Statistical Analysis Plan

Sponsor:	Medivation, Inc., a wholly owned subsidiary of Pfizer Inc
Protocol No:	MDV3800-04
CCI Project ID:	MVE011PC-160116
Protocol Title:	A Phase 1 Open-Label, Two-Arm, Drug-Drug Interaction Study to Evaluate the Effect of Itraconazole and Rifampin on the Pharmacokinetics of Talazoparib in Patients With Advanced Solid Tumors
Version Date:	25 Jan 2018

1.0 Approvals

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

Name of Sponsor Representative / Title:	PPD MPH / Clinical Pharmacology Statistical PPD
Signature of Sponsor Representative / Date:	PPD
Name of Author / Title:	PPD of Data Services – Patient Pharmacology Services
Signature of Author / Date:	PPD

2.0 Table of Contents

3.0 Introduction

This Statistical 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 MDV3800-04.

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 amendment 2 (general) dated 21 Oct 2016 and the final CRF(s) dated 22 Sep 2016.

An approved and signed SAP is a requirement for database lock. This SAP only covers the results that will be processed by the CCI Early Development Services (EDS) Biostatistics Department.

CCI EDS will perform the Pharmacokinetic (PK) and Safety evaluations.

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 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 and Endpoints

5.1 Objectives

5.1.1 Primary Objectives

To assess the effect of P-gp inhibitor (itraconazole) and P-gp inducer (rifampin) on the single-dose PK of talazoparib in patients with advanced solid tumors

5.1.2 Secondary Objectives

To assess the safety and tolerability of a single dose of talazoparib with and without itraconazole or rifampin in patients with advanced solid tumors

5.2 Endpoints

5.2.1 Primary Endpoints

5.2.1.1 Primary PK Parameters

AUC_{inf}, AUC_{last}, C_{max}

5.2.2 Secondary Endpoints

5.2.2.1 Secondary PK Parameters

T_{max}, $T_{1/2}$, k_{el}, CL/F, and V_z/F

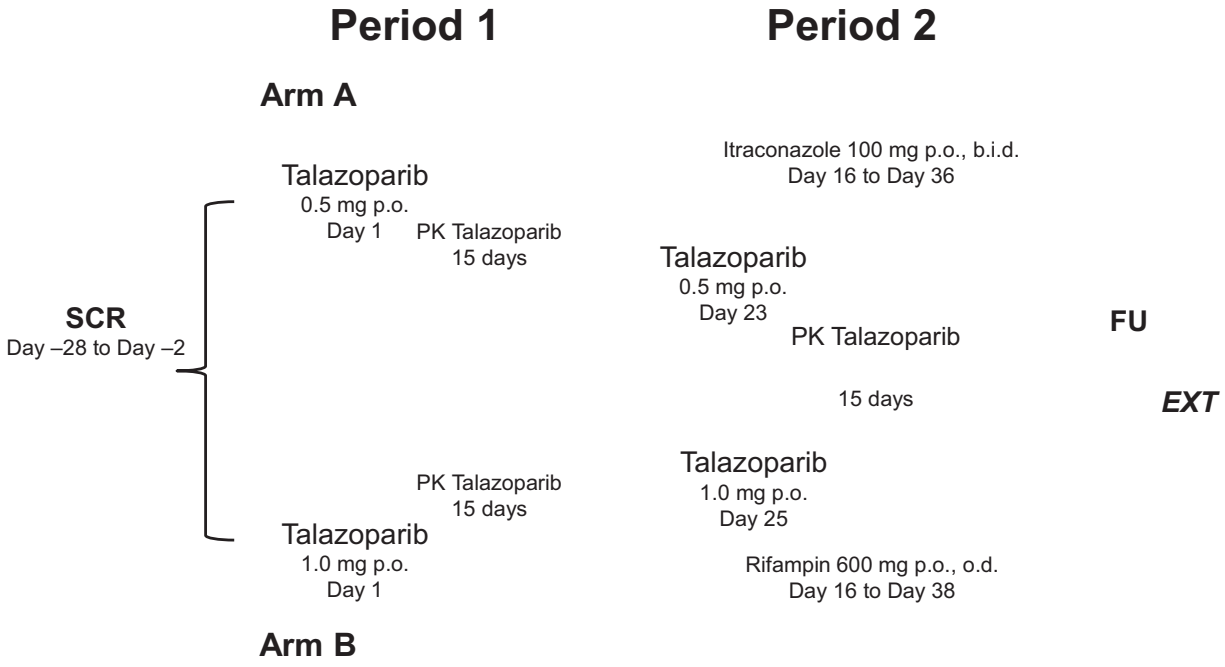
5.2.2.2 Safety Parameters

The safety variables to be measured include but are not limited to: AEs, Clinical laboratory assessments, Vital signs, ECG, Physical examination.

6.0 Study Design

This is a Phase 1, open-label, two-armed, fixed-sequence DDI study in patients with advanced solid tumors for the investigation of the effect of P-gp inhibition and induction on the PK of talazoparib.

Approximately a total of 36 subjects (~18 subjects per arm) are planned to receive a single oral dose of 0.5 mg (Arm A) or 1 mg (Arm B) talazoparib in Period 1 (Day 1 – 15) to assess the PK of talazoparib without P-gp modulation. In Period 2, subjects are planned receive either 100 mg oral itraconazole twice daily for 21 days (Arm A), or 600 mg oral rifampin daily for 23 days (Arm B), respectively. Subjects from the itraconazole arm (Arm A) will receive 0.5 mg talazoparib with the morning dose of the eighth day of itraconazole dosing. Likewise, subjects of the rifampin arm will receive 1.0 mg talazoparib on the tenth day of rifampin dosing. Itraconazole or rifampin will be taken 30 minutes before talazoparib.



6.1 Sample Size Considerations

Based on the population PK analysis, the intra-subject variability was estimated to be 42% in terms of percent coefficient of variation (%CV). With a sample size of 15 evaluable subjects, the precision or half width of 90% CI for Test Reference comparison on a log scale will be 0.259 from the observed difference in means. This calculation is based on an analysis of variance (ANOVA) model including effects of treatment and subjects nested within the sequence. When the true ratio is 1, the equivalence limits are 0.77 and 1.30. Eighteen subjects are planned to be enrolled in each treatment group to allow for 15% of incompletion or loss to follow up to allow for at least fifteen evaluable subjects per arm. Subjects who discontinue prior to completion of both periods may be replaced upon agreement of the Investigator and the Sponsor.

6.2 Randomization

Not applicable

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

Data from all patients for which PK parameters will be obtained will be included in PK Analysis population. Therefore definition of Pharmacokinetic Analysis Population is changed from

"All subjects who have receive 2 doses of talazoparib in Periods 1 and 2, and provide sufficient bioanalytical assessments to calculate reliable estimates of the PK parameters."

to;

"The Pharmacokinetic Analysis Population is defined as all subjects enrolled and treated who have at least 1 of the talazoparib PK parameters."

Additionally, since this is fixed sequence design study, linear mixed effects model that includes treatment as a fixed factor and subject as a random effect (instead of subject nested within sequence) will be fitted to the log transformed PK parameters (AUC_{inf}, AUC_{last} and Cmax).

7.2 Interim Analysis

There will be no formal interim analyses perform for this study. As this is an open label study, data along with Tables/Figures might be reviewed prior database lock.

7.3 Final Analysis

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

After DBL, draft TFL based on final data will be reviewed. 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 CCI 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 Bioanalytical Laboratories, 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.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

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
- Tmax, Tlag, 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.

9.1.2 Unscheduled Measurements

Unscheduled measurements will be included in the listings.

Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Grouping

For PK analysis, data will be grouped as follows: Arm A: talazoparib alone and talazoparib with itraconazole and for Arm B: talazoparib alone and talazoparib with rifampin.

Treatment emergent Adverse events (TEAEs), laboratory values and vital signs will be summarized by the last treatment received, i.e. “Treatment at onset” as follows:

Arm A

- Talazoparib only (Day 1-15)

- Itraconazole only (Day 16 – 22)
- Talazoparib + Itraconazole (Day 23 – end of study)

Arm B
- Talazoparib only (Day 1-15)
- Rifampin only (Day 16 – 24)
- Talazoparib + Rifampin (Day 25 – end of study)

Lab values and vital signs collected at Day 22 (Arm A) and Day 24 (Arm B) will be summarized under 'Talazoparib only'

9.2.2 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations within each period is defined as the last observation recorded before the first study drug administration in each period. In general, baseline is assessed at the day prior to talazoparib treatment. If assessments were taken at the day prior to dosing and predose at the dosing day, the average of all these scheduled measures will be taken for baseline. If a pre-treatment observation is missing in a given period then the screening value may be used.

9.2.3 Treatment Definition

Medication Scheme

	Arm A			Arm B		
Period	**Study day**	**Talazoparib (single dose)**	**Itraconazole (BID)**	**Study day**	**Talazoparib (single dose)**	**Rifampin (OD)**
1	**Day 1**	0.5 mg		Day 1	1 mg	
1	**Days 2-15**			Days 2-15		
NA	**Days 16-22**		100 mg	Days 16-24		600 mg
2	**Day 23**	0.5 mg	100 mg	Days 25	1 mg	600 mg
2	**Days 24-36**		100 mg	Days 26-38		600 mg

Note: OD = once daily, BID = twice daily

The following treatment labels will be used:

Pharmacokinetic Treatment Labels

Treatment Arm	Treatment	
A	'Talazoparib only'	'Talazoparib with Itraconazole'
B	'Talazoparib only'	'Talazoparib with Rifampin'

AEs and Safety Parameter Treatment Labels

Treatment Arm	Treatment		
A	'Talazoparib only'	'Itraconazole'	'Talazoparib with Itraconazole'
B	'Talazoparib only'	'Rifampin'	'Talazoparib with Rifampin'

9.2.4 Other Definitions

General definitions for variables as used in the text.

Change from baseline will be calculated for safety measures, see below.

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

9.2.5 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®.

PK parameter calculations will primarily be done using Phoenix® WinNonlin®.

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 CCI EDS 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. 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

10.1 Safety Population

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

10.2 Pharmacokinetic Population

All subjects who have received any dose of talazoparib and have at least one reportable concentration data.

10.3 PK Analysis Population

The Pharmacokinetic Analysis Population is defined as all subjects enrolled and treated who have at least one of the talazoparib PK parameters.

Analyses	Safety Population	Pharmacokinetic Population	PK Analysis Population
Disposition Summaries	✓		
Safety Assessments	✓		
Baseline Characteristics	✓		
PK Concentrations		✓	
PK Parameters			✓
Linear mixed effects model on primary PK parameters			✓

11.0 Subject Disposition

For each treatment arm, 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 and Violations

Protocol deviations/violations will be listed as per CTMS export. Further protocol deviations will be included in the CSR.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Subject demographics will be summarized descriptively for all subjects by treatment arm. 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 analysis set.

13.2 Medical History

Medical history will be listed by treatment arm.

13.3 Other Baseline Characteristics

Childbearing potential will be listed by treatment arm.

14.0 Prior and Concomitant Medications

Prior and concomitant medication will be listed by treatment arm. 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 by treatment arm.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

- Plasma concentration of talazoparib with and without itraconazole and rifampin, respectively.
- PK Parameters for talazoparib with and without itraconazole and rifampin, respectively

16.2 Pharmacokinetic Parameters

Subjects who experience events that may affect their PK profile (e.g. lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation of sampling time from the nominal time is of sufficient concern or if the concentration is anomalous for any other reason.

The following PK parameters will be calculated as data allows for talazoparib concentrations in plasma:

Primary:

Parameter	Description	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL
AUC_{last}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL
AUC_{inf}	Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% and an r^2 greater than 0.90 are required to retain	AUCINF_obs from WNL If AUC_%Extrap_obs

Parameter	Description	SAS Programming Notes
	AUC_{inf}.	>20% or Rsq ≤ .90 then parameter is deleted

Note: AUCs are calculated using linear up / log down, expressed in units of concentration x time.

Secondary:

Parameter	Description	SAS Programming Notes
T_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL
$T_{1/2}$	Terminal phase half-life expressed in time units. Percent extrapolation less than or equal to 20% and r^2 greater than 0.90 is required to retain $T_{1/2}$.	HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
CL/F	Apparent clearance Percent extrapolation less than or equal to 20% and r^2 greater than 0.90 is required to retain $T_{1/2}$.	CL_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
V_z/F	Apparent volume of distribution during terminal phase Percent extrapolation less than or equal to 20% and r^2 greater than 0.90 is required to retain $T_{1/2}$.	Vz_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted

Additional PK parameters (only in listings):

Parameter	Description	SAS Programming Notes
AUC_{extrap}%	Percentage of AUC_{inf} obtained by forward extrapolation.	AUC_%Extrap_obs from WNL
r^2	Goodness of fit statistic for the terminal phase rate constant (kel)	Rsq from WNL
k_{el}	Rate constant for terminal phase	Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
$k_{el, t(lo)}$	First time point value used in the calculation of k_{el}	Lambda_z_lower from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
$k_{el, t(hi)}$	Last time point value used in the calculation of k_{el}	Lambda_z_upper from WNL

Parameter	Description	SAS Programming Notes
		If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
$k_{el, t(n)}$	Number of time points used in the calculation of k_{el}	No_points_lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted

PK parameters for talazoparib with and without itraconazole/rifampin will be estimated using non-compartmental methods with WinNonlin®.

The PK parameters will be estimated from the concentration-time profiles for all PK population subjects.

In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be set to zero. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, may be set to missing at the discretion of the pharmacokineticist. 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 time may be substituted in order to calculate the PK parameter.

As appropriate, additional PK parameters may be calculated and reported.

16.3 Pharmacokinetic Concentrations

PK samples obtained beyond 10% of the planned time will be included in the listings and could be included in calculation of PK parameters (based on discretion of the pharmacokineticist), however, will be removed from figures and tables reporting mean concentrations per planned sampling times. Pre-dose PK samples collection should occur prior to administration of the investigational product on that day, otherwise will be excluded.

Concentrations Below the Limit of Quantification
In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

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 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.

Concentrations below the lower limit of quantitation (LLOQ) will be set to zero when calculating descriptive statistics. Zero concentrations will be considered as missing in geometric mean calculations.

Individual concentration vs time plots of talazoparib in plasma (using the actual sampling times) will be presented. Arithmetic mean (+/- SD), median and geometric mean concentration vs time curves of talazoparib in plasma (using the planned sampling times for mean plots) will be plotted using both linear and semi-logarithmic scale. Post-dose concentrations < LLOQ will be plotted as zero; pre-dose concentrations < LLOQ will be set to zero. Plots will overlay the treatments within a treatment arm. 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.

All individual subject plasma concentration data will be listed.

16.4 Statistical Summary, Analysis and Drug-Drug Interaction

Listings, figures and summaries will be provided by treatment within treatment arm.

16.4.1 Statistical Analysis of PK Parameters

Statistical analyses will be performed to assess the effect of steady-state itraconazole and rifampin on the PK of talazoparib using the treatment in combination with talazoparib as Test and the treatment with talazoparib only as reference.

Data for each treatment arm will be analyzed separately.

A linear mixed effects model that includes treatment as a fixed factor and subjects as a random factor will be fitted to the log transformed PK parameters (AUC_{inf}, AUC_{last} and C_{max}). A point estimate and the corresponding 90% CI for the difference between least squares means of Test and Reference treatment (Test – Reference) will be calculated. The antilogarithm of this value will be calculated to obtain the point estimate and the 90% CI for the ratio (Test/Reference) of the geometric means on the untransformed scale.

16.4.2 Summary Statistics of PK Parameters

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 parameters. The PK characteristics of T_{max} will be described utilizing the number of observations, minimum, maximum and median.

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

For primary parameters a listing of the individual subject ratios (Test/Reference) will be provided.

Box and whisker plots for individual subject primary parameters will be presented by treatment arm and treatment (separate plots for each treatment arm, both treatments on the same plot) and overlaid with geometric means.

16.4.3 Summary Statistics of Plasma Concentrations

Presentations of concentrations will include summary of concentrations by treatment and nominal time postdose, where the set of statistics will include arithmetic mean, standard deviation, CV, geometric mean, geometric CV, minimum, median, maximum, the number of observations (non-missing concentrations) and the number of observations above or equal to lower limit of quantification.

Summary statistics at a particular time point will not be presented if number of observations above or equal to lower limit of quantification equals 0.

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

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

All summaries will be by treatment within a treatment arm.

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.

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 by treatment at onset. 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.

A frequency table showing number and percentage of subjects falling outside normal ranges will be generated.

Hematology and serum chemistry values 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 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.

A frequency table showing number and percentage of subjects falling in the following categories will be generated:

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

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.

17.1.7 Other Observations Related to Safety

ECOG Performance Status will be listed.

Estimated glomerular filtration rate will be listed.

The results of drug and alcohol screen will be listed.

Weight, height and BMI will be listed.

18.0 References

Clinical Study Protocol. A Phase 1 Open-Label, Two-Arm, Drug-Drug Interaction Study to Evaluate the Effect of Itraconazole and Rifampin on the Pharmacokinetics of Talazoparib in Patients With Advanced Solid Tumors. Version 3.0, Final, 11 Oct 2016.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AUC	Area under the curve
BMI	Body Mass Index
BQL	Below the Quantifiable Limit
CL	Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of variation
DDI	Drug-Drug Interaction
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDS	Early Development Services
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	Lower Limit of Quantification
PK	Pharmacokinetic
QA'd	Quality Assured
QC'd	Quality Controlled
SAP	Statistical Analysis Plan
SDTM	Standard Data Tabulation Model
TEAE	Treatment-emergent Adverse Event
TFL(s)	Tables, Figures and Listings
WNL	WinNonlin

Appendix 2: Schedule of Assessments

Table 1 Schedule of Assessments Arm A (Itraconazole Arm)

	Screening	Baseline	Period 1														
Study Day►	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Ambulatory	X					X	X	X		X		X		X			X
Confinement		X	X	X	X												
Informed consent, SCR Number [1]	X																
ECOG assessment	X	X															
Tumor assessments	X																
Medical history	X	X															
Demographics	X																
Eligibility criteria / confirmation	X	X															
Enrollment		X															
Physical examination	X	X								X[2]							X[2]
Height	X																
Weight	X		X[3]														X
12-Lead ECG	X	X	X[4]														X
Vital signs[5]	X	X	X[4]	X	X					X							X
Adverse event review [6]			X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X[3]	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 [7]	X	X															
Follicle-stimulating hormone [8]	X																
Serum chemistry	X	X		X													X

Table 1 Schedule of Assessments Arm A (Itraconazole Arm)

	Screening	Baseline	Period 1														
Study Day►	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Hematology	X	X		X													X
Coagulation	X																
Urinalysis	X	X		X													X
eGFR Calculation [9]	X	X															
Blood sample for PK [10]			X	X	X	X	X	X		X		X		X			X

1 Informed consent can be obtained on a separate visit
2 Symptom-oriented physical examination
3 On Day 1 pre-dose
4 On Day 1, pre-dose and 2 hours post-dose. Pre-dose ECG is triplicate 1 – 2 minutes apart (all other ECG recordings are single)
5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest
6 SAE will be collected starting from informed consent signature of the subject; non-serious AEs will be collected following the first dose of study drug on Day 1.
7 Collect only for females of childbearing potential.
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 Calculation of the estimated glomerular filtration rate (eGFR) by MDRD equation.
10 For details see Table 3

SCR: screening; HIV: human immunodeficiency virus; PK: pharmacokinetics

Table 1 Schedule of Assessments Arm A (Itraconazole Arm) *continued*

	Period 2																	F/u[1]
Study Day►	16-21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Event▼																		
Ambulatory						X	X	X		X		X		X			X	X
Confinement		X	X	X	X													
Confirmation of eligibility		X																
Physical examination		X[2]								X[2]							X	
Weight			X[3]														X	
12-Lead ECG		X[4]	X[4]	X						X							X	
Vital signs[5]		X[3]	X[3]	X[3]	X[3]					X[3]							X	X
Adverse event review	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
Administer talazoparib			X															
Administer itraconazole	X	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry		X		X						X							X	X
Hematology		X		X													X	X
Urinalysis		X		X													X	X
Blood sample for PK[7]			X	X	X	X	X	X		X		X		X			X	

1 Follow-up visit 20±3 days after the last dose of itraconazole. In the event of early withdrawal of a subject, the follow-up contact should occur no sooner than 30 days after the last dose of talazoparib, unless the subject enrolls directly in the extension study, in which case the follow-up may occur earlier. If the subject is eligible to and chooses to participate in the separate open-label extension study and the screening for the open label extension study occurs within 30 days after the last dose of talazoparib, the follow up visit will not be required.

2 Symptom-oriented physical examination

3 Pre-dose

4 Triplicate ECG (1 to 2 minutes apart); before and 2.5 hours after itraconazole dose on Days 22 and 23 (all other ECG recordings are single in the morning at pre-dose, if applicable)

5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest

6 Itraconazole to be administered 30 minutes before talazoparib

7 For details see Table 3

F/u: follow-up; PK: pharmacokinetics

Table 2 Schedule of Assessments Arm B (Rifampin Arm)

	Screening	Baseline	Period 1														
Study Day►	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Ambulatory	X					X	X	X		X		X		X			X
Confinement		X	X	X	X												
Informed consent, SCR Number[1]	X																
ECOG assessment	X	X															
Tumor assessments	X																
Medical history	X	X															
Demographics	X																
Eligibility criteria / confirmation	X	X															
Enrollment		X															
Physical examination	X	X								X[2]							X[2]
Height	X																
Weight	X		X[3]														X
12-Lead electrocardiogram	X	X	X[4]														X
Vital signs[5]	X	X	X[4]	X	X					X							X
Adverse event review [6]			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
Administer talazoparib			X														
Alcohol breath test	X	X															
Urine drug screen	X	X															
Serology for HIV, hepatitis B and C	X																
Serum pregnancy test [7]	X	X															
Follicle-stimulating hormone [8]	X																
Serum chemistry	X	X		X													X
Hematology	X	X		X													X
Coagulation	X																

Table 2 Schedule of Assessments Arm B (Rifampin Arm)

	Screening	Baseline	Period 1														
Study Day►	–28 to –2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Event▼																	
Urinalysis	X	X		X													X
eGFR Calculation [9]	X	X															
Blood sample for PK [10]			X	X	X	X	X	X		X		X		X			X

1 Informed consent can be obtained on a separate visit
2 Symptom-oriented physical examination
3 On Day 1 pre-dose
4 On Day 1, pre-dose and 2 hours post-dose. Pre-dose ECG is triplicate 1 – 2 minutes apart (all other ECG recordings are single)
5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest
6 SAE will be collected starting from informed consent signature of the subject; non-serious AEs will be collected following the first dose of study drug on Day 1.
7 Collect only for females of childbearing potential.
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 Calculation of the estimated glomerular filtration rate (eGFR) by MDRD equation
10 For details see Table 3

SCR: screening; HIV: human immunodeficiency virus; PK: pharmacokinetics

Table 2 Schedule of Assessments Arm B (Rifampin Arm) ***continued***

	Period 2																	F/u[1]
Study Day►	16–23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	
Event▼																		
Ambulatory						X	X	X		X		X		X			X	X
Confinement		X	X	X	X													
Confirmation of eligibility		X																
Physical examination		X[2]								X[2]							X	
Weight			X[3]														X	
12-Lead electrocardiogram		X[4]	X[4]	X						X							X	
Vital signs[5]		X[3]	X[3]	X[3]	X[3]					X[3]							X	X
Adverse event review	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
Administer talazoparib			X															
Administer rifampin	X	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum chemistry		X		X													X	X
Hematology		X		X													X	X
Urinalysis		X		X													X	X
Blood sample for PK[7]			X	X	X	X	X	X		X		X		X			X	

1 Follow-up visit 20±3 days after the last dose of rifampin. In the event of early withdrawal of a subject, the follow-up contact should occur no sooner than 30 days after the last dose of talazoparib, unless the subject enrolls directly in the extension study, in which case the follow-up may occur earlier. If the subject is eligible to and chooses to participate in the separate open-label extension study, and the screening for the open label extension study occurs within 30 days after the last dose of talazoparib, the follow up visit will not be required

2 Symptom-oriented physical examination

3 Pre-dose

4 Triplicate ECG (1 to 2 minutes apart); before and 2.5 hours after rifampin dose on Days 24 and 25 (all other ECG recordings are single in the morning at pre-dose, if applicable).

5 Vital signs comprise supine blood pressure, heart rate, body temperature, respiratory rate after ≥5 minutes rest

6 Rifampin be administered 30 minutes before talazoparib

7 For details see Table 3

F/u, follow-up; PK, pharmacokinetic.

Talazoparib Pharmacokinetic Sampling Schedule

Sample collection time relative to talazoparib dosing				
Study Day				Time point
Period 1		Period 2		
Arm A	Arm B	Arm A	Arm B	
1		23	25	pre-dose
				+0.50 h
				+1 h
				+2 h
				+4 h
				+8 h
				+12 h
2		24	26	+24 h
3		25	27	+48 h
4		26	28	+72 h
5		27	29	+96 h
6		28	30	+120 h
7		29	31	
8		30	32	+168 h
9		31	33	
10		32	34	+216 h
11		33	35	
12		34	36	+264 h
13		35	37	
14		36	38	
15		37	39	+336 h

Appendix 3: List of End of Text Outputs

Output	Title	Population
	Disposition	
Table 14.1.1	Summary of Subject Disposition	Safety
	Demographics	
Table 14.1.2	Summary of Demographics and Baseline Characteristics	Safety
	Pharmacokinetics	
Table 14.2.1.1	Summary of Talazoparib Plasma Pharmacokinetic Concentrations	PK
Figure 14.2.1.2	Arithmetic Mean (±SD) Talazoparib Plasma Pharmacokinetic Concentrations (linear and semi-log scale)	PK Analysis
Figure 14.2.1.3	Geometric Mean Talazoparib Plasma Pharmacokinetic Concentrations (linear and semi-log scale)	PK Analysis
Figure 14.2.1.4	Median Talazoparib Plasma Pharmacokinetic Concentrations (linear and semi-log scale)	PK Analysis
Figure 14.2.1.5	Individual Talazoparib Plasma Pharmacokinetic Concentrations (linear and semi-log scale)	PK
Table 14.2.2	Summary of Talazoparib Plasma Pharmacokinetic Parameters	PK Analysis
Figure 14.2.3	Box-Whisker-Plots Talazoparib Plasma Pharamacokinetic Parameters	PK Analysis
Table 14.2.4	Statistical Analysis of Effect of Itraconazole/Rifampin on Talazoparib Primary PK Parameters	PK Analysis
	Safety	
Table 14.3.1.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities)	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Relationship to Study Drug	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Severity	Safety
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	Safety
Table 14.3.4	Listing of Abnormal Laboratory Values	Safety
Table 14.3.5.1	Summary of Absolute Laboratory Values	Safety
Table 14.3.5.2	Summary of Laboratory Changes from Baseline	Safety
Table 14.3.5.3	Frequency of Out-of-Range Results for Laboratory Values	Safety
Table 14.3.5.4	Shift Table for Maximum (by CTCAE grade) Change from Baseline of Laboratory Values	Safety

Table 14.3.6.1	Summary of Absolute Vital Signs Values	Safety
Table 14.3.6.2	Summary of Vital Signs Changes from Baseline	Safety
Table 14.3.6.3	Frequency for Change Categories for Vital Signs	Safety
Table 14.3.7.1	Summary of Absolute 12-Lead Electrocardiogram Values	Safety
Table 14.3.7.2	Summary of 12-Lead Electrocardiogram Changes from Baseline	Safety
Table 14.3.7.3	Frequency for Change Categories for 12-Lead Electrocardiogram	Safety

List of End of Text Listings:		
Output	**Title**	**Note**
	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	
	Pharmacokinetics	
Listing 16.2.6.1	Plasma Pharmacokinetic Concentrations	
Listing 16.2.6.2	Plasma Pharmacokinetic Parameters	
Listing 16.2.6.3	Individual Subject Ratios for Primary Pharmacokinetic Parameters	
	Safety	
Listing 16.2.7.1	Adverse Events	
Listing 16.2.7.2	Adverse Events Leading to Permanent Discontinuation	
Listing 16.2.8.1	Clinical Laboratory Results – Hematology	
Listing 16.2.8.2	Clinical Laboratory Results – Chemistry	

List of End of Text Listings:		
Output	**Title**	**Note**
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis	
Listing 16.2.8.4	Clinical Laboratory Results – Pregnancy Test and Hormone	
Listing 16.2.9.1	Vital Signs	
Listing 16.2.9.2	Weight, Height, BMI	
Listing 16.2.10.1	12-Lead Electrocardiogram Results - Parameters	
Listing 16.2.10.2	12-Lead Electrocardiogram Results - Assessments	
Listing 16.2.11	Physical Examination	

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
01 Dec 2017	PPD	Created from template EDSREP 009 T 01 E
20 Dec 2017	PPD	Implemented sponsor comments
09 Jan 2018	PPD	Implemented sponsor comments
16 Jan 2018	PPD	Implemented sponsor comments
24 Jan 2018	PPD	Implemented sponsor comments
25 Jan 2018	PPD	Minor changes based on TC, final version