Statistical Analysis Plan

Medivation Protocol No. MDV3800-02
CCI

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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 Hepatic Impairment

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Version 1.0	06 March 2017	PPD	N/A. This is the original SAP based on the final protocol dated August 9th, 2016.
Version 2.0	9 December 2019	PPD	Amended to include updates from Protocol Amendment (v5.0, September 14, 2018) and add details for planned analysis.

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Glossary and Abbreviations

Abbreviation	Term
$A_{e0-24}\%$	Amount of drug excreted in urine from time 0 to 24 hours expressed as percentage of administered dose
Ae_{0-24}	Amount of unchanged drug excreted into urine from 0 to 24 hours
AE	Adverse Event
ALT	Alanine Aminotransferase/GPT
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
aPTT/PTT	(Activated) Partial Thromboplastin Time
AST	Aspartate Transaminase / GOT
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration time curve from time 0 to 24 hours
AUC_{0-24u}	Area under the free concentration time curve from 0 to 24 hours Unbound AUC_{0-24}
BMI	Body mass index
BQL	Below Quantification Limit
BUN	Blood Urea Nitrogen
C_{0-12ur}	Drug concentration in urine from time 0 to 12 hours
$C_{12-24ur}$	Drug concentration in urine from time 12 to 24 hours
CI	Confidence interval
CL_{CR}	Creatinine Clearance
CL/F	Apparent Oral Clearance
CL_r	Renal Clearance
CL_u/F	Unbound CL/F
cm	Centimeter
C_{max}	Maximum observed plasma concentration
C_{maxu}	Unbound C_{max}
C_{trough}	Plasma trough (pre-dose) concentration
C_{total}	Total plasma concentration of drug
$C_{unbound}$	unbound concentration of drug
CV	Coefficient of variation
D1	Day 1
D2	Day 22
DNA	Deoxyribonucleic acid
ECGs	Electrocardiograms
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 in plasma

Abbreviation	Term
Gamma GT	Gamma-glutamyl transferase or gamma-glutamyl transpeptidase
H or Hr.	Hour
HBsAg	Hepatitis B surface Antigen
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
INR/PT	International Normalized Ratio/Prothrombin time
kg	kilogram
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
m^2	Square meter
MAD	Maximum Administered Dose
Max	Maximum
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
Min	Minimum
mL	Milliliter
MDV3800	Talazoparib
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
ND	Not Done
NS	No Sample
PARP	Poly (ADP-ribose) polymerase
PK	Pharmacokinetic(s)
Rac	Accumulation ratio
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SFU	Safety Follow Up
$t_{1/2}$	Terminal half-life
TB	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings and Figures
T_{max}	Time to C_{max}
CCI	
ULN	Upper limit of normal
V_{0-12ur}	Urine volume from time zero to 12 hours
$V_{12-24ur}$	Urine volume from time 12 to 24 hours
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

Talazoparib (also known as BMN 673 and MDV3800) is a poly (ADP-ribose) polymerase (PARP) inhibitor being developed for the treatment of a variety of human cancers. 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 ($t\frac{1}{2}$) was approximately 89.8 hrs. Following repeated administration at 1 mg/day, the median talazoparib accumulation ratio (Rac) 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 1 mg, 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. Therefore, it seems that the drug is minimally metabolized in the liver following multiple dose intakes. However, the potential effect of hepatic impairment on human PK of talazoparib is not known as most clinical studies exclude patients with liver impairment.

This study is designed to provide pharmacokinetic and safety data following daily administration of talazoparib in cancer patients with varying degrees of hepatic impairment.

The study is carried out in patients with advanced solid tumors with normal liver function and with mild, moderate and severe hepatic dysfunction as classified using the National Cancer Institute Organ Dysfunction Working Group (per the NCI-ODWG) criteria. Based on the results of this study, talazoparib dosing recommendations for patients with impaired liver function may be provided to future treating clinicians.

The dose selected in this study is 0.5 mg/day which is considered a safe dose as it is lower than the Maximum Tolerated Dose (MTD) established in patients with normal hepatic function at 1 mg/day. Talazoparib has also shown clinical efficacy at this dose level in a phase 1 study. Talazoparib will be given for 22 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 or severe hepatic impairment on the pharmacokinetics of talazoparib following daily oral dosing of talazoparib for 22 calendar 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 hepatic 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 advanced solid tumors and impaired hepatic function.

Safety and PK data from patients with mild, moderate and severe hepatic impairment as classified using the NCI-ODWG criteria for hepatic impairment will be compared with a control group consisting of patients with normal hepatic function.

Patients will be assigned to one of four groups based on their hepatic function. Hepatic function defined for each group as per the NCI-ODWG classification is presented in Table 1.

Table 1.   Group Assignment

Group	Description	Patients*
A	**Control, normal hepatic function**: Total bilirubin (TB) and aspartate aminotransferase (AST) ≤ upper limit of normal (ULN)	6 (8)
B	**Mild hepatic dysfunction**: TB ≤ ULN and AST > ULN or TB >1.0 to 1.5 × ULN and any AST value	6 (8)
C	**Moderate hepatic dysfunction**: TB >1.5 to 3.0 × ULN and any AST value	6 (8)
D	**Severe hepatic dysfunction**: TB >3 × ULN and any AST value	6 (0)

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

Study periods include:

- Screening;

- Enrollment (D-1);

- A 22 day treatment period, and

- A safety follow up visit (also called as the End of Study visit) which will occur approximately 30 days (window -3/+10 days) after the last study drug administration or before initiation of a new anticancer therapy, or enrollment into the talazoparib open-label extension (OLE) study, whichever occurs first.

In each group, 6 patients will be treated with a daily oral dose of talazoparib 0.5 mg for at least 22 calendar days counted from Day 1 (date of first study drug administration). If treatment in the group of patients with severe hepatic dysfunction (Group D) is halted due to safety, 2 additional patients will be enrolled in each of Groups A, B and C (total of 8 PK evaluable patients in each group). Therefore, a total of at least 24 patients will be enrolled in the study.

3.1. PK Evaluable Patients

Patients will be considered **PK Evaluable** if they meet all the following criteria:

- Completed the Day 22 visit;

- Missed less than 5 consecutive doses;

- Received at least 10 consecutive days of 0.5 mg talazoparib daily dose immediately preceding D22 visit without dosing interruption;

- At least 85% of total plasma PK samples collection is reported.

Patients who discontinue the study before the completion of the Day 22 assessment and/or who do not meet the above-mentioned criteria may be replaced if needed, upon agreement of the Sponsor.

3.2. Collection of Plasma Concentration

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 (also called the End of Study visit) if the study treatment discontinues earlier than planned.

Blood samples for plasma protein binding evaluation will be collected on Day 1 and Day 22 (2h post-dose).

Urine samples for PK analyses will be collected as a single void at pre-dose on Day 1 and all urine voided after talazoparib dosing on Days 1 and 22 at the intervals of 0-12 hours and 12-24 hours.

The study schema is shown in Figure 1.

Figure 1.   Study Schema
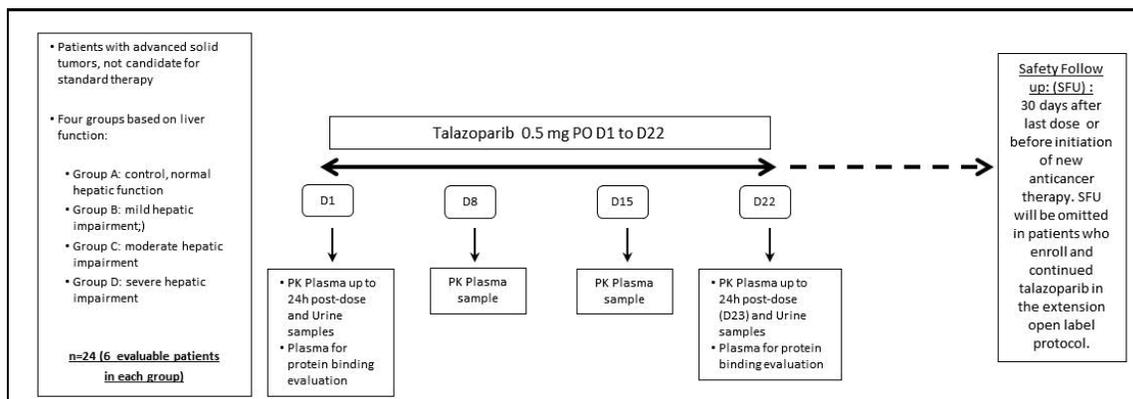
For a detailed description of study procedures, please refer to protocol Section 7 "STUDY VISITS AND ASSESSMENT.

3.3. Study Endpoints

3.3.1. Pharmacokinetic Endpoints

Primary Endpoints

Talazoparib plasma PK parameters: AUC_{0-24}, C_{max}, AUC_{0-24u}, and C_{maxu} at steady state (on Day 22).

Secondary Endpoints

Plasma talazoparib:

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

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

Additional PK parameters will be calculated as applicable.

3.3.2. 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 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 adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), laboratory assessments and Eastern Cooperative Oncology Group (ECOG) performance status.

3.4. Randomization

No randomization will be conducted in the study.

3.5. Sample Size Justification

Patients are assigned to one of four groups, based on hepatic function. The study will enroll 6 PK evaluable patients (evaluability criteria are included in Section 3) with advanced solid tumors per group. If enrollment for severe hepatic dysfunction group is halted due to safety, 2 additional evaluable patients will be enrolled in each of Groups A, B and C (total of 8 evaluable subjects in each group). Therefore at least 24 patients will be enrolled.

Non-evaluable patients may be replaced if needed upon agreement of the Sponsor.

3.6. Data Handling

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

3.6.1. Concentrations Below the Limit of Quantification

In all data presentations (except a few specific scenarios listed below), concentrations below the quantification limit (BQL) will be set to zero. In data listings, BQL values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification). In 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 "."

3.6.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if one 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 enough concern or a concentration has been flagged anomalous by the pharmacokinetics.

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

3.6.3. 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 (i.e., 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 treatment with ≥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 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: For consistency in presentation of data across clinical studies, talazoparib concentration values reported by the respective bioanalytical groups may be converted to other units in the listings. 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, except for 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 time parameters, 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.

4. DATA ANALYSIS

4.1. Analysis Populations

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

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

PK Parameter Analysis Population: All enrolled patients who receive at least 1 dose of talazoparib and who have at least 1 of the talazoparib PK parameters. This analysis population will be used for listings of talazoparib PK parameters for Day 1 and Day 22 and for the Day 1 summary tables and figures for single-dose talazoparib PK parameters.

PK Evaluable Analysis Population: All enrolled patients who meet the PK evaluability criteria listed in Section 3 and provide at least 1 of the talazoparib PK parameters of the primary interest from the Day 22 visit. This analysis population will be used for the summary tables and figures for multiple-dose talazoparib PK parameters.

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

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

4.2. Study Patients

Patient Disposition

Patient disposition will be summarized by hepatic impairment group using the number of enrolled patients. The number and percent of patients who complete and discontinue study will be included in this summary. Additionally, the number and percent of patients included in each analysis population listed in Section 4.1 will be provided. Number and percent of patients continuing open-label extension study will be provided as well.

Patients who fail the screening procedure and the reasons for screen failure will be listed. 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.

Key protocol deviations will be listed by patient and summarized by deviation category as per Pfizer CT40-GSOP.[1]

4.3. Patient Demographics

The demographic will consist of age, gender, race, ethnicity, height (cm), weight (kg), and BMI (kg/m^2). Demographic data analysis will be provided for Safety Population. Individual demographic data will be listed by hepatic impairment group and by patient and summarized by hepatic impairment group.

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. Baseline Definition

For laboratory and vital signs parameters, baseline is defined as the last value measured prior to the first dose of study drug.

For ECGs, baseline is defined as the average value of triplicate ECGs at pre-dose on Day 1.

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

4.5. 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 hepatic impairment group and will be listed by patient. Prior surgery and radiation therapy for cancer, and other procedures will be listed by patient.

4.6. 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 therapy includes any medication used by a patient from 28 days prior to enrollment until 30 days after the last dose of study drug or before initiation of a new

anticancer therapy (standard or investigational treatment) or the first day of OLE study whichever occurs first. Concomitant medications will be those that have a known end date after the first dose of study drug or have a missing end date (Appendix 1: Imputation rules for missing CM dates). 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 will be summarized by hepatic impairment group.

4.7. 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 hepatic impairment group.

4.8. Pharmacokinetic Analysis

4.8.1. 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 hepatic 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 provided as well.

- Summary of plasma concentrations and amount in urine will be presented by hepatic 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 hepatic group for Day 1 and Day 22 (each group on the separate page) in both linear and semi-logarithmic scales.

- Median plasma concentrations time plot (on both linear and semi-log scales) against nominal time postdose by hepatic function groups will be generated for Day 1 and Day 22. All hepatic function groups medians will be presented on the same plot.

- Similarly, arithmetic mean plasma concentrations time plot (on both linear and semi-log scales) against nominal time postdose by hepatic function groups will be generated for Day 1 and Day 22. All hepatic function groups means will be presented on the same plot.

- Unbound fractions (f_u) will be listed and summarized descriptively by hepatic function group.

Care must be taken to ensure that imputed concentrations are only used for the calculation of AUC_{0-24}, AUC_{0-24u}, and C_{trough} PK parameters on Day 22 and are not mistakenly included in any listings, tables, or figures of reported concentrations.

4.8.2. Pharmacokinetic Parameters

PK parameters for talazoparib will be derived for patients in the PK Parameter and PK Evaluable Analysis Population using a non-compartmental model with WinNonlin (Version 6.3 or higher). The following PK parameters will be derived, as applicable (Table 2).

Table 2.   PK Parameters

Parameter	Description	Calculation	Single Dose	Multiple Dose
Ae_{0-24}	Amount of drug excreted in urine from time 0 to 24 hours	$Ae_{0-24} = C_{0-12ur} \cdot V_{0-12ur} + C_{12-24ur} \cdot V_{12-24ur}$	X	X
$Ae_{0-24}\%$	Amount of drug excreted in urine from time 0 to 24 hours expressed as percentage of administered dose	$Ae_{0-24}\% = 100 \cdot Ae_{0-24}/Dose$	X	X
AUC_{0-24}	Area under the free concentration time curve from 0 to 24 hours	By linear trapezoidal rule during the ascending phase and log trapezoidal rule during the descending phase	X	X
AUC_{0-24u}	Unbound AUC_{0-24}	$AUC_{0-24u} = f_u \cdot AUC_{0-24}$	X	X
C_{max}	Maximum observed plasma concentration	Observed data	X	X
C_{maxu}	Unbound C_{max}	$C_{maxu} = f_u \cdot C_{max}$	X	X
C_{trough}[a]	Predose plasma concentration that meet acceptance criteria[a]	Observed data		X
CL/F	Apparent clearance of the drug from plasma after oral administration	$CL/F = Dose/AUC_{0-24}$		X
CL_u/F	Unbound CL/F	$CL_u/F = Dose/AUC_{0-24u}$		X
CL_r	Renal clearance	$CL_r = Ae_{0-24}/AUC_{0-24}$		X
f_u	Fraction of unbound drug	Obtained from measurement of protein binding	X	X
R_{ac}	Accumulation ratio	$R_{ac} = AUC_{0-24} (Day 22)/ AUC_{0-24} (Day 1)$		X
T_{max}	Time of C_{max}	Observed data	X	X

			Single	Multiple
Parameter	Description	Calculation	Dose	Dose

a. Acceptance criteria for C_{trough} on Day 15 and Day 22: received 10 consecutive days of dosing immediately before PK sampling day; Sample drawn within 24 ±2 hrs of the previous dose, and not more than +10 min after the drug administration on the PK collection day. C_{trough} on Day 8: received 7 consecutive days of dosing immediately before PK sampling day; Sample drawn within 24 ±2 hrs of the previous dose, and not more than +10 min after the drug administration on the PK collection day.

Additional PK parameters will be calculated as applicable.

At the discretion of the clinical pharmacologist, missing pre-dose PK sample collections on Day 22 may be imputed from the 24-hour PK sample collections on Day 22 (and vice versa) when a 24-hour sample is present but the pre-dose sample is missing (and vice versa), when steady-state conditions can be assumed, for the purposes of calculating and reporting Day 22 C_{trough}, AUC_{0-24} and AUC_{0-24u}.

Individual plasma and urine PK parameters will be listed (PK Parameter Population) and summarized by hepatic group for Day 1 (PK Parameter Population) and Day 22 (PK Evaluable Population).

PK parameters of talazoparib (T_{max} excluded) will be summarized using arithmetic mean, standard deviation and %CV, geometric mean, geometric %CV, minimum, median, and maximum value. For T_{max} values, 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} (Day 1 (PK Parameter Analysis Population) and Day 22 (PK Evaluable Population)) against hepatic function group will be generated and overlaid with geometric means.

For each hepatic function group, spaghetti plots for individual C_{trough} concentrations against Day 8, Day 15 and Day 22 (X-axis) will be generated. These plots will include only subjects in the PK Evaluable Population with all three C_{trough} collections.

4.8.3. Comparative Analyses of PK Parameters

PK parameters AUC_{0-24}, C_{max}, AUC_{0-24u}, and C_{maxu} on Day 1(PK Parameter Population) and Day 22 (PK Evaluable population) will be natural log-transformed and analyzed using an analysis of variance (ANOVA) model with group as a fixed effect to compare each hepatic impairment group (mild, moderate or severe; Test) with the normal hepatic function group (Reference). Additional analysis will be conducted using an analysis of covariance (ANCOVA) model with hepatic function group as a fixed effect and weight and age as covariates (at the significance level of 0.05). Estimates of the adjusted mean differences (Test/Reference) and corresponding 90% confidence intervals for all listed above PK

parameters will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

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

Exploratory ANOVA/ANCOVA analysis of log transformed PK parameters (AUC_{0-24}, C_{max}, AUC_{0-24u}, and C_{maxu}) Day 1 (PK Parameter Population) and Day 22 (PK Evaluable Population) using hepatic impairment group classified by Child-Pugh Scores may be performed.

The relationship between hepatic functional measures (eg, TB and AST) and selected PK parameters (eg, AUC_{0-24}, C_{max}, AUC_{0-24u} or C_{maxu}) on Day 22 (PK Evaluable Population) may be explored as appropriate.

4.9. Efficacy Analysis

No efficacy analysis is planned in this study.

4.10. Safety Analysis

Safety evaluations will be based on the incidence, intensity, and relatedness of adverse events (AEs), physical examination findings (captured as AEs), 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.

4.10.1. Study Product Exposure/Administration

Study drug exposure/administration will be listed by hepatic impairment group and patient, 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 hepatic impairment group using the Safety Population.

4.10.2. 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, maximum CTCAE grade, and hepatic impairment group. Separate summaries will be created for treatment-emergent treatment related AEs. 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 leading to temporary and permanent study drug discontinuation will be listed by patient.

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

Imputation rules for missing AE dates are included in the Appendix 1.

All death will be displayed by patient.

4.10.3. 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 (ie, end of study visit).

Clinical laboratory test parameters, with associated reference ranges provided by the laboratory, will be listed for individual patients by hepatic group. Clinical laboratory test results outside the laboratory's reference ranges will be flagged with "L" for low and "H" for high. Observed values and changes from baseline visit will be summarized by hepatic impairment group and visit.

Shifts in toxicity from baseline to maximum post-baseline results of laboratory parameters and liver function test elevations will be summarized by hepatic impairment group. 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.

4.10.4. 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 (ie, 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 hepatic group and patient. Other vital signs results will be listed by hepatic impairment group and patient. Summary statistics for observed values and changes from baseline will be displayed by hepatic impairment group and visit.

4.10.5. Resting 12-Lead ECGs

All ECG results will be listed by hepatic impairment group and patient. Observed values and changes from baseline will be summarized by hepatic impairment group and visit.

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

QTc	Borderline (msec)	Prolonged (msec)
Absolute Value	$\geq$450 - <480	$\geq$480
Absolute Change	30-<60	$\geq$60

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

4.10.6. 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.

4.10.7. 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 hepatic impairment group and patient and summarized by hepatic impairment group and visit.

4.11. Interim Analysis

No formal interim analyses are planned for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the study for the purpose of safety and pharmacokinetics assessment and/or supporting clinical development.

4.12. Statistical Programming and Deliverables

All statistical analyses, tables and listings will be generated using SAS (version 9.3 or later) with appropriate documentation and programming validation. Supplemental document will include table of contents of all tables, listings, and figures along with Tables, Listings and Figures shells.

4.13. Changes to the Planned Analysis

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

5. REFERENCES

1.   CT-40 GCSOP Clinical and Medical Controlled Document (Cmcd) Standard Operating
      Procedure.

Appendix 1. Table 1

Domain	Dataset	Label	Imputation Rule
Concomitant Medications	ADCM	Analysis Start Date	Numeric date derived from CM.CMSTDTC. 1. If CM start day is missing and CM start month and year are not missing: if CM start year is the same as the first dose year and CM start month is the same as first dose month, then impute CM start day using the day of first dose. If this leads to a date after the CM end date, use CM end date instead. Otherwise impute the CM start day using the first day of the month. 2. If CM start month is missing and CM start year is not missing: If CM start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the CM end date, use CM end date instead.If CM start year is different from the first dsoe year, use 01 January. 3. If CM start year is missing: impute CM start date using the day of first dose. If this leads to a date after the CM end date, use CM end date instead.
Concomitant Medications	ADCM	Analysis End Date	Numeric date derived from CM.CMENDTC. 1. If end day is missing, and end month and year are not missing: impute the end date using the last day of the month. 2. If end month is missing, and end year is not missing: impute the end date using 31 December as the day and month. 3. If end year is missing and the medication is a prior medication, then impute the end date using the first dose intake date - 1. If the medication is a concomitant medication, then impute end date using the end of follow up date.

Adverse Event	ADAE	Analysis Start Date	Numeric date derived from AE.AESTDTC.
			1. Missing day only:
			  - If the year and the month were same as the year and month of first dosing date,
			    then the day of the first dosing date was assigned to the missing day.
			  - If the year and the month were before the year and month of first dosing date,
			    then the last day of the month was assigned to the missing day.
			  - If the year and the month were after the year and month of first dosing date,
			    then the first day of the month was assigned to the missing day.
			2. Missing day and month or missing month only:
			  -If the year was the same as the year of first dosing date,
			    then the day and month of the first dosing date were assigned to the missing fields.
			  -If the year was prior to the year of first dosing date, then December 31 was assigned to the missing fields.

			-If the year was after the year of first dosing date, then January 1 was assigned to the missing fields. 3. Missing year: -If the year was missing, the onset date was set to the first dosing date, even if the day and month were present. 4. If the imputed AE start date was later than the reported AE stop date, the imputed AE start date was equal to the reported AE stop date.
Adverse Event	ADAE	Analysis End Date	Numeric date derived from AE.AEENDTC. 1. Missing day only: The last day of the month was assigned to the missing day. 2. Missing day and month or missing month only: December 31 was assigned to the missing fields. 3. Missing year: If the year was missing, the stop date was set to the study completion/discontinuation date.