraCT No:	2013-000685-11
Study Drug Names:	niraparib capsules
Development Phase:	1
Date of Original Protocol:	16 June 2017
Date of Amendment 1:	04 October 2017
Date of Amendment 2:	15 January 2018
Version of Protocol:	3

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title (3000-01-003): An Open-Label, Non-Randomized, Multicenter Study to Determine the Pharmacokinetics and Safety of Niraparib Following A Single Oral Dose in Patients with Advanced Solid Tumors and Either Normal Hepatic Function or Moderate Hepatic Impairment

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

PPD

PPD, MD
Medical Director
TESARO

01 / 15 / 2018
Date

INVESTIGATOR'S AGREEMENT

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee/Institutional Review Board, in accordance with the study protocol, the current International Council for Harmonisation Guidelines for Good Clinical Practice, and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Printed Name of Investigator

Investigator's Institution

Signature of Investigator

Date

2. SYNOPSIS

Name of Sponsor/Company: TESARO	
Name of Investigational Product: niraparib (ZEJULA®)	
Name of Active Ingredient: niraparib	
Title of Study: An Open-Label, Non-Randomized, Multicenter Study to Determine the Pharmacokinetics and Safety of Niraparib Following a Single Oral Dose in Patients with Advanced Solid Tumors and Either Normal Hepatic Function or Moderate Hepatic Impairment	
Study Center(s): Multi-Center	
Principal Investigator: PPD, MD	
Studied Period (years): Estimated date first patient enrolled: January 2018 Estimated date last patient completed: November 2018	**Phase of Development:** 1

Objectives:

Primary:

- To characterize the pharmacokinetics (PK) of niraparib and its major metabolite (M1) when administered as a single dose in cancer patients with normal hepatic function compared to patients with moderate hepatic impairment.

Secondary:

- To evaluate the safety of niraparib when administered as a single dose in patients with moderate hepatic impairment.
- To obtain additional safety data through the extension phase, in which patients have the option to continue receiving niraparib.

Rationale for Study:

Niraparib (ZEJULA®) is extensively metabolized and eliminated primarily by hepatic and renal pathways. The purpose of this study is to evaluate pharmacokinetics and safety of niraparib in patients with moderate hepatic impairment, for the purpose of providing recommendations to guide the initial dose and dose titration in this patient population.

Methodology:

This is a Phase 1, open-label, parallel-group, single-dose study in patients with advanced solid tumors and with either normal hepatic function or moderate hepatic impairment.

Patients with solid tumors will be recruited and enrolled within the following groups:

- Group 1: normal hepatic function (total bilirubin [BILI] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN])
- Group 2: moderate hepatic impairment (BILI >1.5 × to 3 × ULN) and any degree of AST elevation

PK Phase

All patients will receive a single dose of 300 mg niraparib administered as 3 × 100 mg capsules on Day 1. Patients will undergo PK sampling up to 168 hours (7 days) following niraparib administration. Pharmacokinetic parameters to be calculated include area under the concentration × time curve calculated to last measured concentration (AUC_{0-t}), area under the concentration × time curve calculated to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to maximum concentration (t_{max}), terminal half-life ($t_{½}$), and apparent total clearance (CL/F). Protein binding parameters to be calculated include fraction of unbound drug (Fu) and clearance of free drug (CLfu/F). The study will be considered complete when the final PK evaluable patient completes all assessments in the PK phase of the study.

Safety will be assessed through adverse event assessment, physical examination, vital sign measurements, clinical laboratory tests, and monitoring of concomitant medications.

AEs are required to be captured through 30 days after cessation of study treatment; SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternative anticancer therapy); and any pregnancies that occur within 180 days post-treatment are to be captured. Study drug-related SAEs and adverse events of special interest (AESIs) will be collected via telephone every 90 ± 14 days after the last dose of study drug until study closeout, or as otherwise indicated in AESI, Section 12.2.7. AESIs must be reported as soon as the investigator becomes aware of them. All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the change(s) observed, until the patient is lost to follow-up or withdraws consent, or until the patient has died.

Extension Phase

On the same day that patients complete the final study assessments for the PK phase, patients may be eligible to continue receiving niraparib in the extension phase of the study, if the investigator believes it is in the best clinical interest of the patient. Patients will receive their first therapeutic dose of niraparib on Cycle 1/Day 1 of the extension phase. Patients will return to the study center during Cycle 1 on Days 8, 15, and 21 to undergo safety assessments (including complete blood counts [CBCs]). Thereafter, patients will return on the first day of every treatment cycle (28 ±3 days) to receive study drug and for safety assessments (including CBCs). Dose modification (dose interruption and/or reduction) may be implemented for any grade toxicity considered intolerable by the patient, and must be implemented for any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 non-hematologic adverse event considered by the Investigator related to study treatment or for hematologic toxicity as outlined in the protocol. Patients may continue in the extension phase until disease progression (assessed by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 and clinical signs and symptoms), unacceptable toxicity, death or discontinuation from the study treatment for any other reason. Patients in the extension phase will be monitored for AEs, SAEs, and AESIs according to the same schedule as the PK phase. At end of study (EOS), safety assessments will be completed. No new capsules will be dispensed at EOS.

Number of Patients (planned): 16 patients (PK-evaluable)
Normal hepatic function (Group 1): 8 patients (PK-evaluable)
Moderate hepatic impairment (Group 2): 8 patients (PK-evaluable)
Patients may be replaced until there are 8 PK evaluable patients in each group of the study.

Diagnosis and Criteria for Inclusion:
All patients:

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Patient, male or female, is at least 18 years of age.
2. Patient has a diagnosis of advanced solid malignancy that has failed standard therapy or for which standard therapy is not likely to provide meaningful benefit, or patient has refused standard therapy.
3. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to1.
4. Patient is able to take oral medications.
5. Female patient, if of childbearing potential, has a negative serum pregnancy test within 72 hours prior to taking study drug and agrees to abstain from activities that could result in pregnancy from enrollment through 180 days after the last dose of study treatment, or be of non-childbearing potential. Non-childbearing potential is defined as (by other than medical reasons):
   - ≥45 years of age and has not had menses for > 1 year.
   - Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pre-study (screening) evaluation.
   - Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use highly effective contraception (see Appendix 1) throughout the study, starting with the screening visit through 180 days after the last dose of study therapy. Information must be captured appropriately within the site's source documents.

   Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
6. Male patient agrees to use an adequate method of contraception and not donate sperm, starting with the first dose of study treatment through 90 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred *contraception* for the patient.
7. Patient is able to understand the study procedures and agrees to participate in the study by providing written informed consent.

Patients with normal hepatic function (Group 1):

Patients screened for the normal hepatic function group must meet the following additional criteria to be eligible for enrollment:

1. Patient has no history of hepatic impairment, including but not limited to chronic Hepatitis C or chronic hepatitis B.
2. Patient has liver function test (LFT) results within normal range:
   - Total bilirubin ≤ ULN
   - Aspartate aminotransferase (AST) ≤ ULN.
   - INR ≤1.5 X ULN unless the patient is receiving anticoagulant therapy and the INR is within therapeutic range of intended use of anticoagulants.

3. Patient has adequate hematologic and renal function as defined below (Note: CBC test should be obtained without transfusion or receipt of colony stimulating factors within 4 weeks before obtaining sample):
    - Absolute neutrophil count ≥1500/μL
    - Platelets ≥100,000/μL
    - Hemoglobin ≥9 g/dL
    - Serum creatinine ≤1.5 × ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation.

Patients with moderate hepatic impairment (Group 2):

Patients screened for the moderate hepatic impairment group must meet the following additional criteria to be eligible for enrollment:

1. Patient has stable, moderate hepatic impairment, defined as:
    - BILI: >1.5 × to 3 × ULN, for at least 2 weeks prior to Day 1
    - AST: Any value
    - INR less than 1.8 unless the patient is receiving anticoagulant therapy and the INR is within therapeutic range of intended use of anticoagulants.
2. Patient has hematologic and renal function as defined below (Note: CBC test should be obtained without transfusion or receipt of colony stimulating factors within 4 weeks before obtaining sample):
    - Absolute neutrophil count ≥1000/μL
    - Platelets ≥75,000/μL
    - Hemoglobin ≥8 g/dL
    - Serum creatinine ≤1.5 × ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation.
3. Patient's hepatic disease is deemed stable by the Investigator (i.e. no clinically significant change in hepatic disease status within 30 days prior to Screening).

Criteria for Exclusion:

Patients will not be eligible for study entry if any of the following criteria are met:

All patients:

1. Patient has undergone palliative radiotherapy within 1 week of study drug administration, encompassing >20% of the bone marrow.
2. Patient is starting chemotherapy within 3 weeks of study drug administration.
3. Patient has a known hypersensitivity to the components of niraparib or excipients
4. Patients who received colony-stimulating factors (e.g. granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF], or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment are not eligible.

5. Patient has persistent chemotherapy associated Grade 2 or greater toxicity except for neuropathy, alopecia or fatigue.
6. Patient has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered "controlled," the patient must have undergone treatment (e.g. radiation or chemotherapy) at least 1 month prior to study entry. The patient must not have any new or progressive signs or symptoms related to the central nervous system [CNS] disease and must be taking ≤ 10 mg of prednisone or equivalent per day or no steroids. Patients who have untreated brain metastases and who are not symptomatic may enroll if the Investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days.
7. Patient has undergone major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
8. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder (other than hepatic impairment) or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy or any psychiatric disorder that prohibits obtaining informed consent.
9. Patient has received a transfusion (platelets or red blood cells) within 3 weeks of receiving niraparib.
10. Female patient is pregnant or is expecting to conceive children while receiving study drug or for up to 180 days after the last dose of study drug. Male patient is expecting to donate sperm or father children while receiving study drug or for up to 90 days after the last dose of study drug.
11. Female patient is breastfeeding or is expecting to breastfeed within 30 days of receiving final dose of study drug (women should not breastfeed or store breastmilk for use, during treatment and for 30 days after receiving the final dose of study treatment).
12. Patient has a known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

NOTE: Exclusion Criteria 13-17 apply only to the PK phase of the study.

13. Patient is currently receiving, or unable to refrain from taking from 4 days prior to dosing until the time of the last PK blood draw, any of the following cytochrome (CYP) 1A2 substrates: alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine, and theophylline.
14. Patient is unable to refrain from any intake of grapefruit or grapefruit juice within 4 days of the first administration of niraparib until the final PK sample collection.
15. Patient is currently receiving, or unable to refrain from taking from 4 days prior to dosing until the last PK blood draw, any of the following P-glycoprotein (P-gp) inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor and verapamil.
16. Patient is taking proton pump inhibitors, antacids, or histamine 2 (H2) blockers within 48 hours prior to niraparib administration, and/or within 6 hours after niraparib administration.

17. Patient has esophagogastrointestinal disease or resection that is likely to interfere with the absorption of niraparib.

Patients with moderate hepatic impairment (Group 2):

Patients screened for the moderate hepatic impairment group who meet any of the following additional criteria will be excluded from the study:

1. Patient has hepatic encephalopathy, severe portal hypertension and/or porto-systemic shunt.
2. Patient has fluctuating or rapidly deteriorating hepatic function as determined by the investigator within the screening period.
3. Patient has acute liver disease caused by drug toxicity or by an infection.
4. Patient has biliary obstruction or other causes of hepatic impairment not related to parenchymal disorder and/or disease of the liver.
5. Patient has esophageal variceal bleeding within the past 2 months.
6. Patient is receiving anticoagulant therapy with warfarin or related coumarins.
7. Patient has a history of hepatic transplant, systemic lupus erythematosus, or hepatic coma.

Investigational Product, Dosage and Mode of Administration:

PK Phase (all patients) (niraparib 300 mg (3 × 100-mg capsules) orally

Extension Phase (patients with normal hepatic function) The starting dose of niraparib will be based on the patient's screening actual body weight or current platelet count. Patients with a screening actual body weight of ≥77 kg **and** current platelet count of ≥150,000/μL at C1D1 (or at screening if done 72 hours prior to C1D1) will take three capsules of 100 mg strength (300 mg/day) at each dose administration. Patients with a screening actual body weight of <77 kg **and/or** current platelet count of <150,000/μL C1D1 (or at screening if done 72 hours prior to C1D1) will take two capsules of 100 mg strength (200 mg) at each dose administration. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation.

Extension Phase (patients with moderately impaired hepatic function: niraparib 200 mg (2 × 100-mg capsules) orally

Duration of Treatment:

PK phase: single dose, one day

Extension phase: once daily (QD) dosing until treatment discontinuation

Reference Therapy, Dosage and Mode of Administration:

None

Criteria for Evaluation:

Pharmacokinetics:

Pharmacokinetic parameters to be assessed include:

- AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinity
- C_{max}: Observed maximum plasma concentration
- t_{max}: Time to C_{max}

- t½: Terminal half-life
- CL/F: Apparent total body clearance

Additional plasma samples will be drawn for the assessment of unbound concentrations of niraparib and M1 (if appropriate). The following will be calculated for protein binding:

- Fu: Fraction of unbound niraparib
- CLfu/F: Clearance of free niraparib

Blood Sample Collection:

Blood (approximately 5 mL per sample) will be collected during the study for PK assessments at the following time points relative to niraparib dosing: predose (within 30 minutes prior to dosing) and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post dose. The following excursions are permitted relative to the protocol-specified PK sampling times. Deviations outside of these time windows must be documented:

- Predose: ≤ 30 minutes
- 1, 2, 3, and 4 hours: ±5 minutes
- 6, 8, and 12 hours: ±15 minutes
- 24 hours: ±30 minutes
- 48 and 72 hours: ±60 minutes
- 120 and 168 hours: ± 120 minutes

The volume of blood collected for PK assessments for each patient during the study will be approximately 65 mL. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual. In brief, blood will be collected into potassium ethylene diamine tetraacetic acid (K_3EDTA) tubes, processed and plasma analyzed by a validated method of liquid chromatography coupled to tandem mass spectrometry detection (LC/MS/MS) for determination of the concentrations of niraparib and M1. The pharmacokinetic parameters will be calculated from the plasma concentration-time profiles. The non-compartmental analysis will be performed using WinNonlin, version 5.1 or higher.

Blood (approximately 5 mL per sample) will be collected during the study for plasma protein binding evaluations at predose (within 30 minutes prior to dosing) and at 3 hours and 168 hours.

Safety:

Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, clinical laboratory results, and monitoring of concomitant medications.

Statistical Methods:

A statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the safety analyses outlined in this section. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report (CSR).

Study completion status will be summarized for all patients. Categories summarized will include those patients who were screened, enrolled, completed the study, or discontinued early (including reason for discontinuation).

Demographic characteristics of all patients enrolled will be summarized descriptively by group and will include age, sex, race, height, and weight.

Protocol deviations will be listed by patient.

Pharmacokinetic Analyses:

The pharmacokinetic population for the evaluation of the PK of niraparib and M1 in patients with normal hepatic function and in patients with hepatic impairment will consist of all patients who receive niraparib and have sufficient evaluable samples for the determination of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Plasma concentrations over time and PK parameters of niraparib will be evaluated after single dose administration. Individual and mean plasma concentrations over time will be plotted by hepatic function group.

Individual patient PK parameter values will be derived by non-compartmental methods using WinNonlin, version 5.1 or higher. Nominal or actual time will be used in the data analysis. Plasma concentrations and PK parameters will be summarized in terms of the number of patients, arithmetic mean, standard deviation (StDev), coefficient of variation, median, minimum and maximum by group.

To assess the effects of hepatic impairment on niraparib PK, linear models will be applied to the log-transformed C_{max}, and AUC_{0-t}, $AUC_{0-\infty}$. The independent variable in the analyses will be liver function (normal hepatic function [control] or moderate hepatic impairment). Point estimates and 90% CIs for differences between means on the log scale will be exponentiated to express the results as ratios of geometric means on the original scale. Patients with normal hepatic function (Group 2) will be used as reference group to which Group 1 will be compared. No adjustments will be made for multiplicity.

Box plots of PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL/F, and CLfu/F) by hepatic function group will be provided.

Similar analyses will be performed on M1 if appropriate.

The effect of hepatic dysfunction on unbound concentrations of niraparib and M1 may be assessed applying a general linear model with a factor for hepatic impairment status.

Safety Analyses:

The safety population will consist of all patients who receive drug.

All data will be summarized by group. Continuous variables will be summarized using descriptive statistics (number of patients, mean, StDev, minimum, median, and maximum). Categorical variables will be summarized using counts of patients and percentages.

All AEs will be listed. The number and percent of patients who experienced an AE will be summarized by timing/treatment for each system organ class (SOC) and preferred term. AEs will also be tabulated accordingly by intensity and causality. Descriptive comparisons of event rates for each group will be presented.

Serious AEs (SAEs) will be listed separately.

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

The adverse events of special interest (AESIs) for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), pneumonitis, embryo-fetal toxicity, and secondary cancer (new malignancies other than MDS/AML). AESIs must be reported to the Sponsor as soon as the Investigator becomes aware of them.

Individual data listings of laboratory test results will be presented. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listing.

Clinical laboratory tests (observed values and changes from baseline) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters (chemistry and hematology).

Individual data listings of vital signs (observed and change from Baseline) will be presented for each patient. Individual clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE listing.

All physical examination findings, including abnormal findings, will be listed.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ADL	activity of daily living
ADP	adenosine diphosphate
AESI	adverse event of special interest
aPTT	activated partial thromboplastin time
AME	absorption, metabolism, and distribution
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
AUC_{0-t}	area under the concentration × time curve calculated to last measured concentration
$AUC_{0-\infty}$	area under the concentration × time curve calculated to infinity
BILI	bilirubin
BRCA	breast cancer (gene)
CI	confidence interval
C_{max}	maximum concentration
CBC	complete blood count
CL_{cr}	creatinine clearance
CL/F	apparent total clearance
CLFu/F	clearance of free niraparib
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	cytochrome 1A2
DNA	deoxyribonucleic acid
ECG	Electrocardiogram

Abbreviation or Specialist Term	Explanation
ECOG	Easter Cooperative Oncology Group
eCRF	electronic case report form
EDTA	ethylene diamine tetraacetic acid
EOS	end of study
FDA	US Food and Drug Administration
Fu	fraction of unbound niraparib
G-CSF	granulocyte colony-stimulating factor
g*BRCA*mut	germline breast cancer gene mutation
g*BRCA*wt	germline breast cancer wild type gene
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
H2	histamine 2
HRD	homologous recombination deficiency
HRDneg	homologous recombination deficiency (negative)
HRDpos	homologous recombination deficiency (positive)
IB	Investigator's Brochure
IC	inhibitory concentration
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC/MS/MS	liquid chromatography-tandem mass spectrometry
LFT	liver function test
M1	major metabolite
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
PARP	poly (ADP-ribose) polymerase
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetics

Abbreviation or Specialist Term	Explanation
PI	Principal Investigator
PO	oral(ly)
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
StDev	standard deviation
$t_{½}$	terminal half-life
t_{max}	time to maximum concentration
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
Vd/F	apparent volume of distribution
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Niraparib

Niraparib (ZEJULA®) is a poly (adenosine diphosphate [ADP]-ribose polymerase) (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Niraparib received FDA approval in March 2017. For more details, refer to ZEJULA® label.[1]

In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-deoxyribonucleic acid (DNA) complexes resulting in DNA damage, apoptosis and cell death. Increased niraparib-induced cytotoxicity was observed in tumor cell lines with or without deficiencies in *BRCA*1/2. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in *BRCA*1/2 and in human patient-derived xenograft tumor models with homologous recombination deficiency that had either mutated or wild type *BRCA*1/2.

Niraparib co-crystallized with the human PARP-1 catalytic domain and was shown to inhibit PARP-1 and PARP-2 activity in vitro with an inhibitory concentration (IC_{50}) of 3.8 and 2.1 nM, respectively. In cultured cells, niraparib inhibited PARP-dependent PARylation stimulated by DNA damage with an IC_{50} of 4 nM and an IC_{90} of 40 nM.

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.

Nonclinical data, including cell-derived and patient-derived xenograph studies demonstrating response to niraparib in both *BRCA* mutated (g*BRCA*mut) and *BRCA* wild-type (g*BRCA*wt) tumors, are discussed in detail in the Investigator's Brochure (IB).

There are 3 ongoing Phase 3 niraparib studies, Study PR-30-5010-C (BRAVO), Study PR-30-5017-C (PRIMA), and Study PR-30-5011-C (NOVA). There isA also 1 ongoing Phase 1/2 study, Study 3000-PN162-01-001 (TOPACIO) and 1 ongoing Phase 2 study, Study PR-30-5020-C (QUADRA).

The ENGOT-OV16/NOVA study[4] is a double-blind, 2:1 (niraparib:placebo) randomized, placebo-controlled study of maintenance treatment with niraparib compared with placebo in patients with platinum- sensitive ovarian cancer who have received at least 2 platinum-based regimens, had a response to their last regimen, and have no measurable disease >2 cm and normal cancer antigen 125 (CA-125) (or >90% decrease) following their last treatment. There were 2 independent patient cohorts comprising patients who have deleterious g*BRCA*mut versus those who have a tumor with high-grade serous histology but without g*BRCA*mut (non-g*BRCA*mut). Patients in the non- g*BRCA*mut cohort are further characterized by tumor HRD status (positive or negative).

A total of 553 patients were randomized into this Phase 3 study at 107 centers worldwide. The study population comprises 203 patients randomized into the g*BRCA*mut cohort and 350 patients randomized into the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut

cohort, 162 had tumors that were defined as HRDpos and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined (HRDnd) for 54 patients.

Demographic and baseline characteristics were well-balanced.

Table 3 shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRD negative (HRDneg) tumors was 6.9 months (95% CI: 5.6, 9.6) in the niraparib arm compared to 3.8 months (95% CI: 3.7, 5.6) in the placebo arm with an HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226).

Table 2: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut Cohort		**non-gBRCAmut Cohort** (regardless of HRD status)		**HRDpos (within non-gBRCAmut cohort)**	
	Niraparib (N=138)	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**	**Niraparib (N=106)**	**Placebo (N=56)**
PFS Median (95% CI)[a]	21.0 (12.9, NR)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	<0.0001		<0.0001		<0.0001	
Hazard Ratio (Nir:Plac) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	
Progression-free survival is defined as the time in months from the date of randomization to progression or death.						

The primary data to support the safety of treatment with niraparib in this proposed indication are derived from the ENGOT-OV16/NOVA main study in which a total of 546 patients received study treatment. Safety presentations for the NOVA study are derived from the analyses included in the clinical study report and include comparisons of the safety profile of niraparib maintenance treatment versus placebo in women with platinum-sensitive recurrent ovarian cancer.

All patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3/4 TEAEs (74% vs 23%), serious adverse events (SAEs) (30% vs 15%), TEAEs leading to treatment interruption (69% vs 5%), TEAEs leading to dose reduction (67% vs 15%), and TEAEs leading to treatment discontinuation (15% vs 2%) were higher for niraparib. There were no on-treatment deaths reported. The incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) in patients who received niraparib (5 of 367; 1.4%) was similar to the incidence in patients who received placebo (2 of 179; 1.1%). MDS/AML and secondary cancers (new malignancies other than MDS or AML) are potential risks of PARP inhibitors.

The selection of the 300 mg starting dose of niraparib for the phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in the ENGOT-OV16/NOVA study was based on data from the Phase 1 MAD study PN001 conducted by Merck & Co. There were no formal Phase 2 dose-ranging studies conducted. The Phase 1 study included both a dose escalation phase to determine the maximal tolerated dose and an expansion arm to further evaluate the selected dose. A total of 104 patients with advanced solid tumors were evaluated in this study, including 60 during dose escalation from 30 mg to 400 mg and 54 during expansion at the 300 mg dose level. The dose escalation stage determined that 400 mg exceeded the maximal tolerated dose (by traditional dose-limiting toxicity evaluations and by using the pooled adjacent violators algorithm). No dose-limiting toxicities were observed at 290 or 300 mg dose levels. In the Phase 3 study, daily niraparib improved progression-free survival (PFS) in a cohort of patients with g*BRCA* mutation as well as in a cohort of patients without g*BRCA* mutation. Within the g*BRCA*mut cohort, the median PFS was 21.0 months in patients on niraparib versus 5.5 months on placebo (hazard ratio [HR], 0.27; $p < 0.0001$). In recurrent ovarian cancer patients, efficacy was assessed in patients with HRD-positive tumors as identified by the Myriad's myChoice HRD test as well in the overall non-g*BRCA* mutation cohort regardless of HRD status. As observed in the g*BRCA*mut cohort, PFS was significantly longer with niraparib in the homologous recombination deficient-positive group of the non-g*BRCA*mut (without germline *BRCA* mutation) cohort (median, 12.9 months vs 3.8 months; HR, 0.38; $p < 0.0001$). Lastly, PFS was significantly improved in the overall non-g*BRCA*mut cohort (median, 9.3 months vs 3.9 months; HR, 0.45; $p < 0.0001$). Secondary endpoints, including chemotherapy-free interval, time to first subsequent therapy (TFST), and progression-free survival 2 (PFS2), confirmed the PFS benefit of niraparib treatment in both cohorts. This provides compelling evidence that niraparib does not diminish responsiveness to subsequent therapy and that the niraparib treatment effect persists. Subsequently in 2017, a recommendation to consider niraparib maintenance therapy in this setting in cases of CR and PR was added to the National Comprehensive Cancer Network (NCCN) guidelines.[5]

The most commonly observed non-hematologic treatment-emergent adverse events (TEAEs) of any National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade were nausea, fatigue, constipation, and vomiting; the majority of the non-hematologic TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (any grade) were anemia (48.5%), thrombocytopenia 66.2%), and neutropenia (31.4%).

TEAEs leading to treatment interruption, reduction or discontinuation 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 second month of therapy. Most patients achieved their individual maximal tolerated dose by the third month. The average dose of niraparib during the study was 206 mg. After Month 3 or 4, new incidents of thrombocytopenia were reported in < 1% of patients. Although Grade 3 or 4 hematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed, and relatively few patients discontinued due to these AEs (discontinuation rate was 3.3% for thrombocytopenia, 1.4% for anemia 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 in patients who were dose reduced to either 200 mg or

100 mg was consistent with PFS for the patients who remained at 300 mg indicating that patients who required dose reduction do not appear to have decreased efficacy relative to those who remain at the 300 mg starting dose.

These data support that each patient has an optimal benefit/risk at their individualized dose. As lower doses are associated with substantial improvements in the incidence of TEAEs while not appearing to compromise efficacy, approaches to quickly transition patients to their individualized optimal dose, particularly patients at the highest risk of grade 3 or 4 thrombocytopenia in cycle 1were further evaluated. In addition, an exploratory analysis was conducted to determine if risk factors could be identified for a subgroup of patients which were associated with higher rates of hematologic toxicity. In the updated analysis, two factors were identified as being associated with thrombocytopenia, baseline platelet count and baseline body weight.

For a complete discussion on the activity and safety of niraparib, refer to the Investigator's Brochure.

5.2. Niraparib Metabolism

In a dose escalation study in cancer patients (PN001), niraparib exhibited linear PK, and dose-proportional exposure (AUC and C_{max}). Moreover, the consistent t_{max} and $t_{½}$ across the range of doses evaluated (30-400 mg) suggest overall dose-independent absorption and clearance. Following repeat administrations of the daily recommended dose of 300 mg, niraparib accumulation on Day 21 was consistent for both AUC and C_{max} (~2-3 folds). Niraparib was shown to be highly orally bioavailable (F ~73%) (PR-30-3015-C). A high-fat meal exhibited a negligible effect on the extent and rate of absorption niraparib (PR-30-5011-C2-FE); therefore, niraparib can be administered with or without food.

Niraparib was moderately protein bound to human plasma (83.0%) (PK002). The apparent volume of distribution (Vd/F) was 1220 L (PR-30-5015-C), indicating an extensive tissue distribution of niraparib. In the population pharmacokinetic analysis of niraparib, the Vd/F was 1074 L in cancer patients. In nonclinical species (PK001), niraparib exhibited a high volume of distribution, i.e. Vd/F ~ 6.9 and 12.3 L/kg in rats and dogs, respectively. It is readily distributed to the brain and cerebrospinal fluid (CSF) of rats and monkeys, respectively (KB-0039-DA-RI and PK004).

A multiple enzyme-mediated metabolism was established in vitro (PK002) and in vivo (absorption, metabolism, and excretion [AME] study PR-30- 5015-C). The carboxylesterases-catalyzed amide hydrolysis was delineated to be the major primary pathway, followed by the UDP-glucuronosyltransferases (UGTs)-mediated glucuronidation and the other minor secondary pathway (i.e. methylation). The major circulating metabolites in humans are the carboxylic acid (M1) and the glucuronides of M1. The metabolic profile seen in humans is consistent with what was detected in the experimental species (rats and dogs) (PK003).

In the AME study in cancer patients using ^{14}C-radioactive niraparib (N = 6, PR-30-5015-C), a mean measured total of 86.2% (ranged from 71.1% to 91.0%) of the radioactive dose was recovered in urine and fecal samples collected daily from 0 to 504 hours (21 days) postdose after single oral administration of ^{14}C-niraparib. Total radioactivity recovered in the urine accounted for 47.5% (ranged from 33.4% to 60.2%) and in the feces for 38.8% (ranged from 28.3% to

47.0%) of the dose. Therefore, the overall recovery in the excreta following the continuous collection up to 21 days was virtually complete, suggestive of minimal long-term retention of niraparib or its metabolites. Moreover, hepatobiliary clearance and renal excretion are the major routes of elimination in humans.

5.3. Rationale for Current Study

Niraparib is extensively metabolized and eliminated primarily by hepatic and renal pathways. The purpose of this study is to evaluate pharmacokinetics and safety of niraparib in patients with moderate hepatic impairment, for the purpose of providing recommendations to guide the initial dose and dose titration in this patient population.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

- To characterize the pharmacokinetics (PK) of niraparib and its major metabolite (M1) when administered as a single dose in cancer patients with normal hepatic function compared to patients with moderate hepatic impairment.

6.2. Secondary Objectives

- To evaluate the safety of niraparib when administered as a single dose in patients with moderate hepatic impairment.
- To obtain additional safety data through the extension phase, in which patients have the option to continue receiving niraparib.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 1, open-label, parallel-group, single-dose study in patients with advanced solid tumors and with either normal hepatic function or moderate hepatic impairment.

Patients with solid tumors will be recruited and enrolled within the following groups:

- Group 1: normal hepatic function (total bilirubin [BILI] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN])
- Group 2: moderate hepatic impairment (BILI >1.5 × to 3 × ULN) and any degree of AST elevation

7.1.1. PK Phase

All patients will receive a single dose of 300 mg niraparib administered as 3 × 100 mg capsules on Day 1. Patients will undergo PK sampling up to 168 hours (7 days) following niraparib administration. Pharmacokinetic parameters to be calculated include area under the concentration × time curve calculated to last measured concentration (AUC_{0-t}), area under the concentration × time curve calculated to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to maximum concentration (t_{max}), terminal half-life ($t_{½}$), and apparent total clearance (CL/F). Protein binding parameters to be calculated include fraction of unbound drug (Fu) and clearance of free drug (CLfu/F). The study will be considered complete when the final PK evaluable patient completes all assessments in the PK phase of the study.

Safety will be assessed through adverse event assessment, physical examination, vital sign measurements, clinical laboratory tests, and monitoring of concomitant medications (Section 12).

7.1.1.1. Fasting and Study Drug Administration for the PK Phase

During the PK Phase of the study, patients should come to the clinic on the morning of Day 1 of the PK period following a 12-hour overnight fast. During the overnight fast, patients are permitted to consume water (but no other beverages) until up to 2 hours prior to dosing of the study drug. Patients may take their routine medications with sips of water.

Patients will receive a single dose (300 mg) of the formulation with approximately 250 ml of water on Day 1 of the PK period. Patients may resume their regular diet 4 hours after taking the study drug.

7.1.2. Extension Phase

On the same day that patients complete the final study assessments for the PK phase, patients may be eligible to continue receiving niraparib in the extension phase of the study, if the investigator believes it is in the best clinical interest of the patient. Patients will receive their first therapeutic dose of niraparib on Cycle 1/Day 1 of the extension phase. For patients with normal hepatic function, the starting dose of niraparib will be based on the patient's screening actual body weight or current platelet count. Patients with a screening actual body weight of ≥ 77 kg and current platelet count of ≥150,000/µL at C1D1 (or at screening if done 72 hours prior to C1D1) will take three capsules of 100 mg strength (300 mg/day) at each dose

administration. Patients with a screening actual body weight of < 77 kg and current platelet count of <150,000/µL at C1D1 (or at screening if done 72 hours prior to C1D1 will take two capsules of 100 mg strength (200 mg) at each dose administration. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation.

Patients with moderately impaired hepatic function will receive an oral daily dose of niraparib 200 mg (2 × 100-mg capsules).

Patients will return to the study center during Cycle 1 on Days 8, 15, and 21 to undergo safety assessments (including complete blood counts [CBCs]). Thereafter, patients will return on the first day of every treatment cycle (28 ±3 days) to receive study drug and for safety assessments (including CBCs). Dose modification (dose interruption and/or reduction) may be implemented for any grade toxicity considered intolerable by the patient, and must be implemented for any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 non-hematologic adverse event considered by the Investigator related to study treatment or for hematologic toxicity as outlined in the protocol. Patients may continue in the extension phase until disease progression (assessed by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 and clinical signs and symptoms), unacceptable toxicity, death or discontinuation from the study treatment for any other reason. At end of study (EOS), safety assessments will be completed. No new capsules will be dispensed at EOS.

Table 4 and Table 5 presents the schedule of assessments. Section 7.5 details the procedures to be performed on each study day/visit.

7.2. Number of Patients

Approximately 16 patients will be enrolled.

7.3. Treatment Assignment

This study is open-label, and all patients will receive niraparib.

7.4. Schedule of Assessments

Table 3: PK Phase Schedule of Assessments

Assessment	Screening	PK Phase							
Day of Procedure	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X								
Inclusion/ exclusion criteria review	X								
Demographics	X								
Medical, surgical, cancer, and medication history	X								
Investigator-assessed tumor assessment[a]	X								
Vital signs	X	X[b]	X						X
Height and weight	X								
ECOG performance status	X								
Clinical laboratory assessments									
CBC[c]	X								X
Serum chemistry	X								X
Coagulation	X								
Pregnancy test	X[d]								X
Urinalysis	X								
Physical exam	X								X
CL_{cr} calculation or Creatinine clearance	X								
Blood sample for PK analysis		X	X	X	X		X		X
Blood sample for plasma protein binding analysis		X							X

Assessment	**Screening**	**PK Phase**							
Day of Procedure	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Concomitant medications/ procedures		Recorded from first dose of study drug through Safety follow-up							
AE monitoring[e]	X	X	X	X	X	X[e]	X	X[e]	X
Niraparib treatment dispensed		X							

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; CLcr = creatinine clearance; CT = computed tomography; ECOG= Eastern Cooperative Oncology Group; EOS = end of study; ICF = informed consent form; MRI = magnetic resonance imaging; PK = pharmacokinetic; SAE = serious adverse event.

[a] RECIST (v1.1) tumor assessment via a CT or MRI scan of clinically indicated areas and evaluation of clinical signs and symptoms should be performed at minimum at screening in the PK Phase and as described in Table 5 for the Extension Phase.

[b] To be collected prior to niraparib dosing

[c] During the extension phase, test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities.

[d] Serum or urine pregnancy test within 72 hours prior to first dose of niraparib

[e] Collection of AEs begins when ICF is signed. AE monitoring on PK Phase Days 5 and 7 may be performed by telephone.

Table 4: Extension Phase Schedule of Assessments

Assessment	**Extension Phase** Cycle 1				Cycle n/Day 1	EOS	Safety Follow-up
Day of Procedure (window)	**1**[a]	8	15	21	1	(+ 7 Days post-treatment)	30 (+ 7 Days)
Investigator assessed tumor assessment[b]					X	X	
Vital signs	X				X	X	X
ECOG	X					X	X
Weight							X
CBC[c]	X	X	X	X	X	X	X
Serum chemistry					X	X	X
Pregnancy test					X	X	X
Urinalysis							X
Physical exam	X				X	X	X
Concomitant medications/ procedures		Recorded from first dose of study drug through Safety follow-up					
AE monitoring[d]	X	X	X	X	X	X	X
Niraparib treatment dispensed	X[e]				X		

[a] May be the same as PK Day 8/End of PK Phase

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; CLcr = creatinine clearance; CT = computed tomography; ECOG= Eastern Cooperative Oncology Group; EOS = end of study; ICF = informed consent form; MRI = magnetic resonance imaging; PK = pharmacokinetic; SAE = serious adverse event.

[b] Tumor assessment via a CT or MRI scan of clinically indicated areas and evaluation of clinical signs and symptoms should be performed at a minimum at screening and, during the extension phase, every three cycles or per the Institution's standard practice. The Investigator will evaluate the patient scans and clinical symptoms to evaluate disease status and progression, discontinue niraparib and initiate subsequent anticancer treatment as necessary.

[c] During the extension phase, test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities.

[d] AEs are required to be captured through 30 days after cessation of study treatment; SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy). Study drug-related SAEs and adverse events of special interest (AESIs) will be collected via telephone every 90 ± 14 days after the last dose of study drug until study closeout, or as otherwise indicated in AESI, Section 12.2.7. AESIs must be reported as soon as the investigator becomes aware of them.

[e] If Cycle 1/Day 1 is the same day as Day 8 of the PK phase, then niraparib treatment must be dispensed after all other assessments (including PK) have been completed.

Table 5: Pharmacokinetic Sampling

Pharmacokinetic Assessments	
Timepoint	**Collection window**
Predose	within 30 minutes prior to dosing
1 hr postdose	± 5 min
2 hrs postdose	± 5 min
3 hrs postdose	± 5 min
4 hrs postdose	± 5 min
6 hrs postdose	± 15 min
8 hrs postdose	± 15 min
12 hrs postdose	± 15 min
24 hrs postdose	± 30 min
48 hrs postdose	± 60 min
72 hrs postdose	± 60 min
120 hrs postdose	± 120 min
168 hrs postdose	± 120 min
Plasma protein binding	
Predose	within 30 minutes prior to dosing
3 hrs postdose	± 5 min
168 hrs postdose	± 120 min

7.5. Assessments by Visit

Assessment details to be performed during the study are described in Section 11 (PK Assessments) and Section 12 (Assessments of Safety). Where PK and vital sign assessments coincide, vital signs should be performed first, then PK (drawn on timepoint).

Concomitant medications/ procedures are to be recorded from first dose of study drug throughout safety follow-up.

7.5.1. Screening Visit (Days -28 to -1)

Screening will take place from Day -28 to Day -1. The following procedures will be performed at the Screening visit:

- Informed consent
- Inclusion/ exclusion criteria review
- Demographics
- Medical, surgical, cancer, and medication history
- Investigator-assessed tumor assessment: Tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of clinically indicated areas should be performed at screening
- Vital signs
- Height and weight
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory assessments (Section 12.1.1)
  - CBC
  - Serum chemistry
  - Coagulation
  - Pregnancy test (serum, to be conducted within 72 hours prior to niraparib dose)
  - Urinalysis
- Physical exam
- Calculation of creatinine clearance (Cl_{cr}) per Cockcroft-Gault as follows:

$$Cl_{cr}\ (mL/min) = \frac{(140 - age) \times weight\ (in\ kg) \times 0.85\ if\ female}{72 \times serum\ creatinine\ (mg/dL)}$$

- AE monitoring

7.5.2. PK Phase

The following procedures and assessments will be completed during the PK phase:

7.5.2.1. Day 1

- Vital signs
- Blood samples for PK determination and for plasma protein binding analysis as described in Table 4 and Section 11
- AE monitoring
- Niraparib dosing

7.5.2.2. Day 2

- Vital signs
- Blood samples for PK determination analysis as described in Table 4 and Section 11
- AE monitoring

7.5.2.3. Day 3

- Blood samples for PK determination analysis as described in Table 4 and Section 11
- AE monitoring

7.5.2.4. Day 4

- Blood samples for PK determination analysis as described in Table 4 and Section 11
- AE monitoring

7.5.2.5. Day 5

- AE monitoring (may be via telephone)

7.5.2.6. Day 6

- Blood samples for PK determination analysis as described in Table 4 and Section 11

7.5.2.7. Day 7

- AE monitoring (may be via telephone)

7.5.2.8. Day 8 / End of PK Phase

- Note that if a patient is continuing onto the extension phase, the Day 8/ end of PK phase may be the same day as Cycle 1/ Day 1/ Extension phase.
  - Vital signs (only if not continuing onto extension phase)
  - Clinical laboratory assessments (Section 12.1.1):
    - CBC
    - Serum chemistry
    - Pregnancy test (serum or urine)

- Physical exam
- Blood samples for PK determination and for plasma protein binding analysis as described in Table 4 and Section 11
- AE monitoring

If a patient is not continuing to Cycle 1/Day 1 in the Extension Phase, then the procedures in the End of Study and Safety Follow Up must be completed.

7.5.3. Extension Phase

Note: During the extension phase, tumor assessment via a CT or MRI scan of clinically indicated areas and evaluation of clinical signs and symptoms should be performed at minimum every three cycles or per the Institution's standard practice. The Investigator will evaluate the patient scans and clinical symptoms to evaluate disease status and progression and initiate subsequent anticancer treatment as necessary.

7.5.4. Cycle 1/ Day 1

In addition to assessments performed for all patients during PK Day 8 (end of PK phase), the following assessments must be performed on Cycle 1/Day 1 for patients continuing onto the extension phase:

- Vital signs
- Physical exam
- CBC (if this does not coincide with Day8/end of PK phase)
- AE monitoring
- Niraparib treatment dispensed (if Cycle 1/Day 1 is the same day as Day 8 of the PK phase, then niraparib treatment must be dispensed after all other assessments [including PK] have been completed).

7.5.4.1. Cycle 1/ Day 8

- CBC (during the extension phase, test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities).
- AE monitoring

7.5.4.2. Cycle 1/ Day 15

- CBC (during the extension phase, test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities).
- AE monitoring

7.5.4.3. Cycle 1/ Day 21

- CBC (during the extension phase, test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities).
- AE monitoring

7.5.4.4. Cycle n/ Day 1

- Vital signs
- Clinical laboratory assessments (Section 12.1.1):
  - CBC (during the extension phase, test complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. Medical and supportive therapy should be optimized for management of toxicities).
  - Serum chemistry
  - Pregnancy text (serum or urine)
- Physical exam
- Tumor assessment via a CT or MRI scan of clinically indicated areas and evaluation of clinical signs and symptoms should be performed at minimum every three cycles or per the Institution's standard practice.
- AE monitoring
- Niraparib treatment dispensed

7.5.4.5. End of Study

- Investigator-assessed RECIST (v. 1.1) tumor assessment (see note above, Section 7.5.3)
- Vital signs
- ECOG
- Clinical laboratory assessments (Section 12.1.1):
  - CBC
  - Serum chemistry
  - Pregnancy test (serum or urine)
- Physical exam
- AE monitoring

7.5.5. Safety Follow-up (30 days [+ 7 days] Post-treatment)

- Physical exam

- Clinical laboratory assessments: may be done at the study center's local laboratory or at a laboratory local to the patient if the laboratory is included on FDA Form 1572:
  - CBC
  - Serum chemistry
  - Pregnancy test (urine)
  - Urinalysis
- Vital signs
- ECOG
- Weight
- AE monitoring: AEs are required to be captured through 30 days after cessation of study treatment; SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternative anticancer therapy); and any pregnancies that occur within 180 days post-treatment are to be captured. Study drug-related SAEs and adverse events of special interest (AESIs) will be collected via telephone every 90 ± 14 days after the last dose of study drug until study closeout, or as otherwise indicated in AESI, Section 12.2.7. AESIs must be reported as soon as the investigator becomes aware of them. All AEs and SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the change(s) observed, until the patient is lost to follow-up or withdraws consent, or until the patient has died.

8. SELECTION AND DISCONTINUATION OF PATIENTS

8.1. Patient Inclusion Criteria

All patients

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Patient, male or female, is at least 18 years of age.
2. Patient has a diagnosis of advanced solid malignancy that has failed standard therapy or for which standard therapy is not likely to provide meaningful benefit, or patient has refused standard therapy.
3. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to1.
4. Patient is able to take oral medications.
5. Female patient, if of childbearing potential, has a negative serum pregnancy test within 72 hours prior to taking study drug and agrees to abstain from activities that could result in pregnancy from enrollment through 180 days after the last dose of study treatment, or be of non-childbearing potential. Non-childbearing potential is defined as (by other than medical reasons):
   - ≥45 years of age and has not had menses for > 1 year.
   - Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon prestudy (screening) evaluation.
   - Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise the patient must be willing to use highly effective contraception (see Appendix 1) throughout the study, starting with the screening visit through 180 days after the last dose of study therapy. Information must be captured appropriately within the site's source documents.

   Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
6. Male patient agrees to use an adequate method of contraception and not donate sperm, starting with the first dose of study treatment through 90 days after the last dose of study treatment.

   Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
7. Patient is able to understand the study procedures and agrees to participate in the study by providing written informed consent.

Patients with normal hepatic function (Group 1)

Patients screened for the control group must meet the following additional criteria to be eligible for enrollment:

1. Patient has no history of hepatic impairment, including but not limited to chronic hepatitis C or chronic hepatitis B.
2. Patient has liver function test (LFT) results within normal range:
   - Total bilirubin ≤ ULN
   - Aspartate aminotransferase (AST) ≤ ULN
   - INR ≤1.5 ULN unless patient is receiving anticoagulant therapy and the INR is within therapeutic range of intended use of anticoagulants.
3. Patient has adequate hematologic and renal function as defined below (Note: CBC test should be obtained without transfusion or receipt of colony stimulating factors within 4 weeks before obtaining sample):
   - Absolute neutrophil count ≥1,500/μL
   - Platelets ≥100,000/μL
   - Hemoglobin ≥9 g/dL
   - Serum creatinine ≤1.5 × ULN or a calculated creatinine clearance (CL_{cr}) ≥60 mL/min using the Cockcroft-Gault equation.

Patients with moderate hepatic impairment (Group 2)

Patients screened for the moderate hepatic impairment group must meet the following additional criteria to be eligible for enrollment:

1. Patient has stable, moderate hepatic impairment, defined as:
   - BILI: >1.5 × to 3 × ULN, for at least 2 weeks prior to Day 1
   - AST: Any value
   - International normalized ratio (INR) ≤1.8 unless the patient is receiving anticoagulant therapy and the INR is within the therapeutic range of intended use of anticoagulants
2. Patient has hematologic and renal function as defined below (Note: CBC test should be obtained without transfusion or receipt of colony stimulating factors within 4 weeks before obtaining sample):
   - Absolute neutrophil count ≥1000/μL
   - Platelets ≥75,000/μL
   - Hemoglobin ≥8 g/dL
   - Serum creatinine ≤1.5 × ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation.

3. Patient's hepatic disease is deemed stable by the Investigator (i.e. no clinically significant change in hepatic disease status within 30 days prior to Screening).

8.2. Patient Exclusion Criteria

Patients will not be eligible for study entry if any of the following criteria are met:

All patients:

1. Patient has undergone palliative radiotherapy within 1 week of study drug administration, encompassing >20% of the bone marrow.
2. Patient is starting chemotherapy within 3 weeks of study drug administration.
3. Patient has a known hypersensitivity to the components of niraparib or excipients
4. Patients who received colony-stimulating factors (e.g. granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment are not eligible.
5. Patient has persistent chemotherapy associated Grade 2 or greater toxicity except for neuropathy, alopecia or fatigue.
6. Patient has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered "controlled," the patient must have undergone treatment (e.g. radiation or chemotherapy) at least 1 month prior to study entry. The patient must not have any new or progressive signs or symptoms related to the central nervous system [CNS] disease and must be taking ≤ 10 mg of prednisone or equivalent per day or no steroids. Patients who have untreated brain metastases and who are not symptomatic may enroll if the Investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days.
7. Patient has undergone major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
8. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder (other than hepatic impairment); nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy or any psychiatric disorder that prohibits obtaining informed consent.
9. Patient has received a transfusion (platelets or red blood cells) within 3 weeks of receiving niraparib.
10. Female patient is pregnant or is expecting to conceive children while receiving study drug or for up to 180 days after the last dose of study drug. Male patient is expecting to donate sperm or father children while receiving study drug or for up to 90 days after the last dose of study drug.

11. Female patient is breastfeeding or is expecting to breastfeed within 30 days of receiving final dose of study drug (women should not breastfeed or store breastmilk for use, during treatment and for 30 days after receiving the final dose of study treatment).
12. Patient has a known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

NOTE: Exclusion Criteria 13-17 apply only to the PK phase of the study.

13. Patient is currently receiving, or unable to refrain from taking from 4 days prior to dosing until the time of the last PK blood draw, any of the following cytochrome (CYP) 1A2 substrates: alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine, and theophylline.
14. Patient is unable to refrain from any intake of grapefruit or grapefruit juice within starting 4 days prior to of the first administration of niraparib until the final PK sample collection.
15. Patient is currently receiving, or unable to refrain from taking from 4 days prior to dosing until the last PK blood draw, any of the following P-glycoprotein (P-gp) inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil.
16. Patient is taking proton pump inhibitors, antacids, or histamine 2 (H2) blockers within 48 hours prior to niraparib administration, and/or within 6 hours after niraparib administration.
17. Patient has esophagogastrointestinal disease or resection that is likely to interfere with the absorption of niraparib.

Patients with moderate hepatic impairment (Group 2):

Patients screened for the moderate hepatic impairment group who meet any of the following additional criteria will be excluded from the study:

1. Patient has hepatic encephalopathy, severe portal hypertension and/or porto-systemic shunt.
2. Patient has fluctuating or rapidly deteriorating hepatic function as determined by the investigator during the screening period.
3. Patient has acute liver disease caused by drug toxicity or by an infection.
4. Patient has biliary obstruction or other causes of hepatic impairment not related to parenchymal disorder and/or disease of the liver.
5. Patient has esophageal variceal bleeding within 2 months.
6. Patient is receiving anticoagulant therapy with warfarin or related coumarins.
7. Patient has a history of hepatic transplant, systemic lupus erythematosus, or hepatic coma.

8.3. Patient Discontinuation Criteria

8.3.1. Discontinuation from treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing all study treatments include the following:

- AE
- Disease progression as determined by the Investigator
- Clinical disease progression based on clinical criteria by Investigator
- Risk to patient as judged by the Investigator and/or the Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or the Sponsor
- Patient request
- Patient becomes pregnant
- Sponsor decision to terminate study
- Death

Details of required niraparib dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity, are provided in Section 9.4

Discontinuation of treatment may be considered for patients who have attained a confirmed complete response (CR) and have had at least 2 cycles of treatment beyond the date when the initial CR was declared.

Patients who discontinue from study treatments will continue to receive follow-up assessments (Table 4) as part of the study unless they are discontinued from the study (Section 8.3.2).

8.3.2. Discontinuation from the Study

Patients may be discontinued from the study for any of the following reasons:

- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Death from any cause
- Loss to follow-up
- Sponsor decision to terminate study
- Investigator's decision

Patients who withdraw from study drug will be asked to continue study visits and assessments as outlined in the schedule of procedures (Table 4). If a patient is lost to follow-up, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are lost to follow-up, at least 3 documented attempts, including 1 via certified mail, should be made to contact the patient before considering the patient lost to follow-up.

8.3.3. Replacement of Patients

Patients may be replaced so that there are 8 PK-evaluable patients per group.

9. TREATMENT OF PATIENTS

9.1. Randomization and Blinding

This is an open-label study, and patients will not be randomized.

9.2. Description of Study Drug

Table 6: Study Treatment

	Study Treatment
Product Name:	niraparib
Dosage Form:	100 mg capsules
Unit Dose	PK phase: 3 capsules of 100 mg (300 mg) Administered on Day 1 only Extension phase: capsules of 100 mg strength administered once daily (QD), 28 day cycles Patients with normal hepatic function: ≥ 77 kg **and** platelet count of ≥150,000/µL: 300 (3 x 100) mg/day <77 kg **and/or** platelet count of <150,000 u/L: 200 mg/day (2 x 100) mg/day Patients with moderately impaired function: 2 capsules of 100 mg (200 mg) Administered once daily (QD), 28 day cycles
Route of Administration	Oral
Physical Description	Capsule
Manufacturer	QS Pharma LLC

Abbreviations: PK = pharmacokinetic; QD; once daily

9.3. Administration

Niraparib will be supplied as 100-mg capsules.

PK Phase: A single dose (3 capsules of 100-mg strength (300 mg/day) will be administered on Day 1.

Extension phase: For patients with normal hepatic function, the starting dose of niraparib will be based on the patient's screening actual body weight or current platelet count. Patients with a screening actual body weight of ≥77 kg **and** current platelet count of ≥150,000/µL at C1D1 (or at screening if done 72 hours prior to C1D1) will take three capsules of 100 mg strength (300 mg/day) at each dose administration. Patients with a screening actual body weight of <77 kg **and/or** current platelet count of <150,000/µL C1D1 (or at screening if done 72 hours prior to C1D1) will take two capsules of 100 mg strength (200 mg) at each dose administration.

Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation.

Extension phase: Patients with moderately impaired hepatic function will receive an oral daily dose of niraparib 200 mg (2 × 100-mg capsules).

Patients will be instructed to take their niraparib dose at the same time each day. Bedtime administration may be a potential method for managing nausea. Patients must swallow and not chew all capsules. The consumption of water and food is permissible.

Niraparib will be dispensed to patients on Day 1 of every cycle (every 28 days) thereafter until the patient discontinues study treatment. The Pharmacy Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib.

9.4. Dose Adjustment Criteria

During the extension phase, study treatment dosing interruptions are permitted in the case of adverse events, medical/surgical events or logistical reasons not related to study therapy (e.g. surgery, unrelated medical events, patient vacation, or holidays). Patients should resume study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Sponsor.

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

Dose interruption of niraparib may be implemented at any time per the Investigator's judgment. See the following sections for permitted duration of interruption prior to required discontinuation from treatment.

Niraparib dose reduction will be allowed based on treatment side effects. Dose reductions to 1 capsule daily (100 mg) will be allowed (Table 8). No further dose reductions will be allowed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

9.4.1. Niraparib Dose Modifications for Adverse Events

During the extension phase, dose modification may be implemented by the treating physician at any time for any grade of toxicity, when deemed in the best interest of the patient. In the case of severe adverse reactions, treatment should be withheld and then resumed per Table 8 and Table 9.

The recommended dose modifications for hematologic adverse reactions are listed in Table 10.

Table 7: Recommended Dose Modifications for Adverse Reactions

Dose level	**Dose for PK Phase**	**Patients with Normal Hepatic Function in the Extension Phase**	**Patients with Normal Hepatic Function in the Extension Phase**	**Dose for Patients with Moderately Impaired Hepatic Function in the Extension Phase**
	All Patients	Patients ≥77 kg **and** with platelet count of ≥150,000/μL	patients <77 kg **and/or** with platelet count of <150,000 u/L will receive 200 mg/day	
Starting dose	300 mg/day	300 mg/day	200 mg/day	200 mg/day
First dose reduction	200 mg/day	200 mg/day	100 mg/day	100 mg/day
Second dose reduction	100 mg/day*	100 mg/day*	N/A	N/A
*If further dose reduction below 100 mg/day is required, discontinue niraparib.				

9.4.2. Niraparib Dose Modifications for Nonhematologic Toxicity

During the extension phase, treatment with niraparib must be interrupted for any treatment-related nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 event. If toxicity is appropriately resolved to Grade 1 or less within 28 days of interruption, the patient may restart treatment with niraparib with a dose level reduction according to Table 9 unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted.

If the toxicity requiring dose interruption has not resolved to CTCAE Grade 1 or less during a maximum 4-week (28-day) dose interruption period, or the patient has already undergone a dose reduction (to a minimum dose of 100 mg QD), or both, the patient must permanently discontinue treatment with niraparib. Once the dose of niraparib has been reduced, any re-escalation must be discussed with the Sponsor.

Table 8: Niraparib Dose Reductions for Nonhematologic Toxicity in Patients with Normal or Impaired Hepatic Function.

Nonhematologic CTCAE ≥ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose per Table 8. Up to 2 dose reductions are permitted.
CTCAE ≥ Grade 3 treatment-related adverse reaction event lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue medication.
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events	

9.4.3. Niraparib Dose Modifications for Hematologic Toxicity

The dose interruption/modification criteria for niraparib for any hematologic toxicities noted during the extension phase will be based on blood counts and are outlined in Table 10 (Normal Hepatic Function) and Table 11 (Impaired Hepatic Function).

If clinically indicated, use of G-CSF is allowed according to current American Society of Clinical Oncology (ASCO) guidelines.[5] If clinically indicated, red blood cell transfusions are allowed according to institutional guidelines.

If the hematologic toxicity does not recover to the specified level within 4 weeks (28 days) of dose interruption and/or the patient has already undergone 1 dose reduction (to a minimum dose of 100 mg QD), then niraparib should be discontinued.

Patients with normal hepatic function requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support may undergo a niraparib dose reduction upon recovery if study treatment is resumed.

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the Sponsor's Medical Monitor.

It is strongly recommended that the patient be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE ≤ Grade 1 within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue niraparib.

The reason for interruption, reduction, or discontinuation of niraparib should be recorded in the eCRF.

Table 9: Management of Hematologic Toxicities in Patients with Normal Hepatic Function

Medical and supportive therapy should be optimized for management of toxicities.	
Platelet count <100,000/µL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume niraparib at the same or reduced dose per Table 8. If platelet count is <75,000/µL, resume at a reduced dose.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume niraparib at a reduced dose. Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil <1,000/µL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL. Resume niraparib at a reduced dose. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hemoglobin <8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hematologic adverse reaction requiring transfusion or hematopoietic growth factor support	For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.
Abbreviations: MDS = myelodysplastic syndrome, AML = acute myeloid leukemia, CBC = complete blood count, MDS = myelodysplastic syndrome, QD = once daily.	

Table 10: Management of Hematologic Toxicities in Patients with Impaired Hepatic Function

Medical and supportive therapy should be optimized for management of toxicities.	
Platelet count <50,000/µL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥75,000/µL. Resume niraparib at the same or reduced dose per Table 8. If platelet count is <25,000/µL, resume at a reduced dose.
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥75,000/µL. Resume niraparib at a reduced dose. Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil <750/µL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1000/µL. Resume niraparib at a reduced dose. Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hemoglobin <7 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until hemoglobin returns to ≥8 g/dL. Resume niraparib at a reduced dose. Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hematologic adverse reaction requiring transfusion or hematopoietic growth factor support	For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume niraparib at a reduced dose.
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.
Abbreviations: MDS = myelodysplastic syndrome, AML = acute myeloid leukemia, CBC = complete blood count, MDS = myelodysplastic syndrome, QD = once daily.	

If clinically indicated, use of G-CSF is allowed according to current ASCO guidelines.[5] If clinically indicated, red blood cell transfusions are allowed according to institutional guidelines.

If the hematologic toxicity does not recover to the specified level within 4 weeks (28 days) of dose interruption and/or the patient has already undergone 1 dose reduction (to a minimum dose of 100 mg QD), then niraparib should be discontinued.

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the Sponsor's Medical Monitor.

It is strongly recommended that the patient be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE ≤ Grade 1 within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue niraparib. The reason for interruption, reduction, or discontinuation of niraparib should be recorded in the eCRF.

9.5. Concomitant Medications and Study Restrictions

Any medication the patient takes during the study other than the study treatments, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

The identity, dose and regimen of all concomitant drugs must be recorded in the eCRF. All such concomitant medications should remain unchanged for 14 days before dosing with study drug and for the duration of the study. Concomitant medication will not be administered 4 hours before or after dose of niraparib.

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the previous visit.

9.5.1. Prohibited Medications

9.5.1.1. PK Phase

During the PK Phase of the study, patients should not be receiving, and must refrain from taking from 4 days prior to dosing and until the time of the last PK blood draw, the following CYP1A2 substrates: alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine, and theophylline.

Patients must not be receiving, and must refrain from taking from 4 days prior to dosing until the time of the last PK blood draw, any of the following P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor and verapamil.

Patients must not be taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to niraparib administration, and/or within 6 hours after niraparib administration.

9.5.1.2. PK and Extension Phases

Patients are prohibited from receiving the following therapies during the screening, PK, and extension phase of this study:

- Antineoplastic systemic chemotherapy, biological therapy, or hormonal therapy
- Chemotherapy or immunotherapy not specified in this protocol
- Investigational agents other than niraparib

- Prophylactic cytokines (e.g., G-CSF). During the extension phase, prophylactic cytokines should not be administered in the first cycle but may be administered in subsequent cycles according to current ASCO guidelines.[5]

If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. The decision to continue the patient on study therapy, however, requires the mutual agreement of the Investigator, the Sponsor, and the patient.

The niraparib safety profile includes thrombocytopenia; therefore, use caution with anticoagulation and antiplatelet drugs.

9.5.2. Study Restrictions

9.5.2.1. Restrictions Specific to Patients with Moderate Hepatic Impairment

Patients enrolled in the moderate hepatic impairment group should be cautioned about the concomitant use of acetaminophen (Tylenol®, Percocet®, or other analgesic combination tablets containing acetaminophen).

Patients with hepatic impairment may receive standard therapy for diseases related to cirrhosis.

9.5.2.2. Dietary and Fluid Restrictions

Patient must refrain from any intake of grapefruit or grapefruit juice within 4 days of the first administration of niraparib until the final PK sample collection.

9.5.2.3. Other Restrictions

Niraparib is known to have properties that require the patient to use contraception. For details, refer to the IB.

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

Patients should maintain a normal diet unless modifications are required to manage an AE, such as diarrhea, nausea, or vomiting.

9.6. Duration of Therapy

A single dose of niraparib is administered on Day 1 of the PK phase of the study, and PK assessments are conducted for 7 days. Following completion of the PK phase, patients may be eligible to continue QD niraparib treatment in an extension phase until the patient meets any of the study withdrawal criteria (Section 8.3).

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug Packaging, Labeling, and Storage

Niraparib 100-mg capsules may be packed in high-density polyethylene bottles with child-resistant closures or in blister cards. The sponsor is exploring a change in packaging configuration to blister cards, which may be implemented at some point during the study.

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-patient specific.

All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed or administered to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

10.2. Study Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. Study drug accountability should be maintained by each site based on capsules dispensed vs. returned to the clinic at each visit and the number days since last visit.

Details of maintaining drug accountability, including information on the accountability log, will be provided in the Pharmacy Manual.

All dispensation and accountability records will be available for Sponsor review. The Study Monitor will assume the responsibility to reconcile the study treatment accountability log. The pharmacist will dispense study treatment for each patient according to the protocol and Pharmacy Manual, if applicable.

10.3. Study Drug Handling and Disposal

At the end of study (EOS), when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving the Sponsor’s approval in writing, the investigational site is responsible for destruction of study drug according to local regulations. If a site does not have the capability for on-site destruction, the Sponsor will provide a return for destruction service to a third party. Both the unused and expired study medication must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

The drug provided for this study is to be used only as indicated in this protocol and only for the patients entered in this study.

11. PHARMACOKINETIC ASSESSMENTS

11.1. Pharmacokinetic Parameters

Pharmacokinetic parameters to be assessed include the following:

- AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinity
- C_{max}: Observed maximum plasma concentration
- t_{max}: Time to C_{max}
- t½: Terminal half-life
- CL/F: Apparent total body clearance

Additional plasma samples will be drawn for the assessment of unbound concentrations of niraparib and M1. The following will be calculated for protein binding:

- Fu: Fraction of unbound niraparib
- CLfu/F: Clearance of free niraparib

11.2. Blood Sample Collection

Blood will be collected during the study for PK assessments and protein binding at the timepoints relative to niraparib dosing as described in Table 6. In total, approximately 80 mL of blood will be collected from each patient.

11.2.1. Pharmacokinetic Assessment

The volume of blood collected for PK assessments from each patient (approximately 5 mL per sample) during the study will be approximately 65 mL. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual. In brief, blood will be collected into potassium ethylene diamine tetraacetic acid (K_3EDTA) tubes, processed and plasma analyzed by a validated method of liquid chromatography coupled to tandem mass spectrometry detection (LC/MS/MS) for determination of the concentrations of niraparib and M1. The pharmacokinetic parameters (Section 11.1) will be calculated from the plasma concentration-time profiles. The non-compartmental analysis will be performed using WinNonlin, version 5.1 or higher.

11.2.2. Plasma Protein Binding

The total volume of blood collected during the study for plasma protein binding from each patient (approximately 5 mL per sample) will be approximately 15 mL. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual. In brief, plasma protein binding will be performed by equilibrium dialysis (MWCO 10kD). At the end of dialysis, aliquots from both compartments will be analyzed to determine the concentration of the unchanged drug using a modified LC/MS/MS method.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety parameters evaluated during the conduct of the study include TEAEs, discontinuations due to AEs, clinical laboratory assessments (including CBC, serum chemistry, and urinalysis), vital signs, physical examination findings, and monitoring of concomitant medications.

12.1.1. Clinical Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (Table 4 and Table 5). These tests will be performed by the local laboratory at the clinical site.

- **Complete blood count:**
  - Hemoglobin
  - White blood cell count
  - Platelets
  - Differential white cell count
- **Serum chemistry:**
  - Sodium
  - Potassium
  - Chloride
  - Creatinine
  - Urea or blood urea nitrogen
  - Glucose
  - Calcium
  - Phosphate
  - Magnesium
  - Total bilirubin
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Total protein
  - Albumin
  - Amylase
  - Lactate dehydrogenase
- **Urinalysis:**
  - Specific gravity
  - Blood
  - Protein
  - Glucose
  - Bilirubin
- **Serum or urine pregnancy testing**

12.1.2. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure, pulse, and temperature), will be performed in accordance with the schedule of assessments (Table 4 and Table 5).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI (see Section 12.2.7), the event should be recorded and reported according to the SAE reporting process (see Section 12.2.5).

12.1.3. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (Appendix 2) in accordance with the schedule of assessments (Table 4 and Table 5). The same observer should assess performance status each time.

12.2. Adverse Events

12.2.1. Definitions

Adverse event (AE): An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered. A TEAE will be defined as any new AE that begins, or any preexisting condition that worsens in severity during the Treatment Period.

Serious adverse event (SAE): A SAE is defined as any untoward medical occurrence that, at any dose as follows:

- Results in death
- Is life-threatening
  - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Any AE that prolongs hospitalization will be considered an SAE.
  - Exception: Preplanned hospitalization (e.g. for observation, protocol compliance, elective procedures, social reasons) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history section of the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is an important medical event(s)
  - Medical and scientific judgement should be exercised in determining whether situations or events should be considered serious adverse events; An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. (See section 12.2.5 for information about SAE reporting)

Treatment-Emergent Adverse Events (TEAEs): Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

Adverse Events of Special Interest (AESI): Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the investigator to the Sponsor is appropriate.

Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure:

- **Abuse:** the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section
- **Accidental /Occupational exposure:** the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e. study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on an SAE Report Form [or designated Special Form] to the Sponsor regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an SAE, an SAE report form must be submitted to the Sponsor within 24 hours of awareness. If there is no AE or SAE, the occurrence must be submitted on the designated Special Form (indicate 'no AE has occurred') as soon as possible.

12.2.2. Assessment of Adverse Events

12.2.2.1. Severity Assessment

All AEs will be assessed by the Investigator for severity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03: 14 June 2010; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each adverse event. The CTCAE v4.03 is available on the NCI/NIH website.

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.2.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

12.2.2.2. Expectedness

The Sponsor will be responsible for determining whether an adverse event is 'expected' or 'unexpected'. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective niraparib Investigator Brochure (IB).

12.2.2.3. Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Definitely related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.
- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.

- Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g. concomitant disease, environmental factors, or other drugs or chemicals).

12.2.3. Collecting and Recording Adverse Events

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as: "How have you been feeling since you were last asked?" The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be monitored through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternative anticancer therapy) and recorded in the eCRF. SAEs will also be reported on an SAE form as described in section 12.2.5 of this protocol. SAEs considered by the Investigator to be related to study medication are reported until the patient is lost to follow-up or until the patient has died.

All AEs, regardless of the source of identification (e.g. physical examination, laboratory assessment, reported by patient), must be documented in the eCRF for each patient from the signing of the ICF for this study up to 30 days after the last dose of study treatment.

Concomitant illnesses that existed before entry into the study will not be considered an AE unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF as well as on the SAE Report Form medical history section.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 12.2.5

12.2.4. Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the specified follow up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in Section 12.2.5.

12.2.5. Reporting of Serious Adverse Events

The Investigator must report all SAEs within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE using the SAE reporting contact information as printed on the SAE forms and in the SAE Completion guidelines. SAEs can be reported after study completion, if the SAE is assessed study-drug related.

For all SAEs, an SAE report form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE report must be completed each time the Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient number, protocol number, and the SAE term(s) and date of awareness. Additionally, only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation, as requested (e.g. hospital reports, consultant reports, death certificates, autopsy reports) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE form. Also, any additional SAE documentation must be a clear photocopy with the patient's personal identifiers removed. The Investigator must sign and date all SAE forms.

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator must promptly respond to queries from the Sponsor.

The *minimum* information required for an initial SAE report are the following:

- Name of person sending the report (i.e. name, address of the Investigator)
- Investigator signature
- Patient identification (screening/randomization number, initials [if permitted by local data privacy regulations], NOT patient name)
  - Protocol number
- Description of SAE with diagnosis if possible
  - Causality assessment
  - Seriousness assessment

The Sponsor (or designee) will confirm receipt of all email reports (as long as the email is not coming from "no reply" domain) within 1 business day.

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator should promptly respond to queries from the Sponsor.

SAE REPORTING CONTACT INFORMATION

Email: PPD

Fax: PPD

Telephone: PPD

12.2.6. Submission and Distribution of Serious Adverse Events

Per regulatory requirements, if an event is assessed by the Sponsor as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor to submit the SUSAR Regulatory Authorities according to applicable regulations.

In addition, the SUSAR will be distributed to the Investigators/sites, utilizing a Council for International Organizations of Medical Sciences (CIOMS) report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) per the governing institutional requirements and in compliance with local laws and guidelines.

12.2.7. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for niraparib are the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies [other than MDS or AML])
- Pneumonitis
- Embryo-fetal toxicity

Reporting AESIs: All occurrences AESIs must be reported to the Sponsor within 24 hours of awareness. If the AESI is serious, it should be reported on an SAE Report Form [*and* designated Special Form]. If the AESI is not serious, it should be reported on the relevant designated Special Form.

AESIs should also be collected and reported as follows:

• MDS and AML along with other secondary cancers should be reported to the Sponsor until death or loss to follow-up.

• Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first).

• Embryo-fetal toxicity should be reported as outlined in Section 12.2.9.

12.2.8. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental occupational exposure with any study treatment must be reported on a Special Situation Form to the Sponsor regardless of whether an AE or SAE has occurred. The form should be submitted as soon as possible, and if there is no AE or SAE, it should be indicated that 'no AE has occurred'. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated

with an SAE, an SAE report form must be submitted to the Sponsor within 24 hours of awareness.

12.2.9. Pregnancy Reporting and Follow-up

The Investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The site will follow-up with the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. The Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome. If an SAE occurred, then the SAE form must be completed and submitted as well.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (Section 12.2.5).

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions, but should be reported to the Sponsor. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form (e.g. maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

13. STATISTICS

A statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the safety analyses outlined in this section. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report (CSR).

13.1. Determination of Sample Size

16 PK-evaluable patients will be enrolled in the study (8 with normal hepatic function and 8 with moderate hepatic impairment). This is a descriptive study and no formal sample size calculations were performed. The proposed sample size is consistent with the recommendations in the FDA document (at least 6 subjects), Guidance for Industry for Hepatic Function studies (Guidance for Industry 2003).

13.2. Study Population

13.2.1. Patient Disposition

Study completion status will be summarized for all patients. Categories summarized will include those patients who were screened, enrolled, completed the study, or discontinued early (including reason for discontinuation).

13.2.2. Demographic Information and Baseline Characteristics

Demographic characteristics of all patients enrolled will be summarized descriptively by group and will include age, sex, race, height, and weight.

13.2.3. Protocol Deviations

Protocol deviations will be listed by patient.

13.2.4. Analysis Populations

The pharmacokinetic population for the evaluation of the PK of niraparib and M1 in patients with normal hepatic function and in patients with hepatic impairment will consist of all patients who receive niraparib and have sufficient evaluable samples for the determination of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

The safety population will consist of all patients who receive drug.

13.3. General Considerations

All data will be summarized by group. Continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation [StDev], minimum, median, and maximum). Categorical variables will be summarized using counts of patients and percentages.

13.4. Pharmacokinetic Analyses

Plasma concentrations over time and PK parameters of niraparib will be evaluated after single dose administration. Individual and mean plasma concentrations over time will be plotted by hepatic function group.

Individual patient PK parameter values will be derived by non-compartmental methods using WinNonlin, version 5.1 or higher. Nominal or actual time will be used in the data analysis. Plasma concentrations and PK parameters will be summarized in terms of the number of patients, arithmetic mean, standard deviation, coefficient of variation, median, minimum and maximum by group.

To assess the effects of hepatic impairment on niraparib PK, linear models will be applied to the log-transformed C_{max}, and AUC_{0-t}, $AUC_{0-\infty}$. The independent variable in the analyses will be liver function (normal hepatic function [control] or moderate hepatic impairment). Point estimates and 90% CIs for differences between means on the log scale will be exponentiated to express the results as ratios of geometric means on the original scale. Patients with normal hepatic function (Group 2) will be used as reference group to which Group 1 will be compared. No adjustments will be made for multiplicity.

Box plots of PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL/F, and CLfu/F) by hepatic function group will be provided.

Similar analyses will be performed on M1 if appropriate.

The effect of hepatic dysfunction on unbound concentrations of niraparib and M1 may be assessed applying a general linear model with a factor for hepatic impairment status.

13.5. Safety Analyses

13.5.1. Adverse Events

All AEs will be listed. The number and percent of patients who experienced an AE will be summarized by timing/treatment for each system organ class and preferred term. AEs will also be tabulated accordingly by intensity and causality. Descriptive comparisons of event rates for each group will be presented.

Serious AEs will be listed separately.

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Individual data listings of laboratory test results will be presented. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listing.

Clinical laboratory tests (observed values and changes from baseline) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters (chemistry and hematology).

Individual data listings of vital signs (observed and change from Baseline) will be presented for each patient. Individual clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE listing.

All physical examination findings, including abnormal findings, will be listed.

13.5.2. Clinical Laboratory Tests

Individual data listings of laboratory test results will be presented. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listing.

Clinical laboratory tests (observed values and changes from baseline) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters (chemistry and hematology).

13.5.3. Vital Signs

Individual data listings of vital signs (observed and change from Baseline) will be presented for each patient. Individual clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE listing.

13.5.4. Physical Examination

All physical examination findings, including abnormal findings, will be listed.

14. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

14.1. Data Quality Assurance

The Sponsor or its designee will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to Good Clinical Practices (GCP) and standard operating procedures (SOPs) for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator or designee.

14.2. Access to Source Data/Documents

An electronic data capture system to manage data collection will be utilized during this trial. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully Code of Federal Regulations (CFR) 21 part 11 compliant.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (e.g. medical records, AE reporting, and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient receiving study treatment.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB) to have direct access to all documents pertaining to the study.

14.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Council on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

14.4. Good Clinical Practice

This study will be conducted in accordance with ICH GCP and the Declaration of Helsinki (Version 2008). The clinical study will also be carried out in keeping with national and local regulatory requirement(s).

14.5. Informed Consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or AEs that may occur. The patient should be informed that he/she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The ICF must be signed and dated; 1 copy will be given to the patient and the Investigator will retain 1 copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC, and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

14.6. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the responsible IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients with appropriate instructions.

14.7. Study Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed, in order to comply with GCP guidelines. On-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and by communications (letter, telephone, and fax).

All unused study treatment and other study materials will be returned to the Sponsor after the clinical phase of the study has been completed.

14.8. Audits and Inspections

Responsible IRB/IEC/Competent Authorities and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

14.9. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Version 2008). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

14.10. Publication Policy

Information regarding publication of study results is contained in the Steering Committee Charter.

15. LIST OF REFERENCES

1. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology.* 1982;5(6):649-655.
2. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med.* 2016.
3. Niraparib (ZEJULA) Prescribing Information. TESARO. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf.
4. Ricks TK, Chiu HJ, Ison G, et al. Successes and Challenges of PARP Inhibitors in Cancer Therapy. *Front Oncol.* 2015;5:222.
5. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.

APPENDIX 1. CONTRACEPTION GUIDELINES

Patients of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 180 days after last dose of study treatment(s):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral route
  - intravaginal route
  - transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, if the preferred and usual lifestyle of the subject

APPENDIX 2. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Description	Grade
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

Source: [1]