Statistical Analysis Plan

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

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	Mar. 6th, 2017	PPD	N/A. This is the original SAP based on the final protocol dated July 18th , 2016.
Version 2.0	February 28 , 2019	PPD	This is amended SAP based on the protocol amendment dated August 31st, 2018. The following updates were made: • Inclusion of additional abbreviations • Updates to definition of evaluability, eligibility criteria, PK assessments and revision of populations for analyses. Additionally SAP was updated to • Reflect Pfizer reporting standards of PK parameters and concentrations. • Statistical model was updated to explore weight and age as covariates • Include exploratory analysis of PK parameters versus renal function (CL_{CR}).

Signature Page

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Glossary and Abbreviations

Abbreviation	Term
Ae_{0-24}	Amount of unchanged drug excreted into urine from 0 to 24 hours
A_e%	Percentage of dose recovered in urine as unchanged
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase / GPT
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
aPTT/PTT	(Activated) Partial Thromboplastin Time
AR	Accumulation ratio
AST	Aspartate Transaminase / GOT
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area Under the concentration time curve from 0 to 24 hours
AUC_{0-24u}	Area under the free concentration time curve from 0 to 24 hours
BMI	Body mass index
BUN	Blood Urea Nitrogen
CI	Confidence interval
CL_{CR}	Creatinine Clearance
CL/F	Apparent Oral Clearance
CL_r	Renal Clearance
CL_u/F	Apparent total clearance of the drug from plasma after oral administration
C_{max}	Maximum plasma concentration
C_{maxu}	Maximum Free Plasma Concentration
C_{trough}	Predose plasma drug concentration
C_{total}	Total plasma concentration of drug
$C_{unbound}$	unbound concentration of drug
CV	Coefficient of variation
D1	Day 1
DNA	Deoxyribonucleic acid
ECG(s)	Electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FDA	Food and Drug Administration
f_u	Fraction of unbound drug
Gamma GT	Gamma-glutamyl transferase or gamma-glutamyl transpeptidase
hr	Hour
HBsAg	Hepatitis B surface Antigen
HIV	Human Immunodeficiency Virus
INR/PT	International Normalized Ratio / Prothrombin time
IU	International Unit

kg	kilogram
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MAD	Maximum Administered Dose
Max	Maximum
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum
mL	Milliliter
MRT	Mean residence time
MTD	Maximum Tolerated Dose
n or N	Number of patients
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PARP	Poly(ADP-ribose) polymerase
PK	Pharmacokinetics
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
Scr, std	Standardized Serum Creatinine
SD	Standard Deviation
SFU	Safety Follow Up
$t_{½}$	Terminal half-life
TEAE(s)	Treatment Emergent Adverse Event(s)
TLFs	Tables, Listings and Figures
T_{max}	Time to C_{max}
CCI	[redacted]
$V_{0\text{-}12ur}$	Urine volume from time zero to 12 hours
$V_{12\text{-}24ur}$	Urine volume from time 12 to 24 hours
WBC	White Blood Cells
WHO	World Health Organization

[redacted]

1 Introduction

Talazoparib (also known as BMN 673 and MDV3800) is a poly(ADP-ribose) polymerase (PARP) inhibitor being developed for the treatment of genetically driven tumors. PARP represents a family of at least 17 enzymes that transfer ADP-ribose groups to target proteins to regulate various cellular processes including deoxyribonucleic acid (DNA) repair. Among them, PARP1 and PARP2 play important roles in DNA repair.

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

The study drug, talazoparib, is a potent, orally bioavailable small molecule poly PARP inhibitor in development for the treatment of a variety of human cancers both as single agent and in combination with DNA-damaging chemotherapy.

The pharmacokinetics (PK) of talazoparib as a single agent were evaluated in 142 adult patients with hematologic malignancies and solid tumors at doses of 0.025 to 2 mg/day administered orally, as a single dose or as multiple doses. The PK was similar in patients of each cancer type and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. Elimination appeared to follow biphasic kinetics. At 1 mg/day, the mean terminal half-life ($t_{½}$) was approximately 89.8 hours. Following repeated daily administration at 1 mg/day, the median talazoparib accumulation ratio ranged from 2.23 to 12.3. Apparent oral clearance (CL/F) of talazoparib appeared to be dose linear. A food-effect study conducted at 0.5 mg/day in healthy volunteers showed that food had no clinically meaningful effect on the extent of absorption (AUC) of talazoparib.

PK studies have shown that overall, plasma talazoparib concentrations increase in a dose-dependent manner. After a daily administration of talazoparib 1mg, it took approximately 3 weeks to reach the steady state. Based on phase 1, in vitro and in vivo preclinical data, talazoparib appears to predominantly excrete via the renal route.

A preliminary population PK analysis was performed with data from patients in two phase 1 studies to assess the effects of renal function on PK parameters of talazoparib. Talazoparib CL/F in patients with mild renal impairment (creatinine clearance [CLCR], 60-89 mL/min) was similar compared with patients with normal renal function (CLCR ≥ 90 mL/min). In patients with moderate renal impairment (CLCR, 30-59 mL/min), the talazoparib CL/F was decreased by 44% from normal, resulting in higher talazoparib exposure. Therefore, based on this preliminary data, patients with moderate or severe renal impairment (CLCR < 60 mL/min) may be at risk of higher exposure to talazoparib.

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

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

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

The dose selected in this study is 0.5 mg/day which is considered a safe dose as it is 50% lower than the Maximum Tolerated Dose (MTD) established in patients with solid tumors in phase 1 study at 1 mg/day. Talazoparib has also shown clinical efficacy at this dose level in a phase 1 study; however, efficacy is not being explored in this study. Additionally, the expected exposures increase in moderate and severe renal impaired patients should not exceed the exposure of maximum administered dose (MAD) of 2 mg/day experienced in the Phase 1 studies. Talazoparib will be given daily for 22 calendar days in order to assess the safety and PK of talazoparib at the steady state.

This statistical analysis plan (SAP) covers the detailed procedures for performing statistical analyses and for producing tables, listings, and figures (TLFs) in the study.

2 Study Objectives

2.1 Primary Objective

- To investigate the effect of mild, moderate and severe renal impairment on the pharmacokinetics of talazoparib following daily oral dosing of talazoparib for 22 days in patients with advanced solid tumors

2.2 Secondary Objective

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

3 Study Design and Methods

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

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

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

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Scr, std})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

(where Scr, std = standardized serum creatinine (mg/dL); age = years)

Patients will be enrolled in parallel and assigned to one of four groups based on their renal function. Renal function defining each group according to the MDRD formula is presented in Table 1.

In each group, 6 evaluable patients will be treated with daily oral doses of talazoparib 0.5 mg for at least 22 calendar days. If treatment in the group of patients with severe renal dysfunction (Group D) is halted due to unacceptable toxicity, 2 additional evaluable patients will be enrolled in each of Groups A, B and C (total of 8 evaluable patients each). Therefore, a total of at least 24 patients will be treated in the study (Table 1).

Table 1 Group Assignment

Group	Description	Patients*

A	**Control, normal renal function**: eGFR ≥ 90 mL/min/1.73m^2	6 (8)
B	**Mild renal impairment:** eGFR ≥ 60 and ≤ 89 mL/min/1.73m^2	6 (8)
C	**Moderate renal impairment:** eGFR ≥30 and ≤ 59 mL/min/1.73m^2	6 (8)
D	**Severe renal impairment:** eGFR ≥15 and ≤29 mL/min/1.73m^2, not on dialysis	6 (0)

* The patient number in the parenthesis will be assigned if Group D is halted due to unacceptable toxicity.

Study periods include:

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

Serial PK plasma samples will be collected at predetermined times on Day 1 and Day 22 up to 24 hours post-dose (Day 2 and Day 23, respectively) for talazoparib concentration measurement during which time the patients will be confined to the clinical research facility. Additionally, trough (pre-dose) samples will be collected on Day 8 and Day 15.

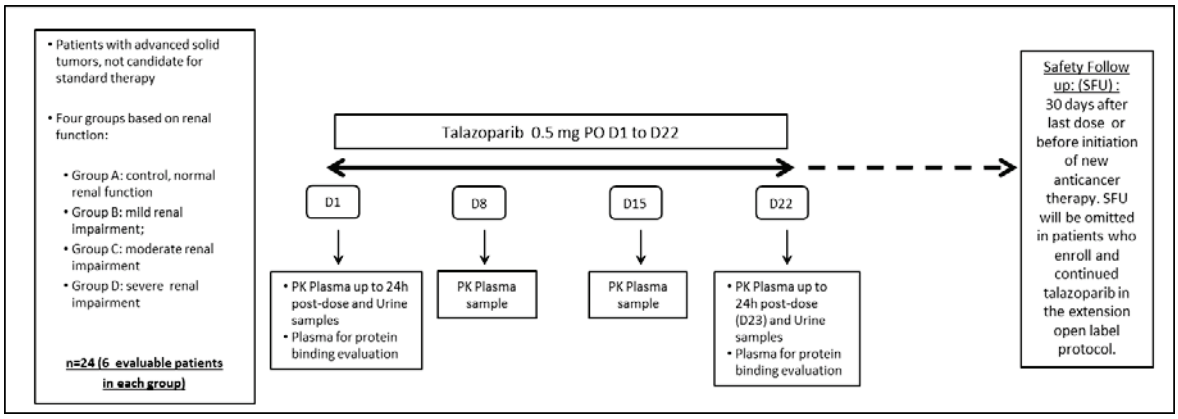
One PK blood sample will also be collected at the Safety Follow up Visit if the study treatment discontinues earlier than planned. Blood samples for plasma protein binding evaluation will be collected on Day 1 and Day 22 (2 hours post dose). Urine samples for PK analyses will be collected as a single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

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

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

Patients who discontinue the study before the completion of the Day 23 assessments and/or who do not meet the above mentioned criteria may be replaced if needed, upon agreement of the Sponsor.

Figure 1 Study Schema



The schedule of procedures and samples for PK assessment are presented in Tables 2 and 3 below, respectively. For a detailed description of study procedures, please refer to protocol Section 7 “STUDY VISITS AND ASSESSMENTS”.

Table 2 Schedule of Procedures

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

[redacted]

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

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

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

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

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

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

6: Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lung, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the

	Pre-screening	Screening	Enrollment	Treatment period: Cycle 01 only									Safety Follow up Visit (=End of Study Visit) (17)
Study Day		**-28 to -2 (1)**	**D-1**	**D1 = First Study Drug Intake (5)**	**D2**	**D3-7**	**D8**	**D9-D14**	**D15**	**D16-D20**	**D21**	**D22**	**D23**	
Window				Within 3 calendar days post D-1		+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days		-3/+10 days

study site or as clinically indicated by symptoms.

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

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

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

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

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

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

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

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

13: Serial plasma pharmacokinetic analysis will be collected at predetermined times on Day 1 and Day 22, during which time the patients will be confined to the clinical research facility. Blood samples for PK bioanalysis will be drawn at the following selected time-points during Day 1 and Day 22: On Day 1 within 60 minutes prior to dose and on Day 22 within 24 h ± 60 minutes from the previous dose (Day 21) but within 60 minutes prior to next dose) then 0.5, 1, 2, 4, 6, 8-12, and 24 hours post-dose. Post-dose samples up to 60 minutes post-dose will be obtained with a window of ± 3 minutes. From after 60 minutes until 12 hours post-dose, samples will be obtained with time margins of ±10 minutes. Thereafter, samples should be obtained within ±60 minutes of the scheduled time points.

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

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

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

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

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

[redacted]

	Pre-screening	Screening	Enrollment	Treatment period: Cycle 01 only									Safety Follow up Visit (=End of Study Visit) (17)
Study Day		**-28 to -2 (1)**	**D-1**	**D1 = First Study Drug Intake (5)**	**D2**	**D3-7**	**D8**	**D9-D14**	**D15**	**D16-D20**	**D21**	**D22**	**D23**	
Window				Within 3 calendar days post D-1		+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days		-3/+10 days

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

[redacted]

Table 3 Samples for PK assessment

PK SAMPLES	Day1							Day 1/ Day 2	D8	D15	D22							D22/ D23
	Pre-Dose	Post-Dose						Post-dose Day 1 = Pre-Dose Day 2	Pre-dose	Pre-dose	Pre-Dose	Post-Dose						Post-dose Day 22
Blood sample for PK	x	x	x	x	x	x	x	x	X	X	x	x	x	x	x	x	x	x
Window	within 60 min	0.5 (+/- 3 min)	1h (+/- 3 min)	2h (+/- 10 min)	4h (+/- 10 min)	6h (+/- 10 min)	8-12h (+/- 10 min)	24h (+/- 60 min)	within 60 min(1)	within 60 min(1)	within 60 min(1)	0.5 (+/- 3 min)	1h (+/- 3 min)	2h (+/- 10 min)	4h (+/- 10 min)	6h (+/- 10 min)	8-12h (+/- 10 min)	24h (+/- 60 min)
Blood sample for protein binding analysis				X (+/- 10 min)										X (+/- 10 min)				
Urine sample for PK	x	x			x							x			x			
Window	within 2 h	0-12 hour (+/- 60 min)			12-24 hour (+/- 60 min)							0-12 hour (+/- 60 min)			12-24 hour (+/- 60 min)			

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

[redacted]

3.1 Study Endpoints

3.1.1 Pharmacokinetic Endpoints

Primary endpoints

Plasma talazoparib: AUC_{0-24}, C_{max}, AUC_{0-24u} and C_{maxu} at steady-state (Day 22).

Secondary endpoints

Plasma talazoparib:

Single dose parameters: AUC_{0-24}, C_{max}, T_{max}, f_u, AUC_{0-24u} and $C_{maxu,}$

Multiple dose parameters: T_{max}, C_{trough}, CL/F, R_{ac}, f_u, CL_u/F

Urine talazoparib:

Single dose parameters: Ae_{0-24} and Ae_{0-24}%.

Multiple dose parameters: Ae_{0-24}, Ae_{0-24}%, and CL_r.

3.1.2 Safety Endpoints

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

The safety will be evaluated based on the assessments of AEs, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), laboratory assessments and Eastern Cooperative Oncology Group (ECOG) performance status.

3.2 Randomization

No randomization will be conducted in the study.

3.3 Sample Size Justification

Patients are assigned to one of four groups, based on renal function. The study will enroll at least 6 evaluable patients with advanced solid tumors per group so at least 24 patients will be enrolled. If enrollment for severe renal impairment group is halted due to unacceptable toxicity profile, 2 additional evaluable patients will be enrolled in each Groups A, B and C (total of 8 evaluable patients each). Patients will be considered evaluable if they are eligible and have (1) completed 22 calendar days of treatment with talazoparib counted from Day 1, regardless of any treatment hold and missed ≤5 consecutive doses of talazoparib, (2) received at least 10 consecutive days of 0.5 mg talazoparib daily dose without dosing interruption prior to Day 22 PK sample collection, (3) completed at least 85% of total plasma PK samples collection and (4) not vomited talazoparib dose on Day 1 and Day 22 of the PK samples collection. Patients who

discontinue the study before the completion of the Day 23 assessments and/or who do not meet the above mentioned criteria may be replaced upon agreement of the Sponsor.

3.4 Data Handling

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied for missing values.

3.4.1 Concentrations Below the Limit of Quantification

In all data presentations (except a few specific scenarios listed below), concentrations below the limit of quantification (BLQ) will be set to zero. In data listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification). For individual concentration vs. time plots on the semi-logarithmic scale, all BQL values will set to missing.

The mean plots will match the summary table results and will not have an observation at a given time point if more than half of the subjects have values BQL.

BQL values will be set to zero when calculating descriptive statistics. Zero concentrations will be considered as missing in geometric mean calculation.

For PK parameter calculations, BQL concentrations will be treated as zero when they occur before the first measurable concentration; all other BQL values will be treated as missing and set to "."

3.4.2 Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

3.4.3 Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular treatment with $\geq$3 evaluable measurements. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be

set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (for example due to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

Concentration Data for Parameter Calculations: The concentration data, as reported by the respective bioanalytical groups, will be used without rounding for all analyses.

Concentration Data Listings: By default, concentration values should be presented in listings exactly as reported by the respective bioanalytical groups. However, in cases where concentration data may be supplied electronically with unrealistic precision, rounded values may be presented. A default of 3 significant figures is suggested, with the exception of T_{max} (2 decimal places).

Parameter Data Listings: The non-compartmental parameters should not be reported to any greater precision than that of the concentration data. A default of 3 significant figures is preferred.

Summary Statistics of PK data: Parameter values (and if applicable, concentration values) should be rounded to the same precision used in data listings prior to any statistical analysis or descriptive summaries.

Descriptive summaries:

- Means, Median – 1 more significant figure than the data
- T_{max} and any other parameters which are direct time observations, median will have the same significant figures as the data
- Standard Deviation – 1 more significant figure than means
- CV% – whole numbers
- Minimum, Maximum – same significant figures as the data

Statistical summaries of PK data:

- Means, Differences, CIs (non-transformed data) – 1 more significant figure than the data
- Ratios, CIs (log transformed data) – 2 decimal places
- Individual differences, ratios and ln ratios – same significant figures as the data.

Study Reports:

Generally, for consistency and to simplify document QC, values presented within tables in a Clinical Study Report will match the data in the source tables.

For reporting of safety data, unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum (min) value, median, and maximum (max) value.

Categorical data will be summarized with frequencies and percentages.

Baseline is defined as the last value measured prior to the first dose of study drug.

Change from Baseline is defined as [Post-baseline Value – Baseline Value].

4 Data Analysis

4.1 Analysis Populations

Safety Population: All patients who received any amount of talazoparib will be included in the safety analyses and listings.

PK Population: All patients who have at least 1 reportable talazoparib concentration. This population will be used for talazoparib plasma and urine concentrations.

PK Analysis Population: All evaluable patients who provide at least 1 of the talazoparib PK parameters of primary interest. This population will be used for the analyses of talazoparib PK parameters.

The frequency and percentage of patients in each population will be summarized by renal impairment group. Patients who are excluded from the analysis populations will be listed by renal impairment group and patient.

Other Analysis Population: The protein-binding analysis will include all eligible patients with at least one adequate PK assessment.

4.2 Study Patients

Patient Disposition

Patient disposition will be summarized by renal impairment group using the number and percent of patients who fail the screening procedure and the reasons for screen failure, the number and percent of patients who complete the study, the number and percent of patients who discontinue the study and the reasons for discontinuation, the number and percent of patients continuing open-label extension study, and the number and percent of patients analyzed for pharmacokinetics and safety. Patient disposition and completion status will be listed for all enrolled patients.

Eligibility status for the study will be listed for all enrolled patients.

Protocol Deviations

Protocol deviations will be identified prior to database lock and may include but are not limited to: significant violations of inclusion/exclusion criteria, noncompliance of the study treatment taken, use of prohibited medications or not following clinical trial protocol procedures that may affect evaluation of the PK profile. Subjects who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

Key protocol deviations will be summarized by deviation category, and all protocol deviations will be listed by patient.

4.3 Patient Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by renal impairment group for the safety population. The demographic and baseline characteristics will consist of age, gender, race, ethnicity, height (cm), weight (kg), and BMI (kg/m^2). Individual demographic and baseline characteristics for the safety population will be listed by patient.

The age is a calculated parameter. Age will be calculated using the patient's date of birth and the patient's informed consent date.

Continuous variables (age, height, weight, BMI) will be summarized by n, mean, SD, Min, median, and Max. Number of patients and percentages will be used to describe categorical (discrete) variables (gender, race and ethnicity).

4.4 Medical/Surgical History and Procedures/Non-Drug Therapies

The presence/absence of any current medical condition and/or other significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.

Initial Diagnosis/cancer history and Medical/surgical history collected at the screening will be summarized by renal impairment group, and will be listed by patient, respectively. Prior surgery and radiation therapy for cancer, and other procedures will be listed by patient.

4.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced Dictionary (September 2015 or later). Prior medications (including prior systemic anti-cancer therapy) will be those that start and end prior to first dose of study drug. Concomitant medications will be those that have a known end date after the first dose of study drug, or have a missing end date. Medications will be listed by patient including Anatomical Therapeutic Chemical (ATC) classification, preferred term and reported term; the start and end dates (or ongoing status); and dose, unit and indication. Medications taken by patients from 30 days prior to Screening until the end of treatment will be included in the listing. Medications will be summarized by renal impairment group.

4.6 Treatment Compliance

Treatment compliance will be assessed based on patients' used and unused study drug containers and their completed study drug diary at Day 8, Day 15 and Day 22. Percent compliance will be calculated by the number of capsules taken during dosing period divided by the expected number of capsules dispensed, multiplied by 100%. Treatment

compliance along with duration of treatment, dose intensity, dose interruption and duration of dose interruption will be listed for all patients and will be summarized by renal impairment group.

4.7 Pharmacokinetic Analysis

The pharmacokinetic analysis will be conducted using the PK population and PK analysis population.

4.7.1 Plasma and Urine Concentrations

Presentations for talazoparib concentrations will include the following:

- Individual listing of plasma concentrations and amount in urine will be sorted by renal function group (present in heading), then subject id, by day and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- Summary of plasma concentrations and amount in urine will be presented by renal function group, day and nominal time postdose, where the set of statistics will include the number of measurements, arithmetic mean, SD and CV, geometric mean, geometric CV, Min, median, Max value and the number of concentrations above the lower limit of quantification.
- Individual concentration vs time plots of talazoparib in plasma (using the actual sampling times) will be presented by renal group for Day 1 and Day 22 (each group on the separate plot) in both linear and semi-logarithmic scales.
- Median plasma concentrations time plot (on both linear and semi-logarithmic scales) against nominal time postdose by renal function groups will be generated for Day 1 and Day 22. All renal function groups medians will be presented in the same plot.
- Similarly, mean plasma concentrations time plot (on both linear and semi-logarithmic scales) against nominal time postdose by renal function groups will be generated for Day 1 and Day 22. All renal function groups mean will be presented in the same plot.
- Median plots of the predose plasma concentrations against day (including Day 8, Day 15, and Day 22) by renal function groups in order to assess the attainment of steady-state (all renal function groups on the same plot).
- Individual plots of the predose plasma concentrations against day (including Day 8, Day 15, and Day 22) by renal function groups.

Additionally, unbound fractions (f_u) will be listed and summarized descriptively by renal function group.

4.7.2 Pharmacokinetic Parameters

PK parameters for talazoparib will be derived for patients in the PK analysis population using a non-compartmental model with WinNonlin. The following PK parameters will be derived, as applicable (Table 4)

Table 4 PK Parameters

Parameter	Description	Calculation	Single Dose	Multiple Dose
Ae_{0-24}	Amount of drug excreted in urine from time 0 to 24 hours	$Ae_{0-24} = C_{0-12ur} \bullet V_{0-12ur} + C_{12-24ur} \bullet V_{12-24ur}$	X	X
$A_e\%$	Percentage of dose excreted in urine as unchanged drug	$\%Dose_{urine} = 100 \bullet Ae_{0-24}/Dose$	X	X
AUC_{0-24}	Area under the concentration time curve from time 0 to 24 hours	By linear trapezoidal rule during the ascending phase and log trapezoidal rule during the descending phase	X	X
CL/F	Apparent clearance of the drug from plasma after oral administration	$CL/F = Dose/AUC_{0-24}$		X
CL_r	Renal clearance	$CL_r = Ae_{0-24}/AUC_{0-24}$		X
C_{max}	Maximum plasma concentration	Observed data	X	X
C_{trough}	Predose plasma concentration	Observed data		X
R_{ac}	Accumulation ratio	AUC_{0-24} (Day 22)/ AUC_{0-24} (Day 1)		X
T_{max}	Time of C_{max}	Observed data	X	X
AUC_{0-24u}	Area under the free concentration time curve from time 0 to 24 hours	$AUC_{0-24u} = F_u \bullet AUC_{0-24}$	X	X
CL_u/F	Apparent clearance	$CL_u/F = F_u \bullet CL/F$		X

	of free drug from plasma after oral administration			
C_{maxu}	Maximum free plasma concentration	$C_{maxu} = F_u \bullet C_{max}$	X	X
f_u	Fraction of unbound drug	$F_u = C_{unbound} / C_{total}$	X	X

Additional PK parameters will be calculated as applicable.

Individual plasma and urine PK parameters will be listed by renal group for Day 1 and Day 22.

PK parameters of talazoparib in plasma (T_{max} excluded) will be summarized by arithmetic mean, standard deviation and CV, geometric mean, geometric CV, minimum, median, maximum value and the number of evaluable patients. T_{max} values will be described utilizing the number of observations, minimum, maximum and median.

Geometric CV% = sqrt(exp(variance of log transformed data)-1)*100

Box and whisker plots for individual subject parameters (AUC_{0-24}, AUC_{0-24u}, C_{max} and C_{maxu}) against renal function group will be presented and overlaid with geometric means.

4.7.3 Comparative Analysis of PK Parameters

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

The comparison of PK parameters (AUC_{0-24}, C_{max}, C_{maxu}, and AUC_{0-24u}) of each renal impairment group to the normal renal function group will be presented as geometric mean, its ratio and 90% CI.

The renal functional measure eGFR calculated according to MDRD formula will be listed for each patient,and summarized by renal impairment group. The relationship between eGFR and selected PK parameters (e.g., AUC_{0-24}, C_{max}, AUC_{0-24u} or C_{maxu}) may be explored graphically as appropriate.

The relationship between PK parameters and renal function [creatinine clearance (CL_{CR})] will be determined by a linear regression model. CL_{CR} values on Day 22 (steady-state) will be used for the PK regression analysis.

Linear regression will be used to analyze the potential relationship between appropriate PK parameters (AUC_{0-24}, CL/F AUC_{0-24u} and CL_u/F) and renal function (CL_{CR}). Estimates of the slope and, intercept, together with their precision (90% CI), and the coefficient of determination will be obtained from the model.

Plots of PK parameters (AUC_{0-24}, CL/F AUC_{0-24u} and CL_u/F) versus renal function (CL_{CR} on Day 22 measurement) will be constructed. A regression line and 90% confidence region for the PK parameters and CL_{CR} will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify subjects from different renal function groups.

4.8 Efficacy Analysis

No efficacy analysis is planned in this study.

4.9 Safety Analysis

Safety evaluations will be based on the incidence, intensity, and relatedness of adverse events (AEs), physical examination findings, study discontinuation information, clinical laboratory tests, ECG, ECOG and vital signs.

Safety variables will be tabulated and presented for all patients in the Safety Population. Adverse events will be summarized by MedDRA system organ class, preferred term and renal impairment group; physical examination will be listed; and change from baseline in clinical laboratory parameters and shifts in toxicity of lab parameters, liver function test elevations, ECG and vital signs parameters will be summarized by renal impairment group.

4.9.1 Study Product Exposure/Administration

Study drug exposure/administration will be listed by patient and renal impairment group, indicating dose date and time and administration start and end dates. Any deviations will be documented. Duration of treatment or duration of exposure, cumulative dose and relative dose intensity will be summarized by renal impairment group using the safety population.

4.9.2 Adverse Events

AEs are collected from first dose of study drug until the Safety Follow-Up Visit (30 days after the last dose of study drug), or before initiation of any new anticancer therapy or enrollment into the talazoparib open-label extension study. Serious AEs (SAEs) will be

collected from the time the patient signs the Patient Informed Consent Form until the end of study visit. All AEs will be coded and classified according to MedDRA (Version 19.1). The intensity of adverse events is judged by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (death) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03, and the relationship to study drug is judged by the investigator as probable, possible or not related. Adverse events occurring prior to the date and time of first dose of study drug are considered non-treatment emergent events. Events occurring after the date and time of the first dose of study drug up to 30 days following the last dose of study drug are considered treatment emergent AEs (TEAEs).

All TEAEs will be summarized as the number and percentage of patients by System Organ Class, Preferred Term and renal impairment group. Separate summaries will be created by severity and by relationship to study drug. If the same AE (preferred term) is reported more than once for the same patient, it will only be counted once in the summary table. For summary tables by severity and relationship to study drug, if the same AE (preferred term) is reported more than once for the same patient, the highest severity grade or the strongest relationship to treatment (probable > possible > not related) will be counted in the summary table.

All AEs will be listed, and a flag will indicate if the AE is treatment emergent or not.

All SAEs will be listed, and a flag will indicate if the SAE is treatment emergent or not.

All AEs and SAEs leading to temporary and permanent study drug discontinuation will be listed by patient.

All death will be displayed by patient.

4.9.3 Clinical Laboratory Assessments

Clinical laboratory parameters, including hematology, coagulation, blood chemistry, urinalysis and urine culture evaluations will be performed at the screening visit, enrollment visit, on Day 8, Day 15 and Day 22 post-dose, and at the safety follow up visit (i.e. end of study visit).

Clinical laboratory test parameters, with associated reference ranges provided by the laboratory, will be listed for individual patients. Clinical laboratory test results outside the laboratory's reference ranges will be flagged with "L" for low and "H" for high. Observed values and change from baseline to each visit will be summarized by renal impairment group at screening/pre-dose (baseline), along visits and at the safety follow up visit**.** Baseline is defined as the last measurement prior to study drug treatment. The toxicity of laboratory parameters will be graded as 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening) or 5 (death) according to the NCI CTCAE v4.03. Shifts in toxicity from

baseline to maximum post-baseline results of laboratory parameters and liver function test elevations will be summarized by renal impairment group.

4.9.4 Vital Signs Assessments

Evaluation of vital signs, including blood pressure, pulse rate, respiratory rate, and weight will be performed at the screening visit, enrollment visit, on Day 8, Day 15 and Day 22 post-dose, and at the safety follow up visit (i.e. end of study visit). Temperature will be performed at the screening visit, enrollment visit and at the safety follow up visit. Temperature will be listed by patient; other vital signs results will be listed for each patient, and summary statistics and change from baseline will be displayed by renal impairment group. Baseline is defined as the last measurement prior to study drug treatment.

4.9.5 Resting 12-Lead ECGs

All ECG results will be listed by patient, and ECGs and change from baseline will be summarized by renal impairment group. Baseline is defined as the average value of triplicate ECGs at pre-dose on Day 1.

The number (%) of subjects with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated by renal impairment group:

QTc	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

QTcF is recommended as the primary correction for QT interval evaluation. In the current study, QTcF will be reported as the primary QT interval correction. QTcB data will be provided for completion.

4.9.6 Physical Examinations

Physical examinations will be performed by qualified personnel at the screening visit, enrollment visit, on Day 8, Day 15 and Day 22 post-dose, and at the safety follow up visit. Physical examination completion (yes/no) will be listed by patient.

4.9.7 ECOG Performance Status

Assessment of ECOG performance status will be performed at the screening visit, pre-dose and the safety follow up visit. ECOG performance status assessment will be listed by patient.

4.10 Interim Analysis

No interim analyses are planned for this study.

4.11 Statistical Programming and Deliverables

All statistical analyses, tables and listings will be generated in SAS (version 9.3 or later) with appropriate documentation and programming validation. The table of contents of all tables, listings, and figures will be presented in a Tables, Listings and Figures shell supplemental document.

4.12 Changes to the Planned Analysis

Any deviation(s) of consequence from the SAP during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document, as appropriate.