Medivation, Inc.

CLINICAL RESEARCH PROTOCOL

Study Title:	A Phase 1, Open-Label Study to Assess the Effects of Talazoparib on Cardiac Repolarization in Patients With Advanced Solid Tumors
Protocol Identifiers:	MDV3800-14 TRIO029
Phase	1
Investigational Product:	Talazoparib (also known as MDV3800, BMN 673)
Indication:	Solid Tumors
Sponsor:	Medivation, Inc. and its Subsidiaries 525 Market Street, 36th Floor San Francisco, CA 94105 Telephone: +1 (415) 543-3470 Fax: +1 (415) 543-3411
Reference Numbers:	United States IND 108,708
Sponsor Medical Monitor:	PPD . PPD , MD Telephone: PPD Mobile: Email:
Original Protocol:	v1.0 – 15 May 2016
Amendment 1	v2.0 – 19 Aug 2016

This study will be conducted according to the principles of Good Clinical Practice as described in International Conference on Harmonisation guidelines, including the archiving of essential documents.

[redacted]

SYNOPSIS

Title of Study: A Phase 1, Open-Label Study to Assess the Effects of Talazoparib on Cardiac Repolarization in Patients With Advanced Solid Tumors

Protocol Identifier: MDV3800-14

Phase of Development: 1

Number of Patients: At least 30 patients

Study Centers: Approximately 12 (United States)

Study Objectives:

Primary:

- To evaluate the effect of talazoparib on cardiac repolarization in patients with advanced solid tumors by assessing the corrected QT interval (QTc)
- To assess the relationship between plasma talazoparib concentrations and the QTc

Secondary:

- To evaluate the safety and tolerability of talazoparib
- To evaluate the effect of talazoparib on non-QT interval electrocardiogram (ECG) parameters (heart rate, RR, PR, QRS intervals, and ECG morphology)
- To evaluate the pharmacokinetics (PK) of talazoparib

Methods: This is a phase 1, open-label safety study of talazoparib (also known as MDV3800, BMN 673), a poly(ADP-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers. This study is designed to evaluate the effects of talazoparib on cardiac repolarization in at least 30 patients with advanced solid tumors with no available standard treatment options. Eligible patients will have continuous 12-lead ECG recordings at baseline (day -1); time-matched PK samples and continuous ECG recordings will be obtained at days 1, 2, and 22. Patients will fast for at least 6 hours before and 2 hours after the dose on days 1 and 22.

On day -1, patients will have continuous 12-lead ECG recording, starting at time 0 (baseline, corresponding to the dosing time on day 1) for 6 hours. On day 1, continuous 12-lead ECG recording will start 45 minutes before administration of talazoparib 1 mg at time 0, and continue through 6 hours postdose. Blood samples for PK will be collected predose and at 1, 2, 4, and 6 hours postdose. On day 2, a 30-minute continuous 12-lead ECG recording and a blood sample for PK will be obtained before the day 2 dose of talazoparib.

On days 3 to 21, talazoparib at 1 mg/day every day will be self-administered orally. On days 8 and 15, patients will return for general assessments.

On day 22, patients will return for steady-state continuous 12-lead ECG recordings, starting 45 minutes before the dose of talazoparib, and continuing for 6 hours postdose. PK samples will be collected predose and at 1, 2, 4, and 6 hours postdose.

ECG data from continuous 12-lead ECG recordings will be submitted for independent central review. After reviewing for data quality, triplicate 10-second ECGs will be extracted from a 5-minute extraction window at each planned time point, beginning 15 minutes before each PK collection time point. ECG recordings will be analyzed for measurement of RR, PR, QRS, and QT intervals and evaluation of ECG morphology.

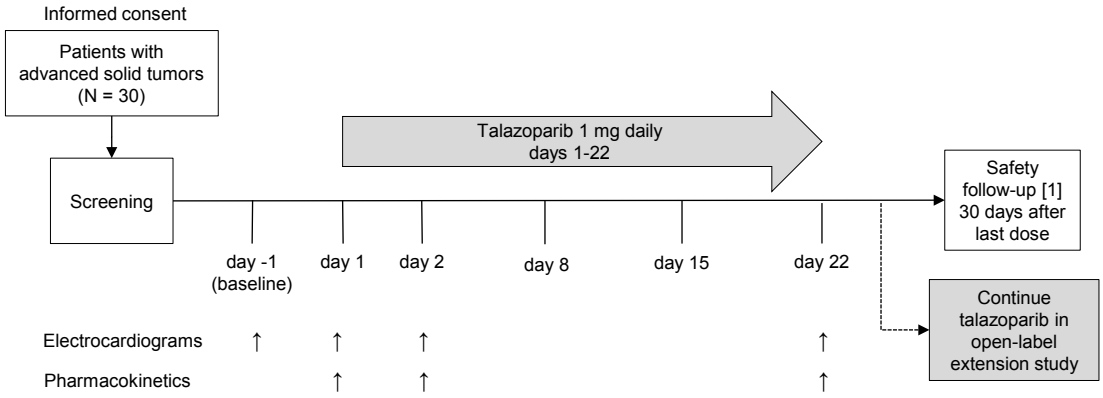
Study periods include screening, baseline (day -1), a 22-day treatment period, and safety follow-up. Safety follow-up will occur approximately 30 days after the last dose of study drug or before initiation of a new antineoplastic therapy, whichever occurs first. For further talazoparib treatment, patients must enroll and initiate continued talazoparib treatment in a separate open-label extension study within 30 days after the last dose of study drug, and in this case, safety follow-up will be omitted and an ECG will be obtained at the time of enrollment in the open-label extension study.

Study Assessments:

Continuous ECGs will be collected on days -1, 1, 2, and 22; single ECGs will be collected at screening and safety follow-up. PK samples will be collected on days 1, 2, and 22. Other general and laboratory assessments will be performed at screening; days -1, 1, 2, 8, 15, and 22; and safety follow-up according to the schedules of activities. Safety will be assessed by adverse events, physical examinations, vital signs, ECGs, and clinical laboratory tests.

No efficacy assessments will be performed for this study. Disease assessments will be performed according to the standard of care at the study site.

Study Schematic:



[1] Safety follow-up will be omitted for patients who enroll and initiate continued talazoparib treatment within 30 days in the open-label extension study; an ECG will be obtained at the time of enrollment in the open-label extension study.

Key Eligibility Criteria:

Patients must have histologically confirmed advanced solid tumors with no available standard treatment options. The Eastern Cooperative Oncology Group (ECOG) performance status score must be ≤ 2 and estimated life expectancy must be ≥ 3 months.

Test Product, Dose, and Mode of Administration:

Talazoparib is provided as the 4-methylbenzenesulfonate (tosylate) salt and has the chemical name (8S,9R) 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-pyrido[4,3,2-de]phthalazin-3-one.

The drug product is a capsule containing talazoparib tosylate and silicified microcrystalline cellulose. The capsules for each dose strength will be provided in dose-specific colors.

Talazoparib 1 mg will be self-administered orally once daily at approximately the same time each day. Talazoparib capsules will be swallowed whole with a glass of water. Patients will fast for at least 6 hours before and 2 hours after the dose on days 1 and 22. Patients may resume eating after the 2-hour postdose PK sample is collected. On other days, talazoparib may be taken with or without food.

Reference Therapy, Dose, and Mode of Administration:

Not applicable.

Duration of Treatment:

Talazoparib treatment will continue through day 22 in this study. For further talazoparib treatment, patients must enroll and initiate continued talazoparib treatment in a separate open-label extension study within 30 days after the last dose of talazoparib. Dose modification guidelines must be followed for managing adverse events as described in Section 8.2.1. Study drug treatment may be discontinued for disease progression based on investigator assessment.

Statistical Methods:

Safety Analyses:

All safety analyses will be performed using the safety population, defined as all patients who receive any amount of talazoparib. The safety of talazoparib will be evaluated by the analysis of incidence of serious and nonserious adverse events, severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in vital signs, ECGs, and clinical laboratory values. Drug exposure will be summarized using descriptive statistics.

Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (eg, leading to permanent treatment discontinuation).

Treatment-emergent safety data will be collected from day 1 (the first dose of study drug) through approximately 30 days after the last dose of study drug, before initiation of a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first.

Laboratory values will be classified by severity using the CTCAE. Laboratory shift tables of baseline results to each subsequent visit will be produced as appropriate.

ECG Analyses: The primary endpoints are to evaluate the effects of talazoparib on Fridericia's corrected QT interval (QTcF); and to evaluate the relationship between the plasma concentration of talazoparib and the change from baseline in QTc, corrected for heart rate based on Fridericia's correction formula (ΔQTcF). Bazett's correction formula (ΔQTcB) will also be evaluated. Changes from time-matched baseline measurements will be calculated and data will be summarized in tabular and graphic formats for each study visit. Assessments include absolute QTc prolongation with QTc > 450 msec, > 480 msec, and > 500 msec and change from baseline in QTc with QTc increase > 30 msec and > 60 msec. The means of each measurement of RR, PR, QRS, and QT intervals will be utilized for statistical analyses. Heart rate will be used to assess QTc endpoints.

ECG morphology and changes from baseline for each planned postbaseline time point will be summarized for all patients. The proportion of patients with any postbaseline change in ECG morphology and the proportion of patients with each type of abnormality will also be summarized.

PK Analyses:

Summary data of plasma talazoparib concentrations will be presented in tabular and graphic formats for each time point. PK parameters such as time to maximum concentration (T_{max}), maximum plasma concentration (C_{max}), and area under the concentration-time curve (AUC) on days 1 and 22 will be calculated. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately.

PK-Pharmacodynamic Analyses:

The correlation between changes in ECG interval measurements from time-matched baseline and the plasma talazoparib concentration will be investigated using a linear mixed-effects model.

Efficacy Analyses:

No efficacy analysis is planned in this study.

Sample Size Considerations:

A sample size of at least 30 evaluable patients will provide 80% power to reject the null hypothesis if the mean change from baseline in QTcF is ≥ 10 msec with a 95% one-sided alpha, assuming a standard deviation of 20 msec. Patients will be enrolled until 30 patients complete day 22, miss ≤ 5 consecutive doses of study drug, have technically adequate ECG recordings, and have at least 80% of specified PK samples collected representing all 3 days of observation (days 1, 2, and 22).

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BRCA	Breast cancer susceptibility gene
BCRP	Breast cancer resistance protein
CFR	Code of Federal Regulations
CL/F	Apparent oral clearance
C_{max}	Maximum plasma concentration
C_{min}	Plasma trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
EC	Ethics committee (global term including institutional review boards, independent ethics committees, research ethics committees, and the like)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	Identification
INR	International normalized ratio
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
PARP	Poly(ADP-ribose) polymerase
P-gp	P-glycoprotein
PD	Pharmacodynamics
PK	Pharmacokinetics
QTc	Corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
SUSAR	Suspected unexpected serious adverse reaction
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States

1 INTRODUCTION

1.1 Background

Talazoparib (also known as MDV3800, BMN 673) is a potent, orally bioavailable, small molecule poly(ADP-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers. PARP inhibitors including talazoparib exert cytotoxic effects by 2 mechanisms: inhibition of PARP1 and PARP2 enzyme activity, and PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription (Murai et al, 2012). Single-agent talazoparib has demonstrated potent antitumor effects in human cancer cell lines harboring gene mutations that compromise DNA repair, as well as in mouse tumor xenograft models (Murai et al, 2014; Shen et al, 2013; Cardnell et al, 2013). Antitumor effects have also been observed in phase 1 studies of talazoparib monotherapy in patients with cancer.

This cardiac safety study will evaluate the effects of talazoparib on cardiac electrophysiology, in particular cardiac repolarization as assessed by the corrected QT interval (QTc).

1.2 Summary of Relevant Clinical Experience With Talazoparib

Approximately 319 patients have received talazoparib in company-sponsored studies as of 30 Nov 2015, including 3 studies in solid tumors and 1 in hematologic malignancies. Studies include a phase 1 study (PRP-001) in advanced solid tumors, a phase 2 study (673-201, ABRAZO) in advanced breast cancer, and a phase 3 study (673-301, EMBRACA) in locally advanced and/or metastatic breast cancer.

1.2.1 Efficacy

PRP-001 is a phase 1, open-label, safety, pharmacokinetics (PK), and dose-escalation (0.025-1.1 mg/day) and expansion (1 mg/day) study of talazoparib monotherapy in 110 patients with advanced or recurrent solid tumors with DNA repair deficiencies. As of 30 Nov 2015, objective responses (complete response, partial response) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) were observed in patients with breast (8 of 18 [44.4%]), ovarian/primary peritoneal (12 of 25 [48%]), and pancreatic (2 of 13 [15.4%]) cancers with deleterious germline breast cancer susceptibility gene (BRCA) mutations. Clinical benefit (complete response, partial response, or stable disease $\geq$ 24 weeks) was observed in 13 of 18 patients (72.2%), 19 of 25 patients (76%), and 4 of 13 patients (30.8%), respectively. In patients with small cell lung cancer, objective responses were observed in 2 of 23 patients (8.7%) and clinical benefit reported in 6 of 23 patients (26.1%).

Additional information on the clinical efficacy of talazoparib is provided in the talazoparib investigator brochure.

1.2.2 Safety

The safety of talazoparib is based on phase 1 and 2 studies in patients with advanced cancer.

Aggregate safety data from 3 of the 5 company-sponsored clinical studies (phase 1 studies PRP-001 and PRP-002, and phase 2 study 673-201; 214 patients total; data as of 30 Nov 2015) provide the basis for the most common treatment-emergent adverse events. The most common adverse events associated with talazoparib (> 20%) were myelosuppression (anemia, thrombocytopenia, neutropenia), gastrointestinal toxicity (nausea, diarrhea, vomiting), and fatigue. The most common grade 3 or higher adverse events and serious adverse events were associated with myelosuppression. A total of 25 of 214 patients had an adverse event that led to death (12 associated with malignancies, 3 disease progression, 2 each lung infection and pneumonia, and 1 each cardiorespiratory arrest, neutropenic sepsis, renal impairment, dyspnea, hypoxia, and respiratory failure). Of these events, none was assessed as related to study drug. Eight of 214 patients discontinued study drug due to an adverse event.

In the ongoing phase 3 study 673-301, an adverse event of veno-occlusive disease of the liver leading to death was assessed as related to talazoparib by the investigator.

Additional information on the clinical safety of talazoparib is provided in the talazoparib investigator brochure.

1.2.3 Pharmacokinetics

The PK of talazoparib as a single agent was evaluated in 142 adult patients with cancer, including 109 patients with solid tumors (PRP-001) and 33 with hematologic malignancies (PRP-002). Doses of 0.025 mg to 2 mg were administered orally as a single dose or as once daily doses. This dose range bracketed the 1 mg/day dose used in ongoing safety and efficacy studies, and provided a framework for assessing dose linearity. As the PK of talazoparib was similar in patients with solid tumors and hematologic malignancies, and no differences were apparent between males and females, the results are summarized collectively.

Oral absorption of talazoparib was rapid and independent of dose after administration of single or once-daily doses. Peak talazoparib concentrations were generally reached approximately 1 to 8 hours postdose. Exposure increased approximately dose-proportionally with increasing doses. At 1 mg/day, the mean half-life was approximately 2 days; the mean apparent volume of distribution was 415 L, indicating extensive extravascular distribution. Steady state was reached in approximately 2 to 3 weeks with daily administration.

Apparent oral clearance (CL/F) of talazoparib appeared to be dose linear, with a mean CL/F across doses of approximately 5 L/h. Renal excretion was a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44% to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady state for doses up to 1 mg/day. Mean renal clearance ranged from 1.38 L/h to 4.96 L/h, independent of dose, suggesting linear urinary elimination kinetics.

Following repeated administration at 1 mg/day, talazoparib accumulated approximately 2.4-fold relative to a single dose. At steady state, the mean maximum plasma concentration (C_{max}) was 21.0 ng/mL, the mean plasma trough concentration (C_{min}) was 3.72 ng/mL, and the mean area under the concentration-time curve (AUC) was 202 ng•h/mL.

PK data from a food-effect study showed that food had no effect on the extent of absorption of talazoparib (AUC), but decreased the rate of absorption (C_{max} was 46% lower and time to C_{max} [T_{max}] was 2.63 hours later); however this reduction in the rate of absorption following a single dose is not clinically relevant because talazoparib accumulates 2.4-fold at steady state after 1 mg once-daily dosing. Furthermore, in nonclinical pharmacology studies, AUC or C_{min} appeared to drive efficacy, not C_{max}; therefore, talazoparib can be taken with or without food. Talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

A preliminary population PK analysis using data from patients in studies PRP-001 and PRP-002 assessed the effects of renal function on the PK of talazoparib. In patients with moderate renal impairment (creatinine clearance [CL_{CR}] 30-59 mL/min), the talazoparib CL/F was decreased by 44% from normal, resulting in higher talazoparib exposure.

The effects of hepatic impairment on talazoparib PK have not been studied.

The potential for talazoparib to affect the PK of other drugs was assessed through in vitro experiments and is described in Section 1.3.2. Additional information on the PK of talazoparib is provided in the investigator brochure.

1.3 Summary of Relevant Nonclinical Experience With Talazoparib

1.3.1 Nonclinical Pharmacology of Talazoparib

The cytotoxic activity of talazoparib was demonstrated in cell culture, and antitumor effects were demonstrated in mouse xenograft models.

In cell-free enzyme assays, talazoparib inhibited PARP1 and PARP2 catalytic activity (Wang et al, 2016). Talazoparib was approximately 3.4- to 8.3-fold more potent than other PARP inhibitors in clinical development (veliparib, rucaparib, olaparib) in inhibiting PARP1 catalytic activity (Shen et al, 2013). In addition, talazoparib was approximately 40-fold more potent than olaparib in stimulating the formation of stable PARP1-DNA complexes (Murai et al, 2014).

In tissue culture studies, talazoparib was cytotoxic to cancer cell lines harboring gene mutations that compromise DNA repair pathways, including MX-1 (BRCA1-mutant) and MDA-MB-468 (PTEN-mutant) mammary cancer cells, LNCaP (PTEN- and ATM-mutant) and PC-3 (PTEN-mutant) prostate cancer cells, and HCT-116 (MLH-1-mutant) colorectal tumor cells. The half-maximal inhibitory concentration (IC_{50}) values of talazoparib in these cancer cell lines were in the single-digit nanomolar or subnanomolar range; in contrast, the IC_{50} values of talazoparib in MRC-5 normal human primary lung cancer cells and other tumor cell lines without reported DNA repair-related mutations were higher (250 nM to

> 1000 nM). The talazoparib IC_{50} for growth inhibition of Capan-1 human pancreatic cancer cells (BRCA2-deficient) was 50- to over 2000-fold lower than the other PARP inhibitors tested (Shen et al, 2013). The higher potency of talazoparib relative to the other PARP inhibitors is thought to be due to the more potent PARP trapping activity seen with talazoparib as opposed to inhibition of PARP catalytic activity (Shen et al, 2015).

Consistent with its antitumor effects in tissue culture, talazoparib demonstrated potent antitumor activity in mouse xenograft models of small cell lung cancer and breast cancer (Cardnell et al, 2013; Shen et al, 2013).

Additional information on the nonclinical pharmacology of talazoparib is provided in the talazoparib investigator brochure.

1.3.2 Nonclinical PK and Metabolism

PK studies in rats and dogs show that talazoparib oral bioavailability was > 43% in rats and > 51% in dogs. A Good Laboratory Practice (GLP) study in dogs demonstrated that the capsule formulation used in clinical studies is approximately 2-fold more bioavailable than the suspension formulation used in nonclinical studies. In general, talazoparib displays greater than or approximately dose-proportional increases in exposure in rats and dogs with no evidence of sex differences.

Studies of [^{14}C]-talazoparib in rats and dogs indicate rapid absorption, wide distribution (greater than total body water), and nearly complete elimination of drug substance (> 90%) by 7 days. Fecal elimination was the main route of elimination in both species, and renal excretion was moderate (21-26%). In a study in rats, [^{14}C]-talazoparib was widely distributed, reaching maximum levels 1 to 4 hours postdose. Excluding the gastrointestinal tract, the highest radioactivity levels were observed in liver and kidney (and the eye uveal tract in albino rats). Tissue radioactivity levels were greater than blood levels in the target organs of talazoparib toxicity (bone marrow, spleen, and thymus) through 7 days. Metabolic profiling of plasma, urine, and feces samples indicated that [^{14}C]-talazoparib is largely cleared via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation.

In vitro metabolism studies in rat, dog, and human hepatic microsomes demonstrated that [^{14}C]-talazoparib has high metabolic stability (> 90%) over 2 hours. A minimal extent or a lack of metabolism for [^{14}C]-talazoparib was observed in the presence of freshly isolated mouse, rat, dog, and human hepatocytes or cryopreserved human hepatocytes. Talazoparib does not appear to be a substrate of any major cytochrome P450 (CYP450) metabolizing enzyme.

Mean binding to human plasma proteins is 78.7%; therefore, it is unlikely that talazoparib will demonstrate clinically significant drug-drug interactions related to displacement from plasma protein binding sites. At therapeutic exposures, talazoparib does not markedly induce or inhibit CYP450 enzymes. Therefore, it is unlikely that talazoparib will demonstrate clinically significant CYP450 inhibition- or induction-based drug-drug interactions when coadministered with corresponding substrates. At therapeutic exposures, talazoparib does

not markedly induce or inhibit any transporters. Therefore, it is unlikely that talazoparib will demonstrate clinically significant drug transporter inhibition-based drug–drug interactions when coadministered with corresponding substrates.

Because talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), plasma talazoparib concentrations may increase or decrease when coadministered with P-gp or BCRP inhibitors or inducers, respectively. Guidelines for concomitant use of talazoparib inhibitors or inducers of P-gp or inhibitors of BCRP are provided in Section 7.3.

Additional information on the nonclinical PK and drug metabolism of talazoparib is provided in the investigator brochure.

1.3.3 Nonclinical Toxicology

Safety pharmacology, single- and repeat-dose toxicity, genotoxicity, embryo-fetal development, and in vitro phototoxicity studies were conducted to evaluate the nonclinical toxicology profile of talazoparib. Repeat-dose toxicity/toxicokinetic studies were conducted with talazoparib utilizing the intended oral route of administration in mice, rats, and dogs. A repeat-dose study with talazoparib was conducted in BALB/c nude mice to select doses and exposures for the mouse xenograft studies.

Five-day, 28-day, and 13-week repeat-dose GLP toxicity and toxicokinetic studies with 28-day recovery periods were conducted in the rat and dog. The major findings are as follows:

- Dose-dependent pancytopenia with bone marrow hypocellularity and depletion of lymphoid tissue in multiple organs was observed and considered possibly due to exaggerated pharmacology of talazoparib based on the higher (relative to baseline) poly(ADP-ribose) (index of PARP1/2 activity) tissue levels in these organs. The hematologic findings were partially reversible and may be readily monitored in the clinic. The toxicities that resulted in mortality in dogs (0.1 mg/kg/day) and some rats (1 mg/kg/day) occurred at $AUC_{0\text{-}24}$ exposures that were > 0.8- and 4-fold higher, respectively, than the exposure at the recommended human dose of 1 mg/day. The toxicities were mainly due to septicemia that resulted from the severe bone marrow and lymphoid depletion.
- A dose-dependent increased incidence of gastrointestinal tract findings of apoptosis/necrosis in the stomach and duodenum was observed. Additional findings at higher doses included reversible villous atrophy and increased apoptosis throughout the gastrointestinal tract, most notably in the small intestine. Gastrointestinal tract toxicities of enteropathy and villous atrophy caused mortality in rats at 3.0 mg/kg/day. Exposures at 3.0 mg/kg/day are significantly higher than the exposures at the recommended human dose.

- Additional findings at the high dose (≥ 1 mg/kg/day) in the 5-day GLP study in rats included focal necrotic changes in the ovarian follicular atresia and hepatocyte necrosis of the liver. These findings were not observed in the 28-day or 13-week repeat-dose studies in rats.
- Atrophy and/or degenerative changes in testes and epididymis and effects on the seminiferous tubules were observed in rats and dogs; the severity correlated with both dose and duration of treatment.

There were no talazoparib-related effects on respiratory or central nervous system parameters after a single oral administration to rats (safety pharmacology studies), or on cardiovascular parameters and electrocardiogram (ECG) evaluations after a repeat-dose oral administration in dogs (repeat-dose toxicity studies). Talazoparib had no effect on ophthalmologic end points in rats or dogs in repeat-dose toxicity studies. Talazoparib was not mutagenic in a bacterial reverse mutation assay, but consistent with the genomic instability of its primary pharmacology, was clastogenic in an in vitro chromosomal aberration assay and in an in vivo micronucleus assay, indicating the potential for genotoxicity in humans. Talazoparib caused fetal malformations, structural variations, and death in an embryo-fetal development study in rats. Based on an in vitro 3T3 neutral red uptake assay, which results in a high incidence of false positives, talazoparib is potentially phototoxic in humans. In conclusion, the main nonclinical toxicologic findings were early hematologic changes, and subsequent bone marrow and lymphoid organ depletion; focal atrophy and degeneration of testes, epididymis, and seminiferous tubules; and dose-dependent apoptosis/necrosis in the gastrointestinal tract and liver after repeat-dose talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. Additional information on the toxicology of talazoparib is provided in the talazoparib investigator brochure.

1.4 Cardiac Safety of Talazoparib

In vitro, talazoparib has an estimated IC_{50} for inhibition of hERG channels of > 100 μM whereas in humans taking 1 mg once daily the mean C_{max} at steady state is 0.055 μM (free C_{max} of 0.0117 μM), indicating low potential for significant inhibition. In vivo, ECG evaluations were conducted in 28-day and 13-week toxicity studies in beagle dogs over a range of doses. No talazoparib-related changes in PR, QRS, QT, QTc, or RR intervals, or heart rate were observed on days 3 or 24 of the dosing phase (28-day study) or day 90 of the dosing phase or day 26 of the recovery phase (13-week study). No rhythm abnormalities or qualitative ECG changes were observed during qualitative assessment of the ECGs in either study.

In phase 1 study PRP-001 (110 patients), ECGs were recorded at baseline, at 3 to 4 hours postdose on days 1 and 35 (dose-escalation phase) or at day 1 of cycle 2 (dose-expansion phase), and at the end of treatment (< 10 days after the last dose of talazoparib), if clinically indicated. ECG interval data were collected retrospectively from these recordings. Of the 96 patients with ECG recordings at baseline and postbaseline based on draft data, 1 patient had a postbaseline QTcF (Fridericia's corrected QT interval) > 500 msec; 1 had a postbaseline QTcF > 480 msec to ≤ 500 msec; and 9 (9.4%) had a postbaseline

QTcF > 450 msec to ≤ 480 msec. One patient had an increase in QTcF from baseline > 60 msec and 6 (6.3%) had an increase in QTcF from baseline > 30 msec to ≤ 60 msec.

These observations indicate that talazoparib has a low risk of QT prolongation or proarrhythmic effects. This study will further assess the effects of talazoparib on cardiac electrophysiology.

1.5 Talazoparib Benefits and Risks Assessment

The dose of talazoparib in this study, 1 mg/day, is supported by nonclinical studies and phase 1 studies in patients with advanced malignancies. Antitumor activity has been observed, and warrants further exploration in a larger patient population. The expected adverse events with talazoparib include myelosuppression, gastrointestinal toxicity, fatigue, and alopecia. Hepatotoxicity, febrile neutropenia, and neutropenic sepsis are potential risks per the investigator brochure Section 7. The activity of talazoparib is being evaluated in multiple indications. The benefit-risk profile of talazoparib is not yet well characterized.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the effect of talazoparib on cardiac repolarization in patients with advanced solid tumors by assessing the QTc
- To assess the relationship between plasma talazoparib concentrations and the QTc

2.2 Secondary Objectives

- To evaluate the safety and tolerability of talazoparib
- To evaluate the effect of talazoparib on non-QT interval ECG parameters (heart rate, RR, PR, QRS intervals, and ECG morphology)
- To evaluate the PK of talazoparib

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

This is a phase 1, open-label safety study of talazoparib, a PARP inhibitor in development for the treatment of a variety of human cancers. This study is designed to evaluate the effects of talazoparib on cardiac repolarization in at least 30 patients with advanced solid tumors with no available standard treatment options. Eligible patients will have continuous 12-lead ECG recordings at baseline (day -1); time-matched PK samples and continuous ECG recordings will be obtained at days 1, 2, and 22. Patients will fast for at least 6 hours before and 2 hours after the dose on days 1 and 22.

On day -1, patients will have continuous 12-lead ECG recording, starting at time 0 (baseline, corresponding to the dosing time on day 1) for 6 hours. On day 1, continuous 12-lead ECG

recording will start 45 minutes before administration of talazoparib 1 mg at time 0, and continue through 6 hours postdose. Blood samples for PK will be collected predose and at 1, 2, 4, and 6 hours postdose. On day 2, a 30-minute continuous 12-lead ECG recording and a blood sample for PK will be obtained before the day 2 dose of talazoparib.

On days 3 to 21, talazoparib at 1 mg/day every day will be self-administered orally. On days 8 and 15, patients will return for general assessments.

On day 22, patients will return for steady-state continuous 12-lead ECG recordings, starting 45 minutes before the dose of talazoparib, and continuing for 6 hours postdose. PK samples will be collected predose and at 1, 2, 4, and 6 hours postdose.

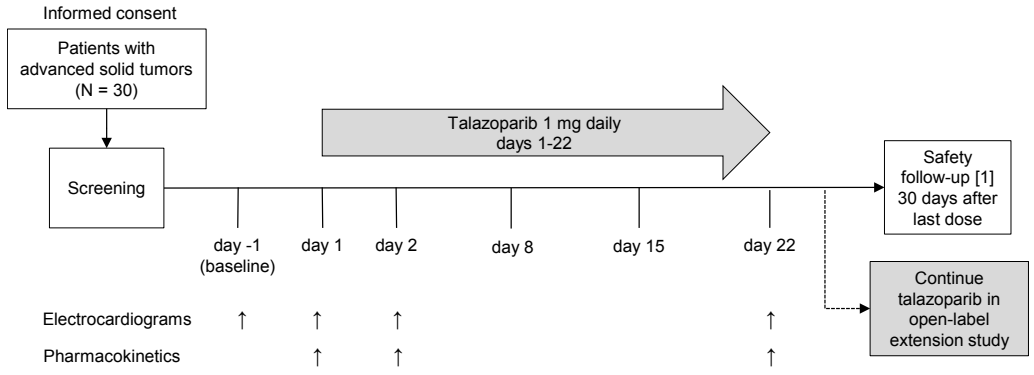
ECG data from continuous 12-lead ECG recordings will be submitted for independent central review. After reviewing for data quality, triplicate 10-second ECGs will be extracted from a 5-minute extraction window at each planned time point, beginning 15 minutes before each PK collection time point. ECG recordings will be analyzed for measurement of RR, PR, QRS, and QT intervals and evaluation of ECG morphology.

Study periods include screening, baseline (day -1), a 22-day treatment period, and safety follow-up. Safety follow-up will occur approximately 30 days after the last dose of study drug or before initiation of a new antineoplastic therapy, whichever occurs first. For further talazoparib treatment, patients must enroll and initiate continued talazoparib treatment in a separate open-label extension study within 30 days after the last dose of study drug, and in this case, safety follow-up will be omitted and an ECG will be obtained at the time of enrollment in the open-label extension study.

3.2 Study Schematic

The study schematic is provided in Figure 1.

Figure 1: Study Schematic



[1] Safety follow-up will be omitted for patients who enroll and initiate continued talazoparib treatment within 30 days in the open-label extension study; an ECG will be obtained at the time of enrollment in the open-label extension study.

3.3 Blinding

All treatments will be open label. All patients, study site personnel (including investigators), and sponsor staff and its representatives will be unblinded to treatment identity. Central reviewers for ECG data are blinded to patient identifiers, treatment, and visit.

3.4 Duration of Study

The total duration of this study will be approximately 1 year.

3.5 Discussion of Study Design

The maximum tolerated dose of talazoparib is 1 mg/day (de Bono et al, 2013) and is defined as the recommended human dose. The talazoparib 1 mg/day dose is being used in this study and is currently being evaluated in ongoing studies in patients with breast cancer, as discussed in Section 1. This study will assess the risk of QT prolongation with serial ECG recordings and time-matched PK measurements. Supratherapeutic doses cannot be administered safely, so a traditional thorough QT study is not feasible. Because talazoparib is clastogenic in vitro and in vivo, it is not possible to conduct the study in healthy volunteers. Therefore, adult patients with advanced solid tumors, representative of the population being evaluated in current and planned phase 2 and 3 studies, will be enrolled.

With chronic dosing at 1 mg/day, plasma talazoparib concentrations reach steady state in 2 to 3 weeks, with about a 2.4-fold accumulation relative to a single dose. Therefore, a 22-day dosing duration will allow most patients to reach steady-state concentrations of talazoparib. ECG recordings will be obtained with time-matched PK samples over a wide range of plasma talazoparib concentrations, after both acute and chronic dosing.

The primary endpoints are to evaluate the effects of talazoparib on QTcF and to evaluate the relationship between the plasma concentration of talazoparib and the change from baseline in QTc, corrected for heart rate based on the QTcF correction formula (ΔQTcF). Bazett's correction formula (ΔQTcB) will also be evaluated. Continuous ECG recordings will be obtained at baseline (day -1), and continuous ECG recordings and blood samples for PK will be obtained on days 1, 2, and 22 (steady state) to obtain ECG recordings over a range of plasma concentrations of talazoparib. Patients will fast for at least 6 hours before and 2 hours after the dose on days 1 and 22 to minimize the variability of C_{max}. For the PK-pharmacodynamic (PD) analysis, a linear mixed effects modeling approach will be used to examine the relationship between the changes from baseline in QTc intervals (ΔQTcF and ΔQTcB) and plasma concentration of talazoparib.

No tumor assessments or other efficacy measures will be collected in this study. Disease assessments may be performed according to the standard of care at the study site.

4 SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1 Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. At least 18 years of age and willing and able to provide informed consent.
2. Histologically or cytologically confirmed advanced solid tumor with no available standard treatment options in the opinion of the investigator.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Estimated life expectancy of ≥ 3 months.
5. Able to swallow the study drug, have no known intolerance to the study drug or excipients, and comply with study requirements.
6. Female patients of childbearing potential (defined in Section 8.2.3) must have a negative pregnancy test at screening and must agree to use a highly effective birth control method (defined in Section 8.2.3) from the time of the first dose of study drug through 45 days after last dose of study drug.
7. Male patients must use a condom when having sex with a pregnant woman or with a woman of childbearing potential from the time of the first dose of study drug through 105 days after last dose of study drug. Contraception should be considered for a nonpregnant female partner of childbearing potential.
8. Male and female patients must agree not to donate sperm or eggs, respectively, from the first dose of study drug through 105 days and 45 days after the last dose of study drug, respectively.
9. Female patients may not be breastfeeding at screening and must not breastfeed during study participation through 45 days after the last dose of study drug.

4.2 Exclusion Criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Use of antineoplastic therapies within 21 days before day -1.
2. Use of any other investigational agent within 21 days before day -1.
3. Have not recovered (recovery is defined as National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] grade ≤ 1) from the acute toxicities of previous therapy, except treatment-related alopecia or laboratory abnormalities otherwise meeting eligibility requirements.
4. Electrolyte abnormality that has not responded to correction, including hypokalemia or hypocalcemia less than the lower limit of normal, or hyperkalemia or hypercalcemia greater than the upper limit of normal (ULN).

5. Major surgery within 14 days before day -1.
6. Diagnosis of myelodysplastic syndrome (MDS) or a hematologic malignancy.
7. Clinically significant cardiovascular disease, including any of the following:
   - Myocardial infarction or symptomatic cardiac ischemia within 6 months before day -1
   - Heart failure, New York Heart Association class II to IV
   - History of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsade de pointes)
   - History of Mobitz II second degree or third degree heart block
   - Atrial arrhythmia (ie, chronic atrial fibrillation or paroxysmal supraventricular tachycardia)
   - Hypotension as indicated by systolic blood pressure < 100 mm Hg at screening or at day -1; a second measurement may be taken after hydration with oral fluids if the first measurement was < 90 mm Hg
   - Bradycardia as indicated by a heart rate of < 50 beats per minute or tachycardia as indicated by a heart rate of > 100 beats per minute on the screening ECG
   - Poorly controlled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at screening
   - Screening QTcF ≥ 450 msec
   - Ventricular pacing (implanted pacemaker or implantable cardioverter-defibrillator [ICD])
   - QRS duration > 119 msec
   - PR interval > 220 msec
8. Significant organ dysfunction as defined by any of the following laboratory abnormalities at screening:
   - Renal: estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 by the MDRD equation (Modification of Diet in Renal Disease [available via www.mdrd.com])
   - Hepatic:
     – Total serum bilirubin > 1.5 times ULN (> 3 × ULN for patients with documented Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation)
     – Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.5 times ULN (if liver function abnormalities are due to hepatic metastasis, then AST and ALT > 5 × ULN)
   - Bone marrow reserve: absolute neutrophil count < 1500/µL, platelets < 100,000/µL, or hemoglobin < 9 g/dL (blood samples collected after ≥ 14 days without growth factor support or transfusion)
9. Gastrointestinal disorder affecting absorption.

10. Current or anticipated use of a strong P-gp inhibitor (eg, dronedarone, quinidine, ranolazine, verapamil, itraconazole, ketoconazole), strong P-gp inducer (eg, rifampin, tipranavir, ritonavir), or strong inhibitor of BCRP (eg, elacridar [GF120918]).
11. Any condition (concurrent disease, infection, or comorbidity) that interferes with ability to participate in the study, causes undue risk, or complicates the interpretation of safety data, in the opinion of the investigator or medical monitor.

5 ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The study periods will include screening, treatment (baseline on day -1 and 22 days of treatment), and safety follow-up. The timing of all study procedures is provided in the schedules of activities (Appendix 1, Appendix 2). Signed informed consent must be obtained before performing any study-specific procedures. The study manual contains the information needed for registering patient status (eg, assigning screening and enrollment numbers, indicating screen failure, and end of treatment).

5.1 Screening Period

The screening period will be from day -29 through day -2. For the purposes of this study, there will be no day 0.

5.1.1 Informed Consent

Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and must document the informed consent process in the patient's source documents.

The informed consent form may be signed before the 28-day screening period.

5.1.2 Screening Identification Numbers

After obtaining signed informed consent, study site personnel will assign a screening identification (ID) number for each potential study participant per the study manual.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent, study site personnel will document the screen failure or consent withdrawal in the patient's source documents. The documentation will include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, and procedures performed.

5.1.3 Screening Procedures

Screening procedures are listed in the schedule of activities in Appendix 1. All procedures must be completed within 28 days before day -1 except as noted.

The investigator will assess the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will request that the sponsor or designee approve the enrollment.

5.2 Treatment Period

5.2.1 Treatment Period Visit Windows

All treatment period visits have a visit window of ±3 days (ie, 3 days before or after the given day), except for days -1, 1, and 2.

5.2.2 Treatment Period Procedures

5.2.2.1 Enrollment

Study site personnel should receive enrollment approval from the sponsor or designee before proceeding with enrollment. An enrollment ID number will be assigned per the study manual. This number will be used to identify the patient for the remainder of the study. Patients must initiate study treatment within 3 business days after enrollment approval.

5.2.2.2 Treatment Period Study Visit Procedures

Day -1 is the day of baseline, and day 1 is the day of the first dose of study drug.

Specified study procedures will be performed at each clinic visit according to the schedule of activities (Appendix 2). The ECG, blood pressure, and PK collection schedule is as follows (Appendix 3):

- Continuous ECG recordings are obtained by attaching the Holter monitor at the start of the collection time point on days -1, 1, 2, and 22. Blood pressure (after supine for 5 minutes) will be obtained 15 to 20 minutes before each PK collection time point. After blood pressure is obtained, the patient should remain supine for 10 to 15 minutes (for continuous ECG recording) before blood samples for PK are collected.
- On day -1 (baseline), ECG recording will start at time 0 (corresponding to the dosing time on day 1) and continue for 6 hours.

- Patients will fast for at least 6 hours before and 2 hours after the day 1 dose.
- On day 1 (within 72 hours of time 0 on day -1, corresponding to the clock time of the first baseline ECG measurement), ECG recording will start at least 45 minutes before the first dose of study drug at time 0, and continue for 6 hours postdose. Blood samples for PK will be collected immediately before the first dose of study drug and at 1, 2, 4, and 6 hours postdose. Patients may resume eating after the 2-hour postdose PK sample is collected.
- On day 2, at 24 hours after the first dose of study drug, ECG recording will start at least 30 minutes before time 0 and continue until the day 2 dose. The day 2 dose should be taken at approximately the same clock time (within 1 hour of time 0) as the day 1 dose. Blood samples for PK will be collected before the dose.
- Patients will fast for at least 6 hours before and 2 hours after the day 22 dose.
- On day 22, ECG recording will start at least 45 minutes before administration of the day 22 dose at time 0, and continue for 6 hours postdose. The day 22 dose should be taken at approximately the same clock time (within 1 hour of time 0) as the day 1 dose. Patients may resume eating after the 2-hour postdose PK sample is collected. Blood samples for PK will be collected immediately before the dose of talazoparib and at 1, 2, 4, and 6 hours postdose.

5.2.3 Unscheduled Visit Procedures

Unscheduled visits may be performed anytime to assess or follow up adverse events or at the request of the patient or investigator. The date and reason for the unscheduled visit must be recorded in the source documentation.

A review of adverse events and changes to concomitant medications or treatments (including herbal therapies) occurring since the previous visit should be performed at unscheduled visits.

Unscheduled visit procedures are listed in Appendix 2. Other study procedures may be performed as clinically appropriate.

5.3 Permanent Treatment Discontinuation

Permanent treatment discontinuation is defined as cessation of study drug treatment administration. After permanent discontinuation, safety follow-up will be per Section 5.4, unless the patient withdraws consent for further follow-up.

Temporary treatment interruption (eg, due to an adverse event) is not considered permanent discontinuation.

The primary reasons for which patients *permanently discontinue* study treatment are listed in Table 1.

Table 1: Primary Reasons for Permanent Treatment Discontinuation

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the investigator or sponsor would lead to undue risk if study treatment were continued (eg, severe drug-induced liver injury [Section 8.2.1.1.1] or MDS/AML [Table 3]). Refer to Section 8.3.1. May or may not be related to disease progression.
Disease progression	Study drug treatment may be discontinued for disease progression based on investigator assessment.
Administration of prohibited concomitant therapy	Refer to Section 7.2.
Patient decision	Patients may permanently discontinue treatment anytime for any reason.
Investigator decision	Protocol treatment may be discontinued if the investigator considers it is in the patient's best interest. This category should be selected if adverse event, disease progression, or administration of prohibited concomitant therapy do not apply and the patient preferred to continue treatment.
Major noncompliance with protocol	The medical monitor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
Loss to follow-up	Refer to Section 5.5.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime for any reason as described in Section 13.6. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

5.4 Safety Follow-Up

Safety follow-up will occur approximately 30 days after the last dose of study drug or before initiation of a new antineoplastic therapy, whichever occurs first. For further talazoparib treatment, patients must enroll and initiate continued talazoparib treatment in a separate open-label extension study within 30 days after the last dose of study drug, and in this case, the safety follow-up will be omitted and an ECG will be obtained at the time of enrollment in the open-label extension study.

In the event that a new antineoplastic therapy is initiated before safety follow-up occurs (eg, a physician not associated with protocol MDV3800-14 initiates the treatment, and study site personnel are not aware of the treatment until afterward), safety follow-up should be scheduled as soon as possible.

Safety follow-up procedures are listed in Appendix 2.

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in Section 8.3.9.

For patients who refuse to come to the clinic for safety follow-up, telephone contact must be attempted and documented to review for adverse events through approximately 30 days after the last study drug treatment, before initiation of a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first. If the patient does not respond to telephone calls, the procedures for loss to follow-up in Section 5.5 should be followed.

5.5 Loss to Follow-Up

Every reasonable effort must be made to contact any patient apparently lost to follow-up during the course of the study to complete study-related assessments and record outstanding data. Following unsuccessful telephone contact, the following should occur:

- An effort to contact the patient by mail using a method that provides proof of receipt should be attempted.
- Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives).
- Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow-up.

Patients who withdraw consent will be considered lost to follow-up for analysis purposes.

6 INVESTIGATIONAL PRODUCT INFORMATION

6.1 General Information

The study drug is talazoparib. The sponsor will provide talazoparib capsules.

6.2 Talazoparib Product Characteristics

Talazoparib is provided as the 4-methylbenzenesulfonate (tosylate) salt and has the chemical name (8S,9R) 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-pyrido[4,3,2-de]phthalazin-3-one. The drug product is a capsule containing talazoparib tosylate and silicified microcrystalline cellulose. The capsules for each dose strength will be provided in dose-specific colors. Additional details will be provided in the pharmacy binder.

6.2.1 Packaging of Talazoparib

Talazoparib study drug is packaged in induction sealed, high-density polyethylene bottles with child-resistant caps.

The label will vary depending on individual country requirements. At minimum, each label typically provides the study protocol number, contents, directions for use and storage, clinical trial statement, sponsor name, batch/lot number, and product retest or expiration date.

6.2.2 Storage of Talazoparib

The drug product should be stored safely and properly in accordance with the study drug label.

6.2.3 Directions for Administration of Talazoparib

The daily dose of talazoparib is 1 mg given orally.

Talazoparib will be administered at the study site on days 1, 2, and 22. Patients will fast for at least 6 hours before and 2 hours after the dose on days 1 and 22. Patients may resume eating after the 2-hour postdose PK sample is collected. On other days, talazoparib may be taken with or without food. The days 2 and 22 doses should be taken at approximately the same clock time (within 1 hour of time 0) as the day 1 dose. On days 3 to 21, patients should self-administer talazoparib orally once daily at approximately the same time each morning. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them.

Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

Dose modifications due to adverse events are described in Section 8.2.1.

Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment (Goodin et al, 2011). Patients should be advised that oral anticancer agents are toxic substances and that (other than the patient) caregivers should always use gloves when handling the capsules.

6.3 Treatment Compliance

Accountability for the study drug capsules will be performed to document compliance with the dosing regimen. Patients will be asked to bring all used and unused study drug bottles to study visits. Study site personnel must make reasonable efforts to obtain used and unused study drug bottles from patients who do not routinely return them at study site visits. Unreturned capsules will be considered to have been taken.

7 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant medications include all vitamins, herbal remedies, and over-the-counter and prescription medications.

7.1 Prior Medications

All prior cancer treatments, other medications taken within 30 days before day -1, and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, must be recorded on the case report form and in the patient's source documents.

7.2 Concomitant Therapy

Concomitant therapy (noninvestigational products) includes any concomitant medications (Section 7), blood transfusions, or radiotherapy used between day -1 and the end of treatment.

Patients will be instructed to consult with the investigator before taking any additional medications (including over-the-counter medications). Supportive medications may be provided prophylactically or therapeutically per investigator discretion, with the exception that granulocyte-colony stimulating factor (G-CSF) is only allowed in the rescue setting. Palliative radiation is allowed but the combination of radiation therapy and talazoparib has not been studied.

Concomitant therapies will be assessed at all clinic visits and must be recorded on the appropriate case report form. If the use of any medication during the study is due to an adverse event, the adverse event must be recorded on the adverse event case report form and in the patient's source documents.

Prohibited medications are described in Table 2. Deviation from these guidelines should occur only if absolutely necessary for the well-being of the patient, and the medical monitor is to be notified to determine whether continued treatment with study drug is permitted.

Study drug must be permanently discontinued upon initiation of any other antineoplastic therapy. Patients who discontinue treatment due to initiation of such therapy will complete safety follow-up per Section 5.4.

Table 2: Prohibited Concomitant Therapies

Medication or Treatment	Comment on Use
Any antineoplastic therapy (including biologic, radionuclide, or cytotoxic chemotherapy	Within 21 days before day -1 through safety follow-up for commercially available or investigational agents.
Other investigational agent (eg, biologic, vaccine, or other agents not approved for marketing)	Within 21 days before day -1 through safety follow-up.
Live bacterial and virus vaccines	Anytime between day -1 and safety follow-up.

7.3 Potential Interactions Between Talazoparib and Concomitant Medications

Guidelines for concomitant use of talazoparib with inhibitors or inducers of P-gp or inhibitors of BCRP are as follows:

- Use of strong P-gp inhibitors (eg, dronedarone, quinidine, ranolazine, verapamil, itraconazole, ketoconazole), P-gp inducers (eg, rifampin, tipranavir, ritonavir), or BCRP inhibitors (eg, elacridar [GF120918]) should be avoided.
- Caution should be used for coadministration of other P-gp inhibitors (eg, amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, felodipine, lopinavir, quercetin), P-gp inducers (eg, avasimibe, carbamazepine, phenytoin, St John's wort), or BCRP inhibitors (eg, cyclosporine, eltrombopag, gefitinib).
- Refer to the following website for a complete list: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inhibitors

8 SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs, ECGs, and clinical laboratory tests.

8.1 Safety Monitoring

The sponsor will periodically monitor safety data during the clinical study in addition to reviewing individual safety case reports, by examining the incidence and severity of adverse events and serious adverse events; changes in vital signs, ECG, and laboratory results; and other data (such as aggregate analysis of data from other talazoparib studies). Any relevant safety concerns will be communicated to the investigators and regulatory agencies, as appropriate.

8.2 Special Safety Considerations

8.2.1 Dose Modification Due to Adverse Events

Talazoparib dose modifications due to adverse events are described in Table 3.

Table 3: Dose Modification of Study Drug Due to Adverse Events

Toxicity	Management of Adverse Events
Grade 1 or 2	No requirement for dose interruption or dose reduction.
Selected hematologic grade 3 or 4 events	
Anemia (hemoglobin < 8.0 g/dL)	Hold talazoparib and monitor weekly until hemoglobin returns to baseline (day 1) grade or better. Implement supportive care per local guidelines. • Talazoparib may be reduced by 1 dose level per Table 4. If anemia persists for > 4 weeks without recovery to baseline grade, refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Neutropenia (ANC < 1000/µL)	Hold talazoparib and monitor weekly until ANC ≥ 1500/µL. Implement supportive care per local guidelines. Resume talazoparib based on the following recovery times: • ≤ 1 week: No change. • > 1 week: Reduce talazoparib by 1 dose level per Table 4. If neutropenia persists for > 4 weeks without recovery to ≥ 1500/µL, refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Thrombocytopenia (platelets < 50,000/µL)	Hold talazoparib until platelets ≥ 75,000/µL. Implement supportive care per local guidelines. Resume talazoparib based on the following recovery times: • ≤ 1 week: No change. • > 1 week: Reduce talazoparib by 1 dose level per Table 4. If thrombocytopenia persists for > 4 weeks without recovery to ≥ 75,000/µL, refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Nonhematologic laboratory grade 3 or 4 events, except abnormal liver tests	Hold talazoparib as follows: ▪ For clinically significant grade 3 laboratory abnormalities, talazoparib may be held. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4 when the laboratory abnormality resolves to grade ≤ 2 (baseline grade for creatinine increases). ▪ For clinically significant grade 4 laboratory abnormalities, hold talazoparib. Resume talazoparib when the laboratory abnormality resolves to grade ≤ 2 (baseline grade for creatinine increases) at a 1 dose level reduction per Table 4. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib should be permanently discontinued for unresolved grade 3 toxicity lasting longer than 2 weeks or for grade 4 toxicity lasting longer than 1 week. Talazoparib must be discontinued if a grade 4 adverse event recurs after study drug treatment resumes.

Toxicity	Management of Adverse Events
Nonlaboratory grade 3 or 4 events	Hold talazoparib as follows: ▪ For clinically significant grade 3 adverse events, hold talazoparib until the adverse event resolves to grade ≤ 1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4. ▪ For clinically significant grade 4 adverse events, hold talazoparib until the adverse event resolves to grade ≤ 1 or baseline. Resume talazoparib at a 1 dose level reduction per Table 4. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved grade 3 toxicity lasting longer than 2 weeks or for grade 4 toxicity lasting longer than 1 week. Talazoparib must be discontinued if a grade 4 adverse event recurs after study drug treatment resumes.
Grade 3 or 4 abnormal liver tests	Hold talazoparib for liver test abnormalities as specified in Table 5. Guidelines for follow-up for possible drug-induced liver injury and for resuming talazoparib after the liver test abnormalities resolve to baseline grade are provided in Section 8.2.1.1. The criteria for permanent discontinuation of talazoparib are provided in Section 8.2.1.1.1. In addition, talazoparib must be discontinued for recurrence of signs and symptoms of hepatitis and/or liver test abnormalities meeting the withholding criteria in Table 5 following rechallenge.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; MDS, myelodysplastic syndrome.

Table 4: Talazoparib Dose Reductions for Toxicity

Talazoparib Dose Level	Talazoparib Dose (mg/day)
Initial dose	**1.0**
First dose reduction	0.75
Second dose reduction	0.50
Third dose reduction	0.25

Dose re-escalation: No dose re-escalation is allowed for this study.

8.2.1.1 Assessment of Abnormal Liver Tests

Patients who develop abnormal liver tests (AST, ALT, total bilirubin), abnormal international normalized ratio (INR) values, or signs or symptoms of hepatitis during the study treatment period may meet the criteria for temporarily withholding or permanently discontinuing study drug treatment as specified in United States Food and Drug Administration (US FDA) Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009). Patients who meet criteria for permanent discontinuation or temporary withholding of study

drug treatment or who do not meet the criteria but who have abnormal liver tests are to be followed up according to the recommendations in this section.

Study drug should be withheld for any liver test abnormality listed in Table 5.

Table 5: Criteria for Temporary Withholding of Study Drug in Association With Liver Test Abnormalities

Baseline AST or ALT Value	**Elevation**
≤ 3 × ULN	> 5 × ULN (ALT or AST ≥ 3 × ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia [≥ 500 eosinophils/µL])
> 3 × ULN	> 8 × ULN
Baseline Total Bilirubin Value	**Elevation**
≤ 1.5 × ULN	> 3 × ULN (> 5 × ULN in patients with a baseline total bilirubin value of > 1.5 × ULN and ≤ 3 × ULN [patients with Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation])

For rechallenge, dose modification may be required per Table 4.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Study drug should be withheld pending investigation of alternative causes of liver injury (Table 6). When withholding study drug, follow-up should continue for possible drug-induced liver injury until the liver test abnormalities resolve to baseline grade.

Rechallenge may be considered at a 1 dose level reduction per Table 4 if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values. The investigator and sponsor should discuss and agree with any decision to rechallenge.

Following rechallenge, patients should be closely monitored for signs and symptoms of hepatitis and/or abnormal liver test results. If signs or symptoms consistent with hepatitis recur or the withholding criteria in Table 5 are met after rechallenge, study drug treatment should be permanently discontinued.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered drug induced.

Table 6: Investigations of Alternative Causes for Abnormal Liver Tests

Recommended tests
Complete blood count with differential to assess for eosinophilia
Serum total immunoglobulin G (IgG), antinuclear antibody (ANA), antismooth muscle antibody, liver kidney microsomal antibody 1 (LKM1), and liver cytosol type 1 antibodies (L-C-1) to assess for autoimmune hepatitis
Serum acetaminophen (paracetamol) concentration
Obtain a more detailed history
Prior and concurrent diseases or illness
Exposure to environmental and/or industrial chemical agents
Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
Prior and concurrent use of alcohol, recreational drugs, and special diets
Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
Obtain viral serologies for hepatitis A, B, C, and E (D if positive for hepatitis B), cytomegalovirus, Epstein-Barr virus, herpes simplex virus
Recommended tests <u>as clinically indicated</u>
Echocardiogram (ECHO)
Serum and urine copper and serum ceruloplasmin
Iron studies (serum iron and ferritin) and transferrin saturation
Serology for celiac disease
Serum alpha-1 antitrypsin
Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
Appropriate liver imaging
Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

8.2.1.1.1 Criteria for Permanent Discontinuation of Study Drug in Association With Liver Test Abnormalities

Study drug should be discontinued permanently if <u>all</u> of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 times ULN (> 5 × ULN if baseline ALT/AST is > 3 × ULN)
2. Total bilirubin increases to > 2 times ULN or INR > 1.5
3. Alkaline phosphatase value does not reach 2 times ULN (note: in the presence of elevated alkaline phosphatase associated with bone metastases, gamma glutamyl transferase [GGT] should be tested and the results should be within the reference range)

4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
   - Congestive heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
   - Alcoholic hepatitis
   - Nonalcoholic steatohepatitis (NASH)
   - Autoimmune hepatitis
   - Wilson disease and hemochromatosis
   - Alpha-1 antitrypsin deficiency

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than those noted above, then it should be determined (based on the patient population and/or severity of the hepatotoxicity or event) whether study drug should be withheld or permanently discontinued as appropriate for the safety of the patient. When study drug is temporarily withheld or permanently discontinued due to a potential drug-induced liver injury, a period of close observation is to commence until the liver test abnormalities return to baseline or normal values. The evaluations listed in Table 7 should be performed.

Table 7: Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests
After the initial liver test abnormality	Within 24 hours
If AST or ALT ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 × ULN), and total bilirubin > 2 × ULN or INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 × ULN) and total bilirubin or INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal.

As drug-induced liver injury is a diagnosis of exclusion, it is important to initiate investigation of alternative causes for abnormal liver tests, which may include consultation with a hepatologist. The medical monitor should be contacted for questions regarding adequate follow-up tests.

8.2.2 Overdose Management

The medical monitor must be contacted in the event of a study drug overdose. An overdose is defined as any dose greater than the protocol-specified dose of talazoparib. In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the mean half-life is 50 hours. No antidote to overdose is known.

All overdose events are to be reported within 24 hours of awareness by the study site according to Section 8.3.6 whether or not the overdose is associated with an adverse event.

8.2.3 Reproductive Considerations

Female Patients

Female patients of childbearing potential must have a negative pregnancy test at screening (serum tested centrally) and safety follow-up (urine or serum tested locally or using a centrally provided kit), and must avoid pregnancy during the study. Urine pregnancy tests must have a limit of detection of 25 IU/L (or equivalent units) for human chorionic gonadotropin. If a pregnancy test is positive, study drug treatment will be discontinued.

Female patients of childbearing potential must use a highly effective form of birth control from the first dose of study drug through 45 days after the last dose of study drug, defined as follows:

- Established use of an oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Established use of an oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal ligation for ≥ 6 months before day -1
- Partner vasectomized for ≥ 6 months before day -1
- Sexual abstinence when in relation to the preferred and usual lifestyle of the patient

Female patients who meet 1 of the following criteria are considered not of childbearing potential:

1. Surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
   OR
2. Postmenopausal, defined as follows:
   - ≥ 55 years of age with no spontaneous menses for ≥ 12 months before day -1
   - < 55 years of age with no spontaneous menses for ≥ 12 months before day -1 and with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/L

Male Patients

Male patients must use a condom when having sex with a pregnant woman or with a woman of childbearing potential from the first dose of study drug through 105 days after the last dose of study drug. Contraception should be considered for a nonpregnant female partner of childbearing potential.

Details regarding the reporting procedures to follow in the event of pregnancy are provided in Section 8.3.10. Instructions regarding sperm or egg donation and breastfeeding are provided in Section 4.1.

8.3 Adverse Event Definitions and Reporting

8.3.1 Adverse Event Definitions

Definitions are provided in this section for adverse events, events of special interest, serious adverse events, treatment-emergent adverse events, suspected unexpected serious adverse reactions (SUSARs), and unexpected adverse events.

Adverse events: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Examples of adverse events include the following:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition
- Development of an intercurrent illness during the study
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately)
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
  - Induces clinical signs or symptoms
  - Requires active intervention
  - Requires interruption or discontinuation of study drug

An adverse event **does not** include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event

- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure)

Serious adverse events: Any adverse event that meets any of the criteria in Table 8 as determined by the investigator or sponsor.

Table 8: Criteria for Serious Adverse Events

Criterion	Comment
Results in death	Death is an outcome, not an adverse event. The primary adverse event resulting in the death should be identified.
Is life threatening (immediate risk of death from the adverse event as it occurred)	Does not include an event that hypothetically might have caused death if it were more severe.
Results in or prolongs an existing inpatient hospitalization	For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure will be identified as the serious adverse event (not the procedure).
Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions	Permanent or substantial disruption of a person's ability to conduct normal life functions.
Results in a congenital anomaly/birth defect	
Important medical events which jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above	Examples include drug-induced bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

Source: US Code of Federal Regulations: 21 CFR 312.32 [75 FR 59961]

Treatment-emergent adverse events: Adverse events observed following administration of the first dose of study drug.

Unexpected adverse events: Adverse events for which the nature or severity is not consistent with the reference safety information.

Suspected unexpected serious adverse reactions (SUSARs): Adverse events assessed as serious, related, and unexpected, which are subject to expedited reporting to regulatory authorities and study investigators.

Adverse events of special interest: Adverse events of special interest are any adverse events (serious or nonserious) identified for ongoing monitoring during the study and require rapid communication by the investigator to the sponsor as described in Section 8.3.6.

8.3.2 Adverse Event Reporting

Safety reporting to regulatory authorities, ethics committees, and investigators will be implemented according to global and country specific regulations.

To elicit adverse event reports from patients, the study site personnel should question the patient in a general way without suggesting specific symptoms.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or stabilizes. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted as described in Section 8.3.9.

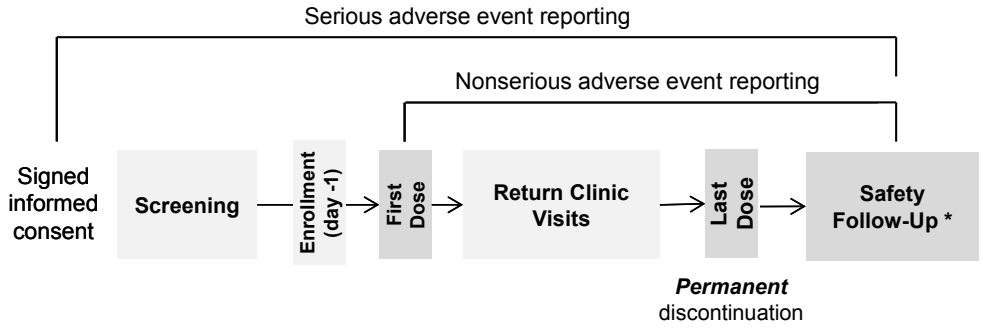
All adverse events, whether or not related to the study drug, must be fully and completely documented on the appropriate form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient or partner will be reported as described in Sections 8.2.2 and 8.3.10, respectively.

8.3.2.1 Adverse Event Reporting Periods

Collection and reporting of adverse event information will begin at the time the patient signs informed consent for serious adverse events and following the first dose of study drug for nonserious adverse events and will continue for all events through safety follow-up (approximately 30 days after the last dose of study drug), before initiation of a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first (Figure 2). Additional reporting instructions for serious adverse events are provided in Section 8.3.6.

Figure 2: Adverse Event Reporting Periods



* Approximately 30 days after last dose of study drug treatment, before a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first.

All adverse events from the time of the first dose of study drug must be documented on the adverse event case report form and in the patient's clinical record. Any event occurring during screening and before the first dose must be documented on the medical history case report form and in the patient's clinical record for any patient who subsequently meets eligibility criteria and proceeds to enrollment.

8.3.3 Assessment of Causal Relationship

The investigator will assess the relationship of an adverse event to study drug treatment according to the criteria in Table 9 and document the relationship in the patient's clinical record.

Table 9: Criteria for Determining Causal Relationship to Study Drug

Relationship	Criteria
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and/or in which other drugs, chemicals, or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

8.3.4 Assessment of Severity (Intensity)

Severity describes the intensity of a specific adverse event (mild, moderate, or severe). The particular event may be of relatively minor medical significance (such as severe headache). Severity is not the same as "serious," which is based on patient/event outcome or action criteria.

Investigators will grade the severity of adverse events according to the CTCAE, version 4. For terms not specified within the CTCAE, the criteria in Table 10 should be used to determine grade of severity.

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

Table 10: Criteria for Determining the Severity (Intensity) of an Adverse Event for Terms Not Specified in CTCAE

Grade	Intensity or Severity	Clinical Description
1	Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening	Life-threatening consequences; urgent intervention indicated
5	Death	Death related to adverse event

Source: Common Terminology Criteria for Adverse Events v4.0

8.3.5 Adverse Events of Special Interest

Adverse events of special interest include a diagnosis of MDS or acute myeloid leukemia (AML) (consistent with events observed with olaparib) and abnormal liver test results. Liver test abnormalities that require reporting are the following:

- AST or ALT ≥ 3 times ULN (> 5 × ULN if baseline ALT/AST is > 3 × ULN) and total bilirubin > 2 times ULN or INR > 1.5
- AST or ALT ≥ 3 times ULN with signs and symptoms consistent with hepatitis and/or eosinophilia (≥ 500 eosinophils/µL)

Adverse events of special interest occurring during the safety reporting period must be reported within 24 hours of awareness by the study site and those occurring after the safety reporting period must be reported within 1 week of awareness, using a serious adverse event report form (contact information provided in Section 8.3.6).

Tissue samples and any other supporting data used to enable the diagnosis of MDS or AML should be submitted for central review if requested.

8.3.6 Serious Adverse Event Reporting

Study site personnel will collect serious adverse event information from the time the patient signs the informed consent form through screen failure or safety follow-up (approximately 30 days after the last dose of study drug), before initiation of a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Using a serious adverse event report form (a sponsor-provided form in the study manual), all serious adverse events must be reported **within 24 hours** of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study drug.

The contact information for submission of serious adverse events, adverse events of special interest, and events of overdose or pregnancy is as follows:

Name:	ProductLife, Ltd.
Fax:	+1-866-488-3347 (US) or designated regional toll-free number
Backup Fax:	+44 (0) 1223 413689 (United Kingdom)
Email:	safety@productlife-group.com
Phone:	+44 (0) 1223 402660

The initial report should include, at minimum, the following:

- Study number (MDV3800-14)
- Site name and number
- Investigator name
- Patient ID number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the serious adverse event (event term, seriousness of the event)
- Causal relationship to the study drug

If the patient died, the report should include the cause of death as the event term (with fatal outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

8.3.7 Clarification in Reporting of Deaths

Information relating to any death at any time during the study (eg, date and primary cause) should be obtained and recorded on the appropriate case report form.

Fatal events (regardless of relationship to study drug) should be reported as serious adverse events during the treatment-emergent safety reporting period defined in Section 8.3.2.

Death per se is not an adverse event but is an outcome of an adverse event. The specific cause of death should be reported whenever possible.

8.3.8 Clarification in Reporting of Disease Progression as an Adverse Event Term

Disease progression is expected in this study population and "disease progression" should not be reported as an adverse event term. When clinical disease progression is identified, the specific clinical event that identifies the disease progression should be reported as the adverse event term for standard adverse event and if applicable, serious adverse event reporting.

8.3.9 Follow-Up of Serious and Nonserious Adverse Events

All adverse events reported during the study should be followed up at appropriate intervals until resolution, or until the event has stabilized, reached a new baseline, or a new antineoplastic therapy is initiated (all follow-up results are to be reported to the sponsor or designee).

Adverse events that remain unresolved at the conclusion of the study may continue to be monitored if warranted based on clinical assessment by the investigator and medical monitor.

Patients should be contacted by phone and written requests as appropriate for adverse event follow-up if they do not come to the clinic for safety follow-up as specified in Section 5.4.

8.3.10 Pregnancy Reporting Procedure

If a female study participant becomes pregnant between the first dose of study drug and 45 days after permanent discontinuation of study drug treatment, or if a male study participant impregnates a partner between the first dose of study drug and 105 days after permanent discontinuation of study drug treatment, the study participant should report the pregnancy to the investigator. The pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site (contact information provided in Section 8.3.6), using the provided reporting forms. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc, should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

8.4 Clinical Laboratory Tests

Routine clinical laboratory tests (hematology, serum chemistry) will be performed according to the schedules of activities (Appendix 1, Appendix 2). Samples will be stored until the specified analyses are completed and then will be destroyed in accordance with standard laboratory practice and applicable local regulations.

A list of the required routine clinical laboratory tests and other evaluations is provided in Table 11. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements.

All clinical laboratory tests will be performed by the central laboratory specified in Form FDA 1572 Section 4 unless otherwise specified. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments.

A local clinical laboratory may be used to evaluate serum chemistry and hematology within 3 days before a scheduled visit. The results of these local laboratory assessments will be used for dosing decisions.

For all patients, a local clinical laboratory may be used to assess samples at unscheduled visits or for urgent care to evaluate an adverse event. Such laboratory data will not be entered into the study database and local laboratories will not be included on Form FDA 1572. Central laboratory samples should be obtained whenever possible during unscheduled visits.

Table 11: Central Laboratory Tests

Hematology	Chemistry	Additional Tests
Hematocrit Hemoglobin Mean corpuscular volume Red blood cell count Platelet count White blood cell count with differential ▪ Total neutrophils ▪ Lymphocytes ▪ Monocytes ▪ Eosinophils ▪ Basophils	Albumin Total protein Alkaline phosphatase ALT (alanine aminotransferase) AST (aspartate aminotransferase) Total bilirubin Blood urea nitrogen Creatinine Glucose (nonfasting) Bicarbonate Calcium Chloride Magnesium Phosphate Potassium Sodium LDH (lactate dehydrogenase)	Urine or serum pregnancy tests for women of childbearing potential [1]

[1] The screening serum pregnancy test will be performed centrally. Other urine or serum pregnancy tests may be performed either locally or using a centrally provided kit.

8.5 Physical Examinations, Vital Signs, and ECGs

The investigator will perform physical examinations according to the schedules of activities (Appendix 1, Appendix 2). Interval medical history will be reviewed as a part of physical examinations.

Physical examinations will include an assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms.

Vital sign measurements will include blood pressure (after supine for 5 minutes), heart rate, respiratory rate, and temperature at the visits noted in the schedule of activities. Blood pressure (after supine for 5 minutes) will be measured 15 to 20 minutes before each PK time point. Weight will be measured at the time of the examination. Height will be measured only at screening.

12-Lead ECGs will be obtained continuously at baseline (day -1) and days 1, 2, and 22, and a single ECG will be obtained at screening and safety follow-up. ECGs will be collected for analysis at specified time points; patients must be supine for 10 minutes before these time points. Additional ECGs may be obtained as necessary per standard of care. For patients who enroll and initiate continued talazoparib treatment in the open-label extension study within 30 days, an ECG will be obtained at the time of enrollment in the open-label study.

9 ASSESSMENT OF SAFETY, PHARMACOKINETIC, AND EFFICACY ENDPOINTS

9.1 Assessment of Safety

The assessment of safety will include adverse events, physical examinations, vital signs, ECGs, and clinical laboratory tests. The procedures for the investigator assessment of adverse events are presented in detail in Section 8. The procedures for clinical laboratory safety tests are presented in Section 8.4, and for physical examinations, vital signs, and ECGs in Section 8.5.

9.2 Assessment of QTc

ECG recordings from continuous 12-lead ECG recordings will be obtained using Holter monitors on days -1, 1, 2, and 22, and will be submitted for independent central review. After reviewing for data quality, triplicate 10-second ECGs will be extracted from a 5-minute extraction window at each planned time point and will be analyzed for measurement of RR, PR, QRS, and QT intervals and evaluation of ECG morphology. A cardiologist will verify the interval durations and perform the morphology analyses. Heart rate will be used to assess QTc endpoints.

9.3 Assessment of PK

Blood samples will be collected according to the schedules of activities (Appendix 2). Samples will be processed as described in the laboratory manual. Plasma talazoparib concentrations will be measured using a validated method.

9.4 ECOG Performance Status

Assessment of ECOG performance status is required to assess patient functional status for study eligibility purposes and will be performed throughout the study according to the schedules of activities (Appendix 1, Appendix 2). Scoring for the assessment is shown in Table 12.

Table 12: ECOG Performance Status

Score	Description of Functional Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken et al, 1982
ECOG, Eastern Cooperative Oncology Group.

9.5 Assessment of Efficacy

No efficacy assessments are planned in this study. Disease assessments will be conducted according to the standard of care at the study site.

10 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1 Statistical and Analytical Plans

The statistical methods and analyses for this study will be described in detail in the statistical analysis plan.

10.2 Analysis Populations

All safety analyses will be performed using the safety population, defined as all patients who receive any amount of talazoparib.

The ECG analysis population is defined as all enrolled patients who receive at least 1 dose of study drug, and have at least 1 available baseline and 1 on-treatment ECG. Patients who do not complete day 22 or who miss > 5 consecutive doses of study drug will be excluded from the analysis of the effects of talazoparib on cardiac repolarization.

The PK population is defined as all patients who receive at least 1 dose of talazoparib and provide at least 1 reportable concentration. The PK analysis population is defined as all patients who have sufficient concentration data to derive at least 1 PK parameter. Additional patients may be excluded from the PK population at the discretion of the pharmacokineticist.

The PK-PD analysis population is defined as all patients in the ECG analysis population who have at least 1 time-matched pair of plasma concentration and ECG measurements obtained at the same nominal time point. Additional details on the PK-PD analysis population are provided in the statistical analysis plan.

10.3 Safety Analyses

All safety analyses will be performed using the safety population, as defined in Section 10.2. Drug exposure will be summarized using descriptive statistics.

The safety of talazoparib will be evaluated by the analysis of incidence of serious and nonserious adverse events, severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in vital signs, ECGs, and clinical laboratory values. Treatment-emergent safety data will be collected from the first dose of study drug treatment through 30 days after the last dose (ie, permanent discontinuation), before initiation of a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first.

Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the CTCAE version 4. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (eg, leading to permanent treatment discontinuation).

Laboratory values will be classified for severity using the CTCAE version 4. Laboratory shift tables of baseline results versus postbaseline results to each subsequent visit will be produced as appropriate.

10.4 ECG Analyses

All ECG analyses will be conducted using the ECG analysis population. The primary endpoints of the study are to evaluate the effects of talazoparib on the QTcF, and to evaluate the relationship between the plasma concentration of talazoparib and the change from baseline in QTc, corrected for heart rate based on the QTcF correction formula (ΔQTcF). The time-matched change from baseline in QTc, corrected for heart rate based on Bazett's correction formula (ΔQTcB), will also be evaluated. Changes from time-matched baseline measurements will be calculated and data will be summarized in tabular and graphic formats

for each study visit. Assessments include absolute QTc prolongation with QTc > 450 msec, > 480 msec, and > 500 msec and change from baseline in QTc with QTc increase > 30 msec and > 60 msec. The means of each measurement of RR, PR, QRS, and QT intervals will be utilized for statistical analyses.

ECG morphology and changes from baseline for each planned postbaseline time point will be summarized for all patients. The proportion of patients with any postbaseline change in ECG morphology and the proportion of patients with each type of abnormality will also be summarized.

10.5 PK Analyses

Summary data of plasma talazoparib concentrations will be presented in tabular and graphic formats for each time point. PK parameters such as T_{max}, C_{max}, and AUC on days 1 and 22 will be calculated.

In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately.

10.6 PK-PD Analyses

The correlation between changes in ECG interval measurements from time-matched baseline and the plasma talazoparib concentration will be investigated using a linear mixed-effects model.

This analysis will be conducted using the PK-PD analysis population.

10.7 Efficacy Analyses

No efficacy analysis is planned in this study.

10.8 Determination of Sample Size

A sample size of at least 30 evaluable patients will provide 80% power to reject the null hypothesis if the mean change from baseline in QTcF is ≥ 10 msec with a 95% one-sided alpha, assuming a standard deviation of 20 msec. Patients will be enrolled until 30 patients complete day 22, miss ≤ 5 consecutive doses of study drug, have technically adequate ECG recordings, and have at least 80% of specified PK samples collected representing all 3 days of observation (days 1, 2, and 22).

11 STUDY COMMITTEES AND COMMUNICATIONS

No formal study committees are planned for this study.

12 LABORATORY REQUIREMENTS

A central laboratory will analyze the clinical laboratory safety samples for this study, unless otherwise noted, as described in Section 8.4. The laboratory manual for this study provides details regarding sample collection procedures and laboratory tests.

13 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

Before initiating the study, the investigator must provide the following documents to the sponsor:

- Fully executed and signed Form FDA 1572
- Fully executed clinical trial agreement
- Current curriculum vitae (also applies to all subinvestigators listed on the Form FDA 1572)
- Financial disclosure (also applies to all subinvestigators listed on the Form FDA 1572)
- Signed protocol signature page
- Signed acknowledgment of receipt of the current investigator brochure
- Ethics committee (EC) approval letter
- EC-approved informed consent form
- Additional documents as necessary per local requirements

If an investigator changes during the course of the study, the sponsor and any local regulatory authorities, as applicable, must first approve the change of investigator and the new investigator must provide the sponsor all of the documents listed above.

The sponsor personnel or representatives may visit the study site, if necessary, before initiation of the study to review information with study site personnel about protocol requirements pertaining to the study drug, case report forms, monitoring, serious adverse event reporting, and other relevant information.

13.1 Ethics

13.1.1 Ethics Committee

Before initiating the study, the investigator will obtain confirmation from the EC that the EC is properly constituted and compliant with all requirements and local regulations.

The investigator will provide the EC with all appropriate material, such as the protocol, current investigator brochure, site-specific informed consent form, and other written information provided to the patients. The study will not be initiated until the investigator obtains appropriate EC approval in writing for the protocol and informed consent document, and copies are received by the sponsor.

EC and health authority approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes. The investigator will provide appropriate reports on the progress of the study to the EC, per local requirements, and to the sponsor or designee in accordance with applicable local regulations.

13.1.2 Ethical Conduct of the Study

This study will be conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including current Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an EC; the study will be conducted by scientifically and medically qualified persons; the anticipated benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will provide written informed consent before any protocol-specific tests or evaluations are performed.

13.1.3 Patient Information and Informed Consent

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator or designee will prepare the informed consent form and provide the documents to the sponsor or designee for approval before submission to the EC. The sponsor and the EC must approve the documents before the investigator implements them.

The investigator will provide copies of the signed informed consent form to each patient and will maintain the signed original document within the patient's clinical record per local requirements. The investigator will also fully document the informed consent process in the patient's source documents.

13.1.4 Maintaining Patient Confidentiality

All reports and patient samples will be identified only by a screening or enrollment ID number and actual initials (if permitted) or mock initials and date of birth (month/year only if no date is permitted) in order to maintain patient confidentiality. Additional patient confidentiality issues are addressed in the clinical trial agreement and in the informed consent form signed by each study participant.

13.2 Data Quality Assurance

13.2.1 Data Management

Clinical data management will be performed by the sponsor or designee according to procedures described in a comprehensive data management plan. The data management plan will include procedures for processing the data from this study, and will describe the responsibilities of the sponsor and designee when clinical data management is provided by an external vendor. In particular, the data management plan will include a list of the standard operating procedures that apply to this study.

Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively. The dictionary versions will be named in the data management plan.

13.2.2 Case Report Forms

The study will use an electronic data capture system. All electronic case report forms will be designed and provided electronically to the site by the sponsor or designee and electronic data capture system vendor. All case report form books are to be filled out completely, reviewed, and signed by the investigator or subinvestigators listed on the Form FDA 1572 or other appropriate local health authority documents.

13.2.3 Study Monitoring

The sponsor or designee will monitor this study in accordance with current GCP guidelines. By signing this protocol, the investigator grants permission to the sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the case report forms, it is mandatory that sponsor representatives (eg, study monitor) have direct access to original source documents (eg, paper or electronic patient records, patient charts, and laboratory reports) needed to verify the entries on case report forms. During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records (paper or electronic) related to the study. The study monitor will be responsible for inspecting the case report forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness and correctness of all case report form entries. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2.4 Study Audits

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

13.3 Investigational Product Accountability

The investigator must maintain accurate records of all study drug supplies received. All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH GCP guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor's drug accountability log or other sponsor-approved pharmacy log
- That study drug is handled and stored safely and properly in accordance with the label and the study protocol
- That study drug is only administered or dispensed to study patients in accordance with the protocol
- That any used or unused drug is returned by the patient at each required visit
- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions as required by the study drug label, accessible only to those authorized by the investigator to dispense these study drugs.
- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.

- The investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative, unless otherwise approved. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request for review and approval before the first onsite destruction. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

13.4 Compensation, Insurance, and Indemnity

In the event of a side effect or injury, appropriate medical care as determined by the investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the patient's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and study staff. No other compensation of any type will be provided by the sponsor. Financial compensation for lost wages, disability, or discomfort due to the study participation or procedures is not available.

13.5 Retention of Records

The investigator must make original study data (paper or electronic) accessible to the study monitor, other authorized sponsor representatives, and regulatory agency inspectors (eg, US FDA) upon request. A file for each patient must be maintained that includes the signed informed consent form and copies of all source documentation related to that patient. The investigator must ensure the reliability and availability of source documents from which the information on the case report form was derived.

Patient identity information recorded will be maintained for at least 15 years on the patient confidentiality log or longer if required by local regulations.

Investigators must maintain all study documentation for at least 2 years following the approval of the drug, or until 2 years after the investigational drug program is discontinued, or longer if required by local regulations. Study documentation includes all essential documents as defined in ICH E6 Guidelines for Good Clinical Practice. The sponsor or designee will notify the investigator when any records may be discarded, but investigators must comply with local regulations.

13.6 Study Termination

The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

The sponsor reserves the right to terminate the study anytime. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator.

If an investigator or the investigator's EC intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason for it.

14 USE OF STUDY INFORMATION AND PUBLICATION

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of Medivation (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. Written approval from the sponsor is required before disclosing any information related to this clinical trial, and no publications initiated by investigators may be published until all protocol-defined primary and secondary endpoints are published in a manuscript. Every attempt will be made to minimize the interval between the completion of data analysis and publication of the study results. Recommendations for the timing of presentation of trial endpoint data and the publication venues (congresses/journals) will be given by the sponsor's Publications Steering Committee.

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

In accord with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator and lead author will be designated by mutual agreement.

Any formal publication of the study in which input of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts or stricter local

criteria (ICMJE, 2015). The sponsor does not compensate for authorship of a publication and all authors will be required to disclose, as part of the publication submission, any potential conflicts of interest, including pertinent financial or personal relationships with the sponsor or related entities, including sponsors of competing products that might be perceived to be a source of bias. Authorship is decided on an individual basis and the sponsor's Publications Steering Committee and sponsor representatives will mutually determine authors and their sequence on individual publications based on the relative contribution of each author to the study and/or publication.

Investigators in this study agree to have their name listed as an investigator in any publication reporting results from this study, whether or not they are an author on the publication.

Professional medical writing support is permissible, and any writing support will be acknowledged in each applicable publication, explaining the role the professional writer had in the drafting of the publication. Medical writing and publications support funded by the sponsor on behalf of investigator authors will be considered as a transfer of value under the reporting requirements of Section 6002 of the Patient Protection Affordable Care Act (PPACA, 2010). Transfer of value will be allocated to authors following sponsor guidelines.

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16 INVESTIGATOR SIGNATURE

MEDIVATION, INC.

A Phase 1, Open-Label Study to Assess the Effects of Talazoparib on Cardiac Repolarization in Patients With Advanced Solid Tumors

Signature of Agreement for Protocol MDV3800-14 Amendment 1 – 19 Aug 2016

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice and the Declaration of Helsinki, and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

Print Study Site Name	Study Site Number
Print Investigator Name	
Investigator Signature	Date

Appendix 1: Study Schedule of Activities: Screening

Study Day	-29 to -2	Comments
General Activities		
Informed consent and screen number	X	Obtain before performing any study-specific procedures. Ensure consent is on the current version of the form approved by the ethics committee. May obtain before the screening window.
Demographics, medical history	X	
Eligibility criteria	X	
Enrollment authorization	X	Obtain approval for the enrollment from the sponsor or designee before proceeding to day -1.
12-lead electrocardiogram	X	Obtain after supine for 10 minutes, read locally to determine eligibility, and submit to the central facility.
Vital signs	X	Measure blood pressure (after supine for 5 minutes), heart rate, respiratory rate, and temperature.
ECOG performance status	X	
Physical examination, weight, height	X	Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).
Pretreatment-emergent serious adverse events review	X	Report serious adverse event information from time of signed informed consent through screen failure.
Prior and concomitant medications	X	
Laboratory Evaluations		Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for results. All laboratory evaluations will be tested centrally.
Serum chemistry, hematology	X	
Serum pregnancy test	X	For women of childbearing potential only.
Blood sample for banking	X	Collect blood sample to be stored for reflex testing for HBV (HBsAg, anti-HBc) and HCV (HCV antibody, reflex testing for HCV RNA if positive).

anti-HBc, hepatitis B core antibody; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Appendix 2: Study Schedule of Activities: Treatment

Study Period or Visit	Treatment							Unscheduled [1]	Safety Follow-Up [2]
Study Day	-1	1	2	3 to 21	8	15	22	Varies	Varies
Window (Days)	na	[3]	na	na	±3	±3	±3	na	-3 to +10
Enrollment ID number	X								
General Activities									
Continuous ECG with Holter monitor [3]	X	X	X				X		
12-Lead ECG [4]									X [4]
Vital signs [5]	X	X	X		X	X	X	X	X
Physical examination, weight [6]	X [6]						X	X	X
ECOG performance status	X						X		X
Adverse events review [7]	X	X	X		X	X	X	X	X
Concomitant medications	X	X	X		X	X	X	X	X
Study drug treatment [8]		X	X	X	X	X	X		
Study drug accountability		X			X	X	X	X (optional)	
Laboratory Evaluations [9]									
Serum chemistry, hematology		X			X	X	X	X [1]	X
Blood sample for PK [10]		X	X				X		
Pregnancy test [11]									X

[1] Anytime necessary to assess or follow up adverse events, at the patient's request, or per investigator decision.

[2] Safety follow-up occurs approximately 30 days after the last dose of study drug or before initiation of a new antineoplastic therapy, whichever occurs first. Phone patients for adverse event follow-up if they do not come to the clinic. For patients who enroll and initiate continued talazoparib treatment in a separate open-label extension study within 30 days after the last dose of talazoparib, safety follow-up will be omitted; an ECG will be obtained at the time of enrollment in the open-label extension study.

[3] On day -1 (time 0, corresponding to the dosing time on day 1), apply Holter monitor and record ECGs for 6 hours. On day 1 (within 72 hours of time 0 on day -1, corresponding to the clock time of the first baseline ECG measurement), start recording ECGs at least 45 minutes before time 0, administer the first dose of study drug at time 0, and continue recording ECGs for 6 hours postdose. On day 2 (24 hours after the first dose of study drug), start recording ECGs at least 30 minutes before day 2 dose. On day 22, start recording ECGs at least 45 minutes before time 0, administer study drug at time 0, and continue recording ECGs for 6 hours postdose. (Appendix 3)

[4] Obtain a single 12-lead ECG (after supine for 10 minutes); obtain at the time of enrollment in the open-label extension study for patients who enroll in that study within 30 days.

[5] Measure blood pressure (after supine for 5 minutes), heart rate, respiratory rate, and temperature at each visit. On days -1, 1, 2, and 22, measure blood pressure (after supine for 5 minutes) 15 to 20 minutes before each PK time point (Appendix 3).

[6] Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms. Measure weight. May be skipped on day -1 if performed within prior 7 days.

[7] Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, before a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first. Collect nonserious adverse event information from day 1 through approximately 30 days after the last dose of study drug, before initiation of a new antineoplastic therapy, or enrollment in the open-label extension study, whichever occurs first.

[8] Administer talazoparib at the study site on days 1, 2, and 22; administer talazoparib on days 2 and 22 at the same clock time as time 0 (±1 hour) on day 1. Instruct patient to self-administer talazoparib at approximately the same time each morning on day 3 through day 21.

Patients will fast for at least 6 hours before and 2 hours after the dose on days 1 and 22. Patients may resume eating after the 2-hour postdose PK sample is collected. On other days, talazoparib may be taken with food or without food.

[9] Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for laboratory results.

[10] Collect blood samples for PK on day 1 immediately before the first dose of study drug and at 1, 2, 4, and 6 hours postdose; on day 2 at 24 hours after the first dose of study drug (and before day 2 dose); and on day 22 predose and at 1, 2, 4, and 6 hours postdose. After obtaining vital signs, patient should remain supine for 10-15 minutes before collecting blood sample for PK (Appendix 3).

[11] For women of childbearing potential only. Perform urine or serum pregnancy test either locally or using a centrally provided kit with a minimum sensitivity of 25 IU/L or equivalent units human chorionic gonadotropin. Discontinue study drug treatment if a pregnancy test is positive.

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ID, identification; na, not applicable; PK, pharmacokinetics.

Appendix 3: Time Points for ECG, Blood Pressure, and PK Assessments

Day	Time Point	Blood Pressure [1]	PK [2]
-1	Attach Holter monitor at time 0 (no dose) [3], [4]	X	
	1 hour	X	
	2	X	
	4	X	
	6	X	
1	Patients will fast for ≥ 6 hours before and 2 hours after day 1 dose		
	Attach Holter monitor ≥ 45 minutes before time 0 [3]		
	Time 0 (first dose of talazoparib, within 72 hours of day -1 time 0)	X	X
	1 hour postdose	X	X
	2 Patients may resume eating after PK sample is collected	X	X
	4	X	X
	6	X	X
2	Attach Holter monitor ≥ 30 minutes before time 0 [3], [4]		
	Time 0 (dose of talazoparib)	X	X
22	Patients will fast for ≥ 6 hours before and 2 hours after day 22 dose		
	Attach Holter monitor ≥ 45 minutes before time 0 [3], [4]		
	Time 0 (dose of talazoparib)	X	X
	1 hour postdose	X	X
	2 Patients may resume eating after PK sample is collected	X	X
	4	X	X
	6	X	X

[1] At 15-20 minutes before each PK time point, measure blood pressure (after supine for 5 minutes).

[2] After obtaining blood pressure, patient should remain supine for 10 to 15 minutes before collecting blood sample for PK.

[3] ECG recordings on days -1, 1, 2, and 22 are continuous ECG recordings by Holter monitor.

[4] Time 0 corresponds to the dosing time on day 1. Administer the dose of talazoparib on days 2 and 22 at the same clock time as time 0 (±1 hour) on day 1.

ECG, electrocardiogram; PK, pharmacokinetics.