AN OPEN-LABEL, RANDOMIZED-SEQUENCE, MULTICENTER, SINGLE-CROSSOVER STUDY TO ASSESS THE RELATIVE BIOAVAILABILITY AND BIOEQUIVALENCE OF NIRAPARIB TABLET FORMULATION COMPARED TO NIRAPARIB CAPSULE FORMULATION IN PATIENTS WITH ADVANCED SOLID TUMORS

Sponsor:	TESARO, a Glaxo Smith Kline Company 980 Great West Road Brentford Middlesex, TW8 9GS UK
Medical Monitor:	Reginald Ewesuedo, MD Senior Medical Director
Sponsor Protocol No.:	3000-01-004
IND No:	100,996
Study Drug Names:	Niraparib capsules, niraparib tablets
Development Phase:	Phase 1
Date of Original Protocol:	26 September 2017
Date of Amendment 1:	05 February 2018
Date of Amendment 2:	06 August 2018
Date of Amendment 3:	29 January 2019
Date of Amendment 4:	18 June 2019
Date of Amendment 5:	22 December 2020
Version of Protocol:	6.0

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.

Confidentiality Statement

All information contained in this document is privileged and confidential to TESARO, a wholly owned subsidiary of Glaxo Smith Kline (GSK). Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors

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 products 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.

_____ _____

Divya Gupta, MD, Senior Medical Director **Date**
on behalf of:
Reginald Ewesuedo, MD
Senior Medical Director
TESARO, a GSK company

INVESTIGATOR'S AGREEMENT

Declaration of the Principal Investigator

Title: An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors

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 Guideline 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

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Institution

_____

Signature of Investigator

_____

Date

Table 1: Summary of Changes for Amendment 5 (Version 6.0)

Header, cover page, and Table 1: Summary of Changes for Amendment 5 (Version 6.0)	Header updated with new version number, cover page updated with new amendment number, version number, and date of approval. Table 1 created to include rationale for this version.	Updated document per best documentation practices
Entire document	Added Stage 3 FE Study. Editorial changes were made throughout the document and to align with the Sponsor's standards and processes.	To assess the effect of a high-fat meal or a fasted state on niraparib PK following a single oral dose of niraparib 300 mg tablet formulation. Editorial changes were made for conformity, clarity, flow, and typographical error correction
Section 1. Synopsis – Studied period (years)	Added date last patient completed in the Stage 3 FE Study PK Phase	To provide an estimated date for last patient completion in Stage 3 FE Study PK phase
Section 1. Synopsis – Primary Objectives Section 5.1. Primary Objectives	New Stage 3 FE Study primary objective defined: to assess the effect of a high-fat meal on niraparib tablet PK	New primary objective for Stage 3 FE Study
Section 1. Synopsis – Secondary Objectives Section 5.2. Secondary Objectives	Included Stage 3 FE Study into the original secondary objective	New secondary objective for Stage 3 FE Study
Section 1. Synopsis – Rationale for Study Section 4.2. Rationale for Study	Detailed rationale for Stage 3 FE Study	New rationale for Stage 3 FE Study
Section 1. Synopsis – Methodology: Overall Study Design Section 6.1. Overall Study Design	Added a brief description of Stage 3 FE Study	New brief description of Stage 3 FE Study
Section 1. Synopsis – Methodology: Pharmacokinetics (PK) Phase Section 6.1. Overall Study Design – PK Phase Section 9.5. Administration	Described cohort-specific dietary instructions, requirements, PK parameters, and sampling intervals for Stage 3 FE Study PK Phase	New information pertinent to Stage 3 FE Study only

Table 1: Summary of Changes for Amendment 5 (Version 6.0) (Continued)

Section 1. Synopsis – Methodology: Extension Phase Section 6.1 Overall Study Design – Extension Phase	Reduced window for Stage 3 FE Study Extension Phase enrollment. Addition of tablet formulation.	To reduce administrative burden. Patients may receive tablet formulation in the Stage 3 FE Study Extension Phase.
Section 1. Synopsis – Figure 1: Study Design: Single-Crossover Study Section 6.1. Overall Study Design – Figure 2: Study Design: Single Crossover Study	Added Stage 3 FE Study	Details the study design for Stage 3 FE Study
Section 1. Synopsis – Number of patients (planned) Section 6.2. Number of Patients	Added Stage 3 FE Study	Provides estimate of patient numbers required for Stage 3 FE Study
Section 1. Synopsis – Inclusion and Exclusion Criteria for Stage 3 PK Phase and Extension Phase Section 7.1.2. Patient Inclusion Criteria (Stage 3 only) Section 7.2.2. Patient Exclusion Criteria (Stage 3 only) Section 7.3.1. Extension Study Patient Inclusion Criteria (Stage 3 only)	Added inclusion and exclusion criteria specific to Stage 3 FE Study PK and Extension Phase	Details the inclusion and exclusion criteria required for patient eligibility to enroll in Stage 3 FE Study PK and Extension Phase
Section 1. Synopsis – Duration of treatment	Added treatment duration for Stage 3 FE Study	New information pertinent to Stage 3 FE Study only
Section 1. Synopsis – Criteria for evaluation: Pharmacokinetics Section 10. Pharmacokinetic Assessments	Added PK parameter t_{lag} for Stage 3 FE Study	Per FDA guidance for industry: Food-Effect Bioavailability and Fed Bioequivalence Studies
Section 1. Synopsis – Criteria for evaluation: Blood Sample Collection Section 10.1. Blood Sample Collection	Provided blood sample collection parameters for Stage 3 FE Study	New information pertinent to Stage 3 FE Study only

Table 1: Summary of Changes for Amendment 5 (Version 6.0) (Continued)

Section 1. Synopsis – Analysis Populations Section 12.1. Analysis Populations	Added new analysis population for Stage 3 FE Study	New patient population to evaluate the PK parameters for Stage 3 FE Study PK Phase
Section 1. Synopsis – Statistical methods: Sample Size Consideration – Stage 3 Section 12.2. Sample Size Consideration	Added required sample size to characterize statistical calculations for Stage 3 FE Study PK Phase	Provides rationale for sample size and statistical calculations criteria for Stage 3 FE Study
Section 1. Synopsis – Statistical methods: Safety Analyses Section 12.3. Safety Analyses	Described safety analyses provisions for patients enrolled in Stage 3 FE Study PK and Extension Phases	Safety analyses expanded to include patients enrolled in Stage 3 FE Study PK and Extension Phases
Section 1. Synopsis – Statistical methods: Safety Analyses Section 11.2.1.4. Adverse Events of Special Interest (AESI)	Removed monitoring requirement for AESIs of pneumonitis and embryo-fetal toxicity	Pneumonitis and embryo-fetal toxicity will be monitored as an ADR and pregnancy outcome, respectively.
Section 1. Synopsis – Statistical methods: Pharmacokinetic Analyses	Added specific requirements related to Stage 3 FE Study	New information pertinent to Stage 3 FE Study only
Section 4.2. Rationale for Study	Included key results from Stage 2 CSR	New information available since last amendment (Amendment 4)
Section 6.1. Overall Study Design	Briefly described of the Stage 3 FE Study cohort design	New information pertinent to Stage 3 FE Study only
Section 6.1. Overall Study Design – Extension Phase	Described patient eligibility criteria for inclusion in Stage 3 FE Study Extension Phase (this study or an alternative study)	New information pertinent to Stage 3 FE Study only
Section 6.1.1. Fasting and Study Drug Administration for the PK Phase	Described specific instructions for patients enrolled in Stage 3 FE Study PK Phase	
Section 6.1.2. General Study Conduct Section 9.5. Administration		
Section 6.3.2. Randomization Scheme	Briefly described the Stage 3 FE Study randomization scheme	New information pertinent to Stage 3 FE Study only

Table 1: Summary of Changes for Amendment 5 (Version 6.0) (Continued)

Section 6.6.1 Schedule of Events – Table 7: Schedule of Events: Study Drug and PK Phase – Stage 3, Table 8: Schedule of Events: Extension Phase (vital signs and weight row and corresponding footnote 10)	New table added for Stage 3 FE Study PK Phase	New information pertinent to Stage 3 FE Study only. Increased vital signs monitoring from 1 week to 4 weeks to ensure they are appropriately monitored to address new PRES and hypertension guidelines.
Section 7.4.1. Discontinuation from Pharmacokinetic Phase	Added that patient must fast for 14 (10+4) hours for both fed and fasted conditions. Further detail on options for continuing to receive niraparib provided.	Clarity. New criteria pertinent to Stage 3 FE Study only.
Section 7.5. Restrictions During Study – #6and #10	Added that patients must be able to fast for 14 (10+4) hours for both PK dosing periods Added restriction #10.	Clarity Prohibits patients enrolled in Stage 3 from taking lipase inhibitors or cholesterol absorption inhibitors.
Section 7.5.1. Lifestyle Considerations	Updated to detail potential photosensitivity associated with niraparib	New Sponsor guidelines due to updated niraparib safety information
Section 8.1. Description of Study Drug – Table 9: Investigational Product	Added Stage 3 FE Study	New information pertinent to Stage 3 FE Study only
Section 11.1.6. Vital Signs	Included heart rate monitoring requirement	New Sponsor guidelines due to updated niraparib safety information
Section 11.2.8. Hypertension, Including Hypertensive Crisis	New safety monitoring requirements for hypertension, and hypertensive crisis added	
Section 6.4.2. Safety Criteria for Adjustment or Stopping Doses During Extension Phase – Table 3: Niraparib Dose Reductions for Non-Hematologic Toxicities Section 11.2.9 – Posterior Reversible Encephalopathy Syndrome	New safety monitoring requirements for PRES added	

Table 1: Summary of Changes for Amendment 5 (Version 6.0) (Continued)

Section 11.2.10. Allergic Reaction	New allergic reaction data added	
Section 11.1.10.6. Pregnancy Screen	Revised language to indicate test should occur prior to PK period 1 only	Clarity
Section 12.4. Pharmacokinetic Analysis	Details specific PK analyses to be conducted for Stage 3 FE Study PK Phase	Clarifies additional requirement for Stage 3 FE Study PK Phase
Appendix E – Guidance on Composition of High-Fat Meal	New appendix added to provide guidance on composition of a high-fat meal	Provides supportive instruction for Stage 3 FE Study

Abbreviations: ADR=adverse drug reaction; AESI=adverse events of special interest; CSR=clinical study report; FDA=Food and Drug Administration; FE=food effect; PK=pharmacokinetic(s); PRES=Posterior Reversible Encephalopathy Syndrome; t_{lag}=time from administration of the dose to the first quantifiable concentration

1. SYNOPSIS

Name of Sponsor/Company: TESARO, a GSK company	
Name of Investigational Product: Niraparib	
Name of Active Ingredient: Niraparib	
Title of Study: An Open-Label, Randomized-Sequence, Multicenter, Single-Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Formulation Compared to Niraparib Capsule Formulation in Patients with Advanced Solid Tumors	
Study center(s): North America (multicenter)	
Studied period (years): Estimated date first patient enrolled: Q4 2017 Estimated date last patient completed in the Stage 1 PK Phase: Q2 2018 Estimated date last patient completed in the Stage 2 PK Phase: Q1 2020 Estimated date last patient completed in the Stage 3 PK Phase: Q2 2021	**Phase of development:** Phase 1

Objectives:

Primary:

- Stage 1: To obtain preliminary assessment of the relative bioavailability (BA) of 300mg niraparib administered as a tablet versus capsule formulation and to estimate the intrasubject variability of niraparib pharmacokinetics (PK)
- Stage 2: To evaluate if the tablet formulation (1×300 mg) of niraparib is bioequivalent (BE) to the capsule formulation (3×100 mg)
- Stage 3: To assess the effect of a high-fat meal on niraparib PK following a single 300 mg dose of the tablet formulation

Secondary:

- Stage 1, Stage 2, and Stage 3: To evaluate the safety of single dose niraparib when administered as a tablet or capsule formulation in patients with advanced solid tumors
- Extension Phase: To evaluate the safety of continuously dosed niraparib in patients with advanced solid tumors.

CCI [redacted]

Rationale for Study:

This study is an open-label Phase 1 study to evaluate the relative BA and BE of niraparib administered as a tablet formulation compared to the reference capsule formulation manufactured by the same process as currently marketed in the United States. Specifically, a 300 mg niraparib tablet will be

compared to 3 niraparib capsules (3×100 mg). In addition, this study will evaluate the effect of a high-fat meal on the PK of the niraparib 300 mg tablet formulation. The Extension Phase will enable patients enrolled in the study to continue to receive treatment with niraparib if they are tolerating it and, in the Investigator's opinion, may receive benefit.

Methodology:

Overall Study Design

This is a multicenter, open-label study in patients with advanced solid tumors. This is a 3-stage, single cohort, randomized-sequence, single-crossover study to assess the relative BA and BE of niraparib tablet formulation relative to the capsule formulation. In addition, Stage 3 of the protocol is a single cohort, randomized-sequence, 2-period, single dose, crossover study to assess effect of food on the PK of the niraparib tablet formulation.

Pharmacokinetics (PK) Phase: In Stages 1 and 2, patients will be randomized 1:1 to receive tablet formulation followed by capsule formulation or capsule formulation followed by tablet formulation. In Stage 3, patients will be randomized 1:1 to receive tablet formulation in a fasted state followed by tablet formulation taken with a high-fat meal or tablet formulation taken with a high-fat meal followed by tablet formulation taken in a fasted state.

Stage 1: Following an 8-hour fast on Day 1 (see Section 6.1.1), patients will receive a single dose of the formulation (tablet [1×300 mg] or capsule [3×100 mg]) followed by a 7-day (+1 day) Washout/PK period followed by a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK period. Patients receiving the tablet in the first treatment period will receive the capsules in the second treatment period and vice versa (see Section 6.1.1). Extensive PK sampling will be carried out after niraparib dosing (see Section 10.1).

Stage 2: Following an 8-hour fast on Day 1 (see Section 6.1.1), patients will receive a single dose of the formulation (tablet [1×300 mg] or capsule [3×100 mg]) followed by a 14-day (+/- 4 days) Washout/PK period, followed by a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK period. Patients receiving the tablet in the first treatment period will receive the capsules in the second treatment period and vice versa (see Section 6.1.1). Extensive PK sampling will be carried out after niraparib dosing (see Section 10.1).

Stage 3: In period 1, patients will receive a single 300 mg niraparib tablet either following a 10-hour fast (see Section 6.1.1) or directly following consumption of a high-fat meal (see Section 6.1.1), followed by a 14-day (+4 days) PK sampling and washout period. In period 2, patients will be crossed over to receive a single 300 mg niraparib tablet in a fasted state or with a high-fat meal, followed by a 7-day PK sampling period. All patients will fast for a minimum of 4 hours postdose in both periods. Patients receiving the tablet in a fasted state in the first treatment period will receive the tablet with a high-fat meal in the second treatment period and vice versa.

In the rare instance where a delay of the entire PK period 2 is needed for any reason beyond the 4-day window specified above, the site must contact the Sponsor's Medical Monitor to discuss the patient circumstances. The Sponsor will then decide if the patient can continue with PK period 2 with a delay. Similarly, should the laboratory results on D15 (the day of niraparib administration in PK Period 2) show changes in organ function such that the original inclusion criteria for laboratory values are no longer met, or in the event of a significant change of patient's clinical status as judged by the Investigator, the site must consult with the Sponsor to discuss the patient's continued participation in PK period 2. Note that sites need not wait for the pre-dose laboratory results to begin PK period 2, but

rather consult the Sponsor once the results are available as needed. Patients who experience emesis within 10 hours of dosing will be discontinued from the PK Phase and will be allowed to be screened for the Extension Phase. Patients who miss critical PK samples will be discontinued from the PK phase; those that meet other criteria for continued niraparib therapy will be eligible to be screened for the Extension Phase (see Section 6.1).

For Stage 1, PK parameters that will be estimated include area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent total body clearance (CL/F), maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), apparent terminal volume of distribution (Vz/F), and BA of tablet formulation relative to the capsule formulation based on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. Relative bioavailability will be assessed based on the ratio of geometric least-squares means of the test (tablet) to reference (capsule). Additionally, the pharmacokinetics of CCI will be determined (Stage 1 only).

For Stage 2, the same PK parameters as above will be estimated. To conclude bioequivalence, the 90% confidence interval (CI) of the ratio of geometric least-squares means of the test (tablet) to reference (capsule) product should be within 0.800-1.250 for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

For Stage 3, the same PK parameters as above will be estimated. In addition, $t_{lag,}$ the time from administration of the dose to the first quantifiable concentration, will be determined, and t_{max} will be compared between the fed and fasted states. The relative bioavailability of the 300 mg niraparib tablet administered with a high-fat meal relative to fasted dosing will be based on the ratio of geometric least-squares means of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

Additional PK parameters may be estimated (e.g., residual area) if deemed appropriate.

Extension Phase: When patients complete the PK Phase of the study (at least 7-days from the beginning of PK period 2), they may be eligible to participate in the Extension Phase (see Section 6.1).

If the patient has met the inclusion criteria and completed the required screening assessments, the starting dose of niraparib in the Extension Phase will be based on the patient's baseline actual body weight or platelet count. Patients with a baseline actual body weight of ≥77 kg and screening platelet count of ≥150,000/µL (obtained after completion of the PK Phase, as part of Extension Phase screening) will take one 300 mg strength tablet or 3×100 mg tablets/capsules at each dose administration (once a day [QD]). Patients with a baseline actual body weight of <77 kg or screening platelet count of <150,000/µL will take one 200 mg strength tablet or 2×100 mg tablets/capsules at each dose administration (QD). For patients whose initial starting dose is 200 mg QD, escalation to 300 mg QD is permitted after 2 cycles of therapy if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and after approval from the Sponsor. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation. If laboratory values at the beginning of Extension Phase are outside of the range specified in the inclusion criteria, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose. Should a patient start the Extension Phase at 100 mg, consideration may be given to escalate to 200 mg after 2 cycles of therapy

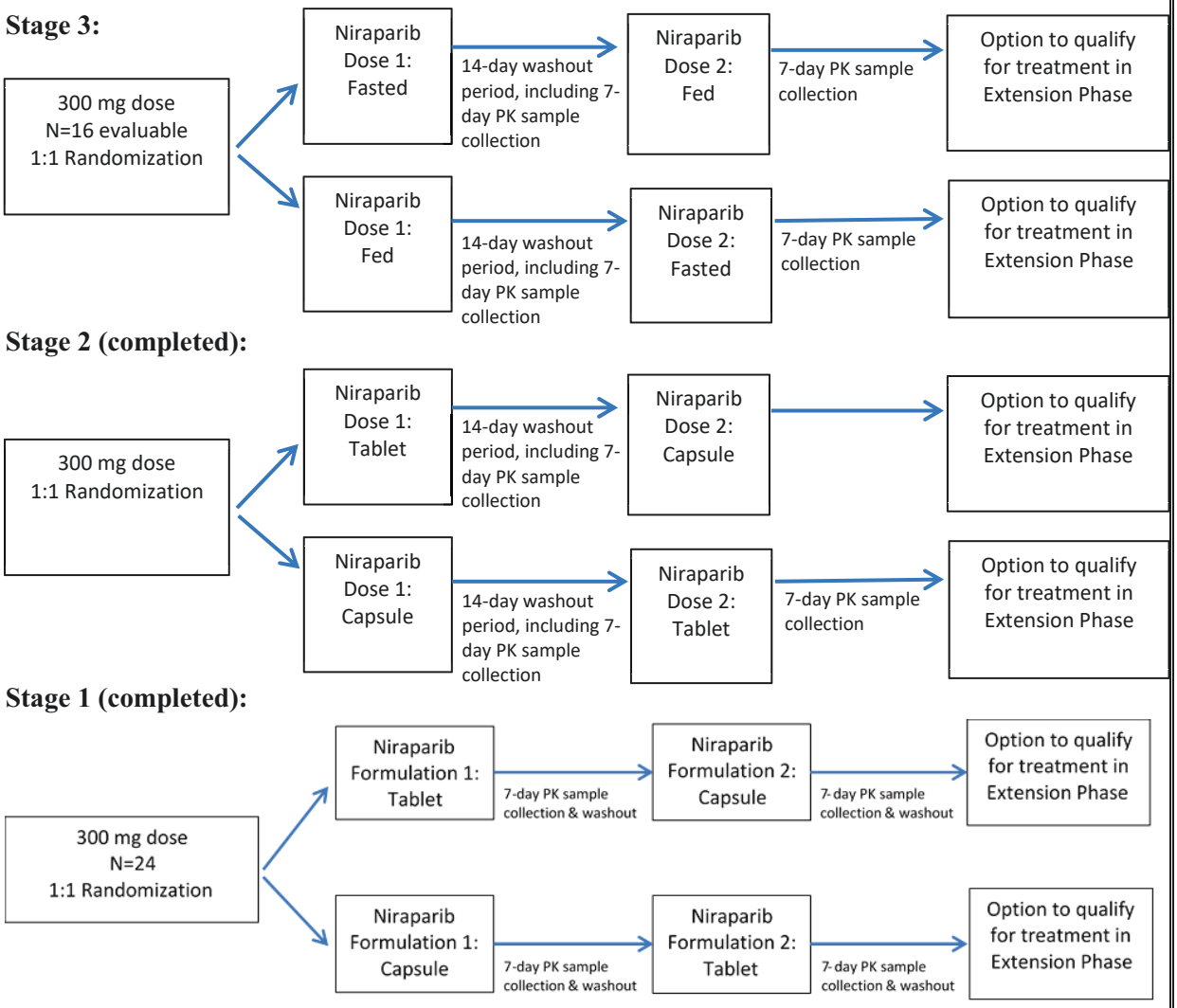
if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and after approval from the Sponsor.

Patients have up to 28 days (21 days for Stage 3 only; up to 28 days may be acceptable following discussion between the Sponsor and Investigator) after completion of the PK Phase to complete the screening assessments and the Extension Phase Screening Visit. A tumor assessment is to be performed prior to the first dose of the Extension Phase (pre-Extension Phase). The pre-Extension Phase tumor assessment need not be completed if the baseline tumor assessment was performed ≤56 days before the first dose of the Extension Phase.

The Cycle 1/Day 1 Visit can occur on the same day as the Extension Phase Screening Visit, dependent upon availability of radiographic results obtained ≤56 days of the first planned dose in the Extension Phase. If the Extension Phase Screening Visit and the Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed by the study personnel prior to study drug administration to ensure eligibility. At the Cycle 1/Day 1 Visit, patients will undergo safety assessments and will receive study drug supply for the duration of 1 cycle (300 mg or 200 mg tablets of niraparib for QD dosing or 3×100 mg or 2×100 mg tablets/capsules of niraparib for QD dosing, depending on availability). It is preferred that patients remain on the same formulation (tablet versus capsule) throughout the Extension Phase. Patients will return on the first day of every treatment cycle (28±7 days) to receive study drug and for safety assessments. Visits will continue approximately every 4 weeks until treatment discontinuation. In line with the niraparib United States Package Insert (US PI), dose interruption (no longer than 28 days) will be allowed based on adverse events (AEs). In addition, dose reductions to 200 mg QD and subsequently to 100 mg QD will be allowed based on AEs (please refer to US PI). Any dose reductions differing from this must be discussed with the medical monitor. Patients can continue in the Extension Phase until the patient meets 1 of the withdrawal criteria (Section 7.4).

End of Treatment (EOT) and Safety Follow-up Visits: The EOT visit will occur within 7 days of the decision to discontinue study drug for any reason. Patients who do not participate in the Extension Phase will also have an EOT visit within 7 days of the decision to discontinue study. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study drug, all assessments required for the Safety Follow-up visit should occur at the EOT visit and this visit will be considered the Safety Follow-up visit. If the first dose of the new anti-cancer therapy occurs >14 days of the decision to discontinue study, the Safety Follow-up visit will occur 30+7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occur first.

Figure 1: Study Design: Single-Crossover Study



Abbreviations: PK=pharmacokinetics

Number of patients (planned):

Stage 1: Approximately 24. Stage 2: Approximately 170 patients will be enrolled to ensure 100 evaluable patients for the BE analysis. Stage 3: Approximately 20 patients will be enrolled to ensure 16 evaluable patients for the FE analysis.

Main Criteria for Inclusion (Stage 1 and 2 only):

PK Phase:

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

1. Patient is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Patient has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, has progressed despite

standard therapy, or for which no standard therapy exists, and who may benefit from treatment with a poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor as assessed by the Investigator. Patients with lymphoma are eligible. Patients with primary central nervous system (CNS) malignancy are eligible provided they do not have new or progressive signs or symptoms, and are not requiring steroid dose exceeding the equivalent of 10 mg of prednisone daily.

3. Patient is at least 18 years of age.
4. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Patient has adequate organ function as defined below (Note: complete blood count [CBC] should be obtained without transfusion or receipt of colony stimulating factors [CSFs], erythropoietin stimulating agents or platelet-stimulating agents within 2 weeks before first dose):
    a. Absolute neutrophil count ≥1,500/μL
    b. Platelets ≥100,000/μL
    c. Hemoglobin ≥9 g/dL (5.6 mM)
    d. Serum creatinine ≤1.5× the upper limit of normal (ULN) or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation.
    e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN
6. Patient has recovered to baseline or Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia or Grade 2 hypothyroidism on a stable dose of thyroid replacement are an exception to this criterion and may qualify for this study). For patients with hematologic, renal or hepatic toxicity from prior therapy inclusion criterion #5 should be applied to determined eligibility.
7. Patient is able to take oral medications.
8. Female patient meets the following criteria:
    a. Patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of non-childbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
    b. Female patient of non-childbearing potential (other than medical reasons) is defined by the following:
        i. ≥45 years of age and has not had menses for >1 year.
        ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
        iii. Had undergone a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study, starting with the Screening

Visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

9. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study drug through 90 days after the last dose of study drug.

   Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

Main Criteria for Inclusion (Stage 3 only):

PK Phase:

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

1. Patient is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Patient has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, has progressed despite standard therapy, or for which no standard therapy exists, and who may benefit from treatment with a PARP inhibitor as assessed by the Investigator. Patients with lymphoma are eligible. Patients with CNS malignancy are eligible provided they do not have new or progressive signs or symptoms and are not requiring steroid dose exceeding the equivalent of 10 mg of prednisone daily.
3. Patient is at least 18 years of age.
4. Patient has an ECOG performance status of 0 to 2.
5. Patient has adequate organ function as defined below (Note: CBC should be obtained without transfusion or receipt of CSFs in the 1 week before obtaining sample.):
   a. Absolute neutrophil count ≥1,000/μL
   b. Platelets ≥100,000/μL
   c. Hemoglobin ≥9 g/dL (5.6 mM)
   d. Serum creatinine ≤1.5× ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation.
   e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
   f. AST and ALT ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN
6. Patient has recovered to baseline or Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia or Grade 2 hypothyroidism on a stable dose of thyroid replacement are an exception to this criterion and may qualify for this study). For patients with hematologic, renal, or hepatic toxicity resulting from prior cancer therapy should meet inclusion criterion #5 for eligibility.
7. Patient is able to swallow and retain oral medication.
8. Female patient meets the following criteria:

a. Female patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of nonchildbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
b. Female patient of nonchildbearing potential (other than medical reasons) is defined by the following:
    i. ≥45 years of age and has not had menses for >1 year.
    ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
    iii. Had undergone a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study, starting with the Screening Visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

9. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study drug through 90 days after the last dose of study drug.

    Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

10. CNS inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following:

    a. No evidence of brain metastases
    b. Untreated brain metastases not needing immediate local therapy
    c. Previously treated brain metastases not needing immediate local therapy
    d. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy
    e. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met:
        i. Time since whole brain radiation therapy (WBRT) is ≥21 days prior to first dose of study drug, time since stereotactic radiosurgery (SRS) is ≥7 days prior to first dose of study drug, or time since surgical resection is ≥28 days.
        ii. Other sites of disease assessable by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) are present
    f. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

11. Patient is able to eat a high-fat meal. See Section 6.1.1.

12. Patient is able to fast for a minimum of 10 hours before start of visit and for an additional 4 hours after study visit. See Section 6.1.1.

Main Criteria for Exclusion (Stage 1 and 2 only):

PK Phase:

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

1. Patient has a known hypersensitivity to the components of niraparib or excipients (see Appendix B).
2. Patient has a known diagnosis of immunodeficiency *(Note: Patients with splenectomy are allowed)*
3. Patient has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered "controlled," the patient must have undergone treatment (eg, 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 disease and must be taking ≤10 mg of prednisone or equivalent per day or no steroids.
4. Patient underwent major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
5. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder; 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, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.
6. 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.
    a. Female patient is breastfeeding or is expecting to breastfeed within 30 days of receiving final dose of study drug (females should not breastfeed or store breastmilk for use, during treatment and for 30 days after receiving the final dose of study drug).
7. Patient has a known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
8. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
9. Patient is unable to refrain from any intake of grapefruit or grapefruit juice within 7 days of the first administration of niraparib until 2 days postdose *(Does not apply for Extension Phase)*.
10. Patient is currently taking any of the following P-glycoprotein inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil, unless the dose and regimen has been stable for at least 14 days prior to first dose and will not change during PK periods 1 and 2 *(Does not apply for Extension Phase)*.

11. Patient taking proton pump inhibitors, antacids, or histamine 2 blockers unless the dose and regimen is stable for at least 14 days prior to first dose and will not change during PK periods 1 and 2. Patients must hold these therapies starting within 8 hours prior to study drug administration until 9 hours after study drug administration *(Does not apply for Extension Phase)*.
12. Patient has gastric, gastro-esophageal, or esophageal cancer; patient is unable to swallow orally administered medication; patient has gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of niraparib.
13. Patient has known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection).
14. Patient has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the Screening Visit) or dependence or is unable to abstain from alcohol for the duration of the study.
15. Patient has had a prior cytotoxic therapy or anticancer monoclonal antibodies (mAbs) within 14 days prior to start of PK Phase. There is no required washout for palliative radiation. For targeted small anti-cancer molecules (eg, tyrosine kinase inhibitors), the required washout is 5 half-lives of the start of PK Phase. Certain hormonal agents are allowed and are listed in Appendix D. For hormonal agents not listed Appendix D, the Site must consult with the Sponsor regarding allowing patient on study. For patient taking hormonal agents, dose and regimen of hormonal agents should have been stable for at least 14 days prior to first dose and is not expected to change during PK periods 1 and 2.
16. Patient has significant pleural effusion or ascites that is expected to require drainage during the PK Phase *(Does not apply for Extension Phase)*.

Main Criteria for Exclusion (Stage 3 only):

PK Phase:

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

1. Patient has a known hypersensitivity to the components of niraparib or excipients (see Appendix B).
2. Patient has a known diagnosis of immunodeficiency *(Note: Patients with splenectomy are allowed)*
3. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
4. Patient underwent major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
5. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder; 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, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.

6. 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.
    a. Female patient is breastfeeding or is expecting to breastfeed within 30 days of receiving final dose of study drug (females should not breastfeed or store breastmilk for use, during treatment and for 30 days after receiving the final dose of study drug).
7. Patient has a known history of MDS or AML.
8. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
9. Patient is unable to refrain from any intake of grapefruit or grapefruit juice within 7 days of the first administration of niraparib until 2 days postdose *(Does not apply for participation in Extension Phase of this study).*
10. Patient is currently taking any of the following P-glycoprotein inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil, unless the dose and regimen has been stable for at least 14 days prior to first dose and will not change during PK periods 1 and 2 *(Does not apply for for participation in Extension Phase of this study)*.
11. Patient is taking a proton pump inhibitor, antacids, or H2 blocker within 48 of dose *(Does not apply for participation in Extension Phase of this study).*
12. Patient has gastric, gastroesophageal or esophageal cancer; patient is unable to swallow orally administered medication; patient has gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of niraparib.
13. Patient has known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen positive status, or suspected active hepatitis C infection).
14. Patient has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the Screening Visit) or dependence or is unable to abstain from alcohol for the duration of the study.
15. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
16. Patient has significant pleural effusion or ascites that is expected to require drainage during the PK Phase *(Does not apply for participation in Extension Phase of this study)*.
17. Patient is currently taking a lipase inhibitor or cholesterol absorption inhibitor, such as orlistat or ezetimibe, respectively. *(Does not apply for participation in Extension Phase of this study)*.

Main Criteria for Inclusion (Stage 1 and 2 only):

Extension Phase:

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

1. Patient has an ECOG performance status of 0 to 2.
2. Patient has adequate organ function as defined below; these criteria must be confirmed within 72 hours of dose 1 in Extension Phase *(Note: CBC should be obtained without transfusion or*

receipt of CSFs, erythropoietin stimulating agents or platelet stimulating factors within 2 weeks before first dose):

a. Absolute neutrophil count ≥1,500/µL
b. Platelets ≥100,000/µL
c. Hemoglobin ≥9 g/dL (5.6 mM)
d. Serum creatinine ≤1.5× the ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation or 24-hour urine creatinine clearance
e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
f. AST and ALT ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN

Note: If laboratory values at the beginning of Extension Phase are outside of the range specified above, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose.

3. Female patient meets the following criteria:

   a. Patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of non-childbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
   b. Female patient of non-childbearing potential (other than medical reasons) is defined by the following:
      i. ≥45 years of age and has not had menses for >1 year).
      ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
      iii. Had a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use highly effective contraception (see Appendix D) throughout the study, starting with the Screening Visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

   Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

4. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study drug through 90 days after the last dose of study drug.

   Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

Main Criteria for Inclusion (Stage 3 only):

Extension Phase:

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

1. Patient has an ECOG performance status of 0 to 2.

2. Patient has adequate organ function as defined below; these criteria must be confirmed within 72 hours of dose 1 in the Extension Phase *(*should be obtained without transfusion or receipt of colony-stimulating factors in the 1 week before obtaining sample*)*:

   a. Absolute neutrophil count ≥1,000/µL
   b. Platelets ≥100,000/µL
   c. Hemoglobin ≥9 g/dL (5.6 mM)
   d. Serum creatinine ≤1.5× ULN or a calculated creatinine clearance of ≥30 mL/min using the Cockcroft-Gault equation.
   e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
   f. AST and ALT ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN

   Note: If laboratory values at the beginning of Extension Phase are outside of the range specified above, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose.

3. Female patient meets the following criteria:

   a. Patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of nonchildbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
   b. Female patient of nonchildbearing potential (other than medical reasons) is defined by the following:
      i. ≥45 years of age and has not had menses for >1 year).
      ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
      iii. Had a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study, starting with the Screening Visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

   Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

4. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study drug through 90 days after the last dose of study drug.

   Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

Investigational product, dosage and mode of administration:

Niraparib 300 mg QD (1×300 mg tablet) orally

Niraparib 200 mg QD (1×200 mg tablet) orally (Stage 1 and 2 only)

Niraparib 100 mg QD (1×100 mg tablet) orally

Reference product, dosage and mode of administration (Stage 1 and 2 only):

Niraparib 300 mg QD (3×100 mg capsules) orally

Duration of treatment:

PK Phase: approximately 15 to 16 days for Stage 1, 18 to 24 days per patient for Stages 2, and 21 to 24 days for Stage 3 of the study, excluding the Screening period

Extension Phase: A patient can continue in the Extension Phase until the patient meets one of the withdrawal criteria.

Reference therapy, dosage and mode of administration: None

Criteria for evaluation:

Pharmacokinetics:

The primary PK parameters for analysis will include AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of niraparib (Stage 1 and 2) and AUC_{0-t} and $AUC_{0-\infty}$ for Stage 3.

Niraparib and CCI (Stage 1 only) PK parameters to be assessed include:

- AUC_{0-t}
- $AUC_{0-\infty}$
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F (niraparib only)
- Vz/F (niraparib only)

Additional PK parameter for Stage 3 only:

- t_{lag}

CCI parameters will only be determined in Stage 1 of the study. Additional PK parameters may be estimated if deemed appropriate. The PK parameters will be calculated from the plasma concentration-time profiles. The non-compartmental analysis will be performed using WinNonlin, version 5.1 or higher. Population PK analysis may be performed on the PK Phase of the study data to inform the dose selection for future studies.

Blood Sample Collection:

During Stage 1 of the study, blood (approximately 5 mL per sample), will be collected during the study for PK assessments at the following time points relative to niraparib dosing (Phase 1): predose (30 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96,120, and 168 hours postdose.

For Stage 2 and Stage 3, PK samples will be drawn at predose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose.

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 to 4 hours: ±5 minutes
- 5 to 8 hours: ±10 minutes
- 12 hours: ±60 minutes
- 24 hours: ±60 minutes
- 48 hours: ±120 minutes
- 72 hours: ±180 minutes
- 96 and 120 hours: ± 240 minutes
- 168 hours: -6/+24 hours

The volume of blood samples collected for PK analysis in the PK Phase would be approximately 160 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 tetra acetic acid (K_3EDTA) tubes, processed and plasma analyzed by a validated method of liquid chromatography coupled to tandem mass spectrometry detection method for determination of analyte concentrations. Samples will be analyzed and reported for niraparib and CCI concentrations in Stage 1. Only niraparib concentrations will be reported for samples collected during Stage 2 and 3.

Safety:

Safety will be assessed based on AEs, physical examinations, vital signs, and clinical laboratory results.

Analysis Populations:

PK Population: All patients who receive at least one dose of niraparib and have at least one measurable niraparib, or niraparib or CCI (Stage 1 only) concentration.

PK Evaluable Population: All patients who complete at least one PK Period and have sufficient concentration data to accurately estimate PK parameters without significant niraparib carryover (baseline concentration >5% of C_{max}) in at least one Period. Patients with carryover will be excluded from the analysis of Period 2, but will be included in the analysis of period 1, as data is available.

BA/BE Evaluable Population: All patients who complete both PK Periods and have sufficient PK sample collection to accurately estimate PK parameters, without significant niraparib carryover (baseline concentration >5% of C_{max}), in both PK Periods. Patients who have significant niraparib carryover in Period 2 will be completely excluded from the BA/BE Evaluable Population.

Food Effect (FE) Evaluable Population: All patients who complete both PK Periods and have sufficient PK sample collection to accurately estimate PK parameters in both periods. Patients meeting non-evaluability criteria per protocol or having significant niraparib carryover (baseline concentration >5% of C_{max}) will be completely excluded from the FE Population.

Safety Population: All patients who receive drug.

Statistical methods:

Sample Size Consideration

Stage 1

No formal sample size calculation was performed for Stage 1. Approximately 24 patients will be enrolled in Stage 1. This sample size is considered adequate for preliminary assessment of the relative bioavailability of the tablet compared to the capsules and for estimating the intra-subject coefficient of variation, after accounting for patient drop-outs and potential carryover.

Stage 2

Based on estimates from Stage 1, 100 BA/BE evaluable patients are required in Stage 2. With 100 evaluable patients, assuming the intra-subject coefficient of variation (CV) is 25% and the true ratio of means is 0.89, there is at least 90% power to demonstrate the bioequivalence (bioequivalence range: 0.800 to 1.250; alpha=0.05). Power calculations were also performed under alternative assumptions for the CV and mean ratio. Assuming the CV is 30% and the true ratio of means is 0.89, with 100 evaluable patients, there is 82% power to demonstrate bioequivalence. Assuming the true ratio is 0.90, the power is 96% and 88% assuming CVs of 25% and 30%, respectively.

The final analysis of bioequivalence will be based on Stage 2 BA/BE evaluable patients only, with a target sample size of 100 evaluable patients. Patients may be identified as non-evaluable due to issues arising during the study conduct, such as:

- emesis within 9 hours of dosing,
- dosing errors,
- patient did not fast prior to dosing,
- missing critical PK sample on Day 8,
- failure to complete both PK periods, and
- significant changes to the patient's medical status that would potentially affect the PK profile as determined by the Sponsor in consultation with the Investigator prior to PK data analysis.

In this patient population, approximately 170 total patients are targeted for enrollment, assuming a 35% non-evaluability rate during the study conduct, and an additional 10% non-evaluability rate during PK analysis. The non-evaluability rate arising during the study conduct will be continuously monitored by the Sponsor and the total number of enrolled patients may be adjusted accordingly with the aim to target the resulting sample size of 100 BA/BE evaluable patients.

Stage 3

Assuming the true ratio of means is 1 and the intra-subject CV is 20% for AUC_{0-t} and $AUC_{0-\infty}$, with 16 evaluable patients, there is approximately 83% probability the 90% CI of the ratio of geometric means will be within 0.800 and 1.250. Based on the results of a FE study conducted using the capsule formulation, an effect of a high-fat meal on C_{max} is possible. The sample size of 16 patients is deemed adequate to characterize this effect. AUC_{0-t} and $AUC_{0-\infty}$ will be the primary parameters for analysis.

The primary analysis will be based on the FE Evaluable Population as it is the most conservative approach, which maximizes the benefits of the crossover design, where each patient serves as their own control. Results for the PK Evaluable Population will also be summarized and reported for this study.

Patients may be identified as non-evaluable due to issues arising during the study conduct, such as:

- dosing errors,
- patient did not follow dietary requirements prior to dose and postdose,
- failure to complete both PK periods, and
- significant changes to the patient's medical status that would potentially affect the PK profile as determined by the Sponsor in consultation with the Investigator prior to PK data analysis.

Patients who experience emesis within 10 hours of dosing or miss sufficient samples to render calculation of AUC unreliable will be discontinued from the PK phase. To account for non-evaluable patients, approximately 20 total patients are targeted for enrollment. The non-evaluability rate arising during the study conduct will be continuously monitored by the Sponsor and the total number of enrolled patients may be adjusted accordingly with the aim to target the resulting sample size of 16 evaluable patients.

Safety Analyses

Data from the Stage 1 PK Phase, Stage 2 PK Phase, Stage 3 PK Phase and Extension Phase will be summarized separately. Summaries will be performed by formulation, fed/fasted state, and dosing period as applicable.

Demographic characteristics will be summarized descriptively and will include age, sex, race, height, and weight.

Protocol deviations will be listed by patient.

All analysis for safety endpoints will be performed in a descriptive manner. Continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation [SD], 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 experience a TEAE will be summarized by timing/treatment for each system organ class and preferred term. AEs will also be tabulated accordingly by intensity and causality.

Serious treatment emergent adverse events (TEAEs) and TEAEs resulting in study discontinuation will be listed separately.

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. 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 drug; serious adverse events (SAEs) are required to be captured through 90 days after cessation of study drug (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) (Section 11.2.1.4) will continue to be monitored until study closeout (unless death or loss to follow-up occurs first). 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.

The AESIs for this study are MDS, AML, 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 or within 24 hours.

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.

In addition, for the Extension Phase, 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 clinically relevant abnormal physical examination findings will be listed.

Pharmacokinetic Analysis

Individual patient PK parameter values will be derived by non-compartmental methods using Phoenix WinNonlin, version 5.1 or higher. Actual time will be used for parameter calculation. The analysis of Stage 1, Stage 2, and Stage 3 will be conducted separately.

During the pharmacokinetic analysis, the following rules will apply:

- Predose sample >5% of C_{max}: profile will be excluded from PK concentration and PK parameters summary and inferential statistics
- Rsq,adj <0.800: $AUC_{0-\infty,}$ λ_z, CL/F, Vz/F, and $t_{1/2}$ will be excluded from descriptive and inferential statistics
- AUC_{0-t} /$AUC_{0-\infty,}$ <0.800: $AUC_{0-\infty}$ and parameters derived from it will be excluded from descriptive and inferential statistics

Planned sampling times will be used to generate the mean concentration-time profiles. Individual and mean plasma concentrations over time will be plotted by formulation in Stage 1 and 2 and by fed/fasted state in Stage 3. Plasma concentrations and PK parameters will be summarized in terms of the number of patients, arithmetic mean, median, SD, coefficient of variation (CV), geometric mean, geometric CV, minimum and maximum by formulation in Stage 1 and 2 and by fed/fasted state in Stage 3, as appropriate. In Stage 3, differences in t_{max} between the fed and fasted state will be assessed and summarized based on the FE Evaluable Population. Details will be provided in the Pharmacokinetic Analysis Plan.

The pharmacokinetic profiles and parameters will be summarized across the PK, PK Evaluable, BA/BE Evaluable, and FE Evaluable populations, as appropriate. Details will be provided in the Pharmacokinetic Analysis Plan.

To assess relative bioavailability/bioequivalence, an analysis of variance model (ANOVA) will be used on logarithmically transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} accounting for the following sources of variation: sequence, subjects nested in sequences, period and treatment. The point estimate and 90% CI for the ratios of the geometric means of the test treatment (tablet) compared to the reference treatment (capsule) will be obtained. Bioequivalence will be claimed if the 90% CI for the ratio of geometric means is between 0.800 and 1.250 for $AUC_{0-\infty}$, AUC_{0-t} and C_{max}. To assess the effect of food in Stage 3, the ratio of geometric means for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of the test treatment (high-fat meal) compared to the reference treatment (fasted state) and corresponding 90% CI will be obtained for $AUC_{0-t,}$, $AUC_{0-\infty}$, and C_{max}.

A population PK analysis may be performed on the PK data from the PK Phase of the study and will be reported separately from the study.

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

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
BA	Bioavailability
BE	Bioequivalence
BP	Blood pressure
BRCA	Breast cancer
CBC	Complete blood count
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent total body clearance
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CRF	Case report form
CSF	Colony stimulating factor
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
FE	Food effect
g*BRCA*mut	Germline *BRCA* mutation
GCP	Good Clinical Practice
HR	Hazard ratio
HRD	Homologous recombination-deficient
IB	Investigator's Brochure
IC_{50}	Median inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous(ly)
K_3EDTA	Potassium ethylene diamine tetra acetic acid
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
mAb	Monoclonal antibody
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
NCI	National Cancer Institute
NIH	National Institute of Health
PARP	Poly(ADP-ribose) polymerase
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PO	Oral(ly)
QD	Once a day
QTc	Corrected QT interval
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious adverse event

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
SD	Standard deviation
SUSAR	Serious Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach C_{max}
t_{lag}	Time from administration of the dose to the first quantifiable concentration
ULN	Upper limit of normal
US PI	United States Package Insert
Vz/F	Apparent terminal volume of distribution

4. INTRODUCTION

4.1. Background

Niraparib is an orally available, potent, highly selective poly (adenosine diphosphate [ADP])-ribose polymerase (PARP)-1 and -2 inhibitor. Niraparib cocrystallized with the human PARP-1 catalytic domain and was shown to inhibit PARP-1 and PARP-2 activity in vitro with a median inhibitory concentration (IC_{50}) of 3.8 and 2.1 nM, respectively.

Niraparib was approved by the Food and Drug Administration in March 2017 and is 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.

4.1.1. Niraparib Nonclinical Studies

The niraparib nonclinical studies are described in detail in the Investigator's Brochure (IB).

4.1.2. Niraparib Clinical Studies

In 2008, a Phase 1 study was initiated in an all solid tumors population to investigate the safety and tolerability of niraparib. Eight (40% [95% CI 19-64]) of 20 BRCA1 or BRCA2 mutation carriers with ovarian cancer had Response Evaluation Criteria in Solid Tumors (RECIST) partial responses, as did two (50% [7-93]) of four mutation carriers with breast cancer. Antitumor activity was also reported in sporadic high-grade serous ovarian cancer, non-small-cell lung cancer, and prostate cancer (Sandhu, 2013).

Clinical studies have shown that PARP inhibitors are active in recurrent ovarian cancer, breast cancer, and prostate cancer (Sandhu, 2013; Fong, 2009; Audeh, 2010; Gelmon, 2011; Kummar, 2012; Ledermann, 2012; Ledermann, 2014). PARP inhibition appears to be most active in patients with g*BRCA mutations* and in patients who are sensitive to platinum-containing therapy. However, clinical benefit has also been observed in g*BRCA* wild-type patients (Sandhu, 2013; Gelmon, 2011; Kummar, 2012; Ledermann, 2012; Ledermann, 2014). In the registrational ENGOT-OV16/NOVA trial, maintenance treatment of patients with recurrent high-grade serous ovarian cancer showed that the PARP-1/2 inhibitor niraparib significantly improved progression-free survival (PFS) in g*BRCA*mut patients (21 months for niraparib vs. 5.5 months for control). Furthermore, in the non-*BRCA*mut population, significant improvement in PFS was also observed (9.3 months for niraparib vs. 3.9 months for placebo, hazard ratio [HR]=0.45, $p < 0.0001$). (Sandhu, 2013; Mirza, 2016) Niraparib has been recently approved in the US for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (Guan, 2017). The niraparib clinical studies are described in detail in the IB.

The safety, tolerability, and PK of niraparib has been evaluated in a series of clinical studies including single-and multiple-dose PK, absorption, metabolism and elimination, and a Phase 3 study (ENGOT-OV16/NOVA), (Mirza, 2016) comprising the QT/QTc and food effect substudy, using the capsule formulation. No clinically significant food effect was observed with the capsule formulation, with no change in niraparib $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ following a high-fat meal, and a 20% reduction in C_{max} when compared to fasted state administration.

Orally-administered niraparib was absorbed with a median time to reach maximum observed plasma concentration (t_{max}) of approximately 2 to 4 hours, highly tissue-distributed, and slowly metabolized and eliminated. The oral BA of niraparib with the capsule formulation is high (absolute BA of the capsule formulation of approximately 73%). Details of the clinical pharmacology of niraparib are described in the niraparib label and IB.

4.1.3. Baseline Platelet Count and Weight as Predictors of Thrombocytopenia in Patients Treated with Niraparib

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial Phase 1 study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180,000 /μL) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the subjects with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of Grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during Cycle 1. In the first 30 days of treatment, a baseline body weight >77 kg is associated with a lower incidence of Grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight<58 kg (43%).

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing Grade ≥3 thrombocytopenia within 30 days after the first dose of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg or baseline platelet count <150,000/μL had a Grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg and a platelet count >150,000/μL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000/μL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000/μL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. Therefore, in the present study in the Extension Phase, patients whose baseline weight is <77 kg or baseline platelet count is <150,000/μL will be treated at the 200 mg starting dose of niraparib.

4.2. Rationale for Study

The approved niraparib drug product is an immediate release hard gelatin capsule dosage form that contains 100 mg of niraparib per capsule. The labelled starting dose for niraparib is 300 mg. Facilitating this dose requires the administration of three 100 mg capsules.

It is the Sponsor's intent to introduce a tablet dosage form that provides the 100 mg, 200 mg and 300 mg dose in single dose strength tablets to reduce the pill burden on the patients.

To this end, the Sponsor has developed a tablet dosage form with the specific intent to provide comparable performance to the approved capsule dosage form. The formulation and manufacturing process of the tablet were selected to produce a tablet with comparable in-vitro performance to the capsule.

This study is an open label Phase 1 study to evaluate the relative BA and BE of niraparib administered as a tablet formulation compared to the reference capsule formulation manufactured by the same process as currently marketed in the United States. Specifically, a 300 mg niraparib tablet will be compared to 3 niraparib capsules (3×100 mg).

Following the PK analysis from the Stage 1 (relative BA), the tablet and capsule formulation were found to have similar bioavailability with the 90% confidence interval (CI) for the least squares geometric mean ratios of the tablet/capsule C_{max}, AUC_{0-t} , and $AUC_{0-\infty}$ falling entirely within 0.800 to 1.250. The inter-subject variability of the tablet formulations' PK parameter estimates appears to be lower than the capsule formulation.

Niraparib PK in Stage 2 of this study was found to be consistent with the values reported in Stage 1 and other studies where niraparib PK was assessed. BE was established between the niraparib tablet (1×300 mg) and capsule (3×100 mg) formulations. The 90% CIs of the least squares geometric mean ratios for tablet compared to capsules fell within the limits of 0.800 and 1.250 for all 3 primary niraparib PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$). Intrasubject variability was low, ranging from 18.1% to 23.7% for the key PK parameters.

In addition, this study will evaluate the effect of a high-fat meal on the PK of the niraparib 300 mg tablet formulation (Stage 3). The Extension Phase of this study will enable patients to continue to receive treatment with niraparib if they are tolerating it and, in the Investigator's opinion, may receive clinical benefit.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study for each Stage is:

- Stage 1: To obtain preliminary assessment of the relative bioavailability of 300mg niraparib administered as a tablet versus capsule formulation and to estimate the intrasubject variability of niraparib PK
- Stage 2: To evaluate if the tablet formulation (1×300 mg) of niraparib is bioequivalent (BE) to the capsule formulation (3×100 mg)
- Stage 3: To assess the effect of a high-fat meal on niraparib PK following a single 300 mg dose of the tablet formulation

5.2. Secondary Objectives

The secondary objective of this study is:

- Stage 1, Stage 2, and Stage 3: To evaluate the safety of single dose niraparib when administered as a tablet or capsule formulation in patients with advanced solid tumors
- Extension Phase: To evaluate the safety of continuously dosed niraparib in patients with advanced solid tumors.

5.3. Exploratory Objectives

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6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a multicenter, open label study in patients with advanced solid tumors. This is a 3-stage, randomized-sequence, single-crossover study to assess the relative BA and BE of niraparib tablet formulation relative to the capsule formulation. In addition, Stage 3 of the protocol is a single cohort, randomized-sequence, 2 period, single dose, crossover study to assess effect of food on the PK of the niraparib tablet formulation.

Pharmacokinetics (PK) Phase: In Stages 1 and 2 patients will be randomized 1:1 to receive tablet formulation followed by capsule formulation or capsule formulation followed by tablet formulation. In Stage 3, patients will be randomized 1:1 to receive tablet formulation in a fasted state followed by tablet formulation taken with a high-fat meal, or tablet formulation taken with a high-fat meal followed by tablet formulation taken in a fasted state.

Stage 1: Following an 8-hour fast on Day 1 (see Section 6.1.1), patients will receive a single dose of the formulation (tablet [1×300 mg] or capsule [3×100 mg]) followed by a 7-day (+1 day) Washout/PK period followed by a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK period. Patients receiving the tablet in the first treatment period will receive the capsules in the second treatment period and vice versa (Figure 2). Extensive PK sampling will be carried out after niraparib dosing (see Section 10.1).

Stage 2: Following an 8-hour fast on Day 1 (see Section 6.1.1), patients will receive a single dose of the formulation (tablet [1×300 mg] or capsule [3× 100 mg]) followed by a 14-day (+/- 4 days) Washout/PK period followed by a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK period. Patients receiving the tablet in the first treatment period will receive the capsules in the second treatment period and vice versa (Figure 2). Extensive PK sampling will be carried out after niraparib dosing (see Section 10.1).

Stage 3: In period 1, patients will receive a single 300 mg niraparib tablet either following a 10-hour fast (see Section 6.1.1) or directly following consumption of a high-fat meal (see Section 6.1.1), followed by a 14-day (+4 days) PK sampling and washout period. In period 2, patients will be crossed over to receive a single 300 mg niraparib tablet in a fasted state or with a high-fat meal, followed by a 7-day PK sampling period. All patients will fast for a minimum of 4 hours postdose in both periods. Patients receiving the tablet in a fasted state in the first treatment period will receive the tablet with a high-fat meal in the second treatment period and vice versa.

In the rare instance where a delay of the entire PK period 2 is needed for any reason beyond the 4-day window specified above the site must contact the sponsor's medical monitor to discuss the patient circumstances, the Sponsor will decide if the patient can continue with PK period 2 with a delay. Similarly, should the laboratory results on D15 in Stage 2 (the day of niraparib administration in PK Period 2) show changes in organ function such that the original inclusion criteria for laboratory values are no longer met, or in the event of a significant change of patient’s clinical status as judged by the Investigator, the site must consult with the Sponsor to discuss the patient's continued participation in PK period 2. Note that sites need not wait for the pre-dose laboratory results to begin PK period 2, but rather consult the Sponsor once the results are available as needed.

In Stage 1 and 2, patients who experience emesis within 9 hours of dosing or who miss a critical PK sample (such as the last PK sample on Day 8 in each Period [Stage 3]) will be discontinued from the PK phase and will be allowed to be screened for the Extension Phase (see Section 6.1).

In Stage 3, patients who experience emesis within 10 hours of dosing or miss sufficient samples to render calculation of AUC unreliable will be discontinued from the PK phase. Patients may also be identified and discontinued from the PK phase as non-evaluable due to issues arising during the study conduct (Section 7.4.1). Patients who are discontinued from the PK phase and meet other criteria for continued niraparib therapy will be eligible to be screened for the Extension Phase (see Section 6.1).

The PK parameters that will be estimated include area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent total body clearance (CL/F), C_{max}, t_{max}, terminal elimination half-life ($t_{1/2}$), apparent terminal volume of distribution (Vz/F), and bioavailability/bioequivalence of the tablet formulation relative to the capsule formulation.

For Stage 2, the same PK parameters as above will be estimated. To conclude bioequivalence, the 90% CI of the ratio of geometric least-squares means of the test (tablet) to reference (capsule) product should be within 0.800 - 1.250 for $AUC_{0-\infty}$ AUC_{0-t} and C_{max}.

For Stage 3, the same PK parameters as above will be estimated. In addition, t_{lag}, the time from administration of the dose to the first quantifiable concentration, will be determined, and t_{max} will be compared between the fed and fasted states. The relative bioavailability of the 300 mg niraparib tablet administered with a high-fat meal relative to fasted dosing will be based on the ratio of geometric least-squares means of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

Additional PK parameters may be estimated (e.g., residual area) if deemed appropriate.

Extension Phase: When patients complete the PK Phase of the study (at least 7 days from niraparib, dose 2), the Sponsor will work with the Investigator to determine if the patient would benefit from continued access to niraparib therapy. Eligibility to participate in the Extension Phase will be at the discretion of the Investigator and Sponsor and will follow review of the study's Extension Phase's respective inclusion criteria and completion of the required screening assessments. Continued treatment in the study will be based on documented evidence of clinical benefit determined by local standard of care disease assessment frequency.

The starting dose of niraparib in the Extension Phase will be based on the patient's baseline actual body weight or platelet count. Patients with a baseline actual body weight of ≥77 kg and screening platelet count of ≥150,000/µL (obtained after completion of the PK phase, as part of Extension Phase screening) will take one 300 mg strength tablet or 3 x 100 mg tablets/capsules at each dose administration (QD). Patients with a baseline actual body weight of <77 kg or screening platelet count of <150,000/µL will take one 200 mg strength tablet or 2 x 100 mg tablets/capsules at each dose administration (QD). For patients whose initial starting dose is 200 mg QD, escalation to 300 mg QD is permitted after 2 cycles of therapy if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and after approval from the Sponsor. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation. If laboratory values at the

beginning of Extension Phase are outside of the range specified in the inclusion criteria, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose. Should a patient start Extension Phase at 100 mg, consideration may be given to escalate to 200 mg after 2 cycles of therapy if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and after approval from the Sponsor.

Patients have up to 28 days (21 days for Stage 3 only; up to 28 days may be acceptable following discussion between the Sponsor and Investigator) after completion of the PK Phase to complete the screening assessments and the Screening Visit.

A tumor assessment is to be performed prior to the first dose of the Extension (pre-Extension Phase). The pre-Extension Phase tumor assessment need not be completed if the baseline tumor assessment was performed ≤56 days before the first dose of the Extension Phase.

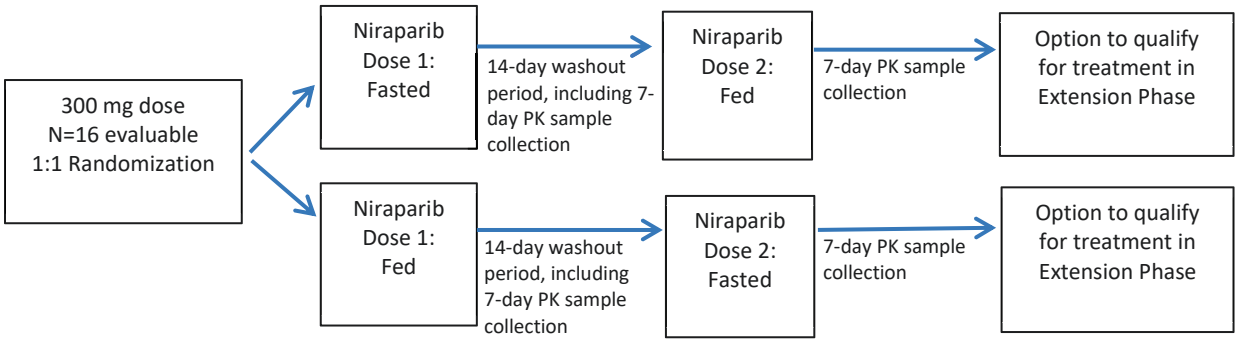
The Cycle 1/Day 1 Visit can occur on the same day as the Extension Phase Screening Visit, dependent upon availability of radiographic results obtained ≤ 56 days of the first planned dose in the Extension Phase. If the Extension Phase Screening Visit and the Cycle 1/Day 1 Visit occur on the same day, the clinical laboratory results will be reviewed by the study personnel prior to study drug administration to ensure eligibility. At the Cycle 1/Day 1 Visit, patients will undergo safety assessments and will receive study drug supply for the duration of 1 cycle (300 mg or 200 mg tablets of niraparib for QD dosing or 3 x 100 mg or 2 x 100 mg tablets/capsules of niraparib for QD dosing, depending upon availability). It is preferred that patients remain on the same formulation (tablet versus capsule) throughout the Extension Phase. Patients will return on the first day of every treatment cycle (28 ± 7 days) to receive study drug and for safety assessments. Visits will continue approximately every 4 weeks until treatment discontinuation. In line with the niraparib US PI, dose interruption (no longer than 28 days) will be allowed based on adverse events (AEs). In addition, dose reductions to 200 mg QD and subsequently to 100 mg QD will be allowed based on AEs (please refer to US PI). Any dose reductions differing from this must be discussed with the medical monitor. Patients can continue in the Extension Phase until the patient meets 1 of the withdrawal criteria.

EOT and Safety Follow-up Visits:

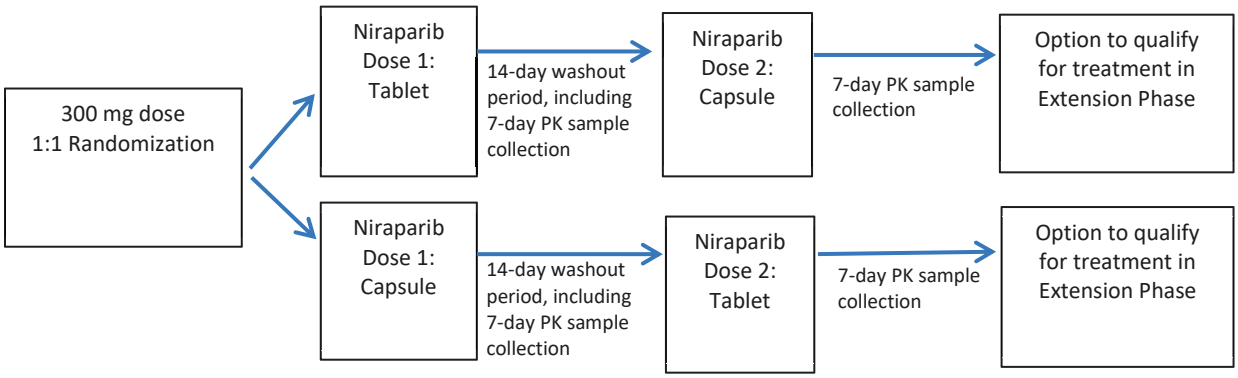
The EOT visit will occur within 7 days of the decision to discontinue study treatment for any reason. Patients who do not participate in the Extension Phase will also have an EOT visit within 7 days of the decision to discontinue study. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety Follow-up visit should occur at the EOT visit and this visit will be considered the Safety Follow-up visit. If the first dose of the new anti-cancer therapy occurs >14 days of the decision to discontinue study, the Safety Follow-up visit will occur 30+7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occur first.

Figure 2: Study Design: Single-Crossover Study

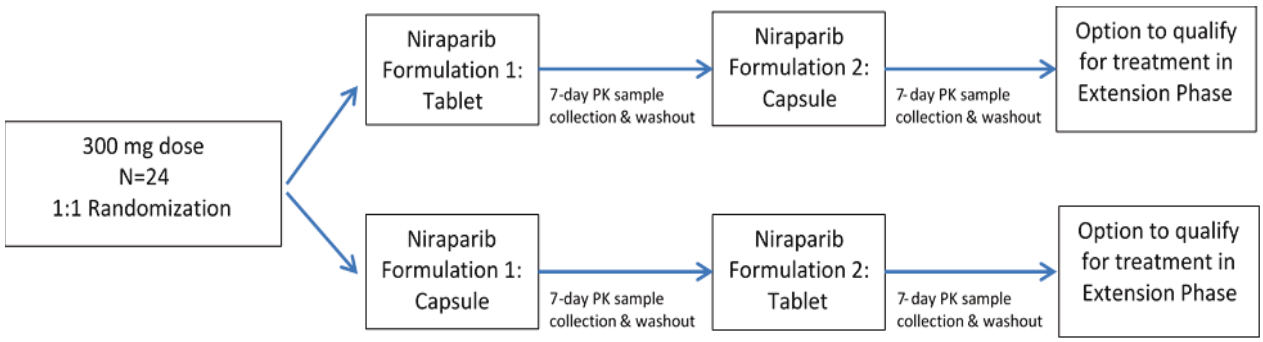
Stage 3:



Stage 2 (completed):



Stage 1 (completed):



Abbreviations: PK=pharmacokinetics

6.1.1. Fasting and Study Drug Administration for the PK Phase

In Stage 1 and 2, during the PK Phase of the study, patients should come to the clinic on the morning of Day 1 of the Study Drug and Washout/PK period and subsequent Study Drug and PK period following an 8-hour overnight fast. During the overnight fast, patients are permitted to consume water (but no other beverages) up to 2 hours prior to dosing of the study drug. Patients may take their routine medications with sips of water. If the patient presents to the clinic and is determined not to be in a fasting state as mandated by the protocol, the dosing needs to be rescheduled.

Patients will receive a single dose of the study drug with approximately 250 ml of water on Day 1 of the Study Drug and Washout/PK period and subsequent Study Drug and PK period. Patients may take sips of water after the single dose and resume their regular diet 4 hours thereafter.

In Stage 3, all patients should arrive at the clinic following an overnight fast for a minimum of 10 hours. For patients taking niraparib with a high-fat meal, the meal (see Appendix E) should start 30 minutes before administration of niraparib. Patients should eat this meal in 30 minutes or less, and every effort should be made for the patient to complete the entire meal.. The dose of niraparib should be taken within 5 minutes of finishing the meal, with 240 mL (8 fluid ounces) of water. Patients taking the drug product in a fasted state should also take it with 240 mL of water. Additional water is allowed except for 1 hour before and 1 hour after drug administration. No food is allowed for at least 4 hours postdose in both treatment periods.

6.1.2. General Study Conduct

This study will consist of a Screening Period (Day -21 to Day -1), a PK Phase (Study Drug and Washout/PK period 1 and Study Drug and PK period 2), an EOT visit, and a Safety Follow-up Visit. When patients complete the PK Phase of the study (at least 7 days from the beginning of PK period 2), they may be eligible to participate in the Extension Phase prior to EOT and Safety Follow-up Visits, following review of the Extension Phase inclusion criteria and completion of the required screening assessments. See Section 6.1.

Following informed consent, all patients will undergo screening procedures within 21 days prior to the first dose of study drug to determine eligibility for study entry. Screening procedures include medical, surgical, cancer, and medication history; complete physical examination, including vital signs, height, and weight; Eastern Cooperative Oncology Group (ECOG) performance status; clinical laboratory assessments (complete blood count [CBC], chemistry, and urinalysis); pregnancy test for women of childbearing potential; baseline tumor assessment and electrocardiogram (ECG).

Once randomized to either capsule to tablet crossover or tablet to capsule crossover, patients will receive a single dose of the formulation (tablet or capsule) in a fasted state (Stage 1 and Stage 2).

Stage 1: Following an 8-hour fast on Day 1 (see Section 6.1.1), patients will receive a single dose of the formulation (tablet [1× 300 mg] or capsule [3× 100 mg]) followed by a 7-day (+ 1 day) Washout/PK period followed by a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK period. Patients receiving the tablet in the first treatment period will receive the capsules in the second treatment period and vice versa (Figure 2). Extensive PK sampling will be carried out after niraparib dosing (see Section 10.1). Blood will be collected during the study for PK assessments at the following time points relative to niraparib dosing: predose (30 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose.

Stage 2: Following an 8-hour fast on Day 1 (see Section 6.1.1), patients will receive a single dose of the formulation (tablet [1× 300 mg] or capsule [3× 100 mg]) followed by a 14-day (+/- 4 days) Washout/PK period followed by a dose of the alternate formulation also in a fasted state, followed by a 7-day Washout/PK period. Patients receiving the tablet in the first treatment period will receive the capsules in the second treatment period and vice versa (Figure 2). Extensive PK

sampling will be carried out after niraparib dosing (see Section 10.1). Blood will be collected during the study for PK assessments at the following time points relative to niraparib dosing: predose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96,120, and 168 hours postdose.

Stage 3: In period 1, patients will receive a single 300 mg niraparib tablet either following a 10-hour fast or directly following consumption of a high-fat meal followed by a 14-day (+4 days) PK sampling and washout period. In period 2, patients will be crossed over to receive a single 300 mg niraparib tablet in a fasted state or with a high-fat meal, followed by a 7-day PK sampling period. All patients will fast for a minimum of 4 hours postdose in both periods. Patients receiving the tablet in a fasted state in the first treatment period will receive the tablet with a high-fat meal in the second treatment period and vice versa. Extensive PK sampling will be carried out after niraparib dosing (see Section 10.1). Blood will be collected during the study for PK assessments at the following time points relative to niraparib dosing: predose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose.

Safety assessments conducted throughout the study include symptom-directed physical examination, vital signs, ECOG performance status, clinical laboratory assessments (CBC, chemistry, and urinalysis) (Section 6.6.1). Laboratory results from D8 (start of PK Period 2) should be reviewed by the site personnel, and significant changes in renal or hepatic function compared to baseline should be discussed with the sponsor.

6.2. Number of Patients

Approximately 24 patients will be enrolled in Stage 1, and approximately 170 will be enrolled in Stage 2 to ensure 100 evaluable patients for BE analysis. Approximately 20 patients will be enrolled in Stage 3 to ensure 16 evaluable patients for the FE analysis.

6.3. Treatment Assignment

6.3.1. Patient Identification

All patients who enter into the screening period of the study (defined as the point at which the patient signs the Informed Consent Form [ICF]) will receive a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. A patient will be considered enrolled when the patient has been consented, screened, and all eligibility criteria have been confirmed in the electronic case report form (eCRF). The patient identification number must remain constant throughout the entire study, and it must not be changed at the time of enrollment.

6.3.2. Randomization Scheme

Randomization will occur centrally using an interactive voice response system/integrated web response system. In Stage 1 and Stage 2, subjects will be assigned randomly in a 1:1 ratio to a dosing sequence: capsule formulation followed by tablet formulation, or vice versa. In Stage 3, subjects will be assigned randomly in a 1:1 ratio to a dosing sequence: dosing after receiving a high-fat meal (fed) followed by dosing after fasting, or vice versa. The period between randomization and Cycle 1/Day 1 should be no longer than 5 calendar days.

6.4. Dose Adjustment Criteria

6.4.1. Safety Criteria for Stopping Doses During PK Phase

During the PK Phase, patients must be discontinued for any treatment-related nonhematologic National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE v.4.03) Grade 3 or 4 AE or serious adverse event (SAE) that the Investigator considers to be related to the administration of niraparib and, in case this resulted in incomplete PK collection. Patients may be permitted to enter the Extension Phase at an appropriately reduced dose.

6.4.2. Safety Criteria for Adjustment or Stopping Doses During Extension Phase

During the Extension Phase, dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient and per the US label. In addition, protocol-defined criteria for dose modification are discussed below.

Treatment must be interrupted for any treatment-related nonhematologic NCI-CTCAE v.4.03 Grade 3 or 4 AE or SAE that the Investigator considers to be related to niraparib administration. If the toxicity is resolved to baseline or ≤Grade 1 within 28 days, the patient may restart treatment with niraparib but with an appropriate dose reduction unless prophylaxis is considered feasible (Table 3). If the event recurs at a similar or worse grade, treatment should be interrupted again, and upon resolution, a further dose reduction must be made. If upon rechallenging with niraparib at the lowest allowable dose, any NCI-CTCAE Grade 3 or 4 AEs, which the Investigator considers to be related to niraparib recur, the patient must be discontinued. At the Investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions, provided that they have not already undergone the maximum number of 2 dose reductions allowed (no more than 2 dose reductions will be permitted). Any dose reductions deviating from this guidance must be discussed with the medical monitor.

Table 3: Niraparib Dose Reductions for Non-Hematologic Toxicities

Event	**Dose**[1]
Initial dose	300 mg QD
First dose reduction for treatment-related NCI-CTCAE v.4.03 Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE v.4.03 Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	100 mg QD
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE ≥28 days	Discontinue study medication
Posterior Reversible Encephalopathy Syndrome (PRES) (see Section 11.2.9)	Discontinue niraparib and treat specific symptoms including hypertension.

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; NCI-CTCAE=National Cancer Institute CTCAE; QD=once daily; PRES=Posterior Reversible Encephalopathy Syndrome; SAE=serious adverse event.
[1] Dose not to be decreased below 100 mg daily.

Management of hematologic toxicities (Guan, 2017) is described in Table 4. For Grade 3 or 4 neutropenia, thrombocytopenia, or anemia, treatment with niraparib must be interrupted with weekly blood counts monitored until recovery to ≤Grade 1. Niraparib should be resumed with a dose level reduction at that time. Cytokines (granulocyte colony stimulating factor [CSF]) may be administered as clinically indicated to manage febrile neutropenia according to local standard of care.

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

Thrombocytopenia is an expected event associated with the use of niraparib and is described in the IB. Thrombocytopenia associated with the use of niraparib resolved upon treatment interruption and/or dose reduction. The occurrence of thrombocytopenia during Cycle 1 requires additional patient monitoring in order to identify hematologic changes early and prevent higher grade thrombocytopenic events. A weekly monitoring of CBC during the first month is mandatory.

If a patient completes the first cycle with no incidence of hematologic toxicity requiring dose interruption or modification, then CBC monitoring will proceed according to protocol every 4 weeks, thereafter. If dose interruption or modification is required at any point on study, weekly CBC will be required for another 4 weeks after the AE has been resolved, to ensure safety of the new dose, after which monitoring every 4 weeks may resume.

It is strongly recommended to refer the patient to the hematologist for further evaluation if (1) transfusions are required on more than 2 occasions in the absence of non-treatment related causes or (2) the treatment-related hematologic toxicities have not recovered to allow retreatment with niraparib after 4 weeks. If a diagnosis of myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML) is confirmed by a hematologist, the patient must permanently discontinue study drug.

Table 4: Management of Hematologic Toxicities

Platelet count < 100,000/µL	First occurrence: • Withhold study medication for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume study medication at same or reduced dose per Table 3. • If platelet count is <75,000/µL, resume at a reduced dose.
	Second occurrence: • Withhold study medication for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume study medication at a reduced dose per Table 3. • Discontinue study medication if 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 once daily.

Table 4: Management of Hematologic Toxicities (Continued)

Neutrophil < 1,000/µL or hemoglobin < 8 g/dL	• Withhold study medication for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL or hemoglobin returns to ≥9 g/dL. • Resume study medication at a reduced dose per Table 3. • Discontinue study medication if neutrophils and/or hemoglobin have 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 once daily.[a]
Hematologic adverse reaction requiring transfusion	• 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. • RBC transfusion is at the discretion of the Investigator • Resume study medication at a reduced dose.
Confirmed MDS/AML	• Permanently discontinue treatment.

Abbreviations: AML=acute myeloid leukemia; CBC=complete blood count; Hb=hemoglobin; MDS=myelodysplastic syndrome; RBC=red blood cell.
[a] If MDS/AML is confirmed, niraparib will be discontinued.

6.5. Criteria for Study Termination

The Sponsor may terminate this study at any time. The Sponsor will notify the Investigators when the study is to be placed on hold, completed, or terminated.

6.6. Study Conduct

6.6.1. Schedule of Events

The schedule of events for the study is provided in Table 5: for Stage 1, Table 6 for Stage 2, Table 7: for Stage 3, and Table 8 for the Extension Phase.

Table 5: Schedule of Events: Study Drug and PK Phase – Stage 1 (COMPLETED)

Cycle/Visit	Screening	Study Drug and Washout/PK Period 1							Study Drug and Washout/PK Period 2						EOT	Safety Follow-up
Day of Procedure	**-21 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**[1]	**9**	**10**	**11**	**12**	**13**	**15**	**+7 days of the decision to discontinue treatment for any reason**[2]	**30 + 7 days post-treatment**[2]
Informed consent	X															
Inclusion/ exclusion criteria review	X															
Randomization	X[3]															
Demographics	X															
Medical, surgical, cancer, and medication history	X															
Laboratory assessments:																
CBC[4]	X	X[5]						X[5]							X	X
Chemistry[6]	X	X[5]						X[5]							X	X
Pregnancy test	X															X
Urinalysis	X															X
ECG	X															X
Complete physical examination	X															X
Symptom-directed physical examination		X[5]						X[5]								
Vital signs and weight	X	X[5]						X[5]								X
Height	X															
ECOG performance status	X	X[5]						X[5]							X	X
Tumor assessment	X[7]															
Niraparib study drug administration		X						X								

Cycle/Visit	Screening	Study Drug and Washout/PK Period 1							Study Drug and Washout/PK Period 2						EOT	Safety Follow-up
Day of Procedure	**-21 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**[1]	**9**	**10**	**11**	**12**	**13**	**15**	**+7 days of the decision to discontinue treatment for any reason**[2]	**30 + 7 days post-treatment**[2]
Pharmacokinetic sample collection		X	X	X	X	X	X	X[8]	X	X	X	X	X	X		
Concomitant medications and procedures	X		Recorded from informed consent through EOT													
Adverse event monitoring[9]	X		Recorded from informed consent through 30 days post-treatment													

Abbreviations: AE=adverse event; AESI=adverse events of special interest; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; MRI=magnetic resonance imaging; PK=pharmacokinetics; SAE=serious adverse event.

[1] Study Drug and PK Period may be delayed up to 1 day if necessary for scheduling purposes.

[2] Patients who do not participate in the Extension Phase of the study will proceed to the EOT visit followed by the Safety Follow-up Visit. Patients participating in the Extension Phase will proceed into screening for the Extension Phase directly after completing the Study drug and PK period.

[3] Patients to be randomized within 5 calendar days of first dose.

[4] CBC to include: Hemoglobin, Platelet count, Mean corpuscular volume, White blood cell count, Differential white blood cell count

[5] Need not be repeated at screening or during the Washout/PK period if done within 72 hours of dosing 1 and 2, respectively.

[6] Chemistry to include: Sodium, Potassium, Magnesium, Chloride, Albumin, Calcium, Amylase, Phosphate, Glucose, Creatinine, Urea or blood urea nitrogen, Total protein, Lactate dehydrogenase, Total bilirubin, Alkaline phosphatase, Aspartate aminotransferase, and Alanine aminotransferase

[7] Tumor assessments may be performed within 28 days of first dose of study drug. Tumor assessments performed outside of the 28 day window but ≤ 56 days of the planned start of the Extension Phase are acceptable. Tumor assessment via a CT or MRI scan of clinically indicated areas should be performed.

[8] PK sample collection for the 168 hour postdose timepoint from the first Study Drug and Washout/PK Period and the predose for the second Study Drug and Washout/PK Period can occur at the same time.

[9] AEs will be collected and recorded for each patient from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug. SAEs are required to be captured through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first). All SAEs assessed by the Investigator as related to the study drug and AESIs will be collected and reported until study closeout (unless death or loss to follow-up occurs first). Any pregnancies that occur within 180 days post-treatment will be reported. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Table 6: Schedule of Events: Study Drug and PK Phase – Stage 2 (COMPLETED)

Cycle/Visit	Screening	Study Drug and Washout/PK Period 1							Study Drug and Washout/PK Period 2							EOT	Safety Follow-up
Day of Procedure	**-21 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**15 (±4)**	**16**	**17**	**18**	**19**	**20**	**22**	**+7 days of the decision to discontinue treatment for any reason[1]**	**30 + 7 days post-treatment[1]**
Informed consent	X																
Inclusion/ exclusion criteria review	X																
Randomization	X[2]																
Demographics	X																
Medical, surgical, cancer, and medication history	X																
Laboratory assessments:																	
CBC[3]	X	X[4]							X[4]							X	X
Chemistry[5]	X	X[4]							X[4]							X	X
Pregnancy test	X																X
Urinalysis	X																X
ECG	X																X
Complete physical examination	X																X
Symptom-directed physical examination		X[4]							X[4]								
Vital signs and weight	X	X[4]							X[4]								X
Height	X																
ECOG performance status	X	X[4]							X[4]							X	X
Tumor assessment	X[6]																

Cycle/Visit	Screening	Study Drug and Washout/PK Period 1							Study Drug and Washout/PK Period 2							EOT	Safety Follow-up
Day of Procedure	**-21 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**15 (±4)**	**16**	**17**	**18**	**19**	**20**	**22**	**+7 days of the decision to discontinue treatment for any reason[1]**	**30 + 7 days post-treatment[1]**
Niraparib study drug administration		X							X								
Pharmacokinetic sample collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications and procedures	X	Recorded from informed consent through EOT															
Adverse event monitoring[7]	X	Recorded from informed consent through 30 days post-treatment															

Abbreviations: AE=adverse event; AESI=adverse events of special interest; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; MRI=magnetic resonance imaging; PK=pharmacokinetics; SAE=serious adverse event.

[1] Patients who do not participate in the Extension Phase of the study will proceed to the EOT visit followed by the Safety Follow-up Visit. Patients participating in the Extension Phase will proceed into screening for the Extension Phase directly after completing the Study drug and PK period. The EOT visit will occur within 7 days of the decision to discontinue study treatment for any reason. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety Follow-up visit should occur at the EOT visit and this visit will be considered the Safety Follow-up visit. If the first dose of the new anti-cancer therapy occurs >14 days of the decision to discontinue study, the Safety Follow-up visit will occur 30+7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occur first.

[2] Patients to be randomized within 5 calendar days of first dose.

[3] CBC to include: Hemoglobin, Platelet count, Mean corpuscular volume, White blood cell count, Differential white blood cell count

[4] Need not be repeated at screening or during the Washout/PK period if done within 72 hours of dosing 1 and 2, respectively.

[5] Chemistry to include: Sodium, Potassium, Magnesium, Chloride, Albumin, Calcium, Amylase, Phosphate, Glucose, Creatinine, Urea or blood urea nitrogen, Total protein, Lactate dehydrogenase, Total bilirubin, Alkaline phosphatase, Aspartate aminotransferase, and Alanine aminotransferase

[6] Tumor assessments may be performed within 28 days of first dose of study drug. Tumor assessments performed outside of the 28 day window but ≤56 days of the planned start of the Extension Phase are acceptable. Tumor assessment via a CT or MRI scan of clinically indicated areas should be performed.

[7] AEs will be collected and recorded for each patient from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug. SAEs are required to be captured through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first). All SAEs assessed by the Investigator as related to the study drug and AESIs will be collected and reported until study closeout (unless death or loss to follow-up occurs first). Any pregnancies that occur within 180 days post-treatment will be reported. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Table 7: Schedule of Events: Study Drug and PK Phase – Stage 3

Cycle/Visit	Screening	Study Drug and Washout/ PK Period 1							Study Drug and Washout/ PK Period 2							EOT	Safety Follow-up
Day of Procedure	**-21 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**15 (+4)**	**16**	**17**	**18**	**19**	**20**	**22**	**+7 days of the decision to discontinue treatment for any reason[1]**	**30+7 days post-treatment[1]**
Informed consent	X																
Inclusion/exclusion criteria review	X																
Randomization	X[2]																
Demographics	X																
Medical, surgical, cancer, and medication history	X																
Laboratory assessments:																	
CBC[3]	X	X[4]							X[4]							X	X
Chemistry[5]	X	X[4]							X[4]							X	X
Pregnancy test[10]	X																X
Urinalysis	X																X
ECG	X																X
Complete physical examination	X																X
Symptom-directed physical examination		X[4]							X[4]								
Vital signs and weight[11]	X	X[4]							X[4]							X	X
Height	X																
ECOG performance status	X	X[4]							X[4]							X	X

Table 7: Schedule of Events: Study Drug and PK Phase – Stage 3 (continued)

Tumor assessment	X[6]																
Confirmation of fasting state[8]		X							X								
Consumption of high-fat meal, as applicable[9]		X							X								
Niraparib study drug administration		X							X								
Pharmacokinetic sample collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications and procedures	X	Recorded from informed consent through EOT															
Adverse event monitoring[7]	X	Recorded from informed consent through 30 days post-treatment															

Abbreviations: AE=adverse event; AESI=adverse events of special interest; BP=blood pressure; CBC=complete blood count; CT=computed tomography; eCRF=electronic case report form; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; MRI=magnetic resonance imaging; PK=pharmacokinetics; SAE=serious adverse event.

[1] Patients who do not participate in the Extension Phase of the study will proceed to the EOT visit followed by the Safety Follow-up Visit. Patients participating in the Extension Phase will proceed into Screening for the Extension Phase directly after completing the Study Drug and PK Period. The EOT visit will occur within 7 days of the decision to discontinue study drug for any reason. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study drug, all assessments required for the Safety Follow-up visit should occur at the EOT visit and this visit will be considered the Safety Follow-up visit. If the first dose of the new anti-cancer therapy occurs >14 days of the decision to discontinue study, the Safety Follow-up visit will occur 30+7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occur first.

[2] Patients may be randomized within 5 calendar days of first dose.

[3] CBC to include: hemoglobin, platelet count, mean corpuscular volume, white blood cell count, differential white blood cell count.

[4] Need not be repeated at Screening or during the Washout/PK Period if done within 72 hours of dosing 1 and 2, respectively.

[5] Chemistry to include: sodium, potassium, magnesium, chloride, albumin, calcium, amylase, phosphate, glucose, creatinine, urea or blood urea nitrogen, total protein, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase

[6] Tumor assessments may be performed within 28 days of first dose of study drug. Tumor assessments performed outside of the 28 day window but ≤56 days before the planned start of the Extension Phase are acceptable. Tumor assessment via a CT or MRI scan of clinically indicated areas should be performed.

[7] AEs will be collected and recorded for each patient from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug. SAEs are required to be captured through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first). All SAEs assessed by the Investigator as related to the study drug and AESIs will be collected and reported until study closeout (unless death or loss to follow-up occurs first). Any pregnancies that occur within 180 days post-treatment will be reported. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

[8] Patient must fast for a minimum of 10 hours prior to start of visit. No food is allowed for at least 4 hours postdose in both treatment periods. Patients should start the high-fat meal (if assigned) 30 minutes before administration of niraparib and eat the meal in 30 minutes or less. The dose of niraparib should be taken

within 5 minutes of finishing the meal, with 240 mL (8 fluid ounces) of water. Patients taking the drug product in fasted state should also take it with 240 mL of water. Additional water is allowed except for 1 hour before and 1 hour after drug administration.

[9] Consumption of high-fat meal in either period 1 or period 2 is determined by patient randomization allocation.

[10] A negative serum or urine pregnancy test is required within 72 hours for females of childbearing potential prior to first dose of study drug for PK period 1 and Extension Phase.

[11] Vital signs include BP, pulse, heart rate, and temperature.

Table 8: Schedule of Events: Extension Phase

Cycle/Visit	Extension Phase Screening	Extension Phase	Extension Phase	EOT	Safety Follow-up
Day of Procedure	**1-28 days**[1]	**Cycle 1 (28 ± 7 days)**[2]	**Cycle 2 and on (28 ± 7 days)**[2]	**+7 days of the decision to discontinue treatment for any reason**[3]	**30 + 7 days post-treatment**[3]
Inclusion/exclusion criteria review	X[2]				
Laboratory assessments:					
CBC[4]	X	Weekly[6]	Monthly	X	X
Chemistry[5]	X	Every other week[6]	Monthly	X	X
Pregnancy test	X				X
Urinalysis					X
ECG					X
Complete physical examination					X
Symptom-directed physical examination including vital signs	X	X[6] (Day 1)	X[6] (Day 1)		
Vital signs and weight[10]	X	Weekly	X[6] (Day 1)	X	X
ECOG performance status	X	X[6] (Day 1)	X[6] (Day 1)	X	X
Tumor assessment	X[7]		X (every 3 cycles)[8]		
Niraparib study drug dispensed		X	X		
Concomitant medications and procedures	Recorded from informed consent through EOT				
Adverse event monitoring[9]	Recorded from informed consent through 30 days post-treatment				X

Abbreviations: AE=adverse event; AESI=adverse events of special interest; BP=blood pressure; CBC=complete blood count; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; MRI=magnetic resonance imaging; SAE=serious adverse event.

[1] When patients complete the PK Phase of the study (at least 7 days from the beginning of PK period 2), they will be eligible to participate in the Extension Phase following re-review of selected entry criteria and completion of the screening assessments. If laboratory values are outside of the range specified in the inclusion criteria, the patient may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose. Patients have 28 days to complete the screening assessments. The Screening Visit and Cycle 1/Day 1 Visit can occur on the same day dependent upon availability of radiographic results obtained ≤ 56 days of the first planned dose in the Extension Phase.

[2] The intent of the 7-day Day 1 window is to allow flexibility in scheduling; please note study drug is dispensed in 31-day increments.

[3] The EOT visit will occur within 7 days of the decision to discontinue study treatment for any reason. Patients who do not participate in the Extension Phase will also have an EOT visit within 7 days of the decision to discontinue study. Should the first dose of a new anti-cancer therapy occur within 14 days of the decision to discontinue study treatment, all assessments required for the Safety Follow-up visit should occur at the EOT visit and this visit will be considered the Safety Follow-up visit. If the first dose of the new anti-cancer therapy occurs >14 days of the decision to discontinue study, the Safety Follow-up visit will occur 30+7 days after the last dose of the study drug, or at the start of any new anti-cancer therapy, whichever occur first.

[4] CBC to include: Hemoglobin, Platelet count, Mean corpuscular volume, White blood cell count, Differential white blood cell count. CBC needs to obtained within 72 hrs prior to starting C1D1 of the Extension Phase and monthly for the next 10 months of niraparib treatment. CBC will be obtained periodically after this time to monitor for clinically significant changes in any hematological parameter during niraparib treatment.

[5] Chemistry to include: Sodium, Potassium, Magnesium, Chloride, Albumin, Calcium, Amylase, Phosphate, Glucose, Creatinine, Urea or blood urea nitrogen, Total protein, Lactate dehydrogenase, Total bilirubin, Alkaline phosphatase, Aspartate aminotransferase, and Alanine aminotransferase. Chemistry needs to obtained within 72 hrs prior to starting C1D1 of the Extension Phase

[6] Need not be repeated if done within 72 hours of dosing Day 1.

[7] Tumor assessment to be performed prior to the first dose of the Extension Phase (pre-Extension Phase). The pre-Extension Phase tumor assessment need not be performed if the baseline tumor assessment was performed ≤56 days before the first dose of the Extension Phase

[8] Tumor assessment via a CT or MRI scan of clinically indicated areas and evaluation of clinical signs and symptoms should be performed during the Extension Phase every three cycles (+/- 7 days) 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.

[9] AEs will be collected and recorded for each patient from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug. SAEs are required to be captured through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first). All SAEs assessed by the Investigator as related to the study drug and AESIs will be collected and reported until study closeout (unless death or loss to follow-up occurs first). Any pregnancies that occur within 180 days post-treatment will be reported. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

[10] Vital signs include BP, pulse, heart rate, and temperature. BP and heart rate will be monitored weekly for the first 4 weeks of the Extension Phase and monthly thereafter.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Inclusion Criteria

7.1.1. Patient Inclusion Criteria (Stages 1 and 2)

PK Phase:

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

1. Patient is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Patient has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, has progressed despite standard therapy, or for which no standard therapy exists, and who may benefit from treatment with a PARP inhibitor as assessed by the Investigator. Patients with lymphoma are eligible. Patients with primary CNS malignancy are eligible provided they do not have new or progressive signs or symptoms, and are not requiring steroid dose exceeding the equivalent of 10 mg of prednisone daily.
3. Patient is at least 18 years of age.
4. Patient has an ECOG performance status of 0 to 2.
5. Patient has adequate organ function as defined below (Note: CBC should be obtained without transfusion or receipt of CSFs, erythropoietin stimulating agents or platelet-stimulating agents within 2 weeks before first dose):
    a. Absolute neutrophil count ≥1,500/μL
    b. Platelets ≥100,000/μL
    c. Hemoglobin ≥ 9 g/dL (5.6 mM)
    d. Serum creatinine ≤1.5× the upper limit of normal (ULN) or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation or 24-hour urine creatinine clearance.
    e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN
6. Patient has recovered to baseline or Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia or Grade 2 hypothyroidism on a stable dose of thyroid replacement are an exception to this criterion and may qualify for this study). For patients with hematologic, renal or hepatic toxicity from prior therapy, inclusion criterion #5 should be applied to determined eligibility.
7. Patient is able to take oral medications.
8. Female patient meets the following criteria:

a. Patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of non-childbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
b. Female patient is of non-childbearing potential (other than medical reasons) as defined by the following:
    i. ≥45 years of age and has not had menses for >1 year).
    ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
    iii. Had undergone a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy, or tubal ligation must be confirmed in the medical records; otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study starting from the Screening visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

    Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

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

7.1.2. Patient Inclusion Criteria (Stage 3 only)

PK Phase:

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

1. Patient is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Patient has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, has progressed despite standard therapy, or for which no standard therapy exists, and who may benefit from treatment with a PARP inhibitor as assessed by the Investigator. Patients with lymphoma are eligible. Patients with CNS malignancy are eligible provided they do not have new or progressive signs or symptoms and are not requiring steroid dose exceeding the equivalent of 10 mg of prednisone daily.
3. Patient is at least 18 years of age.
4. Patient has an ECOG performance status of 0 to 2.
5. Patient has adequate organ function as defined below (Note: CBC should be obtained without transfusion or receipt of CSFs in the 1 week before obtaining sample.):
    a. Absolute neutrophil count ≥1,000/μL

b. Platelets ≥100,000/µL
c. Hemoglobin ≥9 g/dL (5.6 mM)
d. Serum creatinine ≤1.5× ULN or a calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation.
e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
f. AST and ALT ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN

6. Patient has recovered to baseline or Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia or Grade 2 hypothyroidism on a stable dose of thyroid replacement are an exception to this criterion and may qualify for this study). For patients with hematologic, renal, or hepatic toxicity resulting from prior cancer therapy should meet inclusion criterion #5 for eligibility.
7. Patient is able to swallow and retain oral medication.
8. Female patient meets the following criteria:
   a. Female patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of nonchildbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
   b. Female patient of nonchildbearing potential (other than medical reasons) is defined by the following:
      i. ≥45 years of age and has not had menses for >1 year.
      ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
      iii. Had undergone a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study, starting with the Screening Visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

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

Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

10. CNS inclusion - Based on screening brain magnetic resonance imaging (MRI), patients must have one of the following:

a. No evidence of brain metastases
b. Untreated brain metastases not needing immediate local therapy
c. Previously treated brain metastases not needing immediate local therapy
d. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy
e. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if the following criteria are met:
    i. Time since whole brain radiation therapy (WBRT) is ≥21 days prior to first dose of study drug, time since stereotactic radiosurgery (SRS) is ≥7 days prior to first dose of study drug, or time since surgical resection is ≥28 days.
    ii. Other sites of disease assessable by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) are present
f. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

11. Patient is able to eat a high-fat meal See Section 6.1.1.
12. Patient is able to fast for a minimum of 10 hours before start of visit and for an additional 4 hours after study visit. See Section 6.1.1.

7.2. Patient Exclusion Criteria

7.2.1. Patient Exclusion Criteria (Stages 1 and 2)

PK Phase:

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

1. Patient has a known hypersensitivity to the components of niraparib or excipients (please see Appendix B).
2. Patient has a known diagnosis of immunodeficiency *(Note: Patients with splenectomy are allowed).*
3. 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 disease and must be taking ≤10 mg of prednisone or equivalent per day or no steroids.
4. Patient underwent major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
5. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder; 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, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.

6. 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.
    a. 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)
7. Patient has a known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
8. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
9. Patient is unable to refrain from any intake of grapefruit or grapefruit juice within 7 days of the first administration of niraparib until 2 days post-dose *(Does not apply for Extension Phase)*.
10. Patient is currently taking 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, unless the dose and regimen has been stable for at least 14 days prior to first dose and will not change during *PK periods 1 and 2 (Does not apply for Extension Phase).*
11. Patient taking proton pump inhibitors, antacids, or histamine 2 blockers unless the dose and regimen is stable for at least 14 days prior to first dose and will not change during PK periods 1 and 2. Patients must hold these therapies starting within 8 hours prior to study drug administration until 9 hours after study drug administration *(Does not apply for Extension Phase).*
12. Patient has gastric, gastro-esophageal or esophageal cancer; patient is unable to swallow orally administered medication; or patient has gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of niraparib.
13. Patient has known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection).
14. Patient has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the Screening Visit) or dependence or is unable to abstain from alcohol for the duration of the study.
15. Patient has had a prior cytotoxic therapy or anticancer monoclonal antibodies (mAbs) within 14 days prior to start of PK Phase. There is no required washout for palliative radiation. For targeted small anti-cancer molecules (e.g., tyrosine kinase inhibitors), the required washout is 5 half-lives of the start of PK Phase. Certain hormonal agents are allowed and are listed in Appendix D. For hormonal agents not listed in Appendix D, the Site must consult with the Sponsor regarding allowing patient on study. For patient taking

hormonal agents, dose and regimen of hormonal agents should have been stable for at least 14 days prior to first dose and is not expected to change during PK periods 1 and 2.

16. Patient has significant pleural effusion or ascites that is expected to require drainage during the PK Phase *(Does not apply for Extension Phase)*.

7.2.2. Patient Exclusion Criteria (Stage 3 only)

PK Phase:

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

1. Patient has a known hypersensitivity to the components of niraparib or excipients (see Appendix B).
2. Patient has a known diagnosis of immunodeficiency *(Note: Patients with splenectomy are allowed)*
3. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
4. Patient underwent major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
5. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder; 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, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.
6. 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.
    a. Female patient is breastfeeding or is expecting to breastfeed within 30 days of receiving final dose of study drug (females should not breastfeed or store breastmilk for use, during treatment and for 30 days after receiving the final dose of study drug).
7. Patient has a known history of MDS or AML.
8. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
9. Patient is unable to refrain from any intake of grapefruit or grapefruit juice within 7 days of the first administration of niraparib until 2 days postdose *(Does not apply for participation in Extension Phase of this study).*
10. Patient is currently taking any of the following P-glycoprotein inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil, unless the dose and regimen has been stable for at least 14 days prior to first dose and will not change during PK periods 1 and 2 *(Does not apply for participation in Extension Phase of this study).*

11. Patient is taking a proton pump inhibitor, antacids, or H2 blocker within 48 hours of dose *(Does not apply for participation in Extension Phase of this study).*
12. Patient has gastric, gastroesophageal or esophageal cancer; patient is unable to swallow orally administered medication; patient has gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of niraparib.
13. Patient has known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen positive status, or suspected active hepatitis C infection).
14. Patient has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to the Screening Visit) or dependence or is unable to abstain from alcohol for the duration of the study.
15. <THIS EXCLUSION HAS BEEN INTENTIONALLY LEFT BLANK.>
16. Patient has significant pleural effusion or ascites that is expected to require drainage during the PK Phase *(Does not apply for participation in Extension Phase of this study)*.
17. Patient is currently taking a lipase inhibitor or cholesterol absorption inhibitor, such as orlistat or ezetimibe, respectively. *(Does not apply for participation in Extension Phase of this study)*.

7.3. Extension Study Patient Inclusion Criteria (Stage 1 and 2)

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

1. Patient has an ECOG performance status of 0 to 2.
2. Patient has adequate organ function as defined below; these criteria must be confirmed within 72 hours of dose 1 in Extension *(Note: CBC should be obtained without transfusion or receipt of CSFs, erythropoietin stimulating agents or platelet stimulating factors within 2 weeks before first dose)*:
    a. Absolute neutrophil count ≥ 1,500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL (5.6 mM)
    d. Serum creatinine ≤1.5× the ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation or 24-hour urine creatinine clearance
    e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
    f. AST and ALT ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN

Note: If laboratory values at the beginning of Extension Phase are outside of the range specified above, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose.

3. Female patient meets the following criteria:
    a. Patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of non-childbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
    b. Female patient of non-childbearing potential (other than medical reasons) is defined by the following:
        i. ≥45 years of age and has not had menses for >1 year).
        ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
        iii. Had undergone a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy, or tubal ligation must be confirmed in the medical records; otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study, starting from the Screening visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

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

7.3.1. Extension Study Patient Inclusion Criteria (Stage 3 only)

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

1. Patient has an ECOG performance status of 0 to 2.
2. Patient has adequate organ function as defined below; these criteria must be confirmed within 72 hours of dose 1 in the Extension Phase *(*should be obtained without transfusion or receipt of colony-stimulating factors in the 1 week before obtaining sample*)*:
    a. Absolute neutrophil count ≥1,000/µL
    b. Platelets ≥100,000/µL
    c. Hemoglobin ≥9 g/dL (5.6 mM)
    d. Serum creatinine ≤1.5× ULN or a calculated creatinine clearance of ≥30 mL/min using the Cockcroft-Gault equation.
    e. Total bilirubin ≤1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5× ULN of the direct bilirubin.
    f. AST and ALT ≤2.5× ULN unless liver metastases are present, in which case, they must be ≤5× ULN

Note: If laboratory values at the beginning of Extension Phase are outside of the range specified above, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose.

3. Female patient meets the following criteria:
    a. Patient (of childbearing potential) is not breastfeeding, 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 Screening through 180 days after the last dose of study drug, or is of nonchildbearing potential. *Note: A urine pregnancy test may be performed if the serum pregnancy test is not available before dosing.*
    b. Female patient of nonchildbearing potential (other than medical reasons) is defined by the following:
        i. ≥45 years of age and has not had menses for >1 year).
        ii. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon Screening evaluation.
        iii. Had a hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy, oophorectomy or tubal ligation must be confirmed in the medical records, otherwise the patient must be willing to use highly effective contraception (see Appendix C) throughout the study, starting with the Screening Visit through 180 days after the last dose of study drug. Information must be captured appropriately within the site's source documents.

    Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

4. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study drug through 90 days after the last dose of study drug.

Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.

7.4. Patient Withdrawal Criteria

7.4.1. Discontinuation from Pharmacokinetic Phase

Patients may be discontinued from the PK Phase of the study at any time. Specific reasons for discontinuing include the following:

- Unacceptable toxicity
- Vomiting within 10 hours of dose administration
- Loss to follow up
- Disease progression per Investigator's discretion
- It is in the best interest of the patient as judged by the Investigator and/or Sponsor

- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor or other reasons that would make the collected PK data non-evaluable, to include but not limited to:
  - Dosing errors
  - Patient did not fast for a minimum of 10 hours before and for 4 hours after either dosing period
  - Significant changes to the patient's medical status that would potentially affect the PK profile as determined by the Sponsor in consultation with the Investigator prior to data analysis.
- Withdrawal of consent
  - *Note: All reasonable efforts should be made to encourage patients to remain on study even if they withdraw from treatment.*
- Patient becomes pregnant
- Sponsor decision to terminate study
- Death

Those patients deemed to derive clinical benefit from niraparib treatment at the time of final analysis will have the option to continue treatment with niraparib through an alternative study, if available, and at the discretion of the Investigator and Sponsor.

Patients who discontinued from the PK Phase of the study and discontinue niraparib treatment prior to the Extension Phase will continue to receive safety follow-up assessments (Section 6.6.1) as part of the study unless they are discontinued from the study.

7.4.2. Discontinuation from Treatment During Extension Phase

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

- Unacceptable toxicity that cannot be managed by dose modifications
- Loss to follow up
- Disease progression per Investigator's discretion
- It is in the best interest of the patient as judged by the Investigator and/or Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor
- Withdrawal of consent
  - *Note: All reasonable efforts should be made to encourage patients to remain on study even if they withdraw from treatment.*
- Patient becomes pregnant
- Sponsor decision to terminate study
- Death

Details of any required niraparib dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity, are provided in Section 6.4.

Patients who discontinue from treatment will continue to receive follow-up assessments (Section 6.6.1) as part of the study unless they are discontinued from the study.

7.4.3. Discontinuation from the Study

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

- Completion of the required safety follow up
- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study
- Death
- Loss to follow-up
- Sponsor decision to terminate study

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 one via certified mail, should be made to contact the patient before considering the patient lost to follow-up.

7.4.4. Replacement of Patients

Patients will not be replaced during Stage 1. During Stages 2 and 3, the non-evaluability rate arising during the study conduct will be continuously monitored by the Sponsor and the total number of enrolled patients may be adjusted accordingly.

7.5. Restrictions During Study

Restrictions during the study include the following:

1. No other anticancer therapy is permitted during the course of study drug for any patient. If the patient discontinues study drug, this restriction no longer applies. Palliative radiotherapy is allowed for preexisting small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present. Hormonal therapy is allowed provided an agent listed in Appendix D is used. For hormonal agents not listed in Appendix D, the Site must consult with the Sponsor regarding allowing patient on study. For patient taking hormonal agents, dose and regimen of hormonal agents should have been stable for at least 14 days prior to first dose and is not expected to change during PK periods 1 and 2.
2. An increased risk of infection with the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown, so live virus and bacterial vaccines should not be administered to patients in the study.
3. P-glycoprotein inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin,

felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil are not permitted per protocol unless the dose and regimen has been stable for at least 14 days prior to first dose and will not change during PK periods 1 and 2 (does not apply for Extension Phase).

4. Patient taking proton pump inhibitors, antacids, or H2 blocker within 48 of dose *(Does not apply for Extension Phase).*
5. Patients who are blood donors should not donate blood during the study and for 90 days after the last dose of study drug.
6. Patients must be able to fast for 10 hours before and 4 hours after dosing in the 2 PK dosing periods.
7. Patients must avoid alcohol intake during the PK portion of the study.
8. Grapefruit and grapefruit juice is not allowed 7 days before or 2 days after dosing in the PK portion of the study (does not apply for Extension Phase).
9. Administration of blood or platelet transfusion should be avoided during the PK Phase. Should administration of blood products or other colloid solutions become necessary during the PK Phase the site must contact the Sponsor to discuss timing of blood (or other product) administration in relation to the timing of PK sampling.
10. Patient is currently taking a lipase inhibitor or cholesterol absorption inhibitor, such as orlistat or ezetimibe, respectively. *(Does not apply for participation in Extension Phase of this study)*.

7.5.1. Lifestyle Considerations

Cases of photosensitivity have been reported for patients on niraparib treatment. Participants must be informed on measures to decrease exposure to ultraviolet light, such as minimizing time in direct sunlight unless wearing hats and long-sleeves and application of sun protection creams.

8. TREATMENT OF PATIENTS

8.1. Description of Study Drug

Table 9: Investigational Product

	Investigational Product		
	Stage 1 and Stage 2		Stage 3
Product Name:	Niraparib	Niraparib	Niraparib
Dosage Form:	Capsule	Tablet	Tablet
Unit Dose	100 mg per capsule	300 mg per tablet 200 mg per tablet 100 mg per tablet [200 mg and 100 mg tablets for use in Extension Phase]	300 mg per tablet for both PK periods 100 mg per tablet for Extension Phase
Route of Administration	Oral	Oral	Oral
Physical Description	Capsules may be packaged in high-density polyethylene bottles with child-resistant closures or in blister cards	Tablets will be packaged in high-density polyethylene bottles	Tablets will be packaged in high density polyethylene bottles with child resistant closures

8.2. Concomitant Medications

Any medication the patient takes during the study other than the study drugs, 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 also recorded in the eCRF.

At Screening Visit, 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.

8.2.1. Permitted Concomitant Medications

Denosumab and bisphosphonates are allowed while on study.

Prophylactic antiemetics are allowed while on study. Should they be used, the same antiemetic prophylaxis MUST be administered in conjunction with Days 1 and 15 niraparib dosing in the PK Phase and within the same time interval from niraparib administration.

8.2.2. Concomitant Medications Taken with Caution

Niraparib weakly induces cytochrome P450 (CYP)1A2 in vitro and is an insensitive substrate for P-glycoprotein (P-gp); therefore, investigators should be advised to use caution with drugs that are the sensitive substrates for CYP1A2 with a narrow therapeutic range, i.e. theophylline and tizanidine.

8.3. Contraception

Niraparib is known to have properties that require the female patient of childbearing potential to use a highly effective form of contraception. For details on contraceptive guidelines, please refer to Appendix C.

Male patients must use an adequate method of contraception and not donate sperm starting with the first dose of study drug through 90 days after the last dose of study drug (Table 10). For a non-pregnant woman of childbearing potential partner, contraception recommendations should also be considered. Abstinence is acceptable if this is the established and preferred contraception method for the patient.

Patients should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to participate in the study, both male and female patients must adhere to the contraception requirement (described above) for the duration of the study and through 90 and 180 days, respectively, after the last study drug. This applies to female study patients and partners of male study patients. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Table 10: Timing of Contraception and Sperm Donation

Parameter	Timeframe
Contraception use, female patients	Starting with the Screening Visit through 180 days after the last dose of study drug
Contraception use, male patients	Starting with the first dose of study drug through 90 days after the last dose of study drug
Sperm donation	Starting with the first dose of study drug through 90 days after the last dose of study drug

8.4. Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 7.1 and Section 7.2, respectively.

Niraparib will be administered by site personnel at study sites as detailed in Section 9.5.

Study drug accountability will be monitored as detailed in Section 9.6.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Niraparib is a PO available, potent, highly selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate. Niraparib will be supplied as 100 mg capsules and 300, 200, and 100 mg tablets.

9.2. Study Drug Packaging and Labeling

Niraparib 100 mg capsules may be packed in high-density polyethylene bottles with child-resistant closures or in blister cards.

Niraparib 100 mg, 200 mg and 300 mg tablets will be provided in high-density polyethylene bottles. Additional information on packaging can be found in the Pharmacy Manual.

The label text of the study drug will comply with Good Manufacturing Practice and the national legislation to meet the requirements of the United States. The study drug will be open-label and nonpatient-specific.

9.3. Study Drug Storage

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

The pharmacist will dispense study drug for each patient according to the protocol and Pharmacy Manual, if applicable.

9.4. Study Drug Administration

The Pharmacy Manual contains descriptions of the packaging of study drug and instructions for administration of study drug.

9.5. Administration

Niraparib as 100 mg capsules and 300, 200, and 100 mg tablets will be supplied (Table 9). In the Stage 1 and 2 PK Phases, patients will receive a single dose (300 mg) of the study drug (tablet [1× 300 mg] or capsule [3× 100 mg]) in a fasted state (see Section 6.1.1) followed by a 7-day (+1 day) for Stage 1 of the study and a 14-day (+/- 4 days) Washout/PK period for Stage 2 of the study, followed by a dose of the alternate formulation (patients receiving tablets in the first treatment period will receive the capsule in the second treatment period and vice versa).

For Stage 3 during period 1, patients will receive a single 300 mg niraparib tablet either following a 10 hour fast or directly following consumption of a high-fat meal followed by a 14-day (+4 days) PK sampling and washout period. In period 2, patients will be crossed over to receive a single 300 mg niraparib tablet in a fasted state or with a high-fat meal (see Section 6.1.1), followed by a 7-day PK sampling period. Patients receiving the tablet in a fasted state in the first treatment period will receive the tablet with a high-fat meal in the second treatment period and vice versa.

In the Extension Phase, the starting dose of niraparib will be based on the patient's baseline actual body weight or platelet count. Patients with a baseline actual body weight of ≥77 kg and screening platelet count of ≥150,000/μL will take one 300 mg strength tablet or 3 x 100 mg tablets/capsules at each dose administration. Patients with a baseline actual body weight of <77 kg or screening platelet count of <150,000/μL will take one 200 mg strength tablet or 2 x 100 mg tablets/capsules at each dose administration. For patients whose initial starting dose is 200 mg QD, escalation to 300 mg once daily is permitted if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and with Sponsor's approval. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation. If laboratory values at the beginning of Extension Phase are outside of the range specified in the inclusion criteria, the patient may continue to participate in the study only upon Sponsor approval and with consideration for an appropriately reduced dose. Should a patient start the Extension Phase at 100 mg, consideration may be given to escalate to 200 mg after 2 cycles of therapy if no treatment interruption or discontinuation was required during the first 2 cycles of Extension Phase therapy and after approval from the Sponsor.

9.6. Study Drug Accountability

Accountability of the investigational study drugs is under the responsibility of the Investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site based on investigational study drug dispensed versus 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 drug accountability log. The pharmacist will dispense study drug for each patient according to the protocol and Pharmacy Manual, if applicable.

9.7. Study Drug Handling and Disposal

At the end of study, 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 Sponsor 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 onsite destruction, the Sponsor will provide a return for destruction service to a third party. Both the unused and expired study drug 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 medication provided for this study is to be used only as indicated in this protocol and only for the patients entered in this study.

10. PHARMACOKINETIC ASSESSMENTS

The primary PK parameters for analysis will include C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of niraparib (Stage 1 and 2) and AUC_{0-t} and $AUC_{0-\infty}$ in Stage 3. PK parameters to be assessed for niraparib and CCI (Stage 1 only) include the following:

- AUC_{0-t}
- $AUC_{0-\infty}$
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F (niraparib only)
- Vz/F (niraparib only)
- t_{lag} (Stage 3 only)

CCI parameters will only be determined in Stage 1 of the study. Additional PK parameters may be estimated if deemed appropriate. The PK parameters will be calculated from the plasma concentration-time profiles. The noncompartmental analysis will be performed using Phoenix WinNonlin, version 5.1 or higher. Population PK analysis may be performed on the PK Phase of the study data and will be reported separately.

For Stage 3, in addition to the PK parameters above, $t_{lag,}$ the time from administration of the dose to the first quantifiable concentration, will be determined, and t_{max} will be compared between the fed and fasted states. The relative bioavailability of the 300 mg niraparib tablet administered with a high-fat meal relative to fasted dosing will be based on the ratio of geometric least-squares means of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

10.1. 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 (Stage 1): predose (30 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96,120, and 168 hours postdose.

For Stage 2 and Stage 3, PK samples will be drawn at predose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose. 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 to 4 hours: ±5 minutes
- 5 to 8 hours: ±10 minutes
- 12 hours: ±60 minutes
- 24 hours: ±60 minutes
- 48 hours: ±120 minutes

- 72 hours: ±180 minutes
- 96 and 120 hours: ±240 minutes
- 168 hours: -6/+24 hours

The approximate volume of blood samples collected for PK analysis in the PK Phase would be approximately 160 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 tetra acetic acid (K_3EDTA) tubes, processed and plasma analyzed by a validated method of liquid chromatography coupled to tandem mass spectrometry detection (LC-MS/MS) method for determination of analyte concentrations.

10.2. Sample Analysis

Analysis of blood samples includes the following:

- **Blood:** Blood samples will be analyzed for the plasma concentration of niraparib (Stage 1, 2 and 3) and CCI (Stage 1 only) using LC-MS/MS.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety parameters evaluated during the conduct of the study will include treatment-emergent adverse events (TEAEs), discontinuations due to AEs, physical examinations, vital signs, clinical laboratory results, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

11.1.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed at screening/baseline.

11.1.2. Patient Eligibility

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 7.1 and Section 7.2.

11.1.3. Patient Demography

Patient demography consists of age at screening, race, ethnicity, and sex.

11.1.4. Disease History

The following will be documented for disease history, if available:

- Primary Cancer diagnosis
- Date of first diagnosis
- Stage of disease at enrollment (local versus metastatic)
- Information on prior neoadjuvant/adjuvant treatment, if applicable:
  - Agents used in treatment
- Information on previous anticancer treatments:
  - Agents in all subsequent treatments
- Best response for each line of therapy

11.1.5. Medical and Surgical History

Major medical and surgical history (including medication history), including history of thrombocytopenia, neutropenia, leukopenia, or anemia will be collected, if available. Details of any prior malignancy will be collected if available. Medical and surgical history will be obtained by interviewing the patient or by reviewing the patient's medical records.

11.1.6. Vital Signs

Vital signs (blood pressure [BP], pulse, heart rate, and temperature) will be assessed according to the schedule of events (Section 6.6.1).

Body weight and height will be assessed during screening according to the schedule of events (Section 6.6.1).

11.1.7. Physical Examination

A complete physical examination and symptom-directed physical examination will be performed in accordance with the schedule of events.

11.1.8. Concomitant Medications and Procedures

Refer to Section 8.2 for a description of prior and concomitant medications. For prior medications, patients will be asked during the Screening Visit for the PK Phase and the Extension Phase what medications they have taken during the last 30 days. All concomitant medications will be recorded from the time the patient signs the ICF through completion of the study. Medications will be coded according to the most current version of the World Health Organization Drug Dictionary.

11.1.9. Electrocardiogram

All patients will undergo 12-lead ECGs in accordance with the schedule of events (Section 6.6.1). ECGs should be performed prior to blood draws. Patients will be rested for approximately 2 minutes before ECGs are recorded.

11.1.10. Laboratory Assessments

The hematology, chemistry, urinalysis, and pregnancy screening will occur in accordance with the schedule of events (Section 6.6.1). These tests will be performed by the local laboratory at the clinical site.

11.1.10.1. Hematology

Hematology will be measured in accordance with the Schedule of Events (Section 6.6.1). The following values will be obtained/analyzed:

- **CBC:**
  - Hemoglobin
  - Platelet count
  - Mean corpuscular volume
  - White blood cell count
  - Differential white blood cell count

11.1.10.2. Chemistry

Chemistry will be assessed in accordance with the Schedule of Events (Section 6.6.1). The following values will be obtained/analyzed:

- 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

11.1.10.3. Urinalysis

Urinalysis will be assessed in accordance with the Schedule of Events (Section 6.6.1). The following values will be obtained/analyzed:

- Specific gravity
- Leukocyte esterase
- Nitrite
- Blood
- Protein
- Glucose
- Ketones
- Bilirubin

11.1.10.4. Virus Serology

Not applicable.

11.1.10.5. Drug Screen

Not applicable.

11.1.10.6. Pregnancy Screen

A negative serum or urine pregnancy test is required within 72 hours prior to first dose of study drug for PK period 1 and first dose of Extension Phase for females of childbearing potential. Urine pregnancy testing will be performed in accordance with the schedule of events (Section 6.6.1).

11.1.10.7. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Appendix A) in accordance with the schedule of events (Section 6.6.1). The same observer should assess performance status each time.

11.2. Adverse Events and Special Situations

11.2.1. Definitions

11.2.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal 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 a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, 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 after the time of randomization and/or treatment assignment, including baseline or washout periods, even if no study treatment has been administered (see Section 11.2.3 for information about AE collecting and reporting.)

11.2.1.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that, at any dose;

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be captured in medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

**Medical and scientific judgment 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 require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug. (See Section 11.2.5 for information about SAE reporting.)

11.2.1.3. Treatment-Emergent Adverse Event (TEAE)

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.

11.2.1.4. 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.

11.2.1.5. Special Situation: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** is 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:** is 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:** is 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 11.2.5.
- **Accidental /Occupational exposure:** is 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.

11.2.2. Assessment of Adverse Events

11.2.2.1. 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 11.2.1.2. 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.

11.2.2.2. Relationship to Study Intervention

The Investigator must provide a causality assessment regarding the relationship of the event with the study drug and/or study procedure for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product (and/or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.
- Not Related: A causal relationship between the medicinal product (and/or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

11.2.2.3. 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).

11.2.3. Collection and Recording of 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, nonleading question such as, “How have you been feeling since your last study visit?” 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 collected from the signing of the ICF for this study through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first), and recorded in the eCRF. SAEs will also be reported on an SAE form as described in Section 11.2.5 of this protocol. SAEs considered by the Investigator to be related to study medication are reported until study closeout.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by patient), will be collected and recorded in the eCRF for each patient from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History in the eCRF and on the SAE Report Form.

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 appropriate 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 11.2.5.

11.2.4. 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 AE(s) or SAE(s) 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, starts alternate anti-cancer therapy, or until the patient withdraws consent.

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 11.2.5.

11.2.5. Reporting

The Investigator must report all SAEs, and all follow up information to the Sponsor on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE Report Form. If supporting documentation is requested (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including Medical Record number) are removed, and submit the documents

with the SAE Form to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt for all email reports (if received from other than a "no reply" domain) within 1 business day.

The minimum information required for an initial SAE report is:

- Name of person sending the report (ie, name, address of Investigator)
- 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.

SAE REPORTING CONTACT INFORMATION
Email: OAX37649@gsk.com
Fax: +44(0) 208754 7822

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.

11.2.6. Submission and Distribution of Serious Adverse Event Reports

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 to 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.

11.2.7. 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])

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor until study closeout (unless death or loss to follow-up occurs first).
-

11.2.8. Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Preexisting hypertension should be adequately controlled before starting niraparib treatment. While receiving treatment, hypertension should be medically managed with antihypertensive medicinal products with or without niraparib dose adjustment.

BP and heart rate should be monitored at least weekly for the first 2 months of niraparib treatment in the maintenance setting, then monthly for the first year and periodically thereafter during treatment with niraparib. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

11.2.9. Posterior Reversible Encephalopathy Syndrome

There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

11.2.10. Allergic Reaction

Niraparib capsules contain tartrazine, which may cause allergic-type reactions.

11.2.11. Pregnancy

The Investigator must report all pregnancies and the outcomes to the Sponsor. The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Each pregnancy must be reported by the Investigator to the Sponsor on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE, and therefore does not need to be reported as an AE in the eCRF unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow-up all pregnancies, document the course and the outcome, and report this information to the Sponsor on a Pregnancy Outcome Report Form within 24 hours of becoming aware; even if the patient was withdrawn from the study or the study has finished.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE in the eCRF. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth

defect) and reported to the Sponsor within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

11.2.12. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on a Special Situations Report Form to the Sponsor within 5 calendar days of becoming aware of the occurrence, regardless of whether it is categorized as an AE. If the occurrence is associated with an SAE, an SAE Report Form, along with the Special Situations Report Form, must be submitted to the Sponsor within 24 hours of awareness.

12. STATISTICS

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

12.1. Analysis Populations

PK Population: All patients who receive at least one dose of niraparib and have at least one measurable niraparib, or niraparib or CCI (Stage 1 only) concentration.

PK Evaluable Population: All patients who complete at least one PK Period and have sufficient concentration data to accurately estimate PK parameters without significant niraparib carryover (baseline concentration >5% of C_{max}) in at least one Period. Patients with carryover will be excluded from the analysis of Period 2, but will be included in the analysis of period 1, as data is available.

BA/BE Evaluable Population: All patients who complete both PK Periods and have sufficient PK sample collection to accurately estimate PK parameters, without significant niraparib carryover (baseline concentration >5% of C_{max}) in both PK Periods. Patients who have significant niraparib carryover in Period 2 will be completely excluded from the BA/BE Evaluable Population.

FE Evaluable Population: All patients who complete both PK Periods and have sufficient PK sample collection to accurately estimate PK parameters in both periods. Patients meeting non-evaluability criteria or having significant niraparib carryover (baseline concentration >5% of C_{max}) will be completely excluded from the FE Population.

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

12.2. Sample Size Consideration

Stage 1

No formal sample size calculation was performed for Stage 1. Approximately 24 patients will be enrolled in Stage 1. This sample size is considered adequate for preliminary assessment of the relative bioavailability of the tablet compared to the capsules and for estimating the intra-subject coefficient of variation, after accounting for patient drop-outs and potential carryover.

Stage 2

Based on estimates from Stage 1, 100 BA/BE evaluable patients are required in Stage 2. With 100 evaluable patients, assuming the intra-subject coefficient of variation (CV) is 25% and the true ratio of means is 0.89, there is at least 90% power to demonstrate the bioequivalence (bioequivalence range: 0.800 to 1.250; alpha=0.05). Power calculations were also performed under alternative assumptions for the CV and mean ratio. Assuming the CV is 30% and the true ratio of means is 0.89%, with 100 evaluable patients, there is at 82% power to demonstrate bioequivalence. Assuming the true ratio is 0.90, the power is 96% and 88% assuming CVs of 25% and 30%, respectively.

The final analysis of bioequivalence will be based on Stage 2 BA/BE evaluable patients only, with a target sample size of 100 evaluable patients. Patients may be identified as non-evaluable due to issues arising during the study conduct, such as:

- emesis within 9 hours of dosing,
- dosing errors,
- patient did not fast prior to dosing,
- missing critical PK sample on Day 8,
- failure to complete both PK periods, and
- significant changes to the patient medical status that would potentially affect the PK profile as determined by the Sponsor in consultation with the Investigator prior to PK data analysis.

In this patient population, approximately 170 total patients are targeted for enrollment, assuming a 35% non-evaluability rate during the study conduct, and an additional 10% non-evaluability rate during PK analysis. The non-evaluability rate arising during the study conduct will be continuously monitored by the Sponsor and the total number of enrolled patients may be adjusted accordingly with the aim to target the resulting sample size of 100 BA/BE evaluable patients.

Stage 3

Assuming the true ratio of means is 1 and the intra-subject CV is 20% for AUC_{0-t} and $AUC_{0-\infty}$, with 16 evaluable patients, there is approximately 83% probability the 90% CI of the ratio of geometric means will be within 0.800 and 1.250. Based on the results of a FE study conducted using the capsule formulation, an effect of a high-fat meal on C_{max} is possible. The sample size of 16 patients is deemed adequate to characterize this effect. AUC_{0-t} and $AUC_{0-\infty}$ will be the primary parameters for analysis.

The primary analysis will be based on the FE Evaluable Population as it is the most conservative approach, which maximizes the benefits of the crossover design, where each patient serves as their own control. Results for the PK Evaluable Population will also be summarized and reported for this study.

To account for non-evaluable patients, approximately 20 total patients are targeted for enrollment. The final analysis will be based on Stage 3 FE evaluable patients only. Patients may be identified as non-evaluable due to issues arising during the study conduct, such as:

- dosing errors,
- patient did not follow dietary requirements prior to dose and postdose,
- failure to complete both PK periods, and
- significant changes to the patient medical status that would potentially affect the PK profile as determined by the Sponsor in consultation with the Investigator prior to PK data analysis.

Patients who vomit within 10 hours of dosing or miss sufficient samples to render calculation of AUC unreliable will be discontinued from the PK phase; those that meet other criteria for

continued niraparib therapy will be eligible to be screened for the Extension Phase (see Section 6.1). The non-evaluability rate arising during the study conduct will be continuously monitored by the Sponsor and the total number of enrolled patients may be adjusted accordingly with the aim to target the resulting sample size of 16 evaluable patients.

12.3. Safety Analyses

Data from the Stage 1 PK Phase, Stage 2 PK Phase, Stage 3 PK Phase and Extension Phase will be summarized separately. Summaries will be performed by formulation, fed/fasted state and dosing period as applicable. The safety population will consist of all patients who receive drug.

Demographic characteristics will be summarized descriptively and will include age, sex, race, height, and weight.

Protocol deviations will be listed by patient.

All analysis for safety endpoints will be done in a descriptive manner. Continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, and maximum). Categorical variables will be summarized using counts of patients and percentages. All AEs will be coded using the most up-to-date version of MedDRA. NCI-CTCAE v.4.03 will be used to grade the severity of AEs and laboratory abnormalities.

All AEs will be listed. The number and percent of patients who experience a TEAE will be summarized by formulation, fed/fasted state and dosing period as applicable for each system organ class and preferred term. TEAEs will also be tabulated accordingly by intensity and causality.

An analysis of AEs will include the following categories:

- TEAEs
- Drug-related TEAEs
- Grade 3, 4, and 5 TEAEs (presented by grade and overall)
- Grade 3, 4, and 5 drug-related TEAEs (presented by grade and overall)
- TEAEs resulting in study drug discontinuation
- Most commonly reported TEAEs
- Treatment-emergent SAEs
- AESIs

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.

In addition, for the Extension Phase, 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 clinically relevant physical examination findings will be listed.

12.4. Pharmacokinetic Analysis

Individual and mean plasma concentrations over time will be plotted by formulation for the 300-mg dose group in Stage 1 and 2 and by fed/fasted state in Stage 3. Planned sampling times will be used to generate the mean concentration-time profiles.

Individual patient PK parameter values will be derived by non-compartmental methods using WinNonlin, version 5.1 or higher. Actual time will be used in parameter estimation. The analysis of Stage 1, Stage 2, and Stage 3 will be conducted separately.

During the pharmacokinetic analysis, the following rules will apply:

- Predose sample >5% of C_{max}: profile will be excluded from PK concentration and PK parameters summary and inferential statistics
- Rsq,adj <0.800: $AUC_{0-\infty}$, λz, CL/F, Vz/F, and $t_{1/2}$ will be excluded from descriptive and inferential statistics
- AUC_{0-t} /$AUC_{0-\infty}$, <0.800: $AUC_{0-\infty}$ and parameters derived from it will be excluded from descriptive and inferential statistics

Individual and mean plasma concentrations over time will be plotted by formulation in Stage 1 and 2 and by fed/fasted state in Stage 3. The individual plasma concentration versus actual time profiles for each subject, as well as the mean plasma concentration versus scheduled time profiles for each treatment, will be presented graphically on a linear-linear and log-linear scale. Combined individual concentration versus time graphs per treatment will also be presented, together with mean values. Plasma concentrations and PK parameters will be summarized in terms of the number of patients, arithmetic mean, median, SD, coefficient of variation (CV), geometric mean, geometric CV, minimum and maximum by formulation in Stage 1 and 2 and by fed/fasted state in Stage 3, across the PK, PK Evaluable, BA/BE Evaluable and FE Evaluable populations, as appropriate. In Stage 3, differences in t_{max} between the fed and fasted state will be assessed and summarized based on the FE Evaluable Population. Details will be provided in the Pharmacokinetic Analysis Plan.

To assess relative bioavailability/bioequivalence, an analysis of variance model (ANOVA) will be used on logarithmically transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} accounting for the following sources of variation: sequence, subjects nested in sequences, period and treatment. The point estimate and 90% CIs for the ratios of the geometric means of the test treatment (tablet) compared to the reference treatment (capsule) will be obtained. Bioequivalence will be claimed if the 90% CI for the ratio of geometric means is between 0.800 and 1.250 for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. To assess the effect of food for Stage 3, the ratio of geometric means of the test treatment (high-fat meal) and corresponding 90% CI compared to the reference treatment (fasted state) will be obtained for $AUC0_{-t}$, $AUC0_{-\infty}$, and C_{max}.

A population PK analysis may be performed on the PK data from the PK Phase of the study and will be reported separately from the study.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms (CRFs), and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the Sponsor before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. the Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and TESARO's policy on Bioethics.

15.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17. PUBLICATION POLICY

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

18. LIST OF REFERENCES

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5. Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. *Clin Cancer Res.* 2012;18(6):1726-1734.
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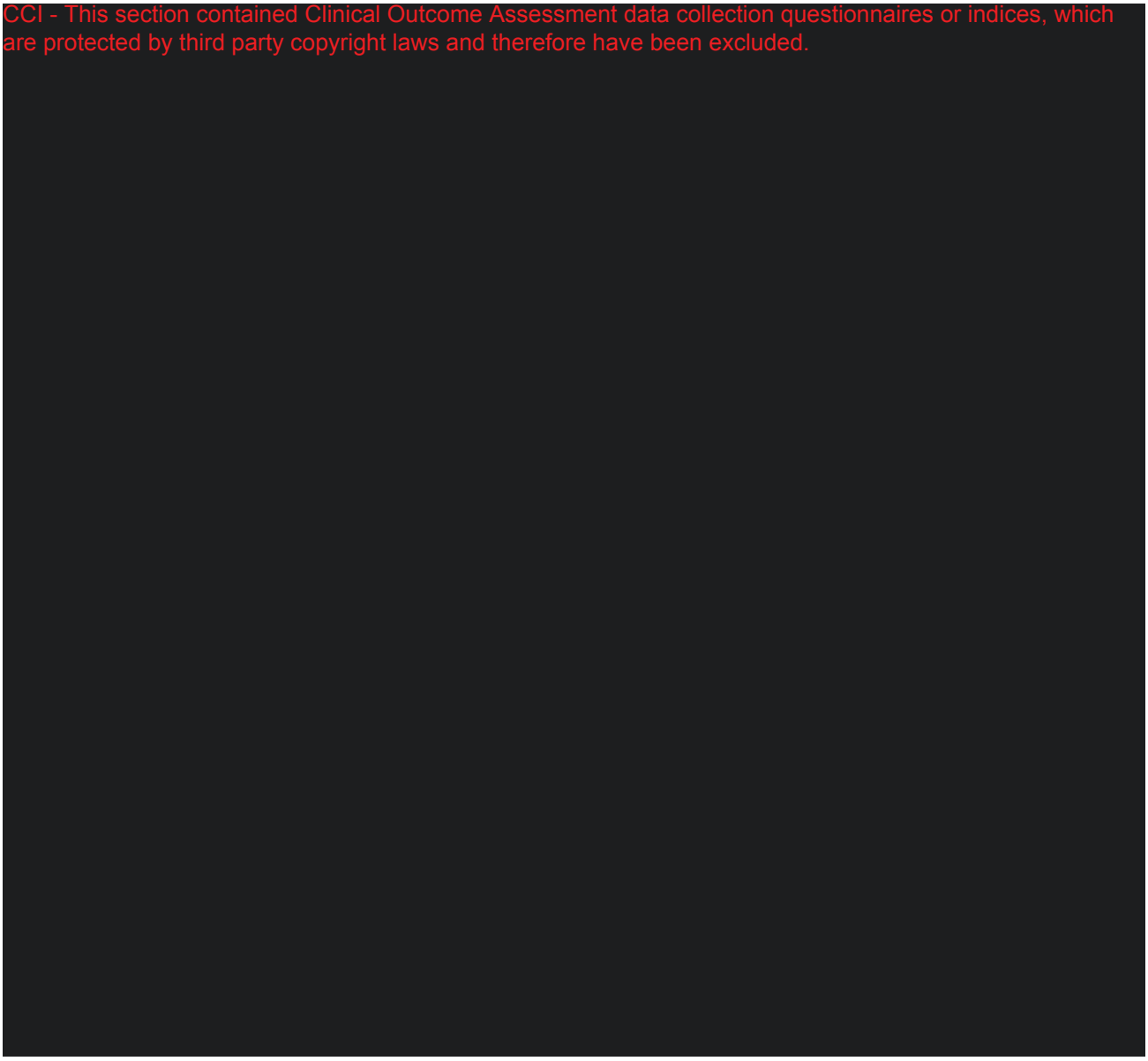
8. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med.* 2016;375(22):2154-2164.
9. Guan J, Lim KS, Mekhail T, Chang CC. Programmed Death Ligand-1 (PD-L1) Expression in the Programmed Death Receptor-1 (PD-1)/PD-L1 Blockade: A Key Player Against Various Cancers. *Archives of pathology & laboratory medicine.* 2017;141(6):851-861.
10. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.
11. FDA. US Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. 2002. Accessed 08 Dec 2020. Available at: https://www.fda.gov/media/70945/download.

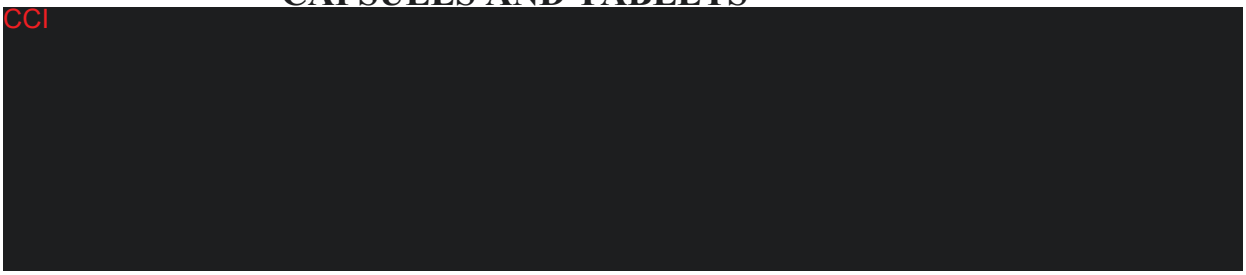
APPENDIX A. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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.



APPENDIX B. COMPONENTS AND EXCIPIENTS OF NIRAPARIB CAPSULES AND TABLETS

CCI



APPENDIX C. CONTRACEPTION GUIDELINES

Patients of childbearing potential who are sexually active and their partners must agree to the use of 2 highly effective form of contraception throughout their participation during the study treatment and for 180 days after last dose of study treatment(s). Acceptable birth control methods include:

- 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 D. PERMITTED HORMONAL THERAPIES

- Anastrozole
- Letrozole
- Exemestane
- Fulvestrant
- Abiraterone acetate
- Enzalutamide
- Goserelin
- Bicalutamide
- Leuprolide

APPENDIX E. GUIDANCE ON COMPOSITION OF HIGH-AT MEAL

During Stage 3 PK periods, patients will receive their niraparib dose in a fasted state or directly after having had a high-fat meal. Below is an example of a high-fat meal, where ≥50% of calories are derived from fat. Substitutions can be made to this meal if the caloric content, volume, and viscosity are maintained.

Example of a high-fat meal:

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600
An Example of a High-Fat Breakfast	• Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk

Source: FDA, 2002