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MEDIVATION

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525 Market Street, San Francisco, CA 94105

A Phase I Open-Label Pharmacokinetics and Safety Study of Talazoparib (MDV3800) in Patients With Advanced Solid Tumors and Normal or Varying Degrees of Renal Impairment

MEDIVATION PROTOCOL: MDV3800-01

PFIZER PROTOCOL: C3441001

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Pfizer Medical Monitor

PPD **MD**

Protocol Version / Date	2.0 / Final 31-Aug-2018
Phase	I
Test Compound	Talazoparib (PF-06944076; formerly known as MDV3800 or BMN673)
Indication	Advanced solid tumors
Sponsor	Medivation, Inc.
EUDRACT #	2016-002536-33
IND #	CCI

MDV3800-01/C3441001/CCI Protocol v. 2.0 – Rationale for Amendment

Version 2.0 of the protocol is an amendment applicable to all sites and performed in order to clarify protocol language and to include new pharmacokinetic data for talazoparib.

Additionally, some administrative changes have been included regarding the Pfizer and CCI teams.

The MDV3800-01/C3441001/CCI protocol was amended as follows:

Document	Version Date	Summary of changes
Protocol version 2.0	31 Aug 2018	• INVESTIGATORS: update of the number of sites based on the current active sites. • CCI AND PFIZER TEAM: administrative changes in teams conformation and signature page. • LIST OF ABBREVIATIONS: inclusion of additional abbreviations. • PROTOCOL SYNOPSIS: update of sections Study Duration, Participating Investigational sites, Background andRrationale, definition of Evaluability, Eligibility criteria, PK assessments and Statistical methods. • SECTION 2. BACKGROUND AND RATIONALE: update of language as per the most recent version of Talazoparib IB. • SECTION 4. STUDY DESIGN: revision of language for clarification. • SECTION 5. PATIENT SELECTION: revision of wording to include updated talazoparib wash out period in females and males. • SECTION 6. STUDY TREATMENT: update of language for clarification. • TABLE 6. INSTRUCTIONS FOR USE OF CONCOMITANT THERAPIES: addition of medications previously included in Section 6.2 *Potential Interactions between Talazoparib and Concomitant Medications* in this table. • TABLE 7. SCHEDULE OF VISITS AND ASSESSMENTS: revision of language for clarification. • SECTION 8. AE REPORTING: update of language for clarification and addition of section “Medication Error”. • TABLE 9. AE REPORTING REQUIREMENTS: update of language for clarification. • TABLE 11. MEDICATION ERROR REPORTING REQUIREMENTS: update of language for clarification.

[redacted]

		• SECTION 9. STATISTICAL CONSIDERATIONS: revision of Population for Analyses. • SECTION 10. ADMINISTRATIVE, ETHICAL AND REGULATORY STANDARDS: revision of the section eData Protection".

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

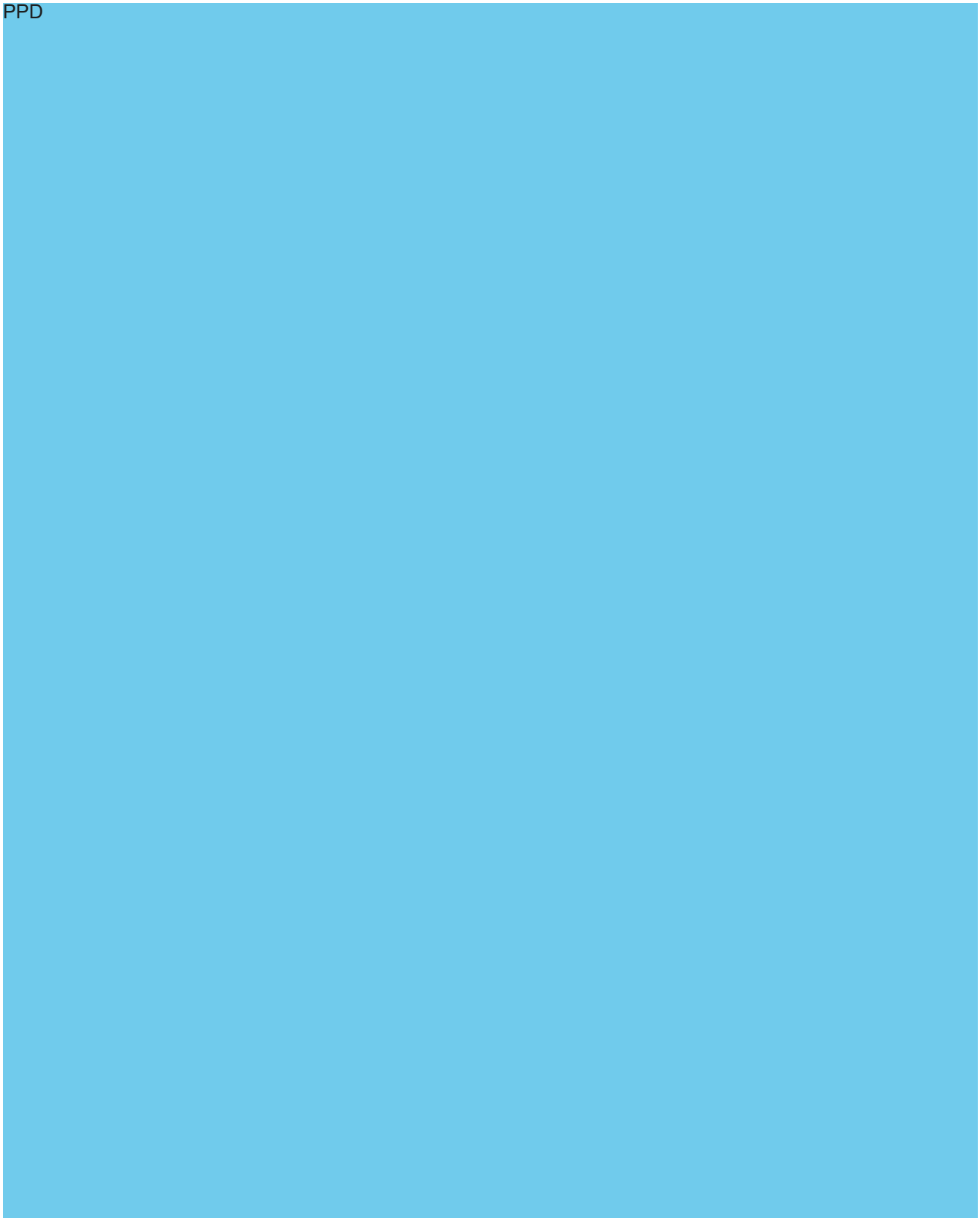
LIST OF FIGURES

[redacted]

INVESTIGATORS

9 sites will participate in the trial. The list of Investigators participating in the study will be maintained in CCI Clinical Trial Management System.

PPD



PROTOCOL SIGNATURE PAGE – Sponsor

This Clinical Study Protocol has been reviewed and approved by the Sponsor representatives listed below. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

PPD **PhD**

PPD

PPD ***Date:*** 31 Aug 2018 20:37:037-0400

PPD **, MD**

PPD **, Safety Risk Lead**

PPD ***Date:*** 31 Aug 2018 16:48:027-0400

PPD

PPD **Date:** 31 Aug 2018 12:50:000-0400

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PPD ***Date:*** 31 Aug 2018 16:26:045-0400

PPD **, MS**

PPD **, Regulatory Affairs**

PPD ***Date:*** 31 Aug 2018 17:49:046-0400

LIST OF ABBREVIATIONS

AE	Adverse Event
Ae%	Percent of dose excreted in urine as unchanged drug
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase / GPT
AML	Acute Myeloid Leukemia
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
aPTT/PTT	(Activated) Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase / SGOT
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area Under the concentration time curve from 0 to 24 hours
$AUC_{0-24,u}$	Unbound AUC_{0-24}
BCRP	Breast cancer resistance protein
BRCA	Breast cancer susceptibility gene
BUN	Blood Urea Nitrogen
CL_{CR}	Creatinine Clearance
CL/F	Apparent Oral Clearance
CL_u/F	Unbound CL/F
C_{max}	Maximum observed plasma concentration
$C_{max,u}$	Unbound C_{max}
C_{trough}	Plasma trough (pre-dose) concentration
CLCR	Creatinine Clearance
CLr	Renal Clearance
CPK	Creatinine Phosphokinase
CRA	Clinical Research Associate
CSR	Clinical Study Report
CT	Computed tomography
CYP450	Cytochrome P450

D1	Day 1
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FDA	Food and Drug Administration
F_u	Fraction of unbound drug in plasma
Gamma GT	Gamma-glutamyl transferase or gamma-glutamyl transpeptidase
GCP	Good Clinical Practices
G-CSF/GM-CSF	Granulocyte/Granulocyte-macrophage colony stimulating factor
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GGT	Gamma glutamyl transferase
h	Hour
HBsAg	Hepatitis B surface Antigen
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Conference for Harmonization
IMP	Investigational medicinal product
INR/PT	International Normalized Ratio / Prothrombin time
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
kg	kilogram

L	Liter
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LDH	Lactate dehydrogenase
MAD	Maximum Administered Dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndrome
mg	Milligram
mL	Milliliter
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
PARP	Poly(ADP-ribose) polymerase
P-gp	P-glycoprotein
PICF	Patient Informed Consent Form
PK	Pharmacokinetics
PR	Partial Response
PS	Performance status
QD	quaque die/every day
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
$S_{cr, std}$	Standardized Serum Creatinine
SFU	Safety Follow Up
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Total Bilirubin
$t_{1/2}$	Terminal half-life
T_{max}	Time to C_{max}
CCI	[redacted]
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of Normal

US	United States
V_z/F	Apparent volume of distribution
WBC	White Blood Cells
WoCP	Women of Childbearing Potential

PROTOCOL SYNOPSIS

Protocol Title	A Phase I Open-Label Pharmacokinetics and Safety Study of Talazoparib (MDV3800) in Patients With Advanced Solid Tumors and Normal or Varying Degrees of Renal Impairment
Protocol #	MDV3800-01/CCI /C3441001
Indication	Advanced solid tumors
Study Duration	• Accrual: approximately 18-24 months • Treatment: 1 cycle defined as 22 calendar days of daily oral intake of talazoparib (counted from day 1) regardless of any treatment hold.
Sponsor	Medivation, Inc.
Participating Investigator Sites	9 sites
Background and Rationale	Talazoparib (PF-06944076; formerly known as BMN 673 or MDV3800) is a potent, orally bioavailable, small molecule poly(ADP-ribose) polymerase (PARP) inhibitor being developed for the treatment of a variety of human cancers both as single agent and in combination with other agents. PARP represents a family of at least 17 enzymes that transfer ADP-ribose groups to target proteins to regulate various cellular processes including deoxyribonucleic acid (DNA) repair. Among them, PARP1 and PARP2 play important roles in DNA repair. PARP inhibitors exert cytotoxic effects by 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity and, (2) PARP trapping, whereby PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription. The single dose pharmacokinetic (PK) of talazoparib has been evaluated in a total of 5 clinical studies, of which 4 were conducted in cancer patients (Studies PRP-001, PRP-002, MDV3800-03, and MDV3800-14) and 1 in healthy subjects (Study 673-103). After administration of a single 1 mg dose of talazoparib capsules to cancer patients, the median time to reach maximum plasma concentration (T_{max}) was ranging from 1.0 to 2.0 hours across studies. The geometric mean C_{max} ranged from 4.35 to 8.79 ng/mL and the geometric mean area under concentration-time curve from time 0 to infinity (AUC_{inf}) ranged from 116 to 196 ng•h/mL. Talazoparib was eliminated slowly with a mean terminal half-life ($t_{½}$) of 89.8 hours. The talazoparib geometric mean apparent volume of distribution (V_z/F) values estimated ranged from 447 to 847 L, which is significantly greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues. The geometric mean apparent oral clearance (CL/F) values estimated for

	talazoparib ranged from 5.12 to 7.71 L/hour (h). The geometric mean renal clearance (CL_r) ranged from 2.76 to 3.44 L/h, indicating that urinary excretion was a major route of elimination for talazoparib. The PK of talazoparib was comparable between patients with cancer and healthy subjects. The PK of talazoparib following multiple oral daily doses was evaluated in a total of 5 studies in patients with cancer (Studies PRP-001, PRP-002, 673-201, 673-301, and MDV3800-14) (Studies 673-201 and 673-301 only included sparse sampling). Following repeated 1 mg QD dosing to steady state, talazoparib was rapidly absorbed with a median T_{max} ranging from approximately 1.0 to 2.0 h across studies. Talazoparib was eliminated slowly, with a geometric mean CL/F ranging from 4.80 to 5.53 L/h. The geometric mean CL_r was 3.34 L/h and 3.32 L/h in Studies PRP-001 and PRP-002, respectively. The talazoparib geometric mean C_{max} values ranged from 11.4 to 19.1 ng/mL and the geometric mean area under the concentration-time curve for a dosing interval (AUC_τ) values ranged from 126 to 208 ng•h/mL. The talazoparib geometric mean steady-state pre dose plasma concentration (C_{trough}) values ranged from 2.99 to 4.95 ng/mL. Following repeated oral dosing, there was a dose proportional increase in the exposure of talazoparib (both Cmax and AUC0-24) across the dose range of 0.025 to 2 mg and the median talazoparib accumulation ratio (Rac) ranged from 2.23 to 12.3. Based on the multiple dosing data and consistent with its observed t½ of 89.8 h, talazoparib plasma concentrations reached steady state around 3 weeks after repeated daily dosing. The effect of food on the talazoparib plasma PK following administration of a single 0.5 mg dose of talazoparib oral capsule formulation in 18 healthy subjects (Study 673-103). Food intake (a high-fat, high-calorie meal) had no impact on the AUC while reduced the Cmax by 46%. Consistent with findings from the food effect study, population PK analysis using data from Studies 673-301, 673-201, PRP-001, and PRP-002 showed food intake decreased absorption rate but had no impact on the extent of the absorption. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is generally driven by total exposure. Therefore, talazoparib can be taken without regard of food. Following oral administration of a single 1 mg dose of 14C-talazoparib to female patients with advanced solid tumors (Study MDV3800-03), a mean of 68.7% and 19.7% of the total administered radioactive dose was recovered in urine and feces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose, while unchanged talazoparib recovered in the feces accounted for 13.6%. No major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived

	entity identified in plasma. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or feces. The identified metabolic pathways of talazoparib in humans include: 1) mono-oxidation; 2) dehydrogenation; 3) cysteine conjugation of mono-desfluoro-talazoparib; and 4) glucuronide conjugation. A population PK analysis for talazoparib was conducted to assess the impact of renal impairment on the CL/F using renal function as a categorical covariate defined by the baseline CLCR. The results of this analysis indicated that talazoparib CL/F was reduced by 14.4% and 37.1% in patients with mild renal impairment (CLCR, 60-89 mL/min) and moderate renal impairment (30 mL/min ≤ CLCR <60 mL/min), respectively, compared to that of patients with normal renal function (CLCR ≥90 mL/min). Due to limited number of severe renal impairment patients (CLCR <30 mL/min), the impact of severe renal impairment on talazoparib CL/F cannot be concluded. Therefore, based on this data, patients with moderate or severe renal impairment (CLCR < 60 mL/min) may be at risk of higher exposure to talazoparib. There is no study prospectively designed with the objective of assessing the potential effect of renal impairment on human PK of talazoparib, as most clinical studies exclude patients with renal impairment and especially those with severe dysfunction. The study will be carried out in patients with advanced solid tumors and with normal, mild, moderate or severe renal function as classified by estimated glomerular filtration rate (eGFR) according to the 2006 Modification of Diet in Renal Disease (MDRD) study equation [available via www.mdrd.com]. This study will contribute to understand the PK of talazoparib in patients with varying degrees of renal impairment and to better understand the exposure profiles in this patient population. Based on the results of this study, talazoparib dosing recommendations for patients with impaired renal function may be provided to future treating clinicians and potential exposure-dependent adverse events (e.g. myelosuppression) may be minimized. The dose selected in this study is 0.5 mg/day which is considered a safe dose as it is 50% lower than the Maximum Tolerated Dose (MTD) established in patients with solid tumors in phase 1 study at 1 mg/day. Talazoparib has also shown clinical activities at this dose level in a phase 1 study; however efficacy is not being explored in this study. Additionally, the expected exposures increase in moderate and severe renal impaired patients should not exceed the exposure of maximum administered dose (MAD) of 2 mg/day experienced in the Phase 1 studies. Talazoparib will be

	given daily for 22 calendar days in order to assess the safety and pharmacokinetics of talazoparib at the steady state.
Objectives	**Primary objective:** To investigate the effect of mild, moderate and severe renal impairment on the PK of talazoparib following daily oral dosing of talazoparib for 22 calendar days in patients with advanced solid tumors. **Secondary objectives:** To evaluate the safety and tolerability of talazoparib in patients with advanced solid tumors and with normal, mild, moderate or severe renal impairment.
Study Design	This is an open-label, non-randomized, multi-center, phase 1 trial to investigate the PK and the safety of talazoparib in patients with advanced solid tumors and impaired renal function. Safety and PK data from patients with mild, moderate and severe renal impairment as classified using the MDRD study formula per FDA guidance, will be compared with a control group consisting of patients with normal renal function. The 4-variable 2006 MDRD equation, expressed as a single equation, is as follows: eGFR (mL/min/1.73 m^2) = 175 x $(S_{cr, std})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American) (where $S_{cr, std}$ = standardized serum Creatinine (mg/dL); age = years) Patients will be enrolled in parallel and will be assigned to one of four groups based on their renal function. Renal function defining each group according to the MDRD formula as follows: • **Group A** (control, normal renal function): eGFR ≥ 90 mL/min/1.73m^2. • **Group B** (mild renal impairment): eGFR ≥ 60 and ≤ 89 mL/min/1.73m^2. • **Group C** (moderate renal impairment): eGFR ≥30 and ≤ 59 mL/min/1.73m^2. • **Group D** (severe renal impairment): eGFR ≥15 and ≤ 29 mL/min/1.73m^2, not on dialysis. In each group, 6 PK evaluable patients will be treated with daily oral doses of talazoparib 0.5 mg for 22 calendar days, regardless of any treatment hold. If enrollment in the group of patients with severe renal dysfunction

	(Group D) is halted due to unacceptable toxicity, 2 additional evaluable patients will be enrolled in each of Groups A, B and C (total of 8 evaluable patients each). Therefore, a total of at least 24 patients will be enrolled in the study. Patients will be considered evaluable for PK analysis (PK evaluable) if they are eligible and have: • Completed 22 calendar days of treatment with talazoparib counted from Day 1, regardless of any treatment hold and missed ≤ 5 consecutive doses of talazoparib, • Received at least 10 consecutive days of 0.5 mg talazoparib daily dose without dosing interruption prior to Day 22 PK sample collection, • Completed at least 85% of total plasma PK samples collection, • Not vomited talazoparib dose on Day 1 and Day 22 of the PK samples collection. Patients who discontinue the study prior to completion of Day 23 assessments and/or who do not meet the above mentioned criteria may be replaced according to Sponsor´s judgment. On Day 1 and Day 22, serial PK plasma samples up to 24 hours post-dose will be collected for talazoparib concentration measurement. *Note: 24h post-dose on Day 1 corresponds to the pre-dose of Day 2; 24h post-dose on Day 22 corresponds to Day 23.* One PK blood sample will also be collected at the Safety Follow up Visit (End of Study Visit), if the study treatment discontinues earlier than planned. Additionally, trough (pre-dose) samples will be collected on Day 8 and Day 15. Blood samples for plasma protein binding evaluation will be collected 2 h post-dose on Day 1 and Day 22. All voided urine will be collected after dosing on Day 1 and Day 22 between the intervals of 0-12h and 12-24h. Pre-dose urine samples for PK analyses will be collected as a single void at pre-dose on Day 1. Patients with no clinically significant toxicities, no contraindications to continue treatment with talazoparib and no disease progression (underlying cancer progression) may be eligible to continue talazoparib treatment on a separate open-label extension study after discussion with the Principal Investigator and obtaining Sponsor permission. Sponsor decision to allow the patient to continue dosing with talazoparib in an open-label extension study will be based on potential overall benefit-risk, patient acceptance to be enrolled in the open-label extension study and other relevant criteria.
Population	<u>Inclusion Criteria</u> Each patient must meet all the following criteria to be considered as eligible to participate in this study:

	1. Signed and dated informed consent form (by the patient or a legally acceptable representative as per the local regulations) obtained prior to initiation of any study-specific procedure and treatment. 2. Female or male of at least 18 years of age. 3. Histologically or cytologically confirmed advanced solid tumor with no available standard approved treatment options in the opinion of the Investigator (i.e. patients who received and failed approved standard therapy or with no effective approved standard therapy available). 4. Eastern Cooperative Oncology Group (ECOG) Performance status (PS) ≤ 2. 5. Expected life expectancy of ≥ 3 months. 6. Able to swallow the study drug (no contra indication to oral agents). 7. Renal function at screening and enrollment as defined by the MDRD equation (available via www.mdrd.com): • Control, normal renal function (Group A): eGFR ≥ 90 mL/min/1.73m^2. • Mild renal impairment (Group B): eGFR ≥ 60 and ≤ 89 mL/min/1.73m^2. • Moderate renal impairment (Group C): eGFR ≥30 and ≤ 59 mL/min/1.73m^2. • Severe renal impairment (Group D): eGFR ≥ 15 and ≤ 29 mL/min/1.73m^2, not on dialysis. Each patient's renal function classification for the study will be based on the assessment made at enrollment, if screening classification is different. 8. Patient has had no clinically significant change in renal status within 3 months prior to screening, according to Investigator's review of clinical patient records. 9. Patient has no unstable renal function, defined as a change in eGFR (calculated with the MDRD equation) of > 25% for patients with mild and moderate renal impaired or as a change in eGFR > 30% for patients with severe renal impaired, from screening to enrollment. 10. If taking concurrent medications for treatment of renal impairment, patient has been on a stable dose of all indicated medication(s) for at least 1 month prior to Day -1 (patient enrollment) and is expected to continue to remain stable during the study. 11. Patient is not currently on hemodialysis and/or peritoneal dialysis for management of chronic kidney disease or acute

	failure/conditions. 12. Adequate other organ function at screening and enrollment as defined by the following criteria: • **Hematology** (blood samples collected after ≥ 14 days without growth factor support, erythropoiesis-stimulating agents or transfusion): - Absolute Neutrophils Count (ANC) ≥ 1.5 x 10^9/L. - Platelets ≥ 100 x 10^9/L. - Hemoglobin ≥ 9 g/dL. • **Liver function:** - Total serum bilirubin ≤ 1.5 x ULN (or ≤ 3 times ULN for patients with documented Gilbert's syndrome or for whom indirect bilirubin concentrations suggest an extra-hepatic source of elevation). - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.5×ULN OR ≤ 5×ULN for patients with liver metastases. 13. Female patients of childbearing potential: a. Must have a negative serum pregnancy test at screening, b. Must agree to use a highly effective birth control method from the time of the first dose of study drug through 7 months after the last dose of study drug, defined as: - 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. - Bilateral tubal ligation ≥ 6 months before enrollment - Placement of an intrauterine device or intrauterine hormone-releasing system. - Sexual partner(s) vasectomized for ≥ 6 months before enrollment. - Sexual abstinence when in relation to the preferred and usual lifestyle of the patient. And c. Must agree to not donate eggs from the time of first talazoparib administration until at least 7 months thereafter. *Note: Female patients not of childbearing potential include those who are surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy with documentation of the*

procedure) or who are post-menopausal, defined as:

- *≥ 55 years of age with no spontaneous menses for ≥ 12 months before enrollment.*
- *< 55 years of age with no spontaneous menses for ≥ 12 months before enrollment and with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/L (or meeting criteria for post-menopausal status by the local laboratory.*

14. Male patients:
    a. Must agree to use a condom when having sex with a pregnant woman or with a non-pregnant female partner of childbearing potential, from 21 days before the first dose of study drug through 4 months after last dose of study drug.

       And

    b. Must agree to not donate sperm from the time of first talazoparib administration until at least 4 months thereafter.
15. Female patients must not be breastfeeding at screening nor during the study participation until 7 months after the last dose of study drug.
16. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

<u>Exclusion criteria</u>

Patients meeting at least one of the following criterion will not be eligible to participate in this study:

1. Treatment within 14 days or five half lives prior to enrollment with any type of systemic anticancer-therapy or any investigational drug, whichever is longer.
2. Have not recovered (recovery is defined as CTCAE grade ≤ 1) from the acute toxicities of previous anticancer standard or investigational therapy, except treatment-related alopecia or laboratory abnormalities otherwise meeting eligibility requirements.
3. Major surgery within 28 days prior to enrollment.
4. Serious accompanying cardiac disorder including the following:
   - Myocardial infarction or symptomatic documented cardiac ischemia within 3 months prior to enrollment.
   - Heart failure New York Heart Association class III or IV at screening.
   - Clinically significant cardiac arrhythmias if not adequately treated or controlled (i.e. by medication, or pacemaker).
   - History of second-degree Mobitz II or third degree heart

	block unless a permanent pacemaker is in place. • Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening and at enrollment (day-1). A second measurement is allowed after hydration with oral fluids if systolic blood pressure < 80 mmHg. • Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG). • Poorly controlled hypertension as indicated by systolic blood pressure > 175 mm Hg or diastolic blood pressure > 105 mm Hg at screening. May be repeated in 15 minutes. • Screening QTcF ≥ 450 msec in males or ≥ 480 msec in females. 5. Active known or suspected brain metastasis or active leptomeningeal disease undergoing or requiring treatment. (asymptomatic brain metastases not currently undergoing treatment are allowed) 6. Symptomatic or impending spinal cord compression or cauda equina syndrome. 7. Has undergone a liver transplant, kidney transplant or nephrectomy. 8. Prior allergic reaction or severe intolerance (meeting the criteria for a serious adverse event, a grade 3 or 4 AE, or permanent treatment discontinuation) to a PARP inhibitor. 9. Known myelodysplastic syndrome. 10. Seropositive for human immunodeficiency virus (HIV). 11. Any serious or unstable medical condition that interferes with ability to tolerate treatment or assessments associated with the protocol. 12. Gastrointestinal disorder affecting absorption. 13. Known or suspected hypersensitivity to any of the talazoparib capsule components. 14. Use of P-gp inhibitor (amiodarone, atorvastatin, azithromycin, carvedilol, clarithromycin, cobicistat, conivaptan, darunavir, diltiazem, diosmin, dronedarone, eliglustat, erythromycin, felodipine, flibanserin, fluvoxamine, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, piperine, propafenone, quercetin, quinidine, ranolazine, ritonavir, saquinavir, schisandra chinensis extract, telaprevir, tipranavir, valspodar and verapamil), P-gp inducer (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort), or inhibitor of BCRP (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag) within 7 days or 5 half lives which ever is longer prior to Day 1. 15. Any condition or reason that interferes with ability to participate

	in the study, tolerate treatment or assessments associated with the protocol, causes undue risk, or complicates the interpretation of safety data, in the opinion of the Investigator or Medical Monitor (e.g. encephalopathy, psychiatric disorders, non-compliance, excessive alcohol consumption, intake of drugs of abuse unless these drugs are medically indicated [e.g. opiates for pain relief]).
Study Treatment	Talazoparib, 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 (provided as the 4-methylbenzenesulfonate [tosylate] salt). Talazoparib will be administered as 0.5 mg orally once daily for 22 days (Day 1 to Day 22).
Efficacy Assessments	Not applicable. Efficacy will not be evaluated in the study. *Note: Screening tumor assessments will be obtained in the event that patients choose to continue talazoparib treatment on a separate open label extension protocol.*
Safety Assessments	Safety assessments and tolerability of talazoparib will be monitored through the evaluation of adverse events (severity according to NCI-CTCAE version 4.03), clinical laboratory tests, vital signs, electrocardiograms (ECGs), ECOG and physical examinations at screening during the 22 days of duration of the study treatment until 30 days after the last study drug administration or before initiation of a new anticancer therapy (standard or investigational treatment) or the first day of the extension protocol whichever occurs first. All assessments will be scheduled as indicated in the Schedule of Visits and Assessments.
PK Assessments	**Blood samples for PK:** Plasma samples will be collected at predetermined time point. • **<u>Day 1 and Day 22:</u>** - Pre-dose: ▪ On Day 1: within 60 minutes prior to dose. ▪ On Day 22: 24h ±60 minutes from the previous dose (Day 21), but within 60 minutes prior to the next dose. - 0.5, 1, 2, 4, 6 h , between 8 and 12 h, and 24 h post-dose (i.e. total of 7 time points). *Note: 24h post-dose on Day 1 corresponds to the pre-dose of Day 2; 24h post-dose on Day 22 corresponds to the sample on Day 23.* Samples up to 60 minutes post-dose will be obtained with a window of ±3 minutes. From after 60 minutes until 12 h post-dose, samples will be obtained with time margins of ±10 minutes. Thereafter, samples should be obtained within ±60 minutes of the scheduled time points. PK blood samples will be collected at the Safety Follow up Visit (End of

	Study visit) if study treatment discontinues earlier than planned. • **Day 8 and Day 15:** pre-dose samples only will be collected 24 h±60 minutes from the previous dose, but within 60 minutes before the next dose on the day of sample collection. **Blood samples for plasma protein binding evaluation:** Blood samples for plasma protein binding evaluation will be collected at 2h post-dose on Day 1 and Day 22. Samples will be obtained with a time margin of ±10 minutes. **Urine Samples for PK:** Urine samples will be collected at the following predetermined time points on Day 1 and Day 22: • Single void at pre-dose on Day 1. • Urine voided after talazoparib dosing on Day 1 and Day 22 at 0-12 h and 12-24 h. A ±60 minute time window applies to the start and end times of urine collection intervals.
Statistical Methods	**Population for Analysis:** The safety population is defined as all patients who received any amount of talazoparib. The PK concentration population is defined as all eligible patients enrolled and treated who have at least 1 reportable plasma talazoparib concentration. The PK parameter analysis population is defined as all evaluable patients enrolled and treated who have at least 1 of the talazoparib PK parameters of primary endpoints interest. **Sample size:** 6 PK evaluable patients will be enrolled per group. If enrollment in the group of patients with severe renal impairment (group D) is halted due to unacceptable toxicity, 2 additional evaluable patients will be enrolled in each Groups A, B and C (total of 8 evaluable patients each). Therefore, a total of at least 24 patients will be enrolled in the study. Patients who discontinue the study prior to completion of Day 23 assessment and/or who do not meet the PK evaluability criteria may be replaced if needed upon agreement of the Sponsor. **Statistical Methods:** • **Safety Analysis:** All safety analyses will be performed using the safety population. 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 (i.e., leading to permanent treatment discontinuation). Treatment-emergent safety data will be collected from Day 1 (the first dose of study drug) through 30 days after the last dose of study drug or before initiation of new anticancer therapy (standard or investigational

	treatment) or the first day of extension protocol, whichever occurs first. Laboratory values will be classified by severity using the NCI CTCAE. Laboratory shift tables of baseline results to each subsequent visit will be produced as appropriate. Change from baseline in laboratory values will be tabulated and summarized graphically. • **Efficacy Analysis:** No efficacy analysis is planned in this study, although baseline tumor assessments will be obtained in the event that patients choose to continue talazoparib treatment in a separate open-label extension study. **PK Analysis**: The PK parameters will be determined from the talazoparib concentration-time data. PK parameters (AUC_{0-24}, C_{max}, $AUC_{0-24,u}$, $C_{max,u}$, C_{trough}, T_{max}, Fu, R_{ac}, Ae%, and CLr) will be calculated by non-compartmental analysis using WinNonlin or another appropriate software. Additional PK parameters will be estimateded/calculated as applicable. PK parameters AUC_{0-24}, C_{max}, $C_{max,u}$, and $AUC_{0-24,u}$ on Days 1 and 22 will be natural log-transformed and analyzed using an analysis of variance (ANOVA) model with group as a fixed effect to compare each renal impairment group (mild, moderate or severe; Test) with the normal renal function group (Reference). Additionally, weight and age will be considered as covariates (at the significance level of 0.05). Estimates of the adjusted mean differences (Test - Reference) and corresponding 90% confidence intervals (CIs) for each comparison will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios on the untransformed scale. Relationship between renal functional measures (e.g. eGFR) and selected PK parameters may be explored graphically, as appropriate. A regression line and 90% confidence region for the PK parameters and renal function will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify subjects from different renal function groups. Linear regression will be used to analyze the potential relationship between selected PK parameters and renal function. Estimates of the slope and, intercept, together with their precision (90% CI), and the coefficient of determination will be obtained from the model.

1. BACKGROUND AND RATIONALE

1.1. Investigational Medicinal Product Overview

1.1.1. Background

Talazoparib (PF-06944076; formerly known as MDV3800 or BMN 673) is a potent, orally bioavailable, small molecule poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers both as single agent and in combination with other agents. PARP represents a family of at least 17 enzymes that transfer ADP-ribose groups to target proteins to regulate various cellular processes including deoxyribonucleic acid (DNA) repair. Among them, PARP1 and PARP2 play important roles in DNA repair.[1]

PARP Inhibitors exert cytotoxic effects by 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, whereby PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription.[2]

DNA instability is an important characteristic of many tumor types; often times a consequence of defects in DNA repair.[3] Although a single DNA repair pathway defect may not be lethal to the cell, the combination of 2 pathway defects may be lethal. This process is termed synthetic lethality.[4] PARP inhibitors induce synthetic lethality in tumor cells bearing mutations and/or deletions in genes involved in homologous recombination or other DNA repair pathways, including BRCA1, BRCA2, FANCA, PTEN, RAD51, MLH1, MSH2, ATM, MRE11, and PALB2.[5–12]

Inhibition of PARP catalytic activity contributes to the process of synthetic lethality, as it results in persistent single-strand breaks that require homologous recombination DNA repair for survival. When trapped, PARP-DNA complexes inhibit DNA repair, replication, and transcription, and are more cytotoxic than unrepaired single-strand breaks because they do not readily dissociate.

The antitumor properties of talazoparib have been demonstrated in nonclinical studies.[7, 13] Talazoparib is more potent at inducing single-agent synthetic lethality of BRCA1- and BRCA2-deficient tumor cells in vitro than any other PARP inhibitors reported to date. Talazoparib inhibited growth of MX-1 human breast cancer cells (BRCA1-deficient) and Capan-1 human pancreatic cancer cells (BRCA2-deficient), with half- maximal inhibitory concentration (IC50) values of 0.3 nM and 5.0 nM, respectively.[7]

Consistent with its antitumor effects in vitro, talazoparib demonstrated antitumor activity in xenograft tumor models in mice. Clinical development of talazoparib is ongoing in various solid tumors as monotherapy at the recommended dose of 1mg/day and in combination with other agents.

1.1.2. Clinical Study Findings with Talazoparib

As of 31 Juanuary 2018, approximately 659 patients and 18 healthy volunteers have received talazoparib at doses up to 2 mg/day in company-sponsored studies in hematologic malignancies and solid tumors.

A phase 1 study in patients with advanced or recurrent solid tumors defined the maximum tolerated dose (MTD) of talazoparib as 1 mg/day. Data from this study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma. A phase 2 and a phase 3 study evaluating single-agent talazoparib in

patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations are ongoing.

The adverse events (AEs) associated with talazoparib are generally identifiable through routine laboratory and clinical monitoring and may be managed by dose reduction or interruption. The most common AEs reported in patients treated with talazoparib as a single agent or in combination are myelosuppression (anemia, neutropenia, thrombocytopenia), gastrointestinal (GI) toxicity (nausea, vomiting, diarrhea), and fatigue. The most common AEs with a severity grade ≥ 3 as per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) were myelosuppression.

1.1.3. Pharmacokinetics of Talazoparib

The single dose pharmacokinetic (PK) of talazoparib have been evaluated in a total of 5 clinical studies, of which 4 were conducted in cancer patients (Studies PRP-001, PRP-002, MDV3800-03, and MDV3800-14) and 1 in healthy subjects (Study 673-103).

After administration of a single 1 mg dose of talazoparib capsules to cancer patients, the median time to reach maximum plasma concentration (Tmax) was ranging from 1.0 to 2.0 hours (h) across studies. The geometric mean Cmax ranged from 4.35 to 8.79 ng/mL and the geometric mean area under concentration-time curve from time 0 to infinity (AUCinf) ranged from 116 to 196 ng•h/mL. Talazoparib was eliminated slowly with a mean t½ of 89.8 h. The talazoparib geometric mean apparent volume of distribution (Vz/F) values estimated ranged from 447 to 847 L, which is significantly greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues. The geometric mean apparent oral clearance (CL/F) values estimated for talazoparib ranged from 5.12 to 7.71 L/h. The geometric mean renal clearance (CLr) ranged from 2.76 to 3.44 L/h indicating that urinary excretion was a major route of elimination for talazoparib. The PK of talazoparib was comparable between patients with cancer and healthy subjects.

The PK of talazoparib following multiple oral daily doses was evaluated in a total of 5 studies in patients with cancer (Studies PRP-001, PRP-002, 673-201, 673-301, and MDV3800-14) (Studies 673-201 and 673-301 only included sparse sampling). Following repeated 1 mg QD dosing to steady state, talazoparib was rapidly absorbed with a median Tmax ranging from approximately 1.0 to 2.0 h across studies. Talazoparib was eliminated slowly, with a geometric mean CL/F ranging from 4.80 to 5.53 L/h. The geometric mean CLr was 3.34 L/h and 3.32 L/h in Studies PRP-001 and PRP-002, respectively. The talazoparib geometric mean Cmax values ranged from 11.4 to 19.1 ng/mL and the geometric mean area under the concentration-time curve for a dosing interval (AUCτ) values ranged from 126 to 208 ng•h/mL. The talazoparib geometric mean steady-state pre dose plasma concentration (Ctrough) values ranged from 2.99 to 4.95 ng/mL.

Following repeated oral dosing, there was a dose proportional increase in the exposure of talazoparib (both Cmax and AUC0-24) across the dose range of 0.025 to 2 mg and the median talazoparib accumulation ratio (Rac) ranged from 2.23 to 12.3. Based on the multiple dosing data and consistent with its observed t½ of 89.8 h, talazoparib plasma concentrations reached steady state around 3 weeks after repeated daily dosing.

The effect of food on the talazoparib plasma PK following administration of a single 0.5 mg dose of talazoparib oral capsule formulation in 18 healthy subjects (Study 673-103). Food intake (a high-fat, high-calorie meal) had no impact on the AUC while reduced the Cmax by 46%. Consistent with findings from the food effect study, population PK analysis using data from Studies 673-301, 673-201, PRP-001, and PRP-002 showed food intake decreased absorption rate but had no impact on the extent of the absorption. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is generally driven by total exposure. Therefore, talazoparib can be taken without regard of food.

Following oral administration of a single 1 mg dose of 14C-talazoparib to female patients with advanced solid tumors (Study MDV3800-03), a mean of 68.7% and 19.7% of the total administered radioactive dose was recovered in urine and feces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose, while unchanged talazoparib recovered in the feces accounted for 13.6%. No major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived entity identified in plasma. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or feces. The identified metabolic pathways of talazoparib in humans include: 1) mono-oxidation; 2) dehydrogenation; 3) cysteine conjugation of mono-desfluoro-talazoparib; and 4) glucuronide conjugation.

At therapeutic exposures, talazoparib did not markedly induce or inhibit cytochrome P450 (CYP450) enzymes or transporters and is therefore unlikely to demonstrate clinically significant CYP450 inhibition- or induction-based drug-drug interactions or drug transporter inhibition-based drug-drug interactions when coadministered with corresponding substrates. However, talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase or decrease when co-administered with P-gp or BCRP inhibitors or inducers, respectively.

Additional information on the chemistry, pharmacology, toxicology, preclinical findings, and clinical experience to date may be found in the talazoparib Investigator's Brochure (IB).

1.2. Study Rationale

1.2.1. Rationale for Conducting the Study

Based on the available data, talazoparib appears to predominantly be excreted via the renal route. A population PK analysis for talazoparib was conducted to assess the impact of renal impairment on the CL/F using renal function as a categorical covariate defined by the baseline CL_{CR}. The results of this analysis indicated that talazoparib CL/F was reduced by 14.4% and 37.1% in patients with mild renal impairment (CLCR, 60-89 mL/min) and moderate renal impairment (30 mL/min ≤ CL_{CR} <60 mL/min), respectively, compared to that of patients with normal renal function (CL_{CR} ≥90 mL/min). Due to limited number of severe renal impairment patients (CL_{CR} <30 mL/min), the impact of severe renal impairment on talazoparib CL/F cannot be concluded. Therefore, based on this data, patients with moderate or severe renal impairment (CL_{CR} < 60 mL/min) may be at risk of higher exposure to talazoparib.

There is no study prospectively designed with the objective of assessing the potential effect of renal impairment on human PK of talazoparib as most clinical studies exclude patients with renal impairment, and especially those with severe dysfunction. This study is designed to provide PK data following daily

administration of talazoparib in cancer patients with varying degrees of renal impairment. The study will be carried out in patients with advanced solid tumors with normal renal function and with mild, moderate and severe renal impairment classified by eGFR according to the 2006 Modification of Diet in Renal Disease (MDRD) study equation [available via www.mdrd.com] [14.]

This study will contribute to understand the PK of talazoparib in patients with varying degrees of renal impairment and to better understand the exposure profiles in this patient population. Based on the results of this study, talazoparib dosing recommendations for patients with impaired renal function may be provided to future treating clinicians and potential exposure-dependent adverse events (e.g. myelosuppression) may be minimized.

1.2.2. Rationale for Regimen and Dose Selection

In previous clinical trials, talazoparib was given as a single dose or as daily multiple doses in patients with various solid tumors and hematological malignancies in doses ranging from 0.025 to 2 mg/day given orally. The established recommended dose is 1 mg/day p.o. and at this dose, the mean $t_{½}$ was 89.8 hours. With daily administrations at this dose, it took approximately 3 weeks to reach the steady state. Based on this, a single dose study in cancer patients is not appropriate as at least a 2 to 3 week washout period would be required to be able to evaluate key PK parameters. In this study, talazoparib will be given daily for 22 calendar days to assess the pharmacokinetics and safety of talazoparib at steady state.

The dose selected in this study is 0.5 mg daily, which is considered safe as it is 50% lower than the MTD established in patients with solid tumors in phase 1 study at 1 mg/day. Talazoparib has also shown clinical activity at the dose to be used in the study in a Phase 1 trial; however efficacy is not being explored in this study; only pharmacokinetics is being evaluated. Additionally, the expected exposures increase in moderate and severe renal impaired patients should not exceed the exposure of Maximum Administered Dose (MAD) of 2 mg/day experienced in the Phase I studies.

2. OBJECTIVES

2.1. Primary Objective

To investigate the effect of mild, moderate and severe renal impairment on the PK of talazoparib following daily oral dosing of talazoparib for 22 calendar days in patient with advanced solid tumors.

2.2. Secondary Objective

To evaluate the safety and tolerability of talazoparib in patients with advanced tumors and with normal, mild, moderate or severe renal impairment.

3. STUDY DESIGN

This is an open-label, non-randomized, multi-center, phase 1 trial to investigate the PK and the safety of talazoparib in patients with various advanced solid tumors and impaired renal function.

Safety and PK data from patients with mild, moderate and severe renal impairment as classified using the MDRD study formula per FDA guidance will be compared with a control group consisting of patients with normal renal function.

The 4 variable 2006 MDRD formula, expressed as a single equation, is as follows:

eGFR (mL/min/1.73 m^2) = 175 x $(S_{cr, std})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

(where $S_{cr, std}$ = standardized serum Creatinine (mg/dL); age = years)

Patients will be enrolled in parallel and assigned to one of four groups based on their renal function. Renal function defining each group according to the MDRD formula is as follows:

- **Group A (control, normal renal function)**: eGFR ≥ 90 mL/min/1.73m^2.
- **Group B (mild renal impairment):** eGFR ≥ 60 and ≤ 89 mL/min/1.73m^2.
- **Group C (moderate renal impairment):** eGFR ≥30 and ≤ 59 mL/min/1.73m^2.
- **Group D (severe renal impairment):** eGFR ≥15 and ≤29 mL/min/1.73m^2, not on dialysis.

In each group, 6 PK evaluable patients will be enrolled. If enrollment in the group of patients with severe renal dysfunction (Group D) is halted due to unacceptable toxicity, 2 additional PK evaluable patients will be enrolled in each of Groups A, B and C (total of 8 PK evaluable patients each). Therefore, a total of at least 24 patients will be enrolled in the study from 9 sites.

All patients will be treated with oral talazoparib given on a daily basis at a dose of 0.5 mg over 22 calendar days (from Day 1 to Day 22 defined as 1 cycle of treatment) regardless of any study treatment hold. Talazoparib administration within this study will be discontinued after 22 days of starting study treatment.

Note: At the End of Study, patients with no clinically significant toxicities, no contraindications to continue treatment with talazoparib, and no disease progression (underlying cancer progression) may be eligible to continue talazoparib treatment in a separate open-label extension study after discussion with the Principal Investigator and obtaining Sponsor permission. Sponsor decision to allow the patient to continue dosing with talazoparib in an open-label extension study will be based on potential overall benefit-risk, patient acceptance and other relevant criteria.

Study periods include:

- Screening
- Enrollment (D-1)
- A 22 calendar day treatment period
- A Safety follow up visit (also considered as the End of Study visit)

Serial PK plasma samples will be collected at predetermined times on Day 1 and Day 22 up to 24 h post-dose (Day 23) for talazoparib concentration measurement. Additionally though (pre-dose) samples will be collected on Day 8 and Day 15.

One PK blood sample will also be collected at the Safety Follow up Visit if the study treatment discontinues earlier than planned. Blood samples for plasma protein binding evaluation will be collected on Day 1 and Day 22 (2h post dose). Urine samples for PK analyses will be collected as a single void at pre-dose on Day 1 and all urine voided after talazoparib dosing on Days 1 and 22 between the intervals of 0-12 h and 12-24 h.

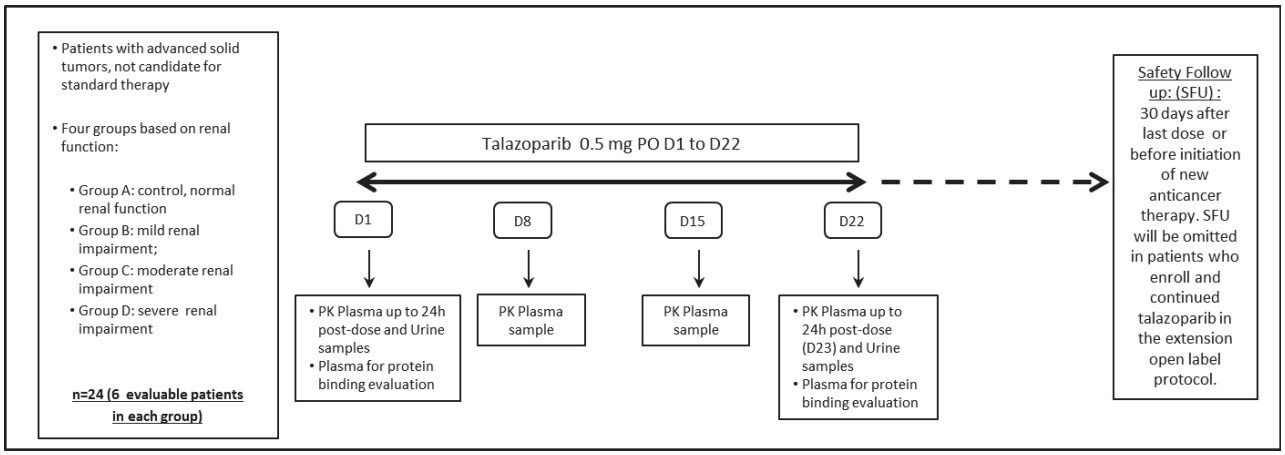
Patients will be considered evaluable for PK analysis (PK evaluable) if they are eligible and have:

- Completed 22 calendar days of treatment with talazoparib counted from Day 1, regardless of any treatment hold and missed ≤5 consecutive doses of talazoparib
- Received at least 10 consecutive days of 0.5 mg talazoparib daily dose without dosing interruption prior to Day 22 PK sample collection
- Completed at least 85% of total plasma PK samples collection
- Not vomited talazoparib dose on Day 1 and Day 22 of the PK samples collection.

Patients who discontinue the study before the completion of the Day 23 assessments and/or who do not meet the above mentioned criteria may be replaced according to the Sponsor's judgment.

[redacted]

Figure 1: Study Schema



4. PATIENT SELECTION

Patients can be enrolled in the study only if the eligibility criteria are met. This study can fulfill its objectives only if appropriate patients are enrolled. Patients who fail to meet ≥ 1 inclusion criterion or fulfill at least one exclusion criteria cannot be enrolled in the study. The sponsor CCI will not grant any eligibility waivers.

If a patient that does not meet the eligibility criteria is incorrectly enrolled, the Investigator should immediately inform the CCI Medical Monitor. The decision about the continuation or discontinuation of these patients on the study will be based on medical judgment, treatment benefit and safety risks for the patient.

4.1. Inclusion Criteria

Each patient must meet all the following criteria to be considered as eligible to participate in this study:

1. Signed and dated informed consent form (by the patient or a legally acceptable representative as per the local regulations) obtained prior to initiation of any study-specific procedure and treatment.
2. Female or male of at least 18 years of age.
3. Histologically or cytologically confirmed advanced solid tumor with no available standard approved treatment options in the opinion of the Investigator (i.e. patients who received and failed standard approved therapy or with no effective standard approved therapy available).
4. Eastern Cooperative Oncology Group (ECOG) Performance status (PS) ≤ 2.
5. Expected life expectancy of ≥ 3 months.
6. Able to swallow the study drug (no contra indication to oral agents).
7. Renal function at screening and enrollment as defined by the MDRD equation (available via www.mdrd.com):
    - Control, normal renal function (Group A): eGFR ≥ 90 mL/min/1.73m^2.
    - Mild renal impairment (Group B): eGFR ≥ 60 and ≤ 89 mL/min/1.73m^2.
    - Moderate renal impairment (Group C): eGFR ≥30 and ≤ 59 mL/min/1.73m^2.

- Severe renal impairment (Group D): eGFR ≥ 15 and ≤ 29 mL/min/1.73m^2, not on dialysis.

Each patient's renal function classification for the study will be based on the assessment made at enrollment, if screening classification is different.

8. Patient has no clinically significant change in renal status within 3 months prior to enrollment, according to Investigator's judgment.
9. Patient has no unstable renal function, defined as a change in eGFR (calculated with the MDRD equation) of > 25% for patients with mild and moderate renal impaired or as a change in eGFR > 30% for patients with severe renal impaired, from screening to enrollment.
10. If taking concurrent medications for treatment of renal impairment, patient has been on a stable dose of all indicated medication(s) for at least 1 month prior to Day -1 and is expected to continue to remain stable during the study.
11. Patient is not currently on hemodialysis and/or peritoneal dialysis for management of chronic kidney disease or acute failure/conditions.
12. Adequate other organ function at screening and enrollment as defined by the following criteria:
    - **Hematology** (blood samples collected after ≥ 14 days without growth factor support, erythropoiesis-stimulating agents or transfusion):
        - Absolute Neutrophils Count (ANC) ≥ 1.5 × 10^9/L.
        - Platelets ≥ 100 × 10^9/L.
        - Hemoglobin ≥ 9 g/dL.
    - **Liver function:**
        - Total serum bilirubin ≤ 1.5 × ULN (or ≤ 3 times ULN for patients with documented Gilbert's syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation).
        - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.5 × ULN OR ≤ 5 × ULN for patients with liver metastases.
13. Female patients of childbearing potential:
    a. Must have a negative serum pregnancy test at screening,
    b. Must agree to use a highly effective birth control method from the time of the first talazoparib administration until at least 7 months thereafter, defined as:

- 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.
- Bilateral tubal ligation ≥ 6 months before enrollment.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Sexual partner(s) vasectomized for ≥ 6 months before enrollment.
- Sexual abstinence when in relation to the preferred and usual lifestyle of the patient.

And

c. Must agree to not donate eggs from the time of first talazoparib administration until at least 7 months thereafter.

Note: Female patients not of childbearing potential include those who are surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy with documentation of the procedure) or who are post-menopausal, defined as:

- *≥ 55 years of age with no spontaneous menses for ≥ 12 months before enrollment.*
- *< 55 years of age with no spontaneous menses for ≥ 12 months before enrollment and with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/L (or meeting criteria for post-menopausal status by the local laboratory).*

14. Male patients:
    - Must agree to use a condom when having sex with a pregnant woman or with a non-pregnant female partner of childbearing potential, from 21 days before the first dose of study drug through 4 months after last dose of study drug.

      And

    - Must agree to not donate sperm from the time of first talazoparib administration until at least 4 months hereafter.
15. Female patients must not be breastfeeding at screening nor during the study participation until 7 months after the last dose of study drug.
16. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

4.2. Exclusion Criteria

Patients meeting at least one of the following criteria will not be eligible to participate in this study:

1. Treatment within 14 days or five half lives prior to enrollment with any type of systemic anticancer-therapy or any investigational drug whichever is longer.
2. Have not recovered (recovery is defined as CTCAE grade ≤ 1) from the acute toxicities of previous anticancer standard or investigational therapy, except treatment-related alopecia or laboratory abnormalities otherwise meeting eligibility requirements.
3. Major surgery within 28 days prior to enrollment.
4. Serious accompanying cardiac disorder including the following:

- Myocardial infarction or symptomatic documented cardiac ischemia within 3 months prior to enrollment.
- Heart failure New York Heart Association class III or IV at screening.
- Clinically significant cardiac arrhythmias if not adequately treated or controlled (i.e. by medication, or pacemaker).
- History of second-degree Mobitz II or third degree heart block unless a permanent pacemaker is in place.
- Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening and at enrollment (Day-1). A second measurement is allowed after hydration with oral fluids if systolic blood pressure < 80 mmHg.
- Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG).
- Poorly controlled hypertension as indicated by systolic blood pressure > 175 mm Hg or diastolic blood pressure > 105 mm Hg at screening. May be repeated in 15 minutes.
- Screening QTcF ≥ 450 msec in males or ≥ 480 msec in females.

5. Active known or suspected brain metastasis or active leptomeningeal disease undergoing or requiring treatment (asymptomatic brain metastases not currently undergoing treatment are allowed).
6. Symptomatic or impending spinal cord compression or cauda equina syndrome.
7. Has undergone a liver transplant, kidney transplant or nephrectomy.
8. Prior allergic reaction or severe intolerance (meeting the criteria for a serious adverse event, a grade 3 or 4 AE, or permanent treatment discontinuation) to a PARP inhibitor.
9. Known myelodysplastic syndrome.
10. Seropositive for human immunodeficiency virus (HIV).
11. Any serious or unstable medical condition that interferes with ability to tolerate treatment or assessments associated with the protocol.
12. Gastrointestinal disorder affecting absorption.
13. Known or suspected hypersensitivity to any of the talazoparib capsule components.
14. Use of a P-gp inhibitor (amiodarone, atorvastatin, azithromycin, carvedilol, clarithromycin, cobicistat, conivaptan, darunavir, diltiazem, diosmin, dronedarone, eliglustat, erythromycin, felodipine, flibanserin, fluvoxamine, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, piperine, propafenone, quercetin, quinidine, ranolazine, ritonavir, saquinavir, schisandra chinensis extract, telaprevir, tipranavir, valspodar and verapamil), P-gp inducer (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort), or inhibitor of BCRP (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag) within 7 days or 5 half lives which ever is longer prior to Day 1.
15. Any condition or reason that interferes with ability to participate in the study, tolerate treatment or assessments associated with the protocol, causes undue risk, or complicates the interpretation of safety data, in the opinion of the Investigator or Medical Monitor (e.g. encephalopathy, psychiatric disorders, non-compliance, excessive alcohol consumption, intake of drugs of abuse unless these drugs are medically indicated [e.g. opiates for pain relief]).

5. STUDY TREATMENT

5.1. Study Treatment Identification

Talazoparib is the only study treatment in the study and is considered an Investigational Medicinal Product (IMP). Talazoparib has the chemical name CCI [redacted] The drug substance is a CCI [redacted] The drug product consists of the drug substance formulated with a pharmaceutically suitable excipient filled into hydroxymethylpropylcellulose capsules.

For the purpose of this trial, the Single Reference Document to be used for talazoparib is the IB.

5.2. Investigational Product Information and Management

5.2.1. Packaging and Labelling

The drug product will be provided as powder-filled, hard gelatin opaque white capsules containing talazoparib at the strength of 0.25 mg calculated as the free-base equivalent. Capsules will be provided free of charge by the Sponsor.

The capsules will be supplied in 30-count induction-sealed high density polyethylene (HDPE) bottles with child-resistant caps.

At minimum, each label typically provides the study protocol number, contents, and directions for use, storage directions, clinical trial statement, Sponsor name, batch/lot number, and product retest or expiration date.

5.2.2. Storage and Dispensation

At the site, talazoparib must be kept in the original container and stored safely and properly in accordance with the study drug label.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

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. Patients should be advised that oral anticancer agents are toxic substances and that caregivers (other than the patient) should always use gloves when handling the capsules.

Receipt and dispensing of trial medication must be recorded by an authorized person at the site.

5.2.3. Accountability, Return and Destruction

The Investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount administered or dispensed to and returned by the patients, and the amount remaining at the conclusion of the trial.

Patients must return all unused medication and empty containers to the Investigator.

[redacted]

The Investigator or designee must retain all unused or expired study supplies in a secure location (separately from medication that needs to be dispensed) for accountability and reconciliation by the Clinical Research Associate (CRA).

Unused study drug will be destroyed on site, per the site's standard operating procedures, ideally after the Sponsor or designee has granted approval for drug destruction and the CRA has accounted for all study drugs in a formal reconciliation process.

If a site is unable to destroy study drug, the site can return unused study drug to a central location for drug destruction upon agreement with the Sponsor or designee.

To ensure adequate records, dispensations, accountability, return / destruction of talazoparib capsules will be documented in a timely manner. Appropriate documents (Drug accountability/destruction log or similar) for this purpose will be provided.

5.3. Study Treatment Administration

5.3.1. Dosage and Administration

The patient should start the study treatment within 3 calendar days after being enrolled in the study. As much as possible, study treatment should start on a weekday that allows D8, D15 and D22-23 visits to fall on a weekday.

All patients enrolled will receive oral talazoparib given on a daily basis at a dose of 0.5 mg (2 capsules of 0.25 mg) over 22 calendar days (from Day 1 to Day 22).

At Day 1, all patients should be given with one bottle containing 30 capsules of talazoparib 0.25 mg. A resupply with a 2nd bottle containing 30 capsules of talazoparib 0.25 mg will occur at D15 for the remaining dosing period (D15-D22).

Talazoparib should be taken at approximately the same time each day in the morning. The patients can self-administer talazoparib at home except on Days 1, 2, 8, 15 and 22. Patients should not take the study drug at home on Days 1, 2, 8, 15 and 22. On those days patients should be instructed to come into the clinic before taking his or her dose of talazoparib and these doses will be administered in the clinic by study staff after completing pre-dose visit assessments. If patient takes the study treatment at home on Day 22 before arriving at the clinic, the patient should be asked to visit the site again on Day 23 to take the study treatment at the clinic. All the study assessments (including PK sampling) initially planned on Day 22 should be collected on Day 23 instead.

On Days 1 and 22 PK sampling days, talazoparib will be swallowed whole, under fasting conditions. Fasting is defined as after an overnight fast of at least 6 hours with no food allowed for at least 4 hours post-dose. Water is allowed as desired. On the other days, talazoparib can be given with or without food.

If a patient vomits a dose, the patient should not take a second dose that calendar day. The patient should resume daily dosing the following day. If a patient misses a dose, he/she should take the dose as soon as possible, but not when more than 12 hours after the missed scheduled dose. If the dose is missed greater than 12 hours, the missed dose should be skipped and the patient should take the next dose when scheduled.

[redacted]

If a capsule is broken or damaged, the capsule should not be used, and brought back to the site for accountability and disposal.

5.3.2. Treatment Compliance

Patients will be instructed to bring all used and unused study drug containers and their completed study drug diary to all clinic visits (Day 8, Day 15 and Day 22) in order to assess the treatment compliance. Site staff will perform accountability of the returned drug and will assess compliance of the patient. Site staff must ensure that the patient clearly understands the directions for self-medication and follows the schedule adequately.

5.3.3. Treatment Duration

The patients will be treated only during 1 cycle, defined as a 22 calendar days counted from Day 1, regardless of any treatment hold.

If Day 22 coincides with a non-working day (e.g. weekend, holiday) it is acceptable to administer study treatment for more than 22 calendar days up until the closest upcoming weekday, up to a maximum of 25 days of treatment.

Patients with no clinically significant toxicities, no contraindications to continue treatment with talazoparib and no disease progression (underlying cancer progression) may be eligible to continue talazoparib treatment on a separate open-label extension study after discussion with the Principal Investigator and obtaining Sponsor permission. Sponsor decision to allow the patient to continue dosing with talazoparib in an open-label extension study will be based on potential overall benefit-risk, patient acceptance to be enrolled in the open-label extension study and other relevant criteria.

5.4. Treatment Schedule Adjustment and Adverse Event Management

5.4.1. General Rules

Regular assessment and monitoring of AEs is required throughout study treatment period and until the Safety Follow up visit, i.e. 30 days after the last dose of study drug or before initiation of a new anticancer therapy (standard or investigational treatment) or the first day of the extension protocol whichever occurs first.

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. For adverse event terms not specifically listed in the NCI CTCAE, the investigator should report the adverse event using the criteria in Table 1 to assess severity.

Table 1: AE grading for toxicities when the AE term is not listed in NCI CTCAE

Grade	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 (e.g. preparing meals, shopping for groceries or clothes).

3	**Severe:** medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g. bathing, dressing and undressing, feeding oneself).
4	**Life threatening** or debilitating consequences, urgent intervention indicated.
5	**Death** related to AE.

Patients will be instructed to notify their study Investigator immediately for any and all toxicities. Assessment of causality (chronology, confounding factors, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the Investigator prior to dose modification and/or delay whenever possible. As a general approach, it is suggested that all AEs be managed with supportive care at the earliest signs of toxicity and before delaying/reducing study drug, when possible and if clinically appropriate.

5.4.2. Dose Modification Due to Adverse Events

5.4.2.1. Assessment of Abnormal Non Liver Tests

Study treatment dose modifications due to adverse events with the exception of liver tests abnormalities are described in Table 2.

Table 2: Talazoparib Treatment Adjustment for Non Liver Test Abnormalities

Non Liver Test Abnormalities	
Grade 1 or 2	No requirement for dose interruption or dose reduction.
Selected grade 3 or 4 hematological toxicity	
Anemia (hemoglobin < 8.0 g/dL)	Hold study treatment and monitor weekly until hemoglobin returns to baseline or better. Implement supportive care per local guidelines. Study treatment should be reduced by 1 dose level to 0.25 mg/day. If Day 22 is reached without recovery, discontinue study treatment and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Neutropenia (ANC < 1000/µL)	Hold study treatment and monitor weekly until ANC ≥ 1500/µL. Implement supportive care per local guidelines. Resume study treatment based on the following recovery times: ✓ ≤ 1 week: No change. ✓ >1 week: Reduce study drug treatment by 1 dose level to 0.25 mg/day. If Day 22 is reached without recovery, discontinue study treatment and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Thrombocytopenia (platelets < 50,000/µL)	Hold study treatment until platelets ≥ 75,000/µL. Implement supportive care per local guidelines. Resume study drug treatment based on the following recovery times: ✓ ≤ 1 week: No change. ✓ >1 week: Reduce study treatment by 1 dose level to 0.25 mg/day. If Day 22 is reached without recovery, discontinue study treatment and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Grade 3 and 4 non hematological toxicity	
Other grade 3 or 4 events, except abnormal liver tests[1]	• For clinically important grade 3 or 4 laboratory abnormalities, study treatment may be held. Resume study treatment when the laboratory abnormality resolves to grade ≤ 2 (baseline grade for creatinine increases). • For clinically significant grade 3 or 4 adverse events, hold study treatment until the adverse event resolves to grade ≤ 2. Resume study treatment at the same dose or reduce by 1 dose level to 0.25 mg/day if the event resolves or improves within 22 days of holding study drug treatment, and can be monitored if it recurs. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Study treatment should be permanently discontinued for unresolved grade 3 or 4 toxicity per investigator decision that continued study drug treatment is not in the patient's best interest.

Note: Dose modifications for liver abnormalities are presented in Table 3.

5.4.2.2. 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 as specified in 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 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.

5.4.2.2.1. Criteria for temporary withholding Talazoparib in Association With Liver Test Abnormalities

Study treatment should be withheld for any liver test abnormality listed in Table 3.

Table 3: Criteria for Temporary Withholding Talazoparib 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 baseline total bilirubin value of > 1.5 × ULN and ≤ 3 × ULN (patients with Gilbert syndrome or for whom indirect bilirubin concentration suggest an extra-hepatic source of elevation)

Note: For re-challenge, dose modification may be required per Table 2.

Study treatment should be withheld pending investigation of alternative causes of liver injury (Table 4). When withholding study treatment, follow-up should continue for possible drug-induced liver injury until the liver test abnormalities resolve to baseline grade. Rechallenge may be considered 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.

Table 4: Investigations of Alternative Causes for Abnormal Liver Tests

Recommended tests:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin 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 as clinically indicated:

- 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)

The investigator and the Sponsor should discuss and agree with any decision to re-challenge. Following re-challenge, patients should be closely monitored for signs and symptoms of hepatitis and/or abnormal liver test results. If signs or symptoms recur with re-challenge, study drug should be permanently discontinued. Re-challenge should never occur if the criteria for permanent discontinuation are clearly met.

5.4.2.2.2. Criteria for Permanent Discontinuation of Talazoparib in Association With Liver Test Abnormalities

Talazoparib should be discontinued permanently if ALL of the following 4 criteria are met (i.e. potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 times ULN (> 5 times ULN if baseline ALT/AST is > 3 times 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 (e.g. 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 talazoparib should be withheld or permanently discontinued as appropriate for the safety of the patient. When talazoparib 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 5 should be performed.

Table 5: Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency of Repeating Liver (AST, ALT, Biliubin (total and direct)) and INR tests
After the initial liver abnormality	**Within 24 hours**
If AST or ALT ≥ 3 x ULN (> 5 x ULN if baseline ALT/AST is 3 x ULN) and total bilirubin > 2 or INR > 1.5	**Every 24 hours until laboratory abnormalities improve**
If AST or ALT ≥ 3 x ULN (>5 x ULN if baseline ALT/AST is 3 x 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**

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. Guidance for such cases is provided in section 8.4.1 Potential Cases of Drug-Induced Liver Injury.

5.5. Study Treatment Discontinuation

By default, patients are treated for 22 calendar days counted from day 1, regardless of any treatment hold. The Investigator will discontinue study treatment before Day 22 if any of the following conditions are met:

- Patient's decision to withdraw study treatment
- Intercurrent illness or a change in patient´s condition or unacceptable toxicity that warrants study treatment discontinuation according to Investigator judgment
- Any event, condition, criterion which would warrant treatment discontinuation according to section 5.4
- Need for additional local and/or systemic non-protocol anticancer therapy or patient receives non-protocol anticancer therapy at any time during the study treatment.
- Progressive Disease
- Lost to follow up
- Death
- Pregnancy
- Investigator's decision
- Medical Monitor's decision
- Sponsor's discontinuation of the study

Permanent treatment discontinuation is defined as permanent cessation of study drug administration. After permanent treatment discontinuation, a Safety Follow up Visit (End of Study visit) will be performed. The Safety Follow up Visit corresponds to the end of study participation.

6. CONCOMITANT TREATMENT AND PROCEDURES

Concomitant therapy includes any medication (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements, etc.) used by a patient from 28 days prior to enrollment until 30 days after the last dose of study drug or the first day of extension study whichever occurs first. Any concomitant medication during the study will be recorded on the eCRF.

In the event of an emergency, any needed medications (even if prohibited per section 6.3) may be prescribed as required, but the CCI Medical Monitor or designee must be notified of the use of any prohibited medication immediately thereafter.

The following sections and Table 6 provide a list of allowed and prohibited medications and instructions on their use.

6.1. Allowed Concomitant Treatments

The Investigator may prescribe concomitant medications during the study as clinically indicated; as long as the prescribed medication is not prohibited by the protocol (refer to section 6.3). Allowed medications include (but are not limited to):

- Anti-emetics, such as dexamethasone, metoclopramide, ondansetron, aprepitant, etc.; anti-diarrheals, such as loperamide hydrochloride; appetite stimulants such as megestrol acetate.

- Supportive medications may be provided prophylactically or therapeutically at the Investigator's discretion, with the exception of that colony stimulating factor (G-CSF or GM-CSF) and erythropoiesis-stimulating agents that are only allowed in the rescue setting (not for primary or secondary prophylaxis). Erythropoietin is allowed if the patient is chronically receiving this drug.
- Bisphosphonates and the monoclonal antibody denosumab are also permitted for treatment, or prophylaxis, of bone metastases as per local standards of care.

6.2. Concomitant Medication for Treatment of Renal Impairment

If the patient is taking concurrent medications for treatment of renal impairment, to be eligible he/she must meet inclusion criterion 10. Also, concurrent medication used for the management of renal impairment will not be taken for at least 4 hours before and 2 hours after talazoparib dosing. During that period, the patient should not take these medications.

6.3. Prohibited Treatments

Patients are prohibited from receiving the following therapies from the time of patient informed consent form (PICF) until the Safety Follow up Visit (End of Study visit):

- Investigational agents other than talazoparib;
- Any additional investigational or commercial anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, endocrine therapy, etc. even when used for non-cancer indications; and,
- Live bacterial and virus vaccines.
- Use of inhibitors or inducers of P-gp and inhibitors of BCRP (see Table 6).

Table 6: Instructions for Use of Concomitant Therapies

Use Category	Medication or Treatment	Comment on Use
Allowed	Antiemetics (i.e., prochlorperazine, dexamethasone, metoclopramide, ondansetron, aprepitant)	Not applicable
	Antidiarrheals (i.e., loperamide hydrochloride)	Not applicable
	Appetite stimulants (i.e., megestrol acetate)	Not applicable
	Anticoagulants	Not applicable
	Bisphosphonates or other antiresorptives such as denosumab for bone disease	Not applicable
	Corticosteroids	Not applicable
	Pain medications, antidepressants, cardiovascular and other medications to treat other medical conditions with the exception of the medications noted in section 6.3	Not applicable
	Antibiotics	Not applicable
	Granulocyte-colony stimulating factor, erythropoietin	Use per American Society of Clinical Oncology (ASCO) guidelines (Smith et al, 2015b), but should not be used prophylactically.
	Palliative radiation therapy only for local pain control, and only if in the opinion of the treating Investigator the patient does not have progressive disease.	Precaution: the combination of radiation therapy and talazoparib has not been studied.
Prohibited	Any standard or investigational antineoplastic systemic therapy (including but not limited to PARP inhibitor, chemotherapy, targeted therapy, biologics, immunotherapy, endocrine therapy, etc.)	Within 4 weeks before enrollment through the Safety Follow up.
	Other investigational agent (i.e., biologic, vaccine, or other agents not approved for marketing)	Within 4 weeks before enrollment through the safety Follow up.
	Live bacterial and virus vaccines	Any time between Day-1 and safety follow-up.
	P-gp inhibitors (amiodarone, atorvastatin, azithromycin, carvedilol, clarithromycin, cobicistat, conivaptan, darunavir, diltiazem, diosmin, dronedarone, eliglustat, erythromycin, felodipine, flibanserin, fluvoxamine, indinavir, itraconazole, ketoconozole, lapatinib, lopinavir, piperine, propafenone, quercetin, quinidine, ranolazine, ritonavir, saquinavir, schisandra chinensis extract, telaprevir, tipranavir, valspodar, and verapamil)	Within 7 days or 5 half lives which ever is longer prior to Day 1 through Safety Follow up.

Use Category	Medication or Treatment	Comment on Use
	P-gp inducers (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort)	Within 7 days or 5 half lives which ever is longer prior to Day 1 through Safety Follow up.
	BCRP inhibitors (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag)	Within 7 days or 5 half lives which ever is longer prior to Day 1 through Safety Follow up.

6.4. Palliative Radiotherapy

Patients may receive palliative radiotherapy before discontinuing study treatment. However, the effect of talazoparib with radiation has not been evaluated.

6.5. Contraception/Reproductive Consideration

Refer to section 8.4.2.1**Error! Reference source not found.** for details regarding the reporting procedures to follow in the event of pregnancy. Instructions regarding sperm or egg donation and breastfeeding are provided in the inclusion/exclusion criteria (section 4).

6.5.1. Females

Women of childbearing potential must have a negative pregnancy test (tested locally) at screening (serum pregnancy test), on Day -1 and at the Safety Follow up (urine or serum pregnancy test) 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 treatment will be discontinued.

In addition, women of childbearing potential must agree to use a highly effective birth control method from the time of first talazoparib administration through 7 months after the last dose of talazoparib. A highly effective contraceptive method is defined as:

- 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 enrollment
- Sexual partner(s) vasectomized for ≥ 6 months before enrollment
- Sexual abstinence when in relation to the preferred and usual lifestyle of the patient.

Note: Female patients not of childbearing potential include those who are surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy with documentation of the procedure) or who are post-menopausal, defined as:

- *≥ 55 years of age with no spontaneous menses for ≥ 12 months before enrollment.*
- *< 55 years of age with no spontaneous menses for ≥ 12 months before enrollment and with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/L (or meeting criteria for post-menopausal status by the local laboratory.*

[redacted]

6.5.2. Males

Male patients must agree to use a condom when having sex with a pregnant woman or with a non-pregnant woman of childbearing potential, from 21 days before the first dose of study drug through 4 months after last dose of study drug.

7. STUDY VISITS AND ASSESSMENTS

7.1. Patient Inclusion

7.1.1. Informed Consent

In compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), US 21 CFR §50 and other applicable local regulations, a properly written and executed (PICF will be obtained for each patient prior to entering the patient into the study.

Prior to any study-specific screening evaluation, the patient or legally acceptable representative (if applicable per local regulation) will be informed of the nature of the study and will be given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the study.

An approved PICF will then be read and signed by the patient (or legally acceptable representative if applicable) and, when required, a witness, and the Investigator or a person designated by the Investigator, as per local regulations. The patient will be provided with a copy of the signed PICF.

The patient may withdraw from the study at any time without prejudicing future medical treatment. In any case, the withdrawal should be clearly documented in the medical charts of the patient.

If a potential patient or legally acceptable representative is illiterate or visually impaired, the Investigator must provide an impartial witness to read the PICF to the patient and must allow for questions. Thereafter, both the patient or legally acceptable representative and the witness must sign the PICF to attest that informed consent was freely given and understood. The PICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB), and the regulatory authorities to have direct access to its data that will be processed according to the confidentiality regulations.

If important new information becomes available that may be relevant to the patient's consent and willingness to continue participation in the study, the PICF will be revised and submitted to IRB for approval/favorable opinion. The new information will be then discussed with the patient in a timely manner and if he/she agrees to continue participation in the study, the revised PICF will be signed and dated and the patient will receive a copy.

In line with each country's applicable regulations, the source should also support the documentation of the consent process, for each patient.

Note: If the patient continues the treatment in the context of the extension study (separate protocol), a new PICF will be obtained.

[redacted]

7.1.2. Patient Enrollment

Details on the process to be followed to enroll the patient in the study can be found in the Registration Eligibility Review and Enrollment Instruction Manual provided to each site.

Patients will be enrolled in one of the four groups based on their renal function, according to section 4.1.

Study treatment should be started within 3 calendar days after enrollment.

7.2. Schedule of Visits and Assessments

Prior to undergoing any study specific procedures not considered standard practice by the institution, patients must read and sign the PICF. Adherence to the schedule of visits and assessments is required and visits should be planned accordingly.

All study visits and procedures are detailed in the Schedule of Visits and Assessments table presented in this section. All study procedures and assessment should be performed irrespective of any treatment hold.

In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK blood sampling will be done after the ECG and vital signs recordings have been conducted, with blood sampling exactly on time. The description of the study assessments is in section 7.4.

[redacted]

Table 7: Schedule of Visits and Assessments

	Pre-screening	Screening	Enrollment	Treatment period: Cycle 01 only									Safety Follow up Visit (=End of Study Visit) (17)
Study Day		**-28 to -2 (1)**	**D-1**	**D1 = First Study Drug Intake (5)**	**D2**	**D3-7**	**D8**	**D9-D14**	**D15**	**D16-D20**	**D21**	**D22**	**D23**	
Window				Within 3 calendar days post D-1		+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days		-3/+10days
Informed consent signature	X													
Demographics, medical, surgical, disease history		X												
Central review of the eligibility criteria ([redacted] and enrollment			X											
Physical Examination (6)		X	X (3)				X		X			X		X
ECOG Performance Status		X	X (3)											X
Height		X												
Weight		X	X (3)				X		X			X		X
Temperature		X	X (3)											X
Respiratory Rate		X	X (3)				X		X			X		X
12-Lead Electrocardiogram		X		X (2)								X (2)		X
Supine Heart Rate and Blood Pressure		X	X (3)				X		X			X		X
Adverse Event Review		X (SAE)	X (SAE)	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X
Talazoparib administration				X (4)	X	X	X (4)	X	X (4)	X	X	X (4)		
Talazoparib compliance							X		X			X		
Serology for HIV		X												
Serum pregnancy test assessed locally **(7)**		X	X											X

	Pre-screening	Screening	Enrollment	Treatment period: Cycle 01 only										Safety Follow up Visit (=End of Study Visit) (17)
Study Day		**-28 to -2 (1)**	**D-1**	**D1 = First Study Drug Intake (5)**	**D2**	**D3-7**	**D8**	**D9-D14**	**D15**	**D16-D20**	**D21**	**D22**	**D23**	
Window				Within 3 calendar days post D-1		+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days		-3/+10days
Follicle-stimulating hormone **(8)**		X												
Serum chemistry **(9)**		X	X (3)				X		X			X		X
eGFR calculation according to MDRD equation		X	X(3)											
Hematology **(10)**		X	X (3)				X		X			X		X
Coagulation/urinalysis **(11)**		X	X (3)											X
Tumor assessments **(12)**		X												
Blood sample for PK **(13)**				X	X		X		X			X	X	X (1 sample only in case of early study treatment discontinuation)
Blood sample for protein binding analysis **(14)**				X								X		
Urine sample for PK **(15)**				X	X							X	X	
Blood sample for banking **(17)**		X												

1: If a transient but clinically significant clinical or laboratory abnormality is seen just prior to enrollment, that the screening period may be extended up to 7 days and if the repeat assessments (e.g. on the Day -1) labs are acceptable/meeting the inclusion criteria, then the patient may be included.

2: Triplicate ECGs (approximately 1-2 minutes apart) assessed locally will be collected at pre-dose and 2 hour post-dose on Day 1 and Day 22. ECG should be done prior to PK drawn with a window of ±10 min.

3: These tests must be done at screening and at enrollment. For patients where enrollment visit is done within 3 days of the screening tests, tests at enrollment can be omitted unless clinically indicated to repeat them.

4: On the days of ambulatory visits, talazoparib will not be taken at home and will be withheld until after the PK sample is collected.

[redacted]

[redacted]

5: The patient should start the study treatment within 3 calendar days after enrollment.

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.

7: For women of childbearing potential only: must have a negative pregnancy test at screening (serum), on day – 1 and at the Safety FU (urine or serum). Urine pregnancy tests must have a limit of detection of 25 IU/L (or equivalent units) for human chorionic gonadotropin. Discontinue study treatment if a pregnancy test is positive.

8: Collect only for females with no spontaneous menses for ≥ 12 months, who are ≤ 55 years old, and who do not have documented surgical sterilization.

9: Serum chemistry includes: Albumin, Alkaline phosphatase, ALT, AST, Total Bilirubin (TB), Bicarbonate, Blood Urea Nitrogen (BUN) (urea), calcium, creatinine, chloride, Gamma GT, glucose, LDH, sodium, phosphate, potassium, total protein, Uric Acid, FSH (for women at screening only and if applicable).

Blood samples for blood chemistry can be drawn within 72 hours prior to dosing.

10: Hematology includes: Erythrocytes, Hematocrit, Hemoglobin, White Blood Cell (WBC), Absolute Neutrophil Count (ANC), Lymphocytes, Platelets.
Blood samples for hematology assessments can be drawn within 72 hours prior to dosing.

11: Coagulation includes: PT or INR, aPTT/PTT.

Urinalysis (dipstick) includes: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, leukocyte esterase. Microscopy is required if dipstick results for blood and leukocyte esterase are positive; Day -1 screening coagulation and urinalysis samples can be taken within 72 hours prior to dosing.

12: Tumor assessment: Initial Tumor imaging must be performed within 28 days prior to enrollment. Scans and other imaging as part of the standard of care for the concerned solid tumor should be performed.

13: Serial plasma PK analysis will be collected at predetermined times on Day 1 and Day 22. Blood samples for PK bioanalysis will be drawn at the following selected time-points during Day 1 and Day 22: pre-dose On day 1 (within 60 minutes prior to dose) and on Day 22 (24 h± 60 minutes from the previous dose (Day21) but within 60 minutes prior to next dose) and then at 0.5, 1, 2, 4, 6, 8-12, and 24 h post-dose. Post-dose samples up to 60 minutes post-dose will be obtained within a window of ± 3 minutes. From after 60 minutes until 12 h post-dose, samples will be obtained with time margins of ±10 minutes. Thereafter, samples should be obtained within ±60 minutes of the scheduled time points.

Note: 24h post-dose on Day 1 corresponds to the pre-dose on Day 2 and 24h post-dose on Day 22 corresponds to the sample on Day 23.

Additionally pre-dose samples on Day 8 and Day 15 will be collected 24 h ± 60 minutes from the previous dose but within 60 minutes before the next dose on the day of sample collection.

14: Blood samples for plasma protein binding evaluation will be collected at 2 hours post-dose on Day 1 and Day 22. Samples will be obtained with a time window of ±10 minutes.

15: Urine samples for PK analyses will be collected as a single void at pre-dose on Day 1. All urine voided after talazoparib dosing on Day 1 and Day 22 will be collected at the intervals of 0-12 h and 12-24 h. The ± 60 minute time window also applies to the start and end times of urine collection intervals.

16: 30 days (-3/+10 days) after the last study drug administration or before initiation of a new anti-cancer therapy (standard or investigational). For patients who enroll and continued talazoparib a separate open label extension protocol within 30 days after the last dose of talazoparib the safety follow up will be omitted.

17: Collect blood sample to be stored for reflex testing for HBV (HBsAg, anti-HBc) and HCV (HCV Ab, reflex testing for HCV RNA if positive).

7.3. Study Visits

7.3.1. Screening Period

The screening period starts with the signature of the PICF and ends when the patient is enrolled. Assessments should be done during the screening period according to the Schedule of Visits and Assessments in section 7.2. All procedures and assessments must be completed within 28 days before enrollment except as noted.

7.3.2. Enrollment Period

Day -1 corresponds to the day of the enrollment of the patient in the study. Tests mandated at enrollment according to

Table 7 need to be repeated even if done at screening, unless otherwise specified.

7.3.3. Treatment Period

Study treatment should begin within 3 calendar days of enrollment. Day 1 is the first day the patient receives study treatment.

Study visits during the treatment period will be done according to the Schedule of Visits and Assessments in section 7.2.

7.3.4. Safety Follow Up Visit (End of Study Visit)

The Safety Follow up visit (also called End of Study visit) must be scheduled approximately 30 days (window -3/+10 days) after the last study drug administration or before initiation of any new anti-cancer therapy, whichever occurs first. The Safety Follow up Visit corresponds to the end of study participation. The primary purpose of this visit is to follow up on any AE ongoing at the time of treatment discontinuation, and to assess any new AEs that may have occurred since treatment discontinuation.

For eligible patients who are enrolled and continued talazoparib in a separate open label extension protocol within 30 days after the last dose of talazoparib, the safety follow up visit will be omitted.

7.3.5. Follow-Up

No follow up visit is planned in the context of this study.

Patients may be eligible to continue talazoparib treatment on a separate open-label extension study (refer to section 5.3.3).

7.4. Description of Study Assessments

7.4.1. Demographics and Medical History

The Investigator will collect and report in the eCRF demographics and complete history of malignant and clinically-significant non-malignant diseases including known hypersensitivity reactions.

7.4.2. Physical Examination and Vital Signs

Physical examination and vital signs collection includes:

- An examination of major body systems
- Height and weight
- Temperature
- Respiratory Rate
- Supine Heart Rate
- Blood Pressure

7.4.3. ECG

Refer to the Schedule of Visits and Assessments in section 7.2.

[redacted]

7.4.4. ECOG Performance Status

Assessment of ECOG PS (Appendix 1) is required to assess patient´s functional status for study eligibility purposes and will be performed throughout the study according to the Schedule of Visits and Assessments (section 7.2).

7.4.5. Laboratory Safety Assessments

The following laboratory safety assessments will be done at screening, enrollment, during the study treatment phase, and at the Safety Follow up Visit (also called End of study visit) according to the Schedule of Visits and Assessments in section 7.2.

- Hematology: Erythrocytes, Hematocrit, Hemoglobin, White Blood Cell (WBC), Absolute Neutrophil Count (ANC), Lymphocytes, Platelets.
- Serum chemistry: Albumin, Alkaline phosphatase, ALT, AST, Total Bilirubin, Bicarbonate, Blood Urea Nitrogen (BUN) (urea), calcium, chloride, creatinine, gamma GT, glucose, LDH, sodium, phosphate, potassium, total protein, Uric Acid, FSH (for women at screening only and if applicable).
- Calculation of eGFR according to MDRD equation at screening and at Day -1.
- Coagulation tests: INR or PT and aPTT/PTT (at baseline and then only if clinically indicated)
- Urinalysis (dipstick): pH, specific gravity, protein, glucose, ketones, bilirubin, blood, leukocyte esterase. Microscopy is required if dipstick results for blood and leukocyte esterase are positive.
- Serum pregnancy test: only in women of childbearing potential at screening
- Serum or urine pregnancy test at enrollment (Day -1), at the Safety Follow up visit and when clinically indicated.
- Serology for HIV (only at screening)
- Blood sample for banking to be stored for reflex testing for HBV (HBsAg, anti-HBc) and HCV (HCV Ab, reflex testing for HCV RNA if positive).

For information on the assessment and collection of AEs refer to section 8 and to the Schedule of Visits and Assessments in section 7.2.

7.4.6. Efficacy Assessments

No efficacy analysis is planned in this study, although screening tumor assessments will be obtained in the event that eligible patients choose to continue talazoparib treatment in the separate open-label extension study.

7.4.7. PK Assessments

Procedures for sample collection, labeling, storage and shipment of PK samples will be described in the study Laboratory Manual. The exact times of each PK sample collection will be recorded in the eCRF. PK samples will be analyzed for talazoparib concentration using a validated LC-MS/MS method.

7.4.7.1. Blood PK samples

Blood samples for PK analyses will be drawn at the following selected time-points:

- Day 1 and Day 22:
  - Pre-dose:
    - On Day 1: within 60 minutes prior to dose
    - On Day 22: 24h ± 60 minutes from the previous dose (Day 21) but within 60 minutes prior to the next dose
  - Post dose: 0.5, 1, 2, 4, 6 h, between 8 and 12 h, and 24 h after taking talazoparib. Post-dose samples up to 60 minutes post-dose will be obtained with a window of ± 3 minutes. From after 60 minutes until 12 hours post-dose, samples will be obtained with time margins of ± 10 minutes. Thereafter, samples should be obtained within ± 60 minutes of the scheduled time points.

  Note: the 24h post -dose sample on Day 1 corresponds to the pre-dose sample on Day 2 and the 24h post-dose sample on Day 22 corresponds to the sample on Day 23.

- Day 8 and Day 15: Pre-dose samples will be collected 24h ± 60 minutes from the previous dose but within 60 minutes before the next dose on the day of sample collection.

  Note: One PK Blood sample will also be collected at the safety follow up if the study treatment discontinues earlier than planned.

7.4.7.2. Urine PK samples

Urine samples for PK analyses will be collected as follows:

- As a single void at pre-dose on Day 1
- All urine voided after talazoparib dosing on Day 1 and Day 22 will be collected between the intervals of 0-12 h and 12-24 h. A ± 60 minute time window applies to the start and end times of urine collection intervals.

7.4.7.3. Blood samples for plasma protein binding evaluation

Blood samples for plasma protein binding evaluation will be collected at 2h post-dose on Day 1 and Day 22. A ± 10 minute window will apply.

[redacted]

Table 8: Samples for PK assessment

PK SAMPLES	Day1							Day 1/ Day 2	D8	D15	D22							D22/ D23
	Pre-Dose	Post-Dose						Post-dose Day 1 = Pre-Dose Day 2	Pre-dose	Pre-dose	Pre-Dose	Post-Dose						Post-dose
Blood sample for PK	x	x	x	x	x	x	x	x	X	X	x	x	x	x	x	x	x	x
Window	within 60 min	0.5 (+/- 3 min)	1h (+/- 3 min)	2h (+/- 10 min)	4h (+/- 10 min)	6h (+/- 10 min)	8-12h (+/- 10 min)	24h (+/- 60 min)	within 60 min**(1)**	within 60 min**(1)**	within 60 min**(1)**	0.5 (+/- 3 min)	1h (+/- 3 min)	2h (+/- 10 min)	4h (+/- 10 min)	6h (+/- 10 min)	8-12h (+/- 10 min)	24h (+/- 60 min)
Blood sample for protein binding analysis				X (+/- 10 min)										X (+/- 10 min)				
Urine sample for PK	x	x			x							x			x			
Window	within 2 h	0-12 hour (+/- 60 min			12-24 hour (+/- 60 min)							0-12 hour (+/- 60 min)			12-24 hour (+/- 60 min			

(1) Pre-dose samples on Day 8, Day 15, and Day 22 will be collected 24h ± 60 minutes from the previous dose but within 60 minutes before the next dose on the day of sample collection.

7.5. Permanent Patient Discontinuation

The Investigator has the right to withdraw a patient from the study at any time. In addition, patients have the right to withdraw from the study at any time for any reason.

Permanent treatment discontinuation is defined as permanent cessation of study drug administration. After permanent discontinuation, a Safety Follow Up Visit (End of Study Visit) will be performed.

The Safety Follow Up Visit corresponds to the End of Study participation.

Should a patient decide to withdraw consent, all efforts will be made to complete and report the observations as thoroughly as possible. The Investigator should contact the patient by telephone or through a visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. Withdrawal should be documented on the initial PICF, and must be dated and signed by the patient and by the Investigator

In the case a patient does not show up for study visits, site staff should make reasonable contact attempts before declaring the patient as lost to follow-up. These attempts need to be documented in the medical records.

8. ADVERSE EVENT REPORTING

8.1. Requirements

Table 9 below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Table 9: Adverse Events Reporting Requirements

Safety Event	Recorded on the CRF	Reported on the SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in Table 9 above that require reporting to Pfizer Safety on the SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an SAE event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see section 8.2.4 below).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

[redacted]

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient.

In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see sections 5.5 and 7.5)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the SAE Report Form, in accordance with section 8.1 above.

8.1.4. Time Period for Collecting AE/ Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient will be as per the Table below:

Table 10: Active Collection Period

Study Period	SAEs (including AESI)	AEs
From the time the patient signs the PICF	Yes	No

From first dose of study drug until the Safety Follow up Visit (30 days after the last dose of study drug) or before initiation of any new anticancer therapy or enrollment into the talazoparib open-label extension study.	Yes	Yes
After the Safety Follow up Visit (End of Study Visit)	If assessed as related to the study drug by the Investigator.	No

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as an AE in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Adverse Event of Special Interest (AESI)

AESIs include a diagnosis of MDS or AML (consistent with events observed with talazoparib) 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)

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

AESIs must be transmitted to Pfizer Safety Unit by completing a SAE form.

8.2.3. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms;
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or,
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.4. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); and,
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or the diagnosis o fa second primary malignancy.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period.
- Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.
- If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see section 8.3).

8.2.5. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g. from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient; and,
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

The intensity of AEs will be classified and recorded according to the NCI CTCAE (v4.03) in the CRF or according to the grading defined in section 5.4.1 if the AE is not specifically listed in NCI CTCAE.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are

termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TB) elevations (> 2 × ULN) by several days or weeks. The increase in TB typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TB values will be elevated within the same lab sample). In rare instances, by the time TB elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST or ALT in addition to TB that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TB baseline values within the normal range who subsequently present with AST or ALT values > 3 × ULN and a TB value > 2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 × ULN or not available;
- For patients with baseline AST or ALT or TB values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Pre-existing AST or ALT baseline values above the normal range: AST or ALT values > 2 times the baseline values and > 3 × ULN; or > 8 × ULN (whichever is smaller).
    - Pre-existing values of TB above the normal range: TB level increased from baseline value by an amount of at least 1 × ULN or if the value reaches > 3 × ULN (whichever is smaller).

Rises in AST/ALT and TB separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hfrom awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST, ALT and TB, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous

analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TB elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 h of investigator awareness.

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hof awareness of the exposure. The

information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 h of the investigator's awareness, using the SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Table 11: Medication Errors Reporting Requirements

Safety Event	Recorded on the CRF	Reported on the SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication error	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a SAE Report Form only when associated with an SAE.

There is no specific treatment in the event of talazoparib overdose, and symptoms of overdose are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow general supportive measures and treat symptomatically.

9. STATISTICAL CONSIDERATIONS

9.1. Populations for Analyses

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

The PK concentration population is defined as all eligible patients enrolled and treated who have at least 1 plasma talazoparib concentration.

The PK parameter analysis population is defined as all evaluable patients enrolled and treated who have at least 1 of the talazoparib PK parameters of primary interest.

9.2. Demographics and Screening Characteristics

Demographics and screening characteristics data will be listed and summarized by each group.

9.3. Protocol Treatment

Duration of treatment, duration of exposure, cumulative dose and relative dose intensity will be summarized by renal impairment group using the safety population.

9.4. Safety Endpoints

The assessment of safety will be made on the safety population and will be based on summaries of AEs, physical examinations (including weight), vital signs, electrocardiograms (ECGs), laboratory evaluations and ECOG performance status.

The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a preferred term and system organ class.

The number and percentage of patients with adverse events will be presented by MedDRA's System Organ Class (SOC) and Preferred Term (PT), relationship to study treatment, severity, seriousness and action taken (e.g., leading to permanent treatment discontinuation).

Detailed listings for all AEs will also be provided.

Laboratory parameters, graded according to the NCI CTCAE v4.03, will be summarized at screening, along visits and at the safety follow up visit. Tables of shifts in toxicity will also be provided.

9.5. Pharmacokinetics Endpoints

Actual PK sampling times and doses will be used for PK parameters calculations.

The following PK parameters will be calculated by non-compartmental analysis using WinNonlin or another appropriate software.

- AUC_{0-24}: area under the concentration time curve from 0 to 24 hours
- C_{max}: maximum observed plasma concentration
- $AUC_{0-24,u}$: unbound AUC_{0-24}
- $C_{max,u}$: unbound C_{max}
- C_{trough}: pre-dose plasma drug concentration
- T_{max}: time of C_{max} estimated directly from the experimental data
- oral unbound CL/FF_u: fraction of unbound drug
- R_{ac}: accumulation ratio

- Ae%: Percentage of dose excreted in urine as unchanged drug
- CL_r: renal clearance

Additional PK parameters will be calculated as applicable.

The concentration-times data of talazoparib in plasma will be separately tabulated.

The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric CV, minimum, median, maximum value and the number of measurements. Concentrations below LLOQ will be set to zero when calculating descriptive statistics. Means at any time will only be reported if the mean ≥ LLOQ; for mean < LLOQ, "missing" is reported in the tables.

The PK characteristics of T_{max} and R_{ac} will be described utilizing minimum, maximum and median. All PK parameters except T_{max} and R_{ac} will be expressed as individual data as well as arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric CV, minimum, median, maximum value and the number of measurements.

PK parameters AUC_{0-24}, C_{max}, $C_{max,u}$, and $AUC_{0-24,u}$ on Days 1 and 22 will be natural log-transformed and analyzed using an analysis of variance (ANOVA) model with group as a fixed effect to compare each renal impairment group (mild, moderate or severe; Test) with the normal renal function group (Reference). Additionally, weight and age will be considered as covaraites (at the significance level of 0.05). Estimates of the adjusted mean differences (Test - Reference) and corresponding 90% CIs for each comparison will be obtained from the model. The adjusted mean differences and the 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios on the untransformed scale.

Relationship between renal functional measures (e.g. eGFR) and selected PK parameters may be explored graphically as appropriate. A regression line and 90% confidence region for the PK parameters and renal function will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify subjects from different renal function groups.

Linear regression will be used to analyze the potential relationship between selected PK parameters and renal function. Estimates of the slope and, intercept, together with their precision (90% CI), and the coefficient of determination will be obtained from the model.

The PK parameters of talazoparib will be summarized descriptively by renal function group and Day. Boxplots of mean, median and individual subject parameters will be made across all the groups for AUC_{0-24}, and C_{max} by Day. Concentrations will be listed and summarized descriptively by PK sampling time and group. Summary profiles (means and medians) of the concentration- time data will be presented with all renal function groups plotted across different groups by Day. Individual subject concentration time profiles will be also presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

[redacted]

9.6. Efficacy Endpoints

No efficacy analysis is planned in this study.

9.7. Sample Size

Patients are assigned to one of four groups, based on renal function.

The study will enroll at least 6 PK evaluable patients with advanced solid tumors per group so at least 24 patients will be enrolled.

If enrollment for severe renal impairment group is halted due to unacceptable toxicity profile, 2 additional evaluable patients will be enrolled in each of Groups A, B and C (total of 8 PK evaluable patients each).

Patients will be considered PK evaluable if they are eligible and have:

- Completed 22 calendar days of treatment with talazoparib counted from day 1, regardless of any treatment hold and miss ≤ 5 consecutive doses of talazoparib,
- Received at least 10 consecutive days of 0.5 mg talazoparib daily dose without dosing interruption prior to Day 22 PK sample collection,
- Completed at least 85% of total plasma PK samples collection,
- Not vomited talazoparib dose on Day 1 and Day 22 of the PK samples collection.

Patients who discontinue the study before the completion of the Day 23 (i.e., 24 h of Day 22) assessment and/or who do not meet the above mentioned criteria may be replaced according to Sponsor´s judgment.

10. ADMINISTRATIVE, ETHICAL AND REGULATORY STANDARDS

10.1. Study Committee

No study committees are planned for this study.

10.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directives 2001/20/EC and 2005/28/EC and the US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. This study will be conducted under ethical, scientific and medical standards that protect the rights of participants which include informed consent, independent review, and post-study medical care.

10.3. Institutional Review Board (IRB)

Each participating institution must provide the review and approval of this protocol, the associated informed consent documents and any recruitment material to an appropriate Institutional Review Board (IRB). The IRB decision concerning the conduct of the study will be made in writing and kept with the Investigator study file. A copy of this decision will also be provided to CCI

Particular attention is drawn to the FDA's requirements for IRBs. By signing the "Statement of Investigator" form (Form FDA 1572), the Investigator provides CCI with the necessary assurance that an IRB is responsible for the initial/continuing review and subsequent approval of the proposed clinical study in accordance with these regulations when applicable.

In compliance with the applicable country regulations, the Investigator is responsible for keeping the IRB informed of the progress with study renewal at least once a year, or more frequently, as required by the IRB. The Investigator must also report any SAE, life-threatening problems or deaths to the IRB as per institutional guidelines and inform the Sponsor according to GCP and applicable local regulations. The IRB must be informed by the Investigator of the termination of the study.

10.4. Compliance with the Protocol and Protocol Amendments

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact CCI or its agents, to request approval of a protocol deviation, as no such authorized deviations are permitted.

When a deviation occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant, CCI and the reviewing IRB must be notified as soon as possible after the emergency situation occurred (ICH E6 GCP 4.5.2 and 21 CFR part 312.66).

A planned deviation from the protocol that is non-emergent and represents a major change in the protocol as approved by the IRB must be considered an amendment and treated as such. Even if the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by CCI /the Sponsor and subsequently approved by the Health Authorities and IRB, it cannot be implemented. All significant

protocol deviations will be recorded and reported in the Clinical Study Report (CSR). Any modifications to the protocol which may impact the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. As previously stated, only amendments that are required to eliminate an immediate hazard to patients for patient safety can be implemented prior to the IRB approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

10.5. Monitoring, Auditing and Inspecting

To ensure compliance with current local regulations and the ICH guidelines, data generated by this study must be available for monitoring, audit or inspection upon request by representatives of the national and local health authorities, CCI /the Sponsor and duly authorized representatives of any entity providing support for this study. On site, they will notably review for AEs and study records and directly compare them with source documents, review regulatory documents, discuss the conduct of the study with the Investigator, verify study drug accountability and confirm that the facilities remain acceptable.

10.6. Recording, Processing and Retention of Data

The investigator is responsible for the preparation and maintenance of adequate case histories designed to record all observations and other relevant data. All patient data reported in the eCRF must be derived from source documents and as such be consistent with the source documents, or the discrepancies must be explained.

Data will be entered and collected via an electronic data capture system (EDC) using eCRFs. EDC is a validated system designed for entry of data in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). Study site staff will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or authorized designee. Only identified and trained users may view the data as their actions will become part of the audit trail.

While study sites will be responsible for data entry, CCI will be responsible for data management of this study, including quality checks.

The eCRF must be completed shortly after the patient's visit. All requested information must be entered on the eCRF. If an item is not available or is not applicable, it must be documented as such. The completed eCRF must be promptly reviewed and approved by the Investigator or authorized designee. In the event of discrepant data, CCI will request data clarification from the sites. The sites will resolve the discrepancy electronically in the EDC system. eCRF and data clarification documentation will be maintained in the EDC system's audit trail.

At the end of the study, the investigator will receive patient data, for their site, in a readable format on CD, DVD, or other similar storage format that must be kept with the study records. Acknowledgement of receipt of the storage disc or similar storage format is required.

The investigator will retain copies of study documentation for a period of at least 15 years from study completion. Additional considerations must be made about complying with applicable local laws, guidelines, etc.

10.7. Data Protection

Patient confidentiality is strictly held in trust by the participating Investigators, their staff, CCI the Sponsor or affiliates. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating patients.

Patient and investigator personal data which may be included in the study database shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data, CCI and the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party. The confidentiality of participating patients will be respected with strict adherence to professional standards and applicable privacy rules (i.e., Health Insurance Portability and Accountability Act [HIPPA] Privacy Rule).

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval by CCI or the Sponsor.

The CCI Medical Monitor or other authorized representatives (CCI /the Sponsor/Regulatory Authorities/Ethics Committees) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the patients in this study. The site will permit access to such records.

10.8. Withdrawal of Informed Consent for Submitted PK Samples

If a patient withdraws his/her consent, the Investigator has the responsibility to notify CCI immediately. CCI will ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed/repatriated and the actions are documented and returned to the study site.

10.9. Insurance of Liabilities

If required, the Investigator may forward to the IRB a copy of the insurance document required by CCI in order to cover his/her liabilities, and those of any other participating parties.

10.10. Use of Information and Publication

All information concerning the study drug or in connection with this study, supplied by CCI /the Sponsor and/or by any other party collaborating with CCI /the Sponsor within this study, and not previously published, is considered confidential and proprietary information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, workbooks (if applicable), case report forms, assay methods, technical methodology, and other technical and scientific data. This confidential information shall remain the sole property of the Sponsor and shall not be disclosed to others without prior written consent from CCI the Sponsor. Information shall not be used except in the performance of this study.

To allow for the use of the information derived from this clinical study and to insure compliance to current regulations, the Investigator is obliged to provide CCI /the Sponsor with complete test results and all data developed in this study. No publication, abstract or presentation of the study will be made without the approval of the Sponsor. CCI /the Sponsor will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. Prior to publication, the authorship list will be agreed upon by CCI /the Sponsor. For the purpose of the efficacy and safety analyses, the names on the author list will be given according to the participation in the concept of the study design as well as accrual input (number of eligible patients accrued) by the Investigators at each center. The maximum number of authors will be determined by the publication policy established by the targeted journal. Abstracts and publications will be submitted to the authors and to the Sponsor at least 30 days prior to the expected date of submission to the intended publisher.

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12. APPENDICES

APPENDIX 1: Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light and sedentary nature, e.g., light housework, 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 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