Clinical Study Protocol: CO-338-098

Study Title:	SEASTAR: A Phase 1b/2, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral Rucaparib in Combination with Other Anticancer Agents in Patients with a Solid Tumor
Study Number:	CO-338-098
Study Phase:	Phase 1b/2
Product Names:	Rucaparib (CO-338) Lucitanib (CO-3810) Sacituzumab Govitecan (IMMU-132; hRS7-SN38) M4344
IND Number:	[redacted]
EUDRA CT Number	[redacted]
Indication:	Advanced, recurrent, or metastatic solid tumors
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
Sponsor Address:	[redacted] [redacted] Telephone Number: [redacted] Facsimile Number: [redacted]
Responsible Medical Officer:	[redacted]

	Date
[redacted]	[redacted]
[redacted]	[redacted]
Amendment 2.0	01 September 2020

PROTOCOL APPROVAL SIGNATURE PAGE

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Date: 01 September 2020

Version: Amendment 2.0

Reviewed and Approved by:

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Clovis Oncology, Inc.

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Clovis Oncology, Inc.

PROTOCOL ACCEPTANCE FORM

Protocol: CO-338-098

Title: SEASTAR: A Phase 1b/2, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral Rucaparib in Combination with Other Anticancer Agents in Patients with a Solid Tumor

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I have carefully read this protocol and agree that it contains all the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH E6(R2) Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature	Date (DD-MMM-YYYY)
Name (printed)	

SPONSOR'S MEDICAL EXPERT FOR THE STUDY

Medical Expert:

[redacted]

Telephone: [redacted]
Facsimile: [redacted]
E-mail: [redacted]

Clinical Investigators, Study Sites, and Laboratories:

This is a multicenter study. Information on investigators, institutions, and laboratories involved in the study are maintained in the clinical study file and can be provided upon request.

SYNOPSIS

Sponsor

Clovis Oncology, Inc.

Name of Finished Products

Rucaparib tablets;
Lucitanib tablets;
Sacituzumab govitecan for infusion;
M4344 tablets

Name of Active Ingredients (respectively)

Rucaparib camsylate (CO-338);
Lucitanib (CO-3810);
Sacituzumab govitecan (IMMU-132);
M4344

Study Title

SEASTAR: A Phase 1b/2, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral Rucaparib in Combination with Other Anticancer Agents in Patients with a Solid Tumor

Study Number

CO-338-098

Study Phase

Phase 1b/2

Background and Study Rationale

This study aims to evaluate the poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, rucaparib, in combination with various other anticancer agents that have a different mechanism of action.

Rucaparib is an inhibitor of PARP enzymes, which play a critical role in base excision repair (BER) of deoxyribonucleic acid (DNA).[1] When PARP function and effective BER are impaired, double-stranded DNA breaks accumulate. In cells deficient in homologous recombination, these breaks cannot be accurately repaired, resulting in synthetic lethality.[2] While mutated breast cancer genes (BRCA)1 and BRCA2 are most commonly associated with homologous recombination deficiency (HRD), other homologous recombination repair (HRR) proteins may be mutated or functionally deficient in ovarian and other cancers. Rucaparib (Rubraca®) is approved in the United States (US) as monotherapy treatment for adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who have been treated with 2 or more prior chemotherapies, and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who have a complete or partial response to platinum-based chemotherapy.[3] Rucaparib is also approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-

sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade EOC, FTC, or PPC who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.[4] In addition, rucaparib is being developed for the treatment of cancer associated with HRD, defined by the presence of a deleterious mutation in BRCA1, BRCA2, or other HRR genes, and/or high percentage of tumor genome with loss of heterozygosity (LOH), which is a phenotypic consequence of HRD.

PARP inhibitors have been explored in combination with chemotherapy; however, such combinations were challenging to administer due to overlapping toxicity, specifically myelosuppression, therefore novel combination approaches with more selective targeted agents are currently thought to have more potential. Combination therapy with a PARP inhibitor would aim to increase accumulation of DNA damage and subsequent dependence on HRR, such as in the combination of a PARP inhibitor with a topoisomerase inhibitor. Agents that inhibit topoisomerase 1, including irinotecan and topotecan, have demonstrated synergy with PARP inhibitors in a variety of human tumor cell lines, including ovarian and breast cancers.[5,6] The PARP inhibitor olaparib has been shown to potentiate the cytotoxicity of SN-38, the active metabolite of irinotecan and topotecan, irrespective of mismatch repair (MMR) status in a variety of MMR-deficient or MMR-efficient cell lines.[7] A clinical study of the PARP inhibitor veliparib combined with topotecan showed a mechanistic interaction between the 2 drugs, resulting in delayed repair of Topo1-mediated DNA damage, despite there being some challenges with overlapping hematologic toxicities.[8] Targeted delivery of SN-38 to cancer cells through administration of an antibody-drug conjugate (ADC) has greater potential for combination therapy with a PARP inhibitor by reducing off-target and additive toxicity. Other combinations would aim to induce a BRCA-like phenotype in order to elicit PARP inhibitor and BRCA-like synthetic lethality, as has been shown to occur in combinations between PARP inhibitors and angiogenesis inhibitors (such as vascular endothelial growth factor [VEGF] inhibitors) and ataxia telangiectasia mutated and Rad3-related (ATR) inhibitors. The combination of a PARP inhibitor with a VEGF inhibitor, which have distinctly different mechanisms of action, have also demonstrated synergistic effects in nonclinical studies (Clovis Oncology, data on file). In addition, a Phase 2 clinical study in patients with recurrent ovarian cancer treated with the PARP inhibitor, olaparib, and an antiangiogenic agent, cediranib, has shown promise.[9] Nonclinical data indicate that ATR inhibition increases sensitivity to PARP inhibition[10] and that defects in ATR signaling may result in synthetic lethality with PARP inhibition.[11] Inhibition of ATR may also be a mechanism to overcome primary and acquired resistance to PARP inhibition.

This study will initially evaluate rucaparib in combination with 3 other anticancer therapies; additional combinations may be added at a later date.

The initial 3 Treatment Arms include the following:

Treatment Arm A: rucaparib and lucitanib; lucitanib is a potent, selective inhibitor of the tyrosine kinase activity of vascular endothelial growth factor receptors, types 1, 2, and 3 (VEGFR1–3); platelet-derived growth factor receptors (PDGFR), types alpha and beta (PDGFRα/β); and fibroblast growth factor receptors (FGFR), types 1, 2, and 3 (FGFR1-3).

Treatment Arm B: rucaparib and IMMU-132 (sacituzumab govitecan); sacituzumab govitecan is an antibody-drug conjugate comprised of a humanized antibody targeting Trop-2 (trophoblast cell-surface antigen-2) linked to SN-38, a potent topoisomerase 1 inhibitor.

Treatment Arm C: rucaparib and M4344; M4344 is a potent ATR inhibitor.

The rucaparib combinations selected for evaluation within this study were carefully chosen based on nonclinical and clinical data, and theoretical concepts to support a potential efficacious synergism. The rationale for each rucaparib combination is provided in the body of the protocol.

Primary Objectives:

Phase 1b of each Treatment Arm

- To evaluate the safety and tolerability of rucaparib in combination with a second anticancer agent and to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of the combination.

Phase 2 of each Treatment Arm

- To evaluate the efficacy of rucaparib in combination with a second anticancer agent by measuring investigator-assessed confirmed best overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 in one or more expansion cohorts evaluating the combination.

Secondary Objectives:

Phase 1b of each Treatment Arm

- To characterize the pharmacokinetics (PK) of rucaparib (Treatment Arm A and Treatment Arm C) and the second anticancer agent (all treatment arms), as well as the metabolites for the second anticancer agent (Treatment Arm B) when rucaparib and the second anticancer agent are co-administered.
- To evaluate the preliminary efficacy of rucaparib in combination with a second anticancer agent in various solid tumors.

Phase 2 of each Treatment Arm

- To evaluate the safety and tolerability of rucaparib in combination with a second anticancer agent.
- To evaluate progression-free survival (PFS) in one or more expansion cohorts.
- To evaluate duration of response (DOR) in one or more expansion cohorts.

Exploratory Objectives:

- To assess tumor tissue biomarkers that correlate with response to the combination.
- To evaluate circulating cell-free tumor DNA (ctDNA) as a molecular marker of response to the combination.
- To evaluate biomarkers associated with resistance to the combination.

- To assess genomic changes over time in plasma and tumor samples.
- To determine steady-state exposure of rucaparib and the second anticancer agent (all treatment arms) by sparse PK sampling.
- To evaluate the development of antidrug antibodies (ADAs) (Treatment Arm B).
- To characterize the PK of metabolites of the second anticancer agent (Treatment Arm C) when rucaparib and the second anticancer agent are co-administered.

Study Design

This is a Phase 1b/2, open-label, study with multiple treatment arms evaluating the safety, tolerability, PK, and preliminary efficacy of rucaparib in combination with a second anticancer therapy in patients with an advanced/metastatic solid malignancy (Phase 1b), followed by evaluation of the combination in one or more specific patient populations in an expansion phase (Phase 2 cohorts).

The description of the study design provided in this synopsis is general across all treatment arms. The specifics of each treatment arm are included in the body of the protocol.

Screening Phase

All patients will undergo screening assessments prior to enrollment. Patients will be required to provide archival tumor tissue or a more recently obtained tissue sample, as well as blood samples, for genomic analysis. Enrollment of eligible patients is described below.

Treatment Phase

Treatment cycles will be 21 or 28 days in length, depending upon the study drug combination; cycles are defined within each specific treatment arm. All patients will be monitored for safety throughout the treatment phase. In addition, all patients will be assessed for disease status per RECIST v1.1 per the time interval specified within each treatment arm until one of the following: radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments.

Phase 1b/ Dose-escalation Phase:

In the Phase 1b portion of each treatment arm, there will be an estimated 6 to 12 dose-escalation cohorts, with a minimum of 3 patients enrolled in each cohort, followed by an expanded evaluation of the RP2D in up to 10 additional patients.

This portion of the study will enroll patients with advanced malignancy who have relapsed following prior treatment or are not eligible for standard of care treatment. Dose escalation will follow a 3+3 design. The starting doses and dose escalation steps are defined for each separate treatment arm within the body of the protocol.

Dose-limiting toxicities (DLTs) are defined according to criteria specified for each combination treatment within the body of the protocol. DLTs will be assessed by the investigator based on toxicity grade (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), clinical significance, and possible relationship to either or both study drug(s) The MTD is defined as the maximum dose combination at which < 33% of patients experience a DLT during Cycle 1 (DLT-

evaluation period). If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation will continue until at least 2 of the 3 to 6 patients treated at a dose level experience a DLT or until the maximum dose to be evaluated is reached, whichever occurs first. If the end of dose escalation is reached due to DLTs, the next lower dose will then be considered the MTD. Alternatively, if the difference between the MTD and the maximally delivered dose is significant (such as 100%), then a more modestly de-escalated dose may be explored (eg, 20% to 50%).

Prior to initiating treatment at each new combined dose level or prior to expanding a cohort, a safety teleconference will be held to review patient data, including, but not limited to, demographics, PK results, study drug combination dosing, concomitant medications, hematology and chemistry, and adverse events (AEs), and then confer and document agreement that dose escalation and/or expanding an existing dose level is/are considered appropriately safe. Safety teleconferences will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites.

The RP2D for evaluation in the Phase 2 portion will be selected based on overall safety and tolerability, PK, as well as any efficacy, if observed. The RP2D may or may not be the same as the MTD identified in the dose-escalation. For example, if the MTD is not reached, if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile of the combination, then the RP2D may be a different, although not higher, dose than the MTD for the combination. Once the RP2D of the combination has been provisionally determined, up to 10 additional Phase 1b patients may be enrolled and treated at the RP2D, in order to further characterize safety, tolerability, and PK and to confirm that this is the optimal dose combination to evaluate in Phase 2.

Phase 2/ Expansion Phase:

Phase 2 of each treatment arm will not commence until the RP2D has been established in Phase 1b. In Phase 2, the study drug combination administered at the RP2D will be evaluated for safety and tolerability, PK, pharmacodynamics, and efficacy in patients as defined for each treatment arm and cohort.

Phase 2 will enroll patients into specified cohorts for each treatment combination, and a Simon 2-stage design[12] will be utilized for each of the planned Phase 2 expansion cohorts.

End of Treatment and Follow-up

Upon treatment discontinuation in either Phase 1b or Phase 2, regardless of reason (with the exception of patient withdrawal or death), patients will have an End of Treatment Visit, and all patients will be followed for at least 28 days after the last dose of study drug.

Patients who discontinue treatment for a reason other than disease progression or death should continue to have tumor scans performed at the interval specified for that treatment arm until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments.

The study will be considered ongoing until all patients have either met one of the

withdrawal criteria (see below) or have withdrawn consent for the study, or the sponsor terminates the study.

Number of Patients

The number of patients anticipated to participate in each treatment arm is variable due to the uncertainty in the number of dose escalation cohorts in Phase 1b and the design in Phase 2. Sample size estimates for Phase 1b and each cohort in Phase 2 are provided in the body of the protocol for each treatment arm.

For Treatment Arm A, total enrollment is anticipated to be up to 135 patients, with up to 55 patients in Phase 1b and up to 80 patients in Phase 2.

For Treatment Arm B, total enrollment is anticipated to be up to 194 patients, with up to 55 patients in Phase 1b and up to 139 patients in Phase 2.

For Treatment Arm C, total enrollment is anticipated to be up to 135 patients with up to 55 patients in Phase 1b and up to 80 patients in Phase 2.

Number of Sites

Three to six sites in the US are expected to participate in the Phase 1b portion of the study; approximately 25 sites globally may be activated to participate in the Phase 2 portion of the study.

Enrollment and Study Treatment

In Phase 1b, eligible patients will be enrolled into cohorts as described above. Enrollment in the Phase 2 portion will be competitive for all treatment arms. If a patient appears to be eligible for more than one treatment arm that is open to enrollment, the investigator will be responsible for selecting the most appropriate treatment arm for the patient.

Patients participating in this study will enroll into either the Phase 1b or Phase 2 portion, but a patient cannot participate in both portions of the same treatment arm. No randomization or blinding is planned in the study.

Patients will be treated with the study drug combination at the doses specified by the Phase 1b dose escalation plan for each combination or the RP2D. Rucaparib will be administered twice a day (BID) continuously up to a maximum dose of 600 mg BID, and the other study drug will be administered as specified within each respective treatment arm.

Withdrawal Criteria

A patient must be discontinued from treatment with study drug if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator, unless patient is still receiving benefit from the study drug(s) according to the investigator, and the patient has provided additional consent.

- Initiation of any other anticancer therapy.
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient. If it is determined that 1 of the study drugs in the combination is posing a safety risk and that study drug is permanently discontinued, administration of the other study drug may continue if none of the other withdrawal criteria have been met and the investigator believes that the patient may continue to receive benefit.
- Any concomitant illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy.
- A positive pregnancy test at any time during the study.

Efficacy Assessments

Tumor assessment measurements will be performed at screening and at treatment arm-specified intervals until objective radiological disease progression. Tumor assessments should be performed at the time of treatment discontinuation if the reason for discontinuation was other than radiologically-confirmed disease progression and the time elapsed since the last assessment is greater than the tumor-assessment interval. Additional tumor assessments should be performed as clinically indicated. Confirmatory scans should be obtained no less than 4 weeks after the initial response.

Disease assessment will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (computed tomography and/or magnetic resonance imaging scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1). Other complementary assessments (X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. Tumor markers should be collected as clinically indicated for the response assessment by RECIST v1.1. For example, a complete response (CR) in an ovarian cancer patient would require normalization of cancer antigen-125 (CA-125).

Tumor response will be interpreted using RECIST v1.1. Disease progression will be determined by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

Patients who discontinue treatment for a reason other than disease progression or death should continue to have tumor scans performed at the interval specified for that treatment arm until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination or specific cohort closure (in Phase 2), or initiation of subsequent anticancer treatments.

Safety Assessments

Safety and tolerability will be assessed based on the following:

- Incidence, type, seriousness, severity, and causality of AEs reported (CTCAE v5.0);
- Clinical laboratory investigations (hematology, chemistry, urinalysis);

- Vital signs (blood pressure, heart rate, and body temperature);
- 12-lead electrocardiograms (ECGs);
- Physical examinations; and
- Eastern Cooperative Oncology Group (ECOG) performance status.

Pharmacokinetic Assessments

Samples for intensive (Phase 1b, Cycle 1) and sparse (Phase 1b and Phase 2) PK assessments will be collected for both study drugs in the combination, with the exception of no intensive rucaparib PK collection in Treatment Arm B.

Statistical Methods

Sample Size

The number of patients anticipated to participate in each treatment arm is variable due to the uncertainty in the number of dose escalation cohorts in Phase 1b and the design in Phase 2.

Each Phase 2 cohort will be evaluated for futility with the option to stop enrollment in the cohort if the prespecified outcomes are not observed. Sample size estimates for Phase 1b and each cohort in Phase 2 are provided in the body of the protocol for each treatment arm.

Efficacy Analysis

The analysis of all efficacy endpoints will be based on the RECIST v1.1 criteria as assessed by the investigator.

Primary Efficacy Endpoint

The primary efficacy endpoint for each cohort in Phase 2:

- Objective response.

Confirmed ORR is defined as the proportion of patients with a documented and confirmed best overall response of CR or partial response (PR) as assessed by the investigator. A confirmed CR or PR is a response that is maintained and documented on a subsequent tumor assessment no less than 4 weeks after initial response. The frequency and percentages of patients with a best overall response of CR, PR, stable disease (SD), or progressive disease (PD) will be summarized. ORR (confirmed CR + PR) will also be summarized with frequencies and percentages. All summaries of response rate will be accompanied by 95% confidence intervals (CIs).

Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Duration of response (DOR; Phase 2),
- Progression-free survival (PFS; Phase 2),
- Objective response (Phase 1b).

PFS will be calculated as 1+ the number of days from the first dose of study drug to documented radiographic progression, according to RECIST v1.1, as determined by the

investigator, or death due to any cause, whichever occurs first. Patients without a documented event of radiographic progression will be censored on the date of their last adequate tumor assessment (ie, radiologic assessment), or date of first dose of study drug if no post-baseline tumor assessments have been performed. Only tumor scans prior to start of any subsequent anticancer treatment are included.

For any Phase 2 patient who reached a best response of CR or PR, DOR will be measured from the date that best response is first recorded until the first date that PD is documented per RECIST v1.1. DOR will be summarized as a time to event variable. For patients who continue treatment post-progression, the first date of progression will be used for the analysis. Patients without a documented event of radiographic progression will be censored on the date of the last adequate tumor assessment.

For both PFS and DOR, the Kaplan-Meier methodology will be used. If able to be estimated, the 50th (median) percentile together with a 95% CI, will be presented. The number of patients with events and the number of patients at risk at each timepoint will be presented, and censored patients will be graphically displayed.

Safety Analyses

All safety analyses will be summarized for the Safety Population separately for each treatment arm. Within a treatment arm, safety analyses will be summarized by dose cohort and pooled for all patients in Phase 1b and by expansion cohort in Phase 2. Safety and tolerability will be assessed based on the following:

- DLTs in the dose-escalation (Phase 1b) portion;
- Incidence, type, seriousness, severity, and causality of AEs reported;
- Clinical laboratory investigations
- Vital signs;
- 12-lead ECGs;
- Physical examinations;
- ECOG performance status.

Pharmacokinetic Analyses

In the Phase 1b portion, blood sampling for PK analyses of both rucaparib and the second study drug will be conducted in all patients. The PK parameters will be determined using non-compartmental methods. Pharmacokinetic parameters, including but not limited to C_{max}, C_{min}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, V_{ss}/F, and CL/F, will be calculated and reported as data allow.

Date of Protocol Amendment 2.0 Approval

01 September 2020

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	
AAG	α1-acid glycoprotein
ACE	angiotensin converting enzyme
ADA	anti-drug antibody
ADC	antibody-drug conjugates
ADCC	antibody-dependent cytotoxicity
ADP	adenosine diphosphate
ADR	adverse drug reactions
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALCOA-C	attributable, legible, contemporaneous, original, accurate, complete
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
ATR	ataxia telangiectasia mutated and Rad3-related
AUC	area under the curve
$AUC_{0\text{-}24h}$	area under the curve from time 0 to 24 hours
$AUC_{0\text{-}inf}$	area under the curve from time 0 to infinity
$AUC_{0\text{-}last}$	area under the curve from time 0 to the last observation
BCRP	breast cancer resistance protein
BER	base excision repair
BICR	blinded independent central review
BID	twice a day
BIW	twice a week
BP	blood pressure
BRCA	breast cancer gene
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
BRCA1/2	breast cancer gene 1 or breast cancer gene 2
$BRCA^{mut}$	deleterious mutations within BRCA
$BRCA^{wt}$	BRCA wild-type
$BRCA^{wt/unk}$	BRCA wild-type unknown

BUN	blood urea nitrogen
CA-125	cancer antigen-125
CDC	complement-mediated cytotoxicity
CBR	clinical benefit rate
CDP	clinical development program
CFR	Code of Federal Regulations
CHK1	checkpoint kinase 1
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration
C_{min}	minimum concentrations
CNS	central nervous system
CO_2/HCO_3^-	bicarbonate
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
ctDNA	circulating cell-free tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand break
DVT	deep venous thrombosis
EC	European Commission
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate

EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EOI	end of infusion
EOT	end of treatment
ESMO	European Society of Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FISH	fluorescence in situ hybridization
FMI	Foundation Medicine Inc.
FSH	follicle-stimulating hormone
FU	follow-up visit
FTC	fallopian tube cancer
gBRCA	germline BRCA
$gBRCA^{wt}$	germline BRCA wild type
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
H_0	null hypothesis
H_1	alternative hypothesis
H&E	hematoxylin and eosin
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
HDPE	high-density polyethylene
HGOC	high-grade ovarian cancer
HGSOC	high-grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HNSTD	highest non-severely toxic dose

HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
IB	Investigator's Brochure
IC_{50}	concentration of inhibitor required for 50% inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
LOH	loss of heterozygosity
LVEF	Left ventricular ejection fraction
MATE	multidrug and toxin extrusion
mCRPC	metastatic castration-resistant prostate cancer
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDCK	Madin-Darby Canine Kidney (cell line)
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition

NCI	National Cancer Institute
NGS	next-generation sequencing
NOAEL	No-Observed-Adverse-Effect-Level
NSCLC	non-small cell lung cancer
NTCP	sodium/taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OC	ovarian cancer
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PD	progressive disease
PDGF	platelet derived growth factor
PDGFR	platelet-derived growth factor receptors
PDX	patient-derived xenograft
PE	pulmonary embolism
PET	positron emission tomography
PFI	platinum-free interval
PFS	progression-free survival
P-gp	P-glycoprotein
PIS	patient information sheet
PK	pharmacokinetic
PPC	primary peritoneal cancer
PPI	proton pump inhibitors
PPK	population pharmacokinetics
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
QD	once a day
QTcF	QT interval corrected using Fridericia's method
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RS	replication stress
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan

SAR	serious adverse drug reaction
SAS	statistical analysis software
SBP	systolic blood pressure
SCLC	small cell lung cancer
SD	stable disease
StD	standard deviation
SI	International System of Units
SN-38	active metabolite of irinotecan
STD	severely toxic dose
STD_{10}	severely toxic dose to 10% of the population
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T3	triiodothyronine
T4	thyroxine
tBRCA	tumor tissue deleterious alteration in BRCA 1 or BRCA 2
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
Topo1	topoisomerase 1
TMA	thrombotic microangiopathy
t_{max}	maximum concentration
TNBC	triple-negative breast cancer
Trop-2	trophoblast cell-surface antigen
TSH	thyroid stimulating hormone
UC	urothelial cancer
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
V/F	apparent volume of distribution
V_{ss}	volume of distribution at steady-state
V_{ss}/F	apparent volume of distribution at steady state
Vz/F	Apparent volume of distribution during terminal phase after oral administration
WBC	white blood cell

WOCBP	women of child bearing potential
WT	wild type

1 INTRODUCTION

1.1 Background

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes play a critical role in base excision repair (BER).[1] When PARP function is impaired, double-stranded deoxyribonucleic acid (DNA) breaks accumulate in the absence of effective BER; in homologous recombination deficient (HRD) cells, these breaks cannot be accurately repaired, resulting in synthetic lethality and cell death.[2] While mutated breast cancer gene 1 (BRCA1) and BRCA2 genes are most commonly associated with HRD, mutations or functional inactivation of other essential homologous recombination repair (HRR) proteins can also cause HRD. In addition, over the past decade, it has been determined that patterns of genomic loss of heterozygosity (LOH), a phenotypic marker of HRD, has been shown to be a biomarker of PARP sensitivity.[13]

The development of PARP inhibitors has advanced steadily over the last few years. There are currently 4 PARP inhibitors marketed in the United States (US), with various clinical indications in ovarian and breast cancer.[3,14,15] While the single-agent activity of many PARP inhibitors has been established in HRD ovarian tumors, the utility of PARP inhibitors in the treatment of patients with HRR-proficient ovarian cancer is less certain given that these tumors generally do not respond as well to monotherapy PARP inhibitor treatment. Combining a PARP inhibitor with agents that inhibit HRR or may induce HRD may represent an effective strategy to sensitize HRR-proficient tumors to PARP inhibitor treatment.[16] Further, in vivo/in vitro data evaluating the synergistic antitumor activity of PARP inhibitors with select targeted agents support several combination strategies.

1.1.1 Rucaparib

Rucaparib is a potent, oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, that play a critical role in BER.[1]

Rucaparib (Rubraca®) is approved in the US for the treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who have been treated with 2 or more prior chemotherapies, and for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[3] Rucaparib is also approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade EOC, FTC, or PPC who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.[4] In addition, rucaparib is being developed for the treatment of cancer associated with HRD, defined by the presence of a deleterious mutation in BRCA1, BRCA2, or other HRR genes, and/or high percentage of tumor genome with LOH, which is a phenotypic consequence of HRD.

A brief overview of data from nonclinical and clinical studies are provided below and described in detail in the rucaparib Investigator's Brochure (IB).

1.1.1.1 Nonclinical Experience

The results from nonclinical studies are consistent with the mechanism of action and pharmacological effects of PARP inhibition.

Pharmacological assessment demonstrated that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3 and has robust and durable in vitro and in vivo activity in multiple BRCA1/2 mutant cell lines and xenograft models. Rucaparib was also active in a BRCA wild-type models, consistent with in vitro data suggesting that rucaparib is active in cells with other defects in HRR through synthetic lethality. In vitro screens suggested that rucaparib has a limited potential for off-target effects.

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs. Rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UDP-glucuronosyltransferase 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1) and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single and repeat dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an in vitro chromosomal aberration assay suggesting potential genotoxicity in humans. Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryo-toxic. Although no rucaparib related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility.[17-20]

1.1.1.2 Clinical Experience

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer with and without evidence of HRD. Rucaparib clinical studies have evaluated (and continue to evaluate) patients with relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer in both the treatment and maintenance settings.

Rucaparib is being evaluated as treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), both as monotherapy and in combination with nivolumab.

Clinical pharmacology studies in patients with advanced solid tumors have evaluated rucaparib drug-drug interactions (DDIs) and mass balance and drug metabolism. Additional

clinical pharmacology studies continue to characterize rucaparib DDIs, as well as rucaparib PK in special populations.

Additional studies of rucaparib as monotherapy and in combination with other anticancer therapies are planned in ovarian, prostate, and bladder cancers, as well as other tumors.

1.1.1.2.1 OVERVIEW OF PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS

Assessment of rucaparib PK in cancer patients showed an approximate dose proportional exposure after once a day (QD) or twice a day (BID) dosing, rapid absorption with C_{max} achieved within 1.5 to 6 hours. The oral bioavailability was 36% and elimination half-life ($t_{1/2}$) was approximately 24 hours. Rucaparib was moderately bound to human plasma proteins in vitro (70%).

At a dose of 600 mg BID rucaparib, steady state was achieved after approximately 1 week with approximately 4-fold accumulation. A high-fat meal increased the C_{max} and area under the curve $(AUC)_{0\text{-}24h}$ of rucaparib by 20% and 38%, respectively, as compared with that under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

In vitro, rucaparib showed slow enzymatic turnover in human liver microsomes and hepatocytes. Recombinant CYP2D6, and to a lesser extent CYP1A2 and CYP3A4, were able to metabolize rucaparib. In cancer patients, M324, a carboxylic acid, was a major inactive metabolite of rucaparib.

Drug interactions with rucaparib as a substrate were assessed in a population PK (PPK) analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultrarapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyper-inducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Concomitant administration of strong CYP1A2 or CYP2D6 inhibitors did not significantly impact rucaparib PK. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play limited role in rucaparib metabolism. Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. No rucaparib dose adjustment is recommended when concomitantly administered with CYP inhibitors or inducers.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for patients who are receiving concomitant treatment with a PPI.

Results from Study CO-338-044 evaluating potential DDI with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on the PK of oral digoxin (a P-gp substrate). Caution should be exercised in the concomitant use of drugs that are sensitive clinical substrates of the above CYP enzymes (refer to the rucaparib IB, Section 6.4).

1.1.1.2.2 OVERVIEW OF EFFICACY

Rucaparib was originally approved by the US Food and Drug Administration (FDA) in December 2016 as monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies. As of May 2018, rucaparib was approved by the European Commission for the same indication with the exception that patients must be intolerant to subsequent platinum-based chemotherapy.[4] The recommended dose of rucaparib is 600 mg BID.

The primary outcome measure on which approval by FDA for the treatment indication was based is investigator-assessed overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), with ORR by central independent radiological review conducted as a supportive analysis. ORR by investigator was 53.8%, while ORR by independent review was 41.5%, confirming the results of investigator assessment for this endpoint.[21] Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months.

In April 2018, rucaparib was approved by the US FDA for the maintenance treatment of adult patients with recurrent EOC, FTC, or PPC who are in a complete or partial response to platinum-based chemotherapy.[3] This approval was based on Study CO-338-014 (ARIEL3), a randomized, placebo-controlled Phase 3 study. In this study, investigator-assessed progression-free survival (invPFS) was the primary efficacy endpoint, with PFS by blinded independent central review (bicrPFS) conducted as a key, stand-alone, secondary endpoint. Overall, rucaparib as maintenance treatment reduced the risk of progression or death by 63.5% (hazard ratio [HR] 0.365 [95% confidence interval (CI), 0.295-0.451]; $p < 0.0001$) in the intent-to-treat (ITT) population, demonstrating a strong treatment effect over placebo. Analysis of non-nested, non-overlapping patient subpopulations indicate that the significant improvement in PFS observed in the ITT population was not driven only by the tBRCA subpopulation (tumor tissue deleterious alteration in BRCA1 or BRCA2) or HRD subpopulation (tBRCA as well as tumors that were non-tBRCA, but with genomic LOH ≥16%). Nearly half (44.6%) of the ITT patients in the rucaparib group showed benefit at 1 year compared to 8.8% in the placebo group.[22] At 18 and 24 months, 32.0% and 26.0%, respectively, of patients who received rucaparib were still progression-free compared to 5.8% and 2.6% in the placebo group, respectively. These investigator-assessed results were confirmed by results of BICR.

1.1.1.2.3 OVERVIEW OF SAFETY

Results of a recent integrated safety analysis in over 1,000 patients with ovarian or prostate cancer who received 600 mg BID rucaparib in the treatment or maintenance setting showed that the most common treatment-emergent adverse events (TEAEs) reported were primarily mild to moderate (Grade 1-2) in severity and included gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increased, decreased appetite, and dysgeusia. The most common TEAE ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue. Section 6.6 of the rucaparib Investigator's

Brochure (IB) serves as guidance to the investigator on adverse drug reactions (ADRs) for rucaparib, based on incidence of TEAEs by all CTCAE grades and by ≥ Grade 3.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI),[23,24] and few patients discontinued rucaparib due to ALT/AST elevations.[22,25] Similarly, elevations in creatinine were self-limiting and generally stabilized over time. The majority of creatinine elevations were Grade 1 or Grade 2. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib were not accompanied by changes in blood urea nitrogen (BUN) and did not lead to discontinuation of rucaparib treatment. Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters (Section 1.1.1.1).

An updated analyses of safety presented in the US prescribing information[3] and the EU Summary of Product Characteristics (SmPC)[4] demonstrate that safety results in ovarian cancer patients treated with rucaparib have remained consistent with those previously reported, and that the safety profile across both the treatment and maintenance indications is consistent.

Effects on cardiac channel activity in vitro and a comprehensive assessment of the effects of rucaparib on electrocardiogram (ECG) parameters in cancer patients demonstrated a low risk of cardiac effects by rucaparib.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESI), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation. Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

More recently, pneumonitis was classified as an AESI. TEAEs of pneumonitis have been reported with PARP inhibitor treatment, including in clinical trials evaluating rucaparib. Currently, however, there is a lack of understanding of a mechanistic link between pneumonitis and PARP inhibitor treatment, and causality assessment is often confounded by lack of a consistent clinical pattern as well as other pre-disposing factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy. Clovis is seeking to better understand whether or not there is a relationship between pneumonitis and rucaparib treatment, hence the AESI designation in order to gather the necessary information to enable a thorough evaluation and assessment.

Pneumonitis and similar events (interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) will be considered an AESI if occurring on treatment or within 28 days after last dose of study drug(s). More information on AESIs is provided in the rucaparib IB.

1.2 Rationale for the Study

PARP inhibitors have been explored in combination with chemotherapy; however, such combinations were challenging to administer due to overlapping toxicity, specifically myelosuppression, therefore novel combination approaches with more selective targeted agents are currently thought to have more potential. Combination therapy with a PARP inhibitor would aim to increase accumulation of DNA damage and subsequent dependence on HRR, such as in the combination of PARP inhibitor with a DNA-damaging chemotherapy, radiation, or targeted therapies that induce HRD. Agents that inhibit topoisomerase 1, including irinotecan and topotecan, have demonstrated synergy with PARP inhibitors in a variety of human tumor cell lines, including ovarian and breast cancers.[5,6] The PARP inhibitor olaparib has been shown to potentiate the cytotoxicity of SN-38, the active metabolite in irinotecan and topotecan, irrespective of mismatch repair (MMR) status in a panel of MMR-deficient or MMR-efficient cancer cell lines.[7] A clinical study of the PARP inhibitor veliparib combined with topotecan showed a mechanistic interaction between the 2 drugs, resulting in delayed repair of Topo1-mediated DNA damage, despite there being some challenges with overlapping hematologic toxicities.[8] Targeted delivery of SN-38 to cancer cells through administration of an antibody-drug conjugate (ADC) has greater potential for combination therapy with a PARP inhibitor by reducing off-target and additive toxicity. Other combinations would aim to induce a BRCA-like phenotype in order to elicit PARP inhibitor and BRCA-like synthetic lethality, as has been shown to occur in combinations between PARP inhibitors angiogenesis inhibitors (such as vascular endothelial growth factor [VEGF] inhibitors) and ataxia telangiectasia mutated and Rad3-related (ATR) inhibitors. The combination of a PARP inhibitor with a VEGF inhibitor, which have distinctly different mechanisms of action, has also demonstrated synergistic effects in nonclinical studies (Clovis Oncology, data on file). In addition, a Phase 2 clinical study in patients with recurrent ovarian cancer treated with the PARP inhibitor, olaparib, and an anti-angiogenic agent, cediranib, has shown promise.[9] Nonclinical data indicate that ATR inhibition increases sensitivity to PARP inhibition[10] and that defects in ATR signaling may result in synthetic lethality with PARP inhibition.[11] Inhibition of ATR may be a mechanism to overcome primary and acquired resistance to PARP inhibition.

This study aims to evaluate the PARP inhibitor, rucaparib, in combination with various agents that have shown promise as an antitumor agent through different mechanisms of action. The rucaparib combinations selected for evaluation within this study were carefully chosen based on nonclinical and clinical data, and theoretical concepts to support a potential efficacious synergism. The rationales for each rucaparib combination are provided in **Section 8.X.3** of each respective treatment arm.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives of this study are as follows:

Phase 1b of each Treatment Arm

- To evaluate the safety and tolerability of rucaparib in combination with a second anticancer agent and to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of the combination.

Phase 2 of each Treatment Arm

- To evaluate the efficacy of rucaparib in combination with a second anticancer agent by measuring investigator-assessed confirmed best overall response rate (ORR) by RECIST v1.1 in one or more expansion cohorts evaluating the combination.

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

Phase 1b of each Treatment Arm

- To characterize the PK of rucaparib (Treatment Arm A and Treatment Arm C) and the second anticancer agent (all treatment arms), as well as the metabolites for the second anticancer agent (Treatment Arm B) when rucaparib and the second anticancer agent are co-administered.
- To evaluate the preliminary efficacy of rucaparib in combination with a second anticancer agent in various solid tumors.

Phase 2 of each Treatment Arm

- To evaluate the safety and tolerability of rucaparib in combination with a second anticancer agent.
- To evaluate progression-free survival (PFS) in one or more expansion cohorts evaluating the combination.
- To evaluate duration of response (DOR) in one or more expansion cohorts.

2.3 Exploratory Objectives

Exploratory objectives in both parts of this study are as follows:

- To assess tumor tissue biomarkers that correlate with response to the combination.
- To evaluate circulating cell-free tumor DNA (ctDNA) as a molecular marker of response to the combination.
- To evaluate biomarkers associated with resistance to the combination.
- To assess genomic changes over time in plasma and tumor samples.
- To determine steady-state exposure of rucaparib and the second anticancer agent (all treatment arms) by sparse PK sampling.
- To evaluate the development of anti-drug antibodies (ADAs) (Treatment Arm B).
- To characterize the PK of metabolites of the second anticancer agent (Treatment Arm C) when rucaparib and the second anticancer agent are co-administered.

3 STUDY DESIGN

3.1 Overall Study Design and Plan

This is a Phase 1b/2, open-label, study with multiple treatment arms evaluating the safety, tolerability, PK, and preliminary efficacy of rucaparib in combination a second anticancer therapy in patients with an advanced/metastatic solid malignancy (Phase 1b), followed by evaluation of the combination in one or more specific patient populations in an expansion phase (Phase 2 cohorts).

- **Phase 1b/ Dose-escalation Phase**: This portion of the study will enroll patients with advanced malignancy who have relapsed following prior treatment or are not eligible for standard of care treatment. Dose escalation will follow a 3+3 design. Patients will receive rucaparib in combination with a second targeted anticancer therapy (defined within the respective treatment arm section) in order to determine the MTD, if possible, and RP2D for the combination. An expanded evaluation of the RP2D may be conducted in up to 10 additional patients in each combination.
- **Phase 2/ Expansion Phase**: In Phase 2, the study drug combination administered at the RP2D will be evaluated for efficacy, safety, tolerability, PK, and pharmacodynamics in patients as defined for each treatment arm and cohort (within Section 8).

Phase 2 of each treatment arm will not commence until the RP2D has been established in Phase 1b. Patients participating in this study will enroll into either Phase 1b or Phase 2, but a patient cannot enroll into both phases of the same treatment arm. This section describes the general features of the study, common to each treatment arm. The specifics of the study design, including schedule of assessments, and patient population with inclusion/ exclusion criteria, of each treatment arm are described in Section 8.

3.1.1 Screening Phase

All patients will undergo screening assessments prior to enrollment; the time frame for screening assessments is specified under the respective treatment arms.

Screening assessments will include, but may not be limited to, demographics and medical history, prior cancer treatments, prior and current medications and procedures, 12-lead ECG, Eastern Cooperative Oncology Group (ECOG) performance status, hematology and chemistry, urinalysis, physical examination, vital signs measurements, radiologic assessment by CT or magnetic resonance imaging (MRI). Patients will be required to provide archival tumor tissue or a more recently obtained tissue sample, as well as blood samples, for genomic analysis. Data from procedures that are considered standard of care and performed before obtaining patient informed consent for the study may be collected and entered into the electronic case report form (eCRF), where allowable. Additional screening procedures may be done as appropriate for a particular combination, the details of which can be found in the schedule of assessments table for each treatment arm.

3.1.2 Enrollment

For Phase 1b, including dose escalation and any RP2D expansion, eligible patients will be enrolled in parallel into open dose-escalation cohorts across the treatment arms. If a patient appears to be eligible for more than one treatment arm that is open to enrollment, the investigator will be responsible for selecting the most appropriate treatment arm for the patient. A limited number of sites (3-6) will enroll patients in the Phase 1b portion of the study. Once the RP2D of the combination has been provisionally established, up to 10 additional patients may be enrolled at the RP2D and treated as part of Phase 1b to further characterize safety, tolerability, efficacy, and PK and confirm that this is the optimal dose combination to evaluate in Phase 2.

Enrollment in the Phase 2 portion for all treatment arms will be competitive. Sites may be actively enrolling in more than 1 treatment arm simultaneously. Sites participating in Phase 1b activities may also enroll patients in Phase 2.

3.1.3 Treatment Phase

Treatment cycles will be 21 or 28 days in length, depending upon the study drug combination; cycles are defined within each specific treatment arm (**Section 8.X.4**).

All patients will be monitored for safety throughout the treatment phase. Assessments will include, but may not be limited to, physical examination, vital signs and weight measurement, hematology, chemistry, concomitant medications, ECOG performance status, disease status assessment, 12-lead ECG, adverse events (AEs) with any associated therapies and procedures, study drug administration and accountability. Urinalysis will be performed as clinically indicated, except where otherwise noted in the schedule of assessments for each treatment arm. Blood samples will also be collected for PK, biomarker, and immunogenicity analyses, as applicable.

All patients will be assessed for disease status by RECIST v1.1 per the time interval specified within each treatment arm in Section 8 (flexibility with scheduling within 1 week prior to planned imaging date is permitted) until 1 of the following occurs:

- radiological disease progression as assessed by the investigator,
- death,
- loss to follow-up,
- withdrawal from study,
- study termination, or
- initiation of subsequent anticancer treatments.

All responses (complete response [CR] or partial response [PR]) must be confirmed with a scan no less than 4 weeks after the initial response.

Disease progression will be determined by RECIST v1.1 (Section 7.3.1). If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST v1.1 per the treatment arm schedule of assessments. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from study treatment and enter into follow-up. However, if the patient has met criteria for radiologic progression by RECIST, but the patient is still receiving benefit from the study drug(s) (eg, patient has mixed radiologic response or is continuing to have symptomatic benefit), according to the investigator, then continuation of treatment will be considered upon discussion with the medical monitor (see Section 5.9).

3.1.3.1 Phase 1b

In the Phase 1b portion of each treatment arm, there will be an estimated 6 to 12 dose-escalation cohorts, with a minimum of 3 patients enrolled in each cohort, followed by an expanded evaluation of the RP2D in up to 10 additional patients.

Dose escalation will follow a 3+3 design (Table 3-1). Rucaparib will be administered BID continuously up to a maximum of 600 mg BID, and the second study drug will be administered as specified within each respective treatment arm in Section 8. The starting doses and escalation plan for each combination treatment is specified in **Section 8.X.4.2.1**.

Dose-limiting toxicities (DLTs) are defined according to criteria specified for each combination treatment and assessed by the investigator, based on toxicity grade (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), clinical significance, and possible relationship to either study drug. DLTs are defined for each combination treatment within **Section 8.X.4.2.1.1**. The MTD for the study drug combination is defined as the maximum dose combination at which < 33% of patients experience a DLT during Cycle 1 (the DLT-evaluation period). If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level (Table 3-1). Dose escalation will continue until at least 2 of the 3 to 6 patients treated at a dose level experience a DLT or until the maximum dose to be evaluated is reached, whichever occurs first. If the end of dose escalation is reached due to DLTs, the next lower dose will then be considered the MTD. Alternatively, if the different between the MTD and the maximally delivered dose is significant (such as 100%), then a more modestly de-escalated dose may be explored (eg, 20% to 50%).

Prior to initiating treatment at each new combined dose level or prior to expanding an existing dose level, a safety teleconference will be held to review patient data, including but not limited to demographics, PK results (if available), study drug combination dosing, concomitant medications, hematology and chemistry, and AEs, and then confer and document agreement that dose escalation and/or expanding an existing dose level is/are considered appropriately safe. Safety teleconferences will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites.

If a patient is not evaluable for MTD within the DLT-evaluation period for reasons other than treatment-related toxicities, an additional patient may be enrolled at the same dose level. If the first dose level exceeds the MTD, other dosing schedules may be explored.

In order to be included in the DLT-evaluable group, a patient in Phase 1b must have received at least 80% of the planned doses of oral study drug(s) (both IV doses for Treatment Arm B) or experienced a DLT within the first cycle of combination treatment (Section 9.2). No dose reductions will be permitted during the DLT-evaluation period, unless the patient has experienced a DLT.

Table 3-1. General Dose Escalation Based on Dose-limiting Toxicities

Number of Patients with DLT at a Given Dose Cohort	Escalation Decision Rule
0 of 3	Enroll 3 patients into next dose cohort
1 of 3	Enroll 3 additional patients to this dose cohort. If none of these 3 patients experiences a DLT, proceed to the next dose cohort. If 1 or more experience a DLT, cease dose escalation. The MTD will be declared.[a]
≥ 2	Stop dose escalation. The MTD may be declared.[a].

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

[a] Enrollment to a lower combination dose level may be initiated.

3.1.3.1.1 DOSE-LIMITING TOXICITY CRITERIA

A DLT is defined according to criteria specified for each combination treatment and assessed by the investigator, based on toxicity grade (according to the NCI CTCAE v5.0), clinical significance, and possible relationship to either study drug (refer to Section 10.7.4 for consideration of causal relationship).

The DLT-evaluation period for the determination of dose escalation is the first cycle of rucaparib combination treatment (the first 21 or 28 days, depending upon the treatment arm).

3.1.3.1.2 RP2D SELECTION AND EXPANSION

The RP2D for evaluation in the Phase 2 portion will be selected based on overall safety and tolerability, PK, as well as any efficacy, if observed. The RP2D may or may not be the same as the MTD identified in the dose escalation. For example, if the MTD is not reached, if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RP2D may be a different, although not higher, dose than the MTD.

Once the RP2D of the combination has been provisionally established, up to 10 additional patients may be enrolled at the RP2D and treated as part of Phase 1b, in order to further characterize safety, tolerability, and PK and confirm that this is the optimal dose combination to evaluate in Phase 2. Since the RP2D may be selected based on evaluation of as few as 3 patients, there is low certainty that the RP2D has a DLT rate that is < 33%. Enrolling additional patients will increase the certainty that the Phase 2 portion of the study is evaluated at a dose with a DLT rate < 33%. If the data from this group of patients in the RP2D expansion differs significantly from those initially treated at this dose, a different dose combination may be evaluated to determine the optimal RP2D.

3.1.3.1.3 PHASE 1B – CYCLE 2 AND BEYOND

Following the DLT-evaluation period in Phase 1b, patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments and PK Assessments within each respective treatment arm section (**Section 8.X.8**).

After Cycle 1 (DLT-evaluation period), recommendations for dose modification for the management of specific AEs are provided within each respective treatment arm section (**Section 8.X.6.4**).

Patients tolerating the investigational treatment(s) at the assigned dose combination for at least 4 cycles may be permitted to escalate to the next highest combination dose level as long as the new dose level is **lower** than that being currently evaluated for safety and tolerability and/or the dose level is the **same or lower** than that determined to be the RP2D, and only after discussion with the study's medical monitor.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study (Section 3.2).

3.1.3.2 Phase 2

Enrollment into the Phase 2 portion may begin when the RP2D is established. Patients in the Phase 2 portion will be assessed for safety and efficacy at the RP2D.

Phase 2 will enroll patients into specified cohorts for each treatment combination, and a Simon 2-stage design[12] will be utilized for each of the planned Phase 2 cohorts. Each cohort will be evaluated with the option to stop enrollment in the cohort if the prespecified confirmed responses are not observed (described in **Section 8.X.9.1**).

The Phase 2 cohorts within each treatment arm are based on nonclinical and clinical data provided in **Section 8.X.3.2** of each respective treatment arm.

Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments and PK Assessments within each respective treatment arm section (**Section 8.X.8**). Recommendations for dose modification for the management of specific AEs are provided within each respective treatment arm section (**Section 8.X.6.4**). Treatment will continue until disease progression, unacceptable toxicity, patient or physician request to

discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study (Section 3.2).

3.1.4 End of Treatment and Safety Follow-up

Upon treatment discontinuation, regardless of reason (with the exception of withdrawal of consent or death), patients will have an End of Treatment Visit, and assessments are specified for each treatment arm in the Schedule of Assessments within **Section 8.X.8**.

All patients will be followed for at least 28 days after the last dose of study drug. Assessments are specified for each treatment arm in the Schedule of Assessments within **Section 8.X.8**

Patients who discontinue treatment for a reason other than disease progression or death should continue to have tumor scans performed at the interval specified for that treatment arm until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments.

An optional tumor biopsy will be collected from patients who experience disease progression and provide appropriate consent.

3.2 Removal of Patients from Therapy or Assessment

A patient must be discontinued from treatment with study drug if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator, unless patient is still receiving benefit from the study drug(s) according to the investigator, and the patient has provided additional consent (see Section 5.9).
- Initiation of any other anticancer therapy.
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient. If it is determined that 1 of the study drugs in the combination is posing a safety risk and that study drug is permanently discontinued, administration of the other study drug may continue if none of the other withdrawal criteria have been met and the investigator believes that the patient may continue to receive benefit.
- Any concomitant illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy.
- A positive pregnancy test at any time during the study.

3.3 End of Study

The study will be considered ongoing until all patients have either met one of the withdrawal criteria (Section 3.2) or have withdrawn consent for the study, or the sponsor terminates the study.

The sponsor may discontinue the study or an individual treatment combination early for any of the reasons noted in Section 11.6.

4 OVERALL STUDY POPULATION SELECTION

Phase 1b of each treatment arm will enroll patients with advanced malignancy who are relapsed to or inappropriate for approved, standard treatment.

Phase 2 will enroll 1 or more specific patient populations defined for each treatment arm (Phase 2 expansion cohorts).

The number of patients estimated to be enrolled into each treatment arm and each Phase 2 cohort are described in **Section 8.X.5** of the respective treatment arms.

4.1 All Patients or All Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion. Women of childbearing potential or male patients of reproductive potential with female partners of childbearing potential must not be considering getting pregnant and must avoid pregnancy during the study and for at least 6 months after the last dose of rucaparib or longer if required for the second study drug, or longer if requested by local authorities.

Female patients of childbearing potential must have a negative serum or plasma pregnancy test result ≤ 3 days prior to administration of the first dose of study drug. In addition, a serum or plasma pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Phase 1b or Phase 2 Treatment Phases and at the time of treatment discontinuation. Pregnancy testing will be conducted locally. Treatment should be discontinued immediately in any woman found to have a positive pregnancy test while taking study drug.

Male patients are required to use a condom during sex with a partner to avoid the possibility of exposure of the partner to study drug, regardless of whether the partner is a woman of childbearing potential or not. Male patients must not make semen donations during treatment and for 6 months following the last dose of study drug(s).

Male patients are considered to be of reproductive potential unless permanently sterile by bilateral orchiectomy or vasectomized with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

Female patients or partners of male patients are considered to be of childbearing potential unless 1 of the following applies:

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy; or
- Is postmenopausal, defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

Female and male patients of reproductive potential must practice highly effective methods (failure rate < 1% per year) of contraception with their partners, if of reproductive potential, during treatment and for 6 months following the last dose of rucaparib or longer if required for the second study drug, or longer if requested by local authorities. Highly effective contraception includes the following:

- Ongoing use of progesterone only injectable or implantable contraceptives;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;
- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable; or
- Male sterilization, with appropriate post vasectomy documentation of absence of sperm in ejaculate.

Patients will be instructed to notify the investigator if pregnancy in either the patient or partner is discovered either during or within 6 months of completing treatment with study drug or longer if required for the second study drug.

4.2 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

5 RUCAPARIB TREATMENT

This section describes the treatment of rucaparib across all treatment arms. The treatment descriptions of the second study drug administered in combination with rucaparib are provided in **Section 8.X.6** of the respective treatment arm.

5.1 Rucaparib Description of Treatment and Storage

Rucaparib camsylate (also known as CO-338; formerly known as PF-01367338 and AG-014447) is an oral formulation. Rucaparib tablets for oral administration will be supplied to the study sites by the sponsor. A brief description of rucaparib is provided below with details in the Pharmacy Manual.

Table 5-1. Description of Rucaparib Tablets

Drug Name	Rucaparib
INN	Rucaparib
Formulation (strengths expressed as free base)	Tablet; film coated; 200 mg (blue, round, debossed with C2), 250 mg (white, diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3).
How Supplied	200 mg, 250 mg, and 300 mg (as free base) strength tablets in 60 count bottles. Patients may receive one or more strengths.
Storage Conditions	15–30°C (59–86°F).

5.2 Rucaparib Packaging and Labeling

Rucaparib tablets are provided in 60-count high-density polyethylene (HDPE) bottles with child resistant caps and should be stored in the provided containers between 15° and 30°C (59 and 86°F). Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle, including a small overage.

Details with respect to packaging and labeling of rucaparib tablets are described in the Pharmacy Manual.

5.3 Blinding/Masking of Treatments

This is an open-label study; the investigational products will not be blinded or masked. All patients enrolled will receive rucaparib in combination with the second study drug in the specified treatment arm.

5.4 Method of Assigning Patients to Treatment Arms

Refer to Section 3.1.2 for a description of the enrollment process.

After confirming that patients fulfill eligibility criteria, the investigator or his/her delegate will enroll patients into the available combination cohorts.

5.5 Preparation and Administration of Rucaparib

For Phase 1b of each treatment arm, rucaparib will be administered orally at the dose and frequency specified by the dose cohort to which the patient is enrolled (see **Section 8.X.4.2.1** of the respective treatment arm).

For Phase 2 of each treatment arm, rucaparib will be administered orally at the RP2D for that combination. As rucaparib is dosed BID, the dose should be administered as close to 12 hours apart as possible, preferably at the same times every day with at least 8 ounces (240 mL) of water starting on Cycle 1 Day 1. Study drug (tablets) may be taken with or without food. Tablets should be swallowed whole without crushing or chewing.

Rucaparib will be provided as 200, 250, and 300 mg [as free base] dose strength tablets. If a patient vomits after dosing, the dose will not be made up; the patient will take their next dose at the regularly scheduled interval.

Treatment will begin on Day 1 of Cycle 1. Patients will be provided a sufficient quantity of rucaparib to last until Day 1 of the next treatment cycle. Patients will be instructed to bring their study drug tablets and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel.

5.6 Dose Modification Criteria for Rucaparib Combinations

Study drug dose modification criteria are described within each specific treatment arm (**Section 8.X.6.4**).

5.7 Treatment Compliance

Documentation of dosing will be recorded in a study-specific dosing diary provided by the sponsor (or designee). Dosing noncompliance is defined as a patient missing > 14 days of study drug within a cycle for 2 consecutive cycles for reasons other than toxicity. The sponsor may require patients meeting noncompliance criteria to discontinue study treatment. Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at the next scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Additional descriptions of compliance for the second study drug are in **Section 8.X.6**, where applicable. Details regarding study drug dispensation and return can be found in the study-specific Pharmacy Manual.

Every effort should be made to ensure patients return to the clinic with their study drug containers/ unused study drug at the end of each cycle of treatment. Study site personnel should conduct a verbal review of dosing with the patient and document the discussion in the patient's medical record. This may serve as source documentation for the purpose of entering dosing data on the appropriate eCRF.

5.8 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation of study drugs provided by the sponsor. The interactive response technology (IRT) system will be used to manage study drug inventory at all sites. In order to function properly, the system will require real time entry of study drug receipt, dispensation, destruction, etc. by study personnel at the study site.

The site is responsible for the return or destruction of study drug supplied by the sponsor. Authorization to destroy study drug at the site that has not been dispensed to a patient (eg, expired study drug), must be requested from the sponsor prior to destruction. All study drug containers must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of hazardous materials. Unused and returned study drug product and containers should be destroyed on-site if possible. If destruction on site is not possible, supply should be returned to the drug depot, following the sponsor's instructions.

During the course of the study and at completion of the study, the number of study drug units (ie, bottles, vials) and containers received, dispensed, returned, and destroyed must be recorded and reconciled. Additional details regarding study drug accountability can be found in the Pharmacy Manual.

5.9 Investigational Treatment beyond Disease Progression

Patients will receive study drug(s) until confirmed radiologic disease progression as assessed by investigator using RECIST v1.1 criteria, unacceptable toxicity, patient or physician request to discontinue, death, initiation of any other anticancer therapy, positive pregnancy test, or termination of the study (refer to Section 3.2).

If a patient receiving study drug(s) has met criteria for confirmed radiologic disease progression by RECIST v1.1, but the patient continues to derive clinical benefit per the investigator, then continuation of study drug(s) may be permitted upon discussion with the medical monitor. In such cases, the documented decision to continue will be made jointly between the investigator and the sponsor (or designee), it must be documented in the patient's chart, and the patient must provide consent within a reasonable timeframe of the documented decision to continue study treatment. Clinical scenarios where continuation of study drug(s) after radiographic progression may be considered include, but are not limited to 1) a patient for whom radiographic progression develops slowly while disease-related symptoms remain well controlled; 2) a patient who experiences progression in a site of disease that is unlikely to adversely affect prognosis (eg, enlargement of a solitary lymph node); or 3) a patient with general disease control, but limited progression in sites of disease that can be managed with local therapies such as surgery or radiation. Patients continuing to receive study drug(s) will continue to have all protocol-required assessments as described in Section 7 and Section 8 of the respective treatment arm.

6 PRIOR AND CONCOMITANT THERAPY

The protocol specification for prior and/or concomitant therapy that are general to all treatment arms are provided below. Additional information or specifications unique to a treatment arm are provided in **Section 8.X.7** of the respective treatment arm.

6.1 Supportive Care

During the study, supportive care (eg, antiemetics, analgesics for pain control, antidiarrheals, thyroid replacement hormone, hematopoietic growth factors, blood products) may be used at the investigator's discretion and in accordance with institutional procedures. Drugs with a known risk for prolonged QT interval and Torsades de Pointes should be avoided. Supportive care must be recorded for each patient in the appropriate section of the eCRF.

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered per standard of care and according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

All procedures performed (eg, thoracentesis, etc.) during the study must be documented on the eCRF.

6.2 Radiotherapy

Palliative radiotherapy on lesions not considered target lesions for tumor evaluation is permitted during the study. Treatment with study drug should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation related toxicity.

6.3 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study, with the exception of palliative radiotherapy and hormonal treatment. Prior treatment with such excluded anticancer therapies must have been completed > 14 days prior to the first dose of study drug or as specified in the treatment arm-specific inclusion/exclusion criteria (**Section 8.X.5**).

Any botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care are prohibited (except those prescribed as supportive care by a health care professional as per Section 6.1).

6.4 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (Study CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used in patients on rucaparib taking concomitant medications that are sensitive clinical substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A (refer to

the rucaparib IB, Section 6.4). Selection of an alternative concomitant medication is recommended.

Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers (refer to rucaparib IB, Section 6.4).

6.5 Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 in vivo. Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin). Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

6.6 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Rucaparib marginally increased digoxin AUC by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

In vitro, rucaparib is a potent inhibitor of MATE-1 and MATE-2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP with concentration of inhibitor required for 50% inhibition (IC_{50}) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (eg, rosuvastatin).

6.7 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on patient attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each patient. Oral and/or intravenous (IV) contrast should be used whenever possible and appropriate, and rectal contrast should only be considered in patients with peritoneal disease. Imaging contraindications and contrast risks should be considered in this assessment. Patients with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate.

The ultimate decision to perform MRI in an individual patient in this study rests with the site radiologist, the investigator and the standard set by the local Independent Ethics Committee (IEC).

6.8 General Restrictions

Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they burn more easily during treatment with rucaparib. When outdoors, patients should use typical precautions such as applying sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

7 METHODS OF DATA COLLECTION

7.1 Medical History and Demographic/ Baseline Characteristics

Basic demographic and baseline characteristics will be collected during screening. In addition to the evaluation of a patient's medical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF. Events that occur after signing of informed consent but prior to initiation of study drug(s), unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF.

The patient's entire oncology history will be collected on the appropriate eCRF including cancer histology, stage, and date of diagnosis, prior surgeries/ treatments received for cancer, dates of treatment administration, best response achieved, date of progression and how assessed, radiology reports, and HRD status.

7.2 Prior and Concomitant Medication Assessments

Medications being used by the patient will be recorded as prior medications during screening and as concomitant medications following receipt of the first dose of study drug through the completion of the last Safety Follow-up Visit after treatment discontinuation. Medication information will be entered in the appropriate eCRF after it is obtained at each study visit.

7.3 Efficacy Evaluations

7.3.1 Disease/ Tumor Assessments

Tumor assessment measurements will be performed at screening and at the end of the treatment arm-specified interval starting with Cycle 1 Day 1 until objective radiological disease progression (refer to **Section 8.X.4.2** for assessment intervals). Tumor assessments should be performed at the time of treatment discontinuation if the reason for discontinuation was other than radiologically-confirmed disease progression and the time elapsed since the last assessment is greater than the tumor-assessment interval. In addition, tumor assessments should be made as clinically indicated. All responses (CR or PR) must be confirmed with a scan no less than 4 weeks after the initial response.

Disease assessment will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (CT and/or MRI scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST). Other complementary assessments (X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline. Investigators should perform scans of other anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status. If a patient has known brain metastases, this disease should be evaluated at each required assessment time. Tumor markers should be collected as clinically indicated for the response assessment by RECIST v1.1. For example, a complete response (CR) in an ovarian cancer patient would require normalization of cancer antigen-125 (CA-125).

Tumor response will be interpreted using RECIST v1.1. Disease progression will be determined by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

Patients who discontinue treatment for a reason other than disease progression or death should continue to have tumor scans performed at the interval specified for that treatment arm until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments.

7.4 Safety Evaluations

7.4.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. During the screening period, unless otherwise required by local regulations, serious adverse events (SAEs) which are related to protocol-mandated assessments will be reported. Once enrolled and study drug is administered, patients will be monitored for all AEs, SAEs, and AESIs (as defined in the respective IBs) during study participation and until last Safety Follow-up Visit(s).

After the last Safety Follow-up Visit(s), only treatment-related SAEs (including serious reports of pneumonitis or similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML, irrespective of causality, need to be reported. Any ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed until resolution or stabilization, death, or until loss to follow up. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (v5.0) and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

7.4.2 Clinical Laboratory Investigations

The clinical laboratory assessments will be general across the combination treatment arms. Any additional laboratory assessment(s) specific to a treatment arm will be described in **Section 8.X.8.2** of the respective arm.

All clinical laboratory samples for safety will be collected and analyzed by the site's local laboratory. The panels of laboratory tests to be performed are presented in Table 7-1.

Laboratory tests will be assessed for all patients at screening, during treatment per the Schedule of Assessments described for the respective treatment arms, and at the End of Treatment Visit, and Safety Follow-up Visit(s), and if toxicities are present.

Laboratory tests performed within the protocol-defined assessment windows (-3 days for each timepoint) do not need to be repeated on the day of the visit. Further, screening laboratory tests performed within 3 days of C1D1 do not have to be repeated at C1D1.

Hematology and chemistry results must be reviewed by the investigator before the start of study drug(s) and throughout the study. Fasting is not required before blood sampling for chemistry tests. Additional and more frequent tests may be performed at the investigator's discretion.

Table 7-1. Laboratory Tests - All Treatment Arms

Hematology	Clinical Chemistry	
Red blood cell (RBC) count	Total protein	Glucose
Hemoglobin	Albumin	Sodium
Hematocrit	Creatinine (eGFR)[a]	Potassium
MCV	Blood urea nitrogen (BUN) or urea	Magnesium
MCH	Bilirubin (total, direct, indirect)	Chloride
MCHC	Alkaline phosphatase (ALP)	Bicarbonate (CO_2/HCO_3^-)
Reticulocyte count	Alanine aminotransferase (ALT)	Calcium
White blood cell (WBC) count	Aspartate aminotransferase (AST)	Phosphorus
Differential with absolute neutrophil count (ANC)	Lactate dehydrogenase (LDH)	Total cholesterol
Platelet count	**Treatment Arm A only:** Thyroid stimulating hormone (TSH) and free triiodothyronine (T3)/free thyroxine (T4)	

Abbreviations: eGFR = estimated glomerular filtration rate; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume.

[a] Estimated GFR using the Cockcroft Gault formula (Appendix 1) or institutional standard formula may also be collected, as clinically applicable.

Urinalysis: performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation or 24-hour urine collection will be performed to assess the abnormal findings. Urinalysis will be performed at screening for all treatment arms, and for Treatment Arm A, at Day 1 and Day 15 for Cycles 1 and 2, Day 1 at cycles thereafter, and at the End of Treatment Visit. Urinalysis may be conducted at other times as clinically indicated.

Pregnancy Testing: Female patients of childbearing potential must have a negative serum or plasma pregnancy test result ≤ 3 days prior to administration of the first dose of study drug. In addition, a blood-based pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Phase 1b or Phase 2 Treatment Phases and at the time of treatment discontinuation.

Local laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out of range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow up to the abnormalities, will be documented on the eCRF as an AE. Refer to Section 10.5 for guidelines on reporting of abnormal laboratory values as AEs.

7.4.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature and will be taken after the patient has been resting for at least 5 minutes during screening, at study visits during the Treatment Phase, and at the End of Treatment Visit, and more often if required in **Section 8.X.8.1** of the respective treatment arm. Oxygen saturation will be measured if clinically indicated.

7.4.4 12-Lead Electrocardiogram

For all patients, local 12-lead ECGs will be taken at screening, Day 1 of each cycle, and at the End of Treatment Visit. ECGs are to be performed at rest in the supine position.

The following will be measured or calculated: heart rate, PR, QRS, QT, QT interval corrected using Fridericia's method (QTcF), and rhythm. The investigator or qualified designee will review the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant).

If it is clinically indicated, ECGs can be performed at other times during the study.

7.4.5 Physical Examinations, Body Weight, and Height

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be performed during screening and at the End of Treatment Visit. Physical examinations at study visits during the Treatment Phase will be limited as clinically indicated.

Height will be measured during the Screening Visit only. Weight will be measured per institutional guidelines during screening, on Day 1 of each cycle, and at the End of Treatment and Follow-up Visits.

7.4.6 ECOG Performance Status

ECOG performance status will be assessed during screening, at study visits during the Treatment Phase, End of Treatment, and Follow-up Visits. The ECOG performance status should be assessed by the same study personnel at each visit, if possible. For eligibility purposes, patients with borderline ECOG performance status should be considered carefully to avoid enrolling patients who may have significant impairment.

7.5 Biomarker Evaluations

7.5.1 Mandatory Tumor Tissue Analysis

Patients must have sufficient archival or more recently obtained formalin-fixed, paraffin-embedded (FFPE) tumor tissue (obtained prior to administration of any study drug) available for molecular analyses. Tumor tissue must be submitted to the sponsor's central laboratory by Cycle 2 Day 1, but the results are not required from the central laboratory prior to enrollment.

Submission of approximately 10 to 15 × 5 μm unstained sections (or equivalent) for biomarker analyses is preferred. FFPE blocks that contain a similar tumor volume are acceptable if sections cannot be prepared locally. Be advised that it may take up to 3 months for block returns to allow the sponsor to have sections made. The tumor tissue sample must be of adequate quality (at least 20% tumor content [≥ 30% is strongly preferred] with a minimum of 80% nucleated cellular content), or a new sample must be obtained. Please check with the sponsor if the sample does not meet all of these requirements. Refer to the Laboratory Manual for details on tissue adequacy, sample collection and handling instructions.

Collection of a tumor tissue sample at or following disease progression until the start of the next treatment is optional; patients must provide additional consent for this optional tumor tissue biopsy sample. If disease progression is caused by appearance of a new lesion(s), the lesion(s) should be prioritized for the optional biopsy. Refer to the Laboratory Manual for details.

The tumor specimens may be sent to 1 or more laboratories and evaluated for alterations in cancer-related genes or other genomic signatures (eg, percentage of genomic LOH) by targeted next-generation sequencing (NGS) or whole genome sequencing. Additional genomic, transcriptional, and/or proteomic profiling may also be performed. The goal of these biomarker analyses is to identify molecular markers associated with response or resistance to the combination of rucaparib and the second study drug.

7.5.2 Plasma ctDNA Analysis

Blood samples will be collected during screening, before dosing on Day 1 of Cycles 1 through 6; subsequent sampling will occur at approximately the same time as radiological imaging and CA-125 sampling, where applicable (± 3-day window), the End of Treatment Visit, and 28-day Follow-up Visit. Sample collection details will be provided in the Laboratory Manual. These samples will be used for ctDNA profiling to assess alterations in genes that may be associated with response and resistance to the combination of rucaparib and the second study drug.

7.5.3 Pharmacogenomics

A blood sample for pharmacogenomics analyses will be collected at Cycle 1 Day 1 (or next visit if not collected at Cycle 1 Day 1) from all patients. Sample collection details will be provided in the Laboratory Manual. Results of actionable alterations may be made available to the investigator, subject to patient's consent.

These samples, if needed, will be used for the evaluation of genes or biomarkers that may affect the PK of rucaparib, the second study drug, or metabolites. Pharmacogenomic samples may also be tested to determine whether any mutations identified from genomic testing are of germline origin. Because the germline analysis will be done near the end of the study, there are no plans to share these results with the investigator and the patient. However, if an actionable mutation, as defined by the American College of Medical Genetics and Genomics (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/), is detected, the incidental finding will be made available to the investigator provided the results are generated from a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory and the patient has consented to receive the results.

7.5.4 Additional Research

The patient will have the option to provide additional consent to allow the sponsor to retain residual samples for future unspecified research.

7.6 Other Study Evaluations

Pharmacokinetic assessments, biomarker evaluations, and other treatment arm-specific data collection are described in **Section 8.X.8** of the respective treatment arm.

8.A TREATMENT ARM A: RUCAPARIB AND LUCITANIB

8.A.1 Angiogenesis Inhibition

Tumor angiogenesis is a complex process through which new blood vessels are formed from the pre-existing vasculature of the tumor and necessary for metastatic dissemination.[26,27] The process of angiogenesis is critically important for maintaining tumor oxygenation, delivery of nutrients, including growth factors and hormones, and tumor metabolic waste removal.[28] Several growth factors are key players in promoting tumor angiogenesis. These growth factors, secreted by tumor cells and/or the tumor microenvironment, stimulate endothelial cells to proliferate and form new blood vessels. They include vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet derived growth factor (PDGF), among others. They regulate fundamental developmental pathways, which make them and their cognate receptors important cancer therapeutic targets.

VEGF, a cytokine that is present in various human tumors and a potent inducer of vascular permeability, plays an important role in tumor angiogenesis.[29,30] Activation of the VEGF/VEGFR pathway promotes endothelial cell growth, migration, and survival; as well, it mediates vessel permeability and mobilizes endothelial progenitor cells. VEGF acts by binding to several high-affinity transmembrane endothelial cell receptors, most notably VEGFR 1 (Flt 1) and VEGFR 2 (KDR). In addition, VEGF binding to VEGFR 3 (Flt 4) expressed on the lymphatic endothelium, initiates lymphangiogenesis, which contributes to tumor growth, invasion, and metastasis.[31] The expression of angiogenic growth factor inhibitors, like VEGF, are upregulated in many tumors, and the activation of the associated growth factor receptors have been shown to correlate with the degree of tumor vascularization; as such VEGF expression has been proposed as a prognostic factor in patient survival.[32] VEGF is therefore considered to be an important therapeutic target in anti-angiogenic cancer therapy strategy, and drugs affecting the function of VEGFRs (eg, ligand interaction or kinase activity) have been developed and approved, with multiple agents and indications.[33-37]

Therapies directed against VEGF and its receptors exert their effects through a number of potential mechanisms, including (1) inhibition of new vessel growth; (2) regression of newly formed tumor vasculature; (3) alteration of vascular function and tumor blood flow; and (4) direct effects on tumor cells.[38,39] The VEGF inhibitor, bevacizumab (AVASTIN®), is approved in combination with platinum-based chemotherapy, followed by single-agent use, for first-line treatment of ovarian cancer and for platinum-sensitive recurrent disease. It has also been shown to benefit patients with recurrent platinum-resistant disease in combination with chemotherapy.[40,41]

Angiogenesis inhibitors, such as VEGFR inhibitors, combined with PARP inhibitors have suggested synergistic effects in nonclinical studies conducted by the sponsor (Clovis, data on file), as well as by other researchers.[42-44] VEGF overexpression has a role in the development of ovarian cancers.[45] It has been hypothesized that combination therapies including angiogenesis inhibitors and PARP inhibitors can induce a higher incidence of hypoxia, a reduction in homologous recombination, and subsequently a higher sensitivity to PARP inhibition.[42] Inhibition of VEGFR3 can also result in down-regulation of BRCA1 and

BRCA2 expression.[46] PARP inhibitors in combination with targeted anti-angiogenic agents have been well-studied in patients with breast and ovarian cancer.[9,47,48]

8.A.2 Lucitanib Background

Overviews of data from nonclinical and clinical studies are provided below and described in detail in the lucitanib IB.

8.A.2.1 Mechanism of Action of Lucitanib

Lucitanib is a potent, selective inhibitor of the tyrosine kinase activity of vascular endothelial growth factor receptors, types 1, 2, and 3 (VEGFR1–3); platelet-derived growth factor receptors (PDGFR), types alpha and beta (PDGFRα/β); and fibroblast growth factor receptors (FGFR), types 1, 2, and 3 (FGFR1–3).

8.A.2.2 Nonclinical Experience

In vivo, the oral administration of lucitanib over a range of well-tolerated doses significantly inhibited tumor growth in subcutaneous xenograft rodent models using a panel of human tumor cell lines or primary patient-derived tumors. In addition, the combination of lucitanib with a PARP inhibitor demonstrated enhanced anti-tumor responses in murine models.

Lucitanib demonstrated anti-angiogenic activity with regard to modification of tumor perfusion, expression changes in tumor vasculature markers in subcutaneous xenograft models, and inhibition of FGF-induced angiogenesis in Matrigel™ implanted mice.

Lucitanib showed no significant inhibition when evaluated in vitro in a broad screen against receptors, ion channels, enzymes, and transporters suggesting that unexpected pharmacological activity is unlikely based on the IC_{50} obtained and on available tissue distribution data.

Lucitanib is metabolized by both oxidative and conjugation routes. The in vitro metabolism of lucitanib was mainly CYP dependent with equal contribution of CYP2C8 and CYP3A4. Based on clinical DDI knowledge and in vitro-in vivo scaling, an increase in lucitanib exposure is expected in case of co-administration of lucitanib with strong inhibitors of CYP3A4 or CYP2C8 and strong dual inhibitors of CYP3A4/CYP2C8. Therefore, concomitant use of lucitanib with these medications is contraindicated. Additionally, the concomitant use of lucitanib with moderate inhibitors of CYP3A4 or CYP2C8 and dual inhibitors of CYP3A4/CYP2C8 is not recommended, and if clinically necessary, should be used with caution. Strong inducers of CYP3A4 may reduce the plasma concentrations of lucitanib and are contraindicated.

At the observed plasma concentrations of lucitanib at 10 mg QD, the risk of clinical DDI with lucitanib as a CYP inhibitor is low. No CYP induction by lucitanib was observed in vitro at clinically relevant lucitanib concentrations.

Lucitanib was shown to be a substrate of P-gp. However, due to its high permeability across Caco-2 cell monolayers, no DDI is expected with drugs that are P-gp inhibitors. Lucitanib

was not a substrate of sodium/taurocholate cotransporting polypeptide (NTCP), organic anion transporting polypeptide (OATP), organic anion transporter (OAT)2, organic cation transporter (OCT)1, or breast cancer resistance protein (BCRP). The potential for lucitanib to cause DDIs with inhibitors of the transporters tested is low. Further, in vitro transporter-inhibition data suggested that lucitanib has a low risk of clinically relevant inhibition of uptake and efflux transporters.

Lucitanib was found to be genotoxic in Ames tests and demonstrated clastogenicity in human lymphocytes in vitro. Although no embryofetal toxicology assessment has been conducted with lucitanib, it is considered a reprotoxicant.

8.A.2.3 Clinical Experience

The initial focus of the lucitanib clinical development program (CDP) was the treatment of patients with advanced/metastatic breast cancer that harbored an FGFR gene alteration. Five Phase 1 and 2 studies have been conducted to evaluate oral lucitanib as monotherapy in the treatment of cancer in patients with predominately FGF alterations. These studies have evaluated the safety, efficacy, pharmacodynamics, and PK of lucitanib at continuous doses ranging from 5 mg QD to 30 mg QD and in intermitted dosing schedules of 21 days on and 7 days off (21/7).

Results from the first study, a Phase 1 dose escalation (Study CL1 80881-007), identified 30 mg QD as the MTD and a RP2D of 20 mg QD; however, due to the incidence of hypertension and proteinuria at the higher dose levels, the recommended dose was reduced to 15 mg QD and later to 10 mg QD for all ongoing lucitanib studies.

Three of the 5 studies (CL2-80881-001 [BIG 2-13/FINESSE], CL2-80881-002 [INES], and CO-3810-025) evaluated lucitanib administration to patients with metastatic breast cancer.

The fifth study (Study E-3810-II-02) was a Phase 2, open-label study of oral lucitanib in patients with advanced/metastatic small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) and FGF, VEGF, or PDGF genetic alterations.

A total of 424 patients received at least 1 dose of lucitanib with 421 patients exposed at or above the recommended monotherapy dose of 10 mg QD.

8.A.2.3.1 Clinical Pharmacology

The clinical PK properties of lucitanib were evaluated following single and multiple daily oral administrations. Lucitanib was rapidly absorbed with a C_{max} reached within 1 to 3 hrs. Following oral administration of lucitanib, C_{max} and AUC_{0-24} increased approximately dose proportionally with relatively high inter-patient variability.

Lucitanib showed a long terminal half-life ($t_{1/2}$) of 31 to 40 hrs, low apparent clearance (CL/F), and moderate apparent volume of distribution (V/F) in patients. At steady state following daily dosing, lucitanib showed approximately 2-fold accumulation.

Lucitanib has high plasma protein binding (99.3%). No major metabolite of lucitanib was observed. The observed transformations of the lucitanib were demethylation, glucuronidation, glucosidation, and hydroxylation.

Based on clinical concentration-QT analysis, no significant drug-related increase in Fridericia-corrected QT interval from baseline (ΔQTcF) was observed following oral administration of 10 mg lucitanib QD.

8.A.2.3.2 Efficacy

Activity was observed across a wide range of tumor types in the lucitanib Phase 1, first-in-human study.[49] In the subsequent Phase 2 studies evaluating lucitanib monotherapy, only modest clinical efficacy was observed in lung and breast cancer patients across all lucitanib clinical studies and at all doses.

The combined efficacy analysis demonstrates an ORR of 9.3% and median PFS of 15.9 weeks (95% CI, 13.4-19.1). The median time to response was 8 weeks (range, 4-96 weeks) and median duration of response of 37.7 weeks (95% CI, 18.4-101.0). Efficacy was not significantly different for the subset of breast cancer patients only (N = 257), with an ORR of 8.9%, clinical benefit rate (CBR) of 18.3%, and median PFS of 14.1 weeks (95% CI, 12.0-16.4).

8.A.2.3.3 Safety

A total of 424 patients received at least 1 dose of lucitanib and were included in a pooled safety analysis.

The most frequently reported (≥ 30%) TEAEs were hypertension, nausea, hypothyroidism, proteinuria, diarrhea, decreased appetite, headache, asthenia/fatigue, and vomiting. Most of these events were assessed as Grade 1 or 2, except for hypertension, where the majority of patients with a hypertension event had a Grade 3 event. The AEs most frequently reported as related to study drug were similar to the most frequently reported AEs (≥ 30%), regardless of severity.

Twenty-six patients (6.1%) had at least one AE with a fatal outcome with none assessed as related to lucitanib treatment. Of the 424 patients in the safety population, 44.3% had at least 1 SAE, with the most frequent SAEs being dyspnea, thrombotic microangiopathy, and hypertension. All-grade hypertension was reported in over 80% of all patients and in over 50% with ≥ Grade 3 severity. Approximately 20% of patients had an TEAE that lead to study drug discontinuation, with hypertension the most common at an incidence of 3.5%.

Overall, the observed clinical risk profile for lucitanib is consistent with its mechanism of action and AE reported for other anti-angiogenic drugs, as well as observations from the nonclinical studies, with AEs mainly targeting the kidney, cardiovascular system, gastrointestinal tract, and thyroid gland.

Adverse drug reactions (ADRs) for lucitanib are presented in the lucitanib IB (Section 6).

8.A.2.3.3.1 Hypertension

Hypertension is a known toxicity associated with VEGF inhibitor treatment, including lucitanib.[50,51]

Hypertension is the most frequently reported treatment-related AE reported for lucitanib monotherapy in Phase 1-2 clinical studies. Rapid increases in blood pressure (BP) from baseline were observed as early as the first few days following initiation of lucitanib. Hypertension is generally manageable through judicious use anti-hypertensive treatment and rarely results in permanent treatment discontinuation. Abnormal BP measurements in the clinic should be repeated within an hour to confirm findings. Additionally, patients should be instructed to self-measure and record their BP at home in a diary log at least 2 times per week while receiving lucitanib treatment. Patient-monitored BP should be followed by the Investigator at all clinic visits to evaluate the effectiveness of any concomitant anti-hypertensive treatment. Guidelines for management of lucitanib-related hypertension are provided in Section 8.A.6.5.1.

8.A.2.3.3.2 Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) has been observed with other anti-angiogenic compounds. If TMA is suspected, lucitanib dosing should be interrupted and a kidney biopsy should be performed, as needed, to confirm the diagnosis; a nephrologist should be consulted, as appropriate. If TMA is confirmed, lucitanib should be permanently discontinued.

8.A.2.3.3.3 Proteinuria

Proteinuria is an identified risk for lucitanib. The glomerular microvasculature in the kidneys is particularly susceptible to injury through direct targeting of VEGF by antiangiogenic therapy. The common occurrence of proteinuria after inhibition of VEGF signaling reflects importance of VEGF in normal renal function. Patients on lucitanib should be monitored for proteinuria as specified in the relevant protocol. Management of treatment-emergent proteinuria is described in Section 8.A.6.5.2.

Detailed information and Guidance for the Investigator is presented in the lucitanib IB.

8.A.3 Rationale for Rucaparib and Lucitanib Combination

Treatment with a PARP inhibitor or the VEGF inhibitor, bevacizumab, has demonstrated benefit in the ovarian cancer setting.[36,52-54] In addition, a Phase 2 clinical study in patients with recurrent ovarian cancer treated with the PARP inhibitor olaparib and the anti-angiogenic agent cediranib has shown promise (see Section 8.A.3.2). The combination of a PARP inhibitor with a VEGF inhibitor, which have distinctly different mechanisms of action, have also shown synergistic effects in nonclinical studies (Clovis Oncology, data on file). In vitro, the ability of rucaparib in combination with lucitanib to inhibit tumor growth was evaluated using a triple negative breast cancer cell line (MDA-MB-436) harboring the BRCA1 gene mutation. All treatment groups demonstrated significant tumor inhibition ($p < 0.0001$), with the rucaparib plus lucitanib combination showing superior activity

compared to lucitanib ($p = 0.0034$) and rucaparib ($p < 0.0001$) alone (Clovis Oncology; data on file).

Further, nonclinical data suggest that restriction of angiogenesis produces a hypoxic state that can subsequently induce a BRCA-like phenotype by decreasing BRCA1 and RAD51 expression.[55] Anti-angiogenesis therapies, including bevacizumab and cediranib, have been shown to induce a higher incidence of hypoxia and genetic instability, a reduction in HRR, and therefore, subsequent sensitivity to PARP inhibition[42,56] The inhibition of VEGFR-3 also results in down-regulation of BRCA1 and BRCA2 expression and can restore chemosensitivity in ovarian cancer models.[46]

PARP inhibitors have demonstrated robust clinical activity in patients with deleterious BRCA1/2-mutant ovarian cancer. However, in patients with ovarian cancer and BRCA wild-type ($BRCA^{wt}$) disease, targeted treatment options remain elusive with research ongoing to define the aberrations responsible for the disease and its progression. Standard chemotherapy, in the form of platinum-based doublet regimens, remains the primary choice of treatment for patients with ovarian cancer who are classified as platinum-sensitive (platinum-free interval [PFI] $\geq$ 6 months). For patients with platinum-resistant disease (PFI $\geq$ 1 month to < 6 months), single-agent chemotherapy is standard, demonstrating only modest response rates. However, in the open-label, Phase 3 AURELIA study, the addition of bevacizumab to chemotherapy demonstrated significant improvement in PFS and the ORR in patients with platinum-resistant ovarian cancer.[57] The median PFS doubled in the combination bevacizumab/chemotherapy group vs chemotherapy alone (6.7 vs 3.4 months; HR 0.48 [95% CI 0.38-0.60]; $p < 0.001$), and the ORR was reported as 27.3% in patients receiving bevacizumab/chemotherapy compared to 11.8% in patients receiving chemotherapy alone. The overall survival benefit was found to be not clinically significant between the groups. An increased incidence of hypertension, proteinuria, gastrointestinal perforation, and fistula/abscess was observed in the bevacizumab/chemotherapy arm compared to chemotherapy alone. A lower incidence of abdominal pain, vomiting, fatigue, and dyspnea were observed in the combination arm, while other toxicities, including hematologic toxicities consistent with the chemotherapy backbone, were generally similar across arms. Despite these encouraging results, other efficacious treatment options that may ameliorate the potential of cumulative toxicities from chemotherapy are needed for patients with platinum-resistant ovarian cancer. Based on nonclinical evidence of synergic activity and activity in ovarian cancer in combination studies of cediranib and olaparib (see Section 8.A.3.2), this study proposes to evaluate the hypothesis that an HRR state can be induced through treatment with antiangiogenic agent, which through use of a PARP inhibitor can induce synthetic lethality and tumor cell death. This Phase 1b/2 study will evaluate the safety, tolerability, and preliminary efficacy of rucaparib in combination with lucitanib in patients with an advanced/metastatic solid tumor or advanced $gBRCA^{wt}$ ovarian cancer.

8.A.3.1 Dose and Duration Rationale

Expected constitutional symptoms of asthenia/fatigue and gastrointestinal associated toxicities, including nausea, diarrhea, vomiting, and abdominal pain, are potentially overlapping with a combination of lucitanib and rucaparib treatment (see Section 1.1.1.2.3 and Section 8.A.2.3.3). Thus, the initial dose cohort (Dose Cohort 1) to be evaluated in

Phase 1b will consist of a rucaparib dose that is ~50% of the approved starting monotherapy dose (ie, 300 mg BID) and a lucitanib dose that is < 40% of the clinical dose used in Phase 2 studies (ie, 4 mg QD). Doses of rucaparib and/or lucitanib less than 300 mg BID and 4 mg QD, respectively, may be evaluated based on unacceptable toxicities observed in Dose Cohort 1.

8.A.3.2 Expansion Cohorts Rationale

PARP inhibitors in combination with anti-angiogenic agents have been well-studied in patients with breast and ovarian cancer.

Liu et al (2014) have shown significant clinical benefit in a Phase 2 combination study in patients with gBRCA-mutated, platinum-sensitive, recurrent ovarian cancer treated with olaparib and cediranib. Cediranib is a potent, selective, orally bioavailable inhibitor of the tyrosine kinases VEGFR-1, VEGFR-2, and VEGFR-3 with additional activity observed against PDGFR and the proto-oncogene, c-kit. The median invPFS for the olaparib and cediranib combination was 17.7 months (95% CI, 14.7-not reached) compared to olaparib alone at 9.0 months (95% CI, 5.7-16.5) (HR 0.418 [95% CI, 0.229–0.763]; p = 0.005).[9] The ORR was 79.6% with olaparib and cediranib (95% CI 1.53-12.22, p = 0.002) compared to 47.8% with monotherapy olaparib. In the subset of patients with platinum-sensitive ovarian cancer, with gBRCA^{wt} or unknown BRCA status (collective called BRCA$^{wt/unk}$) disease, an improvement in PFS was also observed in patients receiving the combination of olaparib and cediranib (16.5 months; 95% CI, 1.8-inf) vs monotherapy olaparib (5.7 months; 95% CI, 5.3-11.2) (HR 0.32; p = 0.008), and an increase in ORR of 76% vs 32%, respectively, was observed (p = 0.006). A greater incidence of Grade 3/4 AEs was observed in the combination arm compared to the monotherapy olaparib arm, including hypertension, fatigue, and diarrhea, with 77% of patients in the olaparib and cediranib arm requiring a dose reduction compared to 27% in the olaparib arm.

In another Phase 1/2 study (ENGOT-OV24/AVANOVA1), the PARP inhibitor niraparib was evaluated in combination with bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. In the Phase 1 portion of the study, 12 patients were enrolled into the single-arm study, where patients received combination bevacizumab (15 mg/kg in 21-day cycles) and niraparib (escalating doses of 100, 200, or 300 mg QD) in a 3+3 dose escalation design. The majority (75%) of the 12 patients enrolled in this dose escalation phase were gBRCA^{wt}. In the Phase 1 portion of the study, an ORR of 45% (1 CR, 4 PRs), disease control rate of 91%, and median PFS of 49 weeks were reported.[58] In the Phase 1 portion of the study a DLT of Grade 3 thrombocytopenia that persisted for ≥ 5 days was observed at the highest dose level (bevacizumab 15 mg/kg IV; niraparib 300 mg QD). Other common toxicities report in Cycle 1 included Grade 3 and 4 AEs of hypertension (42%), anemia (25%, and thrombocytopenia (8.3%). The Phase 2 portion of the study is ongoing and the primary endpoint of PFS has not been reported.

8.A.4 Treatment Arm A Study Design

Treatment Arm A of this study will investigate the safety, tolerability, PK, and efficacy of the PARP inhibitor rucaparib in combination with the angiogenesis inhibitor lucitanib.

As described in Section 3.1, the treatment arm will consist of 2 phases: Phase 1b is a dose-escalation phase primarily to determine the MTD, if possible, and RP2D; and Phase 2 investigates the RP2D for the combination of rucaparib and lucitanib in patients with prespecified tumor types.

For patients enrolled into Treatment Arm A (Phase 1b or Phase 2) of the study, patients will receive rucaparib BID and lucitanib QD continuously in 28-day cycles.

8.A.4.1 Treatment Arm A Screening and Enrollment

All patients will undergo screening assessments, including disease status per RECIST v1.1, prior to enrollment, within the time frame specified by the Schedule of Assessments (Table 8.A-7).

Treatment Arm A will enroll patients who have met all of the inclusion criteria and none of the exclusion criteria presented in Section 8.A.5.2 and Section 8.A.5.3, respectively. The criteria may be different depending upon which phase of Treatment Arm A the patient is enrolled; these phase-specific criteria are indicated, as appropriate.

Phase 1b will enroll patients with an advanced, recurrent, or metastatic solid tumor who have received at least 1 prior line of therapy in this setting. Provided all other eligibility criteria are met, patients with a deleterious gBRCA mutation are permitted to enroll into this Phase 1b portion of Treatment Arm A.

Phase 2 will enroll patients into 1 of 2 cohorts:

Cohort A1: Patients with platinum-sensitive, gBRCA^{wt}, high-grade serous or Grade 2/Grade 3 endometrioid EOC, FTC, or PPC (collectively termed high-grade ovarian cancer [HGOC])

Cohort A2: Patients with platinum-resistant, gBRCA^{wt} HGOC

Patients enrolled into Cohort A1 or A2 (HGOC) will have received at least 1 prior line of platinum-based chemotherapy in the metastatic setting. Cohort A1 will enroll patients with platinum-sensitive disease, defined as disease progression ≥ 6 months after the **most recent** platinum-based chemotherapy, and Cohort A2 will enroll patients with platinum-resistant disease, defined as disease progression ≥ 1 to < 6 months after the **most recent** platinum-based chemotherapy. In addition, Cohort A1 and Cohort A2 will exclude patients with a locally tested and confirmed deleterious gBRCA mutation (ie, patients will be gBRCA^{wt}).

8.A.4.2 Treatment Arm A: Treatment Phase

For both Phase 1b and Phase 2 of Treatment Arm A, patients will visit the study site on Day 1, Day 4, and Day 15 of Cycle 1; on Day 1 and Day 15 of Cycle 2, and on Day 1 of every cycle thereafter (see Table 8.A-7).

Patients will be assessed for disease status per RECIST v1.1 every 8 calendar weeks (± 1 week) for the first 18 months following initiation of combination study treatment

(Cycle 1 Day 1), then every 16 weeks (± 1 week) thereafter until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, or study termination, or initiation of subsequent anticancer treatments. Responses (CR or PR) must be confirmed with a scan no less than 4 weeks after initial response.

8.A.4.2.1 Phase 1b

Phase 1b is based on a standard 3+3 design as described in Section 3.1.3.1. The first dose of combination study treatment (rucaparib and lucitanib) will be administered on Day 1 of Cycle 1; both drugs will be dosed continuously thereafter. The first 28 days of study treatment (Cycle 1) is the DLT-evaluation period. During the DLT-evaluation period, patients will visit the study site on Day 1, Day 4, and Day 15.

The initial combination dose consists of oral rucaparib 300 mg BID and an oral lucitanib 4 mg QD, with both drugs administered continuously. The dose of rucaparib will be escalated in 100-200 mg BID increments up to a maximum of 600 mg BID. The dose of lucitanib will be escalated in 2 mg QD increments up to a maximum of 10 mg QD. Once the initial dose has been evaluated for the first cohort and deemed safe and tolerable, parallel cohorts, where the dose of 1 investigational agent remains the same as in the prior cohort while the dose of the other agent is escalated, may be evaluated going forward. For example, a cohort receiving 400 mg BID rucaparib in combination with 4 mg QD lucitanib may be evaluated in parallel with a separate cohort receiving 300 mg BID rucaparib in combination with 6 mg QD lucitanib. Doses of rucaparib and/or lucitanib less than 300 mg BID and 4 mg QD, respectively, may be evaluated based on unacceptable toxicity observed at the initial dose cohort.

Prior to initiating treatment at each new combined dose level or prior to expanding an existing dose level, a safety teleconference will be held to review patient data, including but not limited to demographics, PK results (if available), study drug combination dosing, concomitant medications, hematology and chemistry, and AEs, and then confer and document agreement that dose escalation and/or expanding an existing dose level is/are considered appropriately safe. Safety teleconferences will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites.

Dose modifications will be made based on clinical judgement and the dose modification guidance in Section 8.A.6.4.

8.A.4.2.1.1 Dose-limiting Toxicity Criteria

A DLT considered for dose escalation in Phase 1b of Treatment Arm A is defined as any of the following occurring within the first 28 days of initiating combination treatment (Cycle 1) that is assessed by the investigator as possibly related to rucaparib and/or lucitanib (refer to Section 10.7.4 for consideration of causal relationship). Where applicable, the event will be assessed, according to NCI CTCAE v5.0.

- Grade 3 or greater febrile neutropenia (ie, fever > 38.3°C with ANC < 1.0×10^9/L) of any duration;
- Grade 3 or 4 neutropenia lasting more than 7 days despite granulocyte colony-stimulating factor (GCSF) administration;
- Grade 3 thrombocytopenia (platelets < 50×10^9/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < 25×10^9/L) ≥ 5 days duration;
- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated) or any anemia (regardless of grade or severity) requiring a blood transfusion;
- Hypertension, defined as systolic blood pressure [SBP] ≥ 160 mmHg and/or diastolic blood pressure [DBP] ≥ 100 mmHg, that does not resolve to ≤ Grade 2 within 14 days despite optimized antihypertensive therapy, or any Grade 4 hypertension (hypertension with life-threatening consequences);
- Grade 3 or greater hyponatremia lasting more than 5 days despite repletion;
- Any nonhematological AE ≥ Grade 3, with the exception of:
  - Nausea, vomiting, and diarrhea well controlled by systemic medication and with duration ≤ 48 hours;
  - Fatigue;
  - Grade 3 ALT or AST not accompanied by concomitant increase in total bilirubin above the upper limit of normal (ULN). Note: any Grade 4 ALT/AST is a DLT.

If a patient is not evaluable for a DLT, then an additional patient may be enrolled. For the definition of evaluability, please refer to Section 9.2.

8.A.4.2.1.2 RP2D Selection and Expansion

As described in Section 3.1.3.1.2, once the RP2D of the combination has been provisionally established, up to 10 additional patients may be enrolled and treated in Phase 1b, in order to further characterize safety, tolerability, and PK and confirm that this is the optimal dose combination to evaluate in the Phase 2 portion.

8.A.4.2.1.3 Phase 1b – Cycle 2 and Beyond

Following the DLT-evaluation period, patients will come into the study site for a visit on Day 1 and Day 15 of Cycle 2, and on Day 1 of every cycle thereafter. Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments (Table 8.A-7) and PK Assessments (Table 8.A-8).

After the 28-day DLT-evaluation period, recommendations for rucaparib and lucitanib dose modification for the management of specific AEs are provided in Section 8.A.6.4 and Section 8.A.6.5, respectively.

Patients tolerating the investigational treatment(s) at the assigned dose combination for at least 4 cycles may be permitted to escalate to the next highest combination dose regimen as

long as the new dose regimen is **lower** than that being currently evaluated for safety and tolerability and/or the dose level is the **same or lower** than that determined to be the RP2D. All individual patient dose-escalation steps must be approved by the study's medical monitor.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other anticancer therapy, positive pregnancy test, or termination of the study (Section 3.2). If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the medical monitor (Section 5.9).

8.A.4.2.2 Phase 2 Cohorts

Upon determination of the RP2D from Phase 1b, Phase 2 will be initiated. In Phase 2, the selected RP2D from Phase 1b will be evaluated using Simon 2-stage designs in separate and parallel cohorts (see Section 8.A.9.1). Patients meeting all eligibility criteria will be enrolled into 1 of 2 cohorts as follows:

Cohort A1: Patients with platinum-sensitive, gBRCA^{wt} HGOC

Cohort A2: Patients with platinum-resistant, gBRCA^{wt} HGOC

The Phase 2 cohorts were chosen due to the potential susceptibility to the combination of rucaparib and lucitanib (Section 8.A.3.2).

The RP2D of the combination of rucaparib and lucitanib may be further adjusted, and/or alternative dosing schedules assessed during Phase 2 based on emerging safety, PK, and efficacy data.

Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments (Table 8.A-7) and PK Assessments (Table 8.A-8).

Dose modification and AE management guidelines in Section 8.A.6.4 and Section 8.A.6.5, respectively, should be followed throughout the Phase 2.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other anticancer therapy, positive pregnancy test, or termination of the study (Section 3.2). If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the medical monitor (Section 5.9).

8.A.4.3 End of Treatment Arm A (both Phases) and Safety Follow-up

Upon treatment discontinuation, regardless of reason (with the exception of withdrawal of consent or death), patients will have an End of Treatment Visit, and assessments are specified for each treatment arm in the Schedule of Assessments within Table 8.A-7. All patients will

be followed for at least 28 days after the last dose of study drug. Safety follow-up assessments are specified for Treatment Arm A in the Schedule of Assessment.

8.A.5 Study Population Selection for Treatment Arm A

8.A.5.1 Treatment Arm A: Number of Patients and Sites

In Phase 1b, it is estimated that up to 55 patients with advanced or metastatic solid tumors will be enrolled, dependent upon the number of dose cohorts enrolled.

In Phase 2, up to 80 patients will be enrolled into the following cohorts:

Cohort A1: Up to 49 patients with platinum-sensitive, gBRCA^{wt} HGOC

Cohort A2: Up to 31 patients with platinum-resistant, gBRCA^{wt} HGOC

Patients will enroll into either Phase 1b or Phase 2, but a patient cannot enroll into both phases of the same treatment arm. For Phase 2, patients will enroll simultaneously across both cohorts based on separate Simon 2-stage designs for each cohort. Enrollment into Phase 2 for each cohort will continue until the required number of patients for each stage is reached (Section 8.A.9.1).

The enrollment of the 2 phases in Treatment Arm A of the study is up to 135 patients. It is planned that 3 to 6 sites in the US are expected to participate in Phase 1b of the study; approximately 25 sites globally may be activated to participate in the Phase 2 portion of the study.

8.A.5.2 Treatment Arm A: Inclusion Criteria

All patients participating in Treatment Arm A must meet all of the following inclusion criteria:

1. Have signed an Institutional Review Board (IRB)/ IEC-approved informed consent form (ICF) prior to any study-specific evaluation;
2. Be ≥ 18 years of age at the time the ICF is signed;
3. Have an ECOG performance status of 0 or 1;
4. Have a life expectancy greater than 3 months per investigator discretion;
5. Have adequate organ function confirmed by the following laboratory values obtained within 14 days prior to first dose of study drug:
   a. Bone Marrow Function:
      i. ANC ≥ 1.5×10^9/L;
      ii. Platelets > 100×10^9/L;
      iii. Hemoglobin ≥ 9 g/dL
      Note: All hematology values must be achieved without the need for transfusion or growth factors ≤ 14 days prior to the planned start of study treatment (C1D1);

b. Hepatic Function
   i. AST and ALT ≤ 3 × institutional ULN; if liver metastases, then ≤ 5 × the institutional ULN;
   ii. Total bilirubin ≤ 1.5 × institutional ULN;
   iii. Albumin ≥ 30 g/L (3.0 g/dL);
c. Renal Function
   i. Creatinine ≤ 1.5 × institutional ULN **OR** estimated glomerular filtration rate (eGFR) ≥ 45 mL/min using the Cockcroft-Gault formula (Appendix 1);
   ii. Less than or equal to 1+ proteinuria. Patients with > 1+ proteinuria on dipstick must perform a 24-hour urine collection demonstrating ≤ 1.0 g over 24 hours;

6. Have left ventricular ejection fraction (LVEF) ≥ 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan evaluation performed during screening using institutional standard;
7. Have measurable disease per RECIST v1.1;
8. Women of childbearing potential must have a negative serum or plasma pregnancy test within 3 days prior to administration of the first doses of study drug;
9. Have sufficient archival or more recently obtained FFPE tumor tissue available for genomic analysis (refer to Section 7.5.1);
10. **Phase 1b**: Have a histologically or cytologically confirmed diagnosis of locally advanced, recurrent, or metastatic solid tumor;
11. **Phase 1b**: Received at least 1 prior line of therapy in the locally advanced, recurrent, or metastatic setting and have progressed on standard therapy. Patients with ovarian cancer associated with a deleterious BRCA1/2 mutation must have received prior treatment with a PARP inhibitor.
12. **Phase 2**: Criteria Specific to the expansion cohorts
    a. Have a histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid EOC, FTC, or PPC;
    b. Received ≥ 1 prior line of platinum-based chemotherapy and have relapsed or progressive disease (PD) as confirmed by radiologic assessment;
    c. Had documented treatment-free interval of ≥ 6 months following the first chemotherapy regimen received;
    d. **COHORT A1:** Have platinum-sensitive disease, defined as disease progression ≥ 6 months after last dose of platinum-based chemotherapy; or
    e. **COHORT A2**: Have platinum-resistant disease, defined as disease progression ≥ 1 to < 6 months after last dose of platinum-based chemotherapy;
    f. Have gBRCA^{wt} ovarian cancer (ie, patients with a deleterious germline mutation in BRCA1 or BRCA2, as determined by a local laboratory that has received an international or country-specific quality standards certification, **are excluded**).

8.A.5.3 Treatment Arm A Exclusion Criteria

Patients who meet any of the following criteria will be excluded from Treatment Arm A:

1. Unable to swallow oral study drug;
2. Have an active second malignancy, ie, patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment.

   Note: Patients with a history of malignancy that has been successfully treated, with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically-cured, low-risk tumors, such as early stage cervical or endometrial cancer are allowed to enroll. Patients receiving anticancer hormonal therapy in the maintenance setting are allowed to enroll.
3. **Phase 2 only:** Have received prior treatment with a PARP inhibitor;

   Note: patients in Phase 1b may have received a prior PARP inhibitor as long it was not the most recent treatment received;
4. Have received prior treatment with an anti-angiogenesis inhibitor(s), with the exception of bevacizumab in combination with chemotherapy and/or as maintenance to treat newly diagnosed disease in the frontline setting;
5. **Phase 2 only:** Have platinum-refractory disease, defined as disease that progressed by radiologic assessment during or within 4 weeks after completing the last dose of the most recent platinum-based therapy;
6. Have a known history of MDS;
7. Have symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic, previously-treated CNS metastases are eligible provided they have been clinically stable (not requiring steroids for at least 8 weeks prior to first dose of study drug) and have had appropriate scans at the screening assessment;
8. Have pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study drug;
9. Have known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C;
10. Have received chemotherapy, radiation, antibody therapy, or other immunotherapy, gene therapy, vaccine therapy, or experimental drugs ≤ 14 days prior to first scheduled dose of study drugs;
11. Have ongoing toxicity from prior cancer treatment ≥ Grade 2 by NCI CTCAE v5.0, except alopecia; additionally, ongoing Grade 2 peripheral neuropathy may be permitted with prior advanced approval from the sponsor;
12. Have had a nonstudy related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first dose of study drug. In all cases, the patient must be sufficiently recovered and stable before treatment administration;

13. Have had a hospitalization for bowel obstruction within 3 months prior to enrollment;
14. Have a history of gastrointestinal or genitourinary fistula, gastrointestinal perforation, or intra-abdominal abscess, unless previously resected, and confirmed to be fully healed with no evidence of recurrence;
15. History of major thromboembolic event, defined as:
    a. Uncontrolled pulmonary embolism (PE);
    b. Deep venous thrombosis (DVT);
    c. Other related conditions, with exception of patients with stable therapeutic anticoagulation for PE or DVT > 3 months prior to enrollment;
16. Have a history of hemoptysis, clinically significant hemorrhage or history of cerebral vascular accident, transient ischemic attack or subarachnoid hemorrhage within 3 months prior to enrollment;
17. Have clinically relevant cardiac arrhythmia, unstable angina or myocardial infarction within 6 months prior to enrollment; congestive heart failure greater than New York Heart Association (NYHA) III, severe peripheral vascular disease, QTcF > 450 msec; or clinically significant pericardial effusion;
18. Have the need for ongoing concomitant administration of strong inhibitors of CYP2C8 or CYP3A4 or strong inducers of CYP3A4 ≤ 7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix 2);
19. Have radiographic evidence of cavitation or necrotic tumors with invasion of adjacent major blood vessels;
20. Have unstable or uncontrolled BP defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg despite optimized anti-hypertensive therapy per investigator judgement, or history of hypertensive crisis. Patients must be willing and able to check and record daily BP readings;
21. Have uncontrolled hypothyroidism defined as thyroid stimulating hormone (TSH) > 5 mIU/mL while receiving optimized thyroid hormone replacement therapy;
22. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:
    a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib study treatment.
    b. Pregnant or breast feeding.
    c. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of study drug.
    d. Male patients who refuse to use condoms during sex during and up to 6 months after study treatment. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib.
23. Have any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.

No waivers of these inclusion or exclusion criteria will be granted by the investigators, the sponsor, or its designee.

8.A.5.4 Patients or Partners of Patients of Reproductive Potential

Refer to Section 4.1.

8.A.6 Study Treatment(s): Treatment Arm A

Refer to Section 5 for rucaparib treatment.

8.A.6.1 Investigational Drug Product – Lucitanib

Lucitanib (also named S 80881, CO-3810, and E-3810) is an oral formulation. Lucitanib tablets for oral administration will be supplied to the study sites by the sponsor. A brief description of lucitanib is provided below with details in the Pharmacy Manual.

Table 8.A-1 Description of Lucitanib

Drug Name	Lucitanib; S 80881, CO-3810, and E-3810
INN	Lucitanib
Formulation (strengths expressed as free base)	Lucitanib (free base) is formulated as film coated immediate release tablets for oral dosing. Tablets are available in strengths of 1 mg (salmon, round), 2 mg (yellow, round), and 5 mg (white, round).
How Supplied	1 mg, 2 mg, and 5 mg (as free base) strength tablets in 30 count bottles. Patients may receive one or more strengths.
Storage Conditions	Tablets should be stored between 15-30°C (59-86°F).

8.A.6.2 Lucitanib Packaging and Labeling

Lucitanib tablets are packaged in 30-count HDPE bottles with a child resistant closure and should be stored between 15°C and 30°C (59°F to 86°F). Patients will be dispensed one or more strengths of each study drug depending on their current doses of the study drug combination. The number of bottles of each strength dispensed will be sufficient to supply 28 days treatment per cycle, including a small overage.

8.A.6.3 Preparation and Administration of Lucitanib

Lucitanib is administered QD. Tablets should be swallowed with water (240 mL or 8 oz) at approximately the same time each day, on an empty stomach (abstain from food 2 hours before and 1 hour after dosing). Lucitanib may be provided as 1 mg, 2 mg, and 5 mg dose strength tablets, as described in Table 8.A-1.

The morning doses of rucaparib and lucitanib, ideally, should be taken at the same time; due to the food restriction for lucitanib dosing, administration should be on an empty stomach, as

stated above. There are no strict requirements regarding the order in which rucaparib and lucitanib should be ingested by the patient; however, on PK days, the 2 medications should be dosed as closely together as possible for convenient PK sampling.

The evening dose of rucaparib can be taken with or without food.

8.A.6.4 Dose Modification and Retreatment Criteria for Rucaparib and Lucitanib

Toxicities should be managed with supportive care and with dose modification for each of the study drugs according to the attribution of causality for the toxicity based on investigator judgement and consultation with the sponsor, as appropriate. A dose modification of rucaparib or lucitanib is permitted, with the other dose remaining constant, if the causality is believed to be related to 1 study drug, but not the other. General management of AEs are described for the rucaparib and lucitanib combination in Table 8.A-2. Management of new or worsening pulmonary symptoms is described in Section 8.A.6.4.1. Management of AEs specific to lucitanib is provided in the following sections and supersedes the dose modifications described in the table below:

- Hypertension – see Section 8.A.6.5.1
- Proteinuria – see Section 8.A.6.5.2
- Hypothyroidism – see Section 8.A.6.5.3
- Decrease in LVEF – see Section 8.A.6.5.4
- Posterior Reversible Encephalopathy Syndrome (PRES) – see Section 8.A.6.5.5

At the discretion of the investigator, the dose of rucaparib and/or lucitanib may be held and/or reduced for Grade 2 toxicity that is attributed to either rucaparib or lucitanib alone, or in combination, and not adequately controlled by concomitant medications and/or supportive care.

If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred for further evaluation, as clinically appropriate. For clinically significant hematology results, bone marrow analysis and/or blood cytogenetic analysis should be considered according to standard hematological practice.

If a patient continues to experience the same toxicity despite multiple dose reduction steps to the lowest allowable dose, or if dosing with either study drug is interrupted for > 21 consecutive days due to the toxicity, study treatment should be discontinued (Section 8.A.6.4.3), unless otherwise agreed upon between the investigator and the sponsor; exceptions are noted in Section 8.A.6.5 (Management of Adverse Events Specific to Lucitanib).

Table 8.A-2 Rucaparib and Lucitanib Dose Modification Criteria and Action Taken

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			Lucitanib		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
Non-hematological Events							
Adverse event or laboratory abnormality	1 or 2	None[a]	N/A	None[a]	None[a]	N/A	None[a]
Adverse event[b]	3 or 4	Hold dose	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE:** Discontinue	Hold dose	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE:** Discontinue
ALT/AST elevation (in the absence of other signs of liver dysfunction)	3	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline within 2 weeks or if levels increase	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE:** Discontinue	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline within 2 weeks or if levels increase	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE:** Discontinue
ALT/AST elevation	4	Hold; monitor LFTs weekly;	≤ Grade 2	Reduce dose[c] Monitor LFTs weekly for 3 weeks after restart of study	Hold dose; monitor LFTs weekly;	≤ Grade 2	Reduce dose[c] Monitor LFTs weekly for 3 weeks after restart of study

Table 8.A-2 Rucaparib and Lucitanib Dose Modification Criteria and Action Taken

				drug			drug
Adverse Event including Laboratory Abnormalities	**Severity (CTCAE Grade)**	**Rucaparib**			**Lucitanib**		
		Treatment Interruption	**Re-treatment**	**Dose Modification**	**Treatment Interruption**	**Re-treatment**	**Dose Modification**
ALT or AST elevations (> 3 × ULN) AND total bilirubin elevation (> 2 × ULN) - suspected DILI [Section 10.9][23,24]	NA	Hold[d]; monitor LFTs weekly	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently discontinued	Hold[d]; monitor LFTs weekly	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently discontinued
Hematological Events							
Adverse event or laboratory abnormality	1 or 2	None[a]	N/A	None[a]	None[a]	N/A	None[a]
Adverse event or laboratory abnormality	3 or 4	Hold dose	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE:** Discontinue	Hold dose	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE:** Discontinue
Anemia	≥ 3	Hold dose[e].	≤ Grade 2	Same or reduced dose[a, c]	Hold dose[e].	≤ Grade 2	Same or reduced dose[a, c]

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice a day; BUN = Blood urea nitrogen; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LFT = liver function test; N/A = not applicable; ULN = upper limit of institutional normal

[a] At the discretion of the investigator, the dose of rucaparib and/or lucitanib may be held and/or reduced for Grade 2 toxicity that is attributed to either

rucaparib or lucitanib alone, or in combination, and not adequately controlled by concomitant medications and/or supportive care.

[b] Exceptions include Grade 3 or 4 nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to institutional guidelines; for management of hypertension, proteinuria, hypothyroidism, decrease in LVEF, or PRES refer to Section 8.A.6.4.

[c] For dose reductions see Table 8.A-3.

[d] Evaluate patient for the presence of confounding factors, including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis, that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as INR should be implemented as indicated. If no alternative cause is identified, study drugs must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

[e] If anemia CTCAE Grade ≥3 persists for > 14 consecutive days, or a dependence upon blood transfusions occurs, then weekly complete blood counts should be performed until resolution of the event. If after 42 days of interruption and anemia has not improved to CTCAE Grade ≤ 1, the patient should be referred to hematologist and analysis of the bone marrow with cytogenetic studies and recommended according to standard practice. Bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

8.A.6.4.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur, or a deterioration of pulmonary function is observed, and/or radiologic abnormality is detected in the lungs, and this occurs in the absence of any clear diagnosis, a diagnostic workup (including high resolution CT scan) in consultation with a pulmonologist should be performed in order to rule out pneumonitis. During this time, treatment with rucaparib may be interrupted or continued per investigator discretion. Lucitanib treatment may also be interrupted or continued per investigator discretion. The contribution of lucitanib should be assessed independently.

Following investigation, if pneumonitis is not confirmed, treatment may be resumed/continued as deemed appropriate by the investigator and in accordance with the study protocol directions for management of AEs. All confirmed events of pneumonitis should be treated as appropriate per medical judgement and institutional guidelines. If the event resolves and retreatment is being considered, please consult the study medical monitor. Retreatment may be resumed at the current or a reduced dose, if appropriate.

Refer to Section 10.7 and Section 10.8 of the protocol for additional information regarding classification and reporting of pneumonitis (and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) as an AESI.

8.A.6.4.2 Rucaparib and/or Lucitanib Dose Reductions

Potential dose reduction steps for rucaparib and lucitanib based on different current doses are shown in Table 8.A-3. Rucaparib and lucitanib dose reductions will occur in step-wise sequence. Doses lower than rucaparib 300 mg BID are not permitted without consultation with the medical monitor, and doses lower than lucitanib 2 mg QD are not permitted.

Unless otherwise specified, dose re-escalation upon resolution of the toxicity to < Grade 1 is permitted upon agreement between the investigator and sponsor.

Table 8.A-3 Rucaparib and Lucitanib Dose Reductions

Rucaparib		Lucitanib	
Current Dosage	**Dose Reduction[a]**	**Current Dosage**	**Dose Reduction[a]**
600 mg BID	500 mg BID	10 mg QD	8 mg QD
500 mg BID	400 mg BID	8 mg QD	6 mg QD
400 mg BID	300 mg BID	6 mg QD	4 mg QD
300 mg BID	200 mg BID[b]	4 mg QD	2 mg QD
-	-	2 mg QD	None permitted

Abbreviations: BID = twice a day; QD = once a day.

Table 8.A-3 Rucaparib and Lucitanib Dose Reductions

Rucaparib		Lucitanib	
Current Dosage	**Dose Reduction[a]**	**Current Dosage**	**Dose Reduction[a]**

[a] No more than 2 dose reductions for the same AE are allowed for either study drug, after which treatment with both study drugs will be discontinued.

[b] Consult with sponsor's medical monitor before reducing the dose of rucaparib to this level.

8.A.6.4.3 Rucaparib and/or Lucitanib Discontinuation

Rucaparib and/or lucitanib should be permanently discontinued for any of the following:

- If a patient continues to experience toxicity despite dose reduction steps to the lowest permissible dose for either study drug (see Table 8.A-3) or if dosing with either study drug is interrupted for > 21 consecutive days due to toxicity, treatment with both study drugs should be discontinued, with the following exceptions:
  - Treatment interruption > 21 days may be allowed if approved by the sponsor. Prior to re-initiating treatment for a patient with a treatment interruption lasting > 21 days, the study medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if treatment is interrupted.
- Confirmed diagnosis of MDS/AML;
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued oral study treatment dosing; or
- Patient with progressive disease. If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria, but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the sponsor (Section 5.9).

8.A.6.5 Management of Adverse Events Specific to Lucitanib

8.A.6.5.1 Management of Treatment-emergent Hypertension

Patients with unstable or uncontrolled hypertension (defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg despite optimized anti-hypertensive therapy per investigator judgement), or have a history of hypertensive crisis are excluded from this rucaparib and lucitanib combination arm (Exclusion Criteria #20).

Pharmacological management of hypertension should be based on the investigator's judgment, and no definite recommendations for an anti-hypertensive agent can be made. However, calcium channel blockers may be preferred as initial treatment based on their rapid action and safety profile. Angiotensin Converting Enzyme (ACE) inhibitors can be considered in case of concomitant proteinuria. In case of rapid elevation of BP, 2 antihypertensive agents should be considered. The use of 3 antihypertensive agents, such as

concomitant use of a renin-angiotensin system inhibitor, calcium channel blocker, and a diuretic drug may be considered based on the investigator's decision. In that case, close surveillance of kidney function and electrolytes is strongly recommended.

Cardiologist and nephrologist advice should be sought when appropriate and especially in the context of hypertension associated AEs such as proteinuria.

Abnormal BP measurements in the clinic should be repeated within an hour to confirm findings and assess clinical significance. Additionally, patients should be instructed to self-measure and record their BP at home in a diary log at least 2 times per week while receiving lucitanib treatment. The patient must be educated before the first intake of study drug on the importance of BP self-monitoring, trained to recognize signs of hypertension, and trained on the importance of contacting the site if BP is greater than 160/100 mmHg at any time. Patient-monitored BP should be followed by the investigator at all clinic visits to evaluate the effectiveness of any concomitant anti-hypertensive treatment.

For purposes of medical history reporting and AE reporting, it is important to follow the NCI CTCAE grading scale, taking into account not only the BP levels, but also the number of anti-hypertensive therapies (Table 8.A-4).

In the case of lucitanib withdrawal, the patient's BP must be monitored in order to adjust and progressively discontinue concomitant anti-hypertensive treatments that were started during the study.

Table 8.A-4 NCI CTCAE Grading Scale for Hypertension

Grade 1	Prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg)
Grade 2	Stage 1 hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg); medical intervention indicated; recurrent or persistent (≥ 24 hrs); symptomatic increase by > 20 mmHg (DBP) or to > 140/90 mmHg if previously within normal limits; monotherapy indicated
Grade 3	Stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Grade 5	Death

Source: NCI CTCAE, v5.0.

Abbreviations: DBP = diastolic blood pressure; hrs = hours; SBP = systolic blood pressure.

First-time Hypertension

If a patient experiences hypertension for the first time after starting the rucaparib and lucitanib combination, the following actions should be taken:

- Initiate anti-hypertensive therapy immediately.
- Immediate use of 2 anti-hypertensive agents can be considered in case of rapid elevation of BP. The antihypertensive agent can be adjusted over a period of 14 days. The patient should be followed by the investigator at least once per week to evaluate the response to anti-hypertensive treatment. During this period, interruption of lucitanib or dose modification is not necessary.
- If BP decreases to < 140/90 mmHg within 14 days, continue lucitanib at the same dose.

Previously-controlled Hypertension Worsens to Grade 2

If a patient with previously-controlled hypertension experiences worsening in BP values after starting the rucaparib and lucitanib combination, with SBP from 140 to 159 mmHg and/or DBP from 90 to 99 mmHg, the following actions should be taken:

- Review all current antihypertensive treatment and intensify/ adapt as needed. Immediate dose and therapeutic class optimization should be performed. Up to 3 anti-hypertensive agents may be considered.
- The anti-hypertensive agent can be adjusted over a period of 14 days. The patient should be followed by the investigator at least once per week to evaluate the response to anti-hypertensive treatment. During this period, interruption of lucitanib or dose modification is not necessary.
- If BP decreases to < 140/ 90 mmHg within 14 days, continue lucitanib at the same dose and maintain anti-hypertensive treatment, as appropriate.

Persistent Grade 2 Hypertension Despite Optimized Treatment

If after starting the rucaparib and lucitanib combination, a patient has persistent hypertension with SBP from 140 to 159 mmHg and/or DBP from 90 to 99 mmHg, despite optimized anti-hypertensive treatment of ≥ 14 days and assured compliance, the following actions should be taken:

- **Reduce lucitanib** to next lower dose level (see Table 8.A-3), or if at 2 mg QD lucitanib, **withhold lucitanib treatment**.
- Ensure adequate control of BP below 140/90 mmHg including increasing the dose of the current antihypertensive agent(s) (if appropriate) and/or initiation of additional antihypertensive agents, as appropriate.

- Allow up to 14 days for BP to be controlled to baseline or Grade < 2.
- If BP does not reduce to < 140/ 90 mmHg after 14 days, **lucitanib should be reduced again**, unless if at 2 mg QD lucitanib, whereby **withhold lucitanib treatment**.
    - Allow an additional 14 days for BP to be controlled to baseline or Grade < 2.
    - If BP decreases to < 140/90 mmHg within 14 days, resume lucitanib at the reduced dose.
    - If BP does not reduce to < 140/ 90 mmHg within the additional 14 days, **lucitanib should be withheld for up to 14 days**.
    - If BP remains at ≥ 140/90 mmHg after withholding lucitanib for 14 days, approval by the study's medical monitor is required prior to re initiating lucitanib treatment.

Confirmed Grade 3 Hypertension with No Hypertension-related Symptoms and No More than 1 Risk Factor

If after starting the rucaparib and lucitanib combination, a patient has confirmed hypertension with SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg, with no hypertension-related symptoms and no more than 1 risk factor (defined as comorbidities that may increase hypertension-related complications, eg, diabetes and/ or coronary artery disease), the following actions should be taken:

- Continue lucitanib therapy.
- Immediately start anti-hypertensive treatment or optimize current anti-hypertensive treatment.
    - Allow up to 48 hours for BP to be controlled (BP < 140/ 90 mmHg), with close follow-up by the treating physician.
    - If BP does not reduce to < 140/90 mmHg within 48 hours, **lucitanib should be reduced to next lower dose level**, or if at 2 mg QD lucitanib, withhold lucitanib treatment.
    - If BP does not reduce to < 140/90 mmHg within 48 hours despite lucitanib dose reduction and optimal anti-hypertensive therapy, **withhold lucitanib**.
        - If BP decreases to < 140/90 mmHg within 14 days, **resume lucitanib at next lower dose level**, or if withheld while receiving 2 mg QD lucitanib, resume at 2 mg QD.
        - If BP is not controlled < 140/90 mmHg) within 14 days after interruption of lucitanib and despite optimal anti-hypertensive treatment, **lucitanib should be permanently discontinued**.

Confirmed Grade 3 Hypertension with Mildly Symptomatic Hypertension, Several Risk Factors, or Receiving 2 Anti-hypertensive Agents

If after starting the rucaparib and lucitanib combination, a patient has confirmed hypertension with SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg, in addition to any one of the following:

1. mildly-symptomatic hypertension, defined as symptoms of headache, facial flushing, etc. in the absence of additional cardiac, neurological findings or major renal complications; or
2. several risk factors (defined as comorbidities that may increase hypertension-related complications, eg, diabetes and/ or coronary artery disease)

then the following actions should be taken:

- **Withhold lucitanib treatment**. Immediate use of 2 or 3 anti-hypertensive agents may be considered in patients with no history of hypertension. For patients already on 2 anti-hypertensive agents, with assured compliance, modification of the current anti-hypertensive therapy and/or adding a third agent should be considered.
  - The patient should be followed by the investigator closely to evaluate the response to anti-hypertensive treatment.
  - Allow up to 14 days for BP to be controlled (BP < 140/90 mmHg).
  - If BP decreases to < 140/90 mmHg within 14 days, **resume lucitanib at next lower dose level (**Table 8.A-3**)**, or if withheld while receiving 2 mg QD lucitanib, resume at 2 mg QD.
  - If BP does not reduce to < 140/90 mmHg within 14 days, **lucitanib should be permanently discontinued**.

Confirmed Hypertensive Crisis with Life-threatening Consequences

If after starting the rucaparib and lucitanib combination, a patient has confirmed hypertensive crisis, defined as an increase in BP of ≥ 180 mmHg SBP and/ or ≥ 120 mmHg DBP) that can lead to life-threatening consequences (eg, cerebral stroke), then **lucitanib treatment must be permanently discontinued**.

8.A.6.5.2 Management of Treatment-emergent Proteinuria

Patients will be regularly monitored for proteinuria by dipstick. Patients with early signs of proteinuria by dipstick (2+) should be closely monitored and proteinuria evaluated quantitatively (24 hrs protein excretion or protein-to-creatinine ratio).

Proteinuria will be graded NCI CTCAE v5.0, as presented in Table 8.A-5.

Table 8.A-5 NCI CTCAE Grading Scale for Proteinuria

Grade 1	1+ proteinuria; urinary protein < 1.0 g/24 hours
Grade 2	2+ proteinuria; urinary protein ≥ 1.0 to 3.4 g/24 hours

Grade 3	Urinary protein ≥ 3.5 g/24 hours

Source: NCI CTCAE, v5.0.
Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Guidelines for management of lucitanib-related proteinuria are listed in Table 8.A-6.

Table 8.A-6 Management of Lucitanib-related Proteinuria

Adverse Event	Severity (CTCAE Grade)	Dose Modification Action
Proteinuria, first onset	≥ 2	**Withhold lucitanib;** monitored proteinuria by dipstick weekly at the investigational site. Upon recovery of proteinuria to Grade ≤ 1, resume lucitanib at the same dose; continue to monitor via dipstick.
Proteinuria, second onset	≥ 2	**Withhold lucitanib;** perform quantitative assessment of 24-hr urinary protein. Upon recovery of proteinuria to Grade ≤ 1, resume lucitanib at the next lower dose; or if at 2 mg QD, resume at 2 mg QD.
Proteinuria, third onset	≥ 2	Repeat assessments and dose modifications as outlined above.
Proteinuria, fourth onset	≥ 2	If proteinuria ≥ Grade 2 recurs following dose reductions to 2 mg QD, or if there is no recovery within 30 days at 2 mg QD, **discontinue lucitanib treatment permanently.**

Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once a day.

8.A.6.5.3 Management of Subclinical Hypothyroidism

Plasma TSH and thyroid hormones levels should be measured, as part of clinical chemistry testing per the Schedule of Assessments (Table 8.A-7). Treatment with levothyroxine 50 µg/day is recommended for patients with TSH values above 5 mIU/L, even if triiodothyronine (T3) and thyroxine (T4) are normal. Study drug dose modifications are not necessary.

8.A.6.5.4 Management of Decrease in Left Ventricular Ejection Fraction

In case of observed decrease in LVEF or symptoms of heart failure, the following guidelines should be followed:

- Perform ECHO or MUGA, as appropriate.

- If no signs of heart failure and LVEF ≥ 45% OR absolute drop from baseline ≤ 15 ejection fraction percentage points, then continue lucitanib at the same dose level, and repeat the LVEF assessment.
- Patient is symptomatic OR LVEF < 45% OR absolute drop from baseline > 15 ejection fraction percentage points, then hold lucitanib until resolution (LVEF ≥ 50% and asymptomatic). If resolution occurs within 3 weeks, lucitanib can be resumed at a reduced dose (Table 8.A-3), otherwise discontinue lucitanib permanently.
- No recovery OR LVEF < 20%, then discontinue lucitanib permanently and maintain follow-up as per Section 10.8.

8.A.6.5.5 Management of Posterior Reversible Encephalopathy Syndrome

If a patient presents with symptoms suggestive of PRES, eg, persisting headache not responsive to usual analgesics, confusion, visual symptoms, seizures and coma, immediately **withhold lucitanib** and consider performing all relevant clinical and radiological examinations (eg, neurological consultation, MRI) to ensure early diagnosis and treatment of this syndrome. A follow-up MRI should be performed to confirm the diagnosis of PRES, and if confirmed, lucitanib must be permanently discontinued.

8.A.6.6 Treatment Arm A Study Drug Compliance and Accountability

Rucaparib treatment compliance is described in Section 5.7, and lucitanib compliance will be recorded analogously. Study drug accountability is described in Section 5.8.

8.A.7 Prior and Concomitant Therapy

Refer to Section 6 for prior and concomitant therapy restrictions and information that is general across all treatment arms of this study. Additional information specific to the rucaparib and lucitanib combination arm are described in this section.

Due to the known risk of hypertension with lucitanib treatment, sites should counsel patients on limiting salt intake to less than 4 g/day.

8.A.7.1 Other Concomitant Medications

Drugs with a known risk for prolonged QT interval and Torsades de Pointes should be avoided.

For the rucaparib and lucitanib combination arm, strong inhibitors of CYP2C8 or CYP3A4 are contraindicated during the study. Should acute treatment with a strong inhibitor of CYP2C8 be deemed necessary, lucitanib must be temporarily withheld. Lucitanib may be resumed after a minimum of 7 days of ending the acute treatment with a strong inhibitor of CYP2C8. Concomitant administration of strong inducers of CYP3A4 are not permitted at any time during treatment. Moderate CYP2C8 and CYP3A4 inhibitors are not recommended. Strong inducers of CYP3A4 may reduce the plasma concentrations of lucitanib and should be avoided. Refer to Appendix 2.

8.A.8 Study Procedures and Methods for Treatment Arm A

8.A.8.1 Schedule of Assessments: Treatment Arm A

Table 8.A-7 summarizes the procedures and assessments to be performed for all patients in Treatment Arm A (Phase 1 and Phase 2).

Table 8.A-8 summarizes the timing of collection of PK samples for all patients in Treatment Arm A.

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, written informed consent must be obtained from each potential patient prior to any study activities (see Section 11.2). The information on the IRB/IEC-approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand.

The screening period begins with the first study-specific procedure, performed outside standard of care, and only after written consent for study participation has been provided.

Additionally, patients participating in the optional tumor tissue biopsy at the time of radiologic disease progression/treatment discontinuation must provide additional written consent for this procedure.

All procedures and assessments are to be completed within ± 3 days of the scheduled time unless otherwise stated.

Table 8.A-7 Schedule of Assessments for All Patients in Treatment Arm A (Phase 1b and Phase 2)

	Screening Phase			Treatment Phase (28-day cycles ± 3 days)				Post Treatment Phase	
				Cycles 1 and 2			Cycles 3+		
Study Day	**Day -56 to Day -1**	**Day -28 to Day -1**	**Day -14 to Day -1**	**Day 1**	**Day 4[a]**	**Day 15**	**Day 1**	**End of Treatment**	**28-day Safety FU[b]**
Procedure[c]									
Informed Consent	X								
Medical/Oncology History (Section 7.1)	X								
Tumor Tissue Sample (Section 7.5.1)[d]	X								
Physical Examination (Section 7.4.5)		X		X			X	X	X
Vital Signs (Section 7.4.3)		X		X	X	X	X	X	X
12-lead ECG (Section 7.4.4)		X		X			X	X	
LVEF Assessment (Section 8.A.8.2.1)		X							
Prior/Concomitant Medications/Procedures (Section 7.2)[e]		X		X	X	X	X	X	X
Disease Assessment/Tumor Scans[f] (Section 7.3.1)		X					X	X	
ECOG Performance Status		X		X			X	X	X
Hematology (Section 7.4.2)			X	X		X	X	X	X
Chemistry, including TSH and T3/T4 (Section 7.4.2 and Section 8.A.8.2.2)			X	X		X	X	X	X
Urinalysis (Section 7.4.2)			X	X		X	X	X	
Serum or plasma Pregnancy Test (WOCBP only) (Section 7.4.2)			X	X			X	X	
CA-125 Measurement for HGOC patients (Section 7.5.2)[g]			X	X			X	X	
Pharmacogenomics Blood Sample (Section 7.5.3)[h]				X					

Table 8.A-7 Schedule of Assessments for All Patients in Treatment Arm A (Phase 1b and Phase 2)

	Screening Phase			Treatment Phase (28-day cycles ± 3 days)				Post Treatment Phase	
				Cycles 1 and 2			Cycles 3+		
Study Day	**Day -56 to Day -1**	**Day -28 to Day -1**	**Day -14 to Day -1**	**Day 1**	**Day 4[a]**	**Day 15**	**Day 1**	**End of Treatment**	**28-day Safety FU[b]**
Procedure[c]									
Blood Sample for ctDNA Analysis (Section 7.5.2)[i]		X		X			X	X	X
Blood Sample for AAG Analysis (Section 8.A.8.2.2)				X					
Rucaparib and Lucitanib Administration[j]				X	X	X	X		
Adverse Events[k] (Sections 10.7 and 10.8)	(X)	(X)	(X)	X	X	X	X	X	X
Post-progression Tumor Tissue Biopsy (Section 7.5.1)[l]								X	
Blood Samples for PK	Refer to Table 8.A-8 for sampling schedule								

Abbreviations: AAG = α1 acid glycoprotein; AML = acute myeloid leukemia; CA-125 = cancer antigen 125; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; OC = ovarian cancer; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndrome; PK = pharmacokinetics; T3 = free triiodothyronine; T4 = free thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

[a] Patients are required to have a study visit on Day 4 of Cycle 1 only. There is no ± 3 day window for this visit.

[b] Follow-up Visit should occur 28 days (±7) from the last dose of study drug or can be performed on the date of discontinuation if that date is at least 28 days from last dose, whichever is later. Chemistry and hematology are only necessary at FU Visit, if toxicities are present. The follow up visit should be conducted in person.

[c] The study visit window in the treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the patient's investigational product supply. Only 1 cycle of oral study drug will be dispensed to the patient on Day 1 of each cycle.

[d] The tumor tissue sample must be adequate for genomic testing. If archival tissue sample is inadequate or unavailable, a more recently obtained tissue sample will be required prior to administration of study drug. Refer to the Laboratory Manual for details on tissue adequacy, sample collection and handling instructions.

[e] Patients taking warfarin should have INR monitored regularly per standard clinical practice (Section 6.5). Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice (Section 6.6).

[f] Disease assessments to consist of clinical examination and appropriate imaging techniques per RECIST will occur every 8 calendar weeks (up to ±1 week prior is permitted) for the first 18 months following initiation of combination study treatment, then every 16 weeks until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, or study termination. Other complementary studies may be performed if clinically indicated. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. End-of-Treatment scans not required if disease progression determined and patient is not continuing study treatment.

[g] CA-125 measurement should be performed for patients with ovarian cancer at screening and on Day 1 of every subsequent cycle, at treatment discontinuation, as clinically indicated. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and ctDNA sampling.

[h] If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter.

[i] Day 1 (before dosing) of Cycle 1 through Cycle 6 and at the same time as radiological imaging and CA-125 sampling (where feasible), at the End of Treatment, and at the 28-day Follow-up Visit. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and CA-125 (for ovarian cancer patients).

[j] First dose of both study drugs in Cycle 1 should be administered within 3 days after a patient having been confirmed as meeting the enrollment criteria. Administration is continuous (not just the days specified in the table). Refer to Section 5.5 (rucaparib) and Section 8.A.6.3 (lucitanib) for administration guidelines. Study treatment continues in 28-day cycles until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study.

[k] AEs, SAEs, and AESIs that occur after first administration of study drug through to 28 days after last dose of study drug(s). In addition, SAEs that were related to a screening procedure will also be recorded. Ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed to resolution or stabilization. After the Safety Follow-up, only SAEs considered as potentially study-drug related (including serious reports of pneumonitis and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML, regardless of causality, will be recorded in the eCRF.

[l] An optional tumor biopsy may be collected at or following disease progression until the start of the next treatment. Additional consent is required. Refer to the Laboratory Manual for details on sample collection and handling instructions.

Table 8.A-8 Pharmacokinetic Sample Collections in Treatment Arm A (Phase 1b and Phase 2)

Study Visit		Lucitanib PK	Rucaparib PK
Cycle 1 (Phase 1b[a])	D15[b]	Predose[c]	Predose[c]
		Post-morning dose: 0.5, 1, 1.5, 2.5, 4, 6 and 8 hrs	Post-morning dose: 0.5, 1, 1.5, 2.5, 4, 6 and 8 hrs
	D16[d]	Predose[c]	_
Cycle 2-4 (Phase 1b[a] and Phase 2)	D1	Predose[c]	Predose[c]

Abbreviations: D = Day; hrs = hours; PK = pharmacokinetics.

[a] Phase 1b includes patients in the dose-escalation phase and the RP2D expansion.

[b] On Cycle 1 Day 15, doses of rucaparib and lucitanib must be taken at the same time on an empty stomach, ie, at least 2 hours prior and 1 hour after any meal. For Phase 1b for Cycle 1 Day 15, a time window of ±5 minutes for specimen collections up to 2 hours and ±15 minutes from 2.5 to 8 hours.

[c] Predose refers to collection prior to the morning dose of both rucaparib and lucitanib. The predose specimen collection may be performed 30 minutes before taking the next dose of study drug.

[d] Patients do not need to stay overnight for Cycle 1 Day 16. A time window of ±1 hour for specimen collection (of lucitanib) is permitted 24 hours after the Cycle 1 Day 15 dose of lucitanib and within 30 minutes before taking the next dose.

Notes: Collection of the actual time(s) of dose administration is essential for both rucaparib and lucitanib.

Refer to the (Treatment Arm A) Laboratory Manual for details on sample handling and processing.

8.A.8.2 Methods of Data Collection: Arm A

See Section 7 for methods of data collection that are general across all treatment arms of this study. Additional information specific to the rucaparib and lucitanib combination arm are described in this section.

8.A.8.2.1 Left Ventricular Ejection Fraction Assessment

LVEF will be assessed by ECHO or MUGA during screening. Patients must meet the LVEF criteria (Inclusion Criteria #6). If it is clinically indicated, LVEF assessments can be performed at other times during the study.

8.A.8.2.2 Additional Clinical Laboratory Investigations

In addition to the laboratory assessments described in Section 7.4.2, the following will be tested at the same timepoints as chemistry testing: TSH, free triiodothyronine (T3; fT3), free thyroxine (T4, fT4), TSH with reflexive fT3 and fT4 if TSH is abnormal on treatment.

A blood sample for α1-acid glycoprotein (AAG) analysis will be taken predose on Day 1 of Cycle 1 for all patients.

8.A.8.2.3 Pharmacokinetic Sample Collection

For all patients in Phase 1b and Phase 2, plasma samples are to be collected for trough level PK analysis of oral study drug within 30 minutes before the morning dose of rucaparib and daily dose of lucitanib on Day 1 of Cycles 2, 3, and 4. Plasma samples are to be collected approximately 12 hours after the last oral dose of rucaparib and approximately 24 hours after the last dose of lucitanib, but prior to the next oral dose (ie, typically within 30 minutes prior to dosing). If study drug dosing is temporarily withheld on a day where PK specimens were to be collected, plasma samples for rucaparib and lucitanib PK should still be collected at the nominal collection days and times prior to the originally planned dosing.

On Day 15 of Cycle 1, an intensive PK sampling collection will commence after the morning dose of rucaparib and daily dose of lucitanib on an empty stomach (see Section 8.A.6.3). On this day, these 2 doses should be taken together to facilitate PK sampling. Plasma samples will be taken as indicated in Table 8.A-8. For Phase 1b for Cycle 1 Day 15, a time window of ± 5 minutes for specimen collections up to 2 hours and ± 15 minutes from 2.5 to 8 hours. Patients do not need to stay overnight for Cycle 1 Day 16. A time window of ± 1 hour for specimen collection at the 24-hour timepoint is permitted.

A central laboratory will be used for bioanalysis of plasma rucaparib and lucitanib concentration measurement. Please refer to the Laboratory Manual for details on collection and processing of blood PK samples.

8.A.9 Planned Statistical Methods: Treatment Arm A

The statistical methods that are general across treatment arms are described within Section 9.

The determination of sample sizes for Treatment Arm A, Phase 1b and Phase 2 cohorts are described below.

8.A.9.1 Determination of Sample Size

The total enrollment planned for evaluation of rucaparib in combination with lucitanib is up to 135 patients.

Phase 1b is based on a standard 3+3 dose-escalation design, and the overall sample size depends on the occurrence of safety findings, specifically, DLTs, observed at the different dose regimens. A minimum of 6 and maximum of approximately 55 patients across all dose cohorts may be enrolled. Additional patients may be enrolled to evaluate other dose levels or schedules as described in Section 8.A.4.2.1. Additional patients may be enrolled into a particular dose cohort if a patient already enrolled into that same dose cohort does not meet the criteria for the DLT-evaluable population, defined in Section 9.2.

A Simon 2-stage design will be used to evaluate efficacy (confirmed overall response of CR or PR) of rucaparib in combination with lucitanib in each of the Phase 2 cohorts. The sample sizes for each Phase 2 cohort was determined based on a null hypothesis (H_0), which specifies a response proportion that if not reached (response is less than that specified), further investigation would not be warranted, and an alternative hypothesis (H_1), which specifies a response proportion that if observed would warrant further investigation of the rucaparib and lucitanib combination treatment in the corresponding cohort.

Phase 2 Cohort A1: Patients with Platinum-sensitive, gBRCA^{wt} HGOC

Up to 49 patients (31 patients enrolled in Stage 1 and 18 patients enrolled in Stage 2) will be used to evaluate efficacy. After the first 31 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 10 of these 31 patients have a confirmed overall response (CR or PR per investigator assessment), the sponsor and key participating investigators will evaluate overall benefit:risk for patients and determine whether or not to continue further enrollment. If 11 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 18 patients in Stage 2 will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.35$;
- H_1: $p \geq 0.50$; and
- 80% power at significance level = 0.10 (one-sided).

If Stage 2 is fully enrolled and ≥ 22 out of 49 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and lucitanib combination warrants consideration of further investigation in patients with platinum-sensitive, $BRCA^{wt}$ ovarian cancer.

Phase 2 Cohort A2: Patients with Platinum-resistant, $gBRCA^{wt}$ HGOC

Up to 31 patients (16 patients enrolled in Stage 1 and 15 patients enrolled in Stage 2) will be used to evaluate efficacy. After the first 16 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 1 of these 16 patients have a confirmed overall response (CR or PR per investigator assessment), the sponsor and key participating investigators will evaluate overall benefit:risk for patients and determine whether or not to continue further enrollment. If 2 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 15 patients in Stage 2 will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.10$;
- H_1: $p \geq 0.25$; and
- 80% power at significance level = 0.10 (one-sided).

If Stage 2 is fully enrolled and ≥ 6 out of 31 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and lucitanib combination warrants consideration of further investigation in patients with platinum-resistant, $BRCA^{wt}$ ovarian cancer.

8.B TREATMENT ARM B: RUCAPARIB AND SACITUZUMAB GOVITECAN

8.B.1 Antibody-drug Conjugates

Antibody-drug conjugates (ADC) are a class of potent bioconjugated drugs designed to target specific cells in patients with cancer. They are produced by linking the unique targeting capabilities of a monoclonal antibody with a cytotoxic chemotherapy agent. Such targeting methods often provide a selective advantage for localizing these agents to tumors, with improved therapeutic responses as compared to the agent alone, but careful development and evaluation are required. Paramount is that the conjugate preserves the activity of the cytotoxic agent without compromising the antibody's ability to bind to its target. Secondly, the therapeutic agent should be active at relatively low concentrations, preferably nanomolar levels. This requirement reflects the fact that for antibody conjugates to be active, they need not only to deliver the therapeutic agent selectively to the tumor, but the conjugate must be internalized into the tumor cell, with the agent being released in an active form.

ADCs are gaining interest as a targeted therapy, since they should discriminate between the normal tissue and tumor tissue, which generally expresses higher levels of the antibody target. Brentuximab vedotin (Adcetris®), an anti-CD30 monoclonal antibody attached to the cytotoxic agent, monomethyl auristatin E (MMAE), is approved in both the US and EU for the treatment of relapsed Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL).[59,60] A second ADC, trastuzumab emtansine (T-DM1; Kadcyla®), which consists of the recombinant anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody trastuzumab (Herceptin®) conjugated to the cytotoxic agent, emtansine (DM1), is approved in the US for the treatment of patients with HER2-positive metastatic breast cancer who have received prior treatment with trastuzumab and a taxane chemotherapy.[61]

8.B.2 Sacituzumab Govitecan Background

Sacituzumab govitecan (IMMU-132) is a novel ADC that is composed of the following 3 components:

1. The humanized monoclonal antibody, hRS7 IgG1κ, which binds to Trop-2 (trophoblast cell-surface antigen, also known as EGP-1, epithelial glycoprotein-1).

   Trop-2 is a cell surface, transmembrane calcium signal transducer glycoprotein belonging to the TACSTD gene family, which is highly expressed in many epithelial cancers, particularly metastatic sites,[62] with much lower expression in normal tissues.[63] Trop-2 has been implicated in oncogenesis, often being found in more aggressive tumors.[64] The antibody was initially developed as a murine monoclonal antibody by the immunization of mice with a fresh specimen of a human lung cancer. The properties of the parent murine antibody have been extensively described.[65-70]

2. The camptothecin-derived agent, SN-38, a topoisomerase 1 inhibitor.

   SN-38 is the active metabolite of irinotecan (camptothecin-11; Camptosar®), which is approved as treatment for metastatic colorectal cancer.[71] Only 5% of irinotecan is converted to the active SN-38 form by esterase activity residing primarily in the liver, though there are also esterases in the tumor that can cleave irinotecan to SN-38.[72] SN-38 is not soluble in aqueous media, and hence the reason a water-soluble irinotecan derivative was prepared.
3. A linker, with the company designation CL2A, which binds SN-38 to the antibody.

8.B.2.1 Mechanism of Action of Sacituzumab Govitecan

Sacituzumab govitecan (IMMU-132) is an ADC composed of hRS7, a humanized IgG1κ monoclonal antibody, SN-38, a camptothecin analog, and CL2A, a linker which couples SN-38 to hRS7.

Trop-2 is a cell surface antigen overexpressed in many epithelial cancers and has been linked to aggressive disease and poor prognosis. The antibody component binds to Trop-2 such that the ADC concentrates on tumor cell surfaces. SN-38 is the active metabolite of irinotecan and a topoisomerase I inhibitor that induces single-stranded DNA breaks during replication. If unrepaired, these breaks progress to double-stranded DNA breaks and results in cell death. The CLA2 linker is unique in that it is subject to pH-dependent hydrolysis. Following internalization of the ADC-antigen complex, SN-38 is released in the acidic lysosome and kills the target cells.[73,74] In addition, SN-38 can be cleaved from extracellular, surface-bound ADC due to the acidic pH of the tumor microenvironment. The released drug diffuses into neighboring cells in an antigen-independent manner, and this leads to death of cells in the immediate proximity of the target-expressing cells. These 2 mechanisms of action combine to enable sacituzumab govitecan to target and kill cancer cells that over-express Trop-2, as well as, other cells in the tumor with low or no Trop-2 expression.

8.B.2.2 Nonclinical Experience

8.B.2.2.1 Pharmacology

In vitro cytotoxicity of sacituzumab govitecan was assessed in 6 different cell lines representative of several different epithelial tumors; PC-3 (prostate), Calu-3, COLO 205, Capan-1, SK-MES-1 and BxPC-3. In general, the IC_{50} values ranged from 1.95 nM to 23.14 nM.[75]

In vivo preclinical testing of sacituzumab govitecan was performed in nude mouse-human cancer xenograft models using a variety of different human cancer cell lines, eg, NSCLC, colorectal, pancreatic, gastric, squamous cell lung, and triple-negative breast cancer (TNBC) cancers.[75-77] Pronounced antitumor activity and significant inhibition of tumor growth was shown in all xenograft models, with the exception of a single squamous cell lung cancer xenografts, where sacituzumab govitecan was superior to saline or unconjugated hRS7, but not superior to a nonspecific antibody or irinotecan at the MTD.

8.B.2.2.2 Pharmacokinetics

Toxicokinetic analysis of the 3-month repeat-dose study in Cynomolgus monkeys showed a dose-related exposure with no relevant gender differences. SN-38G readily appeared in serum with mean t_{max} ranging from 4.0 to 12 hours after the first dose. On average the Free SN-38 exposure was 2.26% and 1.52% of the Total SN-38 exposure, respectively, based on the AUC_{0-168} and C_{max} values.

8.B.2.2.3 Toxicology

In acute toxicity studies in Swiss-Webster Mice, sacituzumab govitecan at doses of up to 750 mg/kg/dose (ie, cumulative doses of up to 1500 mg/kg) caused minimal loss (< 10%) in body weight. There was no evidence of hematological toxicity, and no abnormal histology findings. Transient increases in hepatic transaminases were observed that returned to normal by the end of the study.

In Cynomolgus monkeys, sacituzumab govitecan administered 50 mg/kg/dose (human equivalent dose [HED] = 16 mg/kg/dose) for 4 treatment cycles (Days 1 and 8 of a 21-day cycle) was considered a No-Observed-Adverse-Effect-Level (NOAEL) and 120 mg/kg/dose administered 3 days apart was associated with lethality. In monkeys, target organs included the female reproductive tract, skin (hair loss, pigmentation), kidney (periarteritis), lymphoid organs (lymphoid depletion), bone marrow (reduced cellularity) with concomitant reductions in red cells, white cells and platelets and the gastrointestinal tract (necrosis, erosions, inflammation, fibrosis, hemorrhage, edema).

Local tolerance was evaluated in the Good Laboratory Practice (GLP)-compliant monkey studies. Although changes were observed at the injection site, the study pathologist interpreted these findings as related to procedural trauma and not the test article. These changes consisted of mild to moderate perivascular hemorrhage, moderate hemorrhage in the dermis and subcutis, and minimal to mild perivascular mixed cell infiltration.

SN-38 was negative for mutagenicity in a bacterial reverse mutation test and was found to be clastogenic in an in vitro mammalian cell micronucleus test. Neither the carcinogenicity, nor effects of sacituzumab govitecan on fertility, early embryonic development or pre- and post-natal development have been assessed. However, SN 38 is a camptothecin and hence might be carcinogenic. Furthermore, SN-38 is a known developmental toxicant.[71]

8.B.2.3 Clinical Experience

To date, the clinical experience with sacituzumab govitecan is derived from 3 ongoing clinical studies. IMMU-132-01 is a Phase 1/2 multi-center US study that was originally designed to obtain initial safety and dose-finding data of sacituzumab govitecan monotherapy in patients with advanced relapsed/refractory metastatic epithelial cancers, including ovarian, TNBC, prostate (hormone refractory), lung (non-small cell and small-cell), head and neck (squamous cell), esophageal, gastric, colorectal, pancreatic, hepatocellular, renal (clear cell) and urinary bladder cancers. This study was expanded with a Phase 2 portion that only enrolled patients with TNBC, lung (non-small cell and small-cell), or urothelial cancer (UC). Both phases of the study are closed to enrollment. The Phase 1 portion of the study has been

completed, while there are still patients under follow-up in the Phase 2 portion. Based on encouraging data noted in the TNBC cohort of IMMU-132-01, a Phase 3 randomized, controlled study was initiated, IMMU-132-05. In addition, based on activity noted in the UC cohort of IMMU-132-01, a Phase 2 study (IMMU-132-06) in metastatic UC was recently initiated (not yet described in the sacituzumab govitecan IB). Recruitment in both IMMU-132-05 and IMMU-132-06 studies is ongoing.

Twenty-five patients were included in the Phase 1 portion of IMMU-132-01, with sacituzumab govitecan doses as high as 18 mg/kg given on Day 1 and 8 of a 21-day treatment cycle.[78] Neutropenia was the dose-limiting toxicity at this level, with the MTD declared to be 12 mg/kg. Most of the other AEs at all dose levels were Grade 2 or lower. Fatigue, alopecia and occasional mild to moderate diarrhea were some of the more common non-hematological toxicities, with 2 patients reporting a rash. While 12 mg/kg was considered the MTD, there was tendency for patients treated at this level to have delays in their dose schedule, as well as dose reductions. Ultimately, 10 mg/kg (days 1 and 8 of a 21-day cycle) was selected for further development.

As of November 2018 (after the release of the current sacituzumab govitecan IB v6, dated 28 Sept 2018), a total of 650 patients have been treated with sacituzumab govitecan in the 3 clinical studies with the majority treated at the 10-mg/kg dose level.

8.B.2.3.1 Efficacy

Efficacy in the relevant populations, using recently-published data, are shown below.

Triple-negative Breast Cancer

As of 30 Jun 2017, 110 patients with TNBC were enrolled in Study IMMU-132-01 who have had at least 2 prior therapies in the metastatic setting and were treated at the 10 mg/kg dose of sacituzumab govitecan had an assessable radiographic response measured by RECIST v1.1. Based on best response, there were 3 confirmed CRs and 33 confirmed PRs, resulting in a current ORR of 34% (37/110); the clinical benefit rate (CR + PR + stable disease [SD] > 6 months) was 45%.[79] Kaplan-Meier graphs of PFS and overall survival (OS) generated for all treated patients show current estimated median values of 5.5 and 12.7 months, respectively.

Urothelial Cancer

Based on data presented at the European Society for Medical Oncology (ESMO) conference in 2017, Tagawa, et al[80] reported an ORR of 34% in 41 relapsed metastatic UC patients. Majority of patients had received platinum therapy with 14 of the 41 having received immunotherapy prior to entering the study. Patients had a median duration of response of

12.6 months, a median PFS of 7.1 months (95% CI, 5.0-10.7) and a median OS of 16.1 months (95% CI, 10.5-17.7).

8.B.2.3.2 Safety

Based on recently updated results, internal to the sponsor of sacituzumab govitecan, the safety profile of sacituzumab govitecan was characterized based on 420 patients with various epithelial cancers in the Overall Safety Population in Study IMMU-132-01. The most frequent AEs by MedDRA (Medical Dictionary for Regulatory Activities) system organ class (SOC) were gastrointestinal disorders (91%), followed by general disorders and administration site conditions (76%), and blood and lymphatic system disorders (66%). Infections occurred in 43% of patients. The most frequent AEs by preferred term of any NCI CTCAE grade were nausea (67%), diarrhea (62%), fatigue (53%), vomiting (44%), alopecia (42%), anemia (41%), and neutropenia (41%). Febrile neutropenia occurred in 6%. Serious adverse events were experienced by 40% of patients; the most frequent were febrile neutropenia (4%), diarrhea, pneumonia, and vomiting, (3% each), and dyspnea, nausea, and neutropenia (2% each).

8.B.2.3.2.1 Risks Associated with Antibody Administration

When any antibody product is administered, the possibility of an allergic reaction, such as itching, erythema, hives, or anaphylaxis, which can manifest as bronchospasm or hypotension, needs to be considered. A physician should be available and supplies of epinephrine, antihistamine, and corticosteroid should be readily accessible when a patient receives sacituzumab govitecan infusion. In the event of an anaphylactic reaction, sacituzumab govitecan infusion should be stopped immediately and permanently discontinued. A patient who has such an allergic reaction should not receive additional sacituzumab govitecan. Other reversible and non-life-threatening potential side effects associated with antibody administration include constitutional symptoms such as chills, fever, myalgia, and malaise. These side effects can be treated symptomatically (refer to Section 8.B.6.5.1 for management of infusion-related reactions).

8.B.2.3.3 Pharmacokinetics and Immunogenicity

Four analytes were measured to characterize the PK of the sacituzumab govitecan: 1) total antibody (hRS7 + hRS7-SN-38); 2) free SN-38 (the cytotoxic payload, not covalently bound to sacituzumab govitecan); 3) SN-38 glucuronide (SN-38G, an inactive metabolite of SN-38, not covalently bound to sacituzumab govitecan); and 4) total SN-38 (free SN-38 + hRS7-SN-38). Furthermore, an analytical method for the detection of anti-IMMU-132 antibodies has been established to support the assessment of immunogenicity.

The clinical pharmacology of SN-38 once released from sacituzumab govitecan is considered comparable to that of SN-38 released from irinotecan.

Serial PK samples were available for 55 patients of the metastatic TNBC target population in Study IMMU-132-01, and peak/trough samples were available for 4 patients. Since all sampled patients were part of the target population, they had received a sacituzumab govitecan starting dose of 10 mg/kg; but some patients had PK samples taken after dose

reduction to 7.5 mg/kg. Concentration-time curves, shown for sacituzumab govitecan (IMMU-132), free SN-38, and total SN-38, appeared to be approximately parallel with a slight delay in C_{max} for free SN-38.

The metabolism of sacituzumab govitecan is mediated by both catabolism of the antibody and metabolism of the released payload, SN-38. Since the protein portion of sacituzumab govitecan is expected to be catabolized into individual amino acids in vivo, metabolism studies were not conducted for the antibody component. The metabolism of SN-38 is well described in the literature.[71,72,81] Briefly, SN-38 is highly (~95%) bound to human plasma proteins, predominantly albumin.[71] SN-38 can be conjugated to glucuronide in the liver by UGT1A1 forming the inactive metabolite SN-38G. Literature suggests that SN-38 may also be metabolized by CYP3A4; however, clinical implications of this finding have not yet been evaluated. UGT1A1 activity is reduced in people with genetic polymorphisms that lead to reduced enzyme activity, such as the UGT1A1*28 polymorphism. Metabolism of SN-38 is impaired in patients with such UGT1A1*28 polymorphisms.[71]

Studies of the excretion of sacituzumab govitecan have not been conducted. SN-38 and SN-38G are reported to be primarily excreted through the hepatobiliary route, with lesser amounts detected in the urine.[71,72,81]

8.B.3 Rationale for Rucaparib and Sacituzumab Govitecan Combination

Agents that inhibit topoisomerase 1, including irinotecan, have demonstrated synergy with PARP inhibitors in a variety of human tumor cell lines, including ovarian and breast cancers.[5,6] The combination of a PARP inhibitor (including rucaparib) and sacituzumab govitecan demonstrated synergistic growth inhibition, increased double-stranded DNA breaks, and accumulation of cells in the S-phase of the cell cycle when assessed in human TNBC cell lines.[82] These effects were observed regardless of BRCA1 or 2 mutation status. Taken together, these data support the rationale for the evaluation of the combination of rucaparib and sacituzumab govitecan clinically.

It is notable that a study of the PARP inhibitor, veliparib, combined with the topoisomerase 1 inhibitor, topotecan, showed a mechanistic interaction between the 2 drugs, resulting in delayed repair of Topo1-mediated DNA damage, despite there being some difficulties with synergistic hematologic toxicities.[8] In addition, the PARP inhibitor, olaparib, has been shown to potentiate the cytotoxicity of SN-38, the active metabolite in irinotecan and topotecan, irrespective of MMR status in a variety of MMR-deficient or MMR-efficient cell lines.[7]

8.B.3.1 Dose and Duration Rationale

Because synergistic effects as well as additive toxicities are possible, dose escalation for this combination will begin with starting doses lower than the established or recommended single-agent dose for either study drug. As safety and efficacy for oral rucaparib have been established using BID dosing, and the dosing schedule for sacituzumab govitecan (Day 1 and Day 8 in 21-day cycles) has been established in prior single-agent studies, these schedules will be followed in the current study. The starting doses will be oral rucaparib 300 mg BID with IV sacituzumab govitecan 6 mg/kg on Day 1 and Day 8 of each cycle. Modulation of

the doses of each study drug, rather than their schedules, is the intended approach to investigating the MTD and RP2D for the combination of rucaparib and sacituzumab govitecan.

8.B.3.2 Expansion Cohorts Rationale

As previously described, favorable nonclinical data for this combination in both TNBC and ovarian cancer support the inclusion of patients with these underlying tumors. Clinical data for sacituzumab govitecan in advanced, metastatic UC have demonstrated significant and durable responses in patients with heavily pre-treated disease (Section 8.B.2.3.1). Genomic LOH is a biomarker of HRD that has been associated with PARP inhibitor sensitivity in ovarian cancer, and an analysis of The Cancer Genome Atlas (TCGA) demonstrated that many UC tumors have high genomic LOH (Clovis, data on file). Allowing prior treatment with a PARP inhibitor for the ovarian cancer patients reflects evolving treatment patterns and provides for the evaluation of possible restoration of sensitivity to PARP inhibition imparted by this combination.

8.B.4 Treatment Arm B Study Design

Treatment Arm B of this study will investigate the safety, tolerability, PK, and efficacy of the PARP inhibitor, rucaparib, in combination with the ADC, sacituzumab govitecan (IMMU-132).

As described in Section 3.1, the treatment arm will consist of 2 phases: Phase 1b is dose-escalation phase primarily to determine the MTD and RP2D; and Phase 2 investigates the RP2D for the combination of rucaparib and sacituzumab govitecan in patients with prespecified tumor types.

For patients enrolled into Treatment Arm B (Phase 1b or Phase 2) of the study, patients will receive oral rucaparib BID continuously and IV sacituzumab govitecan on Days 1 and 8 of 21-day cycles.

8.B.4.1 Treatment Arm B: Screening and Enrollment

All patients will undergo screening assessments, including disease status per RECIST v1.1, prior to enrollment, within the time frame specified by the Schedule of Assessments (Table 8.B-6). In addition to the tumor tissue collection for genomic analysis, Trop-2 expression analysis will also be conducted.

Treatment Arm B will enroll patients who have met all of the inclusion criteria and none of the exclusion criteria presented in Section 8.B.5.2 and Section 8.B.5.3. The criteria may be different depending upon which phase of Treatment Arm B the patient is enrolled; these phase-specific criteria are indicated, as appropriate.

Phase 1b will enroll adult patients with previously-treated, locally-advanced unresectable or metastatic TNBC; previously-treated locally-advanced, or metastatic UC; or relapsed, platinum-resistant ovarian cancer. Patients with an advanced, recurrent, or metastatic solid

tumor with documented evidence of a deleterious alteration in BRCA1, BRCA2, PALB2, RAD51C, and/or RAD51D are also eligible for the Phase 1b portion of the study.

Phase 2 will enroll patients into 1 of 3 cohorts:

Cohort B1: Patients with locally-advanced unresectable or metastatic TNBC

Cohort B2: Patients with locally-advanced or metastatic UC

Cohort B3: Patients with relapsed, platinum-resistant ovarian cancer

Patients enrolled into Cohort B1 will have a diagnosis of either locally advanced unresectable or metastatic TNBC refractory to or relapsing after at least 1 prior standard-of-care chemotherapy regimen for unresectable, locally advanced or metastatic breast cancer. Phase 2 patients may have received no more than 3 prior therapies. Earlier adjuvant or neoadjuvant treatment for more limited disease will qualify as one of the prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within 12 months of adjuvant therapy. Eligible patients will have received prior treatment with a taxane in either the adjuvant or metastatic setting.

Patients enrolled into Cohort B2 will have locally advanced or metastatic UC and will have received 1 or 2 prior standard of care treatment regimens (eg, cisplatin- or carboplatin-containing chemotherapy and/or immune checkpoint inhibitor) for advanced or metastatic disease.

Patients enrolled into Cohort B3 will have relapsed, high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer that is resistant (progression-free interval < 6 months after their last dose of platinum) to the most recently administered platinum-based therapy. These patients will have received ≤ 1 line of treatment for platinum-resistant disease.

8.B.4.2 Treatment Arm B: Treatment Phase

For both Phase 1b and Phase 2 of Treatment Arm B, patients will visit the study site on Day 1, Day 8, and Day 15 of Cycle 1 and Cycle 2, and on Day 1 and Day 8 of every cycle thereafter (see Table 8.B-6).

Patients will be assessed for disease status per RECIST v1.1 at screening, every 6 weeks (± 1 week) for the first 24 weeks, and then every 9 weeks (± 1 week) thereafter until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, or study termination, or initiation of subsequent anticancer treatments. Responses (CR or PR) identified prior to 24 weeks will be confirmed at the next scheduled scanning timepoint (6 weeks later). For responses identified after 24 weeks, confirmatory scans should be obtained no less than 4 weeks after the initial response.

8.B.4.2.1 Phase 1b

Phase 1b is based on a standard 3+3 design as described in Section 3.1.3.1. The first dose of combination study treatment (rucaparib and sacituzumab govitecan) will be administered on Day 1 of Cycle 1. The first 21 days of study treatment (Cycle 1) is the DLT-evaluation period. During the DLT-evaluation period, patients will come into the study site for a visit on Day 1, Day 8, and Day 15.

The initial combination dose consists of oral rucaparib 300 mg BID, administered continuously, in combination with IV sacituzumab govitecan 6 mg/kg administration on Days 1 and Day 8 of a 21-day cycle. The dose of rucaparib will be escalated in 100 mg BID increments up to a maximum of 600 mg BID. The dose of sacituzumab govitecan will be escalated in increments of 2 mg/kg, up to a maximum dose of 10 mg/kg. Once the initial dose has been evaluated for the first cohort and deemed safe and tolerable, parallel cohorts, where the dose of 1 investigational agent remains the same as in the prior cohort while the dose of the other agent is escalated, may be evaluated going forward. For example, a cohort receiving 400 mg BID rucaparib in combination with 6 mg/kg sacituzumab govitecan may be evaluated in parallel with a separate cohort receiving 300 mg BID rucaparib in combination with 8 mg/kg sacituzumab govitecan. Doses of rucaparib and/or sacituzumab govitecan less than 300 mg BID and 6 mg/kg IV, respectively, may be evaluated based on unacceptable toxicity observed at the initial dose cohort.

Prior to initiating treatment at each new combined dose level or prior to expanding an existing dose level, a safety teleconference will be held to review patient data, including but not limited to demographics, PK results (if available), study drug combination dosing, concomitant medications, hematology and chemistry, and AEs, and then confer and document agreement that dose escalation and/or expanding an existing dose level is/are considered appropriately safe. Safety teleconferences will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites.

Dose modifications will be made based on clinical judgement and the dose modification guidance provided in Section 8.B.6.4.

8.B.4.2.1.1 Dose-limiting Toxicity Criteria

A DLT considered for dose escalation in Phase 1b of Treatment Arm B is defined as any of the following occurring within the first 21 days of initiating combination treatment (Cycle 1) that is assessed by the investigator as possibly related to rucaparib and/or sacituzumab govitecan (refer to Section 10.7.4 for consideration of causal relationship). Where applicable, event will be assessed, according to the NCI CTCAE v5.0.

- Grade 3 or greater febrile neutropenia (ie, fever > 38.3°C with ANC < 1.0×10^9/L) of any duration;
- Grade 3 or 4 neutropenia lasting more than 7 days despite GCSF administration;

- Grade 3 thrombocytopenia (platelets < 50×10^9/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < 25×10^9/L) ≥ 5 days duration;
- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated) or any anemia (regardless of grade or severity) requiring a blood transfusion;
- Any nonhematological AE ≥ Grade 3, with the exception of:
  - Nausea, vomiting, and diarrhea if well controlled by systemic medication and with duration ≤ 48 hrs;
  - Fatigue;
  - Grade 3 ALT or AST not accompanied by a concomitant increase in total bilirubin above the ULN. Note: any Grade 4 ALT/AST is a DLT.
- Any Grade 3 or greater infusion-related reaction that fails to resolve within 4 hours despite optimal medical management.

If a patient is not evaluable for a DLT, then an additional patient may be enrolled. For the definition of evaluability, please refer to Section 9.2.

8.B.4.2.1.2 RP2D Selection and Expansion

As described in Section 3.1.3.1.2, once the RP2D of the combination has been provisionally established, up to 10 additional patients may be enrolled and treated in Phase 1b, in order to further characterize safety, tolerability, and PK and confirm that this is the optimal dose combination to evaluate in the Phase 2 portion.

8.B.4.2.1.3 Phase 1b – Cycle 2 and Beyond

Following the DLT-evaluation period, patients will come into the study site for a visit on Day 1, Day 8 and Day 15 of Cycle 2, and on Days 1 and 8 of every cycle thereafter. Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments (Table 8.B-6) and PK Assessments (Table 8.B-7).

After the 21-day DLT-evaluation period, recommendations for rucaparib and sacituzumab govitecan dose modification for the management of specific AEs are provided in Section 8.B.6.4.

Patients tolerating the investigational treatment(s) at the assigned dose combination for at least 4 cycles may be permitted to escalate to the next highest combination dose regimen as long as the new dose regimen is **lower** than that being currently evaluated for safety and tolerability and/or the dose level is the **same or lower** than that determined to be the RP2D. All individual patient dose-escalation steps must be approved by the study's medical monitor.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other anticancer therapy, positive pregnancy test, or termination of the study (Section 3.2). If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to

derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the medical monitor (Section 5.9).

8.B.4.2.2 Phase 2 Cohort

Upon determination of the RP2D from Phase 1b, Phase 2 will be initiated. In Phase 2, the selected RP2D from Phase 1b will be evaluated using Simon 2-stage designs in separate and parallel cohorts (see Section 8.B.9.1). Patients meeting all eligibility criteria will be enrolled into 1 of 3 cohorts as follows:

Cohort B1: Patients with locally-advanced unresectable or metastatic TNBC

Cohort B2: Patients with locally-advanced or metastatic UC

Cohort B3: Patients with relapsed, platinum-resistant ovarian cancer

The Phase 2 cohorts were chosen due to the potential susceptibility to the combination of rucaparib and sacituzumab govitecan (Section 8.B.3.2).

The RP2D of the combination of rucaparib and sacituzumab govitecan may be further adjusted, and/or alternative dosing schedules assessed during Phase 2 based on emerging safety, PK, and efficacy data.

Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments (Table 8.B-6) and PK Assessments (Table 8.B-7).

Dose modification guidelines in Section 8.B.6.4 should be followed throughout the Phase 2.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other anticancer therapy, positive pregnancy test, or termination of the study (Section 3.2). If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the medical monitor (Section 5.9).

8.B.4.3 End of Treatment Arm B and Safety Follow-up

Upon treatment discontinuation, regardless of reason (with the exception of withdrawal of consent or death), patients will have an End of Treatment Visit, and assessments are specified for each treatment arm in the Schedule of Assessments within Table 8.B-6. All patients will be followed for at least 28 days after the last dose of study drug. Safety follow-up assessments are specified for Treatment Arm B in the Schedule of Assessment.

8.B.5 Study Population Selection for Treatment Arm B

8.B.5.1 Treatment Arm B: Number of Patients and Sites

In Phase 1b, it is estimated that up to 55 patients will be enrolled, dependent upon the number of dose cohorts enrolled.

In Phase 2, up to 139 patients will be enrolled into the following cohorts:

Cohort B1: Up to 53 patients with metastatic TNBC

Cohort B2: Up to 53 patients with locally-advanced or metastatic UC

Cohort B3: Up to 33 patients with relapsed, platinum-resistant ovarian cancer

Patients will enroll into either Phase 1b or Phase 2, but a patient cannot enroll into both phases of the same treatment arm. For Phase 2, patients will enroll across all cohorts based on separate Simon 2-stage designs for each cohort. Enrollment into Phase 2 for each cohort will continue until the required number of patients for each stage is reached (Section 8.B.9.1)

The enrollment of the 2 phases in Treatment Arm B of the study is up to 194 patients. It is planned that 3 to 6 sites in the US are expected to participate in Phase 1b of the study; approximately 25 sites globally may be activated to participate in the Phase 2 portion of the study.

8.B.5.2 Treatment Arm B: Inclusion Criteria

All patients participating in Treatment Arm B must meet all of the following inclusion criteria:

1. Have signed an IRB/IEC-approved ICF prior to any study-specific evaluation;
2. Be ≥ 18 years of age at the time the ICF is signed;
3. Have an ECOG performance status of 0 or 1;
4. Have a life expectancy greater than 3 months per investigator discretion;
5. Has adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug:
   a. Bone Marrow Function:
      i. ANC ≥ 1.5×10^9/L;
      ii. Platelets > 100×10^9/L;
      iii. Hemoglobin ≥ 9 g/dL
      Note: All hematology values must be achieved without the need for transfusion or growth factors ≤ 14 days prior to the planned start of study treatment (C1D1);
   b. Hepatic Function
      i. AST and ALT ≤ 3 × ULN; if liver metastases, then ≤ 5 × the institutional ULN;
      ii. Total bilirubin ≤ 1.5 × institutional ULN;
      iii. Albumin ≥ 30 g/L (3.0 g/dL);
   c. Renal Function
      i. Creatinine ≤ 1.5 × institutional ULN **OR** estimated eGFR ≥ 45 mL/min using the Cockcroft-Gault formula (Appendix 1);

ii. Less than or equal to 1+ proteinuria. Patients with > 1+ proteinuria on dipstick must perform a 24-hour urine collection demonstrating ≤ 1.0 g over 24 hours;

6. Have measurable disease per RECIST v1.1;
7. Women of childbearing potential must have a negative serum or plasma pregnancy test within 3 days prior to administration of the first doses of study drug;
8. Have sufficient archival or more recently obtained FFPE tumor tissue available for genomic analyses (refer to Section 7.5.1);
9. **For Phase 1b and Phase 2**, has 1 of the following 4 diagnoses (a through d):
   a. TNBC histologically- or cytologically-confirmed by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH), and
      i. Is refractory to or has relapsed following 1 to 3 prior standard of care chemotherapy regimens for unresectable, locally advanced, or metastatic disease. Earlier adjuvant or neoadjuvant treatment for more limited disease will qualify as one of the prior regimens if the development of unresectable, locally advanced, or metastatic disease occurred within 12 months of adjuvant therapy.

         Note: While patients participating in Phase 2 are limited to 3 prior regimens, patients participating in Phase 1b are allowed to have received more than 3 prior chemotherapy regimens.
      ii. Must have received a taxane, regardless of disease stage (adjuvant, neoadjuvant, or advanced) when it was given. Patients who have contra-indications or are intolerant to taxanes are eligible provided they received at least 1 cycle of a taxane and demonstrated intolerance or contra-indication during or at the end of that cycle of treatment.
      iii. Prior platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer is allowed, provided there was no evidence of disease progression during the platinum chemotherapy.
      iv. Prior platinum received as potentially curative treatment for a prior cancer (eg, ovarian cancer) or as adjuvant/neoadjuvant treatment for breast cancer is allowed, provided ≥ 12 months have elapsed between the last dose of platinum-based treatment and treatment with study drugs.
      v. **Phase 2 only:** must have received prior therapy with an anthracycline unless contraindicated or declined by the patient.
      vi. **Phase 1b only:** Patients with TNBC associated with a deleterious BRCA mutation must have received prior treatment with a PARP inhibitor (either olaparib or talazoparib). **Phase 2 only:** Patients with TNBC cannot have received prior treatment with a PARP inhibitor.
   b. Histologically or cytologically confirmed locally advanced (tumor, node, metastasis [TNM] staging of T4b and any N; or any T and N2-3) or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureter, urinary bladder, or urethra). Mixed transitional/non-transitional cell histologies are allowed.
      i. Has received 1 or 2 prior standard of care treatment regimens (eg, cisplatin- or carboplatin-containing chemotherapy and/or immune checkpoint inhibitor) for

advanced or metastatic disease and had confirmed radiologic disease progression during or following the most recent treatment.
Note: Patients participating in Phase 1b are allowed to have received more than 2 prior chemotherapy regimens, including platinum.

ii. Neoadjuvant or adjuvant treatment for muscle invasive disease will be considered a treatment regimen if radiologic disease progression occurred ≤ 12 months from the start of treatment.

iii. No more than 1 prior platinum-containing chemotherapy regimen for advanced disease permitted. A change of platinum within the same regimen will be considered 1 prior platinum-containing chemotherapy.

iv. Patients must have received platinum-based chemotherapy (cisplatin or carboplatin), if eligible, and treatment with a PD-1/PD-L1 inhibitor, if eligible. These agents may have been administered as 2 separate regimens or as 1 combined regimen.

v. Patients with transitional cell carcinoma of the urothelium are eligible regardless of BRCA-mutation status. Prior treatment with a PARP inhibitor is only allowed for those patients enrolled into the Phase 1b portion of the study. Patients in the Phase 2 portion of the study cannot have received prior treatment with a PARP inhibitor.

c. Histologically confirmed diagnosis of high-grade serous or Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer and relapsed or PD confirmed by radiology.

i. Has received ≥ 2 prior chemotherapy regimens, was resistant to most recently administered platinum-based treatment (ie, disease progression < 6 months after last dose of platinum) and has received ≤ 1 treatment for platinum-resistant disease.

ii. Must have received prior treatment with bevacizumab-containing chemotherapy for platinum-resistant disease OR not be eligible to receive bevacizumab in this setting due to prior exposure in an earlier treatment setting OR not currently be eligible for treatment with bevacizumab.

iii. Patients with platinum-refractory disease, ie, disease that progressed during or within 4 weeks after completing last platinum-based treatment are excluded.

iv. Has treatment-free interval of ≥ 6 months following the first chemotherapy regimen received.

v. Patients with platinum-resistant disease are eligible regardless of BRCA-mutation status. Prior treatment with a PARP inhibitor is permitted but not required.

10. For Phase 1b only: A previously-treated, advanced, recurrent, or metastatic solid tumor with documented evidence of a deleterious alteration in BRCA1, BRCA2, PALB2, RAD51C, and/or RAD51D from tissue or plasma ctDNA testing.

8.B.5.3 Treatment Arm B Exclusion Criteria

Patients who meet any of the following criteria will be excluded from Treatment Arm B:

1. Unable to swallow oral study drug;
2. Have an active second malignancy, ie, patient known to have potentially fatal cancer present for which he/ she may be (but not necessarily) currently receiving treatment;

   Note: Patients with a history of malignancy that has been successfully treated, with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically-cured low-risk tumors, such as early stage cervical or endometrial cancer are allowed to enroll. Patients receiving anticancer hormonal therapy in the maintenance setting are allowed to enroll.
3. Have received prior treatment with any PARP inhibitor, with the following exceptions:
   a. Patients participating in Phase 1b are permitted to have had prior treatment with a PARP inhibitor;
   b. Patients with TNBC associated with a deleterious BRCA mutation who are participating in Phase 1b must have received prior treatment with a PARP inhibitor (either olaparib or talazoparib);
   c. Ovarian cancer patients participating in Phase 2 are permitted to have had prior treatment with a PARP inhibitor;
4. Have previously received treatment with irinotecan, topotecan, or any derivative in any formulation;
5. Have a known history of MDS;
6. Have symptomatic and/or untreated CNS metastases. Patients with asymptomatic, previously-treated CNS metastases are eligible provided they have been clinically stable (not requiring steroids for at least 8 weeks prior to first dose of study drug) and have had appropriate scans at the screening assessment;
7. Have a history of Gilbert's disease;
8. Have a known history of unstable angina, myocardial infarction, or congestive heart failure present within 6 months of randomization or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy;
9. Have a prior history of gastrointestinal perforation within 6 months of the first scheduled study drug dose;
10. Have known HIV or AIDS-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C;
11. Have active chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) or hospitalization for bowel obstruction within 3 months prior to planned enrollment.
12. Have received chemotherapy, radiation, gene therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior to the first scheduled dose of study drugs, OR antibody therapy or other immunotherapy ≤ 4 weeks prior to first scheduled dose of study drugs,

13. Have ongoing toxicity from prior cancer treatment ≥ Grade 2 by NCI CTCAE v5.0, except alopecia; additionally, ongoing Grade 2 peripheral neuropathy may be permitted with prior advanced approval from the sponsor;
14. Have had nonstudy-related minor surgical procedures ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first scheduled dose of study drug. In all cases, the patient must be sufficiently recovered and stable before treatment administration;

    Note: placement of a port, catheter or central line is considered study-related.
15. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:
    a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib study treatment.
    b. Pregnant or breast feeding.
    c. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of study drug.
    d. Male patients who refuse to use condoms during sex during and up to 6 months after study treatment. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib.
16. Have any serious or unstable concomitant systemic disorder incompatible with the clinical study (eg, substance abuse, psychiatric disturbance, or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism).
17. Have any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.

No waivers of these inclusion or exclusion criteria will be granted by the investigators, the sponsor, or its designee.

8.B.5.4 Patients or Partners of Patients of Reproductive Potential

Refer to Section 4.1.

8.B.6 **Study Treatment(s): Arm B**

Refer to Section 5 for rucaparib treatment.

8.B.6.1 Investigational Drug Product – Sacituzumab Govitecan

Sacituzumab govitecan (also known as IMMU-132 and hRS7-SN38) is an IV formulation. Sacituzumab govitecan for IV administration will be supplied to the study sites by the sponsor. A brief description of sacituzumab govitecan is provided below with details in the Pharmacy Manual.

Table 8.B-1 Description of Sacituzumab Govitecan

Drug Name	Sacituzumab govitecan; IMMU-132; hRS7-SN38
INN	Sacituzumab govitecan
Formulation:	10 mg/mL is formulated in 25 mM MES buffer, pH 6.5, together with the other excipients (25 mM trehalose, 0.01% Polysorbate 80). It is then lyophilized and filled at 200 mg/vial.
How Supplied	50-mL clear colored glass vials containing 200 mg of sacituzumab govitecan as a sterile, non-pyrogenic powder.
Storage Conditions	The sterile, non-pyrogenic powder should be stored between 2 and 8°C (35.6-46.4°F). Since the formulated drug product contains no preservative, vials should be used only once and within 8 hrs of reconstitution.

8.B.6.2 Sacituzumab Govitecan Packaging and Labeling

Sacituzumab govitecan will be supplied by the sponsor in 50-mL clear colored glass vials containing 200 mg of sacituzumab govitecan as a sterile, non-pyrogenic powder (Table 8.B-1). The vials and outer carton will be labeled according to national regulations for investigational products.

Details with respect to packaging and labeling of sacituzumab govitecan for infusion are described in the Pharmacy Manual.

8.B.6.3 Preparation and Administration of Sacituzumab Govitecan

8.B.6.3.1 Preparation

The refrigerated sacituzumab govitecan vial should be brought to room temperature, without heating, prior to reconstitution. Sacituzumab govitecan should be reconstituted with 0.9% sodium chloride (normal saline). The 200 mg of powder in each vial can be reconstituted with 20 mL of normal sterile saline (10 mg/mL). Only saline should be used for reconstitution as other buffers have not been studied in stability. The reconstituted solution should be gently shaken and allowed to dissolve for up to 15 minutes. Appropriate use of aseptic technique should be employed.

Calculate the prescribed dose in mg based on the patient's body weight at the beginning of EACH cycle (or more frequently for > 10% change in body weight or if required by institutional policy).

After determining the amount of reconstituted sacituzumab govitecan that will be needed for the patient's dose, the necessary amount of reconstituted sacituzumab govitecan should be withdrawn from the vial(s) and injected into a glass or plastic evacuated infusion container (bag) slowly and without shaking to minimize foaming of the contents. Dilution with normal saline should be accomplished so the final sacituzumab govitecan concentration range is 1.1 to 3.4 mg/mL (total volume should not exceed 500 mL). A sample drug preparation chart for a 70-kg patient is provided in Table 8.B-2 with 200 mg/vials and 250 mL bags of normal

saline as the infusion container. The saline-reconstituted sacituzumab govitecan study drug is stable for up to 8 hrs at room temperature.

Initiate the infusion within 1 hour of reconstitution/dilution. If infusion is delayed beyond 1 hour, refrigerate at 2 to 8°C for no more than 8 hours from reconstitution/dilution prior to infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration. If infusion does not begin within 8 hours after reconstitution/dilution, dispose of the original preparation and prepare a new infusion bag by reconstitution and dilution from new vials. Discard any unused portion in the vial. The product does not contain a preservative.

Any amount of reconstituted sacituzumab govitecan that is not used for patient administration must be discarded appropriately.

Table 8.B-2 Sacituzumab Govitecan Preparation for 10 mg/kg Dosing (Assume 70-kg Patient)

Total Dose needed	**700 mg (200 mg/vial)**
Vials required	4
Volume of saline to be used for reconstitution	20 mL
Volume after reconstitution of each vial with USP saline	80 mL
Volume withdrawn for Scheduled Dose	70 mL
Dilute with Normal Saline	180 mL
Total volume dispensed	250 mL
Final concentration	2.8 mg/mL

Abbreviations: USP = United States Pharmacopeia.

It is preferable for both PK and non-PK study visit days (Day 1 or Day 8) for a patient to first dose with rucaparib or for the site staff to ascertain prior dosing of rucaparib (if taken at home prior to the visit), prior to initiation of the sacituzumab govitecan infusion. When predose PK samples are indicated for both study drugs (refer to Table 8.B-7), the patient should be reminded to hold their morning dose of rucaparib prior to the site visit.

8.B.6.3.2 Preventative Medications

Infusion-related Reactions: For prevention of infusion-related reactions, premedication with antipyretics and H1 and H2 blockers should be administered before each sacituzumab govitecan infusion. Corticosteroids (hydrocortisone 50 mg or equivalent oral or IV) may be administered prior to subsequent infusions if the patient had experienced an infusion-related reaction with a previous infusion.

Nausea, Vomiting: Sacituzumab govitecan is considered to be moderately emetogenic. Premedication with a 2-drug antiemetic regimen is recommended. If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant), and dexamethasone (10 mg oral or IV). Anticipatory nausea can be treated

with olanzapine. Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated.

8.B.6.3.3 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) will be assessed prior to the first infusion of sacituzumab govitecan in Cycle 1 and every 15 ± 5 minutes for the first hour and then every 30 minutes until completing IV administration, at completion, and then 30 minutes post infusion. In absence of significant changes, this may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion.

8.B.6.3.4 Intravenous Administration of Sacituzumab Govitecan

Do not administer as an IV push or bolus. Sacituzumab govitecan is administered intravenously as a slow infusion as described below.

IV access must be well established prior to initiating infusion. At the time of dosing, the IV line will be connected to an infusion container with the prepared volume of sacituzumab govitecan. Either gravity or an infusion pump may be used. Only normal saline should be used as the infusion base solution, since the compatibility of sacituzumab govitecan with other infusion diluents has not been examined.

The initial infusion should proceed slowly. If vital signs remain stable and in the absence of infusion reactions, the infusion rate can be incrementally advanced following suggested guidelines given in Table 8.B-3, and following completion, the intravenous line should be flushed slowly with 20 mL normal saline and the end of infusion time recorded. In the event of infusion reactions or vital sign changes, the infusion rate may be slowed, interrupted or terminated, as considered appropriate by the managing physician.

Table 8.B-3 Infusion Rate Guidelines for Patients Remaining Stable in Absence of Hypersensitivity or Infusion-related Events

Infusion Rate	Infusion #1	Subsequent Infusions
Initial rate (first 15 minutes)	50 mg/hr, or less	100 – 200 mg/hr
Incremental rate (advance every 15-30 minutes)	50 mg/hr	100 – 200 mg/hr
Maximum recommended rate	500 mg/hr	1000 mg/hr

8.B.6.4 Dose Modification and Retreatment Criteria for Rucaparib and Sacituzumab Govitecan

Toxicities should be managed with supportive care and with dose modification for each of the study drugs according to the attribution of causality for the toxicity based on investigator judgement and consultation with the sponsor as appropriate. A dose modification of rucaparib or sacituzumab govitecan is permitted, with the other dose remaining constant, if

the causality is believed to be related to 1 study drug but not the other. General management of specific AEs are described for the rucaparib and sacituzumab govitecan combination are provided in Table 8.B-4. Management of new or worsening pulmonary symptoms is described in Section 8.B.6.4.1.

The protocol allows aggressive medical management of patients in order to avoid dose reduction and dose delay as much as possible. Growth factors should be initiated according to guidelines below and may be used prophylactically as clinically indicated. For patients who could be considered high risk for neutropenia (those who experienced febrile neutropenia or Grade 3-4 neutropenia with prior treatments), use of growth factors may be initiated early on and used prophylactically as early as Cycle 1, except during the DLT period for those patients participating in Phase 1b.

At the discretion of the investigator, the dose of rucaparib and/or sacituzumab govitecan may be held and/or reduced for Grade 2 toxicity that is attributed to either rucaparib or sacituzumab govitecan alone, or in combination, and not adequately controlled by concomitant medications and/or supportive care.

If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred for further evaluation, as clinically appropriate. For clinically significant hematology results, bone marrow analysis and blood cytogenetic analysis should be considered according to standard hematological practice.

If a patient continues to experience the same toxicity despite multiple dose reduction steps to the lowest allowable dose, or if dosing with either study drug is interrupted for > 21 consecutive days (or if 2 consecutive infusions are missed) due to the toxicity, study treatment should be discontinued, unless otherwise agreed upon between the investigator and the sponsor. If either rucaparib or sacituzumab govitecan is interrupted for greater than 21 days, the patient may be discontinued from the study (Section 8.B.6.4.3).

Table 8.B-4 Dose Modification and Retreatment Criteria for Rucaparib and Sacituzumab Govitecan

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			Sacituzumab Govitecan		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
Non-hematological Events							
Adverse event or laboratory abnormality	1 or 2	None[a]	N/A	None[a]	None	N/A	None[a]
Nausea, vomiting, or diarrhea despite maximal systemic antiemetic/antidiarrheal medication administered in standard doses according to institutional guidelines. See Section 8.B.6.5	3 or 4	Hold dose	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[b] **3rd occurrence of same AE:** Discontinue	Hold dose	≤ Grade 2	**1st occurrence:** 25% reduction[b] **2nd occurrence of same AE:** 50% reduction[b] **3rd occurrence of same AE:** Discontinue
Grade 4 non-hematologic toxicity of any duration, **OR** Other ≥ Grade 3 non-hematologic toxicity persisting >48 hours despite optimal medical management, **OR** At time of scheduled infusion, ≥ Grade 3 non-hematologic toxicity, which has delayed dosing by 1 week	3 or 4	Hold dose	≤ Grade 2	**1st or 2nd occurrence** of same AE: Reduce dose[b] **3rd occurrence of same AE:** Discontinue	Hold dose	≤ Grade 2	**1st or 2nd occurrence** of same AE: Reduce dose[b] **3rd occurrence of same AE:** Discontinue

Table 8.B-4 Dose Modification and Retreatment Criteria for Rucaparib and Sacituzumab Govitecan

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			Sacituzumab Govitecan		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
ALT/AST elevation (in the absence of other signs of liver dysfunction)	3	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline to ≤ Grade 2 within 2 weeks or if levels increase	≤ Grade 2	**1st or 2nd occurrence**: Reduce dose[b] **3rd occurrence**: Discontinue	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline to ≤ Grade 2 within 2 weeks or if levels increase. If not recovered within 3 weeks: discontinue	≤ Grade 2	**1st occurrence**: 25% reduction[b] **2nd occurrence**: 50% reduction[b] **3rd occurrence**: Discontinue
ALT/AST elevation	4	Hold; monitor LFTs weekly;	≤ Grade 2	**1st or 2nd occurrence**: Reduce dose[b] **3rd occurrence**: Discontinue	Hold; monitor LFTs weekly;	≤ Grade 2	**1st occurrence**: 25% reduction[b] **2nd occurrence**: 50% reduction[b] **3rd occurrence**: Discontinue
ALT or AST elevations (> 3 × ULN) AND total bilirubin elevation (> 2 × ULN) - suspected DILI [Section 10.9][23,24]	NA	Hold[c]; monitor LFTs weekly;	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently	Hold[c]; monitor LFTs weekly;	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently

Table 8.B-4 Dose Modification and Retreatment Criteria for Rucaparib and Sacituzumab Govitecan

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			Sacituzumab Govitecan		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
				discontinued			discontinued
Hematological Events							
Adverse event or laboratory abnormality	1 or 2	None[a]	N/A	None[a]	None	N/A	None[a]
Anemia	≥ 3	Hold dose[d].	≤ Grade 2	Same or reduced dose[a, c]	Hold dose[d].	≤ Grade 2	Same or reduced dose[a, c]
Severe neutropenia, Grade 4 neutropenia ≥7 days, **OR** Grade 3 febrile neutropenia (absolute neutrophil count <1000/mm^3 and fever ≥38.5°C), **OR** At time of scheduled infusion, ≥ Grade 3 neutropenia which has delayed dosing by 1 week	3 or 4	Hold dose	≤ Grade 2; Growth factors should be used as clinically indicated	**1st occurrence:** Same dose and add GCSF **2nd occurrence:** Reduce dose[b] **3rd occurrence:** Discontinue	Hold dose	≤ Grade 2; Growth factors should be used as clinically indicated	**1st occurrence:** Same dose and add GCSF **2nd occurrence:** 25% reduction[b] **3rd occurrence:** Discontinue
Severe neutropenia that fails to recover to ≤ Grade 2 within 3 weeks	3 or 4	Hold dose	Fails to recover to ≤ Grade 2 within 3 weeks	Discontinue	Hold dose	Fails to recover to ≤ Grade 2 within 3 weeks	Discontinue

Table 8.B-4 Dose Modification and Retreatment Criteria for Rucaparib and Sacituzumab Govitecan

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			Sacituzumab Govitecan		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
At time of scheduled infusion, ≥ Grade 3 non-neutropenic hematologic event which delays dose by 1 week and fails to recover ≤ Grade 2	3 or 4	Hold dose	≤ Grade 2	**1st occurrence:** Same dose **2nd occurrence:** Reduce dose[b] **3rd occurrence:** Discontinue	Hold dose	≤ Grade 2	**1st occurrence:** Same dose **2nd occurrence:** 25% reduction[b] **3rd occurrence:** Discontinue

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice a day; CTCAE = Common Terminology Criteria for Adverse Events; LFT = liver function test; MDS = myelodysplastic syndrome; N/A = not applicable; ULN = upper limit of normal.

[a] At the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity that is attributed to rucaparib and not adequately controlled by concomitant medications and/or supportive care.

[b] For dose reductions see Table 8.B-5.

[c] Evaluate patient for the presence of confounding factors, including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis, that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as INR should be implemented as indicated. If no alternative cause is identified, study drugs must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

[d] If anemia CTCAE Grade ≥3 persists for > 14 consecutive days, or a dependence upon blood transfusions occurs, then weekly complete blood counts should be performed until resolution of the event. If after 42 days of interruption and anemia has not improved to CTCAE Grade ≤ 1, the patient should be referred to hematologist and analysis of the bone marrow with cytogenetic studies and recommended according to standard practice. Bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

8.B.6.4.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur, or a deterioration of pulmonary function is observed, and/or radiologic abnormality is detected in the lungs, and this occurs in the absence of any clear diagnosis, a diagnostic workup (including high resolution computed tomography [CT] scan) in consultation with a pulmonologist should be performed in order to rule out pneumonitis. During this time, treatment with rucaparib may be interrupted or continued per investigator discretion. Sacituzumab govitecan treatment may also be interrupted or continued per investigator discretion. The contribution of sacituzumab govitecan should be assessed independently.

Following investigation, if pneumonitis is not confirmed, treatment may be resumed/continued as deemed appropriate by the investigator and in accordance with the study protocol directions for management of AEs. All confirmed events of pneumonitis should be treated as appropriate per medical judgement and institutional guidelines. If the event resolves and retreatment is being considered, please consult the study Medical Monitor. Retreatment may be resumed at the current or a reduced dose, if appropriate.

Refer to Section 10.7 and Section 10.8 of the protocol for additional information regarding classification and reporting of pneumonitis (and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) as an AESI.

8.B.6.4.2 Rucaparib and/or Sacituzumab Govitecan Dose Reduction

Potential dose reduction steps for rucaparib and sacituzumab govitecan based on different current doses are shown in Table 8.B-5. Rucaparib and sacituzumab govitecan dose reductions will occur in step-wise sequence. Doses lower than rucaparib 300 mg BID are not permitted without consultation with the medical monitor, and doses lower than sacituzumab govitecan 3 mg/kg are not permitted.

Table 8.B-5 Rucaparib and Sacituzumab Govitecan Dose Reductions

Rucaparib		Sacituzumab Govitecan		
			Dose Reduction[a]	
Current Dosage	Dose Reduction[a]	Current Dosage	25%	50%
600 mg BID	500 mg BID	10 mg/kg	7.5 mg/kg	5 mg/kg
500 mg BID	400 mg BID	8 mg/kg	6 mg/kg	4 mg/kg
400 mg BID	300 mg BID	6 mg/kg	4.5 mg/kg	3 mg/kg
300 mg BID	200 mg[b] BID	-	-	

Abbreviations: BID = twice a day; QD = once a day.

[a] No more than 2 dose reductions for the same AE are allowed for either study drug, after which treatment with both study drugs will be discontinued.

Table 8.B-5 Rucaparib and Sacituzumab Govitecan Dose Reductions

Rucaparib		Sacituzumab Govitecan		
			Dose Reduction[a]	
Current Dosage	Dose Reduction[a]	Current Dosage	25%	50%

[b] Consult with sponsor's medical monitor before reducing the dose of rucaparib to this level.

8.B.6.4.3 Rucaparib and/or Sacituzumab Govitecan Discontinuation

Rucaparib and sacituzumab govitecan should be permanently discontinued for any of the following:

- If a patient continues to experience toxicity despite dose reduction steps to the lowest permissible dose for either study drug (see Table 8.B-5) or if dosing with either study drug is interrupted for > 21 consecutive days due to toxicity, treatment with both study drugs should be discontinued, with the following exceptions:
  - Treatment interruption > 21 days may be allowed if approved by the sponsor. Prior to re-initiating treatment for a patient with a treatment interruption lasting > 21 days, the study medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if treatment is interrupted.
- Confirmed diagnosis of MDS/AML;
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued study treatment dosing; or
- Patient with progressive disease. If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the sponsor (Section 5.9).

8.B.6.5 Management of Adverse Events Specific to Sacituzumab Govitecan

8.B.6.5.1 Infusion-related Reactions

Infusion-related reactions are defined as symptoms that occur during and within the first 6 hours after the infusion of sacituzumab govitecan. Symptoms can include: fever, chills, rigors, arthralgias, myalgias, urticaria, pruritus, rash, diaphoresis, hypotension, dizziness, syncope, hypertension, dyspnea, cough, and wheezing, as well as severe hypersensitivity reactions including anaphylactic reactions. Infusion-related reactions should be treated in accordance with best clinical practices and standard institutional guidelines. Because of the potential for life-threatening infusion-related reactions, sacituzumab govitecan should only be administered in a setting in which appropriately trained medical staff, emergency equipment and medications are available in the event that resuscitation is required. NCI

CTCAE v5.0 is used to grade the severity of all infusion related AEs. Premedication for the prevention of infusion-related reactions is described in Section 8.B.6.3.2.

Grade 3 and Grade 4 Events

Grade 3 and Grade 4 infusion-related reactions can include severe or clinically significant cardiopulmonary events and severe allergic reactions such as symptomatic bronchospasm and anaphylactic reactions. Grade 3 infusion-related reactions are defined as those which are prolonged and do not improve with symptomatic treatment and/or brief interruption of treatment, reactions that recur following treatment, and reactions that require hospitalization. Grade 4 reactions include potentially life-threatening reactions, requiring urgent intervention. Severe allergic and anaphylactic reactions should be treated in accordance with best clinical practices and standard institutional guidelines. If Grade 3 or Grade 4 infusion-related reactions occur, sacituzumab govitecan should be permanently discontinued.

Grade 2 Events

Grade 2 infusion-related reactions are defined as those that require infusion interruption and respond to symptomatic treatment; prophylactic medications are indicated for ≤ 24 hours. For Grade 2 infusion-related reactions, the infusion should be interrupted for at least 15 minutes until symptoms resolve. After symptoms resolve, the infusion should be resumed at a slower infusion rate. Recommended infusion rates are provided in Table 8.B-3. For recurrent Grade 2 infusion reactions that fails to recover within 6 hours, despite optimal management, permanently discontinue sacituzumab govitecan.

8.B.6.5.2 Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea are frequent sacituzumab govitecan-associated toxicities. Appropriate treatment, including, as needed, fluid and electrolyte replacement, is required to minimize the risk of serious consequences such as dehydration. Instructions for sacituzumab govitecan dose reduction for treatment-related gastrointestinal toxicities are provided in Section 8.B.6.4.

Nausea and Vomiting

Instructions for the use of premedications for prophylactic treatment of nausea and vomiting and anticipatory nausea are provided in Section 8.B.6.3.2. Do not hold the dose of sacituzumab govitecan for Grade 3 nausea unless Grade 3 nausea persists despite maximal optimal medical management (see Table 8.B-4). Patients should be treated for delayed nausea and vomiting on Days 2 and 3 with 5-HT3 receptor antagonist (ondansetron or palonosetron) monotherapy and other agents if needed. Steroids may be added if symptoms do not resolve with these other agents. Consider olanzapine for persistent or anticipatory nausea; an olanzapine dose of 2.5 mg or 5 mg at bedtime is recommended.

Diarrhea

Dietary modification should be recommended for the management of diarrhea, including a bland diet, small frequent meals, adequate fluid intake of clear liquids to maintain hydration,

and discontinuation of lactose-containing foods and drinks and alcohol. Loperamide should be administered at the onset of treatment-related Grade 1 or Grade 2 diarrhea, at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. If diarrhea is not resolved after 24 hours, add diphenoxylate/atropine.

If diarrhea persists, add octreotide 100 to 150 mcg subcutaneous three times per day. For Grade 3 or Grade 4 diarrhea, the patient should be hospitalized and treated with IV fluids and octreotide. Antibiotics can be administered as clinically indicated.

Patients who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (eg, abdominal cramping, diarrhea, salivation) can receive appropriate premedication (eg, atropine) for subsequent treatments.

8.B.6.5.3 Neutropenia

Complete blood cell counts must be obtained prior to each sacituzumab govitecan infusion and should be administered if absolute neutrophil counts (ANC) meet the following criteria:

- Day 1: ANC > 1500/mm^3
- Day 8: ANC > 1000/mm^3

The routine prophylactic use of growth factors is not recommended; however, they may be used in patients who have experienced febrile neutropenia or Grade 3 or Grade 4 neutropenia following previous infusions. Growth factors may also be administered in the setting of neutropenia in patients at high risk of poor clinical outcomes, including those with prolonged neutropenia, ANC <100/mm^3, febrile neutropenia, and serious infections.

During the DLT-evaluation phase (Cycle 1 for patients in Phase 1b), transfusions may not be used as prophylaxis and should only be used to treat cytopenia considered to be dose-limiting.

8.B.6.6 Treatment Arm B Study Drug Compliance and Accountability

Rucaparib treatment compliance is described in Section 5.7. Study drug accountability is described in Section 5.8.

Each dose of IV sacituzumab govitecan will be prepared by a pharmacist or authorized designee and transferred to an infusion set, in accordance with the protocol and applicable local safe handling procedures. The IV infusion will be monitored by the investigator or designee. Treatment compliance will be monitored by drug accountability, and any preparation of infusion deviations (refer to Section 8.B.6.3.4) will be recorded on the patient's eCRF.

8.B.7 Prior and Concomitant Therapy

See Section 6 for prior and concomitant therapy restrictions and information that is general across all treatment arms of this study. Additional information specific to the rucaparib and sacituzumab govitecan combination arm are described in this section.

See Section 8.B.6.3.2 regarding premedication prior to infusion of sacituzumab govitecan for prevention of infusion reaction.

8.B.7.1 Immunosuppressive Agents

With the exception of the preventative medication described in Section 8.B.6.3.2, immunosuppressive agents are prohibited. However, inhaled or topical steroids, and adrenal replacement steroid doses of up to 20 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. Patients are permitted the use of topical, ocular, intra articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses of up to 20 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded.

8.B.7.2 Other Concomitant Medications

Patients may be medicated during treatment with sacituzumab govitecan as indicated in the judgment of the treating physician to control potential infusion or hypersensitivity responses (see Section 8.B.6.3.2). For anaphylactic reactions, appropriate medical measures (eg, epinephrine, antihistamines, hydrocortisone, and IV fluids) should be taken. Such a patient should not receive additional sacituzumab govitecan and should be discontinued from the study.

As described in Section 8.B.6.5.3, patients receiving sacituzumab govitecan who experience neutropenia will be prescribed growth factors as clinically indicated, including prophylactically. Other hematopoietic growth factors or blood transfusions are allowed at physician's discretion. During the DLT-evaluation phase (Cycle 1 for patients in Phase 1b), transfusions may not be used as prophylaxis and should only be used to treat cytopenia considered to be dose-limiting.

8.B.8 Study Procedures and Methods for Treatment Arm B

8.B.8.1 Schedule of Assessments: Treatment Arm B

Table 8.B-6 summarizes the procedures and assessments to be performed for all patients in Treatment Arm B (Phase 1b and Phase 2).

Table 8.B-7 summarizes the timing of collection of PK and immunogenicity samples for all patients in Treatment Arm B.

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, written informed consent must be obtained from each potential patient prior to any study activities (see Section 11.2). The information on the IRB/IEC-approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand.

The screening period begins with the first study-specific procedure, performed outside standard of care, and only after written consent for study participation has been provided.

Additionally, patients participating in the optional tumor tissue biopsy at the time of radiologic disease progression/treatment discontinuation must provide additional written consent for this procedure.

All procedures and assessments are to be completed within ± 3 days of the scheduled time unless otherwise stated.

Table 8.B-6 Schedule of Assessments for All Patients in Treatment Arm B (Phase 1b and Phase 2)

Study Day	Screening Phase			Treatment Phase (21-day cycles ± 3 days)					Post Treatment Phase	
				Cycles 1 and 2			Cycles 3+			
	Day -56 to Day -1	Day -21 to Day -1	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	End of Treatment	28-day Safety FU[a]
Procedure[b]										
Informed Consent	X									
Medical/Oncology History (Section 7.1)	X									
Tumor Tissue Sample (Section 7.5.1 and Section 8.B.8.2.1)[c]	X									
Physical Examination (Section 7.4.5)		X		X			X		X	X
Vital Signs (Section 7.4.3 and Section 8.B.6.3.3)[d]		X		X	X	X	X	X	X	X
12-lead ECG (Section 7.4.4)		X		X			X		X	
Prior/Concomitant Medications/Procedures (Section 7.2)[e]		X		X	X	X	X		X	X
Disease Assessment/Tumor Scans[f] (Section 7.3.1)		X					X		X	
ECOG Performance Status		X		X			X		X	X
Hematology (Section 7.4.2)			X	X	X	X	X		X	X
Chemistry (Section 7.4.2)			X	X	X	X	X		X	X
Urinalysis (Section 7.4.2)			X							
Serum or plasma Pregnancy Test (WOCBP only) (Section 7.4.2)			X	X			X		X	
CA-125 Measurement for OC patients[g] (Section 7.3.1)			X	X			X		X	
Pharmacogenomics Blood Sample (Section 7.5.3)[h]				X						

Table 8.B-6 Schedule of Assessments for All Patients in Treatment Arm B (Phase 1b and Phase 2)

Study Day	Screening Phase			Treatment Phase (21-day cycles ± 3 days)					Post Treatment Phase	
				Cycles 1 and 2			Cycles 3+			
	Day -56 to Day -1	Day -21 to Day -1	Day -14 to Day -1	Day 1	Day 8	Day 15	Day 1	Day 8	End of Treatment	28-day Safety FU[a]
Procedure[b]										
Blood Sample for ctDNA Analysis (Section 7.5.2)[i]		X		X			X		X	X
Rucaparib Administration[j]				X	X	X	X	X		
Sacituzumab govitecan Administration[j]				X	X		X	X		
Adverse Events[k] (Sections 10.7 and 10.8)	(X)	(X)	(X)	X	X	X	X	X	X	X
Post-progression Tumor Tissue Biopsy (Section 7.5.1)[l]									X	
Blood Sample for PK (Phase 1b)	Refer to Table 8.B-7 for sampling schedule									

Abbreviations: AML = acute myeloid leukemia; CA-125 = cancer antigen 125; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; MDS = myelodysplastic syndrome; OC = ovarian cancer; PK = pharmacokinetics; WOCBP = women of child-bearing potential.

[a] Follow-up Visit should occur 28 days (±7) from the last dose of study drug or can be performed on the date of discontinuation if that date is at least 28 days from last dose, whichever is later. Chemistry and hematology are only necessary at FU visit, if toxicities are present. The FU Visit should be conducted in person.

[b] The study visit window in the treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the patient's investigational product supply. Only 1 cycle of oral study drug will be dispensed to the subject on Day 1 of each cycle.

[c] The tumor tissue sample must be adequate for genomic testing. If archival tissue sample is inadequate or unavailable, a more recently obtained tissue sample will be required prior to enrollment. Refer to the Laboratory Manual for details on tissue adequacy, sample collection and handling instructions.

[d] Vital signs should be assessed prior to the first infusion of sacituzumab govitecan in Cycle 1 and every 15 ± 5 minutes for the first hour and then every 30 minutes until completing IV administration, at completion, and then 30 minutes post infusion. In absence of significant changes, this may be reduced with subsequent doses to prior to infusion, at 30 minutes, and then at completion.

[e] Patients taking warfarin should have INR monitored regularly per standard clinical practice (Section 6.5). Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice (Section 6.6).

[f] Disease assessments to consist of clinical examination and appropriate imaging techniques per RECIST v1.1 will occur every 6 weeks for the first 24 weeks, and then every 9 weeks until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination. Other complementary studies may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. End-of-Treatment scans not required if disease progression determined and patient is not continuing study treatment.

[g] CA-125 measurement should be performed for patients with ovarian cancer at screening and on Day 1 of every subsequent cycle, at treatment discontinuation, as clinically indicated. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and ctDNA sampling.

[h] If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter.

[i] Day 1 of Cycle 1 through Cycle 6 and at the same time as radiological imaging and CA-125 sampling (for OC patients) thereafter, at the End of Treatment, and 28-day Follow-up Visit. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and CA-125 (for OC patients).

[j] First dose of both study drugs in Cycle 1 should be administered within 3 days after enrollment. Rucaparib administration is continuous (not just the days specified in the table). Refer to Section 5.5 (rucaparib) and Section 8.B.6.3 (sacituzumab govitecan) for administration guidelines. Study treatment continues in 21-day cycles until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study. For sacituzumab govitecan dosing, disease assessments (at the end of Cycles 2, 4, 6, 8, 10, and onward) must be completed and reviewed prior to the start of the next cycle. Rucaparib dosing is continuous unless interrupted or stopped for toxicity.

[k] AEs, SAEs, and AESIs that occur after first administration of study drug through to 28 days after last dose of study drug(s). In addition, SAEs that were related to a screening procedure will also be recorded. Ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed to resolution or stabilization. After the Safety Follow-up, only SAEs considered as potentially study drug related (including serious reports of pneumonitis and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML, regardless of causality, will be recorded in the eCRF.

[l] An optional tumor biopsy may be collected at or following disease progression until the start of the next treatment. Additional consent is required. Refer to the Laboratory Manual for details on sample collection and handling instructions.

Table 8.B-7 Pharmacokinetic and Immunogenicity Sample Collections in Treatment Arm B (Phases 1b and 2)

Study Visit		Sacituzumab govitecan PK[a] (All Phase 1b and Phase 2)	Sacituzumab govitecan Immunogenicity (All Phase 1b and Phase 2)	Rucaparib PK (All Phase 1b and Phase 2)
Cycle 1	D1	Predose[b] and 30 min (±5 min) post EOI.	Predose[b]	-
	D8	Predose[b] and 30 min (±5 min) post EOI.	-	Predose[b]
Cycle 3, 5, 7	D1	Predose[b] and 30 min (±5 min) post EOI.	Predose[b]	Predose[b]
	D8	Predose[b] and 30 min (±5 min) post EOI.	-	-
Every 4 cycles after Cycle 7 (eg, 11, 15, etc)	D1	Predose[b] and 30 min (±5 min) post EOI.	Predose[b]	-
	D8	Predose[b] and 30 min (±5 min) post EOI.	-	-
EOT Visit	N/A	X	X	-
Safety Follow-up Visit		X	X	-

Abbreviations: D = Day; EOI = End of Infusion; EOT = End of Treatment; hrs = hours; N/A = not applicable; PK = pharmacokinetics.

[a] Analyses of sacituzumab govitecan and metabolites (SN-38, SN-38G, Total SN-38, total antibody).

[b] Predose refers to collection prior to the morning dose of both rucaparib and sacituzumab govitecan. For rucaparib, the predose should be collected within 30 minutes before the morning dose. If the morning dose on the PK sampling day is on hold or delayed, the predose sample still needs to be collected at approximately 12 hours after the previous dose, if possible. For sacituzumab govitecan, the predose samples should be collected just prior to the administration from the contralateral arm (Section 8.B.8.2.4).

Notes: Collection of the actual time(s) of dose administration on the day prior to the PK Visit (rucaparib only) and during the PK Visit (rucaparib and sacituzumab govitecan) is essential for PK assessment.

Refer to the (Treatment Arm B) Laboratory Manual for details on sample handling and processing.

8.B.8.2 Methods of Data Collection: Treatment Arm B

See Section 7 for methods of data collection that are general across all treatment arms of this study. Additional information specific to the rucaparib and sacituzumab govitecan combination arm are described in this section.

8.B.8.2.1 Biomarker Analyses

The tumor tissue collected for genomic analysis (see Section 7.5.1) will also be used to evaluate the expression of Trop-2 by IHC. The messenger RNA (mRNA) and/or protein levels of Trop-2 may also be evaluated using additional assays.

8.B.8.2.2 Pharmacokinetic and Immunogenicity Evaluations

Samples for rucaparib and sacituzumab govitecan PK and immunogenicity assessments will be collected for all patients, as described in Table 8.B-7. For sacituzumab govitecan, corresponding serum samples designated for either PK or immunogenicity assessments may also be used for either of those analyses, if necessary (eg, insufficient sample volume to complete testing). If dosing is held for toxicity or any other reason on a PK Visit day, plasma samples for rucaparib PK and predose serum samples for sacituzumab govitecan PK and immunogenicity assessments should still be collected on the days and times specified in Table 8.B-7 and below.

8.B.8.2.3 Rucaparib Pharmacokinetic Sample Collection

For all patients, plasma samples are to be collected for trough level PK analysis of oral study drug within 1 hour before the morning dose of rucaparib on Day 8 of Cycle 1 and Day 1 of Cycles 3, 5, 7, as described in Table 8.B-7. Plasma samples are to be collected approximately 12 hours after the last oral dose, but prior to the next oral dose (ie, typically within 1 hour prior to dosing).

A central laboratory will be used for bioanalysis of plasma rucaparib concentration measurement. Please refer to the Laboratory Manual for details on collection and processing of blood PK samples.

8.B.8.2.4 Sacituzumab govitecan Pharmacokinetic Sample Collection

For all patients in Phase 1b and Phase 2, PK samples will be collected for sacituzumab govitecan predose and 30 minutes after the end of infusion on Day 1 and Day 8 of Cycles 1, 3, 5, 7, and every 4 cycles thereafter (eg, Cycle 11, 15, etc.), as well as the End of Treatment Visit and Safety Follow-up Visit, as described in Table 8.B-7.

All time points are relative to the start of IV treatment administration. All on-treatment time points are intended to align with days on which IV treatment is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the IV dose is subsequently delayed, then an additional pre-dose sample should not be collected.

Blood samples should be drawn from a site other than the sacituzumab govitecan IV infusion site (ie, contralateral arm) on days of infusion. All samples collected predose should be collected just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted, the interruption details will also be documented on the eCRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of PK sample collection and processing will be provided to the site in the Laboratory Guidelines. Serum concentration analyses for sacituzumab govitecan will be performed by validated bioanalytical method(s).

8.B.8.2.5 Sacituzumab govitecan Immunogenicity Assessments

Samples for sacituzumab govitecan immunogenicity assessments will be collected for all patients predose on Day 1 Cycles 1, 3, 5, 7, and every 4 cycles thereafter (eg, Cycle 11, 15, etc), at the End of Treatment, and at the Safety Follow-up Visit, as described in Table 8.B-7.

The serum samples will be analyzed for anti-sacituzumab govitecan drug antibodies (ADA) by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to sacituzumab govitecan. The immunogenicity (and corresponding drug exposure) data from these samples will be reported as part of a patient's overall immunogenicity assessment.

Selected serum samples may be analyzed by an exploratory method that measure sacituzumab govitecan or detect ADA for technology exploration purposes; exploratory results will not be reported. Further details of immunogenicity sample collection and processing will be provided to the site in the Laboratory Manual.

8.B.9 Planned Statistical Methods: Treatment Arm B

The statistical methods that are general across treatment arms are described within Section 9.

The determination of sample size for Treatment Arm B, Phase 1b and Phase 2 cohorts are described below.

8.B.9.1 Determination of Sample Size

The total enrollment planned for evaluation of rucaparib in combination with sacituzumab govitecan is up to 194 patients.

Phase 1b is a standard 3+3 dose-escalation design and the overall sample size depends on the occurrence of safety findings, specifically, DLTs, observed at the different dose levels. Up to 55 patients across all dose levels may be enrolled. Additional patients may be enrolled to evaluate other dose levels or schedules as described in Section 8.B.4.2.1. Additional patients may be enrolled into a particular dose cohort if a patient already enrolled into that same dose cohort does not meet the criteria for the DLT-evaluable Population, defined in Section 9.2.

A Simon 2-stage design will be used to evaluate efficacy (confirmed overall response of CR or PR) of rucaparib in combination with sacituzumab govitecan in each of the Phase 2 cohorts. The sample sizes for each pre-specified tumor cohorts in Phase 2 were determined based on a null hypothesis (H_0), which specifies a response proportion that if not reached (response is less than that specified), further investigation would not be warranted, and an alternative hypothesis (H_1), which specifies a response proportion that if observed would warrant further investigation of the rucaparib and sacituzumab govitecan combination treatment in the corresponding cohort.

Phase 2 Cohort B1: Patients with locally-advanced unresectable or metastatic TNBC

Up to 53 patients (24 patients enrolled in Stage 1 and 29 patients enrolled in Stage 2) will be treated to assess efficacy. After the first 24 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 7 of these 24 patients have a confirmed overall response (CR or PR per investigator assessment), the sponsor and key participating investigators will evaluate overall benefit:risk for patients and determine whether or not to continue further enrollment. If 8 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 29 patients will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.30$;
- H_1: $p \geq 0.50$; and
- 90% power at significance level = 0.05 (one-sided).

If Stage 2 is fully enrolled and ≥ 22 out of 53 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and sacituzumab govitecan combination warrants consideration of further investigation in patients with metastatic TNBC.

Phase 2 Cohort B2: Patients with locally-advanced or metastatic UC

Up to 53 evaluable patients (24 patients enrolled in Stage 1 and 29 patients enrolled in Stage 2) will be treated to assess efficacy. After the first 24 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 7 of these 24 patients have a confirmed overall response (CR or PR per investigator assessment), the sponsor and key participating investigators will evaluate overall benefit:risk for patients and determine whether or not to continue further enrollment. If 8 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 29 patients will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.30$;

- H_1: $p \geq 0.50$; and
- 90% power at significance level = 0.05 (one-sided).

If Stage 2 is fully enrolled and ≥ 22 out of 53 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and sacituzumab govitecan combination warrants consideration of further investigation in patients with locally-advanced or metastatic UC.

Phase 2 Cohort B3: Patients with relapsed, platinum-resistant ovarian cancer

Up to 33 evaluable patients (22 patients enrolled in Stage 1 and 11 patients enrolled in Stage 2) will be treated to assess efficacy. After the first 22 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 2 of these 22 patients have a confirmed overall response (CR or PR per investigator assessment), the sponsor and key participating investigators will evaluate overall benefit:risk for patients and determine whether or not to continue further enrollment. If 3 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 11 patients will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.10$;
- H_1: $p \geq 0.30$; and
- 90% power and at significance level = 0.05 (one-sided).

If Stage 2 is fully enrolled and ≥ 7 out of 33 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and sacituzumab govitecan combination warrants consideration of further investigation in patients with relapsed, platinum-resistant ovarian cancer.

8.C TREATMENT ARM C: RUCAPARIB AND M4344

8.C.1 Ataxia telangiectasia mutated and Rad3-related (ATR) Inhibition

The protein kinase ataxia telangiectasia mutated and Rad3-related (ATR) is recruited to junctions of single-stranded and double-stranded DNA, which most commonly arises at sites of replication stress (RS). If left unresolved, this structure rapidly collapses to form a double-strand break (DSB), which can lead to deleterious chromosomal rearrangements or cell death. RS occurs during S-phase when the cell's DNA replication machinery encounters a fragile region of DNA or an unresolved lesion. Treatment of cells with DNA-damaging agents can lead to very high levels of RS as cells progress to S-phase without resolving damage incurred by such agents. The RS pathway is closely associated with a DSB repair pathway mediated by the protein kinase ataxia telangiectasia mutated (ATM)[83] due to frequent interconversion of damaged structures within the cell and because the apical kinases, ATR and ATM, share many downstream substrates. It has been demonstrated that inhibition of ATR in response to RS can lead to activation of ATM and a compensatory DNA repair and survival response.[84] However, for many cancer cells, this compensatory pathway is not available, as ATM signaling is often defective. This most commonly arises from loss-of-function mutations in p53, a principal substrate for ATM, but can also occur from loss of ATM expression or defective activation of ATM.[85-88] Such defects in ATM signaling can cause a dependence on ATR for survival from the RS caused by treatment with DNA-damaging agents.[84,89-93] Accordingly, it is expected that an ATR inhibitor will sensitize many cancer cells to the cytotoxic effects of various DNA-damaging agents. In contrast, noncancer cells have been shown to tolerate combinations of ATR inhibitors and DNA-damaging agents with just a transient increase in growth arrest.[84] High levels of RS are evident in some cancer cells, even in the absence of a DNA-damaging agent resulting from expression of oncogenes that drive dysregulated replication, a hypoxic environment, or from defects in other repair pathways. This high RS in cancer cells can drive a reliance on ATR for survival and, accordingly, ATR inhibitors may have benefit as monotherapy.[94-98]

8.C.2 M4344 Background

Overviews of data from nonclinical and clinical studies are provided below and described in detail in the M4344 IB. M4344 was initially developed under the name "VX 803" by Vertex Pharmaceuticals Incorporated.

8.C.2.1 Mechanism of Action of M4344

M4344 is a potent ATR inhibitor with high selectivity over other kinases and sensitizes many human cancer cell lines to the cytotoxic effects of various DNA-damaging agents. ATR and its downstream kinase CHK1 checkpoint kinase 1 (CHK1), are activated by DNA replication stress and DNA damage, thereby arresting cell-cycle progression allowing time for appropriate damage repair and completion of replication. ATR/ CHK1 blockade prevents DNA damage-induced cell-cycle arrest, resulting in inappropriate entry into mitosis, chromosome aberrations, unequal partitioning of the genome, and ultimately apoptosis.

8.C.2.2 Nonclinical Experience

8.C.2.2.1 Nonclinical Pharmacology

M4344 is a potent and selective inhibitor of ATR kinase. In cellular assays, M4344 blocked ATR activity and showed single-agent cytotoxic activity against some cancer cell lines. Noncancer cells tolerate ATR inhibition with only a transient growth arrest, as attributed to compensatory signaling mediated by ATM. M4344 showed better potency as a single-agent in a panel of cancer cells that harbored the Alternative Lengthening of Telomeres mechanism of telomere maintenance than those with a telomerase mechanism of telomere maintenance.

As monotherapy, orally administered M4344 inhibited tumor growth in a mouse xenograft model of colorectal cancer with defective ATM and expression of oncogenes that drive high RS levels. In combination, M4344 was well tolerated and enhanced the antitumor effects of the DNA-damaging agents cisplatin, carboplatin, irinotecan, and gemcitabine in a dose-dependent manner in mouse xenograft models.

8.C.2.2.2 Nonclinical Pharmacokinetics

M4344 was observed to have a high intrinsic permeability with an apparent permeability coefficient of 19.2×10^{-6} cm/sec (A to B) and 32.1×10^{-6} cm/sec (B to A) in wild-type Madin-Darby Canine Kidney (WT-MDCK) cells. Significant directional efflux of M4344 was observed (efflux ratio of 26.7) at a concentration of 1 μM in the multi-drug resistant protein-1 (MDR-1) transfected MDCK cell line.

Following oral administration, M4344 was rapidly absorbed and exposure increased with dose in rats and dogs. The oral bioavailability in rats, dogs, and cynomolgus monkeys was 49.5%, 67% and 34%, respectively. M4344 was well distributed into tissues after oral administration with a volume of distribution of 0.99 L/kg to 1.84 L/kg in mouse, rat, dog, and monkey.

In vitro protein binding of M4344 was assessed in mouse, rat, dog, and monkey plasma, and to human serum albumin and AAG over the range of 0.15 to 15 μM. A moderate/ high free fraction was observed in all species with indications for saturation of binding at the highest test item concentration of 15 μM, which is not caused by a strong affinity to AAG. In human plasma, M4344 has an average free fraction of 0.319.

M4344 was rapidly taken up into cryopreserved hepatocytes in vitro. The low effect of inhibitors of the transporters OATP-1B1, OATP-1B3 and OCT-1 suggests these transporters do not contribute significantly to the hepatic uptake of M4344.

The primary routes of metabolism for M4344 include CYP3A4 and aldehyde oxidase. All the metabolites detected in human hepatocyte incubations were detected in the in vivo samples from either rat or dog, except the metabolite M11, and latterly the probable aldehyde oxidase simple mono-oxidation product M26 (VRT-1363170)

A low potential for DDI was predicted based on minimal inhibition or induction of CYP isozymes by M4344. UGT1A1-mediated metabolism of bilirubin in human microsomes was

inhibited by M4344 (IC_{50} = 8.36 μM) and its metabolite M26 (IC_{50} = 1.1 μM). In Caco-2/TC7 cells, M4344 was found to inhibit P-gp with an IC_{50} of 39 μM and inhibit BCRP with an IC_{50} of 4.2 μM.

8.C.2.2.3 Toxicology

GLP 28-day toxicology studies were conducted following twice a week (BIW) administration of M4344 of up to 30 mg/kg in rats and up to 4 mg/kg in dogs. The identified hematological toxicity included reductions in white blood cell and red blood cell mass; lymphoid depletion, decreased lymphocytes/extramedullary hematopoiesis in the spleen; extramedullary hematopoiesis in the liver. Testicular toxicity was observed in both species. In addition, gastrointestinal toxicity was reported in dogs. These toxicities are considered reversible. A severely toxic dose to 10% of the population (STD_{10}) in rats was not determined; the highest non-severely toxic dose (HNSTD) in dogs was 2 mg/kg BIW.

M4344 did not affect cardiovascular endpoints in anaesthetized guinea pigs or in conscious dogs at tolerated doses in dedicated cardiovascular studies. M4344 was not mutagenic in a GLP 5-strain bacterial reverse mutation study. An initial photosafety assessment indicated that M4344 absorbs in the ultraviolet-visible range of the electromagnetic radiation spectrum and additional assessments of photosafety are planned for the appropriate phase of clinical development.

8.C.2.3 Clinical Experience

To date, the clinical experience with M4344 is derived from ongoing Study MS201922-0001 (Study 0001), an open-label, first-in-human (FIH) study comprising 3 active Parts (Parts A, A2, and B1). Part A is a dose-escalation study in patients with advanced solid tumors to investigate the safety, tolerability, and PK, as well as establish the MTD and/or RP2D of single-agent M4344 administered BIW and in addition, as QD or BID dosing in Part A2. Part B1 is a dose-escalation study in patients with advanced solid tumors to investigate the safety, tolerability, and PK, as well as establish the MTD and/or RP2D of M4344 administered in combination with carboplatin.

As of 25 May 2018, 40 patients in Part A have received M4344 at doses ranging from 10 to 1,200 mg BIW and 13 patients in Part B1 have received M4344 at doses between 350 mg and 500 mg on Day 2 and Day 9 of a 21-day cycle in combination with carboplatin, administered on Day 1.

8.C.2.3.1 Clinical Pharmacology

Preliminary human PK of M4344 in patients are available for Parts A and B1 from Study 0001. The PK of M4344 was characterized by a moderately fast absorption (maximum concentration [t_{max}] between 1 and 4 hours) followed by a rapid biphasic decline in most patients ($t_{1/2}$of approximately 4 hours). Exposure estimates increased in a roughly dose-proportional manner with increasing dose and with no evidence of study drug accumulation after BIW dosing. The variability in C_{max} and AUC was high and similar on Days 1 and 8 for Part A. The apparent plasma clearance of the drug after oral administration (CL/F) and apparent volume of distribution during terminal phase after oral administration (Vz/F) were

large, ~400 L/hour (approximately 5-times hepatic blood flow) and ~30 L/Kg respectively, suggesting low bioavailability.

The PK of M4344 in Part B1, in combination with carboplatin, were consistent with those observed in Part A.

In all studies, M4344 was administered on an empty stomach, and the effect of food on the absorption of M4344 is currently unknown.

As rucaparib is a weak clinical inhibitor of CYP3A using oral midazolam as a substrate, and both CYP3A4 and aldehyde oxidase are primarily involved in M4344 metabolism, a clinically significant effect of rucaparib on M4344 PK is not expected.

8.C.2.3.2 Efficacy

Preliminary efficacy data (data cut-off date: 25 May 2018) are summarized for 40 patients in Study 0001 Part A (single-agent therapy) and 13 patients in Part B1 (M4344 and carboplatin AUC5). In Part A, 6 of 40 patients (15.0%) had stable disease (SD) as the best overall response; no patients had CR or PR. One patient reporting SD for > 2 years. In Part B1, 4 of 13 patients (30.8%) had SD as the best overall response; no patients had CR or PR.

8.C.2.3.3 Safety

Preliminary safety data (data cut-off date: 25 May 2018) are summarized for 40 patients in Study 0001 Part A who received single-agent therapy at doses ranging from 10 to 1,200 mg BIW and 13 patients in Study 0001 Part B1 who received M4344 at doses of 350 to 500 mg (Days 2 and 9 of a 21-day cycle) in combination with carboplatin at the dose AUC5 (Day 1).

In Part A, all but 1 patient receiving M4344 BIW had AEs, and 36 of 40 patients (90.0%) had at least 1 AE (any Grade) considered by the investigator to be related to study drug treatment. The most common AE was nausea, occurring in 67.5% of patients. Other AEs occurring in at least 25% of patients were vomiting (19 patients, 47.5%), fatigue (17 patients, 42.5%), aspartate aminotransferase increased, and constipation (both 12 patients, 30.0%), blood bilirubin increased (11 patients, 27.5%), and alanine aminotransferase increased (10 patients, 25.0%). Twenty-six patients (65.0%) had AEs of Grade 3 or higher. The most common AE of Grade 3 or higher was blood bilirubin increased (11 patients, 27.5%; in patients treated with ≥ 700 mg). Additionally, a total of 6 patients (15.0%) reported Grade 3 or higher AEs of ALT increased, and 7 patients (17.5%) Grade 3 or higher AEs of AST increased. One patient in Part A had an AE leading to death (death-unknown cause). The investigator noted that this death was related to cancer, not to M4344.

In Part B1, all treated patients had AEs; all patients also reported AEs that were considered by the investigator to be related to M4344 and AEs that were considered by the investigator to be related to carboplatin. The most commonly reported AE was fatigue (10 patients [76.9%]). Twelve patients (92.3%) reported an AE of Grade 3 or higher; the most common was neutropenia (7 patients [53.8%]).

Treatment-emergent AEs that led to discontinuation of study drug in Study 0001 Part A occurred in 13 patients (32.5%), the most common TEAEs leading to discontinuation were blood bilirubin increased and nausea (both reported in 3 patients [7.5%]).

Treatment-emergent AEs that led to discontinuation of study drug in Study 0001 Part B1 occurred in 2 patients (15.4%) in the M4344 500 mg and carboplatin AUC5 group: both patients (15.4%) reported events of neutropenia; and events of thrombocytopenia and ALT increased were reported in 1 patient each (7.7%).

Based on evaluation of safety data from Study 0001, elevations in hepatic transaminases (ALT and AST) have been established as a new important potential risk associated with the administration of M4344.

For M4344, elevation of hepatic transaminases and bilirubin are defined as a treatment-emergent AESIs. Elevations were seen in doses greater than 700 mg BIW. Details on AESIs for M4344 can be found in the current M4344 IB and reporting procedures are in Section 10.10.

In Part A, DLTs confirmed in dose escalation meetings occurred in 3 of 40 patients in the safety set. One patient in the 1,050-mg group had DLTs of ALT and AST increased, blood bilirubin increased, and neutropenia. Two patients in the 1,200-mg group had a DLT of blood bilirubin increased. No DLTs occurred at M4344 doses from 10 to 700 mg BIW.

In Part B1, DLTs confirmed in dose escalation meetings occurred in 4 of 13 patients in the safety set. All DLTs were reported in patients receiving M4344 500 mg and AUC5 carboplatin. Three patients had a DLT of neutropenia; DLTs of febrile neutropenia, gastrointestinal inflammation, thrombocytopenia, and vomiting were reported in 1 patient each.

8.C.2.3.3.1 Adverse Drug Reactions for M4344

Hyperbilirubenemia

M4344 causes hyperbilirubinemia via dose-dependent inhibition of bilirubin glucuronidation by UGT1A1 that has not impaired hepatic function (other than bilirubin metabolism). Before this mechanism was known, increased blood bilirubin and hyperbilirubinemia were reported as DLTs in 3 patients. These 3 events were also reported as SAEs and resulted in study drug withdrawal. After the mechanism of hyperbilirubinemia was determined based on a review of clinical and nonclinical data and outside expert assessment, the definition of a DLT was revised in a 2016 protocol amendment to exclude increases in bilirubin that are assessed as arising from inhibition of bilirubin glucuronidation, as long as the bilirubin level remains below 15 mg/dL (257 µmol/L). After this revision, no DLTs were reported. Overall, DLTs occurred in 3 of 21 patients (14.3%) in the DLT evaluable set; these were the 3 patients experiencing significant hyperbilirubinemia prior to the revision of the DLT definition. This effect has been observed at doses ≥ 300 mg BIW M4344. The onset of increased blood bilirubin is within 1 day of administration of the drug and may be severe (ie, Grade ≥ 3), although elevation of bilirubin due to M4344 has not resulted in any adverse consequences. The incidence of increased blood bilirubin as an SAE is also dose dependent and has been

reported at doses ≥ 700 mg BIW. Both patients in the 1,200 mg BIW dose group, the highest M4344 dose administered in Study 001 Part A, had DLTs of blood bilirubin increased or hyperbilirubinemia. These were also reported as SAEs.

Nausea and Vomiting

In Study 001 Part A, nausea occurred in 67.7% of patients and vomiting in 47.5%. These events have usually been non-serious, Grade 1 or Grade 2. Many of the events of nausea and vomiting occurred on the same day as M4344 administration.

8.C.3 Rationale for Rucaparib and M4344 Combination

PARP inhibitors capitalize upon synthetic lethality by impairing the repair of single-stranded DNA breaks, leading to DNA double-strand breaks, which cannot be repaired efficiently in BRCA1/2 mutant cancers. It has been postulated that PARP inhibitor therapy could be optimized by interfering with cell-cycle checkpoint signaling, thereby further modulating the DNA repair activity. ATR and its downstream kinase CHK1 are activated by DNA replication stress and DNA damage, thereby arresting cell-cycle progression allowing time for appropriate damage repair and completion of replication. ATR/CHK1 blockade prevents DNA damage-induced cell-cycle arrest, resulting in inappropriate entry into mitosis, chromosome aberrations, unequal partitioning of the genome, and ultimately apoptosis.

To this end, it has been postulated that a combination of rucaparib with M4344 could potentially bring about synergistic antineoplastic effects. ATR is recruited to DNA damage lesions during the S and G2 phases of the cell cycle, where it coordinates a series of responses, including checkpoint activation and DNA repair by homologous recombination. PARP inhibition results in double-strand DNA breaks in S-phase and requires ATR activity for efficient DNA repair. Nonclinical data indicate that ATR inhibition increases sensitivity to PARP inhibition[10] and that defects in ATR signaling can potentially result in synthetic lethality with PARP inhibitors.[11] Inhibition of ATR may be a mechanism to overcome primary and acquired resistance to PARP inhibition.

8.C.3.1 Dose and Duration Rationale

The starting doses for the combination of M4344 and rucaparib are selected to provide a safety margin relative to previous clinical experience of each agent as monotherapy and further supported based on preclinical xenograft studies.

A dose-escalation study is currently ongoing to evaluate the safety, tolerability, and PK, as well as establish the MTD and RP2D of M4344 when administered as a single agent in patients with advanced solid tumors (Study 0001). Starting doses were explored in Parts A and A2. A 100-mg dose administered BID (200 mg daily) was selected as the starting dose for Part A2. This starting dose in Part A2 was based on the available clinical experience in 36 patients treated with up to the 1,200 mg BIW dosing schedule in Part A. In Part A, DLTs confirmed in dose escalation meetings occurred in 3 of 40 participants in the safety set (1 patient who received 1,050 mg BIW M4344 and 2 patients who received 1,200 mg BIW M4344). No DLTs were observed at M4344 doses of 10 to 700 mg BIW. The 1,200 mg BIW

schedule results in a total weekly dose of 2,400 mg. A 100-mg dose administered BID results in a total weekly dose of 1,400 mg and is therefore expected to be a tolerable starting dose. The RP2D is still being determined.

Expected gastrointestinal-associated toxicities of nausea, vomiting, and toxicities associated with myelosuppression, such as neutropenia, are potentially overlapping with a rucaparib and M4344 treatment. Additionally, M4344 exposure is associated with dose-dependent hyperbilirubinemia; as well, elevations in hepatic transaminases (ALT and AST) have been established as a new important potential risk associated with the administration of M4344, and rucaparib is associated with transaminase elevation. Given these potentially overlapping toxicities, the initial dose cohort to be evaluated in the Phase 1b will consist of a dose of rucaparib at 50% of the marketed monotherapy starting dose (ie, 300 mg BID) and a dose of M4344 (ie, 50 mg QD) that is 25% of the starting dose in the current monotherapy M4344 Phase 1, part A2 study (100 mg BID). Pharmacokinetic/pharmacodynamic modeling results further suggest that the selected starting M4344 dose of 50 mg QD would result in steady-state plasma exposure of unbound M4344 that is 50% lower than the minimum biologically active exposure in a mouse xenograft model. Incremental increases are planned as described in Section 8.C.4.2.1. Doses of rucaparib and/or M4344 less than aforementioned dose levels or including less frequent dosing or administered on a modified dosing schedule may be evaluated based on unacceptable toxicities observed the initial dose cohort.

8.C.3.2 Expansion Cohorts Rationale

After Phase 1b and determination of the RP2D, the study will evaluate 2 cohorts: patients with ovarian cancer who have progressed on prior PARP inhibitor treatment and patients with solid tumors harboring a deleterious ATM alteration or ATM loss (eg, 0% protein staining based on an IHC assay) who are more susceptible to ATR inhibition.

PARP inhibitors have been well studied in patients with ovarian cancer; therefore, ovarian tumors were selected for inclusion as a Phase 2 expansion cohort. A nonclinical study of olaparib in combination with AZD6738, an ATR inhibitor, was evaluated in a $BRCA^{mut}$ patient-derived xenograft (PDX) model of ovarian cancer.[99] Targeting the ATR/ CHK1 Axis with PARP inhibition results in tumor regression in $BRCA^{mut}$ ovarian cancer models. The authors found that the PARP inhibitor treatment resulted in early activation of ATR/ CHK1 and that the combination PARP inhibitor with the ATR inhibitor was synergistic in suppressing $BRCA^{mut}$ high-grade serous ovarian cancer (HGSOC). In the PDX model, PARP inhibitor and ATR inhibitor combination led to significantly more tumor regression, with 57% of mice having a complete remission compared to no complete remissions in the single-agent PARP inhibitor treatment, and only 14% in the PARP inhibitor and CHK1 inhibitor combination, the other combination being studied. The combination of a PARP inhibitor and ATR inhibitor may have activity in tumors that are PARP inhibitor resistant due to homologous recombination restoration by targeting earlier events in HRR, for example ATM/ATR phosphorylation at sites of DNA damage.

Additionally, there is scientific rationale that a combination of an ATR inhibitor and rucaparib may be effective in tumors harboring a deleterious ATM alteration or ATM loss. The ATR is the primary mediator of an important DNA damage surveillance and repair

pathway that responds to RS.[100] Replication stress arises when the cell's DNA replication machinery attempts to copy through an unresolved damage lesion. Such events are common after cells are treated with DNA-damaging agents. Left unresolved, RS can lead to DSB and cell death. The RS pathway is closely associated with a DSB repair pathway mediated by ATM.[83] Inhibition of ATR in noncancer cells has been shown to lead to activation of a compensatory ATM-mediated response that protects cells from the lethal consequences of unrepaired RS.[84] In contrast, many cancer cells depend on ATR for survival from DNA damage as a result of defects in the ATM-signaling pathway and/or as a result of high background levels of RS that can arise from a number of mechanisms, including expression of certain oncogenes.[85-88] Such defects in ATM signaling can cause a dependence on ATR for survival from RS caused by treatment with DNA-damaging agents.[84,89-93] Accordingly, while noncancer cells have been shown to tolerate combinations of ATR inhibitors and DNA-damaging drugs, it is expected that an ATR inhibitor will sensitize many cancer cells to various DNA-damaging agents.[84] High levels of RS are evident in some cancer cells even in the absence of DNA-damaging agents. This can result from expression of oncogenes that drive dysregulated replication, a hypoxic environment, or from defects in other DNA repair pathways. This high RS in cancer cells can drive a reliance on ATR for survival and thus, ATR inhibitors may have benefit as single agents.[94-98]

8.C.4 Treatment Arm C Study Design

Treatment Arm C of this study will investigate the safety, tolerability, PK, and preliminary efficacy of the PARP inhibitor, rucaparib, in combination with the ATR inhibitor, M4344.

As described in Section 3.1, the treatment arm will consist of 2 phases: Phase 1b is a dose-escalation phase primarily to determine the MTD and RP2D of the combination of rucaparib and M4344; and Phase 2 investigates the RP2D for the combination of rucaparib and M4344 in patients with prespecified tumor types.

For patients enrolled into Treatment Arm C (Phase 1b or Phase 2) of the study, patients will receive rucaparib BID and M4344 QD or BID continuously in 28-day cycles.

8.C.4.1 Treatment Arm C Screening and Enrollment

All patients will undergo screening assessments, including disease status per RECIST v1.1, prior to enrollment, within the time frame specified by the Schedule of Assessments (Table 8.C-4).

Treatment Arm C will enroll patients who have met all of the inclusion criteria and none of the exclusion criteria presented in Section 8.C.5.2 and Section 8.C.5.3, respectively. The criteria may be different depending upon which phase of Treatment Arm C the patient is enrolled; these specific criteria are indicated, as appropriate.

Phase 1b will enroll adult patients with a locally advanced or metastatic solid tumor that has progressed on standard treatment.

Phase 2 will enroll patients into 1 of 2 cohorts:

Cohort C1: Patients with ovarian cancer that have progressed on prior PARP inhibitor therapy

Cohort C2: Patients with locally advanced or metastatic solid tumor with a deleterious ATM alteration or ATM loss (eg, 0% protein staining based on an IHC assay)

Patients enrolled into Cohort C1 will have received prior monotherapy PARP inhibitor treatment as their most recent treatment and have confirmed PR or CR or stable disease for ≥ 6 months on PARP inhibitor prior to disease progression. Maintenance PARP inhibitor treatment following chemotherapy or other treatment is considered an eligible PARP-inhibitor regimen.

8.C.4.2 Treatment Arm C: Treatment Phase

For both Phase 1b and Phase 1 of Treatment Arm C, patients will visit the study site on Day 1 and Day 15 of Cycles 1 and 2, and on Day 1 of every cycle thereafter (see Table 8.C-4).

Patients will be assessed for disease status per RECIST v1.1 every 8 calendar weeks (±1 week) for the first 18 months following initiation of combination study treatment (Cycle 1 Day 1), then every 16 weeks (±1 week) thereafter until radiological disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study termination, or initiation of subsequent anticancer treatments. Responses (CR or PR) must be confirmed with a scan no less than 4 weeks after initial response.

8.C.4.2.1 Phase 1b

Phase 1b is based on a standard 3+3 design as described in Section 3.1.3.1. The first dose of combination study treatment (rucaparib and M4344) will be administered on Day 1 of Cycle 1. The first 28 days of study treatment (Cycle 1) is the DLT-evaluation period. During the DLT-evaluation period, patients will come into the study site for a visit on Day 1 and Day 15.

The initial combination dose consists of oral rucaparib 300 mg BID and oral M4344 50 mg QD. The dose of rucaparib will be escalated in 100 mg BID increments up to a maximum of 600 mg BID. The dose of M4344 will be first increased to 50 mg BID, then increased in increments of 50 mg or 100 mg QD or BID to a maximum dose of 500 mg BID. Once the initial dose has been evaluated and deemed safe and tolerable, parallel cohorts, where the dose of 1 investigational agent remains the same as in the prior cohort while the dose of the other agent is escalated, may be evaluated going forward. For example, a cohort receiving 400 mg BID rucaparib in combination with 50 mg QD M4344 may be evaluated in parallel with a separate cohort receiving 300 mg BID rucaparib in combination with 50 mg BID M4344. In the event that QD or BID dosing of M4344 in combination with BID dosing of rucaparib is not tolerable, alternative dosing schedules may be explored. For example, M4344 may be administered less frequently (eg, evaluation of QD dosing only or administration 2 or 3 times weekly) or a treatment interruption may be introduced (eg, M4344 administered on Days 1 to 14 only). All decisions regarding evaluation of an

alternative dosing schedule will be made between the sponsor and investigators based on available safety, and PK data.

Prior to initiating treatment at each new combined dose level or prior to expanding an existing dose level, a safety teleconference will be held to review patient data, including but not limited to demographics, PK results (if available), study drug combination dosing, concomitant medications, hematology and chemistry, and AEs, and then confer and document agreement that dose escalation and/or expanding an existing dose level is/are considered appropriately safe. Safety teleconferences will include study investigators, the sponsor's medical monitor, and may include other representatives or designees of the sponsor and the study sites.

Dose modifications will be made based on clinical judgement and the dose modification guidance provided in Section 8.C.6.4.

8.C.4.2.1.1 Dose-limiting Toxicity Criteria

A DLT considered for dose escalation in Phase 1b is defined as any of the following occurring within the first 28 days of initiating combination treatment (Cycle 1) that is assessed by the investigator as possibly related to rucaparib and/or M4344 (refer to Section 10.7.4 for consideration of causal relationship). Where applicable, event will be classified, according to NCI CTCAE v5.0.

- Grade 3 or greater febrile neutropenia (ie, fever > 38.3°C with ANC < 1.0×10^9/L) of any duration;
- Grade 3 or 4 neutropenia lasting more than 7 days despite GCSF administration;
- Grade 3 thrombocytopenia (platelets < 50×10^9/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < 25×10^9/L) ≥ 5 days duration;
- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated) or any anemia (regardless of grade or severity) requiring a blood transfusion;
- Any nonhematological AE ≥ Grade 3, with the exception of:
  - Nausea, vomiting, and diarrhea well controlled by systemic medication and with duration ≤ 48 hrs;
  - Fatigue;
  - Grade 3 ALT or AST not accompanied by a concomitant increase in total bilirubin above the ULN. Note: any Grade 4 ALT/AST is a DLT;
  - Increases in indirect bilirubin assessed as arising from inhibition of bilirubin glucuronidation by UGT1A1, provided bilirubin remains below 15 mg/dL (257 µmol/L).

If a patient is not evaluable for a DLT, then an additional patient may be enrolled. For the definition of evaluability, please refer to Section 9.2.

8.C.4.2.1.2 RP2D Selection and Expansion

As described in Section 3.1.3.1.2, once the RP2D of the combination has been provisionally established, up to 10 additional patients may be enrolled and treated in Phase 1b, in order to further characterize safety, tolerability, and PK and confirm that this is the optimal dose combination to evaluate in the Phase 2 portion.

8.C.4.2.1.3 Phase 1b – Cycle 2 and Beyond

Following the DLT-evaluation period, patients will come into the study site for a visit on Day 1 and Day 15 of Cycle 2, and on Day 1 of every cycle thereafter. Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments (Table 8.C-4) and PK Assessments (Table 8.C-5).

After the 28-day DLT-evaluation period, recommendations for rucaparib and M4344 dose modification for the management of specific AEs are provided in Section 8.C.6.4.

Patients tolerating the investigational treatment(s) at the assigned dose combination for at least 4 cycles may be permitted to escalate to the next highest combination dose regimen as long as the new dose regimen is **lower** than that being currently evaluated for safety and tolerability and/or the dose level is the **same or lower** than that determined to be the RP2D. All individual patient dose-escalation steps must be approved by the sponsor's medical monitor.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other anticancer therapy, positive pregnancy test, or termination of the study (Section 3.2). If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the medical monitor (Section 5.9).

8.C.4.2.2 Phase 2 Cohorts

Upon determination of the RP2D from Phase 1b, Phase 2 will be initiated. In Phase 2, the selected RP2D from Phase 1b will be evaluated using Simon 2-stage designs in separate and parallel cohorts (see Section 8.C.9.1). Patients meeting all eligibility criteria will be enrolled into 1 of 2 cohorts as follows:

Cohort C1: Patients with ovarian cancer that has progressed on prior PARP inhibitor therapy

Cohort C2: Patients with locally advanced or metastatic solid tumor associated with a deleterious ATM alteration or ATM loss (eg, 0% protein staining based on an IHC assay)

The Phase 2 cohorts were chosen due to the potential susceptibility to the combination of rucaparib and M4344 (Section 8.C.3.2).

The RP2D of the combination of rucaparib and M4344 may be further adjusted, and/or alternative dosing schedules assessed during Phase 2 based on emerging safety, PK, and efficacy data.

Patients will be monitored for safety, PK, and efficacy as outlined in the Schedule of Assessments (Table 8.C-4) and PK Assessments (Table 8.C-5).

Dose modification guidelines in Section 8.C.6.4 should be followed throughout the Phase 2.

Patients will be treated until disease progression, unacceptable toxicity, patient or investigator request to discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study (Section 3.2). If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the medical monitor (Section 5.9).

8.C.4.3 End of Treatment Arm C and Safety Follow-up

Upon treatment discontinuation, regardless of reason (with the exception of withdrawal of consent or death), patients will have an End of Treatment Visit, and assessments are specified for each treatment arm in the Schedule of Assessments within Table 8.C-4. All patients will be followed for at least 28 days after the last dose of study drug. Safety follow-up assessments are specified for Treatment Arm C in the Schedule of Assessments.

8.C.5 Study Population Selection for Arm C

8.C.5.1 Treatment Arm C: Number of Patients and Sites

In Phase 1b, it is estimated that up to 55 patients will be enrolled, dependent upon the number of dose cohorts enrolled.

In Phase 2, up to 80 patients will be enrolled into the following cohorts:

Cohort C1: Up to 40 patients with ovarian cancer that has progressed on prior PARP inhibitor therapy

Cohort C2: Up to 40 patients with locally advanced or metastatic solid tumor associated with a deleterious ATM alteration or ATM loss based on IHC. (**Note**: no more than 10 patients with ATM loss will be enrolled).

Patients will enroll into either Phase 1b or Phase 2, but a patient cannot enroll into both phases of the same treatment arm. For Phase 2, patients will enroll simultaneously across both cohorts based on separate Simon 2-stage designs for each cohort. Enrollment into Phase 2 for each cohort will continue until the required number of patients for each stage is reached (Section 8.C.9.1).

The enrollment of the 2 phases in Treatment Arm C of the study is approximately 135 patients. It is planned that 3 to 6 sites in the US are expected to participate in Phase 1b of

the study; approximately 25 sites globally may be activated to participate in the Phase 2 portion of the study.

8.C.5.2 Treatment Arm C: Inclusion Criteria

All patients participating in Treatment Arm C must meet all of the following inclusion criteria:

1. Have signed an IRB/IEC-approved ICF prior to any study-specific evaluation;
2. Be ≥ 18 years of age at the time the ICF is signed;
3. Have an ECOG performance status of 0 to 1;
4. Have life expectancy of at least 3 months per investigator discretion;
5. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug:
   a. Bone Marrow Function
      i. ANC ≥ 1.5×10^9/L;
      ii. Platelets > 100×10^9/L;
      iii. Hemoglobin ≥ 9 g/dL
      Note: All hematology values must be achieved without the need for transfusion or growth factors ≤ 14 days prior to the planned start of study treatment (C1D1);
   b. Hepatic Function
      i. AST and ALT ≤ 3 × institutional ULN; if liver metastases, then ≤ 5 × the institutional ULN;
      ii. Total bilirubin ≤ 1.5 × institutional ULN;
      iii. Albumin ≥ 30 g/L (3.0 g/dL).
   c. Renal Function
      i. Creatinine ≤ 1.5 × institutional ULN **OR** eGFR ≥ 45 mL/min using the Cockcroft-Gault formula (Appendix 1);
      ii. Less than or equal to 1+ proteinuria. Patients with ≥ 1+ proteinuria on dipstick must perform have a 24-hour urine collection demonstrating ≤ 1.0 g over 24 hours;
6. Have sufficient archival or more recently obtained FFPE tumor tissue available for genomic analysis (refer to Section 7.5.1);
7. **Phase 1b**: Have a histologically or cytologically confirmed solid tumor that is locally advanced or metastatic and has progressed on standard treatment;
8. **Phase 1b**: Have disease that is evaluable per RECIST v1.1;
9. **Phase 2**: Criteria specific to Phase 2 cohorts:
   a. Have locally advanced or metastatic disease that has progressed on standard treatment;
   b. Have measurable disease as defined by RECIST v1.1;
   AND

c. **For Cohort C1**:
   i. Have EOC, FTC, or PPC that has progressed following monotherapy PARP inhibitor treatment (rucaparib, olaparib, niraparib, or talazoparib);
   ii. PARP inhibitor must have been the last treatment received; maintenance PARP inhibitor treatment following chemotherapy or other treatment is also considered an eligible PARP inhibitor regimen;
   iii. Must have had confirmed PR or CR or SD ≥ 6 months on PARP inhibitor treatment prior to disease progression;
   iv. Must have disease that can be biopsied prior to receiving study drug treatment;

d. **For Cohort C2:**
   i. Must have been previously tested and identified to have a deleterious ATM alteration from tissue or plasma ctDNA results, per local CLIA-certified laboratory. Deleterious ATM alterations include protein truncating mutations, large protein-truncating rearrangements, splice site mutations, and homozygous deletions. Missense mutations would only be acceptable if the variant is classified as "pathogenic" or "likely pathogenic", OR
   ii. Must have ATM loss (eg, 0% protein staining) based on an IHC assay performed in a local CLIA-certified laboratory.

8.C.5.3 Treatment Arm C Exclusion Criteria

Patients who meet any of the following criteria will be excluded from Treatment Arm C:

1. Unable to swallow oral study drug;
2. Have active second malignancy, ie, patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment;

   Note: Patients with a history of malignancy that has been completely treated, with no evidence of active cancer for 3 years prior to enrollment, or patients with surgically-cured low-risk tumors, such as early-stage cervical or endometrial cancer are allowed to enroll. Patients receiving anticancer hormonal therapy in the maintenance setting are allowed to enroll.
3. **For Phase 2, Cohort C2**: Have had prior treatment with any PARP inhibitor;
4. Have symptomatic and/or untreated CNS metastases. Patients with asymptomatic, previously-treated CNS metastases are eligible provided they have been clinically stable (not requiring steroids for at least 8 weeks prior to first dose of study drug) and have had appropriate scans at the screening assessment;
5. Have known HIV or AIDS-related illness, or history of chronic hepatitis B or C, with the exception of patients with sustained virologic response after completion of treatment for hepatitis C;
6. Have received chemotherapy radiation, antibody therapy, or other immunotherapy, gene therapy, vaccine therapy, or experimental drugs ≤ 14 days prior to first dose of study drugs;

7. Have ongoing toxicity from prior cancer treatment ≥ Grade 2 by NCI CTCAE v5.0, except alopecia; additionally, ongoing Grade 2 peripheral neuropathy may be permitted with prior advanced approval from the sponsor;
8. Has had a nonstudy-related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to first scheduled dose of study drug. In all cases, the patient must be sufficiently recovered and stable before treatment administration;
9. For female patients of childbearing potential and all male patients, the following are exclusion criteria, as applicable:
    a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 6 months after the last dose of rucaparib study treatment;
    b. Pregnant or breast feeding;
    c. Women of childbearing potential must not be considering getting pregnant during the study and for 6 months following the last dose of study drug;
    d. Male patients who refuse to use condoms during sex during and up to 6 months after study treatment. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib;
10. Have any serious or unstable concomitant systemic disorder incompatible with the clinical study (eg, substance abuse, psychiatric disturbance, or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism);
11. Have a known history of MDS;
12. Have any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study;
13. Are receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4 that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study;
14. Cannot comply with restrictions for medications or food. Specifically, any subject who must continue on daily antacid therapy, such as, but not limited to, daily proton pump inhibitor (PPI) therapy or daily H2 blocker therapy;
15. Patients of reproductive potential (male and female) must practice an effective method of contraception during treatment and for 6 months following the last dose of rucaparib.

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee.

8.C.5.4 Patients or Partners of Patients of Reproductive Potential

Refer to Section 4.1.

8.C.6 **Study Treatment(s): Arm C**

Refer to Section 5 for rucaparib treatment.

8.C.6.1 Investigational Drug Product – M4344

M4344 (formerly known as VX-803) is an oral formulation. M4344 tablets for oral administration will be supplied to the study sites by the sponsor. A brief description of M4344 is provided in Table 8.C-1 with details in the Pharmacy Manual.

Table 8.C-1 Description of M4344

Drug Name	M4344
INN	M4344
Formulation	M4344 is formulated as immediate release 50 mg tablets for oral administration. Tablets are off-white to yellow and round.
How Supplied	50 mg tablets in bulk bottles, each containing 20 tablets.
Storage Conditions	Tablets should be stored ≤ 25°C with no freezing allowed.

8.C.6.2 M4344 Packaging and Labeling

The sponsor will supply 50 mg M4344 tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for M4344 will be included in the Pharmacy Manual.

8.C.6.3 Preparation and Administration of M4344

M4344, in combination with rucaparib, will be administered orally QD or BID on an empty stomach (abstain from food 2 hours before and 1 hour after dosing) at approximately the same time each day and at the same time as rucaparib. There are no strict requirements regarding the order in which rucaparib and M4344 should be ingested by the patient; however, on PK days, the 2 medications should be dosed as closely together as possible for convenient PK sampling. Administration conditions may be revised based on emerging data regarding food effect on PK of M4344 from other studies.

8.C.6.4 Dose Modification and Retreatment Criteria for Rucaparib and M4344

Toxicities should be managed with supportive care and with dose modification for each of the study drugs according to the attribution of causality for the toxicity based on investigator judgement and consultation with the sponsor, as appropriate. A dose modification of rucaparib or M4344 is permitted, with the other dose remaining constant, if the causality is believed to be related to 1 study drug, but not the other. General management of specific AEs are described for rucaparib and M4344 in Table 8.C-2. Management of new or worsening pulmonary symptoms is described in Section 8.C.6.4.1.

At the discretion of the investigator, the dose of rucaparib and/or M4344 may be held and/or reduced for Grade 2 toxicity that is attributed to either rucaparib or M4344 alone, or in combination, and not adequately controlled by concomitant medications and/or supportive care.

If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred for further evaluation, as clinically appropriate. For clinically significant hematology results, bone marrow analysis and blood cytogenetic analysis should be considered according to standard hematological practice.

If a patient continues to experience the same toxicity despite multiple dose reduction steps to the lowest allowable dose, or if dosing with either study drug is interrupted for > 21 consecutive days due to the toxicity, study treatment should be discontinued, unless otherwise agreed upon between the investigator and the sponsor. If either rucaparib or M4344 is interrupted for greater than 21 days, the patient may be discontinued from the study (Section 8.C.6.4.3).

Table 8.C-2 Dose Modification and Retreatment Criteria for Rucaparib and M4344

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			M4344		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
Non-hematological Events							
Adverse event or laboratory abnormality	1 or 2	None[a]	N/A	None[a]	None[a]	N/A	None[a]
Adverse event or laboratory abnormality[b]	3 or 4	Hold dose	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE**: Discontinue	Hold dose	≤ Grade 2	**1st occurrence**: 25% reduction[c] **2nd occurrence of same AE**: 50% reduction[c] **3rd occurrence of same AE**: Discontinue
ALT/AST elevation (in the absence of other signs of liver dysfunction)	3	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline to ≤ Grade 2 within 2 weeks or if levels increase	≤ Grade 2	**1st occurrence**: Same dose[a] **2nd occurrence of same AE**: Reduce dose[c] **3rd occurrence of same AE**: Discontinue	Continuation of dosing permitted provided total bilirubin is < ULN and ALP is < 3 x ULN; monitor LFTs weekly; Hold if levels do not decline to ≤ Grade 2 within 2 weeks or if levels increase. If not recovered within 3 weeks: discontinue	≤ Grade 2	**1st occurrence**: 25% reduction[c] **2nd occurrence**: 50% reduction[c] **3rd occurrence**: Discontinue

Table 8.C-2 Dose Modification and Retreatment Criteria for Rucaparib and M4344

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			M4344		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
ALT/AST elevation	4	Hold; monitor LFTs weekly.	≤ Grade 2	Reduce dose[c] Monitor LFTs weekly for 3 weeks after restart of study drug; **If > 2nd occurrence**: Discontinue	Hold; monitor LFTs weekly.	≤ Grade 2	**1st and 2nd occurrence**: 50% reduction[c] **3rd occurrence**: Discontinue
ALT or AST elevations (> 3 × ULN) AND total bilirubin elevation (> 2 × ULN) - suspected DILI [Section 10.9][23,24]	NA	Hold[d]; monitor LFTs weekly;	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently discontinued	Hold[d]; monitor LFTs weekly;	≤ Grade 1 (or baseline)	Subject to investigation: reduce dose[c] If DILI is confirmed, treatment should be permanently discontinued
Hematological Events							
Adverse event or laboratory abnormality	1 or 2	None	N/A	N/A	None	N/A	N/A
Adverse event (excluding exceptions below)	3 or 4	Hold dose	≤ Grade 2	**1st occurrence**: Same dose **2nd occurrence of same AE**: Reduce dose[b] **3rd occurrence of same AE**: Discontinue	Hold dose	≤ Grade 2	**1st occurrence**: 25% reduction[c] **2nd occurrence of same AE**: 50% reduction[c] **3rd occurrence**: Discontinue

Table 8.C-2 Dose Modification and Retreatment Criteria for Rucaparib and M4344

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			M4344		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
Anemia	≥ 3	Hold dose[e]	≤ Grade 2	Same or reduced dose[a, c]	Hold dose[e].	≤ Grade 2	Same or reduced dose[a, c]
Instructions Specific to M4344							
Neutropenia	Grade ≥3	Instruction specific to M4344			Hold dose	Resume upon recovery to ≤ Grade 1 within 3 weeks. growth factors should be used as clinically indicated.	Resume at same dose if recovered within 7 days[a]
Grade 4 Neutropenia > 7 days or febrile neutropenia of any duration (fever > 38.3°C with ANC < 1.0×10^9/L)	Grade 4	Instruction specific to M4344			Hold dose	Resume upon recovery to ≤ Grade 1 within 3 weeks. growth factors should be used as clinically indicated	**1st occurr**ence: 25% reduction[c]; add growth factors **2nd occurrence**: 50% reduction[c] **3rd occurrence**: Discontinue
Hyperbilirubinemia	Grade 3	Instruction specific to M4344			Hold dose	≤ Grade 2 with dose held for ≤ 14 days	**1st occurrence**: 25% reduction[c] **2nd occurrence**: 50% reduction[c] **3rd occurrence**: Discontinue

Table 8.C-2 Dose Modification and Retreatment Criteria for Rucaparib and M4344

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib			M4344		
		Treatment Interruption	Re-treatment	Dose Modification	Treatment Interruption	Re-treatment	Dose Modification
Hyperbilirubinemia	Grade 4	Hold	≤ Grade 2	Reduce dose[c]; monitor LFTs weekly for 3 weeks	Hold	≤ Grade 2	**1st or 2nd occurrence**: 50% reduction[c] **3rd occurrence**: Discontinue

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice a day; CTCAE = Common Terminology Criteria for Adverse Events; LFTs = liver function tests; MDS = myelodysplastic syndrome; N/A = not applicable; QD = once a day; ULN = upper limit of normal.

[a] Dosing of either study drug may be resumed at either the same dose or a lower dose, at the discretion of the investigator.

[b] Exceptions include Grade 3 or 4 nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to institutional guidelines.

[c] For dose reductions see Table 8.C-3.

[d] Evaluate patient for the presence of confounding factors including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as INR should be implemented as indicated. If no alternative cause is identified, study drug must be permanently discontinued. Patients should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

[e] If anemia CTCAE Grade ≥3 persists for > 14 consecutive days, or a dependence upon blood transfusions occurs, then weekly complete blood counts should be performed until resolution of the event. If after 42 days of interruption and anemia has not improved to CTCAE Grade ≤ 1, the patient should be referred to hematologist and analysis of the bone marrow with cytogenetic studies and recommended according to standard practice. Bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

8.C.6.4.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening unexplained pulmonary symptoms suggestive of pneumonitis (including, but not limited to, dyspnea) occur, or a deterioration of pulmonary function is observed, and/or radiologic abnormality is detected in the lungs, and this occurs in the absence of any clear diagnosis, a diagnostic workup (including high resolution computed tomography [CT] scan) in consultation with a pulmonologist should be performed in order to rule out pneumonitis. During this time, treatment with rucaparib may be interrupted or continued per investigator discretion. M4344 treatment may also be interrupted or continued per investigator discretion. The contribution of M4344 should be assessed independently.

Following investigation, if pneumonitis is not confirmed, treatment may be resumed/continued as deemed appropriate by the investigator and in accordance with the study protocol directions for management of AEs. All confirmed events of pneumonitis should be treated as appropriate per medical judgement and institutional guidelines. If the event resolves and retreatment is being considered, please consult the study Medical Monitor. Retreatment may be resumed at the current or a reduced dose, if appropriate.

Refer to Section 10.7 and Section 10.8 of the protocol for additional information regarding classification and reporting of pneumonitis (and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) as an AESI.

8.C.6.4.2 Rucaparib and/or M4344 Dose Reduction

Potential dose reduction steps for rucaparib and M4344 based on different current doses are shown in Table 8.C-3. Rucaparib and M4344 dose reductions will occur in step-wise sequence. In the event that the initial dose level exceeds the MTD, other dosing schedules may be explored.

Table 8.C-3 Rucaparib and M4344 Dose Reductions

Rucaparib		M4344		
Current Dosage	Dose Reduction[a]	Current Dosage	Dose Reduction[a]	
			25%	50%
600 mg BID	500 mg BID	500 mg BID	750 mg daily (350 mg AM, 400 mg PM)	250 mg BID
500 mg BID	400 mg BID	400 mg BID	300 mg BID	200 mg BID
400 mg BID	300 mg BID	300 mg BID	450 mg daily (200 mg AM, 250 mg PM)	150 mg BID
300 mg BID	200 mg BID[b]	200 mg BID	150 mg BID	100 mg BID
-	-	100 mg BID	150 mg daily (50 mg AM, 100 mg PM)	50 mg BID

Table 8.C-3 Rucaparib and M4344 Dose Reductions

Rucaparib		M4344		
Current Dosage	Dose Reduction[a]	Current Dosage	Dose Reduction[a]	
			25%	50%
-	-	50 mg BID	None permitted	50 mg QD
-	-	50 mg QD	None permitted	

Abbreviations: AM = morning (dose); BID = twice a day; PM = evening (dose); QD = once a day.

[a] No more than 2 dose reductions for the same AE are allowed for either study drug, after which treatment with both study drugs will be discontinued.

[b] Consult with sponsor's medical monitor before reducing the dose of rucaparib to this level.

8.C.6.4.3 Rucaparib and/or M4344 Discontinuation

Rucaparib and M4344 should be permanently discontinued for any of the following:

- If a patient continues to experience toxicity despite dose reduction steps to the lowest permissible dose for either study drug (see Table 8.C-3) or if dosing with either study drug is interrupted for > 21 consecutive days due to toxicity, treatment with both study drugs should be discontinued, with the following exceptions:
  - Treatment interruption > 21 days may be allowed if approved by the sponsor. Prior to re-initiating treatment in a patient with a treatment interruption lasting > 21 days, the study medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if treatment is interrupted;
- Confirmed diagnosis of MDS/AML;
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued oral study treatment dosing; or
- Patient with progressive disease. If a patient receiving study drug has met criteria for radiologic disease progression by RECIST v1.1 criteria but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted after discussion with the sponsor (Section 5.9).

8.C.6.5 Treatment Arm C Study Drug Compliance and Accountability

Rucaparib treatment compliance is described in Section 5.7, and M4344 compliance will be recorded analogously. Study drug accountability is described in Section 5.8.

8.C.7 Prior and Concomitant Therapy

Refer to Section 6 for prior and concomitant therapy restrictions and information that is general across all treatment arms of this study. Additional information specific to the rucaparib and M4344 combination arm are described in this section.

8.C.7.1 Other Concomitant Medications

Drugs with a known risk for prolonged QT interval and Torsades de Pointes should be avoided.

Because the drug interaction profile of M4344 has not yet been fully characterized, caution should be used when co-administration of medications with M4344. As M4344 is primarily metabolized by CYP3A4 and aldehyde oxidase. For this reason, concomitant administration with potent inhibitors or inducers of CYP3A4 should be avoided.

- Strong CYP3A4 inhibitors include (but are not limited to): clarithromycin, itraconazole, ketoconazole, hepatitis C virus and HIV protease inhibitors, nefazodone, posaconazole, telithromycin, voriconazole, grapefruit juice
- Strong CYP3A4 inducers include (but are not limited to): carbamazepine, rifampin, phenobarbital, phenytoin, St. John's wort

Caution should be used with moderate CYP3A4 inhibitors or inducers (Appendix 2). Alternative medications are recommended.

Drug-drug interactions based on inhibition or induction of aldehyde oxidase have not been well characterized in the literature and the risk of altered drug exposure when administered with potent inhibitors or inducers of aldehyde oxidase is not well understood.

The risk for M4344 as a potent perpetrator drug via inhibition or induction of CYPs, is predicted to be low. There is a moderate theoretical risk for transporter-mediated DDIs with P-gp or BCRP. M4344 and one of its metabolites have the potential to inhibit UGT1A1 at clinical exposures reached with twice weekly dosing (see Section 8.C.2.2).

The solubility of M4344 is expected to decrease significantly at higher pH values. Therefore, concomitant administration of acid-modifying agents such as proton-pump inhibitors, H2 receptor antagonists, and antacids should be discontinued.

8.C.8 Study Procedures and Methods for Treatment Arm C

8.C.8.1 Schedule of Assessments: Treatment Arm C

Table 8.C-4 summarizes the procedures and assessments to be performed for all patients in Treatment Arm C (Phase 1 and Phase 2).

Table 8.C-5 summarizes the timing of collection of PK and pharmacodynamic samples for all patients in Treatment Arm C.

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, written informed consent must be obtained from each potential patient prior to any study activities (see Section 11.2). The information on the IRB/IEC approved consent form should be translated and communicated in the language the patient (or legally authorized representative) can understand.

The screening period begins with the first study-specific procedure, performed outside standard of care, and only after written consent for study participation has been provided.

Additionally, patients participating in the optional tumor tissue biopsy at the time of radiologic disease progression/treatment discontinuation must provide additional written consent for this procedure.

All procedures and assessments are to be completed within ±3 days of the scheduled time unless otherwise stated.

Table 8.C-4 Schedule of Assessments for All Patients in Treatment Arm C (Phase 1b and Phase 2)

Study Day	Screening Phase			Treatment Phase (28-day cycles ± 3 days)			Post Treatment Phase	
				Cycles 1 and 2		Cycles 3+		
	Day -56 to Day -1	Day -28 to Day -1	Day -14 to Day -1	Day 1	Day 15	Day 1	End of Treatment	28-day Safety FU[a]
Procedure[b]								
Informed Consent	X							
Medical/Oncology History (Section 7.1)	X							
Tumor Tissue Sample (Section 7.5.1)[c]	X							
Physical Examination (Section 7.4.5)		X		X		X	X	X
Vital Signs (Section 7.4.3)		X		X	X	X	X	X
12-lead ECG (Section 7.4.4)		X		X		X	X	
Prior/Concomitant Medications/Procedures (Section 7.2)[d]		X		X	X	X	X	X
Disease Assessment/Tumor Scans (Section 7.3.1)[e]		X				X	X	
ECOG Performance Status		X		X		X	X	X
Hematology (Section 7.4.2)			X	X	X	X	X	X
Chemistry (Section 7.4.2)			X	X	X	X	X	X
Urinalysis (Section 7.4.2)			X					
Serum or plasma Pregnancy Test (WOCBP only) (Section 7.4.2)			X	X		X	X	
CA-125 Measurement for OC patients (Section 7.5.2)[f]			X	X		X	X	
Pharmacogenomics Blood Sample (Section 7.5.3)[g]				X				

Table 8.C-4 Schedule of Assessments for All Patients in Treatment Arm C (Phase 1b and Phase 2)

Study Day	Screening Phase			Treatment Phase (28-day cycles ± 3 days)			Post Treatment Phase	
				Cycles 1 and 2		Cycles 3+		
	Day -56 to Day -1	Day -28 to Day -1	Day -14 to Day -1	Day 1	Day 15	Day 1	End of Treatment	28-day Safety FU[a]
Procedure[b]								
Blood Sample for ctDNA Analysis (Section 7.5.2)[h]		X		X		X	X	X
Rucaparib and M4344 Administration[i]				X	X	X		
Adverse Events[j] (Sections 10.7 and 10.8)	(X)	(X)	(X)	X	X	X	X	X
Post-Treatment Tumor Tissue Biopsy (Section 7.5.1)[k]							X	
Blood Samples for PK	Refer to Table 8.C-5 for sampling schedule							

Abbreviations: AML = acute myeloid leukemia; CA-125 = cancer antigen 125; ctDNA = circulating tumor deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; MDS = myelodysplastic syndrome; OC = ovarian cancer; PK = pharmacokinetics; WOCBP = women of child-bearing potential.

[a] Follow-up Visit (FU) should occur 28 days (±7) from the last dose of study drug, whichever is later, or can be performed on the date of discontinuation if that date is at least 28 days from last dose. Chemistry and hematology are only necessary at FU Visit, if toxicities are present. The follow up visit should be conducted in person.

[b] The study visit window in the treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the subject's investigational product supply. Only 1 cycle of oral study drug will be dispensed to the subject on Day 1 of each cycle.

[c] The tumor tissue sample must be adequate for genomic testing. If archival tissue sample is inadequate or unavailable, a more recently obtained tissue sample will be required prior to administration of study drug. Refer to the Laboratory Manual for details on tissue adequacy, sample collection and handling instructions.

[d] Patients taking warfarin should have INR monitored regularly per standard clinical practice (Section 6.5). Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice (Section 6.6).

[e] Tumor scans to be performed every 8 calendar weeks (±1 week) after start of study treatment on Day 1 of Cycle 1 until radiological disease progression. Disease progression will be determined by RECIST v1.1. Patients with OC who meet GCIG CA-125 criteria for disease progression should have a

radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

[f] CA-125 measurement should be performed for patients with ovarian cancer at screening and on Day 1 of every subsequent cycle, at treatment discontinuation, as clinically indicated. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and ctDNA sampling.

[g] If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter.

[h] Day 1 of Cycle 1 through Cycle 6 and at the same time as radiological imaging and CA-125 sampling (where feasible), at the End of Treatment, and the 28-day Follow-up Visit. If a patient discontinues treatment for reasons other than disease progression, then a sample should be taken at the same time as radiological imaging and CA-125 (for ovarian cancer patients).

[i] First dose of both study drugs in Cycle 1 should be administered within 3 days after enrollment. Administration is continuous (not just the days specified in the table). Refer to Section 5.5 (rucaparib) and Section 8.C.6.3 (M4344) for administration guidelines. Study treatment continues in 28-day cycles until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, initiation of any other cancer therapy, positive pregnancy test, or termination of the study.

[j] AEs, SAEs, and AESIs that occur after first administration of study drug through to 28 days after last dose of study drug(s). In addition, SAEs that were related to a screening procedure will also be recorded. Ongoing SAEs, AESIs, or treatment-related Grade 3/4 AEs will be followed to resolution or stabilization. After the Safety Follow-up, only SAEs considered as potentially study drug related (including serious reports of pneumonitis and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML, regardless of causality, will be recorded in the eCRF.

[k] An optional tumor biopsy may be collected at or following disease progression until the start of the next treatment. Additional consent is required. Refer to the Laboratory Manual for detailed on sample collection and handling instructions.

Table 8.C-5 Pharmacokinetic and Pharmacodynamic Sample Collections in Treatment Arm C (Phase 1b and Phase 2)

Study Visit		Pharmacodynamics	M4344 PK	Rucaparib PK
Cycle 1 (Phase 1b[a])	D1[b]	Predose[c] and Post-morning dose: 2.5 hrs	Post-morning dose: 0.5, 1, 1.5, 2.5, 4, 6 and 8 hrs	N/A
	D15[b]	Predose[c] and Post-morning dose: 2.5 hrs	Predose[c] and Post-morning dose: 0.5, 1, 1.5, 2.5, 4, 6 and 8 hrs	Predose[c] and Post-morning dose: 0.5, 1, 1.5, 2.5, 4, 6 and 8 hrs
Cycle 2-4 (Phase 1b[a] and Phase 2)	D1	–	Predose[c]	Predose[c]

Abbreviations: D = Day; hrs = hours; N/A = not applicable; PK = pharmacokinetics.

[a] Phase 1b includes patients in the dose-escalation phase and the RP2D expansion.

[b] Doses of rucaparib and M4344 must be taken at the same time on an empty stomach, ie, at least 2 hours prior and 1 hour after any meal. For Phase 1b for Cycle 1 Day 1 (M4344) and Day 15, a time window of ±5 minutes for specimen collections up to 2 hours and ±15 minutes from 3 to 8 hours.

[c] Predose refers to collection prior to the morning dose of both rucaparib and M4344. The predose specimen collection should be performed within 30 minutes before taking the next dose of study drug.

Notes: Collection of the actual time(s) of dose administration is essential for both rucaparib and M4344 (this includes the time of the last administration before the D1 and D15 predose samples).
Refer to the (Treatment Arm C) Laboratory Manual for details on sample handling and processing.

8.C.8.2 Methods of Data Collection: Arm C

See Section 7 for methods of data collection that are general across all treatment arms of this study. Additional information specific to the rucaparib and M4344 combination arm are described in this section.

8.C.8.2.1 Pharmacokinetic Sample Collection

For all patients in Phase 1b and Phase 2, plasma samples are to be collected for trough level PK analysis of oral study drug within 1 hour before the morning dose (ie, typically within 30 minutes prior to dosing) of rucaparib and M4344 on Day 15 of Cycle 1 (Phase 1b) and on Day 1 of Cycles 2, 3, and 4 (both phases). Plasma samples are to be collected approximately 12 hours after the last oral dose of rucaparib and approximately 12 hours (BID) or 24 hours (QD) after the last oral dose of M4344.

In addition, for all patients in Phase 1b, intensive PK samples will be collected for M4344 on Day 1 and Day 15 of Cycle 1, and for rucaparib on Day 15 of Cycle 1 (a). For Phase 1b for Cycle 1 Day 1 (M4344) and Day 15 (both study drugs), a time window of ±5 minutes for specimen collections up to 2 hours and ±15 minutes from 3 to 8 hours.

Date and time of dose of rucaparib and M4344 are to be recorded on the eCRF for doses taken on PK sample days, as well as date and time for the last rucaparib and M4344 administrations taken prior to the predose samples (both Phase 1b and Phase 2), together with the date/time of all plasma PK samples.

A central laboratory will be used for bioanalysis (concentration measurements) of plasma rucaparib and/or M4344 and its metabolites. Please refer to the Laboratory Manual for details on collection and processing of blood PK samples.

Samples obtained for PK analyses may be used for the future metabolite identification and/or other exploratory evaluations.

8.C.8.2.2 Pharmacodynamic Sample Collection

Blood samples will be collected at the indicated time points (Table 8.C-5) for pharmacodynamic analyses. Biomarkers of PARP and/or ATR inhibition such as γH2AX, which is a biomarker associated double-strand DNA breaks, will be analyzed in these samples. Details on the collection, processing, and shipment of these samples are in the Laboratory Manual.

8.C.9 Planned Statistical Methods: Treatment Arm C

The statistical methods that are general across treatment arms are described within Section 9.

The determination of sample size for Treatment Arm C, Phase 1b and Phase 2 cohorts are described below.

8.C.9.1 Determination of Sample Size

The total enrollment planned for evaluation of rucaparib in combination with M4344 is approximately 135 patients.

Phase 1b is based on a standard 3+3 dose-escalation design, and the overall sample size depends on the occurrence of safety findings, specifically, DLTs, observed at the different dose regimens. A minimum of 6 and maximum of approximately 55 patients across all dose cohorts may be enrolled. Additional patients may be enrolled to evaluate other dose levels or schedules as described in Section 8.C.4.2.1. Additional patients may be enrolled into a particular dose regimen if a patient already enrolled into that same dose regimen does not meet the criteria for the DLT-evaluable population, defined in Section 9.2.

A Simon 2-stage design will be used to evaluate efficacy (confirmed overall response of CR or PR) of rucaparib in combination with M4344 in each of the Phase 2 cohorts. The sample sizes for each Phase 2 cohort were determined based on a null hypothesis (H_0), which specifies a response proportion that if not reached (response is less than that specified), further investigation would not be warranted, and an alternative hypothesis (H_1), which specifies a response proportion that if observed would warrant further investigation of the rucaparib and M4344 combination treatment in the corresponding cohort.

Phase 2 Cohort C1: Ovarian Cancer Patients who have Progressed on Prior PARP Inhibitor Therapy

Up to 40 patients (22 patients enrolled in Stage 1 and 18 patients enrolled in Stage 2) will be used to evaluate efficacy. After the first 22 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 2 of these 22 patients have a confirmed overall response (CR or PR per investigator assessment), the sponsor and key participating investigators will evaluate overall benefit:risk for patients and determine whether or not to continue further enrollment. If 3 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 18 patients will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.10$;
- H_1: $p \geq 0.25$; and
- 80% power at significance level = 0.05 (one-sided).

If Stage 2 is fully enrolled and ≥ 8 out of 40 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and M4344 combination warrants consideration of further investigation in patients with ovarian cancer previously-treated with a PARP inhibitor.

Phase 2 Cohort C2: Patients with a Solid Tumor Associated with a Deleterious ATM Alteration or ATM Loss

Up to 40 patients (22 patients enrolled in Stage 1 and 18 patients enrolled in Stage 2) will be used to evaluate efficacy. After the first 22 patients either a) complete 16 weeks of study treatment or b) discontinue study treatment prior to completing 16 weeks, an interim (Stage 1) analysis will be performed. If ≤ 2 of these 22 patients have a confirmed overall response (CR or PR per investigator assessment), then the sponsor and key participating investigators will evaluate overall benefit:risk for patients in both the ATM alteration and ATM loss subgroups and determine whether or not to continue further enrollment. If 3 or more patients in Stage 1 have a confirmed overall response, then enrollment of the additional 18 patients in Stage 2 will be completed.

Characteristics of this design include:

- H_0: $p \leq 0.10$;
- H_1: $p \geq 0.25$; and
- 80% power at significance level = 0.05 (one-sided).

If Stage 2 is fully enrolled and ≥ 8 out of 40 total patients have a confirmed overall response, then per the design, the null hypothesis is rejected, and the rucaparib and M4344 combination warrants consideration of further investigation in patients with a solid tumor associated with a deleterious ATM alteration or ATM loss.

9 PLANNED STATISTICAL METHODS: ALL TREATMENT ARMS

The statistical methods described within this section are general across treatment arms. The determination of sample size for each treatment arm, as well as additional analyses or deviations from the descriptions below are described in **Section 8.X.9** of the respective treatment arm and/or will be described in the statistical analysis plan (SAP) for this study.

9.1 General Considerations

For Phase 1b, summary tables will generally present data by dose cohort and by all patients enrolled. For Phase 2, summary tables will present data by expansion cohort.

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

The Kaplan Meier methodology will be used to summarize time-to-event variables.

Unless otherwise specified, all data will be used to their maximum possible extent but without any imputations for missing data. Unless otherwise specified, baseline is defined as the last measurement prior to the first dose of study drug.

All statistical analyses will be conducted with the statistical analysis software (SAS®) System, Version 9.3 or higher. Further details around the statistical analyses planned in this study will be outlined in the SAP.

9.2 Analysis Populations

- **DLT-evaluable Population** (Phase 1b): All patients in Phase 1b who have either received at least 80% of the planned doses of rucaparib and the second study drug (for Treatment Arm B, both planned infusions of the second study drug must be received) without having experienced a DLT or who experienced a DLT during Cycle 1. If a patient withdraws from the study without having met any of these criteria, then an additional patient will be enrolled in that dose cohort.
- **Safety Population**: All patients who have received at least 1 dose of rucaparib or the second study drug. This will be the primary population for analyses of safety for Phase 1b and for each expansion cohort in Phase 2.
- **Efficacy Population**: All patients who have received at least 1 dose of rucaparib or the second study drug and who have measurable disease per RECIST v1.1 at baseline. This will be the primary population for analyses of efficacy in Phase 1b and each expansion cohort in Phase 2.

9.3 Demographics and Baseline Characteristics

All demographic (eg, age, race, and ethnicity as allowed by local regulations) and baseline characteristics will be summarized for the Safety Population, separately for Phase 1b and Phase 2. The following variables, as appropriate, will be summarized with frequency tabulations:

- Time since diagnosis (months): > 12 to 24, > 24
- Baseline laboratory parameters: graded based on CTCAE
- Molecularly defined subgroups based on HRD and other definitions as appropriate;
- If applicable, progression-free interval following the last platinum regimen received (months); 0-6, > 6;
- Number of prior anticancer regimens; also split out by
  - Number of prior chemotherapy regimens
  - Number of prior platinum-based regimens.

Descriptive statistics may also be used to summarize the continuous variables.

9.4 Efficacy Analyses

The analysis of all efficacy endpoints will be based on the RECIST v1.1 criteria as assessed by the investigator and performed using the Efficacy Population.

9.4.1 Efficacy Endpoints

The primary efficacy endpoint for each expansion cohort in Phase 2:

- Objective response.

Secondary efficacy endpoints include:

- Duration of response (DOR; Phase 2),
- Progression-free survival (PFS; Phase 2),
- Objective response (Phase 1b).

9.4.2 Primary Efficacy Analysis

The primary efficacy endpoint for each expansion cohort in Phase 2 will be analyzed by calculating the ORR. ORR is defined as the proportion of patients with a documented and confirmed best overall response of CR or PR as assessed by the investigator. A confirmed CR or PR is a response that is maintained and documented on a subsequent tumor assessment no less than 4 weeks after initial response.

The frequency and percentages of patients with a best overall response of CR, PR, SD, or PD will be summarized. ORR (confirmed CR + PR) will also be summarized with frequencies and percentages. All summaries of response rate will be accompanied by 95% CIs. Objective response as a secondary endpoint for Phase 1b of the study will be analyzed in a similar manner as for the Phase 2 efficacy analysis.

9.4.3 Secondary Efficacy Analyses

9.4.3.1 Progression-free Survival

PFS will be calculated as 1+ the number of days from the first dose of study drug to documented radiographic progression, according to RECIST v1.1, as determined by the investigator, or death due to any cause, whichever occurs first. Patients without a documented event of radiographic progression will be censored on the date of their last adequate tumor assessment (ie, radiologic assessment), or date of first dose of study drug if no post-baseline tumor assessments have been performed. Only tumor scans prior to start of any subsequent anticancer treatment are included.

The Kaplan-Meier methodology will be used to summarize PFS. If able to be estimated, the 50th (median) percentile together with a 95% CI, will be presented. The number of patients with events and the number of patients at risk at each timepoint will be presented, and censored patients will be graphically displayed.

9.4.3.2 Duration of Response

For any Phase 2 patient who reached a best response of CR or PR, DOR will be measured from the date that best response is first recorded until the first date that PD is documented per RECIST v1.1. DOR will be summarized as a time to event variable. For patients who continue treatment post-progression, the first date of progression will be used for the analysis. Patients without a documented event of radiographic progression will be censored on the date of the last adequate tumor assessment.

The Kaplan-Meier methodology will be used to summarize DOR. If able to be estimated, the 50th (median) together with a 95% CI, will be presented. The number of patients with events and the number of patients at risk at each timepoint will be presented and censored patients will be graphically displayed.

9.5 Safety Analyses

All safety analyses will be summarized for the Safety Population separately for each treatment arm. Within a treatment arm, safety analyses will be summarized by dose cohort and pooled for all patients in Phase 1b and by expansion cohort in Phase 2.

Safety endpoints are incidence of AEs, clinical laboratory abnormalities, and dose modifications.

AEs, clinical laboratory results, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/ procedures will be tabulated and summarized.

9.5.1 Safety Endpoints

The primary safety endpoint for Phase 1b is the incidence of Grade 3 or 4 AEs and clinical laboratory abnormalities defined as dose-limiting toxicities DLTs.

Secondary safety endpoints (both Phase 1b and Phase 2) include the incidence of AEs, clinical laboratory abnormalities, vital signs, and ECG results.

9.5.2 Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v5.0. TEAEs are defined as AEs with onset date on or after the date of first dose of study drug until 28 days after the last dose of study drug.

The number and percentage of patients who experienced TEAEs for each SOC and preferred term will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

Separate tables will be presented as follows:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs (rucaparib and/ or second study drug);
- Serious TEAEs;
- Treatment-related serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study drug (rucaparib and/ or second study drug);
- TEAEs resulting in interruption/delay of study drug (rucaparib and/ or second study drug); and
- TEAEs resulting in dose reduction of study drug (rucaparib and/ or second study drug).

The incidence of TEAEs will be summarized by relationship to study drug (rucaparib and/ or second study drug) according to the following categories: “treatment-related,” or “not treatment-related”. If a patient experiences multiple occurrences of the same AE with different relationship categories for one study drug, the patient will be counted once, as a relationship category of treatment related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a

missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least 1 TEAE of the given grade will be summarized.

9.5.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology and chemistry. The laboratory values will generally be presented in International System of Units (SI). The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug or the last Safety Follow-up Visit, whichever is later. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum, and last value during the on-treatment period.

Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (ie, those that meet Grade 3 or Grade 4 criteria according to CTCAE).

9.5.4 Vital Sign Measurements

The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug or the last Safety Follow-up Visit, whichever is later. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, standard deviation [StD], minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, StD, minimum, median and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

9.6 Pharmacokinetic Analysis

In the Phase 1b portion, blood sampling for PK analyses of both rucaparib and the second study drug will be conducted in all patients. The PK parameters will be determined using non-compartmental methods. Area under the curve from time zero to the last observation ($AUC_{0\text{-last}}$) will be calculated using the trapezoid rule. The $t_{1/2}$ and the AUC from time 0 to infinity ($AUC_{0\text{-inf}}$) will be calculated from the estimated k_{el}, as appropriate. Other parameters to be determined are C_{max}, C_{min}, t_{max}, V_{ss}/F, and CL/F, which will be estimated and reported, as data allow.

9.7 Exploratory Analysis

Tumor tissue and blood specimens will be used for pharmacodynamic assessment of rucaparib and/or the second study drug activity to explore biomarkers that may be predictive of response or resistance to rucaparib and/or the second study drug. Biomarkers and changes in biomarker status may also be investigated for associations with rucaparib and/or the second study drug exposure and safety.

The goal of the exploratory analyses is to assess potential relationships between biomarkers and the efficacy and safety of the study drug combination. The biomarkers to be evaluated include, but are not limited to, genomic alterations in tissue and blood, genomic LOH, other expression or genomic signatures, circulating growth factors and/or cytokines, and where applicable, PK parameters. Where possible, changes in these biomarkers from pretreatment to timepoints during and post-treatment will also be evaluated. Given the exploratory nature of these analysis, no formal hypothesis testing is planned.

9.8 Interim Analysis

An interim analysis of ORR by RECIST v1.1 criteria per investigator for each Phase 2 cohort will be performed as specified for each treatment arm. Enrollment in the cohort may continue while the interim analysis is being prepared. If the continuance criteria are not met, the sponsor and key investigators will evaluate the overall benefit:risk for patients and provide a recommendation whether further enrollment should continue.

Additionally, at any point throughout the study, the study may be terminated early due to unacceptable safety risk assessed by emerging data, or unacceptable toxicity observed. The sponsor may terminate the treatment arm or study electively or if required by regulatory decision. If the treatment arm or study is terminated prematurely, the sponsor will notify the investigators and regulatory agencies of the decision and reason for termination. Investigators will be required to notify the IRBs and IECs, accordingly.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a non-leading question (eg, "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). Symptoms reported spontaneously by the patient during the physical examination would also qualify as an AE (and hence documented on the AE eCRF, not on the physical examination eCRF, which is reserved for physical signs or findings).

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (or, occurs after informed consent is given and prior to dosing if the SAE is related to a study procedure) that:

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drug through 28 days after last dose of either study drug) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity
- Results in a congenital anomaly or birth defect
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

10.3 Definition of Adverse Events of Special Interest

AESIs (serious or nonserious) are defined as AEs of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study sponsor to other parties (eg, regulators) might also be warranted.

AESIs for rucaparib include MDS, AML and any AE of pneumonitis (including the following similar event terms: interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia). Details on AESIs for M4344 can be found in the current M4344 IB. There are

no specified AESIs for either lucitanib or sacituzumab govitecan within the respective IBs for these drugs.

All AESIs, irrespective of causality assessment and severity, are to be reported to the sponsor within 24 hours (see Section 10.10 for reporting instructions).

10.4 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care);
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward);
- Overdose of either study drug or concomitant medication unless associated with an SAE. However, the event should still be captured as a nonserious AE on the appropriate eCRF page;
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE or an SAE;
- Events that meet the SAE criteria (as outlined in Section 10.2) and occur after informed consent but before the first dose of study drug, which are considered unrelated to screening procedures.

10.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess and document the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality;
- Intervention for management of the abnormality is required;
- At the discretion of the investigator should the abnormality be deemed clinically significant.

10.6 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the course of the study, study drug(s) should be held immediately.

Pregnancy is not considered to be an AE or SAE; however, all pregnancies and partner pregnancies occurring during study participation or within 6 months of last dosing must be reported to the sponsor using the Pregnancy Report Form within the same timelines as for an SAE.

All pregnancies will be followed through to outcome. Once the outcome of a pregnancy is known, the Pregnancy Outcome Report Form will be completed and reported to the sponsor.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/ AESI processes using the appropriate AE or SAE/ AESI forms.

10.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Events that occur after signing of informed consent but prior to initiation of study drug(s), unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF. Any AE that occurs after first dose of study drug(s) through 28 days after receiving the last dose of study drug(s), will be recorded on the AE eCRF. After the 28-day reporting window after discontinuation of assigned treatment, only SAEs assessed as related to study drug(s) (including serious reports of pneumonitis and similar events, ie, interstitial lung disease, alveolitis, necrotizing alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and all AESIs of MDS and AML, irrespective of causality, need to be reported. AEs of pneumonitis and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, should only be reported as an AESI up to, but not beyond, the Post-treatment Follow-up Visit (28 days after the last dose of study drug(s). Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.8.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

Each AE is to be evaluated for **causal relationship** to the investigational drug(s), severity, and seriousness. The action taken and the outcome must also be recorded.

SAEs and AESIs that occur during the study or within 28 days after receiving the last dose of study drug(s), whether or not related to study drug(s), must be reported immediately (ie, **within 24 hours** of knowledge of the event or additional information for a previously

reported event) to the sponsor/SAE designee. The contact information for reporting of SAEs/AESIs can be found on the SAE/ AESI Reporting Form.

10.7.1 Onset Data of Adverse Events

The onset date is the date that the event or the signs or symptoms related to the event started.

10.7.2 Resolution Date of Adverse Events

The resolution date is the date that the event or the signs / symptoms related to the event resolved or resolved with sequelae or enter the resolution date as the date when the patient has reached a new baseline if event is not expected to resolve.

10.7.3 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, v5.0 .[101]

Severity is not the same as serious.

For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Life-threatening events require urgent intervention to prevent death
- Fatal events are events that lead to the patient's death

10.7.4 Causal Relationship of Adverse Events to Study Drug

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge with the study drug(s) (Table 10-1).

Table 10-1. Causal Relationship of Adverse Events to Study Drug

Not Related to Study Drug	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.). • It does not follow a reasonable temporal sequence from administration of the study drug. • It does not follow a known pattern of response to study drug. • It does not reappear or worsen when study drug is restarted. • An alternative explanation is likely, but not clearly identifiable.
Related to Study Drug	• An AE that is difficult to assign to alternative causes. • It follows a strong or reasonable temporal sequence from administration of study drug. • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. • It follows a known response pattern to study drug. • It is confirmed with a positive rechallenge or supporting laboratory data.

10.7.5 Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug (note all that apply)

- None
- Dose reduced/delayed
- Study drug temporarily interrupted
- Study drug permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Recovering/ Resolving/ Improving

- Ongoing
- Death
- Lost to follow-up

10.8 Follow-Up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 28 days after the last dose of study drug(s). Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, death, or until lost to follow-up. After the 28-day window, treatment-related SAEs (including serious reports of pneumonitis and similar events, ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia, if considered to be related to study drug), and AESIs of MDS and AML, irrespective of causality, need to be reported.

10.9 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs must be reported as SAEs (see Section 10.10 for reporting details).

Potential drug-induced liver injury is defined as:

1. ALT or AST elevation > 3 × ULN

AND

2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum or plasma alkaline phosphatase)

AND

3. No other immediately apparent possible causes of ALT/AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

10.10 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting

It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report. For reporting SAEs/AESIs or pregnancies, use the applicable report forms. The contact information for reporting of SAEs and AESIs can be found on each of the forms.

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the US FDA, according to 21 Code of Federal Regulations (CFR) 312.32; to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

The sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

11 STUDY ADMINISTRATION

11.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol and applicable Standard Operating Procedures (SOPs) and in compliance with International Council for Harmonisation (ICH) E6(R2); FDA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki. The ethical principles underlying European Union Directives 2001/20/EC, 2005/28/EC, Eudralex Volume 10, and the US Code of Federal Regulations, (21CFR Parts 50, 54, 56, and 312), and applicable local requirements.

The principal investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB/IEC, and local health authority (where applicable), except where necessary to eliminate an immediate hazard(s) to the trial patients.

Noncompliance with the protocol, SOPs, Good Clinical Practice (GCP), and/or applicable regulatory requirement(s) by an investigator/institution, or by members(s) of sponsor staff or its representatives will lead to prompt action by the sponsor to secure compliance. If monitoring and/or auditing identifies serious noncompliance on the part of an investigator/institution, the sponsor will take steps to secure compliance or terminate the investigator/institutions participation in the study. When an investigator/institution's participation is terminated because of noncompliance, the sponsor will promptly notify the regulatory authority(ies).

All potential serious breaches of GCP must be reported to the sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

11.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval prior to the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 (or equivalent) when participating in a US Investigational New Drug (IND) study and provide the completed form according to written instructions to the sponsor (or designee). In addition, local statement of investigator documents must be provided where required. Each investigator must submit to the sponsor (or designee) financial disclosure information if required by national law and/or local regulations.

The study will be registered on www.clinicaltrials.gov, European Clinical Trials Database (EudraCT), and other applicable study registry systems as appropriate. Data generated from this study must be handled in accordance with any laws, rules, and regulations related to the privacy of personal data or medical information applicable in the jurisdiction where the data is processed, including without limitation, the US Health Information Portability and Accountability Act of 1996 (HIPAA), and its implementing regulations, and the EU General Data Protection Regulation 2016/679 (GDPR).

11.1.2 Institutional Review Board or Independent Ethics Committee Approval

This protocol, the IB for each study drug, and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) must be reviewed and approved by IECs/IRBs before study start. This also applies to protocol amendments (note: this applies to substantial amendments in the EU).

The sponsor will supply relevant data for the investigator to submit the study protocol and additional study documents to the IRB/IEC. The study protocol will be submitted review and approval by an IEC/ IRB, according to national law and/or local regulations, and will provide the IRB/IEC with all appropriate materials.

Verification of the IEC's/IRB's unconditional approval of the study protocol and the written ICF will be transmitted to the sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review and approval.

No patient will be admitted to the study until appropriate IRB/IEC approval of the study protocol and ICF/patient information sheet (PIS) have been received, the investigator has

obtained the signed and dated informed consent form, and the eligibility criteria has been satisfied and confirmed.

The principal investigator will submit appropriate reports on the progress of the study to the IEC/ IRB at least annually in accordance with applicable national law and/ or local regulations and in agreement with the policy established by the IRB/IEC and sponsor.

The IRB/IEC must be informed by the principal investigator of all subsequent study protocol amendments (substantial amendments in the EU) and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study, according to institutional policies.

11.2 Patient Information and Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from all patients participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

The ICF, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IRB/IEC and be acceptable to the sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version used and approved by the relevant IRB/IEC. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legally-authorized representatives [where acceptable according to national law and/or local regulations], if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. Both the patient and the person explaining the study and with whom the patient can discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original ICF will be filed in the investigator file unless otherwise agreed. The process of obtaining informed consent will should be documented in the patient's source documents. The date when a patient's informed consent was actually obtained will be captured in the patient's CRF.

11.3 Patient Confidentiality

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient identifiers such as initials, year of birth, and an identification code (ie, not names) should be recorded on any form submitted to the sponsor and the IRB/IEC, as far as permitted by applicable local requirements. The investigator must record all screened and enrolled patients in the eCRF. The investigator must maintain a list with the identity of all treated patients, but not intended for use by the sponsor.

The investigator agrees that all information received from the sponsor or designee including, but not limited to, the IB, this protocol, eCRFs, the protocol specified treatment, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

Discontinuation of treatment does not necessarily indicate study discontinuation for a patient. Samples collected for research will continue to be used unless the patient explicitly withdraws consent for their use. If the patient withdraws consent to continue in the study or discontinues the study for another reason, it will be documented on the appropriate eCRF. A patient may withdraw consent to participate in an additional part of a study that has an additional consent (ie, optional tumor biopsy) yet continue to participate and be treated/ followed in the main part of the study.

11.4 Study Monitoring

On behalf of the sponsor, a contract research organization (CRO) or contract monitor will contact and visit the investigator at the study site prior to the entry of the first patient (unless the sponsor or the CRO has worked with the site recently in the same or comparable indication, the site location and facilities have not changed significantly, and the potential investigator/site are in good standing with respect to previous regulatory compliance, in such cases this initial visit may be waived) and at appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit. Representatives from the sponsor may also contact and visit the investigators and monitor data during the study.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (ie, the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs; however, the principal investigator retains the ultimate responsibility for the quality and integrity of data generated by the site.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file.

11.5 Case Report Forms and Study Data

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the eCRF should be consistent with the data recorded on the source documents.

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study site personnel and delegation list" must be kept current throughout the study. Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant EDC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding EDC and completing eCRFs is included in the investigator files. All questions or comments related to electronic capture should be directed to the assigned monitor.

11.6 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate a treatment arm and/ or the entire study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating all or part of the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

The sponsor reserves the right to discontinue all or part of the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

A treatment arm or the entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study;
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the treatment arm or study unnecessary or unethical;

- The stated objectives of the treatment arm or study are achieved; or
- The sponsor discontinues the development of study medication.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented.

If all or part of the study is terminated prematurely, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The investigators will promptly inform their IRB/IEC, providing the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

11.7 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB/IEC must be informed of all amendments (note: substantial amendments in the EU) and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

11.8 Retention of Study Documents

The study site will maintain a study file, which should contain all documents defined in the ICH E6(R2) Guidelines for GCP. The investigator should have control of all essential documents generated by the site. Source documents must be maintained, ALCOA-C (attributable, legible, contemporaneous/complete, original, accurate, and complete) used. Any changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (via an audit trail). The investigator must implement procedures to ensure the integrity of any data generated.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or its designees. The investigator should have control of and continuous access to the eCRF data.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by

the applicable regulatory requirement(s) or if needed by the sponsor. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the sponsor. Copies of original documents should fulfill the requirements for certified copies. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in writing of the new responsible person and/or the new location. The sponsor will inform the investigator, in writing, when the study-related records are no longer needed.

All clinical study information should be recorded, handled and stored in a way that allows accurate reporting, interpretation and verification, irrespective of the media used.

The sponsor and the investigator will maintain a record of the location(s) of their respective essential documents including source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version history, search and retrieval.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

11.9 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Aspects of the study that are essential to ensure human subject protection and reliability of study results should be the focus of these procedures.

11.9.1 Changes to the Protocol and Deviations

The investigator may not deviate from the protocol unless necessary to eliminate immediate hazards to the patient. A deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable. Any deviation must be documented in the source documents and reported to the sponsor.

11.9.2 Study Site Training and Ongoing Monitoring

Each investigator and the site personnel for this study will be trained by the sponsor and/ or a designee (ie, a CRO) on the design, conduct, procedures, and administrative aspects of this study. This may include, but is not limited to, on-site training, Investigator Meeting(s), and/ or tele/ videoconferencing. Training may be ongoing as refresher, to address specific items, or to introduce changes in the study.

In accordance with Code of Federal Regulations 21 CFR 312.56, ICH GCP E6(R2), 2001/20/EC, 2005/28/EC, and local regulations, the clinical monitor will periodically inspect

via direct access to records, all eCRFs, study documents, medical records (office, clinic, or hospital) for patients in this study (anonymity is to be preserved), research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the investigator must inform the sponsor of these restrictions before initiation of the study.

11.9.3 Direct Access to Source Data/ Documents for Audits and Inspections

The sponsor and investigator sites are to maintain a record of locations of essential documents and study source documents. The storage systems used during the study and for archiving (irrespective of media used) must provide for documentation identification, version history, search, and retrieval. Members of the sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA, European Medicines Agency (EMA), or other regulatory agencies, including IRB/IEC representatives may also conduct an audit or inspection of the study. If informed of such an activity, the investigator should notify the sponsor immediately. The investigator will ensure that the auditors and inspectors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files and electronic records are available, if requested.

11.10 Clinical Study Report

A clinical study report (CSR) will be prepared, regardless of whether the study is completed or terminated early, under the responsibility and supervision of the sponsor and signed by the sponsor's chief medical officer, head of biostatistics, and head of regulatory affairs; thereby indicating their agreement with the analyses, results, and conclusions of the CSR. The CSR will be provided to the regulatory agency(ies) as required by the applicable regulatory requirements.

11.11 Publication and Disclosure Policy

All data generated from this study will be maintained by the sponsor. All data generated from this study, and all information furnished by the sponsor, the investigators, and other participating study groups shall be held in strict confidence. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the sponsor. Any collaborative publications will be authored in accordance with the applicable guidelines (eg, International Committee of Medical Journal Editors [ICJME]).[102] Written permission to the investigator will be contingent on the review of the statistical analysis and manuscripts/abstract by the sponsor and participating cooperative groups, and will provide for nondisclosure of the sponsor and

cooperative groups confidential or proprietary information. In all cases, the parties agree to provide all manuscripts or abstracts to all other parties 60 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

11.12 Investigator Oversight

The investigator has a responsibility for supervising any individual or party to whom they delegate study related duties or functions conducted at the study site. This includes the services of any party or individual retained by the investigator for this purpose. All staff delegated study responsibilities must be documented on an approved Delegation of Authority log for the study and this filed with the essential documents. In addition, the investigator must ensure that delegated staff are qualified by training, experience and licensure (as applicable). The investigator should implement procedures to ensure integrity of the study-related duties, functions performed, and any data generated.

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13 APPENDICES

Appendix 1 Cockcroft-Gault Formula

Estimated Glomerular Filtration Rate (GFR)

Estimated GFR using serum creatinine value is at screening and may be collected each time clinical chemistry testing occurs.

$$\text{Male } CL_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}$$

$$\text{Female } CL_{cr} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}\right] \times 0.85$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL; the calculated units are mL/min.[103]

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times \textit{Constant}}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women.

Appendix 2 Example Inhibitors and Inducers of CYP2C8 and CYP3A4 (not an inclusive list)

CYP Enzyme	Strong Inhibitor (Contraindicated)	Moderate Inhibitor (Use with Caution)
CYP2C8	gemfibrozil	teriflunomide
CYP3A	boceprevir clarithromycin cobicistat conivaptan danoprevir and ritonavir diltiazem grapefruit juice[a] idelalisib indinavir and ritonavir itraconazole ketoconazole lopinavir and ritonavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) nefazodone nelfinavir posaconazole ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir troleandomycin voriconazole	aprepitant cimetidine ciprofloxacin clotrimazole crizotinib cyclosporine dronedarone erythromycin fluconazole erythromycin imatinib tofisopam verapamil
CYP Enzymes	**Dual Inhibitor (Contraindicated)**	**Dual Inhibitor (Use with Caution)**
CYP3A and CYP2C8	clopidogrel verapamil teriflunomide	trimethoprim ticargrelor

CYP Enzyme	Strong Inducer (Contraindicated)
CYP3A	carbamazepine enzalutamide mitotane phenytoin rifampin St. John's Wort

Source: US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers[104]

[a] The effects of grapefruit juice vary widely among brands, thus can be classified as both a strong and moderate inhibitor depending on concentration, quantity consumed, and preparation. Patients should be advised to avoid.