Protocol C3441037

A PHASE 1, OPEN LABEL, CROSSOVER STUDY TO ESTABLISH BIOEQUIVALENCE BETWEEN THE PROPOSED SOFT GEL TALAZOPARIB CAPSULE FORMULATION AND THE CURRENT TALAZOPARIB COMMERCIAL FORMULATION AND TO ESTIMATE THE FOOD EFFECT ON PHARMACOKINETICS OF THE PROPOSED TALAZOPARIB SOFT GEL CAPSULE FORMULATION IN PARTICIPANTS WITH ADVANCED SOLID TUMORS

Statistical Analysis Plan (SAP)

Version: **3.0**

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Below table details the summary of changes made to the previous version of this document.

Table 1. Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	November 10, 2020	PPD	Not Applicable
2.0	August 3, 2021	PPD	The primary purpose of the amendment is to incorporate initial design assumptions reassessment during the trial. The previous estimation of power/sample size was based on the AUC_{24} variance of the current commercial formulation as no clinical data was available for the proposed soft gel capsule formulation and assumed ratio 1.07.
3.0	January 31, 2022	PPD	The primary purpose of the amendment is to update criterion # 6 for participant pk evaluability. From the requirement that on the last 3 days IP is taken under protocol specified fed/fasted condition to the requirement that only on the last day of a treatment period (intensive PK day collection), IP is taken under the protocol-specified fed/fasted condition. The rationale is as below: Food effect of talazoparib has been evaluated in Study 673-103 included in the Talazoparib 2018 NDA 2.7.1 SBS. Food intake delayed talazoparib absorption with significantly lower C_{max} (996.3 vs 1849 pg/mL) and prolonged T_{max} (4 vs 1 hour) in fed conditions compared to fast conditions. So, we have to control patients' compliance to the fast/fed requirement on the specific heavy PK collection day. Talazoparib's efficacy is found to be driven by total exposure (AUC). Since AUC_{inf} were not affected (61065 vs 62551 pg•h/mL) and plasma profiles from 12 to 24 hours post-dose were overlapping for the two conditions, it's unnecessary for us to control the compliance in the earlier times.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3441037. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

Talazoparib (PF-06944076, formerly known as MDV3800 or BMN 673) is a potent, orally bioavailable, small molecule PARP (poly ADP-ribose polymerase) inhibitor. TALZENNA™ (talazoparib) (0.25 mg and 1 mg capsules) was approved in a number of countries, including the United States, and EU, and is under review with anticipated approvals in other countries for the treatment of adult patients with deleterious or suspected deleterious gBRCAm HER2-negative locally advanced or metastatic breast cancer. Talazoparib is under development for a variety of human cancers both as a single agent and in combination with other agents.

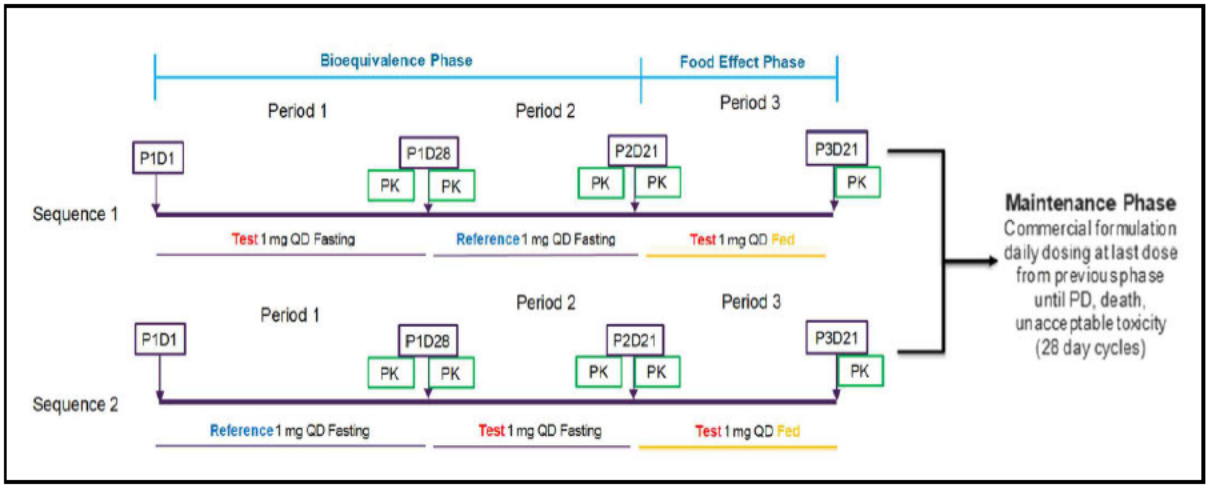
This study will be conducted to support the bridging of the current commercial capsule with the proposed talazoparib soft gel capsule formulation, and to explore the potential food effect on the pharmacokinetics of the proposed talazoparib soft gel capsule formulation.

2.1. Study Design

2.1.1. Overall Design

This will be a Phase 1, open label, 2-sequence, crossover study to establish the BE of the current commercial formulation (Generation 3.1 talazoparib capsules) to the proposed talazoparib liquid-filled soft gelatin capsule (soft gel capsule) formulation after multiple dosing under fasting conditions in participants with advanced solid tumors. In addition, the effect of food on the PK of the proposed talazoparib soft gel capsule formulation will be evaluated in fixed sequence after the 2 BE assessment periods. An overview of the study design is shown in Figure 1.

Figure 1. Study Design



2.1.2. Number of Participants

Approximately 46 participants will be enrolled into the study intervention to ensure at least 22 PK-evaluable participants who complete Periods 1 and 2 for the BE phase and at least 12 PK-evaluable participants who complete the food effect evaluation phase. Initial number of 46 participants is estimated based on 52% non-evaluable rate and might be adjusted during enrollment if non-evaluable rate changes.

When approximately 12 evaluable participants complete both Periods 1 and 2, initial assumptions (AUC_{24} variability and point estimate) for power/sample size calculation may be reassessed. Sample size may be increased; however, the total number of participants to be enrolled in the study may not exceed approximately 88 participants.

Eligible participants are considered PK-evaluable for a treatment period if they meet all the following criteria:

- Have had at least 21 consecutive days of continuous 1 mg QD dosing of IP (regardless of formulation) on the last day of a treatment period.
- Have stable renal function (≤25% change in CLCR between 2 visits) and acceptable renal function (CLCR >60 mL/min).
- On the day of full PK sampling, drug administration occurs between 20 and 28 hours after the previous dose.
- On the day of full PK sampling, no vomiting within 4 hours post dosing.
- >85% of the PK samples are available for valid analysis (including pre-dose and 24-hr sample).
- On the last day of a treatment period, IP is taken under the protocol-specified fasting/fed condition.

2.1.3. Intervention Groups and Duration

Participants will be randomly assigned to 1 of 2 sequences to receive Treatments A, B and C in different order as shown below (Table 2). The first 2 periods will be for BE assessment, with the first period being 28 days and the following periods being 21 days. Period 3 will be a 21 day period to evaluate the food effect on the PK of the proposed talazoparib soft gel capsule formulation that will be included in the fixed sequence after the 2 BE assessment periods (for participants who can tolerate one high-fat/high-calorie meal). Participants must have received 21 consecutive days of continuous 1 mg QD drug administration to be considered as completers of a treatment period, before moving on to the next scheduled treatment. When dose interruptions or missed doses occur, participants may repeat a treatment period for 21 days up to 2 additional times in order to qualify as completers. Participants who have repeated a period 2 times but still cannot meet PK evaluable criteria,

need a dose reduction, have unstable renal function, have experienced renal function worsening to moderate/severe renal impairment during the study, or have completed the food effect assessment, will be rolled over to the maintenance phase which will consist of repeating 28 day cycles of treatment with the current commercial formulation.

Table 2. Study Schematics

Sequence	*Period 1*	*Period 2*	*Period 3*
1 (23 participants)	*B*	*A*	*C*
2 (23 participants)	*A*	*B*	*C*

Treatment A: current commercial talazoparib formulation 1 mg once daily given under fasting condition (reference for BE evaluation).

Treatment B: the proposed talazoparib soft gel capsule formulation 1 mg once daily given under fasting condition (test for BE evaluation, reference for food effect evaluation).

Treatment C: the proposed talazoparib soft gel capsule formulation 1 mg once daily given with food (on the PK sampling day, high-fat/high-calorie meal will be administered in the clinical sites prior to the administration of the proposed talazoparib soft gel capsule formulation; test for food effect evaluation).

2.2. Study Objectives

2.2.1. Primary Objective(s)

- *To establish the BE of the proposed talazoparib soft gel capsule formulation to the current commercial formulation (Gen 3.1 talazoparib capsules) after multiple dosing under fasting condition.*
- *To estimate the effect of food on the PK of the proposed talazoparib soft gel capsule formulation after multiple dosing.*

2.2.2. Secondary Objective(s)

- *To characterize the talazoparib plasma PK parameters for all treatments.*
- *To evaluate the safety and tolerability of the proposed talazoparib soft gel capsule formulation.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The alternative hypothesis of bioequivalence (H_1: $\theta_L <= \mu_T - \mu_R <= \theta_U$), and the null hypothesis of inequivalence (H_o: $\mu_T - \mu_R < \theta_L$ or $\mu_T - \mu_R > \theta_U$) can be expressed as the following two separate one-sided hypotheses:

H_{OA}: $\mu_T - \mu_R < \theta_L$
H_{1A}: $\theta_L <= \mu_T - \mu_R$

H_{OB}: $\mu_T - \mu_R > \theta_U$
H_{1B}: $\mu_T - \mu_R <= \theta_U$

where μ_T and μ_R represent the average bioavailability on a log scale for the Test and Reference products respectively and [θ_L, θ_U] defines the bioequivalence range.

4.2. Statistical Decision Rules

The two one-sided hypotheses are tested at the α= 0.05 levels of significance for log-transformed AUC_{24} and C_{max} by constructing the 90% confidence interval for the ratio between the test and reference geometric means.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration in at least 1 treatment period.

5.1.2. Parameter Analysis Set

The PK parameter population is defined as all PK-evaluable participants randomized and treated who have primary PK parameter of AUC_{24} or C_{max} in at least 1 treatment period.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.

5.4. Treatment and Disposition of Participants

Participant evaluation groups will show end of study participant disposition and will show which participants were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for participant discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

5.5. Other Analysis Sets

None.

5.6. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

5.7. Protocol Deviations

Participants who experience events that may affect their PK profile (eg, 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 in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed prior to database closure.

5.7.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess participants against the inclusion and exclusion criteria as outlined in the protocol.

5.7.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

Treatment-emergent safety data will be defined as events from the first dose of study treatment through approximately 28 days after the last dose of study drug, or upon initiation of new antineoplastic therapy, whichever occurs first.

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

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of talazoparib will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for talazoparib (if possible) from the concentration-time data using standard non-compartmental methods:

Table 3. Non-compartmental PK Parameters

PK Parameter	Analysis Scale	Talazoparib
AUC^{24}	ln	A, D
AUC_{last}[a]	ln	D
C_{max}	ln	A, D
T_{max}	R	D
C_{trough}[b]	ln	D
CL/F	ln	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), a=Calculated when the last measurable PK sample is not taken at 24 hours postdose, b=Predose sample from a PK-evaluable participant.

6.3.2. PD Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

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

7.1. 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).

7.2. Deviations, Missing Concentrations and Anomalous Values

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

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

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

7.3. Pharmacokinetic Parameters

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

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

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular 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 particular parameter if more than 50% of the data are NC.

If an individual participant has a known biased estimate of a PK parameter (for example due to an unexpected event such as vomiting occurring at or before 2 times the median T_{max}), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Bioequivalence of PK parameters will be determined by constructing 90% confidence intervals around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

8.2. Statistical Analyses

8.2.1. Primary Endpoint(s)

To assess BE, natural log transformed AUC24 and Cmax after multiple dosing on the last day of Periods 1 and 2 will be analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Treatment A (commercial formulation given under fasting condition) will be the Reference treatment while Treatment B (the proposed talazoparib soft gel capsule formulation under fasting condition) will be the Test treatment.

To assess food effect, natural log transformed AUC_{24} and C_{max} after multiple dosing on the last day of Treatments B and C will be analyzed using a mixed effect model with sequence and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Treatments B (the proposed talazoparib soft gel capsule formulation under fasting condition) is the Reference treatment while Treatments C (the proposed talazoparib soft gel capsule formulation given under fed conditions) is Test treatment.

If initial design assumptions are reassessed during the trial, additional sensitivity analysis of BE will be performed by combining estimators from 2 stages using Cui, Hung, Wang 1999.[1] The 90% CI will be constructed using combined weighted estimate and standard error from 2 stages.[1]

As Asian participants have approximately 20% lower exposure and >50% overall non-evaluable rate is expected (high likelihood that participant will be evaluable in one period only), sensitivity analyses to assess effect of enrolled Asian participants on the bioequivalence/food effect will be performed. Results from the final statistical model/analysis will be included in the CSR.

Residuals from the model will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

8.2.2. Secondary Endpoint(s)

The PK parameters AUC_{24}, AUC_{last}, C_{max}, C_{trough}, CL/F, and T_{max} on the last day of Periods 1 to 3 will be summarized descriptively by treatment. Concentrations will be listed and summarized descriptively by treatment, and PK sampling time. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. C_{trough} on 3 consecutive days within Periods 1 and 2 will be compared to assure steady state is reached.

Table 4. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{24} C_{max} AUC_{last} C_{trough},	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
CL/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

For AUC_{24} and C_{max} a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for individual PK participant parameters (AUC_{24} and C_{max}) will be presented by treatment and overlaid with geometric means.

Presentations for talazoparib concentrations will include:

- A listing of all concentrations sorted by participant ID, treatment and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by treatment and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale).

Individual concentration time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) per scale].

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering study treatments.

8.3.1. Demographic and Clinical Examination Data

A break-down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Participants' in accordance with the sponsor reporting standards.

8.3.2. Discontinuation(s)

Participant discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.3.3. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by treatment.

8.3.4. Laboratory Data

The baseline measurement is the last predose measurement taken prior Period 1, Day 1 dose.

Laboratory data will be listed and assessed against the criteria specified in the sponsor reporting standards.

8.3.5. Vital Signs Data

Vital Signs data will be databased and available upon request.

8.3.6. ECG Data

ECG data will be databased and available upon request.

8.3.7. Other Safety Data

None.

8.3.8. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.4. Screening and Other Special Purpose Data

Coagulation (INR PT,aPTT) or as clinically indicated and FSH potential will be obtained at Screening.

If this data is brought in-house, then it will be listed.

CCI [redacted]

9. REFERENCES

1. Cui L, Hung HM, Wang SJ, et al. Modification of sample size in group sequential clinical trials. Biometrics. 1999, 55:853-7.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

For Bioequivalence assessment:

```
proc mixed data=tab.pk;
where period in (1 2);
        class seq period trt participant;
        model l&var=seq period trt/ ddfm=KR;
        random participant(seq) /participant=participant(seq);
        lsmeans trt;
        estimate 'Test vs Reference' trt -1  1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
A = the commercial formulation given under fasting condition (Reference);
B = the proposed talazoparib soft gel capsule formulation under fasting condition (Test)  */;
```

For Food-effect assessment:

```
proc mixed data=tab.pk;
where trt in (“B” “C”);
        class seq trt participant;
        model l&var=seq trt/ ddfm=KR;
        random participant(seq) /participant=participant(seq);
        lsmeans trt;
        estimate 'Test vs Reference' trt -1  1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
B = the proposed talazoparib soft gel capsule formulation under fasting condition
(Reference);
C = the proposed talazoparib soft gel capsule formulation given with high-fat/high-calorie
meal (Test)  */;
```