CLINICAL STUDY PROTOCOL: CO-338-111

Study Title:	CATCH-R: A Rollover Study to Provide Continued Access to Clinical Therapy with Rucaparib
Study Number:	CO-338-111
Study Phase:	Phase 3/3b
Product Name:	Rucaparib (CO-338)
IND Number:	[redacted]
EUDRACT Number	[redacted]
Indication:	Multiple solid tumor types
Investigators:	Multicenter
Sponsor Name:	Clovis Oncology, Inc.
Sponsor Address:	[redacted] Telephone Number: [redacted] Facsimile Number:
Responsible Medical Officer:	[redacted] Telephone: [redacted] E-mail: [redacted]

Protocol Version	**Date**
Original Protocol:	05 August 2020

Confidentiality Statement

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol: CO-338-111

Title: CATCH-R: A Rollover Study to Provide Continued Access to Clinical Therapy with Rucaparib

Date: 05 August 2020

Version: Original Protocol

Reviewed and Approved by:

[redacted] Clovis Oncology, Inc.

[redacted] Clovis Oncology, Inc.

[redacted] Clovis Oncology, Inc.

[redacted] Clovis Oncology, Inc.

PROTOCOL ACCEPTANCE FORM

Protocol:	CO-338-111
Title:	CATCH-R: A Rollover Study to Provide Continued Access to Clinical Therapy with Rucaparib
Date:	05 August 2020
Version:	Original Protocol

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

Investigator's Signature and Date (dd Month yyyy)

Name (printed)

SPONSOR'S MEDICAL EXPERT FOR THE STUDY

[redacted]

[redacted]

Telephone:
Facsimile:
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.

PROTOCOL SYNOPSIS

Sponsor: Clovis Oncology, Inc.
Name of Finished Product: Rucaparib tablets
Name of Active Ingredient: Rucaparib camsylate (CO-338)
Study Title: CATCH-R: A Rollover Study to Provide Continued Access to Clinical Therapy with Rucaparib
Study Number: CO-338-111
Study Phase: Phase 3/3b
Study Duration: This study is open to patients who participate in current and future studies with rucaparib. Patients receiving study treatment will remain enrolled from the time of informed consent through 28 days after receiving their last dose of rucaparib. Those patients in long-term follow-up (LTFU) will remain enrolled from the time of informed consent until withdrawal of consent, death, loss to follow up, or study closure by the sponsor. The end of the study is defined as the date of the last study visit or follow up for the last patient on study, or study closure by the sponsor. Overall, it is estimated that the study duration will be approximately 5 years.
Background and Study Rationale: CO-338-111 (CATCH-R) is an open-label, rollover study designed to provide continued access to study treatment for patients with a solid tumor who have participated in a Clovis-sponsored clinical study (the parent studies) of rucaparib that is being closed. Eligible patients for continued treatment are those who are tolerating and deriving clinical benefit from study treatment in the parent study, and who would, in the opinion of the investigator, benefit from continued treatment. Patients for whom LTFU data were being collected in a parent study may also enroll in this study to enable complete collection of such LTFU data in the event the parent study has been closed.
Study Objectives • Provide ongoing rucaparib treatment to patients who participated in a Clovis-sponsored study and who are assessed as continuing to benefit from rucaparib at the time of study closure; • Collect serious adverse events (SAEs) and adverse events of special interest (AESIs); • Collect long-term follow-up (LTFU) data, as applicable based on parent study objectives.

Study Design:

This is a multicenter, open-label rollover study providing rucaparib as treatment across multiple solid tumor types for patients previously enrolled in a Clovis-sponsored study (the parent study) and who, in the opinion of the investigator, would benefit from continued treatment following closure of the parent study. This study is also designed to continue collection of LTFU data following closure of the parent study(ies).

This study will enroll patients who are continuing rucaparib treatment and/or for whom LTFU data are being collected following participation in a Clovis-sponsored study that is being closed.

Patients continuing on rucaparib will receive the same treatment at the start of this study as they last received in the parent study, or may receive a different dose per investigator decision and available dose strength tablets. It is anticipated that patients will have received approximately a minimum of 6 months rucaparib treatment in the parent study before rolling into this study. Those patients who have consented to LTFU will be followed for data collection, as applicable based on parent study objectives.

Patients will be assessed for disease status/progression per institutional standard of care. Patients will be monitored for safety according to standard practice at the participating institutions. Adverse events (AEs) should be monitored; however, only SAEs and AESIs will be reported per Clovis Pharmacovigilance (PV) requirements and captured in the Clovis PV database.

Treatment will continue until the patient no longer receives benefit, in the opinion of the investigator, unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or study closure by the sponsor.

Patients receiving rucaparib will have all protocol-required assessments specified in the Schedule of Assessments until the discontinuation of treatment, with a final safety assessment approximately 28 days following the last dose of study treatment (Post-treatment Follow-up Visit). Ongoing SAEs and AESIs at the time of the Post-treatment Follow-up Visit will be followed until either resolution or stabilization, death, or until loss to follow-up. After the safety follow-up window (including patients enrolled in LTFU only), only SAEs considered as potentially related to study drug (including serious reports of pneumonitis or associated events, if considered to be related to study drug), and AESIs of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) irrespective of causality, will be reported.

Patients will be followed approximately every 12 weeks for collection of LTFU data, as applicable based on parent study objectives, until death, withdrawal of consent, loss to follow-up, or until closure of this study by the sponsor.

Number of Patients and Sites:

The number of sites and the number of patients who participate in this rollover study is open and is dependent upon the number of eligible patients enrolled in current and future rucaparib studies who tolerate rucaparib, derive clinical benefit, and wish to continue treatment and/or LTFU portions of this study.

Key Inclusion Criteria:

Eligible patients must be currently enrolled in a Clovis-sponsored study of rucaparib that is being closed and have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF); are currently tolerating and benefitting from rucaparib treatment in the parent study, as assessed by the investigator, or have discontinued treatment and be in follow-up for collection of LTFU data; have demonstrated compliance with the parent study requirements and are able and willing to comply with the necessary study visits and assessments as part of the rollover study; and for patients continuing treatment with rucaparib, have not received any intervening anticancer therapy since discontinuing the parent study.

Key Exclusion Criteria:

Patients will be excluded from receiving further rucaparib treatment if they have been permanently discontinued from rucaparib in the parent study for any reason. Women of childbearing potential (WOCBP) must not be considering getting pregnant during continued treatment and for 6 months following the last dose of rucaparib. Male patients with female partners of reproductive potential or who are pregnant who refuse to use effective contraception during treatment and for 3 months following the last dose of rucaparib are excluded. Male patients who are considering making semen donations during treatment or within 3 months following the last dose of rucaparib will also be excluded.

Randomization:

No randomization or blinding will be performed in the study.

Study Treatment:

Patients continuing rucaparib treatment will receive the same dose last received in the parent study, or may receive a different dose per investigator decision and available dose strength tablets. Treatment will continue until the patient no longer receives benefit, in the opinion of the investigator, unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or study closure by the sponsor.

Rucaparib: Rucaparib tablets must be swallowed whole and may be taken with or without food. Rucaparib may be provided as 200 mg, 250 mg, and/or 300 mg dose strength tablets.

Dose reductions and/or treatment interruptions are permitted per investigator decision. Refer to the current Investigator's Brochure (IB) or regional prescribing information for comprehensive information on rucaparib.

Withdrawal Criteria (for patients enrolled to receive study treatment):

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

- Consent withdrawal for any reason at the patient's own request or, where acceptable according to national law and/or local regulations, at the request of their legally authorized representative;
- Progression of patient's underlying cancer as assessed by the investigator per institutional guidelines, unless the patient continues to derive clinical benefit from rucaparib according to the investigator, the investigator has consulted with the sponsor's medical officer or designee, and the patient has provided additional consent for treatment beyond progression at the next study visit;
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient;
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and require discontinuation of therapy;
- Noncompliance by the patient with protocol mandated procedures;
- The study is terminated; or
- A positive pregnancy test result for a female patient at any time during study treatment.

A patient must be discontinued from LTFU if consent is withdrawn.

Disease Status Assessments:

No efficacy measures will be collected.

Disease assessments should be performed according to institutional standard of care per investigator and evaluated locally for patient treatment decisions.

Safety Assessments:

Patients will be monitored for safety through 28 days following the last dose of rucaparib according to standard practice at the participating institution. SAEs and AESIs will be reported per Clovis PV requirements and captured in the Clovis PV database.

Long-term Follow-up Data Collection

Patients for whom LTFU data are being collected, as applicable based on parent study objectives, should be followed approximately every 12 weeks until death, loss to follow-up, withdrawal of consent, or until closure of this study by the sponsor.

Date and cause of death will be recorded in the Death electronic Case Report Form (eCRF) provided by the sponsor.

Date of Protocol Approval (Original):

05 August 2020

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	
AE	adverse event
AESI	adverse event of special interest
ALCOA+	A framework for ensuring data integrity and good documentation practices defined as Attributable, Legible, Contemporaneous, Original or Certified Copy, Accurate, and 'Plus' (+) Complete, Consistent, Enduring, and Available
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
CFR	Code of Federal Regulations (United States)
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
DILI	drug-induced liver injury
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System

LFT	liver function test
LTFU	long-term follow-up
MATE	multidrug and toxin extrusion
MDS	myelodysplastic syndrome
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OCT	organic cation transporter
PK	pharmacokinetic(s)
PMDA	Japanese Pharmaceuticals and Medical Devices Agency
PV	pharmacovigilance
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Background

This study is an open-label, rollover study for patients with a solid tumor previously treated in a Clovis-sponsored clinical study evaluating rucaparib.

1.1.1 Investigational Product under Study – Rucaparib

Refer to the current rucaparib Investigator's Brochure (IB) for mechanism of action, approval history, and nonclinical and clinical experience.

1.2 Study Rationale

1.2.1 Known and Potential Risks and Benefits to Patients

The potential risks and benefits to patients enrolled in this protocol are understood to be the same as those described for the parent study. Participation in the treatment phase of this study is limited to those patients who are tolerating and deriving clinical benefit from study treatment. Refer to the current IB or regional prescribing information for comprehensive information on rucaparib.

1.2.2 Rationale for the Design

This protocol is designed to provide patients currently benefitting from rucaparib treatment in a Clovis-sponsored clinical study with continued access to treatment for as long as they continue to benefit. Patients in long-term follow-up (LTFU) in a parent study may also enroll in this study for continued data collection, as applicable based on parent study objectives.

1.2.3 Dose Rationale

The dose administered at the start of this study will be the same as that received by the individual patient at the time of discontinuation from the parent study, or as deemed appropriate by the investigator for an individual patient and based on available dosage strengths.

1.2.4 Rationale for Duration of Treatment

This is a rollover study designed to provide continued access to rucaparib for patients who have participated in a Clovis-sponsored clinical study (the parent studies) of rucaparib that is being closed. Eligible patients for continued treatment are those who are tolerating and deriving clinical benefit from study treatment in the parent study, and who would, in the opinion of the investigator, benefit from continued treatment. Where applicable based on parent study objectives, patients for whom LTFU data was being collected in a parent study may also enroll in this study to enable collection of such LTFU data in the event the parent study has been closed.

2 STUDY OBJECTIVES

Study objectives are as follows:

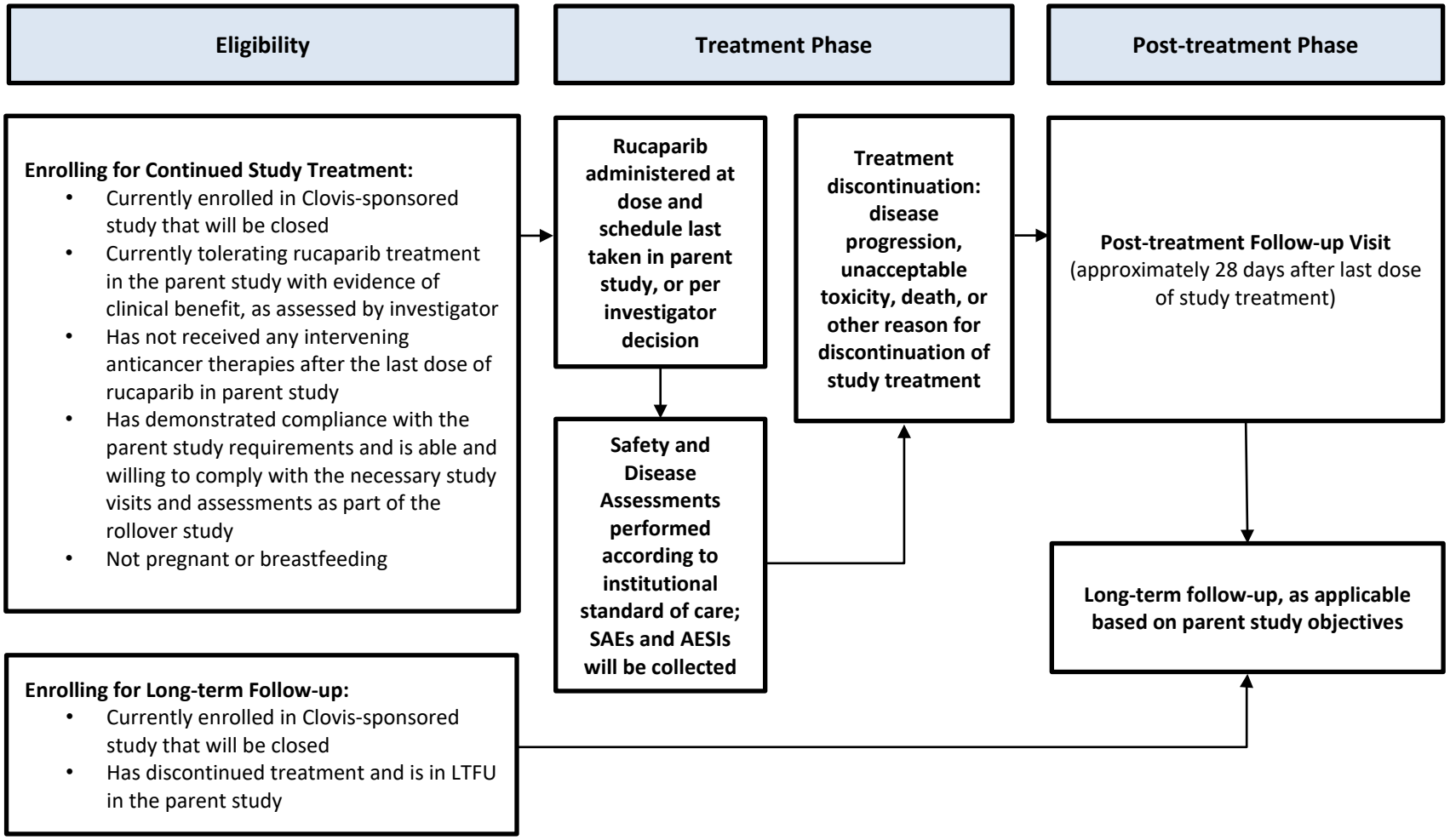
- Provide ongoing rucaparib treatment to patients who participated in a Clovis-sponsored study and who are assessed as continuing to benefit from rucaparib at the time of study closure;
- Collect serious adverse events (SAEs) and adverse events of special interest (AESIs);
- Collect long-term follow-up (LTFU) data, as applicable based on parent study objectives.

3 STUDY DESIGN

3.1 Study Schema

The study schema in Figure 3-1 summarizes the treatment design of the study.

Figure 3-1 Study Schema



Abbreviations: AESI = adverse event of special interest; LTFU = long-term follow-up; SAE = serious adverse event.

3.2 Description of Study Design

Patients enrolled in this study are required to have completed an End-of-Treatment (EOT) Visit with associated assessments as specified in the Clovis-sponsored parent study. Patients who are no longer receiving treatment and are in LTFU in the parent study may enroll into the LTFU portion of this study, as applicable based on parent study objectives, without repeating the EOT visit.

Signing of a new Informed Consent Form (ICF) will be required for all patients. For patients receiving continued treatment in this study, consent will be obtained prior to the EOT Visit in the parent study.

All patients will retain the patient identification number assigned to them in the parent study.

3.2.1 Treatment Phase

The starting dose of rucaparib administered at initiation of this study will be the same as the last dose received in the parent study, or as deemed appropriate by the investigator and based on available dose strength tablets. The first treatment in the rollover study will begin at the next scheduled treatment visit following the EOT Visit in the parent study.

Safety and disease assessments should be performed according to institutional standard of care practices. Suggested assessments include monitoring for adverse events (AEs), complete blood count, pregnancy test for women of childbearing potential (WOCBP; required), disease assessments, laboratory assessments (clinical chemistry, urinalysis), vital signs, and rucaparib accountability (required). See Section 7.1.

Patients enrolled to receive continued rucaparib may be treated until disease progression, as assessed by the investigator, unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or study closure by the sponsor.

If a patient demonstrates disease progression per investigator assessment while receiving treatment with rucaparib but continues to derive clinical benefit, then continuation of treatment beyond progression is permitted based on investigator decision and patient consent. If a patient continues treatment post-progression, all study assessments should be continued per institutional standard of care. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

The first and last dates of dosing should be captured in the electronic Case Report Form (eCRF). SAEs and AESIs will be reported per Clovis Pharmacovigilance (PV) guidelines and captured in the Clovis PV database.

3.2.2 Post-Treatment Phase

Upon treatment discontinuation in this study, regardless of reason (with the exception of withdrawal of consent or death), patients should return to the clinic for post-treatment safety monitoring assessments approximately 28 days (± 7) after the last dose of rucaparib has been administered in this study. Assessments should be performed per institutional standard of

care at the Post-treatment Follow-up Visit. Suggested assessments include monitoring for AEs, complete blood count, pregnancy test for WOCBP (required), disease assessments, laboratory assessments (clinical chemistry, urinalysis), vital signs, and rucaparib accountability (required). See Section 7.1.

The date and reason for treatment discontinuation should be captured in the eCRF.

Ongoing SAEs and AESIs at the time of the Post-treatment Follow-up Visit should be followed until resolution or stabilization has been determined, death, or loss to follow-up.

After the 28-day Post-treatment Follow-up Visit, only SAEs considered as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Post-treatment Follow-up Visit, AESIs of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the Post-treatment Follow-up Visit (28-days after the last dose of rucaparib).

If a patient begins a subsequent anticancer therapy, the sponsor will terminate collection of SAEs.

3.2.3 Long-term Follow-up

If applicable based on parent study objectives, patients who have discontinued treatment in this or the parent study, regardless of reason, and have provided consent, should have LTFU data collected approximately every 12 weeks relative to the last dose of rucaparib until death, loss to follow-up, withdrawal of consent, or study closure. This data should be collected in the eCRF.

3.3 Data Monitoring Committee

There will not be a Data Monitoring Committee in this study.

3.4 Removal of Patients From Therapy or Assessment

A patient must be discontinued from protocol-prescribed treatment if any of the following apply:

- Consent withdrawal, for any reason, at the patient's own request or at the request of their legally-authorized representative (where acceptable according to national law and/or local regulations). The reason must be documented and describe the aspect(s) of the study for which consent is withdrawn (eg, continued treatment, all participation);

- Patient with progressive disease: If a patient receiving rucaparib has met criteria for disease progression per institutional guidelines, but continues to derive clinical benefit per the investigator, continuation of treatment may be permitted. Treatment should be discontinued when it is determined by the investigator that no further benefit can be achieved.
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient;
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy;
- Noncompliance by the patient with protocol-mandated procedures;
- The study is terminated; or
- A positive pregnancy test result for a female patient at any time during study treatment.

If the patient withdraws consent to continue in the study or discontinues the study for another reason, it should be documented on the appropriate eCRF.

The sponsor may terminate the study early for any of the reasons noted in Section 10.6.

3.5 End of Study

The end of the study is defined as the date of the last study visit or follow up for the last patient on study, or study closure by the sponsor.

4 STUDY POPULATION

4.1 Number of Patients and Sites

The number of sites and the number of patients who participate in this rollover study is dependent upon the number of eligible patients enrolled in current and future rucaparib protocols who tolerate rucaparib, derive clinical benefit, and wish to continue treatment and/or LTFU portions of this study.

4.2 Inclusion Criteria

Eligible patients must meet the following inclusion criteria:

1. Patient is currently enrolled in a Clovis-sponsored study of rucaparib that is being closed;
2. Patient either:
   a. Is currently tolerating a rucaparib treatment regimen in the parent study with evidence of clinical benefit, as assessed by the investigator, or
   b. Has discontinued treatment and is being followed for collection of LTFU data in the parent study;
3. Patient has demonstrated compliance with the parent study requirements, as assessed by the investigator, and patient is able and willing to comply with the necessary study visits and assessments as part of the rollover study;
4. Patient has provided written informed consent prior to enrolling in this rollover study;

5. For patient enrolling to continue receiving treatment in this rollover study, has not received any intervening anticancer therapy since the last dose of rucaparib in the parent study.

4.3 Exclusion Criteria

Patients considered for continued treatment with rucaparib in this study who meet any of the following criteria will be excluded from the study:

1. Patient has been permanently discontinued from study treatment in the parent study for any reason;
2. For female patients of childbearing potential, the following are exclusion criteria:
   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 (see Section 4.4).
   b. WOCBP who are pregnant or breastfeeding or who have a positive pregnancy test ≤ 3 days prior to the first dose of rucaparib within this study. WOCBP must not be considering getting pregnant during the study and for 6 months following the last dose of rucaparib.
3. For male patients, the following are exclusion criteria:
   a. Refusal to use highly effective method of contraception or to practice true abstinence during treatment and for 3 months after the last dose of rucaparib.
   b. Male patients must not donate semen during treatment and for 3 months following the last dose of rucaparib.
4. Presence of any other condition that may, in the opinion of the investigator, make the patient inappropriate for continuation of rucaparib treatment.

4.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion for patients enrolled to receive study treatment. WOCBP 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 (female patients) or 3 months (partners of male patients of reproductive potential) after the last dose of rucaparib or longer if requested by local authorities.

Female patients of childbearing potential must have a negative pregnancy test result ≤ 3 days prior to administration of the first dose of rucaparib in this study. In addition, a pregnancy test must be performed ≤ 3 days prior to Day 1 of every cycle during the Treatment Phase 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 rucaparib.

Male patients are required to use a condom during sex with a partner to avoid the possibility of exposure of the partner to rucaparib, regardless of whether the partner is a WOCBP or not, or who are pregnant. Male patients must not make semen donations during treatment and for 3 months following the last dose of rucaparib.

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 one 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 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 requested by local authorities.

Male patients must practice highly effective methods (failure rate < 1% per year) of contraception with their female partners, if of reproductive potential, during treatment and for 3 months following the last dose of rucaparib or longer if requested by local authorities.

Highly effective contraception includes:

- 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.

Female patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib, and male patients will be instructed to notify the investigator if pregnancy is discovered in their female partner either during or within 3 months of completing treatment with rucaparib (refer to Section 8.5).

4.5 Compliance With Inclusion/Exclusion Criteria

All inclusion/exclusion criteria must be met for the prospective participant to enroll. Neither the investigator, nor the sponsor/designee, may allow a prospective participant who has not met the inclusion/exclusion criteria to enter the study.

5 STUDY TREATMENT

5.1 Description of Investigational Product and Storage

5.1.1 Rucaparib

A brief description of the investigational product is provided in Table 5-1.

Table 5-1 Description of Study Treatment

Drug Name:	Rucaparib
INN:	Rucaparib
Formulation:	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).

Abbreviation: INN = International Nonproprietary Name.

5.2 Packaging and Labeling

5.2.1 Rucaparib

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°C and 30°C (59°F and 86°F). Patients will be dispensed one or more strengths depending on their dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply at least one 28-day treatment cycle, including a small overage (see Section 5.4.1).

Study drug containers containing rucaparib tablets will be labeled according to national regulations for investigational products and inventory will be managed by the use of Interactive Response Technology (IRT).

5.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; the investigational product will not be blinded.

5.4 Preparation and Administration of Protocol-specified Treatment

5.4.1 Rucaparib

The investigator or designee will be responsible for distributing rucaparib tablets to all patients.

The dose of rucaparib is that which was last received in the parent study, or as deemed appropriate by the investigator and based on available dose strength tablets. Patients may take rucaparib with or without food. Each dose should be taken with water. Tablets should be swallowed whole without crushing or chewing. Tablet strength combinations shall be determined by the IRT.

Patients should take rucaparib doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (ie, does not take it within 4 hours of the scheduled time), he/she should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

More than 1 cycle of rucaparib can be dispensed, if deemed appropriate by the investigator (see Section 7.1). Patients will be instructed to bring their rucaparib tablets and all containers (empty, partially used, and/or unopened) to the next scheduled visit for reconciliation by site personnel.

5.5 Dose Modifications of Protocol-specified Treatment

Doses of rucaparib may be interrupted or delayed for toxicity and other protocol-specified criteria. Dose reductions are permitted for rucaparib. Treatment may be discontinued due to withdrawal of consent, unacceptable toxicity, disease progression, or termination of the study, whichever occurs first.

The date of last dose and reason for discontinuation should be captured on the appropriate eCRF; dose modifications (ie, interruption, reduction, and/or re-escalation) are not required to be recorded.

Refer to the current IB or regional prescribing information for comprehensive information on rucaparib.

Dose interruption and re-treatment of rucaparib are to be based on the criteria presented in Table 5-2.

Table 5-2 Dose Interruption and Re-Treatment Criteria for Rucaparib

Adverse Event including Laboratory Abnormalities	Severity (CTCAE Grade)	Rucaparib	
		Treatment Interruption	Re-treatment
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	≤ NCI-CTCAE Grade 2
ALT/AST elevation	4	Hold	≤ NCI-CTCAE Grade 2
ALT or AST elevations (> 3 × ULN) AND Total bilirubin (> 2 × ULN) - Suspected DILI [Section 8.8]	NA	Hold[a]; Monitor LFTs weekly If DILI is confirmed, treatment should be permanently discontinued	≤ NCI-CTCAE Grade 1 (or baseline)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; INR = international normalized ratio; LFT = liver functions test; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

[a] 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, rucaparib 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.

5.5.1 Rucaparib Dose Modification Criteria

The rucaparib dose may be reduced as needed, per investigator decision. Refer to Section 5.1.1 for available dose strengths.

Dose escalation upon resolution of toxicity to ≤ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)[1] Grade 1 is permitted at the discretion of the investigator.

5.5.1.1 Management of anemia

If anemia CTCAE Grade ≥ 3 occurs and persists for > 14 days, or a dependence upon blood transfusions occurs, then weekly complete blood counts are recommended until resolution of the anemia to ≤Grade 1. If after 42 days of treatment interruption anemia has not improved to Grade ≤ 1, a referral to a hematologist and analysis of the bone marrow according to institutional standard practice is recommended.

Refer to Sections 8.3 and 8.6 of the protocol for additional information regarding classification and reporting of MDS or AML as an AESI.

5.5.1.2 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.

Following investigation, if pneumonitis is not confirmed, treatment with rucaparib 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 with rucaparib is being considered, please consult the study Medical Monitor. Retreatment with rucaparib may be resumed at the current or a reduced dose, if appropriate.

Refer to Sections 8.3 and 8.6 of the protocol for additional information regarding classification and reporting of pneumonitis (and related events) as an AESI.

5.5.2 Rucaparib Discontinuation

Treatment should be continued until it is determined by the investigator that no further clinical benefit can be achieved.

Rucaparib should be permanently discontinued for any of the following:

- Confirmed diagnosis of MDS or AML;
- Pregnancy (see Section 8.5)

5.6 Treatment Compliance

Dosing diaries will not be used in this study. Study site personnel should review dosing information with the patient (or legally authorized representative, where acceptable according to national law and/or local regulations) 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, where acceptable according to national law and/or local regulations) will be instructed to keep all unused tablets and containers (empty, partially used, and/or unopened) for accountability at scheduled clinic visits.

Every effort should be made to ensure patients return rucaparib containers/unused rucaparib 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.

5.7 Accountability of Protocol-specified Treatment

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

During the study and at completion of the study, the number of investigational product units and containers received, dispensed, returned, and destroyed must be recorded and reconciled.

6 PRIOR AND CONCOMITANT THERAPY

Medications taken, procedures performed (eg, thoracentesis, etc.), and supportive care given during the study will not be documented in the eCRF.

6.1 Supportive Care

Supportive care (eg, antiemetics; analgesics for pain control; growth factors, etc) may be used at the investigator's discretion and in accordance with institutional procedures.

6.2 Anticancer or Experimental Therapy

No other anticancer therapy (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 receiving treatment with rucaparib, with the exception of palliative radiotherapy.

6.3 Radiotherapy

Palliative radiotherapy is permitted during the study. Treatment with rucaparib should be held prior to initiation of radiation therapy and until the patient has recovered from any radiation-related toxicity.

6.4 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo cytochrome P450 (CYP) interaction 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 medicines that are sensitive clinical substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A (see Appendix 1).

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.

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. Herbal and complementary therapies are discouraged because of unknown side effects and potential drug interactions.

Rucaparib marginally increased digoxin area under the concentration-time curve (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 multidrug and toxin extrusion (MATE1) and MATE2-K, a moderate inhibitor of organic cation transporter (OCT)1, and a weak inhibitor of OCT2. As inhibition of these transporters could decrease 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 breast cancer resistance protein (BCRP) with a concentration at which 50% maximal inhibitory response is observed (IC50) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (eg, rosuvastatin).

6.7 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 STUDY PROCEDURES AND METHODS

7.1 Schedule of Assessments

Table 7-1 summarizes the procedures and assessments to be performed for all patients.

Study procedures and assessments should be performed as close as possible to the scheduled time.

Table 7-1 Schedule of Assessments

Procedure[a]	Prior to EOT in Parent Study	Treatment Phase Cycle X Day 1	Post-Treatment Phase	
			Post-treatment Follow-up[b]	Long-term Follow-up[c]
Informed Consent[d] (Section 7.2)	X			
Adverse Events[e] (Sections 8.6 and 8.7)		The Investigator should monitor and educate patients on possible AEs observed with rucaparib; only SAEs and AESIs will be reported in Clovis PV database		X
Complete Blood Count		Institutional standard of care practices per Investigator		
Clinical Chemistry, Urinalysis, Vital Signs		Institutional standard of care practices per Investigator		
Pregnancy Test[f] (WOCBP only) (local lab) (Section 7.3.2.2)		X	X	
Disease Assessments (Section 7.3.1)		Institutional standard of care practices per Investigator		
Rucaparib Dispensation/Administration/Accountability[g] (Section 5.7)		X	X	
Long-term Follow-up Data Collection (Section 7.3.3)				X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AML = acute myeloid leukemia; eCRF = electronic Case Report Form; EOT = end of treatment; LTFU = long-term follow-up; MDS = myelodysplastic syndrome; PV = pharmacovigilance; SAE = serious adverse event, WOCBP = women of childbearing potential.

[a] Treatment cycles are 28 days. Unless otherwise specified, all assessments are to be completed as close as possible to the scheduled time point. Data to be entered in the appropriate electronic Case Report Form (eCRF) include enrollment, dosing, discontinuation, survival/death, and long-term follow-up (LTFU). Dose modifications, hematology/clinical chemistry assessments, and pregnancy testing are not required to be entered.

[b] Post-treatment safety follow-up visit should occur approximately 28 days (±7) from the last dose of rucaparib, or can be performed on the date of discontinuation if that date is at least 28 days from last dose.

[c] Patients who have discontinued treatment, regardless of reason, and provide consent, should have LTFU data collected approximately every 12 weeks relative to the last dose of rucaparib until death, loss to follow-up, withdrawal of consent, or study closure, as applicable based on parent study objectives. This data will be captured in the eCRF.

Table 7-1 Schedule of Assessments

[d] Patients rolling over to continued treatment with rucaparib in this study will sign consent prior to the End-of-Treatment (EOT) Visit of the parent study. Patients rolling over from LTFU in the parent study will sign consent prior to the first LTFU visit in the rollover study.

[e] Adverse events (AEs) will be monitored but only serious AEs (SAEs)/adverse events of special interest (AESIs) are collected per Clovis Pharmacovigilance (PV) guidelines and reported in the Clovis PV database through 28 days after last dose of rucaparib (Post-treatment Follow-up Visit). Ongoing SAEs and AESIs at the time of the Post-treatment Follow-up Visit will be followed to resolution, stabilization, or lost to follow-up. After this visit, only SAEs considered as potentially related to study drug (including serious reports of pneumonitis or associated events, if considered to be related to study drug), and AESIs of MDS and AML irrespective of causality, will be reported. If a patient discontinues from treatment in the rollover study and begins a subsequent anticancer therapy, the sponsor will terminate collection of SAEs.

[f] Women of childbearing potential (WOCBP) must have a negative pregnancy test result ≤ 3 days prior to the first dose of rucaparib in this study. A pregnancy test must be performed ≤3 days prior to Day 1 of every cycle from Cycle 2 and beyond during the treatment phase. Testing may be performed per institutional standard of care during treatment, and results must be reviewed prior to commencing a new cycle of rucaparib. A pregnancy test must be performed at the EOT Visit of the parent study and the Post-treatment Follow-up Visit of the rollover study. See Section 8.5 for reporting a positive pregnancy result.

[g] More than 1 cycle of rucaparib can be dispensed, if deemed appropriate by investigator. Patients will be instructed to bring their rucaparib tablets and all containers (empty, partially used, and/or unopened) to each scheduled visit for reconciliation by site personnel.

7.2 Informed Consent Timing

Informed consent must be obtained from each patient prior to entering the rollover study. General aspects of informed consent are described in Section 10.2.1 and the informed consent process is described in Section 10.2.2. Informed consent can be obtained in written format, as possible. For patients in active treatment in the parent study, informed consent can be obtained prior to the EOT Visit in the parent study. For patients in LTFU in the parent study, it is not necessary to repeat the EOT Visit, but informed consent must be obtained before the first LTFU visit in this study.

7.3 Methods of Data Collection

SAEs and AESIs that occur after informed consent will be collected through 28 days after the last dose of rucaparib for patients receiving treatment in this study. Only SAEs/AESIs will be reported in the Clovis PV database.

After the 28-day Post-treatment Follow-up Visit, only SAEs considered as potentially related to rucaparib should be reported per Clovis PV requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Post-treatment Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the Post-treatment Follow-up Visit (28-days after the last dose of rucaparib).

Hematology, clinical chemistry, urinalysis, vital signs, and disease assessments should be performed locally per institutional standard of care practices. Pregnancy testing will be performed locally per institutional standard of care at screening (the EOT Visit of parent study), before initiation of each treatment cycle, and at the Post-treatment Follow-up Visit of this study.

7.3.1 Disease Status Evaluations

Target and non-target lesions will be evaluated for evidence of progression based on institutional standard of care practices for the purpose of determining continued benefit of study treatment. Tumor assessment data will not be entered in the eCRF.

Tumor assessment will be performed according to institutional standard of care practices until disease progression, as assessed by the investigator, discontinuation for reasons other than progression, loss to follow up, withdrawal from study, death, or study closure.

7.3.2 Safety Evaluations

7.3.2.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients, including monitoring and management of all AEs experienced, and for compliance with the protocol to ensure study integrity. Only SAEs and AESIs occurring from the time of informed consent through 28 days after the last dose of rucaparib will be reported in the Clovis PV database.

After the post-treatment 28-day follow-up window, only SAEs considered as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Post-treatment Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the Post-treatment Follow-up Visit (28-days after the last dose of rucaparib).

Any ongoing SAEs and AESIs will be followed until resolution or stabilization.

If a patient discontinues from treatment in the rollover study and begins a subsequent anticancer therapy, the sponsor will terminate collection of SAEs.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 8.

7.3.2.2 Clinical Laboratory Investigations

Laboratory tests will be performed for all patients during treatment, the Post-treatment Follow-up Visit, and if toxicities are present, according to institutional standard of care practices, per investigator.

Pregnancy testing for WOCBP must be reviewed by the investigator before the start of treatment with rucaparib and ongoing throughout the study when testing occurs.

Data will be recorded in source documentation at the site and not entered into the eCRF. SAEs/AESIs will be reported to the sponsor and captured in the Clovis PV database.

Additional and more frequent tests may be performed at the investigator's discretion.

In studies treating female patients:

Pregnancy Test: Female patients of childbearing potential must have a pregnancy test result ≤ 3 days prior to first dose of rucaparib in this study (a negative result is required before

dosing can begin), ≤ 3 days prior to Day 1 of every cycle during treatment, and at the Post-treatment Follow-up Visit. A positive pregnancy test during participation in the treatment phase of the study must be reported to the sponsor. Refer to Section 8.5 for details.

Local laboratory reports should be reviewed by the investigator or delegated physician.

7.3.3 Long-term Follow-up Data

Patients will be followed approximately every 12 weeks for collection of LTFU data until death, lost to follow-up, withdrawal of consent, or until closure of this study by the sponsor, as applicable based on parent study objectives.

Date and cause of death will be recorded in the Death eCRF provided by the sponsor.

8 ADVERSE EVENT MANAGEMENT

8.1 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 monitor 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.

8.2 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 investigational product through 28 days after last dose) 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; or
- Is an important medical event that may not result in death, is not life-threatening, or does not require hospitalization but may be considered an SAE when, based on appropriate medical judgment, it 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.

8.3 Definition of an Adverse Event of Special Interest

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.

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the sponsor **within 24 hours** of knowledge of the event (see Section 8.6 for reporting instructions).

Report any AE of pneumonitis, or any of the following AEs, irrespective of causality assessment and severity, as an AESI within 24 hours using the study Serious Adverse Event Form and the applicable procedures as outlined in Section 8.6:

- Pneumonitis
- Interstitial lung disease
- Pulmonary fibrosis
- Acute interstitial pneumonitis
- Alveolitis necrotizing
- Alveolitis
- Hypersensitivity pneumonitis
- Organizing pneumonia

8.4 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 investigational product 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 SAE; and
- Events that meet the SAE criteria (as outlined in Section 8.2) and occur after informed consent but before the first dose of investigational product, which are considered unrelated to protocol-mandated screening procedures.

8.5 Pregnancy or Drug Exposure During Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with investigational product(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a study patient or partner of a study patient during study participation or within 6 months of the last dose for female patients, and within 3 months of last dose for partners of male study patients, must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE.

All pregnancies will be followed through to outcome, if possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form is to 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 SAE/AESI forms.

If any female partner becomes pregnant by a male study patient while he is receiving rucaparib, or within 3 months after the last dose of rucaparib, she will be asked to provide optional consent to allow follow-up until final outcome/delivery to determine if rucaparib has any effect on the pregnancy and fetal development.

8.6 Recording of Serious Adverse Events and Adverse Events of Special Interest

Any SAE/AESI that occurs after signing informed consent through 28 days after receiving the last dose of investigational product is to be reported to the sponsor and captured in the PV database.

After the 28-day Post-treatment Follow-up Visit, only SAEs assessed as potentially related to study drug should be reported per Clovis PV requirements and captured in the Clovis PV database. This includes serious reports of pneumonitis or associated events, if considered to be related to study drug.

After the 28-day Post-treatment Follow-up Visit, AESIs of MDS and AML, irrespective of causality, should be reported per Clovis PV requirements and captured in the Clovis PV database.

- AESIs of pneumonitis or associated events should only be reported up to, but not beyond, the Post-treatment Follow-up Visit (28-days after the last dose of rucaparib).

Information on the follow-up of SAEs, and AESIs is provided in Section 8.7.

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 SAE is to be evaluated for causal relationship to the investigational drug, 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 investigational product, whether or not related to investigational product, 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.

8.6.1 Onset Date of Serious Adverse Events and Adverse Events of Special Interest

The onset date is the date that the event or the signs/symptoms attributed to the event started.

8.6.2 Resolution Date of Serious Adverse Events and Adverse Events of Special Interest

The resolution date is the date that the event or the signs/symptoms attributed to the event resolved or resolved with sequelae or it is the date when the patient has reached a new baseline if the event is not expected to resolve.

8.6.3 Intensity of Serious Adverse Events and Adverse Events of Special Interest

The severity of each SAE and AESI will be graded using NCI-CTCAE, v5.0 or later[1]

"Severity" is not the same as "serious".

For SAEs and AESIs 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; or
- Fatal events are those events that lead to the patient's death.

8.6.4 Causal Relationship of Serious Adverse Events and Adverse Events of Special Interest to Investigational Product

Medical judgment should be used to determine the cause of the SAE or AESI considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the SAE or AESI, temporal relationship to the investigational product(s), and dechallenge or rechallenge with the investigational product(s) (Table 8-1).

Table 8-1 Causal Relationship of Serious Adverse Events and AESIs to Investigational Product

Not Related to Investigational Product	• An SAE or AESI 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 investigational product; • It does not follow a known pattern of response to investigational product; • It does not reappear or worsen when investigational product is restarted; or • An alternative explanation is likely, but not clearly identifiable.

Related to Investigational Product	• An SAE or AESI that is difficult to assign to alternative causes; • It follows a strong or reasonable temporal sequence from administration of investigational product; • 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 investigational product; or • It is confirmed with a positive rechallenge or supporting laboratory data.

8.6.5 Outcome and Action Taken

The investigator will record the action taken and outcome for each SAE/AESI according to the following criteria:

Action Taken with Investigational Product (note all that apply)

- None;
- Dose reduced/delayed;
- Investigational product temporarily interrupted;
- Investigational product permanently discontinued; and/or
- Other (specify).

Outcome

- Recovered;
- Recovered with sequelae;
- Recovering/ Resolving/ Improving;
- Ongoing;
- Death; or
- Lost to follow-up.

8.7 Follow-up of Serious Adverse Events and Adverse Events of Special Interest

SAEs and AESIs occurring during the study are to be followed up in accordance with good medical practice until resolution or stabilization, death, or until lost to follow-up; or, if a chronic condition, until fully characterized through 28 days after the last dose of investigational product. After the 28-day window, SAEs considered as potentially related to study drug (including serious reports of pneumonitis or associated events, if considered to be

related to study drug), and AESIs of MDS and AML irrespective of causality, should be reported.

8.8 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria,[2] must be reported as SAEs (see Section 8.6 for reporting details).

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 × upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum 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.

8.9 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/AESIs or pregnancies 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 United States (US) Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); 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 investigational product(s) 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.

9 STATISTICAL METHODS

9.1 Patient Disposition

For patients receiving continued treatment, the date and reason for patient discontinuation from treatment a will be recorded in the eCRF.

For patients in LTFU, appropriate follow-up data will be recorded in the eCRF.

9.2 Demographics and Baseline Characteristics

No additional demographic data will be collected in this study, as the patient demographics are captured in the parent study.

9.3 Efficacy Analysis

No efficacy data will be collected in this study.

9.4 Safety Analysis

No safety analyses will be conducted. SAEs and AESIs will be reported per PV requirements and captured in the Clovis PV database.

10 STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

10.1.1 Good Clinical Practice

The study will be conducted in accordance with the protocol and applicable standard operating procedures (SOPs); and in compliance with applicable guidelines including:

- International Council for Harmonisation (ICH) E6(R2);
- The FDA Code of Federal Regulations (21 CFR Parts 11, 50, 54, 56, and 312);
- EU Directives 2001/20/EC, 2003/94/EC, 2005/28/EC; 536/2014; and
- All applicable local requirements, and in accordance with the ethical principles of the Declaration of Helsinki.

Significant noncompliance with the protocol, SOPs, Good Clinical Practice (GCP), and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the 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's/institution's participation in the study. When an investigator's/institution's participation is terminated because of significant noncompliance, the sponsor will promptly notify the regulatory authority(ies) and other appropriate parties (eg, IRB/IEC).

All potential serious breaches of GCP must be reported to the sponsor or designee within 24 hours. 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 participants 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 site personnel where sanctions have been invoked or where there has been scientific misconduct (eg, debarment).

10.1.2 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to applicable regulatory agencies for approval prior to the study start. No patient will begin study-specific screening 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 Application [IND] study. In addition, local statement of investigator documents must be provided where required. Each investigator must submit to the sponsor (or designee) financial disclosure information for studies under a US IND or if required by national law and/or local regulations.

The study will be registered on regionally-relevant registries, including www.clinicaltrials.gov, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), and other applicable clinical study registry systems as required. Data generated from this study must be handled in accordance with any laws, rules, and regulations related to the privacy of personal data or personal health information applicable in the jurisdiction where the data are processed, including without limitation, the United States Health Information Portability and Accountability Act of 1996 (HIPAA), and its implementing regulations, and the European Union General Data Protection Regulation 2016/679 (GDPR).

10.1.3 Institutional Review Board or Independent Ethics Committee Approval

The protocol, all protocol amendments, and any material to be provided to the patient (such as the ICF, Patient Information Sheets (PIS), or descriptions of the study used to obtain informed consent) must be reviewed and approved by an IRB/IEC before study start, according to national law and/or local regulations. There must be proof of submission of the IB to the IRB/IEC.

The sponsor will supply relevant information to the investigator to use for submission of the study protocol and additional study documents to the IRB/IEC.

Verification of the IRBs/IEC's approval of the study protocol and the written ICF will be transmitted to the sponsor by the investigator or by other means as determined between the investigator and the sponsor.

No patient will begin study-specific procedures until appropriate IRB/IEC approval of the study protocol and ICF/PIS has been received and the investigator has obtained the patient's legally-effective ICF/PIS.

The investigator will submit appropriate reports on the progress of the study to the IRB/IEC at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IRB/IEC.

The IRB/IEC must be informed by the investigator of all 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.

10.2 Patient Information and Consent

10.2.1 General Aspects of Informed 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, the Declaration of Helsinki, and local requirements.

The ICF, prepared by the investigator with the assistance of the sponsor, must comply with all applicable regulations, be approved along with the study protocol by the IRB/IEC, and be acceptable to the sponsor.

It is the responsibility of the investigator to obtain legally-effective informed consent from each patient participating in this study (or their legally-acceptable representative) after adequate explanation of the aims, methods, objectives, and potential hazards of the study, answering all questions from the patient regarding the study, and prior to undertaking any study-related procedures.

10.2.2 Informed Consent Process

The patient must be provided with the patient information, if applicable, and the most current IRB/IEC-approved ICF. The investigator or their designee shall discuss with each patient the nature of the study, its requirements, and that participation is voluntary and may be terminated at any time by the investigator or participant. To participate in the study, informed consent must be obtained from each prospective patient prior to any protocol-specific activities.

The ICF must be in language fully comprehensible to the prospective patient. Patients or legally-authorized representatives (where acceptable according to national law and/or local regulations) 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. The patient and the person conducting the informed consent discussion for the study will

personally sign and date the ICF in addition to any other required signatures (if applicable). A copy of the signed ICF will be provided to the patient or legally-authorized representative and the original will be filed in the investigator's file. The process of obtaining informed consent will be documented in the patient's source documents. The date when a patient's informed consent was obtained will be captured in the patient's source documents and eCRF. The patient will need to re-consent if the ICF is updated during the study, such as after an amendment to the protocol, if mandated by the IRB/IEC.

10.3 Patient Confidentiality

The investigator must assure that each patient's anonymity is strictly maintained and that the identities are protected from unauthorized parties. Only identification codes (ie, no names or, in some regions, initials or date of birth) according to country regulations will be recorded on any form submitted to the sponsor and the IRB/IEC. The investigator must have a list where the identity of all study participants can be found, but not intended for use by the sponsor.

10.4 Study Monitoring

The sponsor, or contract research organization (CRO) or contract monitor acting on the sponsor's behalf, will have routine contact or visit the investigator during the study and through site closure. The monitor will perform a study closeout visit, which may be conducted remotely.

In accordance with ICH GCP and local regulations, the clinical monitor will periodically review eCRFs, study documents, and medical records (office, clinic, or hospital) for patients in this study (anonymity is to be preserved). 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, or as they occur should new or temporary measures be instituted.

The investigator must ensure provision of sufficient time, reasonable space, and adequate number of qualified personnel during monitoring visits, if applicable. The monitor will verify adherence to the study protocol and the completeness, consistency, and accuracy of data recorded on the eCRF and other documents; however, the investigator retains ultimate responsibility for the quality and integrity of data generated by the site. Aspects of the study that are essential for human patient protection and safety and the reliability of study data shall be confirmed. The investigator will make all source data (ie, the various study records, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) and eCRFs for the entire study period available to the monitor. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification). Should access to source documents and data temporarily be limited or restricted (eg, due to public quarantine), the investigator will inform the monitor upon awareness of the temporary conditions.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any issues detected in the course of the study are resolved. Contact information for the study monitor is located in the investigator file.

10.5 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 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, according to the principles of Attributable, Legible, Contemporaneous, Original or Certified Copy, Accurate, and 'Plus' (+) Complete, Consistent, Enduring, and Available (ALCOA+), 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, handwritten initials, delegated tasks, and dates of delegations for all individuals delegated responsibility on this study. This "study site personnel and delegation list" must be kept current throughout the study.

Clinical data will be entered into a 21 CFR Part 11-compliant EDC system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Data collection for the rollover study and entered into eCRF will include, but are not limited to:

- Enrollment (patient number [indicating parent study], informed consent)
- Dosing (date of first and last dose)
- Discontinuation (date and reason)
- Survival/Death (date and cause)
- Long-term follow-up

Laboratory data and investigator observations on the results and any other clinically-significant test results are to be documented in the source documents, but are not required to be entered into the eCRF.

Full information regarding EDC and completing eCRFs is included in the investigator files. All questions or comments related to EDC should be directed to the assigned monitor.

10.6 Study Termination and Site Closure

The sponsor, the investigator/institution, or IRB/IEC reserve the right to terminate the study at any time. Should this be necessary, the sponsor and investigator will arrange discontinuation procedures. In terminating 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 terminate the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if any of the following applies:

- 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 study unnecessary or unethical;
- The objectives applicable to this study are achieved; or
- The development of the investigational product is discontinued.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow up must be recorded in source documents and the eCRF. All reasons for discontinuation of treatment must be documented.

If 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).

10.7 Study Protocol Amendments

Protocol amendments must be made only with the prior approval of the sponsor, except where necessary to eliminate an immediate hazard(s) to the study participants. Agreement from the investigator must be obtained for all protocol modifications and changes to the informed consent document. The IRB/IEC must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the applicable regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines. Managing protocol deviations is described in Section 10.9.1.

10.8 Retention of Study Documents

The study site will maintain a study file, which will contain all documents defined in the ICH E6(R2) Guideline for Good Clinical Practice. The investigator will have control of all essential documents generated by the site. Source documents must be maintained and ALCOA+ documentation practice used. Any changes to source data will be traceable, will not obscure the original entry, and will be explained if necessary (via an audit trail). The investigator must implement procedures to ensure the integrity of any data generated.

The sponsor and 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. 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, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable inspections or audits from regulatory authorities, the IRB/IEC, and the sponsor or its designees.

The investigator shall retain records and documents, including signed ICFs, pertaining to the conduct of the study for a period of 25 years after study completion. However, these documents will be retained for a longer period of time if required by applicable local regulatory requirement(s), institutional policies, or if required 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 shall be destroyed without the agreement of the sponsor. Copies of original documents will 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 will be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification, irrespective of the media used.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site; but at a minimum, for the period defined by the applicable regulatory requirements.

10.9 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

10.9.1 Protocol 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's data nonevaluable. Any deviation must be documented in the source documents and reported to the sponsor and to the IRB/IEC according to institutional and sponsor requirements.

10.9.2 Study Site Training

Each investigator and the site personnel for this study will be trained by the sponsor and/or a designee (ie, a CRO) on ICH GCP and on the design, conduct, procedures, and administrative aspects of this study. This training may include, but is not limited to, on-site training or tele/videoconferencing. Training may be ongoing as refresher, to address specific items, or to introduce changes in the study. When site staff join after study training has been conducted, the investigator is responsible for ensuring that the new staff member is trained.

10.9.3 Quality Assurance Audits and Inspections

An audit of a clinical center may be conducted by a quality assurance auditor appointed by the sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. IRB/IEC representatives may also conduct an audit of the study at any time.

Representatives of the FDA, European Medicines Agency (EMA), or other regulatory agencies may conduct an inspection of the study at any time. If informed of such an inspection, the investigator will notify the sponsor immediately.

10.9.4 Direct Access to Source Data/Documents for Audits and Inspections

The investigator will ensure that the auditors or inspectors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all paper and electronic study files and audit trails are available, if requested. It is important that the investigator(s) and their staff cooperate with the quality assurance auditor or regulatory authority inspector during the audit or inspection.

10.10 Clinical Study Report

A clinical study report (CSR)/abbreviated CSR (aCSR) will be prepared if required for regulatory purposes.

10.11 Publication and Disclosure Policy

All information for the study provided by the sponsor or designee to the investigator, including, but not limited to, the IB, this protocol, eCRFs, the protocol-specified treatment, and any other study information, will 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.

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 study 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 [ICMJE]).[3] Written permission to the investigator will be contingent on the review of the statistical analysis and manuscript/abstract by the sponsor and participating cooperative groups, and will provide for nondisclosure of the 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 timeframe will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

10.12 Investigator Oversight

The investigator has full responsibility for supervising any individual or party to whom they delegate study-related duties and functions conducted at the study site, including satellite locations. The responsibility for supervision includes the services of any party or individual retained by the investigator for this purpose, regardless of location. All staff-delegated study responsibilities must be documented on an approved study site personnel and delegation log for the study and this log filed with the essential documents. In addition, the investigator must ensure that delegated staff are qualified by documented education, training, experience and licensure (as applicable). The investigator will implement procedures to ensure integrity of the study-related duties, functions performed, and any data generated.

11 REFERENCE LIST

1. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. 27 November 2017; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.
2. US Department of Health and Human Services, Food and Drug Administration, CDER, CBER. Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed 15 December 2014.
3. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. December 2017; http://www.icmje.org/recommendations/.
4. US Department of Health and Human Services, Food and Drug Administration, CDER. Draft Guidance for Industry: Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications. October 2017; https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf.

12 APPENDICES

Appendix 1 Examples of Sensitive Clinical Cytochrome P450 (CYP) Substrates

CYP Enzyme	Sensitive Substrates[a]
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine
CYP2C9	celecoxib
CYP2C19	S-mephenytoin, omeprazole
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Source: Draft FDA Guidance on Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications, 2017.[4] More example drugs can be found at the FDA's website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450; DDI = drug-drug interaction; FDA = Food and Drug Administration.

[a] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.