CLINICAL STUDY PROTOCOL

A Phase 1 Open-Label Study of ^{14}C-Labeled Talazoparib in Patients With Advanced Solid Tumors

[redacted]

Sponsor Code: MDV3800-03
[redacted] Code: MVE010PC-160106
EudraCT Number: 2016-001394-33
IND Number: 108708

Investigational Product	Talazoparib
Clinical Phase	1
Indication to be studied	Advanced solid tumors
SPONSOR	Medivation, Inc. and its Subsidiaries 525 Market Street, 36th Floor San Francisco, CA 94105 USA
CONTRACT RESEARCH ORGANIZATION	[redacted] Germany
CLINICAL SITE	PPD Hungary
PRINCIPAL INVESTIGATOR	Prof. PPD MD Fax PPD Phone PPD E-mail PPD
PROTOCOL AUTHOR	Dr. PPD Medical Writer, [redacted]

Version Final 3.0, 07-Oct-2016

This study will be performed in compliance with the principles of Good Clinical Practice.

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 **Clinical Pharmacology & DMPK**

Signature: ***Date:***

PPD

PPD

PPD **MD**

PPD **Drug Safety & Pharmacovigilance**

PPD

Date:

PPD

PPD **PhD**

PPD **Biostatistics**

Signature: **Date:**

PPD

PPD

PPD **MD**

PPD

PPD **Early Development**

PPD

Date:

PPD

PPD **Regulatory Affairs**

PPD

Date:

PPD

PROTOCOL SIGNATURE PAGE – Principal Investigator

I have read this protocol, and I agree that it contains all necessary details for me and my staff to conduct this study as described.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as an Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

PPD **MD**

Principal Investigator

PPD .....

PPD .....

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (See Appendix 8.2.3), the Principal Investigator will complete a "Serious Adverse Event Form" and forward, within 24 hours of awareness, to Medivation Medical Monitor and to Medivation's Safety vendor, [redacted] as noted below:

Name:	[redacted]
Fax:	[redacted]
	[redacted]
	[redacted] (Hungary)
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Phone:	[redacted]

Medivation Medical Monitor:

Name:	PPD MD
Telephone:	PPD
Mobile:	PPD (24-hr Contact Number)
Email:	PPD

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SYNOPSIS

Study Title

A PHASE 1 OPEN-LABEL STUDY OF ^{14}C-LABELED TALAZOPARIB IN PATIENTS WITH ADVANCED SOLID TUMORS

Short Study Title

^{14}C-Talazoparib Mass Balance Study

Study Codes

Sponsor Code:	MDV3800-03
[redacted] Code:	MVE010PC-160106
EudraCT Number:	2016-001394-33
IND Number:	108708

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Principal Investigator

Prof. PPD MD
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Objectives

Primary:

- To determine the time course of excretion of ^{14}C-radioactivity in urine and feces following a single 1 mg oral dose of talazoparib containing 100 µCi ^{14}C-talazoparib.
- To determine the recovery of ^{14}C radioactivity as a percentage of the administered dose.
- To determine the plasma pharmacokinetics (PK) of talazoparib and/or potential metabolites.
- To determine the PK of total radioactivity of ^{14}C-talazoparib, ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, $T_{1/2}$, CL/F, and V_d/F) in plasma and whole blood.

Secondary:

- To assess the safety and tolerability of a single dose of 1 mg talazoparib containing 100 µCi ^{14}C-talazoparib.
- To determine the percentage of ^{14}C radioactivity of talazoparib associated with erythrocytes and whole blood over time.
- To determine the amount of talazoparib in urine and feces.
- To estimate the amount and probable structure of any significant metabolites of talazoparib in plasma, urine and feces.

Design and Treatments

This is a Phase 1, single-center, open-label study evaluating the mass balance of talazoparib after a single dose of 1 mg talazoparib 100 µCi (3.7 MBq) ^{14}C-talazoparib; subjects may elect to continue treatment on an extension protocol.

The study is planned to enroll at total of up to approximately 6 patients in order to obtain the data in at least 4 evaluable patients at a single Phase 1 unit. Patients will receive a single dose of 1 mg talazoparib oral solution containing approximately 100 µCi ^{14}C-talazoparib on Day 1 after an overnight fast of at least 8 hours. No food will be allowed for at least 2 hours post-dose.

Within this food-restricted period the consumption of water is allowed.

The patients will remain at the clinic for approximately 21 days. If scintillation count data are available, patients, on an individual basis, may be discharged prior to Day 22, if any of the following conditions are met:

- ≥ 90% of the administered radioactivity is recovered in the urine and feces (accounting for radioactivity in vomitus, if applicable)
- The daily total excreted radioactivity is 1% or less of the administered dose on 2 consecutive days. Shipments for daily Quick Count will start on Day 10

If a patient meets either of these conditions prior to the morning of Day 22, collection of blood, urine, and feces may be stopped following completion of all scheduled 24-hour collections for that day. At the conclusion of the blood, urine, and feces collection, the patients will be discharged following completion of any safety procedures scheduled at termination.

If an individual patient does not demonstrate a cumulative amount of radioactivity recovered in urine and feces ≥ 90% or has not met the daily total excretion criteria of 1% or less of the administered dose on 2 consecutive days, following consultation with the Sponsor, the Investigator may ask patient to return to the clinic on Day 28 for a 24 h collection of urine and feces. If, by Day 29, the patient has still not met release criteria, a discussion between the Sponsor and the Investigator will be conducted for possibility to collect additional 24 h collection of urine and feces on Day 35.

Patients participating in this study with no clinically significant toxicities may be eligible to continue treatment on a separate extension protocol after discussion with the Principal Investigator and obtaining Sponsor permission. Decision to allow the patient to continue dosing with unlabeled (non-radioactive)

talazoparib in an open label study will be based on potential overall benefit-risk to patients, and patient eligibility for enrollment in the open-label extension study.
Safety data for all patients who had received any amount of talazoparib will be analyzed in the safety analyses.

Study Assessments

Safety and tolerability of talazoparib will be monitored through evaluation of adverse events, clinical laboratory tests, vital signs, electrocardiogram (ECG) recordings and physical examinations.
Serial PK blood, urine, and feces samples for talazoparib (plasma) and total radioactivity (whole blood, plasma, urine, feces, and vomitus, if applicable) analysis will be collected at predetermined times after the single oral dose administration, up to 504 hours (21 days), during which time the patients will be confined to the clinical research facility. Blood samples for plasma total radioactivity and for PK analysis of talazoparib and/or potential metabolite profiles and concentrations will be collected at pre-dose and 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264, 336, 384, 432 and 504 hours post-dose. Whole blood samples for total radioactivity will be collected at pre-dose and 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264, 336, 384, 432 and 504 hours post-dose. Urine and feces samples will be collected for the analysis of total radioactivity and for analysis for talazoparib and/or metabolites. Urine samples will be collected at pre-dose and during 0–8 hour and 8–24 hour post-dose intervals on Day 1 and then continue in 24-hour intervals through Day 22. Feces samples will be collected pre-dose and post-dose at 24-hour intervals through the morning of Day 22. Additional blood samples for PK analysis may be taken at the prolongation observation period and additional (unscheduled) and follow-up visit(s). During these visits, all urine and feces for total radioactivity analysis will be collected.

Key Eligibility Criteria

This study will enroll patients with certain advanced solid tumors (i.e. platinum-resistant ovarian carcinoma, cervical adenocarcinoma, small cell lung carcinoma and triple-negative breast cancer) who are at least 18 years of age and provide informed consent. Patients must abstain from the use of any prescription or nonprescription drugs or supplements with potential P-glycoprotein (P-gp) interaction within 7 days or 5 half-lives (whichever is longer) before Day 1. Patients must not have eGFR (estimated glomerular filtration rate) ≤ 50 mL/min/1.73 m^2 by MDRD (Modification of Diet in Renal Disease) equation at screening and baseline, human immunodeficiency virus (HIV), hepatitis B, or hepatitis C. Patients who had major surgery within 8 weeks, or received any investigational drug within 4 weeks before screening are excluded. Female and male patients of childbearing potential must agree to use a highly effective birth control method starting on 21 days before the administration of talazoparib through 45 and 105 days after last dose of study drug, respectively.

Duration of Study

Approximately 3-4 weeks for each patient.

Sample Size Considerations

The study is planned to enroll a total of up to 6 patients in order to obtain the data in at least 4 evaluable subjects. This sample size is consistent with typical study designs for phase 1 mass balance studies for PK evaluation. Patients who discontinue before 85% of total drug is recovered from urine and feces may be replaced upon agreement of the Investigator and the Sponsor.

Test Product, Dose, and Mode of Administration

Talazoparib, chemical name (8S,9R) CCI [redacted]

Patients will receive a single dose of 1 mg talazoparib oral solution containing approximately 100 μCi of ^{14}C-talazoparib as a single dose.

Reference Therapy, Dose, and Mode of Administration

Not applicable. All patients will receive talazoparib.

Statistical Methods

Pharmacokinetic Analyses

Radioactivity in urine and feces will be measured and reported as the percentage of the administered radioactivity excreted at each time interval and the total percent of dose excreted in urine and feces. talazoparib and/or potential metabolites will be also quantified in urine and feces and reported. Renal clearance will be calculated.

Non-compartmental pharmacokinetic parameters will be calculated from the plasma and whole blood radioactivity concentration versus time data. Unchanged talazoparib and/or potential metabolites in plasma will be measured and reported. Non-compartmental pharmacokinetic parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, $T_{1/2}$, CL/F, and V_d/F) will be calculated from the plasma and whole blood concentration time data.

Efficacy Analyses

No efficacy analyses are planned in this study, although baseline tumor assessments will be obtained in the event that patients choose to continue talazoparib treatment on a separate extension protocol.

Safety Analyses

All safety analyses will be performed using the safety population, defined as all patients who received any amount of talazoparib. Safety will be evaluated using summaries of adverse events (AEs), physical examinations (and weight), vital signs, ECG recordings, and laboratory evaluations.

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

Treatment-emergent safety data will be collected from Day 1 (the first and only dose of study drug) through 14 days after the last day of mass balance phase and at least 30 days after Day 1 or before initiation of new cytotoxic chemotherapy, new investigational treatment, or the first day of extension protocol, whichever occurs first.

Laboratory values will be classified by severity using the CTCAE Version 4. Change from baseline in laboratory values will be tabulated and summarized graphically.

Table 1 Schedule of Assessments

Study Day►	-21 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	FUP[1]
Event▼																									
Informed consent, screening number [2]	X																								
ECOG assessment	X	X																							
Medical history	X																								
Demographics	X																								
Eligibility criteria	X	X																							
Check-in questions		X																							
Physical examination	X	X[3]								X[3]							X[3]							X	
Height	X																								
Weight	X	X																						X	
Temperature	X	X																						X	
Respiratory rate	X	X		X[4]																				X	
12-Lead ECG (triplicates)	X	X	X[5]																					X	
Supine heart rate, blood pressure	X	X	X[5]	X[4]						X							X							X	
Adverse event review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer talazoparib			X																						
Alcohol breath test	X	X																							
Urine drug screen	X	X																							
Serology for HIV, hepatitis B and C	X																								
Serum pregnancy test[6]	X	X																						X	
Follicle-stimulating hormone [7]	X																								
Serum chemistry	X	X		X[4]																				X	
Hematology	X	X		X[4]																				X	
Coagulation	X																								
Urinalysis	X	X		X[4]																				X	

Table 1 Schedule of Assessments

Study Day►	**-21 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**FUP[1]**
Event▼																									
eGFR calculation [8]	X	X																							
Urine collection		X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Feces collection		X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for PK			X[11]	X	X	X	X	X		X		X		X			X		X		X			X	
Collection of vomitus (if applicable)			X																						
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

1 Follow-up within 14 days after the last day of mass balance phase and at least 30 days after Day 1 or the first day of extension protocol, whichever occurs first; this follow-up can be an onsite visit or a phone call

2 Informed consent can be signed before the screening window.

3 Targeted, symptom oriented physical examination

4 To be performed on Day 2, 24 h after talazoparib dose on Day 1

5 On Day 1 at pre-dose and 2 hour post-dose.

6 Collect only for females

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

8 Calculation of the estimated glomerular filtration rate (eGFR) by MDRD equation

9 Only one blank urine sample will be collected within 12 hours prior to study drug administration (Day-1 or Day 1 pre-dose)

10 Only one blank fecal sample will be collected within 48 hours prior to study drug administration (Day -1 or Day 1 pre-dose)

11 On talazoparib dosing day, collect blood sample for PK as shown in Table 3

FUP: follow-up; ECOG: Eastern Co-Operative Oncology Group [Performance Status]; HIV: human immunodeficiency virus; PK: pharmacokinetic.

Table 2 Study Schedule of Activities for Patients Staying Beyond 21 Days

	Study Day		
For patients who do not meet release criteria by Day 22	**23 to 27**	**28 to 29**	**FUP[1]**
For patients who do not meet release criteria by Day 29	**30 to 34**	**35 to 36**	
Event▼			
Physical examination		X	
Weight		X	
12-lead electrocardiogram		X	
Supine heart rate, blood pressure		X	
Adverse event review	X	X	X
Concomitant medication review	X	X	X
Serum chemistry		X	
Hematology		X	
Urinalysis		X	
Fecal collection[2]		X	
Urine collection [2]		X	
Blood sample for PK		X	

1 Follow-up within 14 days after the last day of mass balance phase and at least 30 days after Day 1 or the first day of extension protocol, whichever occurs first. This follow-up can be an onsite visit or a phone call.

2 Patients will return to the unit on Day 28 until Day 29 for 24-hour urine and feces collection. In cases if the release criteria are still not met, the observation period may be prolonged to Day 35 and Day 36, respectively (see Section 3.1.3.3).

Table 3 Talazoparib Pharmacokinetic Sampling Schedule

Sample collection time relative to dosing		Blood†	Urine †	Feces †
Study Day	**Time point**			
1	pre-dose	X	X	X
	+0.50 h	X	X (0 - 8 h)	X (0 - 24 h)
	+1 h	X		
	+2 h	X		
	+4 h	X		
	+8 h	X		
	+12 h	X	X (8 - 24 h)	
2	+24 h	X		
3	+48 h	X	X (24 - 48 h)	X (24 - 48 h)
4	+72 h	X	X (48 - 72 h)	X (48 - 72 h)
5	+96 h	X	X (72 - 96 h)	X (72 - 96 h)
6	+120 h	X	X (96 - 120 h)	X (96 - 120 h)
7			X (120 - 144 h)	X (120 - 144 h)
8	+168 h	X	X (144 - 168 h)	X (144 - 168 h)
9			X (168 - 192 h)	X (168 - 192 h)
10	+216 h	X	X (192 - 216 h)	X (192 - 216 h)
11			X (216 - 240 h)	X (216 - 240 h)
12	+264 h	X	X (240 - 264 h)	X (240 - 264 h)
13			X (264 - 288 h)	X (264 - 288 h)
14			X (288 - 312 h)	X (288 - 312 h)
15	+336 h	X	X (312 - 336 h)	X (312 - 336 h)
16			X (336 - 360 h)	X (336 - 360 h)
17	+384 h	X	X (360 - 384 h)	X (360 - 384 h)
18			X (384 - 408 h)	X (384 - 408 h)
19	+432 h	X	X (408 - 432 h)	X (408 - 432 h)
20			X (432 - 456 h)	X (432 - 456 h)
21			X (456 - 480 h)	X (456 - 480 h)
22	+504 h	X	X (480 - 504 h)	X (480 - 504 h)
*28**	*+648 h*	*X*	*X (648 - 672 h)*	*X (648 - 672 h)*
*35**	*+816 h*	*X*	*X (816 - 840 h)*	*X (816 - 840 h)*

† Identification of metabolites of talazoparib will be pursued if applicable

* Only in case of prolonged in-house stay due to low radioactivity recovery (see Section 3.1.3.3)

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ADL	Activities of daily living
ADME	Absorption, distribution, metabolism and excretion
ADP	Adenosine diphosphate
AE	Adverse event
ALARA	As low [radioactive burden] as reasonably achievable
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-HBc+	anti-hepatitis B core antigen, positive test result
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BER	Base excision repair
BRCA	Breast cancer susceptibility gene
CL_{CR}	Creatinine clearance
CPK	Creatine phoshokinase
CPMP	Committee for Proprietary Medicinal Products; current name: Committee for Medicinal Products for Human Use (CHMP)
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Co-Operative Oncology Group [Performance Status]
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg+	Hepatitis B surface antigen, positive test result
HCV+	Hepatitis C virus, positive test result
HIV+	Human immunodeficiency virus, positive test result
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiological Protection
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LSC	Liquid scintillation counting
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MGMT	Methylguanine methyltransferase
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association

PARP	Poly(ADP ribose) polymerase
PDF	Portable document format
P-gp	P-glycopotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PT	Prothrombin time
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WMA	World Medical Association
β-hCG	β human chorionic gonadotropin

Note: Definitions of pharmacokinetic (PK) parameters are provided in Section 3.8.3

1. INTRODUCTION

1.1 Background

Talazoparib (also known as MDV3800, BMN 673) is a potent, orally bioavailable, small molecule poly(ADP-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers. PARP inhibitors, including talazoparib, exert cytotoxic effects via two mechanisms, catalytic inhibition of PARP1 and PARP2, and PARP trapping, a process in which PARP protein bound to an inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription.

Talazoparib is cytotoxic to human cancer cell lines harboring gene mutations that compromise DNA repair, an effect referred to as synthetic lethality. In breast cancer MX-1 cells that are breast cancer susceptibility gene (BRCA)1-deficient, talazoparib inhibits cell growth in vitro and inhibits tumor growth and/or induces tumor regression in mouse xenografts. Antitumor activity was also demonstrated in small cell lung cancer (SCLC) cell lines and xenograft models; single-agent talazoparib reduced tumor growth to a similar extent as cisplatin in two independent SCLC xenograft models.

Nonclinical studies demonstrated increased cytotoxic effects when talazoparib was combined with certain DNA damaging chemotherapies such as alkylating agents or topoisomerase I inhibitors. Non-cytotoxic concentrations of temozolomide greatly enhanced the cytotoxic effects of talazoparib in tissue culture studies using prostate, leukemia, and Ewing sarcoma cells. Enhancement of talazoparib cytotoxic effects results from temozolomide induced cytotoxic DNA adducts that can be removed by O6 methylguanine methyltransferase (MGMT) and also potentially lethal DNA adducts that are dependent on the base excision repair (BER) response. Temozolomide induces numerous sites for PARP-DNA complexes to form and become trapped by talazoparib. Similarly in an SCLC xenograft model in mice, combination treatment with talazoparib plus temozolomide resulted in a marked enhancement of antitumor effects compared with that observed with either agent alone. Tissue culture studies of talazoparib in combination with the active metabolite of irinotecan, SN38, also demonstrated enhanced pharmacologic effects of combination versus single agent treatment.

For further details on topics in this section refer to the current Investigator's Brochure (IB) [1].

1.1.1 Nonclinical Studies

The main nonclinical toxicology findings with talazoparib were early hematologic changes and subsequent bone marrow and lymphoid organ depletion, as well as focal atrophy and degeneration of testes after repeat-dose talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern. The hematologic findings were generally reversible and the early hematologic changes represent sensitive and early markers of target organ toxicity.

1.1.2 Clinical Studies

As of 30 Nov 2015, approximately 319 patients with hematologic malignancies and solid tumors and 18 healthy volunteers have received talazoparib at doses up to 2 mg/day. The majority of available efficacy and safety data was obtained from studies

in 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.

1.1.2.1 Pharmacokinetics

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

Oral absorption of talazoparib was rapid and independent of dose after administration of single or once-daily doses. Peak talazoparib concentrations were generally achieved approximately 1 to 8 hours post-dose. Elimination appeared to follow biphasic kinetics, with a mean half-life ($T_{1/2}$) that ranged from 52.9 to 229 hours. The mean $T_{1/2}$ of talazoparib showed some evidence of decreasing with increasing dose. At 1 mg/day, the mean $T_{1/2}$ was approximately 2 days. With daily administration, it took approximately 2 to 3 weeks to reach steady state.

The apparent volume of distribution (V/F) of talazoparib appeared to decrease with increasing dose. At 1 mg/day, the mean V/F was 415 L, or approximately 10-fold greater than total body water (42 L), which is indicative of extensive extravascular distribution[2]. In vitro protein binding data showed that talazoparib is 78.7% bound to human plasma proteins.

No clinical studies have investigated penetration of talazoparib into the brain or cerebrospinal fluid. Talazoparib showed negligible penetration across the blood-brain barrier in rats.

Apparent total body clearance (CL/F) of talazoparib appeared to be dose linear. The mean CL/F across doses was approximately 5 L/hr. Clinical data showed that renal excretion is a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44 to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady-state for doses up to 1 mg/day. Mean renal clearance ranged from 1.38 to 4.96 L/h, independent of dose, suggesting linear urinary elimination kinetics. The extent of metabolism was also minimal in nonclinical studies. Following oral administration of ^{14}C-talazoparib to rats and dogs, talazoparib was cleared primarily via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation. In vitro metabolism studies in human hepatic microsomes demonstrated that ^{14}C-talazoparib has high metabolic stability (> 90%) over 2 hours. A minimal extent or a lack of metabolism for ^{14}C-talazoparib was observed in the presence of freshly isolated human hepatocytes or cryopreserved human hepatocytes.

Following administration at 1 mg/day, talazoparib accumulated approximately 2.4-fold relative to a single dose. At steady state, the mean maximum observed plasma concentration (C_{max}) was 21.0 ng/mL, the mean plasma trough concentration (C_{min}) was

3.72 ng/mL, the mean area under the concentration-time curve (AUC) was 202 ng•h/mL, and the mean peak-to-trough ratio was approximately 6.

Food Effect

A food-effect study (673-103) involving administration of a single 0.5 mg dose of talazoparib to 18 healthy male subjects both under fasting conditions and with a high-fat, high-calorie meal showed that food had no effect on the extent of absorption (AUC). Food decreased the rate of absorption (C_{max} was 46% lower and T_{max} was 2.63 hours later); however this reduction in the rate of absorption following a single dose is not clinically relevant because talazoparib accumulates 2.4-fold at steady state after 1 mg once-daily dosing. Furthermore, it is thought that AUC or C_{min} drives efficacy, not C_{max}; therefore, talazoparib can be taken with or without food. Talazoparib is being administered without regard to meals in ongoing safety and efficacy trials.

Pharmacokinetics in Special Populations

A preliminary population PK analysis was performed with data from patients in studies PRP-001 and PRP-002 to assess the effects of renal function on PK parameters of talazoparib. Talazoparib apparent systemic clearance (CL/F) in patients with mild renal impairment (creatinine clearance [CL_{CR}], 60-89 mL/min) was similar compared with patients with normal renal function (CL_{CR} ≥ 90 mL/min). In patients with moderate renal impairment (CL_{CR}, 30-59 mL/min), the talazoparib CL/F was decreased by 44%, resulting in higher talazoparib exposure. Therefore, patients with moderate or severe renal impairment (CL_{CR} < 60 mL/min) may be at risk of elevated exposure ≥50%) to talazoparib.

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

Drug-Drug Interaction

Talazoparib is unlikely to demonstrate clinically significant cytochrome P450 (CYP450) inhibition- or induction-based drug-drug interactions or drug transporter inhibition-based drug-drug interactions when co-administered with corresponding substrates. However, talazoparib is a substrate for P-glycoprotein (P-gp) and the 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.

Efficacy

Preliminary data demonstrated objective responses and/or likely clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer with deleterious germline mutations; SCLC; and Ewing's sarcoma. A Phase 2 study and a Phase 3 study in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations are both ongoing. Efficacy data are not yet available.

The efficacy signals of talazoparib observed in the treatment of cancers with and without BRCA mutations warrant the continued development of talazoparib as a single agent at doses of 1 mg/day and support the hypothesis for enhanced cytotoxicity of talazoparib by the addition of DNA damaging agents.

Safety

The most common adverse events (AEs) associated with talazoparib collected in 214 patients participating three clinical studies (PRP-001, PRP-002, and 673-201) were myelosuppression (anemia, neutropenia, thrombocytopenia), gastrointestinal toxicity (nausea, vomiting, diarrhea), and fatigue. The most common National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 AEs and serious adverse events (SAE) were associated with myelosuppression.

A total of 25 of 214 patients had SAEs that led to death (12 associated with malignancies, 3 disease progression, 2 each lung infection and pneumonia, and 1 each cardiorespiratory arrest, neutropenic sepsis, renal impairment, dyspnea, hypoxia, and respiratory failure). Of these, none was assessed as related to the study drug.

Adverse events leading to dose interruptions occurred in approximately 45%, 49%, and 57% of patients in company-sponsored studies PRP-002 and PRP-001, and investigator-sponsored study NCT02049593 (combination treatment), respectively. Adverse events leading to dose reductions occurred in approximately 6% of patients in PRP-002, more than 17% of patients in PRP-001, and more than 20% of patients in NCT02049593. Most dose modifications were due to myelosuppression.

Potential risks associated with talazoparib include hepatotoxicity, neutropenic sepsis, and febrile neutropenia.

1.2 Study Rationale

The aim of this trial is to evaluate the metabolism and mass balance (i.e., recovery) of talazoparib, to identify the major route(s) of talazoparib elimination, to identify talazoparib metabolites in plasma, urine and feces and to determine the plasma concentration-time profiles of talazoparib and its metabolites in humans.

The need for mass balance trials in anticancer drug development has recently been emphasized by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the ICH S9 and EU guidelines on the evaluation of anticancer medicinal products [2,4].

1.2.1 Radioactively labeled dose (Mass Balance) of Talazoparib

Administration of an oral solution containing 100 µCi ^{14}C-talazoparib is considered to be appropriate to reach the objectives of this study.

The oral administration 100 µCi (3.7 MBq) ^{14}C-talazoparib yields an estimated effective radiation burden of 0.3 mSv and which is within the accepted limits of up to 1 mSv according to the International Commission on Radiological Protection (ICRP), 2007, Guidelines for Category 2a studies[5,6].

The Hungarian National Institute for Quality- and Organizational Development in Healthcare and Medicines (GYEMSZI) accepts an exposure of humans to ionizing radiation using unsealed radioactive products in human trials up to an effective dose of 1 mSv (in adults), in accordance with national Hungarian standard MSZ 62-7 (2011)[7], local regulations 16/2000 EüM and 23/1997 NM and EU guidance[8].

1.2.2 Unlabeled dose of talazoparib

As of 30 Nov 2015, approximately 250 patients have received 1 mg of talazoparib once daily in multiple dose studies. Based on this experience, 1 mg QD was found to be sufficiently well-tolerated in the oncology population and is considered the recommended single-agent dose. As this study includes only a single dose, without the accumulation that occurs after multiple doses, the proposed 1 mg dose is expected to be generally well-tolerated. See the Investigator's Brochure for additional details.

1.2.3 Study Population Rationale

Talazoparib has shown clinical activity in advanced solid tumor patient populations and is being developed further as a treatment for several cancers; a mass balance study in cancer patients is thus justified. In the present study, the patient population will be limited to neoplastic diseases which were already included in previous clinical trials with talazoparib, i.e. patients with platinum-resistant ovarian carcinoma, cervical adenocarcinoma, small cell lung carcinoma and triple-negative breast cancer. After first administration of the ^{14}C-labeled investigational medicinal product (IMP) and the completion of all assessments related to absorption, distribution, metabolism and excretion (ADME) and mass balance, select study subjects may have the option to continue treatment with daily unlabeled (non-radioactive) talazoparib in an open label extension study after evaluation by the Principal Investigator (PI) and approval of Sponsor; a separate extension protocol will be prepared for this purpose.

2. OBJECTIVES

2.1 Primary

- To determine the time course of excretion of ^{14}C radioactivity in urine and feces following a single 1 mg oral dose of talazoparib containing 100 µCi ^{14}C-talazoparib.
- To determine the recovery of ^{14}C radioactivity as a percentage of the administered dose.
- To determine the plasma PK of talazoparib and/or potential metabolites.
- To determine PK of total radioactivity of ^{14}C-talazoparib ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, $T_{1/2}$, CL/F, and V_d/F) in plasma and whole blood .

2.2 Secondary

- To assess the safety and tolerability of a single dose of 1 mg talazoparib containing 100 µCi ^{14}C-talazoparib.
- To determine the percentage of ^{14}C radioactivity of talazoparib associated with erythrocytes and whole blood over time.
- To determine the amount of talazoparib in urine and feces.
- To estimate the amount and probable structure of any significant metabolites of talazoparib in plasma, urine and feces.

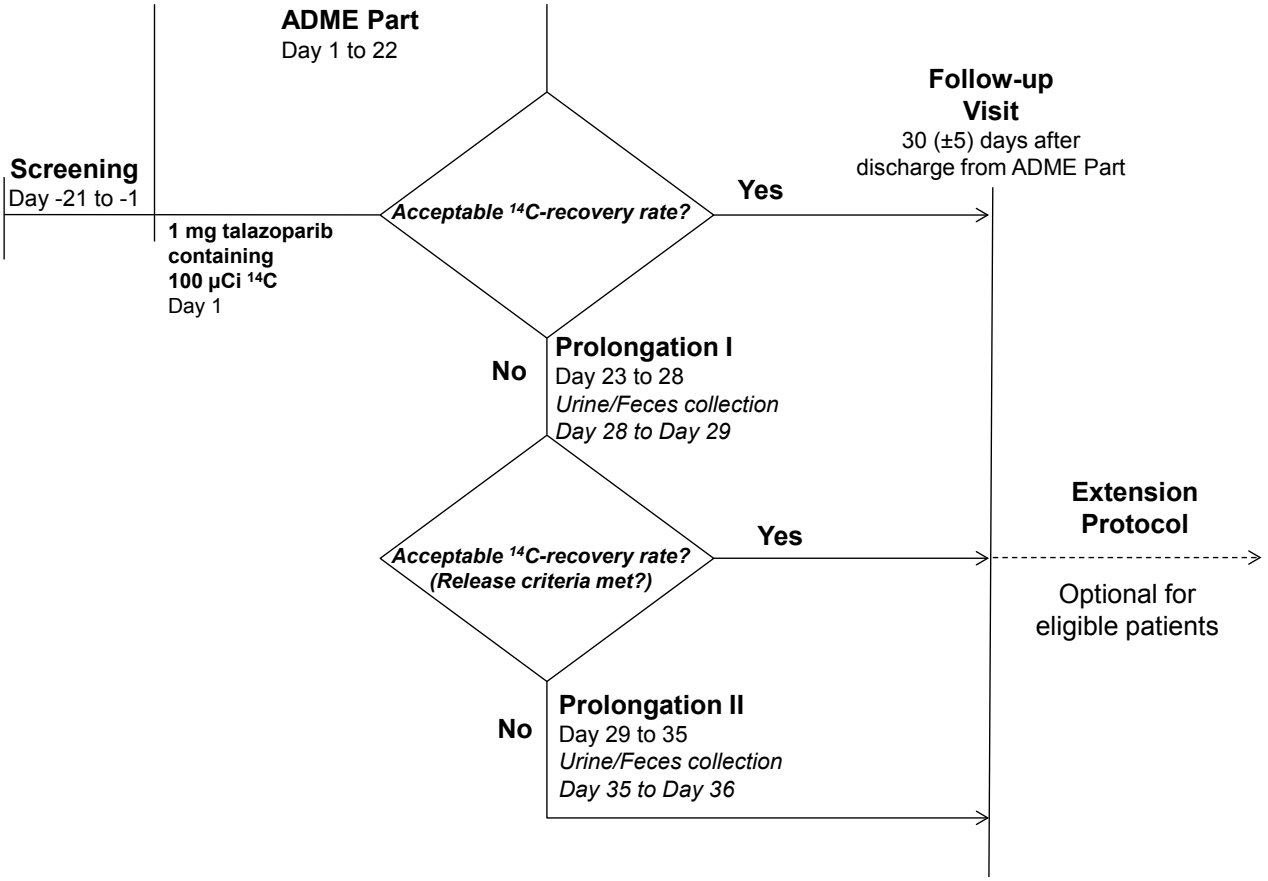
3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Type of Study

This is a Phase 1, single-center, open-label, mass balance study with ^{14}C-radiolabeled talazoparib in at least 6 patients with advanced solid tumors who qualify for treatment with talazoparib. Each eligible patient will receive an oral solution of 1 mg of talazoparib containing100 µCi of ^{14}C-radiolabeled talazoparib. Patients who complete the mass-balance part in this clinical study will have the option to continue treatment on an open-label extension protocol (Figure 1).

Figure 1 Study Design



3.1.2 Screening Period

Patients will sign the study-specific informed consent form (ICF) prior to any study-specific screening procedures being performed within 21 days before dosing of talazoparib on Day 1. The written informed consent will be obtained for all patients, regardless of their eligibility for the study.

Eligibility screening will consist of the assessments as presented in the schedule of assessments (Table 1). Patients may be enrolled if they are eligible according to the inclusion and exclusion criteria (Section 3.4). Details on the conduct of study-related assessments are given in Section 3.8.

3.1.3 Treatment Period

3.1.3.1 Baseline

Eligible patients will enter the clinical unit on Day –1 (one day before administration of talazoparib). Assessments will be performed as shown in the schedule of assessments (Table 1) and as detailed in Section 3.8.

Once all baseline activities of Day –1 have been concluded and pending eligibility criteria have been confirmed patients will be eligible for enrollment and administration of talazoparib on Day 1.

3.1.3.2 Mass-Balance Part

Patients will receive 1 mg of talazoparib as an oral solution that contains 100 µCi (3.7 MBq) of ^{14}C-labeled talazoparib in the morning of Day 1. PK of radiolabeled compound will be performed together with potential metabolite profiling in blood, urine, feces as shown in Table 3.

Assessments of safety and tolerability will be conducted according to the schedule of assessments (Table 1).

Patients will be confined from Day –1 on and will be discharged from the study unit on Day 22 (504 h post-dose) after all study-related procedures have been concluded, assuming that the recovery of the radioactive material satisfies the conditions listed below (Section 3.1.3.3).

3.1.3.3 Early Discharge and Prolongation

Patients will be discharged on Day 22, if any of the following conditions are met:

- ≥ 90% of the administered radioactivity is recovered in the urine and feces (accounting for radioactivity in vomitus, if applicable)
- The daily total excreted radioactivity is 1% or less of the administered dose on 2 consecutive days. Shipments for daily Quick Count will start on Day 10.

Patients may be discharged on an individual basis prior to Day 22, if scintillation counts data are available and the above listed conditions are met. If the patient meet this early criteria prior to the morning of Day 22, collection of blood, urine, and feces may be stopped following completion of all scheduled 24-hour collections for that day. At the conclusion of the blood, urine, and feces collection, and completion of the same safety procedures as scheduled for Day 22 (in lieu of Day 22) the patients will be discharged.

If an individual patient does not demonstrate a cumulative amount of radioactivity recovered in urine and feces ≥ 90% or has not met the daily total excretion criteria of 1% or less of the administered dose on 2 consecutive days, following consultation with the Sponsor, the Investigator may ask patient to return to the clinic on Day 28 for a 24 h collection of urine and feces (Table 2). If, by Day 29, the patient has still not met release criteria, a discussion between the Sponsor and the Investigator will be conducted for possibility to collect additional 24 h collection of urine and feces from Day 35 to Day 36 (Table 2).

3.1.3.4 Follow-up

Follow-up will be performed within 14 days after the last day of the mass balance phase and at least 30 days after Day 1, or the first day of extension protocol, whichever occurs first. This follow-up can be an onsite visit or a phone call (Table 1 and/or Table 2).

3.2 Extension Protocol

Patients participating in this study with no clinically significant toxicities may be eligible to continue talazoparib treatment on a separate open-label extension protocol outside of this study.

Decision to allow the patient to continue dosing with talazoparib in an open-label study will be based on potential clinical benefit and patient eligibility for enrollment to the open-label extension study.

3.3 Discussion of Study Design

This is a clinical study to investigate the metabolism, excretion pattern, and mass balance of talazoparib following the administration of ^{14}C-talazoparib. The terminal half-life of talazoparib at 1 mg is approximately 2 days. Urine and feces collection for up to 21 days should ensure that >90% of the dose is excreted. Talazoparib is being developed for the treatment of a variety of solid tumors either as a single agent or in combination with established therapies. No blinding, comparator treatment or randomization was considered necessary for this study. No formal sample size calculation has been carried out. The administration of the ^{14}C-IMP is based on the ALARA principle (as low radioactive burden as reasonably achievable) set forth in the 96/29/EURATOM directive.

For dose justification and risk-benefit assessment, please see Section 1.2.

3.4 Selection of Study Population

The study is planned to enroll a total of 6 patients with advanced solid cancer in order to obtain data in at least 4 evaluable subjects.

3.4.1 Inclusion Criteria

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

1. At least 18 years of age and willing and able to provide informed consent.
2. Histologically confirmed advanced solid tumor (limited to platinum-resistant ovarian carcinoma, cervical adenocarcinoma, small cell lung carcinoma or triple-negative breast cancer) judged by the Investigator to not be appropriate for standard therapy.
3. Eastern Co-Operative Oncology Group (ECOG) performance status ≤ 2 at screening and Day –1.
4. Expected life expectancy of ≥ 3 months.
5. Able to swallow the study drug and comply with study requirements.
6. Female subjects may be enrolled if they are

a. considered not of childbearing potential including those who are surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy ≥6 months before enrollment, with documentation of the procedure) or who are post-menopausal, defined as:

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

or

b. of childbearing potential using a highly effective form of contraception from screening or at least 21 days prior to study drug administration (whichever is earlier) until 45 days after last intake of study medication and having a negative serum pregnancy test at Screening and Day -1 defined as at least one of the following:

- Established use of an oral, intravaginal, or transdermal combined (estrogen an 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
- Sexual partner(s) vasectomized for ≥ 6 months before enrollment
- Sexual abstinence when in relation to the preferred and usual lifestyle of the subject

and

c. do not donate eggs from the time point of IMP administration until at least 45 days thereafter.

7. Males with partners of childbearing potential may be enrolled if they

   a. use a condom when having sex with a pregnant woman or with a woman of childbearing potential from 21 days before the first dose of study drug through 105 days after last dose of study drug. Contraception should be considered for a nonpregnant female partner of childbearing potential.

   and

   b. do not donate sperm from the time point of study drug administration until at least 105 days thereafter.

8. Female patients must not be breastfeeding at screening and during the study participation until 45 days after the last dose of the study drug.
9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

3.4.2 Exclusion Criteria

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

1. Treatment within 14 days or five half-lives prior to dosing with any type of systemic anticancer therapy or any investigational agent, whichever is longer.
2. Major surgery within 8 weeks before screening.
3. Serious accompanying disorder or impaired organ function, including the following:

   a. Cardiac:

   - Myocardial infarction or symptomatic cardiac ischemia within 6 months before enrollment.
   - Heart failure of severity grade class III or IV according to New York Heart Association (NYHA) within 3 months before enrollment.
   - Clinically significant cardiac arrhythmias if not adequately treated or controlled (e.g. by medication, or pacemaker).
   - History of Mobitz II second degree or third degree heart block unless a permanent pacemaker is in place.
   - Hypotension as indicated by systolic blood pressure < 86 mm Hg at screening or Day –1.
   - Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram (ECG) at screening.
   - 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 if initial reading is believed to be atypical for the patient.
   - Screening QTcF ≥ 450 ms in males or ≥ 480 ms in females.

   b. Renal: eGFR (estimated glomerular filtration rate) ≤ 50 mL/min/1.73 m^2 by MDRD (Modification of Diet in Renal Disease) equation [available via www.mdrd.com]) at screening and Day –1
   c. History or nephrectomy or renal transplant
   d. Clinically significant renal disease within three months of enrollment.
   e. Total serum bilirubin > 1.5 times upper limit of normal (ULN); (> 3 times ULN for patients with Gilbert's syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation)
   f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.5 times ULN
   g. Bone marrow reserve: neutrophils < 1500/µL, platelets < 100,000/µL, or hemoglobin < 9 g/dL (blood samples collected after ≥ 14 days without growth factor support or transfusion).
   h. Albumin < 3.0 g/dL.

4. Symptomatic or impending spinal cord compression or cauda equina syndrome.
5. Non-healing wound, ulcer, or bone fracture, not including a pathological bone fracture caused by a pre-existent pathological bone lesion.
6. Known myelodysplastic syndrome.
7. Patients with the following serologies should be excluded: HBsAg+ or anti-HBc+;

HCV+; HIV+.

8. Serious or unstable medical condition that interferes with ability to tolerate treatment or assessments associated with the protocol.
9. Gastrointestinal disorder affecting absorption.
10. Known hypersensitivity to any of the talazoparib solution components.
11. Use of a strong P-gp inhibitor (e.g., dronedarone, quinidine, ranolazine, verapamil, itraconazole, ketoconazole), strong P-gp inducer (e.g. rifampin, tipranavir, ritonavir), or strong inhibitor of BCRP (e.g., elacridar [GF120918]) within 7 days or 5 half-lives, whichever is longer, before Day 1. Patients must also abstain from the use of any other prescription or nonprescription drugs or supplements with potential P-glycoprotein (P-gp) and BCRP interaction within 7 days or 5 half-lives (whichever is longer) before Day 1.
12. Any condition or reason that interferes with ability to participate in the study, causes undue risk, or complicates the interpretation of safety data, in the opinion of the Investigator or Sponsor (e.g. non-compliance, excessive alcohol consumption, intake of drugs of abuse unless these drugs are medically indicated [e.g. opiates for pain relief]).

3.5 Removal of Subjects from Therapy or Assessment

Participation in the study is strictly voluntary. A patient has the right to withdraw from the study at any time for any reason.

The Investigator has the right to terminate participation of a patient for any of the following reasons:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Intolerable toxicity as evidenced by the occurrence of severe AEs, or SAEs
- Non-compliance that is likely to affect the validity of the data obtained from the subject.

If a subject withdraws or is removed from further study participation end-of-treatment and follow-up visits will be conducted as described in Section 3.1.3.4.

The main objectives of this study can be pursued after the dosing with the ^{14}C-radiolabeled drug on Day 1. Provided that the collection of the PK and mass-balance samples is completed, the subject will not be withdrawn from the main analysis.

If a patient is withdrawn from the study, the Sponsor will be informed immediately. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator until satisfactory health has returned.

Patients who discontinue before 85% of total drug is recovered from urine and feces may be replaced upon agreement of the Investigator and the Sponsor.

The decision regarding the replacement of subjects will be documented.
The Investigator will make every effort to ensure that non-completers and dropouts who have received study drug complete the safety follow-up assessments.

3.6 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the IMP, e.g., due to:
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings.
- Sponsor's decision.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor's IMP.

Health authorities and IECs (Independent Ethics Committees) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of health authorities.

3.7 Treatments

3.7.1 Treatments Administered

Patients will only receive a single 1 mg dose of talazoparib containing 100 µCi ^{14}C-labeled talazoparib on Day 1. No other doses of talazoparib will be administered throughout the remainder of this study.

3.7.2 Identity of Investigational Product

Active substance: Talazoparib, chemical name (8S,9R) [redacted]

Indication: Advanced solid tumors

Dose: 1 mg talazoparib and 100 µCi ^{14}C-talazoparib, once

Note: Preparation of the ^{14}C-radiolabeled and unlabeled IMP will be carried out according to the guide on Good Manufacturing Practice (GMP) for the manufacturing of active pharmaceutical ingredients.

For details concerning drug storage and drug accountability see Appendix 8.1.

3.7.3 Treatment Assignment

After obtaining informed consent, patients will be screened according to the inclusion and exclusion criteria. Enrolled patients will receive a unique patient number (01 to 06) prior to dosing. The patient number will ensure identification throughout the study. Replacement patients will receive the number of the patient to be replaced, increased by 10 (e.g. 11 replacement number for patient number 01), and will be administered the same treatment.

Patients who drop out or withdraw for any reason without completing all screening evaluations successfully, will be considered as “screening failures“. The Investigator or authorized designee will keep a screening log of all patients screened in order to assess the numbers and characteristics of the excluded patients, and the reasons for their exclusion.

3.7.4 Selection and Timing of Doses in the Study

The dose of 1 mg talazoparib is the MTD for daily administration and considered to be the recommended single-agent dose.

Details on preparation and administration of study drug will be provided in the pharmacy manual.

A solution for oral administration containing 1 mg talazoparib together with 100 µCi of ^{14}C-labeled talazoparib will be administered in the morning of Day 1 (Table 1).

3.7.5 Meals During the Study

Subjects will be required to be fasting overnight from at least 8 hours before until at least 2 hours after the administration of talazoparib. Within this food-restricted period the consumption of water is allowed.

All safety laboratory assessments (clinical chemistry, hematology and coagulation) should be performed in a fasted condition of the patients (i.e. overnight, before breakfast).

3.7.6 Blinding

Not applicable. This is an uncontrolled, open-label clinical study.

3.7.7 Concomitant Medication and Other Restrictions During the Study

Patients must abstain from the use of inhibitors or inducers of P-gp or BCRP within 7 days or 5 half-lives (whichever is longer) before Day 1 (see FDA: Table of Substrates, Inhibitors and Inducers).

Note: Restrictions that apply to the period before admission are described in the eligibility criteria in Section 3.4.

3.7.8 Treatment Compliance

Talazoparib will be administered orally by the Investigator or his/her designee. Compliance will be confirmed by bioanalytical assessment of the IMP in blood, urine, and feces samples.

The exact times of study drug administration and the number of units administered will be recorded in the eCRF.

3.8 Pharmacokinetic, Efficacy and Safety Measurements and Variables

3.8.1 Pharmacokinetic, Efficacy and Safety Measurements Assessed

3.8.1.1 Pharmacokinetic Measurements

3.8.1.1.1 Blood Sampling

For PK of talazoparib, for potential metabolite profiling of talazoparib and assessment of total ^{14}C-radioactivity blood samples will be taken as outlined in the PK sampling schedule (Table 3). The exact times of each blood collection will be recorded in the eCRF.

The details of sample acquisition, processing, storage and shipment will be issued in a laboratory manual.

3.8.1.1.2 Urine Collection

During the intervals defined in PK sampling schedule (Table 3), urine will be collected for the analysis of talazoparib, and potential metabolites or degradation products for the analysis of total radioactivity and for quick counts of total radioactivity. The subjects will be instructed to empty their bladders completely before study drug administration and at the end of each collection interval. A blank urine sample will be collected within 12 hours prior to study drug administration. The exact times of urine collection and the total urine volume of each entire interval will be recorded in the eCRF.

The details of sample acquisition, processing, storage and shipment will be issued in a laboratory manual.

3.8.1.1.3 Feces and Vomitus Collection

During the intervals defined in PK sampling schedule (Table 3), all fecal excretions (and vomitus, if applicable) will be collected for the analysis of talazoparib, and potential metabolites products for the analysis of total radioactivity, for quick counts of total radioactivity and/or for metabolite profiling. A blank fecal sample will be collected within 48 hours prior to study drug administration. The exact times of feces collection and the fecal weight of each entire interval will be recorded in the eCRF. This applies also to vomitus, if applicable.

The details of sample acquisition, processing, storage and shipment will be issued in a laboratory manual.

3.8.1.2 Efficacy Measurements

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 on a separate extension protocol.

3.8.1.3 Safety Measurements

Safety and tolerability assessments will consist of AEs, clinical laboratory, vital signs, 12-lead ECG, and physical examination. Assessments will be performed in accordance with the schedules of assessments (Table 1 and Table 2).

3.8.1.3.1 Adverse Events

Adverse events will be recorded following the first dose of study drug until completion of the follow-up visit. Any clinically significant observations in results of clinical laboratory, 12-lead ECGs, vital signs or physical examinations will be recorded as AEs.

A treatment-emergent AE (TEAE) is defined as any event not present prior to administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

Treatment-emergent safety data will be collected from Day 1 (the first and only dose of study drug) through 14 days after the last day of mass balance phase and at least 30 days after Day 1 or before initiation of new cytotoxic chemotherapy, new investigational treatment, or the first day of extension protocol, whichever occurs first.

An AE which occurs prior to (the first) administration of the study drug will be considered a pre-treatment AE and documented on the medical history eCRF.

At several time points before and after drug administration, subjects will be asked non-leading questions to determine the occurrence of AEs. Subjects will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously during the course of the study will be recorded. Events that meet serious criteria will be reported as detailed in Appendix 8.2.

All answers will be coded by the Investigator using the Medical Dictionary for Regulatory Activities (MedDRA; most recent version) for AEs and will be recorded in the AEs Record. Details on the rating of the severity of the AEs and relationship to the study treatment are given in Appendix 8.2.

Pregnancy of female subjects and female partners of male subjects will be monitored along with follow-up, if warranted (see also Appendix 8.3).

3.8.1.3.2 Eastern Co-Operative Oncology Group Performance Status (ECOG)

The performance status will be determined according to the ECOG Performance Status scale [9]:

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 or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

3.8.1.3.3 Clinical Laboratory

The below listed tests will be performed by the local laboratory at time points indicated in the schedule of assessments (Table 1 and Table 2).

Clinical Laboratory Tests			
Hematology and Coagulation	**Serum Chemistry**	**Urinalysis**	**Additional Tests**
Hemoglobin Hematocrit Erythrocytes	Sodium Potassium Chloride	pH Specific gravity Color	Serology: anti- HIV-1/2, HbsAg and anti-HBc, HCV
Platelets Leukocytes Neutrophils Eosinophils Lymphocytes	Calcium Inorganic phosphate Urea Creatinine (including calculation eGFR)	Protein Glucose Ketones Hemoglobin (erythrocytes)	FSH test Collect only for females with no spontaneous menses for ≥12 months, who are <55 years old, and who do not have documented surgical sterilization.
Monocytes Basophils INR* aPTT* PT*	Total bilirubin Direct bilirubin§ ALT AST GGT ALP LDH CPK Triglycerides* Total cholesterol* Total protein* Albumin* Glucose	Leukocytes Microscopic analysis, if urine is positive for protein, leukocytes or hemoglobin	Serum pregnancy test for women of childbearing potential, including women whose last menstruation was less than 1 year before screening
			Urine drugs of abuse test including but not limited to cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates
			Alcohol breath test.

* At screening only

§ Direct bilirubin will be measured only if total bilirubin is higher than upper limit of normal range

The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate the clinically significance according to the applicable [redacted] SOP. Detailed information about follow-up of abnormal laboratory results is given in Appendix 8.2.2.2.

3.8.1.3.4 Vital Signs

Systolic and diastolic blood pressure and pulse will be recorded in supine position after the subject has been resting for at least 5 minutes in a sitting or semi recumbent position. These assessments will be made using an automated device. Body temperature and respiratory rate will be measured subsequently.

3.8.1.3.5 Electrocardiogram

A standard 12-lead ECG will be recorded in triplicates after the subject has been resting for at least 5 minutes in a supine position. The ECG will be recorded using an ECG machine equipped with computer based interval measurements. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTc-interval (Fridericia's) and the interpretation of the ECG profile by the Investigator.

3.8.1.3.6 Physical Examination

A complete physical examination will be performed consisting of all body systems (with the exception of genitalia, anus/rectal, and breast examinations, which will only be performed if medically indicated). Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.

3.8.1.4 Total of Blood Volume

During the course of this clinical study, a maximum volume of approximately 320 mL blood will be collected for PK and safety assessments. In this calculation a maximum prolonged observation period is taken into account (Section 3.1.3.3).

If deemed necessary by the Investigator, additional blood samples for safety or PK analysis may be taken at additional (unscheduled) and follow-up visit(s) up to an additional volume of 30 mL.

3.8.2 Appropriateness of Measurements

The assessments, which will be made in this study are standard for mass-balance studies, and generally recognized as reliable, accurate and relevant.

3.8.2.1 Timing of Assessments

For PK, pre-dose samples will be obtained between waking up and dosing. Post-dose samples up to 60 minutes post-dose will be obtained with a time window of ±1 minute. 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 ±30 minutes of the scheduled time points. The ±30 minutes time window also applies to the start and end times of urine collection intervals.

For safety, pre-dose assessments will be performed between waking up and dosing. Post-dose assessments will be performed with time margins of ±60 minutes of the planned scheme time.

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.

3.8.3 Pharmacokinetic, Efficacy and Safety Variables

3.8.3.1 Pharmacokinetic Parameters

Plasma and whole blood as appropriate, the following PK parameters will be calculated as data allows for talazoparib and/or metabolite concentrations in plasma and for

radioactivity in plasma and whole blood (i.e. nanogram equivalents from radioactivity). PK variables will be computed using WinNonlin Professional or another appropriate software. As appropriate, additional PK parameters may be calculated and reported. A complete list of PK parameters will be provided in the Statistical Analysis Plan (SAP).

C_{max}	Maximum observed plasma/whole blood concentration
T_{max}	Time to attain maximum observed plasma/whole blood concentration
$AUC_{0\text{-}last}$	Area under the plasma concentration-time curve up to time t, where t is the last point with concentrations above the lower limit of quantitation (LLOQ)
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_{last}/k_{el}$, where C_{last} is the last measurable plasma concentration
k_{el}	Terminal elimination rate constant
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{el}$
CL/F	Clearance
V_d/F	Volume of distribution at terminal phase

PK parameters derived from metabolite profiling will be evaluated if applicable.

3.8.3.2 Urine

The following parameters will be calculated as data allows form individual urine concentration of talazoparib and/or metabolites and radioactivity in urine (i.e., nanogram equivalent from radioactivity counts) using non-compartmental approaches. Appropriate validated PK software (e.g., Phoenix WinNonlin or SAS) will be used.

C_{urine}	Urine concentration
Ae_{urine}	Amount excreted during each collection interval, calculated as C_{urine} x urine volume
$CumAe_{urine}$	Cumulative amount of drug excreted in urine
$\%Dose_{urine}$	Percentage of dose recovered in urine over the collection interval
$Cum\%Dose_{urine)}$	Cumulative percent of dose recovered in urine
CLr	Renal clearance calculated as $CLr = CumAe_{urine}/AUC_{0\text{-}last}$

3.8.3.3 Feces

The following parameters will be calculated as data allows form individual concentration of talazoparib and/or metabolites and radioactivity in feces (i.e. nanogram equivalent from radioactivity counts) using non-compartmental approaches. Appropriate validated PK software (e.g. Phoenix WinNonlin or SAS) will be used.

C_{feces}	Fecal concentration
Ae_{feces}	Amount excreted during each collection interval, calculated as Curine x fecal weight
$CumAe_{feces}$	Cumulative amount of drug excreted in feces
$\%Dose_{feces}$	Percentage of dose recovered in feces over the collection interval
$Cum\%Dose_{feces}$	Cumulative percent of dose recovered in feces
$CumAe_{vomit}$	Cumulative amount of drug excreted in vomitus
$Cum\%Dose_{total}$	Cumulative percent of dose recovered in urine and feces

3.8.3.4 Analysis of Mass Balance

Mass balance will be calculated as the percent of total administered radioactivity recovered in urine and feces.

For the purpose of calculating mass balance, the amount of administered radioactivity is defined as the total radioactivity in the dosing solution minus any radioactivity lost due to non-collected vomitus (if any occurred), adsorption to the dosing cup, etc.

3.8.3.5 Metabolic Profiling

Details regarding metabolic profiling, as well as results and a report (if applicable), will be prepared under separate cover by [redacted]

3.8.3.6 Efficacy Variable(s)

Not applicable.

3.8.3.7 Safety Variables

The safety variables to be measured include but are not limited to the variables as given below. A complete list of safety variables will be provided in the SAP.

- AEs
- Clinical laboratory
- Vital signs
- ECG
- Physical examination

3.8.4 Drug Concentration Measurements

Talazoparib and potential metabolites will be analyzed using a validated LC-MS/MS method. ^{14}C-quick counts will be performed in urine and feces to assess the discharge criteria in the ADME part (at least 90% recovery). Less than 1% excretion in urine plus feces per 24-h interval on at least 2 consecutive days will be assessed by a validated LSC method. Total ^{14}C in whole blood, plasma, urine and feces will be analyzed using validated LSC methods.

Metabolite profiling and identification will be done in plasma, urine and feces, if applicable.

3.9 Statistical Procedures and Determination of Sample Size

3.9.1 Analysis Populations

3.9.1.1 Safety Population

All subjects who have received at least 1 dose of talazoparib.

3.9.1.2 Pharmacokinetic Population

All subjects who have received talazoparib, including the radiolabeled IMP, and provided sufficient bioanalytical assessments to calculate reliable estimates of the PK parameters. The concentrations of talazoparib (and potential metabolites) in blood, urine and/or feces will be displayed for the safety population.

3.9.2 Statistical and Analytical Plan for Pharmacokinetic and Safety Evaluation

An SAP will be generated by the Biostatistics Department of [redacted] the SAP will be finalized prior to database lock. Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the Section “Changes in Planned Analysis” in the Clinical Study Report.

3.9.2.1 Demographic and Other Baseline Characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using MedDRA terms.

3.9.2.2 Pharmacokinetic Evaluation

The concentration-times courses of total radioactivity in whole blood and plasma and of talazoparib in plasma and – if appropriate – of its metabolites 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 standard deviation (re-transformed standard deviation of the logarithms),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 post-dose time will only be reported if the mean ≥ LLOQ; for mean < LLOQ, “missing” is reported in the tables. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration vs time curves of total radioactivity in whole blood and plasma and of talazoparib in plasma and – if appropriate – of its metabolites in plasma (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted using both linear and semi-logarithmic scale. Post-dose concentrations < LLOQ will not be plotted; pre-dose concentrations < LLOQ will be set to zero. The amount (%) of talazoparib and – if appropriate – its metabolites excreted into urine and feces will be graphically illustrated

for each sampling interval as well as for the whole sampling period (bar charts for the individual data and for the arithmetic means including standard deviation).

PK parameters of total radioactivity in whole blood and plasma and of talazoparib in plasma and of its metabolites in plasma (T_{max} excluded) will be summarized by arithmetic mean, standard deviation and CV, geometric mean, geometric standard deviation, geometric CV, minimum, median, maximum value and the number of evaluable observations. The PK characteristics of T_{max} will be described utilizing minimum, maximum and median as well as frequency counts. In calculation of PK parameters, pre-dose concentrations < LLOQ are set to zero; all post-dose concentrations < LLOQ are set as missing value.

The same method will be used for the analysis of the drug related radioactivity in blood, plasma, urine and feces. Summary statistics and bar charts will be provided for the cumulative excretion of total radioactivity in urine, feces, vomitus (if applicable) and urine plus feces (plus vomitus [if applicable]) to assess mass balance of total radioactivity.

For total radioactivity the ratio of whole blood to plasma based on $AUC_{0\text{-inf}}$, C_{max} and $AUC_{0\text{-last}}$ will be calculated and summarized.

To determine the percentage of radioactivity associated with erythrocytes in whole blood over time (calculated only for time points that whole blood is collected), the following will be calculated:

The amount of radioactivity in plasma versus whole blood, adjusted for the hematocrit, at the specific time points of comparison Xe/Xb= 1-[Cp*(1-Hct)/Cb], where Xe and Xb stand for amount of radioactivity in erythrocyte or plasma, respectively, and Cp and Cb stands for radioactivity concentration in plasma and blood, respectively. Hematocrit values for Days –1, 1 and 22 will be averaged for use in this calculation.

Additional analyses of the concentrations of talazoparib and its metabolites (if applicable) in plasma, urine, and feces (vomitus, if applicable) as determined by radio-chromatographic methods as well as the corresponding PK parameters will be reported under separate cover.

3.9.2.3 Evaluation of Safety and Tolerability

All safety analyses will be performed using the safety population, defined as all patients who received talazoparib. Safety will be evaluated using summaries of AEs, physical examinations (and weight), vital signs, ECG recordings, and laboratory evaluations.

3.9.2.3.1 Adverse Events

Adverse events will be coded to preferred term and system organ class using MedDRA and classified by severity using NCI CTCAE. The number and percentage of patients with AEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (e.g. leading to permanent treatment discontinuation).

3.9.2.3.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

Laboratory values will be classified by severity using the CTCAE. Change from baseline in laboratory values will be tabulated and summarized graphically, where applicable.

3.9.2.3.3 Vital Signs and Electrocardiograms

Vital signs and ECG parameters will be listed and they will be presented descriptively, where applicable.

3.9.2.3.4 Physical Examination

Clinically significant changes will be considered as AEs.

3.9.3 Determination of Sample Size

At least 6 patients will be enrolled to target 4 evaluable subjects. This sample size is consistent with typical study designs for Phase 1 mass balance studies for PK evaluation.

3.10 Data Quality Assurance

The study may be audited to assess adherence to the Clinical Study Protocol (CSP) and Quality System. During the conduct of the study, process-related audits may be performed as well. An audit certificate will be provided in the appendices of the final Clinical Study Report (CSR) outlining the audit performed and other related activities.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant regulatory requirements. eCRF entries will be verified with the source documentation, if applicable.

Regulatory authorities, the IEC and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at [redacted] for all documents that are generated in relation with the study.

An explanation will be given for all missing, unused and spurious data in the relevant sections of the CSR.

4. ETHICS

4.1 Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, subject information and ICF, any other written information to be provided to the subject, subject recruitment procedures, if any, IB, information about payments and compensation available to subjects, if not mentioned in the subject information, the Investigator's current curriculum vitae and/or other documentation evidencing qualifications, and other documents as required by the regulatory authorities and IEC will be submitted. The submission letter will clearly identify (by study identification number, including version, EudraCT no., title and/or date of the document) which documents have been submitted. Written approval/favorable opinion must be obtained from regulatory authorities/IEC prior to commencement of the study.

During the study, the Investigator must promptly in accordance with local requirements report the following to the IEC (central or local IEC, as applicable): updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the study status and other documents as required by the local IEC.

Substantial amendments must not be implemented before approval/favorable opinion of the IEC, unless necessary to eliminate hazards to the subjects.

The Investigator must maintain an accurate and complete record of all submissions made to the IEC. The records should be filed in the Investigator's study file and copies must be sent to the Sponsor.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments[10].

This study is also designed to comply with ICH E6 Guideline for GCP (ICH Harmonised Tripartite Guideline, E6: Guideline for Good Clinical Practice [CPMP/ICH/135/95], Jan, 1997)[11], the EU Clinical Trial Directive 2001/20/EC (Directive of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct, 4th April 2001)[12], Commission Directive 2005/28/EC[13] and the applicable regulatory requirements.

ICH adopted guidelines and other relevant international guidelines, recommendations and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present in the clinical site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

The Investigator will be responsible for the medical follow up of the subjects.

4.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures and risks of study participation in local language. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

The ICF contains information about the objectives of the study, about the procedures followed during the study and about the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions. In addition, insurance coverage provided during the study is explained. The subjects will have to sign the ICF before any study related procedures are started. The Investigator will retain the original of each subject's signed consent form at the study site.

Additionally, the process of obtaining informed consent should be documented in the subject's source documents.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC, and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

The elements addressed in the ICF are according to the ICH E6 Guideline for GCP (CPMP/ICH/135/95) [11].

4.4 Privacy

All personal details will be treated as confidential by the Investigator and involved site and [redacted] and handling of personal data will be in compliance with the local data protection and privacy regulations.

The Investigator will particularly pay attention that source documents or additional documents handed over to the Sponsor obscure subject names and other confidential personal details, as per local regulations.

5. STUDY ADMINISTRATIVE STRUCTURE

5.1 Distribution of Activities

Preparation of study drug

The study drug will be prepared at [redacted] Netherlands.

Laboratory assessments

The analysis of talazoparib and/or possible metabolites in plasma (and urine and feces) samples will be performed at the [redacted] USA or its designated USA partner.

The analysis of whole blood, plasma, urine and feces for total radioactivity will be conducted at the [redacted] Netherlands).

The analysis of quick counts will be conducted at the [redacted] Netherlands).

Metabolite profiling (if applicable) in plasma, urine and feces samples will be conducted at [redacted] USA or its designated USA partner.

The analysis of clinical laboratory samples will be performed at the local safety laboratory as detailed in the laboratory manual.

The design of the eCRF will be prepared with the computer program Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA) by the Database Programming Department of [redacted]

Data management

Data management will be performed with the computer programs Oracle Clinical (Oracle, Redwood Shores, Redwood City, CA, USA), SAS for Windows® (SAS Institute Inc., Cary, NC, USA) and [redacted]

Statistics

An SAP will be provided by the Biostatistics Department of [redacted] The safety analysis and the statistical evaluation of PK and PD parameters will be conducted by the Biostatistics Department of [redacted] Non-compartmental analyses (NCA) will be performed with WinNonlin™ Professional, Version 6.3 or higher. Statistical analysis will be performed with the computer program SAS for Windows® (SAS Institute Inc., Cary, NC, USA).

CSR writing

The CSR, structured in accordance with the guideline 'Structure and Content of Clinical Study Reports - ICH E3[14], will be written by [redacted]

5.2 Documentation

5.2.1 Archiving

All documents concerning the study will be kept on file in the Central Archives of [redacted] for at least 15 years after conduct of the study. The Sponsor will receive the completed eCRFs (upon request, as PDF file).

5.2.2 Recording of Data in Source Documents and CRFs

All data will be recorded as source data first and entered later into the eCRF. A Data Management Plan will be written by the Data Management Department of [redacted] which will be finalized prior to performing any data validation.

6. CONFIDENTIALITY AND PUBLICATION POLICY

By signing this CSP, the Investigator reaffirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her, or resulting from this study. He/She will only divulge such information as may be necessary to the IEC and the members of the staff and the subjects who are involved in this study.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and [redacted]

7. REFERENCES

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5. ICRP, 2007. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann. ICRP 37 (2-4)
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9. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol.1982;5:649-55.
10. WMA Declaration of Helsinki (18th WMA General Assembly 1964), revised at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013
11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E6: Guideline for Good Clinical Practice (CPMP/ICH/135/95), Jan 1997
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13. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
14. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), Nov 1995
15. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Note for Guidance on Clinical Safety Data Management, June 1995
16. Common Terminology Criteria for Adverse Events v4.0 (CTCAE), US department of Health and Human Services, National Institutes of Health, National Cancer Institute 2009

8. APPENDICES

8.1 Drug Accountability

Upon receipt of the study drug, it will be inspected and counted by the Investigator or the responsible pharmacist. If necessary, all study drug will be re-packed per dosing occasion, and labeled according to [redacted] SOPs.

The study drug will be kept in the [redacted] Pharmacy or in a locked and secured storage facility accessible only to those authorized by the Investigator to dispense the study drug.

The responsible pharmacist will keep an inventory. This will include a description of the formulation and the quantity of study drug received for the study and a record of what is dispensed, to whom and when.

Preparation of the study drug will be performed at [redacted] by a licensed expert on radioactivity.

On termination of the study the Investigator or delegate will conduct a final inventory of the study drug supply and will record the results of this inventory in the Drug Accountability Form. Unused study drug will be returned to the Sponsor at the end of the study or will be locally destroyed according to [redacted] standard procedures.

8.2 (Serious) Adverse Events Evaluation and Reporting

The safety management of this study will comply with all applicable national and international regulatory requirements and adhere to the full requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, October, 1994)[15].

8.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the 'Note for Guidance on clinical safety data management: definitions and standards for expedited reporting' (ICH topic E2A).[15]

SAEs will be collected from the time the subject signs Informed Consent. Non-serious AEs will be collected from the time the subject receives first dose of study drug.

The Investigator will report in the eCRF all AEs observed, spontaneously reported or noted (verbally or e.g. in a diary) by subjects. In addition, trial subjects will be questioned by site personnel about AEs at regular intervals using standard non-leading questions, such as "have you experienced anything new or different since your previous study visit?"

Grading of severity, clinical significance, causality and seriousness will be determined by the Investigator using the CTCAE scale and will be reported in the eCRF.

8.2.2 Grading of Severity

The severity of AEs will be graded using the most current version of the Common Terminology Criteria for Adverse Events (CTCAE) 5-point scale[16]:

- **Mild (Grade 1):** Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2):** Minimal, local or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL). Intervention may or may not be indicated.
- **Severe (Grade 3):** Medically significant but not necessarily life-threatening; severe is not the same as serious; determination of serious vs. life-threatening will be based upon subject's condition / anticipated outcome, e.g. serious is usually reserved for an event which poses an immediate threat to subject's life or could pose a threat to subject's life if not treated promptly
- **Life-threatening (Grade 4):** Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)** related to AE.

It is emphasized that the term severe is a measure of severity: thus a severe AE is not necessarily "serious" as per regulatory definition. For example, itching for several days may be rated as severe, but may not meet regulatory definition of 'serious' (Section 8.2.3).

8.2.2.1 Grading of Relationship (Causality)

The relationship of any AE to the study drug will be assessed and graded as related or not related as following:

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

8.2.2.2 Test results and physical examination findings

Test findings and physical examination findings can result in AEs if they are:

- Associated with accompanying symptoms
- Requires additional diagnostic testing or medical/surgical intervention, and /

- Leads to a change in study dosing or discontinuation of the study medication; results in the addition of significant additional concomitant drug treatment or other therapy
- Leads to any of the outcomes included in the definition of a SAE
- Is considered to be an AE by the Investigator

Reporting an AE should not be triggered by:

- Merely needing to repeat an abnormal test, or,
- Any abnormal test result that is determined to be an error, e.g. it is not reproducible or sustainable on repeat.

8.2.3 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- **Results in death**
- **Is life-threatening** (This refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- **Requires inpatient hospitalization** for a medical reason or prolongation of existing hospitalization (This refers to hospital admission required for treatment of the AE).

Note: This does not include confinement in a skilled nursing unit; rehabilitation facility; the clinical research unit; or confinement due to a planned reason unrelated to study

- **Results in persistent or significant disability/incapacity**
- **Is a congenital anomaly/birth defect**
- **An important medical event** (Medically Significant Event) that is considered by the Investigator to be serious but that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events include but are not limited to intensive treatment in an Emergency Department or at the site for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered 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; or development of drug dependency or drug abuse.

SAEs will be collected from the time the subject signs Informed Consent until 30 days post dosing. SAEs that are related to the investigational drug and continue beyond the normal collection period (i.e., are ongoing at the time a subject exits the study) will be

followed until resolution or until stabilized with sequelae. SAEs that begin after the subject's participation in the study is complete, but that the Investigator considers to be related to study drug, may be reported at any time.

The Investigator or clinical site personnel must notify Medivation's vendor [redacted] and Medivation's Medical Monitor of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical site personnel becoming aware of the event.

The Investigator will provide the initial notification by sending a completed "Serious Adverse Event Report Form", which must include the Investigator's assessment of the relationship of the event to investigational drug, and must be signed by the Investigator.

In addition, notification is sent by the Investigator to the IEC, and the subject's General Practitioner, if applicable.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly as per all SAEs to Medivation's vendor [redacted] and Medivation Medical Monitor.

<u>All SAE (initial and follow-up) reports should be sent to the SAE reporting contacts provided on Page 4.</u>

8.2.4 Suspected Unexpected Serious Adverse Reactions

A SAE the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product) and which has reasonable relationship to IMP administration is called a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The Sponsor (Medivation Drug Safety) will determine which talazoparib SAEs meet regulatory reporting requirements as a SUSAR. Medivation Drug Safety will:

1. Submit all SUSARs to the applicable local regulatory authority (Hungary)
2. Issue SUSARs to [redacted] and/or Investigator whose responsibility will be to report the SUSAR to the applicable IEC

Talazoparib SUSARs will derive from this study as well as other talazoparib clinical studies for cross-reporting to local regulatory authority.

8.2.5 Follow-up of Adverse Events

Follow-up of AEs will continue until resolution, stabilization or death. In case of ongoing AEs at the moment of database closure, the data obtained at the moment of database closure will be used in the statistical analysis. The follow-up of the AE will be documented in the source documents and will be described in the final report only if considered relevant by the Investigator.

8.3 Pregnancy

Pregnancies occurring up to 90 days after the completion of the study drug must be reported to the Investigator. The subject should be counseled by a specialist, to

discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known.

The Investigator should report all pregnancies of female clinical study subjects to Medivation's vendor [redacted] within 24 hours of becoming aware of them using the Pregnancy Reporting Form as per the contact information provided on Page 4: ***SAE Contact Information.***

If the Investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to Medivation's vendor [redacted] within 24 hours of obtaining written consent from the pregnant partner.

[redacted] must report all pregnancies (subject or subject partner) to the Sponsor. Pregnancy outcome will also be reported to the Sponsor within 24 hours of awareness. The Investigator will make arrangements for the partner to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the partner should continue until the outcome of the pregnancy is known.