Statistical Analysis Plan

Sponsor:	Medivation, Inc., a wholly owned subsidiary of Pfizer Inc
Protocol No:	MDV3800-03 (C3441003)
Project ID:	MVE010PC-160106
Protocol Title:	A Phase 1 Open-Label Study of ^{14}C-Labeled Talazoparib in Patients With Advanced Solid Tumors
Version Date:	16-Jun-2017

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	PPD PhD PPD Clinical Pharmacology & DMPK
Signature of Sponsor Representative / Date:	PPD
Name of Sponsor Representative / Title:	PPD PhD PPD Biostatistics
Signature of Sponsor Representative / Date:	PPD PPD
Name of Author / Title:	PPD PPD of Data Services
Signature of Author / Date:	PPD

2.0 Table of Contents

Contents

3.0 Introduction

This [redacted]cal Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Medivation, Inc., a wholly owned subsidiary of Pfizer Inc., Protocol MDV3800-03 (C3441003).

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol 3.0 dated 07-Oct-2016 (including all amendments up to this protocol date) and the final CRF(s) dated 04-Jan-2017.

An approved and signed SAP is a requirement for database lock.

This SAP only covers the results that will be processed by the [redacted] Biostatistics Department.

[redacted] will perform the Pharmacokinetic (PK), and Safety evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in section 9.8.2 of the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 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 and PK of talazoparib and/or potential metabolites.

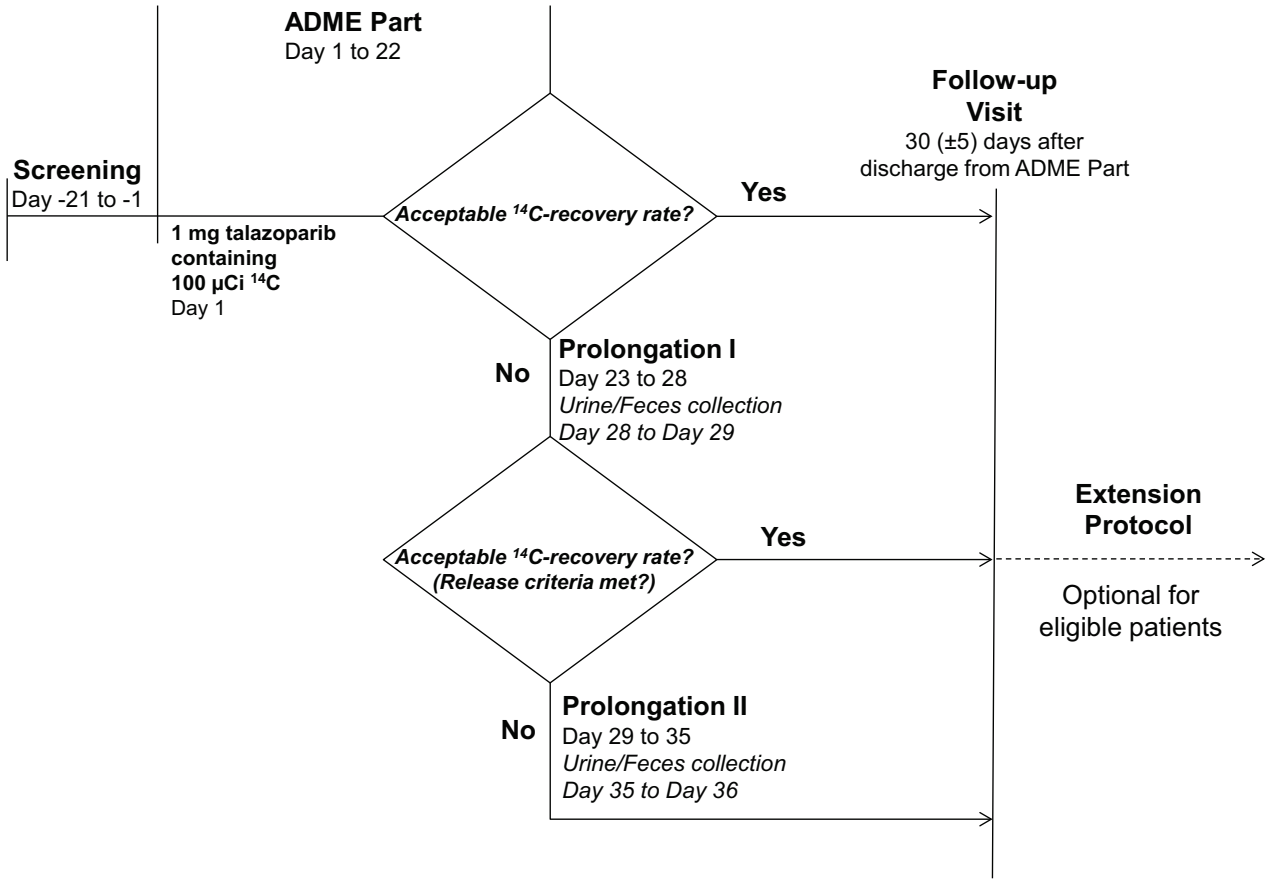
5.2 Secondary

- 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.

6.0 Study Design

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 containing 100 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



6.1 Sample Size Considerations

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.

6.2 Randomization

This is a nonrandomized study.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

There will be no interim analyses or summaries of data provided prior to the delivery of the full set of TFLs.

7.3 Final Analysis

Draft TFLs will be provided prior to database lock (DBL). These TFL will be based on data as received so far, and might not be the final clean data. This set will serve to support data review, and comments might be provided to the [redacted] team prior to DBL.

After DBL, draft TFL will be sent for review again which will be based on final data. After final comments have been incorporated, the TFLs will be finalized and incorporated in the first Draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the [redacted] Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. Database will not be locked until the identified issues are resolved. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters and summary statistics, with the exception of t_{max} (2 decimal places), and CV% and N which will be whole numbers (0 decimal places).

For all summaries, the mean and median will be presented to one decimal place greater than the data, standard deviation to two greater than the data, and the minimum and maximum will be presented to the same number of decimal places as the data. Frequency percentages will be presented with one decimal.

9.1.2 Imputation

Unless otherwise noted data will not be imputed.

9.1.3 Descriptive Statistics

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. Percentages by categories will be based on the number of subjects exposed.

For categorical data the categories will be presented in the tables exactly as they appear in the CRF / Database. No data manipulation will be done for presentation purposes.

9.1.4 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the study drug administration. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping Definition

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.

No subject grouping will be performed.

9.2.3 Other Definitions

Variable	Dataset	Definition/Calculation	Note
Change from Baseline	All	Post-dose Observation minus Baseline Observation	
Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date	
Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1	
TEAE	AE	AE is a TEAE if the AE Date/Time is greater than the Dose Date/Time	

9.2.4 ADaM Datasets

The following Analysis Data Model (ADaM) datasets will be programmed to support TFL output:

ADSL: subject level analysis dataset

ADEX: exposure analysis dataset

ADAE: adverse event analysis dataset

ADPC: pharmacokinetic concentration analysis dataset

ADPP: pharmacokinetic parameter analysis dataset

ADEG: ECG analysis dataset

ADLB: laboratory analysis dataset

ADVS: vital signs analysis dataset

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® version 6.3 or higher (Pharsight, Inc.).

PK computations or summaries may also be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the Pfizer CSR template. The layout of Tables, Figures and Listings (TFLs) will be according to the [redacted] standards.

Table shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the [redacted] project statistician. Other changes to the shells may be out of scope. The TFLs will be provided in rtf format, individual files for each table, figure or listing compiled to one Word document.

10.0 Analysis Sets

Analyses	Safety population	PK population	PK analysis population
Disposition Summaries	✓		
Safety Assessments	✓		
Baseline Characteristics	✓		
PK Concentrations		✓	
PK Parameters			✓

10.1 Safety population

The safety population set will consist of all subjects who have received at least 1 dose of talazoparib. This set will be used for the safety data summaries, and baseline characteristic summaries.

10.2 Pharmacokinetic

10.2.1 PK population (PK)

The PK population was defined as all patients who receive talazoparib and have at least 1 sample with sufficient concentration data.

10.2.2 PK analysis population (PK Analysis)

The PK analysis population was defined as all patients who had sufficient concentration data to derive at least 1 PK parameter.

11.0 Subject Disposition

The number and percentage of subjects dosed, and members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

12.0 Protocol Deviations

Protocol deviations will be listed.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Subject demographics will be summarized descriptively for all subjects. The summary will include the subjects' age at informed consent (in years), gender, race, ethnicity, weight (in kg) at baseline, height (in cm), and BMI (in kg/m^2) at baseline. Demographics will be summarized for the safety set.

13.2 Medical History

Medical history will be listed.

13.3 Other Baseline Characteristics

ECOG performance status will be listed.

Childbearing potential will be listed.

Estimated glomerular filtration rate will be listed.

The results of drug and alcohol screen will be listed.

14.0 Prior and Concomitant Medications

Prior and concomitant medication will be listed. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If a partial date allows a medication to be considered concomitant it will be categorized as such.

15.0 Treatment Compliance and Exposure

Exposure data will be listed.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

- Plasma concentration of talazoparib and potential metabolites
- ^{14}C-Radioactivity concentration in plasma and whole blood (ng eq/mL)
- PK parameters for Talazoparib or metabolites (if applicable) and ^{14}C-radioactivity in plasma and whole blood
- Amount of ^{14}C-radioactivity excreted in urine (% of dose), and amount of ^{14}C-radioactivity excreted in feces (% of dose)
- Amount of ^{14}C-radioactivity excreted in vomitus (% of dose), if applicable
- Recovery of ^{14}C-radioactivity as a percentage of the administered dose

Plasma and Whole Blood (LC/MS method and radioactivity count)

As appropriate, the PK parameters will be calculated as data allows for talazoparib and/or metabolite concentrations in plasma by LC/MS and for radioactivity data in plasma and whole blood (i.e., nanogram equivalents from radioactivity) using noncompartmental approaches. PK variables will be computed using WinNonlin. The definition for each PK parameter is listed in the following tables. Actual elapsed sampling times relative to [^{14}C]-talazoparib (100 µCi) oral administration will be used for the estimation of PK metrics.

Parameter	Analyte/Specimen	Description	SAS Programming Notes
C_{max}	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Maximum {plasma / whole blood} concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.	Cmax from WNL
T_{max}	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Time to maximum {plasma / whole blood} concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL
$AUC_{0\text{-last}}$	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Area under the concentration-time curve (time 0 to time of last quantifiable concentration) using linear up/log down method.	AUClast from WNL
$AUC_{0\text{-inf}}$	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Area under the serum concentration-time curve (time 0 to infinity) using linear up/log down method. Percent extrapolation less than or equal to 20% is required to retain AUCinf.	AUCINF_obs from WNL If AUC_%Extrap_obs >20% then parameter is flagged
%AUC	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Percentage of estimated part for the calculation of AUC.	AUC_%Extrap_obs from WNL
λ_z	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three points and an r^2 greater than 0.80 are required to retain λz.	Lambda_z from WNL If Rsq ≤ .80 then parameter is flagged
$t_{1/2}$	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Terminal phase half-life, calculated as ln(2)/ λz , expressed in time units. Percent extrapolation less than or equal to 20% and r2 greater than 0.80 is required to retain t1/2.	HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .80 then parameter is flagged

Parameter	Analyte/Specimen	Description	SAS Programming Notes
CL/F	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Apparent total plasma or serum clearance of drug after oral administration	CL_F_obs from WNL, ($Dose_{po}/AUC_{0-inf}$). If AUC_%Extrap_obs >20%, then parameter is flagged
V_d/F	talazoparib/Plasma, total ^{14}C/Plasma, total ^{14}C/Blood	Apparent volume of distribution during terminal phase after oral / extravascular administration	Vz_F_obs from WNL

Urine and Feces:

The following parameters will be calculated as data allows from individual urine and feces concentration of talazoparib and/or metabolites by LC/MS method and radioactivity counts in urine and feces (i.e., nanogram equivalents from radioactivity counts) using non-compartmental approaches. PK variables will be computed using SAS.

Urine

Parameter	Analyte/Specimen	Description	SAS Programming Notes
Ae_{t1-t2}	talazoparib/Urine, total ^{14}C/Urine	Amount excreted into urine during each collection interval (t1-t2). Calculated by multiplying the concentration by the volume collected for each interval.	Concentration $(ng/mL)_{ti-t2}$*$volume(mL)_{t1-t2}$
f_e/f_{t1-t2}	talazoparib/Urine, total ^{14}C/Urine	Fraction of orally administered drug excreted into urine over the collection interval	Ae_{t1-t2} /dose(mg)
Ae_{0-t}	talazoparib/Urine, total ^{14}C/Urine	Total amount of drug excreted into urine to time t, obtained by adding the amounts excreted over each collection interval.	Summation $_{t1-tn}$(Concentration $(ng/mL)_{ti-t2}$*$volume(mL)_{t1-t2}$)
F_e/f	talazoparib/Urine, total ^{14}C/Urine	Fraction (%) of the administered dose excreted into urine.	Ae_{0-t}/dose(mg)*100
CLr	talazoparib/Urine	Renal clearance of unchanged talazoparib	Quotient of the cumulative urinary excretion of the unchanged drug up to time t of last sample; CLr= Ae_{0-t} / AUC_{0-last}

Feces

Parameter	Analyte/Specimen	Description	SAS Programming Notes
Ae_{t1-t2}	talazoparib/Feces, total ^{14}C/ Feces	Amount excreted into feces during each collection interval (t1-t2). Calculated by multiplying the concentration by the weight collected for each interval.	Concentration $(ng/mL)_{ti-t2}$* $weight(mg)_{t1-t2}$
f_e/f_{t1-t2}	talazoparib/Feces, total ^{14}C/ Feces	Fraction of orally administered drug excreted into feces over the collection interval	Ae_{t1-t2} /dose(mg)
Ae_{0-t}	talazoparib/Feces, total ^{14}C/ Feces	Total amount of drug excreted into feces to time t, obtained by adding the amounts excreted over each collection interval.	Summation $_{t1-tn}$(Concentration $(ng/mL)_{ti-t2}$* $weight(mg)_{t1-t2}$)
F_e/f	talazoparib/Feces, total ^{14}C/ Feces	Fraction (%) of the administered dose excreted into feces.	Ae_{0-t}/dose(mg)*100

16.2 Pharmacokinetic Concentrations

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 tabulated and presented graphically.

The times courses of total radioactivity in urine and feces will be tabulated and presented graphically.

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 the lower limit of quantitation (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 arithmetic 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.

16.3 Pharmacokinetic Parameters

PK parameters of total radioactivity in whole blood and plasma and of talazoparib in plasma and of its metabolites (if applicable) 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. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled (nominal) time may be substituted in order to calculate the PK parameter.

Summary statistics and figures will be provided for the cumulative excretion of ^{14}C talazoparib and 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

$$X_e/X_b = 1-[C_p*(1-Hct)/C_b],$$

where X_e and X_b stand for amount of radioactivity in erythrocyte or plasma, respectively, and C_p and C_b 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 for Hct.

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.

17.0 Safety Analyses

17.1 Safety Variables

The following safety variables will be summarized:

- Adverse Events (AEs)
- Vital Signs, including weight
- Electrocardiograms (ECG)
- Clinical Laboratory Evaluations
- Physical Examination

17.1.1 Adverse Events

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

All AE summaries will include only treatment emergent adverse events. Treatment-emergent adverse events are those which occur after the first dose of study drug.

A breakdown of the number and percentage of subjects reporting each adverse event, categorized by system organ class and preferred term will be presented. Counting will be done by subject only, not by event; subjects will only be counted once within each system organ class or preferred term.

A summary of events reported, categorized by relationship to study drug, will be provided. Subjects with multiple events within a particular system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class or preferred term. Relationship to study drug is categorized as recorded on the CRF.

A summary of events reported, categorized by severity as recorded on CRF, will also be provided. Subjects with multiple events within a particular system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

A listing of adverse events leading to early discontinuation will be provided.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:00 for a start time and 23:59 for end times

- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date
- Missing AE start date will be assumed to be after treatment for the determination of TEAE

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events will be provided.

17.1.3 Laboratory Data

Clinical laboratory data will be presented using Système International (SI) units (also used in the SDTM Controlled Terminology).

All laboratory data will be listed with flagging of values outside the normal ranges. A separate listing, including clinically significant values outside of the standard reference ranges, will be prepared.

Hematology and serum chemistry values will be classified by severity using the CTCAE. Data will be summarized descriptively. Change from baseline in laboratory values will be tabulated. A Shift table showing number and percentage of maximum change from baseline (CTCAE grade) will be presented.

Pregnancy test results (Human Chorionic Gonadotropin - HCG) and hormone tests (Follicle Stimulating Hormone - FSH) will be listed.

17.1.4 Vital Signs

Descriptive statistics will be provided to summarize vital signs and changes from baseline at each scheduled time.

All Vital Signs, including repeats in response to abnormalities, will be listed. A flag for those values that are judged clinically significant will be included.

17.1.5 Electrocardiograms

Descriptive statistics will be provided to summarize ECG parameters and changes from baseline at scheduled time. A frequency table showing number and percentage of subjects falling in the following categories:

QT [ms], QTcF [ms] Interval:

- New absolute values >450, >480 and >500
- Changes from baseline >30 and >60

Heat Rate (HR) [bpm]:

- Decrease from baseline >25% and to a HR < 50
- Increase from baseline >25% and to a HR > 100

PR Interval [ms]:

- Increase from baseline >25% and to a value >200

QRS Duration [ms]:

- Increase from baseline >25% and to a value >100

ECG parameters and assessments will be listed. A flag for those values that are judged clinically significant will be included.

17.1.6 Physical Examinations

Physical examination assessments will be listed. A flag for those values that are judged clinically significant will be included.

References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A Phase 1 Open-Label Study of ^{14}C-Labeled Talazoparib in Patients With Advanced Solid Tumors. Version 3.0, Final, 07 Oct 2016.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBL	Database lock
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDS	Early Development Services
HCT	Hematocrit
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	Lower Limit of Quantification
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TFL(s)	Tables, Figures and Listings
WNL	WinNonlin

Appendix 2: 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																								

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▼																									
Serum chemistry	X	X		X[4]																				X	
Hematology	X	X		X[4]																				X	
Coagulation	X																								
Urinalysis	X	X		X[4]																				X	
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.

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 .

Table 1 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

Appendix 3: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	**Title**	**Population Set**
Disposition and Compliance		
Table 14.1.1	Summary of Subject Disposition	Safety
Table 14.1.2	Summary of Demographics and Baseline Characteristics	Safety
Pharmacokinetic and Radioactivity		
Table 14.2.1.1	Summary Pharmacokinetic Concentrations - Plasma	PK
Figure 14.2.1.2	Arithmetic Mean (±SD) Pharmacokinetic Concentrations (linear and semi-log scale)	PK
Figure 14.2.1.3	Individual Pharmacokinetic Concentrations (linear and semi-log scale)	PK
Table 14.2.2	Summary Radioactivity Concentrations - Plasma and Whole Blood	PK
Table 14.2.3.1	Summary of Pharmacokinetic Parameters-Plasma	PK Analysis
Table 14.2.3.2	Summary of Pharmacokinetic Parameters-Urine and Feces	PK Analysis
Table 14.2.3.3	Summary of Pharmacokinetic Parameters – Renal Clearance	PK Analysis
Table 14.2.3.4	Summary of Talazoparib Cumulative Recovery - Urine and Feces	PK Analysis
Table 14.2.4.1	Summary of Radioactivity Parameters - Plasma and Whole Blood	PK Analysis
Table 14.2.4.2	Summary of Radioactivity Parameters - Urine and Feces	PK Analysis
Table 14.2.4.3	Summary of Radioactivity Cumulative Recovery - Urine and Feces	PK Analysis
Figure 14.2.4.4	Arithmetic Mean (±SD) Cumulative Excretion	PK
Figure 14.2.4.5	Individual Cumulative Excretion	PK
Table 14.2.5.1	Summary Percentage of ^{14}C Radioactivity Associated with Erythrocytes in Whole Blood	PK
Figure 14.2.5.2	Arithmetic Mean (±SD) Percentage of ^{14}C Radioactivity Associated with Erythrocytes in Whole Blood	PK

Figure 14.2.5.3	Individual Percentage of ^{14}C Radioactivity Associated with Erythrocytes in Whole Blood	PK
Adverse Events		
Table 14.3.1.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Severity	Safety
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	Safety
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR	
Safety Assessments		
Table 14.3.4	Listing of Abnormal Laboratory Values	Safety
Table 14.3.5.1	Summary of Laboratory and Changes from Baseline	Safety
Table 14.3.5.2	Shift Table for Maximum (by CTCAE grade) Change from Baseline of Laboratory Values	Safety
Table 14.3.6	Summary of Vital Signs and Changes from Baseline	Safety
Table 14.3.7.1	Summary of 12-Lead Electrocardiogram Values and Changes from Baseline	Safety
Table 14.3.7.2	Frequency for Change Categories for 12-Lead Electrocardiogram	Safety

List of End of Text Listings:	
Output	**Title**
Disposition and Compliance	
Listing 16.2.1.1	Subject Disposition
Listing 16.2.1.2	Medical History
Listing 16.2.1.3	ECOG Performance Status
Listing 16.2.1.4	Childbearing Potential
Listing 16.2.1.5	Estimated Glomerular Filtration Rate
Listing 16.2.1.6	Drug Screen
Listing 16.2.1.7	Alcohol Breath Test

Listing 16.2.1.8	Prior and Concomitant Medications
Listing 16.2.2	Protocol Deviations
Listing 16.2.3	Analysis Sets
Listing 16.2.4	Subject Demographics
Exposure	
Listing 16.2.5	Study Drug Administration
Pharmacokinetic and Radioactivity	
Listing 16.2.6.1.1	Pharmacokinetic Concentrations - Plasma
Listing 16.2.6.1.2	Pharmacokinetic Concentrations and Parameters - Urine
Listing 16.2.6.1.3	Pharmacokinetic Concentrations and Parameters - Feces
Listing 16.2.6.2.1	Radioactivity Concentrations - Plasma and Whole Blood
Listing 16.2.6.2.2	Radioactivity Concentrations and Parameters - Urine
Listing 16.2.6.2.3	Radioactivity Concentrations and Parameters - Feces
Listing 16.2.6.3.1	Pharmacokinetic Parameters - Plasma
Listing 16.2.6.3.2	Pharmacokinetic Parameters – Urine and Feces
Listing 16.2.6.3.3	Talazoparib Cumulative Recovery - Urine and Feces
Listing 16.2.6.4.1	Radioactivity Parameters - Plasma and Whole Blood
Listing 16.2.6.4.2	Radioactivity Parameters – Urine and Feces
Listing 16.2.6.4.3	Radioactivity Cumulative Recovery - Urine and Feces
Listing 16.2.6.5.1	Individual and Mean Hematocrit
Listing 16.2.6.5.2	Radioactivity Associated with Erythrocytes in Whole Blood
Adverse Events	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Early Termination
Safety Assessments	
Listing 16.2.8.1	Clinical Laboratory Results – Hematology
Listing 16.2.8.2	Clinical Laboratory Results – Chemistry
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Pregnancy Test and Hormone
Listing 16.2.9	Vital Signs
Listing 16.2.10	12-Lead Electrocardiogram Results
Listing 16.2.11	Physical Examinations

Appendix 4: Shells for Post-Text Tables, Figures and Listings

Shells are provided in a separate document.

18.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
16-Jun-2017	PPD	