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

Study Intervention Number:	PF-06944076
Study Intervention Name:	Talazoparib
US IND Number:	CCI [redacted]
EudraCT Number:	2020-006101-35
Protocol Number:	C3441037
Phase:	1
Short Title: A Phase 1 bioequivalence study between the current commercial formulation and the proposed soft gel capsule formulation of talazoparib, and food effect study for the proposed talazoparib soft gel capsule formulation in participants with advanced solid tumors	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	22 June 2021	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. In addition, previously issued Protocol Administrative Change Letters and clarifications were incorporated in this amendment. All modifications are summarized below. • The cover page is updated with the EudraCT number due to the inclusion of sites in European Union. • Synopsis, Sections 4.1, 9.2 and 9.4.2 are updated to include the reassessment of initial design assumptions and potential sample size revision. • Section 4.1 is updated to clarify the definition of unstable renal function. • Section 5.1, #2b is updated to clarify criteria for participants with ovarian cancer, #2c is updated to clarify criteria for participants with NSCLC with EGFR mutations. • Section 5.2, #18 and 21 are updated to clarify the washout periods for compounds with long half-lives. • Section 6.2, #8 is updated to clarify the number of units required for sample retention to align with the FDA guidance. • Section 10.9 Appendix 9 is added to list the drugs with long half-lives and no potential for DDI with talazoparib.
Original protocol	29 July 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country healthy authorities and IRBs/ECs and any protocol administrative clarification letter.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 bioequivalence study between the current commercial formulation and the proposed soft gel capsule formulation of talazoparib, and food effect study for the proposed talazoparib soft gel capsule formulation in participants with advanced solid tumors

Rationale

In order to facilitate greater flexibility in batch size production, a proposed talazoparib liquid-filled soft gelatin capsule (hereafter referred as "soft gel capsule") formulation is currently being developed. The drug substance will be dissolved into a fill consisting of polyethylene glycol, glycerol and tocopherol. The fill will be encapsulated into a shell consisting of gelatin, sorbitol, glycerol and pigments. 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.

Objectives, Estimands, and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• 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.	• Plasma AUC_{24} and C_{max} of talazoparib after multiple dosing under fasted conditions. • Plasma AUC_{24} and C_{max} of talazoparib after multiple dosing under fed condition.
Secondary:	**Secondary:**
• To characterize the relevant talazoparib plasma PK parameters for all treatments. • To evaluate the safety and tolerability of the proposed talazoparib soft gel capsule formulation.	• Plasma CL/F, T_{max}, AUC_{last}, and C_{trough} of talazoparib after multiple dosing for all treatments. • Incidence of AEs characterized by type, severity (graded by NCI CTCAE version 5.0), timing, seriousness and relationship to study treatment.

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.

Number of Participants

Approximately 46 participants will be enrolled into the study intervention to ensure at least 22 PK-evaluable participants for the BE phase and at least 12 after 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.

Intervention Groups and Duration

Participants will be randomly assigned to 1 of 2 sequences to receive Treatment A, B and C in different order as shown below. 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 1mg 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.

Treatment Sequence	Period 1	Period 2	Period 3
1 (n=23 in total)	B	A	C
2 (n=23 in total)	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)

Data Monitoring Committee or Other Independent Oversight Committee: No

This study will not use a DMC.

Statistical Methods

Sample Size Estimation

It is estimated that 22 participants will be required to provide 90% power that the 90% CI for the Test/Reference ratio of talazoparib AUC_{24} falls within the 80-125% acceptance interval for bioequivalence. Additionally, with 22 participants the probability that Test/Reference ratio for C_{max} will fall within 80%-125% is estimated to be 86%. These estimates are based on the assumption that the true ratio between Test and Reference treatments for AUC_{24} and C_{max} is 1.07 and 1.1 and also assumes within subject standard deviations of 0.407 and 0.17 for $\log_e C_{max}$ and $\log_e AUC_{24}$ respectively, as obtained from rifampin and itraconazole cohorts from study MDV3800-04.

Participants who withdraw from the study or fail to provide evaluable samples may be replaced at the discretion of the sponsor.

Primary Endpoints

To assess BE, natural log transformed AUC_{24} and C_{max} after multiple dosing on the last day of treatment Period 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 Test treatment.

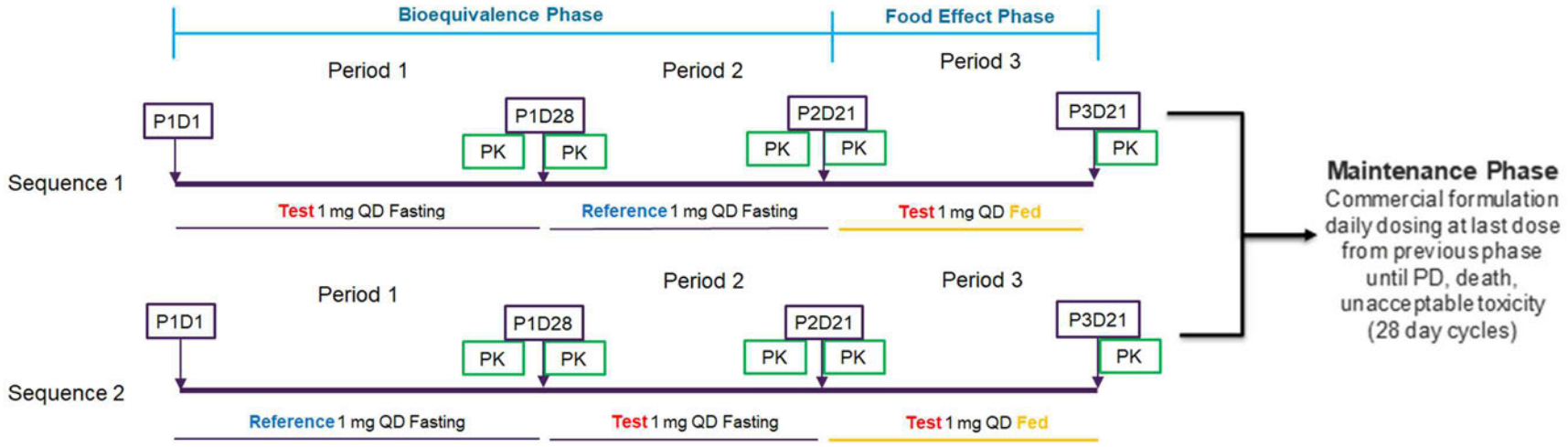
To assess food effect, natural log transformed AUC_{24} and C_{max} after multiple dosing on the last day of treatment B and C will be analyzed using a mixed effect model with sequence and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (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. Treatment B (the proposed talazoparib soft gel capsule formulation under fasting condition) will be the Reference treatment while Treatment C (the proposed talazoparib soft gel capsule formulation given with high fat/high-calorie meal) will be the 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].

Secondary Endpoints

Safety analyses will be performed on the safety population using AE data. The number and percentage of participants with AEs will be presented by MedDRA system organ class and preferred term, relationship to IP, and severity. 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. Descriptive statistics will be used.

1.2. Schema


Bioequivalence Phase
Food Effect Phase
Period 1
Period 2
Period 3
P1D1
P1D28
P2D21
P3D21
PK
Sequence 1
Test 1 mg QD Fasting
Reference 1 mg QD Fasting
Test 1 mg QD Fed
Sequence 2
Reference 1 mg QD Fasting
Test 1 mg QD Fasting
Test 1 mg QD Fed
Maintenance Phase
Commercial formulation daily dosing at last dose from previous phase until PD, death, unacceptable toxicity (28 day cycles)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Bioequivalence and Food Effect Phases

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1**			**Period 2**			**Period 3**		
		Day 1	**Day 27**	**Day 28[r]**	**Day 1**	**Day 20**	**Day 21[r]**	**Day 1**	**Day 21[r]**	**Day 22[t]**
Visit Window (Days)	**Day -28 to Day -1**	**0**	**-/+ 2**	**-/+ 2**	**0**	**-2/+7**	**-2/+7**	**0**	**-2/+7**	**-2/+7**
Informed consent	X									
Demography/ Medical / Oncology history[a]	X									
Physical examination[b]	X	X[q]		X			X		X	
ECOG[c]	X									
Vital Signs[d]	X	X[q]		X			X		X	
Hematology[e]	X	X[q]		X			X		X	
Blood chemistry[e]	X	X[q]		X			X		X	
Coagulation[e]	X		As clinically indicated							
Urinalysis	X	X[q]		X			X		X	
FSH	X									
Serum/urine pregnancy test[f]	X	X[q]		X			X		X	
Contraception check	X	X[q]		X			X		X	
12-Lead ECG[g]	X									

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1			Period 2			Period 3		
		Day 1	Day 27	Day 28[r]	Day 1	Day 20	Day 21[r]	Day 1	Day 21[r]	Day 22[t]
Visit Window (Days)	**Day -28 to Day -1**	**0**	**-/+ 2**	**-/+ 2**	**0**	**-2/+7**	**-2/+7**	**0**	**-2/+7**	**-2/+7**
Disease assessment (±7 day SOC imaging window)[h]	X								X	
Randomization		X								
IP dispensation		X			X[s]			X[s]		
IP administration[i]			Oral daily dosing							
IP compliance check via web portal (1 day prior to visit)[j]				X			X		X	
IP bottle return / accountability[k]				X			X		X	
Blood sampling for talazoparib PK[l]			X	X	X	X	X	X	X	X
High fat, non-fasting meal[m]									X	
CCI [redacted]										
Concomitant medications / treatment(s)[o]	X	X		X	X		X	X	X	X
Serious and nonserious AE monitoring[p]	X	X		X	X		X	X	X	X

a. Includes history and other disease/conditions/illness (active or resolved); oncology history includes cancer type and stage, cancer surgery. cancer radiation and prior anti-cancer therapies; and gene mutation (eg, BRCA status if known) will be recorded.
b. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Full physical examination at screening and brief exams at subsequent visit. See Section 8.2.1
c. Performance score is a clinical assessment of a participant's physical abilities at a specified time point.
d. Blood pressure, heart rate, temperature and weight (height is only reported at screening). See Section 8.2.2.

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1			Period 2			Period 3		
		Day 1	Day 27	Day 28[r]	Day 1	Day 20	Day 21[r]	Day 1	Day 21[r]	Day 22[t]
Visit Window (Days)	Day -28 to Day -1	0	-/+ 2	-/+ 2	0	-2/+7	-2/+7	0	-2/+7	-2/+7

e. Chemistry, hematology and coagulation (coagulation: screening only and as clinically indicated thereafter): must be performed at Screening, Period 1 Day 28 and Periods2-3 Day 21; Day 1 of each maintenance cycle and EOT. Laboratory tests may be repeated as clinically indicated. See Section 10.2 for the listing of safety assessments.
f. Serum/urine pregnancy check will be performed at screening, P1D1, P1D28, P2D21,P3D21; Day 1 of each maintenance cycle, and EOT.
g. Clinically significant abnormal findings at screening will be recorded on the medical history. ECG will also be performed as clinically indicated. Clinically significant abnormal findings during treatment should be recorded and followed as AEs. See Section 8.2.3.
h. Imaging schedules will be per SOC for respective tumor diagnosis but no later than every 6-12 months or as clinically indicated to monitor for continued benefit on treatment. .
i. IP administration: Daily 1 mg PO at approximately the same time each morning. Day 1 will be the first day of dosing. On the visit days with PK assessment, participants will take IP at the site approximately 24 hours after the previous dose and within 10 minutes after the collection of pre-dose blood sample; On other days without PK assessment, participants will be instructed to self administer- IP and maintain an eDiary for compliance (recording timing of each dose and fasting condition, and any missed or vomited doses); In Periods 1 to 2, IP should be taken under fasting condition; In Period 3, IP should be taken under fed conditions. Participants need to have taken at least 21 consecutive days of continuous daily dosing of IP (regardless of formulation) on the last day of a treatment period to be considered a completer of that treatment. Otherwise, the treatment needs to be extended within the allowed window or repeated for 21 days (-2/+7 days). See additional details in Sections 6.1.1 for fasting/fed condition requirement, guidance on missed doses or IP administered outside of the allowed window, and scenarios when participants will rollover to the maintenance phase of the study.
j. The site should review participant's eDiary IP compliance on and one day before the site visit day to check for missed doses/out of window dosing and follow the guidance on missed doses and IP administered outside of the allowed window, detailed in Section 6.1.1.
k. Bottles will be returned and compliance checked with e-Diary dosing compliance from the web portal prior to PKs to ensure required daily 1 mg dosing.
l. Serial blood sample (4 mL) each will be collected at predose on Day 27 of Period 1 and Day 20 of Periods 2 and predose and 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, and 24 hours postdose on Day 28 of Period 1 and Day 21 of Period 2 to 3, respectively. If visit windows are utilized, PK sampling visits must be adjusted so they occur on consecutive days. Refer to PK Sampling Schedule Table below and Section 8.5 for details.
m. High fat meal will be started within 30 minutes prior to dosing and finish before drug administration. On non-site visit days of Period 3, IP will be taken after a proper breakfast. See Section 6.1.1. Participants who cannot tolerate a high fat meal can be excluded from the food effect phase and roll over to the maintenance phase.
C
C
I [redacted]
o. Concomitant medications/treatments will be reported 28 days prior to Day 1 and up to EOT. See Section 6.5.
p. Serious and non-serious AE information will be reported from the time of signed informed consent through a minimum of 28 days after the last dose of IP. Refer to Section 8.3.1 regarding the reporting timeframe for SAEs.
q. If assessments were performed within 7 days prior to Period 1 Day 1 and within 3 days for serum/urine pregnancy test, repeat assessments are not required except for BUN and creatinine.

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1			Period 2			Period 3		
		Day 1	Day 27	Day 28[r]	Day 1	Day 20	Day 21[r]	Day 1	Day 21[r]	Day 22[t]
Visit Window (Days)	**Day -28 to Day -1**	**0**	-/+ 2	-/+ 2	**0**	-2/+7	-2/+7	**0**	-2/+7	-2/+7

r. 24 hour PK collection: occurs on Day 1 of the following period prior to drug administration. P1 Day 28 visit and P2 Day 21 visit occur on the day immediately after P1 Day 27 visit and P2 Day 20 visit, respectively. Participants should consider staying at the study site or a local hotel the night before this visit and the night of this visit if they do not live close to the study site.
Repeat Period 1: Period 1 can be repeated for 21 days instead of 28 days, if 21 consecutive days of continuous daily dosing is met.

s. If a period will be repeated, new bottles of the same treatment should be dispensed on the last treatment day (i.e. Day 28 for period 1 and Day 21 for period 2 and 3) instead of Day 1.

t. Period 3 Day 22 will be the completion of the BE and food-effect phase of this study, if discontinuation is planned at this time, complete all the assessments under EOT. If participant will continue treatment, complete Period 3 Day 22 PK sample and any assessment for Day 1 of the first Maintenance Cycle which will not be performed on Period 3 Day 21. IP dispensed will be the reference formulation for the maintenance cycles. Period 3 Day 22 is also Cycle 1 Day 1 for the Maintenance Cycle Phase. If discontinuation is performed after completion of the Period 3 (Day 22= EOT), a final post-treatment safety assessment is required 28 (+7) days after the last dose of IP. If participant is continuing on study after Period 3, the Maintenance Cycle Phase schedule should be followed.

PK Sampling Schedule on PK Visits

Visit Days	Time Points	Window of Acceptability
Period 1 Day 27* Period 2 Day 20*	Predose PK Collection	24 ± 2 hours from dose on prior day and before the dosing time on the PK sampling day
Period 1 Day 28 Period 2 Day 21** Period 3 Day 21**	Predose PK Collection	24 ± 2 hours from dose on prior day and before the dosing time on the PK sampling day
	Talazoparib Dose	Within 10 minutes after the predose PK sample collection
	0.5 hours PK Collection	±3 minutes
	0.75 hours PK Collection	±5 minutes
	1 hours PK Collection	±6 minutes
	1.5 hours PK Collection	±9 minutes
	2 hours PK Collection	±12 minutes
	4 hours PK Collection	±24 minutes
	6 hours PK Collection	±36 minutes
	8 hours PK Collection	±48 minutes
	24 hours PK Collection***	±60 minutes and before the dosing time on the same day, ie, Day 1 in the following period

*PK sampling visits can occur between Day 25 to Day 29 for period 1, and can occur between Day 18 and Day 27 for period 2 while continuing daily drug administration to accommodate scheduling convenience and compliance as described in the footnotes of the SoA.

**PK sampling on Period 1 Day 28 and Period 2 Day 21 occur on the days immediately after Period 1 Day 27 visit and Period 2 Day 20 visit, respectively; PK sampling on Period 3 Day 21 can occur between Day 19 and Day 28 while coninuitng daily drug administration to accommodate scheduling convenience and compliance as described in the footnotes of the SoA.

***24 hours PK on Day 28 for Period 1 and Day 21 on Periods 2 and 3 is the same PK sample as predose PK on Day 1 in the following period.

Maintenance Phase

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Maintenance Cycles (Cycle =28 Days) Day** [h]	**End of Treatment**	**End of Study**[i]
Visit Windows (Days)	**±3 days**	**+7 days**	
Brief physical examination	X	X	
ECOG[a]	X	X	
Vital signs[b]	X	X	
Blood chemistry[c]	X	X	
Hematology[c]	X	X	
Coagulation[c]	As clinically indicated		
Serum/urine pregnancy test	X	X	
Contraceptive check	X	X	
Disease assessment(±7 day SOC imaging window)[d]	X	X	
IP dispensation	X		
IP administration[e]	Oral daily dosing		
IP bottle return/accountability	X	X	
Concomitant medications/ treatments[f]	X	X	
Serious/non-serious adverse event monitoring[g]	X	X	X

a. ECOG at Day 1 of maintenance phase and EOT
b. Blood pressure, pulse/heart rate, oral temperature, and weight. See Section 8.2.2.
c. Chemistry, hematology, and coagulation (if clinically indicated): must be performed Day 1 of each maintenance cycle and EOT. Laboratory tests may be repeated as clinically indicated. See Section 10.2 for the listing of safety assessments and SoA for timing and frequency.
d. Imaging schedules will be per SOC for respective tumor diagnosis but no later than every 6-12 months or as clinically indicated to monitor for continued benefit on treatment.
e. IP dose will be taken on the days of the clinic visits at the clinic. Participants will be instructed to take their capsule at the same time each day compared to the day before and keep a diary for compliance. Safety assessment should be reviewed prior to starting the next IP cycle.
f. Concomitant medications/treatments will be recorded up to EOT. See Section 6.5.
g. Serious and non-serious AE information will be collected through a minimum of 28 (+7) days after the last dose of IP. Refer to Section 8.3.1 for the reporting time frame of SAEs.
h. At the discretion of the investigator, patients who are stable can be followed every 8 weeks. All tests and assessments outlined in the schedule of activities must be conducted at that visit.
i. EOS: the last date of safety follow-up 28 (+7) days after the last dose of IP, contact may be either by phone call or clinic assessment.

2. INTRODUCTION

Talazoparib (PF-06944076, formerly known as MDV3800 or BMN 673) is a potent, orally bioavailable, small molecule PARP inhibitor. TALZENNA™ (talazoparib) (0.25 mg and 1 mg capsules) was approved in several 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.

2.1. Study Rationale

CCI [redacted] The recommended dose of talazoparib is 1 mg administered orally QD with or without food. Dosing interruptions or dose reductions of talazoparib to 0.75 mg, 0.5 mg or 0.25 mg QD are allowed to manage AEs with the use of the 0.25 mg commercial capsule.

In order to facilitate greater flexibility in batch size production, a proposed talazoparib liquid-filled soft gelatin capsule (hereafter referred as "soft gel capsule") formulation is currently being developed. The drug substance will be dissolved into a fill consisting of polyethylene glycol, glycerol and tocopherol. The fill will be encapsulated into a shell consisting of gelatin, sorbitol, glycerol and pigments. 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 PK of the proposed talazoparib soft gel capsule formulation.

2.2. Background

Talazoparib is a potent and specific inhibitor of PARP1 and PARP2 that play important roles in DNA repair. PARP inhibitors exert cytotoxic effects by 2 mechanisms: inhibition of PARP catalytic activity and PARP trapping. Inhibition of PARP catalytic activity results in persistent single strand DNA breaks that culminate in accumulation of double-stranded DNA breaks, necessitating homologous recombination-mediated DNA repair for cell survival. PARP trapping prevents talazoparib bound PARP protein complexes from readily dissociating from DNA, thereby inhibiting DNA repair, replication, and transcription, resulting in double strand DNA breaks and consequent cytotoxicity. PARP inhibitors induce synthetic lethality in tumor cells that bear mutations and/or deletions in genes involved in homologous recombination or some other DNA repair pathways. In BRCA1 and BRCA2 deficient cells, treatment with a PARP inhibitor results in cell cycle arrest and apoptosis.

PARP inhibitors have been approved to treat patients with advanced or metastatic breast, ovarian and pancreatic cancers who have been identified with germline BRCA mutations, ie, olaparib (Lynparza®), rucaparib (Rubraca®), niraparib (Zejula®), talazoparib (TalzennaTM). PARP inhibitors have also been approved to treat patients without BRCA

mutations, for example in the maintenance setting in ovarian cancer. The major indications for which PARP inhibitors have been approved are described below.[2,3,4,5]

The most recent indication was approved for olaparib on December 2019 by the FDA for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.[2]

Indications for maintenance therapy in patients with ovarian, fallopian tube, and peritoneal adenocarcinoma for patients with recurrent disease, BRCA-associated mutations, and with ≥2 lines of chemotherapy were approved initially in 2014 (olaparib, 2017,2018), and for other PARP inhibitors in 2016 (rucaparib, 2018) and 2017 (niraparib, 2019). [2,3,4,5]

Olaparib is indicated for the following indications in ovarian, fallopian tube, and primary peritoneal cancer: maintenance treatment of recurrent ovarian cancer and advanced gBRCA mutated ovarian cancer after 3 or more lines of chemotherapy.[2]

Other PARP inhibitors such as rucaparib and niraparib are also indicated in the maintenance and advanced setting in patients with platinum sensitive, relapsed or progressive advanced high grade epithelial ovarian, fallopian tube or primary peritoneal cancer based on data from the large ARIEL and NOVA trials respectively. [3,4]

PARP inhibitors were approved for patients with gBRCA positive, advanced or metastatic HER2-negative breast cancer in 2018 (olaparib), and 2018 (talazoparib).[2,5]

Talazoparib is highly potent at inducing single agent synthetic lethality of BRCA1 and BRCA2 deficient tumor cells in vitro . Consistent with its cytotoxic effects in tissue culture studies, talazoparib demonstrated antitumor activity in xenograft tumor models. Potent tumor activity was observed at an oral daily dose <1 mg/kg/day. Complete suppression of growth of BRCA1-deficient tumors (ie, MX1 model) was achiveved in a 3-month study when talazoparib was dosed at 0.165 mg/kg. These in vitro and in vivo activities suggest that talazoparib may have clinical activity in patients with BRCA mutated breast cancer.

In Study PRP001, a Phase 1, first in human, single-arm, open-label dose escalation study of once daily talazoparib (BMN 673) in patients with advanced or recurrent solid tumors with DNA repair deficiencies, a total of 110 patients were treated with talazoparib at doses ranging from 0.025 to 1.1 mg/day. During the dose escalation phase of the study, 2 of the 6 patients enrolled in the talazoparib 1.1 mg/day dose level experienced a dose limiting toxicity: one was Grade 4 thrombocytopenia, the other was Grade 3 thrombocytopenia requiring >5 days off study treatment. Therefore, 1 mg/day was considered the maximum tolerated dose and recommended Phase 2 dose. Between the dose escalation and dose expansion portions of the study, a total of 77 patients were treated with talazoparib at the 1 mg/day dose level in Study PRP001 which was generally well tolerated and warranted further evaluation in patients with solid tumors with DNA repair deficiencies. As a result, talazoparib has been dosed at 1 mg/day in subsequent studies in patients with solid tumors,

including the phase 2 and 3 breast cancer studies ABRAZO, EMBRACA, and currently ongoing investigator-initiated research trials.

The class of PARP inhibitors has demonstrated a risk for dose-dependent reversible myelosuppression and gastrointestinal toxicity, and these events were observed in studies where patients received 1mg/day talazopirib monotherapy. Study drug-related TEAEs occurring in ≥20% of patients in the talazoparib 1 mg/day population were anemia (45.8%), fatigue (36.1%), nausea (32.5%), neutropenia (21.9%), and alopecia (20.1%). Grade 3 or 4 drug-related TEAEs occurring in ≥5% of patients were anemia (34.1%), neutropenia (13.9%), thrombocytopenia (10.6%), and platelet count decreased (5.4%).

2.2.1. Clinical Overview

Talazoparib is currently approved and in development for the treatment of a variety of cancers. Approximately 1212 patients have received talazoparib in company-sponsored studies as of the data cutoff date of the most recent investigator's brochure (30 September 2019).

The single dose PK of talazoparib have been evaluated in a total of 7 clinical studies, of which 6 were conducted in cancer patients (Studies PRP-001, PRP-002, MDV3800-01, MDV3800-03, MDV3800-04, and MDV3800-14) and 1 in healthy subjects (Study 673-103). After administration of a single 1 mg dose of talazoparib capsules to cancer patients, the median T_{max} ranged from 1.0 to 2.0 hours across studies. The geometric mean C_{max} ranged from 4.35 to 8.79 ng/mL and the geometric mean AUC_{inf} ranged from 116 to 220 ng•hr/mL. Talazoparib was eliminated slowly with the geometric mean CL/F values ranging from 4.55 to 7.71 L/hr and the mean $t_{½}$ ranging from 62.4 to 98.1 hours, while the $t_{½}$ of 62.4 hours might be an underestimate as the PK sampling time was only up to 168 hours postdose in the corresponding study. The talazoparib geometric mean V_z/F values estimated ranged from 447 to 847 L, which is significantly greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues.

The PK of talazoparib following multiple oral daily doses was evaluated in a total of 6 studies in patients with cancer (Studies PRP-001, PRP-002, 673-201, 673-301, MDV3800-01, and MDV3800-14), and Studies 673-201 and 673-301 only included sparse sampling. Following repeated 1 mg QD dosing of talazoparib capsules in cancer patients, talazoparib was rapidly absorbed with a median T_{max} ranging from approximately 1.0 to 2.0 hours. The geometric mean C_{max} values ranged from 11.4 to 19.1 ng/mL and the geometric mean AUC_{24} values ranged from 126 to 208 ng•hr/mL. The talazoparib geometric mean C_{trough} values ranged from 2.99 to 4.95 ng/mL. The geometric mean CL/F ranged from 4.80 to 5.53 L/hr, with a mean plasma $t_{½}$ of 57.8 hours (Study PRP-001), which may be an underestimate as the last PK sampling time was at 168 hours postdose.

Based on the multiple dosing data from Studies PRP-001 and PRP-002 and consistent with its observed $t_{½}$ of 89.8 hours (Study MDV3800-03), talazoparib plasma concentrations reached steady state around 3 weeks after repeated daily dosing. The median accumulation ratio ranged from 2.33 to 5.15 following repeated oral administration of 1 mg dose.

The talazoparib plasma exposure (AUC_{24}) and C_{max} increased in a dose-proportional manner over the dose range of 0.025 to 2 mg QD.

2.3. Benefit/Risk Assessment

The doses of talazoparib in this protocol are supported by nonclinical studies and clinical studies in patients with advanced malignancies. Talazoparib has shown anti-tumor activity in patients with breast, ovarian, peritoneal and pancreatic cancers, as described in the background and talazoparib Investigator's Brochure. Talazoparib is currently approved for use in patients with metastatic breast cancer with germline BRCA mutations.

The expected AEs with talazoparib include myelosuppression, gastrointestinal toxicity, fatigue, and alopecia. Hepatotoxicity, febrile neutropenia, and neutropenic sepsis are potential risks per the Investigator's Brochure, Section 7. The activity of talazoparib as monotherapy and in combination with other agents is being evaluated in multiple indications. Based on the available safety and efficacy data, the overall benefit risk profile of talazoparib remains favorable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of talazoparib may be found in the Investigator's Brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) talazoparib		
Potential risks associated with talazoparib include the following: MDS, AML and myelosuppresion.	The potential risks are based on safety data summarized in product label and the investigator's brochure for talazoparib.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). Conduct safety assessment (eg, hematology) according to the SoA. Investigator can provide unplanned assessment as clinically indicated.

2.3.2. Benefit Assessment

Talazoparib has shown anti-tumor activity in patients with breast, ovarian, peritoneal and pancreatic cancers, as described in the background and talazoparib Investigator's Brochure. The benefit of talazopairb for individual pariticipants with solid tumors may include:

- Potential clinical benefit of receiving talazoparib during study.
- Participants in this study will contribute to the process of developing a new formulation for talazoparib.
- Medical assessment (eg, physical exams, ECGs, labs, etc.) associated with study procedures and health care provider visits will be more frequent compared to standard of care.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with talazoparib are justified by the anticipated benefits that may be afforded to participants with solid cancer tumors.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• 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.	• Plasma AUC_{24} and C_{max} of talazoparib after multiple dosing under fasted conditions. • Plasma AUC_{24} and C_{max} of talazoparib after multiple dosing under fed condition.
Secondary:	**Secondary:**
• To characterize the talazoparib plasma PK parameters for all treatments. • To evaluate the safety and tolerability of the proposed talazoparib soft gel capsule formulation.	• Plasma CL/F, T_{max}, AUC_{last}, and C_{trough} of talazoparib after multiple dosing for all treatments. • Incidence of AEs characterized by type, severity (graded by NCI CTCAE version 5.0), timing, seriousness and relationship to study treatment.

4. STUDY DESIGN

4.1. 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 soft gel capsule formulation after multiple dosing under fasting conditions in participants with advanced solid tumors, and to explore the potential food effect on the pharmacokinetics of the proposed talazoparib soft gel capsule formulation. 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 period. 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 (>25% change in CLCR between 2 visits which is considered clinically significant by the investigator and will require a dose reduction), have experienced renal function worsening to moderate/severe renal impairment (CLCR dropped to <60 mL/min) during the study, or have completed the food effect assessment, will be allowed to roll over to the maintenance phase which will consist of repeating 28 day cycles of treatment with the current commercial formulation. The maintenance phase consists of repeating 28 day cycles of treatment with the current commercial formulation.

Participants will be randomly assigned to 1 of the 2 sequences shown in Table 1.

Table 1. Treatment Sequences

Treatment Sequence	Period 1	Period 2	Period 3
1 (n= 23 in total)	B	A	C
2 (n= 23 in total)	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)

Approximately 46 participants (23 per sequence) will be enrolled into the study intervention to ensure at least 22 PK-evaluable participants for the BE phase and at least 12 after 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, 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.

Participants will be randomized 1:1 to receive treatments in sequence 1 or 2. Participants who are still on 1 mg daily after the completion of the first 2 periods and can tolerate one high-fat/high-calorie meal will receive treatment C in period 3 to evaluate the food effect on the PK of the proposed talazoparib soft gel capsule formulation. On the day before the last treatment day of each period, a pre-dose PK sample will be collected. On the last treatment day of each period, participants will undergo serial PK sampling for 24 hours. Participants who have had less than 21 consecutive days of continuous QD dosing of IP (regardless of formulation) on the last day of a treatment period will be considered non-completers of that treatment period (Period X). PK assessment will not be performed for non-completers of a treatment periods, but other scheduled activities will be performed per the SoA. After completion of Period X, instead of moving on to the next treatment, the same treatment in Period X will be repeated until participants have received at least 21 consecutive daily doses of IP on the last day of the treatment period (ie, considered as completers).

4.2. Scientific Rationale for Study Design

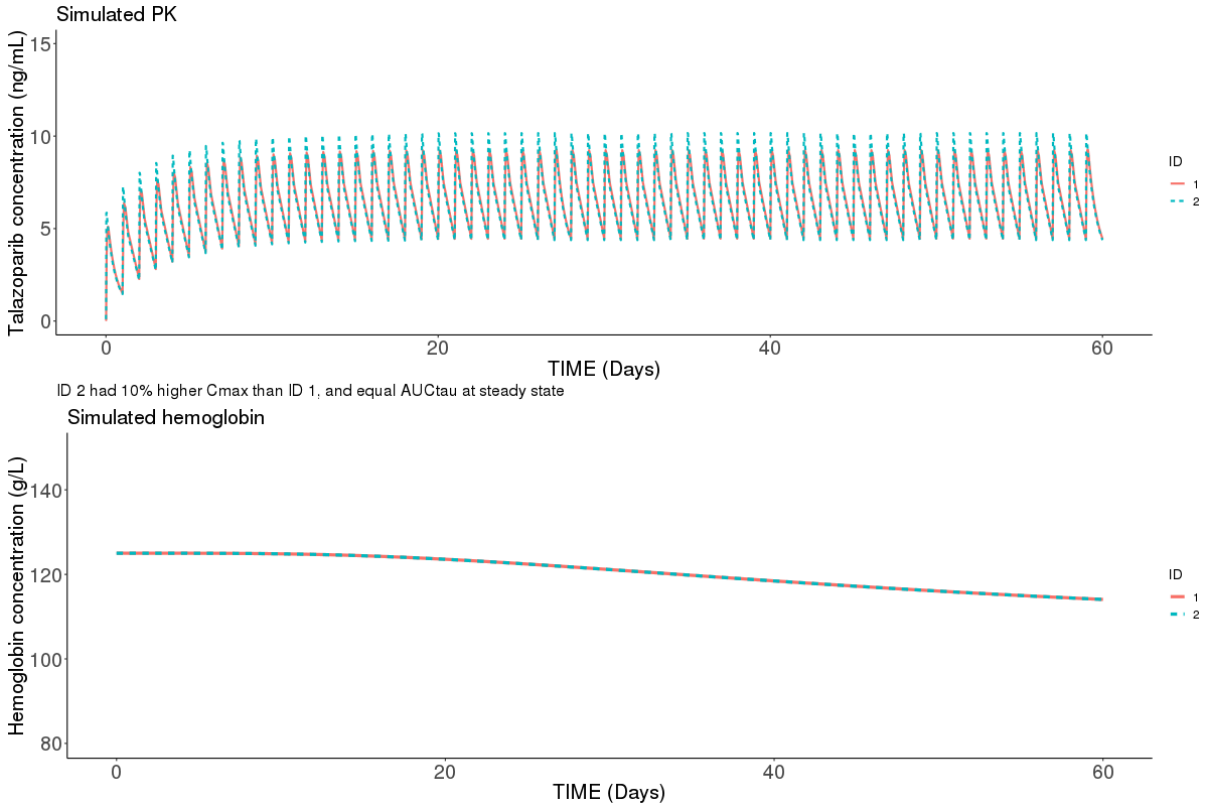
Talazoparib is clastogenic and therefore it is unacceptable to enroll healthy participants for this study. All clinical studies administering talazoparib should be conducted in cancer patients for whom there is potential benefit to offset this risk. Cancer patients who will likely benefit from talazoparib treatment and have good disease control will be recruited to minimize dropouts through progression of disease because of the long duration of treatment (at least 70 days). The selected participant population will include patients with advanced solid tumors that are not amenable for treatment with curative intent who may benefit from treatment with talazoparib.

Due to the selected participant population, a single-dose study is not feasible as the long elimination half-life (t½, 89.9±57.6 hours) of talazoparib would require too long a washout duration with no treatment to be ethical in a cancer patient population setting. Due to high PK variability of talazoparib in cancer patients, (total variability of 47-62% for C_{max} and 32%-42% for AUC [PRP-002 and MDV3800-04 with N>18], single dose studies), a parallel study design would require a large sample size (>100 participants per arm) and therefore would not be feasible. Collectively, inherent properties of talazoparib limit the acceptable BA/BE assessment options to a multiple-dose crossover design in cancer patients. In order to achieve 90% power that the 90% CI for the Test/Reference ratio of talazoparib C_{max} fall within the 80-125%, a full replicate design (TRTR, RTRT) with 40 evaluable participants would be required. Due to the treatment length of this design (at least 84 days), the non-evaluable rate was estimated to be ~65% and approximately 114 participants need to be enrolled, rendering the implementation of this design non-feasible. In addition, C_{max} is not considered a main driver for the efficacy and safety events of talazoparib as illustrated below.

If the C_{max} of the proposed formulation is lower than that of the current commercial formulation, it is not expected to have an impact on efficacy. In the preclinical studies, in MX1 tumors xenograft model, dosing talazoparib at 0.166 mg/kg BID schedule showed a better anti-tumor effect profile compared to dosing talazoparib at 0.33 mg/kg QD schedule. This suggests C_{max} is not the driver for efficacy. This study result led to the registrational Phase 3 study (Study C3441009; EMBRACA) being conducted with talazoparib taken without regard to food intake, as food had no effect on the AUC even though it reduced talazoparib C_{max} by 46%. Consistently, in the USPI talazoparib is recommended to be given with or without of food.

The lack of impact of higher C_{max} on safety was evaluated using ER modeling. Myelosuppression-related AEs are the main side effects of talazoparib treatment and Anemia was reported for 49.2% of patients (Module 2.7.4 NDA 211651 seq 001). Thus, Anemia was selected as a representative safety endpoint for ER modeling to evaluate the impact of C_{max} increase on the safety profile of talazoparib. Simulations were conducted to compare the projected PK profile based on the assumed ratio between the two formulations (10% higher C_{max} for the proposed formulation) and the time course of Anemia (Figure 1). Patient ID 1 represented the population typical talazoparib PK profile; Patients ID 2 had 10% higher C_{max} and same AUC_{24} compared to Patient ID1. As shown in Figure 1, limited increase of C_{max} would not have significant impact on the safety profile of talazoparib (Anemia) when AUC remains the same.

Figure 1. Simulated PK and Pharmacodynamics (Hemoglobin) Profiles After 1 mg QD Talazoparib



Therefore, since C_{max} is not considered a driver for efficacy and safety, and to ensure operational feasibility, a two-way crossover study powered to show 90% CI for the Test/Reference ratio of talazoparib AUC_{24} within the 80-125% acceptance interval for BE was selected.

In order to assess the steady state PK of talazoparib to demonstrate BE, lengthy continuous treatment with talazoparib at 1 mg QD before PK sampling is required. Participants who undergo a dose reduction before the PK sampling will not be included in the PK evaluable population, and participants with dosing interruptions before the PK sampling need to continue talazoparib treatment until the steady state is reached for PK sampling. In addition, disease progression necessitating coming off the study before completing all PK evaluation days may also preclude participants from completing the BE assessment period. With this longer study duration, there could be higher rates of disease progression and dose reduction leading to a higher non-evaluable rate. In addition, the longer the study duration, the higher the likelihood of drug administration non-compliance, leading to higher PK non-evaluable rate. Therefore, to minimize the treatment duration, the study was designed to be 28 days for Period 1 to ensure attainment of steady state, and 21 days for Periods 2 and 3, which is shown to be adequate for steady-state BE and food effect evaluation based on the simulation results below. In addition, three pre-dose PK samples will be collected on consecutive days in period 1 and 2 to show attainment of steady state for BE assessment.

To investigate the shortest adequate treatment durations prior to PK assessment for steady state BE evaluation, simulations were conducted using the final popPK model submitted in the original NDA 211651 (PMAR-EQDD-C344a-DP4-840). Using the proposed treatment duration for each period, simulations were performed for fixed sequence with the second administered formulation having known bioavailability (F1) changes (10% or 5% increase or 10% or 5% decrease in F1 relative to the first administered formulation). Population typical CL and lower 5 percentile CL were used to represent typical participants and participants with lower CL (slower elimination and longer half-life). In the simulation, formulation 1 was administered from Day 1 to Day 28, and formulation 2 was administered from Day 29 to Day 56. PK parameters obtained on Day 14 of Period 2 (ie, Day 42) for the second formulation were compared to those obtained on Day 28 of Period 1 and the AUC ratio obtained was compared to the true difference in F1 used for simulation to illustrate the accuracy of the determination of true formulation effect on bioavailability. In addition, the second formulation had extended dosing to Day 28 for Period 2 (ie, Day 56) in the simulation to further demonstrate whether the steady state for the second formulation was achieved on Day 14 of Period 2 by comparing the results for Day 14 and Day 28 of Period 2 respectively.

Table 2 exhibits the simulation results. When the formulation with 10% higher F1 was administered in Period 3, the ratio of AUC_{24} obtained on Day 14 in Period 2 (Day 42) vs AUC_{24} obtained on Day 28 of Period 1 (Day 28) exhibited 9.9% and 9.8% increase when population typical CL and the lower 5 percentile CL were used in the simulation, respectively. AUC_{24} ratio was similar between Day 42 and Day 56, which indicates that no meaningful improvement in accuracy is achieved with additional 14 days of treatment in Period 2. The same results were observed for the simulated formulation with 5% higher or 5% lower or 10% lower F1 case scenarios. These simulation results suggest that following 28-day treatment of the first formulation, a minimum of 14-day treatment duration for the following periods is needed for steady state BE and food effect evaluation, and therefore 21-day treatment for period 2 and 3 is adequate for steady-state BE and food effect evaluation.

Table 2. Evaluation of Pharmacokinetic Sample Collection Days on the Determination of Steady state AUC_{24}

Simulation Scenarios	PK Sampling Days	Population typical CL (6.37 L/h)	Population lower 5 percentile CL (4 L/h)
		AUC_{24} Ratio	
10% increase in F1	Day 42	1.099	1.098
	Day 56	1.1	1.103
5% increase in F1	Day 42	1.05	1.05
	Day 56	1.05	1.053
10% decrease in F1	Day 42	0.902	0.907
	Day 56	0.9	0.903
5% decrease in F1	Day 42	0.951	0.955
	Day 56	0.95	0.953

Source Data: IMPROVE Artifact ID CP1:FI-1892098.
Simulation was conducted as original formulation dosed daily from Day 1 to Day 28, followed with new formulation from Day 29 to Day 56. The new formulation was assumed to have 10% or 5% higher F1 or 10% or 5% lower F1 compared to the old formulation, respectively, in the simulation scenarios. PK sampling was collected on Days 28, 42, and 56. The AUC on Days 42 and 56 were compared to Day 28.

In order to support the bridging of the soft gel capsule formulation to the current commercial formulation, the same food intake condition should be used. The current talazoparib commercial formulation is administered without regard to food intake. Generally, BE studies are conducted under fasting condition according to the FDA guidance for the industry "*Assessing the Effects of Food on Drugs in INDs and NDAs —Clinical Pharmacology Considerations"*. Therefore, in the first 2 periods to establish BE, talazoparib will be taken under fasting condition.

With the current commercial formulation, C_{max} and T_{max} was affected by food intake although administration with food did not affect AUC. Since the food effect on the soft gel capsule formulation is unknown, a 3rd period was added to assess the food effect. The test meal recommended by the FDA is a high fat meal, chosen as the physiological conditions induced by a high-fat meal generally provides the greatest effect on gastrointestinal physiology and the maximum effect on the systemic availability of the drug.

In pre-clinical studies, talazoparib was shown to be clastogenic, indicating potential for genotoxicity in humans. Based on findings from animal studies, talazoparib can cause embryo-fetal harm and may compromise male and female fertility. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

CCI [redacted]

4.2.1. Participant Input Into Design

Participant input into the study design, dosing, procedures and duration feasibility has been elicited and incorporated into the protocol as appropriate.

4.3. Justification for Dose

According to FDA guidance, when several doses of a drug that exhibit linear PK will be marketed, the highest clinically recommended dose should be used unless safety concerns necessitate a lower dose.[6] The highest clinically recommended dose strength of talazoparib is 1 mg taken as a single oral daily dose in the approved indication (deleterious or suspected deleterious gBRCAm HER2-negative locally advanced or metastatic breast cancer). Therefore, the highest approved dose strength, 1 mg QD, was chosen for this study.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the End of Study visit.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial globally after collection of the final data point for primary and secondary study objectives.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 (or the minimum country specific age of consent if >18) and 70 years, inclusive, at Visit 1 (Screen 1).

Type of Participant and Disease Characteristics:

2. Histological diagnosis of recurrent, locally advanced or metastatic solid tumor that is not amenable for treatment with curative intent.

a. Solid tumors with known or likely pathogenic germline or somatic tumor gene defect (eg, one or more BRCA1 or BRCA2 gene defect except for ovarian cancer) that would benefit from PARPi therapy per current approvals for the tumor indication or supported by strong scientific evidence. Gene mutation determined by local assessment and classification using a test of either germline or tumor DNA which was performed in a CAP/CLIA certified (or comparable local or regional certified) laboratory.

b. Received at least 1 prior SOC regimen, if it exists, as appropriate for the respective tumor type unless deemed unsuitable or declined these therapies; ovarian cancer participants must have at least 1 prior cytotoxic chemotherapy regimen, including at least 1 line of platinum-based therapy. Participants (except for those with ovarian cancer) must not have had disease progression within 6 months of initiation of platinum containing regimen;

   - Participants with ovarian cancer must not have progressed during or within 1 month after the last dose of the most recent platinum-based chemotherapy;

   - Participants with ovarian cancer previously treated with ≤2 prior cytotoxic chemotherapy regimens, participants must have had disease progression within 6 months after the last dose of platinum-based chemotherapy, also termed "platinum-resistant recurrent disease"

   - Participants with ovarian cancer previously treated with >2 prior cytotoxic chemotherapy regimens, ie, platinum sensitive recurrent disease is allowed;

   - Any treatment regimen that began with cytotoxic chemotherapy and continued with another regimen for maintenance therapy following best response to initial cytotoxic regimen will count as one line of prior therapy.

c. Participants with NSCLC harboring B-Raf proto-oncogene (BRAF) v600 mutations, ALK and c-ros oncogene 1 (ROS1) translocation/rearrangements, or epidermal growth factor receptor (EGFR) mutations must have received the appropriate targeted therapy as approved by the relevant health authority.

3. ECOG performance score of 0-1.

4. Adequate bone marrow function, as defined as:

- ANC ⩾1500 cells/mm^3

- Platelets ≥100,000 cells/mm^3

- Hemoglobin ≥10.0 g/dL

5. Adequate renal function, as defined as:

- A CLCR ≥60 mL/min by Cockcroft-Gault formula or as: CLCR={[(140–age) × weight)]/(72 × SCR)} × 0.85 (if female), where CLCR is measured in mL/min, age is expressed in years, weight in kilograms, and SCR in mg/dL; Other methods for calculating CLCR can be used as long as the same method is used for the entire study;

- No documented CLCR <60 mL/min and no change in CLCR >25% in the past 4 weeks.

6. Adequate hepatic function, as defined as:

- AST and ALT ⩽2.5 × ULN; if liver function abnormalities are due to hepatic metastasis, then AST and ALT ⩽5 × ULN;
- Total bilirubin ⩽1.5 × ULN (⩽3 × ULN for Gilbert's syndrome);

7. Life expectancy of at least 12 weeks.

8. Able to swallow capsules whole without breaking apart or crushing.

9. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Informed Consent:

10. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. For ovarian participants: Non-epithelial tumors or ovarian tumors with low malignant potential (ie, borderline tumors) or mucinous tumors.

2. Toxicities from previous anti-cancer therapies must be resolved to NCI CTCAE <Grade 2, except for alopecia, sensory neuropathies ≤Grade 2, or other Grade ≤2 AEs not constituting a safety risk, based on investigator's judgment, are acceptable.

3. Diagnosed with MDS or AML.

4. Active infection requiring systemic therapy within 2 weeks of enrollment.

5. Transfusions or hematopoietic growth factors within 2 weeks of enrollment.

6. Any major surgery within 4 weeks of enrollment.

7. Any condition in which active bleeding or pathological conditions may carry a high risk of bleeding (eg, known bleeding disorder, coagulopathy or tumor involvement with major vessels).

8. Known or suspected brain metastasis or active leptomeningeal disease undergoing or requiring treatment. Asymptomatic brain metastases currently not undergoing treatment are allowed.

9. Spinal cord compression is allowed if definitive treatment was provided and participant has stable disease 4 weeks prior to randomization.

10. In the opinion of the investigator, any clinically significant gastrointestinal disorder affecting absorption (eg, malabsorption syndrome, uncontrolled inflammatory bowel disease, PUD, requires hyperalimentation, or prior surgical procedures effecting absorption.

11. Inability to swallow capsules or any known hypersensitivity to Talzenna™ (talazoparib) or any of the product components.

12. Clinically significant cardiovascular disease:

- Myocardial infarction or symptomatic cardiac ischemia within 6 months of randomization;

- New York Heart Association Class III or IV congestive heart failure;

- History of clinically significant ventricular arrhythmias (history of sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes) within 1 year prior to randomization.

- History of Mobitz II second degree or third degree heart block unless a permanent pacemaker is present.

- Hypotension: systolic blood pressure <80 mm Hg at screening;

- Bradycardia: HR of <45 beats per minute at screening on electrocardiogram;

- Uncontrolled hypertension: systolic blood pressure >170 mm Hg or diastolic >105 mm Hg at screening; rescreening is allowed after adequate blood pressure control is achieved.

13. Women of childbearing potential who are pregnant, breast-feeding or plan to conceive during study participation.

14. Women of childbearing potential who are unwilling or unable to use highly effective methods of contraception as appropriate as outlined in this protocol for the duration of the study and for 7 months after the last dose of IP.

15. Fertile male participants with female partners of reproductive potential or pregnant partners, unwilling to use a condom (even after vasectomy) during treatment and for at least 4 months after the last dose of IP.

16. Known history of testing positive for HIV, AIDS, positive HBV surface antigen, positive HCV RNA, or positive COVID-19 viral test. Asymptomatic patients with no active COVID-19 infection detected but positive antibody tests, indicating past infection, are allowed.

17. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

18. Prior anti-cancer therapy within 2 weeks or 5 half-lives prior to randomization (whichever is longer). Prior anti-cancer treatments with 5 half-lives longer than 30 days and no evidence of drug-drug interaction (DDI) with talazoparib require a 30-day washout period. See Section 10.9 Appendix 9 for more details on DDI potential.

19. Current or anticipated use of P-gp inhibitors, BCRP inhibitors, and P-gp inducers within 2 weeks or 5 half-lives prior to randomization (whichever is longer). See Section 6.5 for more details.

20. Prior radiation within 2 weeks of randomization. Prior palliative radiotherapy to metastatic lesions(s) is permitted, provided it has been completed at least 2 days prior to enrollment and no clinically significant toxicities are expected (eg, mucositis, esophagitis).

Prior/Concurrent Clinical Study Experience:

21. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives prior to randomization (whichever is longer). Prior treatments with 5 half-lives longer than 30 days and no evidence of DDI with talazoparib require a 30-day washout period.

Diagnostic Assessments:

22. QTc interval >470 msec. If the baseline uncorrected QT interval is >470 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

Other Exclusions:

23. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restriction

Bioequivalence and Food-effect Phase

On non-site visit days, in the first 2 periods, participants must abstain from all food and drink (except water) at least 2 hours prior to drug administration and remain fasting after drug administration for at least 2 hours. In period 3, participants will start a formal breakfast within 30 minutes prior to drug administration.

High fat meal will be started within 30 minutes prior to dosing and finish before drug administration. On non-site visit days of Period 3, IP will be taken after a proper breakfast. Participants who cannot tolerate a high fat meal can be excluded from the food effect phase and roll over to the maintenance phase.

On site visit day, the requirement for food intake is described in detail in Section 6.1.1.

Maintenance Phase

No meal or dietary restrictions.

5.3.3. Caffeine, Alcohol and Tobacco

Bioequivalence and Food-effect Phase

Participants will abstain from caffeine containing products for 48 hours prior to and for the duration of the PK sampling days.

Participants will abstain from alcohol for 72 hours prior to and after drug administration on PK sampling days. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for laboratory tests. Walking at a normal pace will be permitted.

Maintenance Phase

No caffeine, alcohol and tobacco restrictions.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IP/enrolled in the study. Screen failure data are collected and remain as source.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened for the following reasons: to repeat tests for eligibility, out of the screening window due to scheduling logistics, and unexpected delays with test completion. Rescreened participants should be assigned the next available number at the site; therefore, each rescreening should have a different participant identification number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to soft gel capsule formulation of talazoparib and TALZENNA™, the term investigational product (IP) may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Intervention Name	**Liquid–filled soft gel capsule formulation of talazoparib**	**Talzenna**
ARM Name (group of patients receiving a specific treatment	Test	Reference
Type	Drug	Drug
Dose Formulation	liquid-filled soft gel capsule	capsule
Unit Dose Strength(s)	1 mg	1 mg, 0.25 mg
Dosage Level(s)	1 mg	1 mg, 0.75 mg, 0.50 mg, 0.25 mg
Route of Administration	Oral	Oral
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Pfizer	Pfizer
Packaging and Labeling	Study intervention will be provided in a bottle. Each	Study intervention will be provided in a bottle. Each

Intervention Name	Liquid–filled soft gel capsule formulation of talazoparib	Talzenna
	bottle will be labeled as per country requirement.	bottle will be labeled as per country requirement.
Current/Former Name(s) or Alias(es)	PF-06944076	PF-06944076

6.1.1. Administration

Bioequivalence and Food Effect Phases

On the visit days with PK assessment, participants will take IP at the site approximately 24 hours after the previous dose and within 10 minutes after the collection of pre-dose blood sample. After drug administration, an examination of the oral cavity is required to verify that a participant has swallowed the IP. On other days without PK assessment, participants will be instructed to self-administer IP at approximately the same time each morning and maintain an eDiary for compliance (recording timing of each dose, fasting/fed condition, vomited dose and missed dose). In Period 1 to 2, participants will take either the current commercial talazoparib capsule formulation or the proposed talazoparib soft gel capsule formulation 1 mg QD under fasting condition (Table 1). In Period 3, participants will take the proposed talazoparib soft gel capsule formulation under fed condition.

Treatment A (current commercial talazoparib capsule formulation 1 mg once daily, fasting): Following a fast of at least 2 hours (or overnight fasting on site visit days), participants will receive daily 1 mg current commercial formulation of IP in the morning at approximately the same time. Participants will remain fasting for at least 2 hours after IP administration.

Treatment B (the proposed talazoparib soft gel capsule formulation 1 mg once daily, fasting): Following a fast of at least 2 hours (or overnight fasting on site visit days), participants will receive daily 1 mg proposed soft gel capsule formulation of IP in the morning at approximately the same time. Participants will remain fasting for at least 2 hours after IP administration.

Treatment C (the proposed talazoparib soft gel capsule formulation 1 mg once daily, with food): Participants will start a formal breakfast within 30 minutes prior to and finish breakfast before administration of daily 1 mg proposed soft gel capsule formulation of IP. On site visit days with PK assessment, high-fat/high-calorie meal will be administered in the clinical sites prior to the administration of the proposed talazoparib soft gel capsule formulation. The breakfast will be high-fat (approximately 50% of total caloric content of the meal) high-calorie (approximately 800-1000 calories with 150, 250, and 500-600 calories from protein, carbohydrate and fat, respectively) meal. At least 80% of the full meal must be consumed prior to administration of IP. Examples for the meal are shown Table 3 below. Substitutions in these test meals can be made as long as the meal provides a similar amount of calorie from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

Water is permitted until 1 hour prior to investigational product administration. Water may be consumed without restriction beginning 1 hour after dosing.

Table 3. High-Fat Meal Example

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600
Example of a High-Fat Breakfast	2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 ounces of whole milk. 2 slices of buttered toast, cottage cheese (90 g), buffalo milk (8 oz), an apple. (avocado and nuts can be substitutes)

50% of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.

Safety assessments should be reviewed prior to starting the next period of IP treatment. On Period 1 Day 1 (treatment sequence 2) or Period 2 Day 1 (treatment sequence 1), participants should be observed after dosing for any events over the first 2 hours.

Guidance on missed doses and IP administered outside of the allowed window:

- If vomiting occurs within 2 hours after drug administration, it will be considered as a missed dose. Participants should not make up vomited doses; dosing should resume on the next calendar day unless otherwise instructed.
- If participants have had less than 21 consecutive days of continuous QD dosing of IP (regardless of formulation) on the last day of a treatment period, they will be considered non-completers of that treatment period (Period X). Otherwise the treatment needs to be extended within the allowed window or repeated for 21 days (-2/+7). PK assessment will not be performed for non-completers of a treatment period, but other scheduled activities for D28 visit (period 1) or Day 21 visit (period 2 and 3) will be performed per the SoA and new bottles of IP (same treatment as Period X) will be dispensed on D28 or D21 visit instead of Day 1. After the completion of Period X, instead of moving on to the next treatment, the same treatment in Period X will be repeated for 21 days (-2/+7 days). In this situation, where Period X gets repeated to ensure 21 continuous days of dosing prior to PK assessment, the repeated period will get noted as Period Xa, and then if repeated a second time as Period Xb. Please note the visit windows shown in the SoA (-2/+2 days for period 1 and -2/+7 days for period 2 and 3) allow the treatment to be extended to meet 21 (-2/+7) continuous days instead of repeating a period.
- Participants must complete a given treatment period before they can enter the next scheduled period.
- If the participant has repeated a period twice due to a missed dose (original plus 2 repeat periods, a total of 3 for the same period), the participant should discontinue the

BE/food effect Phase and roll over to the Maintenance Cycle Phase schedule (SoA). The sponsor reserves the right for taking participants off treatment due to compliance issue.

- On the visit days with PK assessment, participants will take IP at the site approximately 24 hours after the previous dose (ie, nominal time). Drug administration outside of ±2 hours of nominal time will be recorded as a protocol deviation. If drug administration occurs >28 hours from the previous dose (ie, >4 hours after nominal time) or <20 hours from the previous dose (ie, <4 hours before nominal time), PK assessment will not be performed on that day and the participant will need to take at least 2 more daily doses at the nominal time before performing the scheduled activities; as long as the visit occurs within (+4 day) window of the original schedule.
- If a participant forgets his daily dose of IP at the time he/she typically takes it, but remembers it later on the same day, the dose may be taken on that day. As long as the delayed dosing occurs at least 2 days before PK sampling day, the treatment schedule will remain unchanged. If this occurs within 2 days before PK sampling day, the treatment will need to be extended by at least 2 days before the PK sampling visit. Any dose that is missed (not taken on the same day of the intended time) should be skipped and should not be made up on the following day.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements) during the first 2 hours after dosing.

Participants who have repeated a period 2 times but still cannot meet PK evaluable criteria, need a dose reduction, have unstable renal function, or have experienced renal function reduction to moderate/severe renal impairment during the study, or have completed the food effect assessment will roll over to the maintenance phase which will consist of repeating 28 day cycles of treatment with the current commercial formulation.

Maintenance Phase

Participants will continue the same dosage as the last dose from the BE and/or Food Effect Phase, whichever is later, with the commercial formulation. There are no specific dosing restrictions during the maintenance phase. IP may be taken with or without food.

During BE, food-effect, and maintenance phase of the study, participants will be instructed to self-administer their IP according to the provided administration instructions, store the IP at home at 20°C to 25°C (68°F to 77°F), return all unused IP/bottles to the site, and record study-specific details and any deviations from instructions in a diary provided for the study.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment. Participants should be advised that oral anticancer agents (ie, talazoparib) are toxic substances and that other caregivers should always use gloves when handling the capsules.

3. Only participants enrolled in the study may receive IP and only authorized site staff may supply or administer study intervention. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

4. Any excursions from the IP label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the IP to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the IP must be quarantined and not used until Pfizer provides permission to use the IP. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. IP should be stored in their original containers.

7. Site staff will instruct participants on the proper storage requirements for take-home IP.

8. The following are the BA/BE retain requirements:
   - Stored by the investigator site
   - Stored under conditions consistent with product labeling
   - Stored in an area segregated from the area where testing is conducted
   - Stored with access limited to authorized personnel
   - Minimum of 4 (30 count bottles), per lot of the test article and reference standard
   - The subject dosing and retention sample containers must be identical in formulation, manufactured lot, and packaging and labeling presentation.
     For non-US sites, there may be local country regulations (eg, import license restrictions of subject dosing containers only) which prevent distribution of the retention sample containers; they may be stored at a 3rd party vendor location contracted by test site.
     Each reserve sample shall be retained at the investigator site for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not

approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was used.

9. The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor approved equivalent. All IP will be accounted for using a IP accountability form/record. All IP that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned IP must not be redispensed to the participants. to the participants.

10. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

The IP will be dispensed using an IRT drug management system at each visit. A qualified staff member will dispense the IP via unique container numbers in the bottles provided, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the IP in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

See the IP manual for instructions on how to prepare the IP for administration. IP should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of PARP inhibitor agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Participant numbers will be assigned as participants are screened for the study. Investigative sites will utilize IRT to assign randomization numbers and in accordance with the randomization numbers, the participant will receive the study treatment regimen.

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT/IWR system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

The study specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

This will be an open label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. Potential bias will be reduced by the following steps: central randomization, competitive enrollment.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

IP will be dispensed at the study visits summarized in the SoA.

Returned IP must not be re-dispensed to the participants.

The study specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Intervention compliance will be assessed at each visit. Compliance will be assessed by counting returned capsules. For home IP self-administration, a diary will be provided to the participant to aid in compliance with the dosing instructions. Participants should be instructed by the site to enter data in the diary in real-time. The site should review participants' eDiary IP compliance on add and 1 day before the site visit day to check for missed doses/out of window dosing and follow the guidance on missed doses and IP administered outside of the allowed window. Data entered in the diary by the participant will be compared with drug accountability done by the site prior to performing serial PK samplings/prior to dispensing additional IP. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

Bottles will be returned and compliance checked with eDiary dosing compliance from the web portal prior to PKs to ensure required daily 1 mg dosing.

Dosing compliance is critical to obtaining quality PK results for the BE and food effect phase of this study.

During the Maintenance Phase, compliance is defined as 80% of the total doses for each cycle. See Section 8.3.10 for Medication Errors.

6.5. Concomitant Therapy

The following concomitant medications are prohibited during the study:

- P-gp inhibitors: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar, and verapamil, atorvastatin, azithromycin, conivaptan, curcumin, cyclosporine, diltiazem, diosmin, eliglustat, elacridar, eltrombopag, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract.

- P-gp inducers: avasimibe, carbamazepine, phenytoin, rifampin, and St. John's Wort.

- BCRP inhibitors: curcumin, cyclosporine, elacridar, and eltrombopag.

Alternative therapies should be considered whenever possible. If usage of any of the above treatment is deemed medically necessary, consultation and agreement with the sponsor is required prior to treatment initiation as appropriate dose modification of IP may be needed. Please refer to FDA website: (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2) and University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/) for DDI potential with P-gp and BCRP and contact the sponsor when new concomitant medications are used.

Concomitant use of any systemic anti-cancer therapy for disease under study is not allowed during study participation.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

All concomitant treatments taken during the study must be recorded with indication, daily dose, unit and frequency, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

6.6. Dose Modification

This protocol allows for dose modifications from the currently outlined dosing schedule, but the maximum daily dose will not exceed 1 mg. Dose modifications for talazoparib due to adverse events are described in Table 6.

Dose Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment with or without dose reduction based on severity and clinical presentation. Recommended dose reductions are indicated in Table 4 and Table 5.

If a participant requires a dose reduction, the talazoparib commercial formulation will be utilized and dispensed. Reduction may necessitate an additional entry into IRT to request a formulation change. Dose reductions will be in increments of 0.25 mg/dose, therefore, participant may need to self-administer more than 1 capsule for the reduced dose which will be supplied as 0.25 mg capsules (eg, 0.75 mg = 3 capsules daily, 0.50 mg = 2 capsules daily, 0.25 mg = 1 capsule daily) with 30 capsules per bottle. Treatment with IP should be discontinued if more than three dose reductions are required.

Table 4. Dose Reduction Levels for Adverse Reactions

Dose Level	Dose
Recommended starting dose	1 mg (one 1 mg commercial formulation or the proposed talazoparib soft gel capsule formulation once daily
First dose reduction	0.75 mg (three 0.25 mg commercial formulation capsules) once daily
Second dose reduction	0.50 mg (two 0.25 mg commercial formulation capsules) once daily
Third dose reduction	0.25 mg (one 0.25 mg commercial formulation capsule) once daily

After dose reduction, re-escalation is not allowed. Treatment-emergent hematological and non-hematological events will be managed by the following dose modifications.

Table 5. Dose Modification and Management Due to Adverse Reactions

Toxicity	Management of Adverse Events
Grade 1 or 2 Selected hematologic and nonhematologic grade 3 or 4 events	No requirement for dose interruption or dose reduction.

Table 5. Dose Modification and Management Due to Adverse Reactions

Toxicity	Management of Adverse Events
Anemia (hemoglobin <8.0 g/dL)	Hold talazoparib and monitor weekly until hemoglobin returns to baseline (day 1) grade or better. Implement supportive care per local guidelines. Talazoparib may be reduced by 1 dose level per Table 4. If anemia persists for >4 weeks without recovery to baseline grade, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Neutropenia (ANC <1000/µL)	Hold talazoparib and monitor weekly until ANC ≥1500/µL. Implement supportive care per local guidelines. Reduce talazoparib by 1 dose level per Table 4. If neutropenia persists for >4 weeks without recovery to ≥1500/µL, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Thrombocytopenia (platelets <50,000/µL)	Hold talazoparib until platelets ≥50,000/µL. Implement supportive care per local guidelines. Reduce talazoparib by 1 dose level per Table 4. If thrombocytopenia persists for >4 weeks without recovery to ≥50,000/µL, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Nonhematologic laboratory grade ≥3 events except abnormal liver tests	Hold talazoparib as follows: • For clinically significant grade 3 laboratory abnormalities talazoparib may be held. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4 when the laboratory abnormality resolves to grade ⩽2(baseline grade for creatinine increases). • For grade 4 laboratory abnormalities, hold talazoparib. Resume talazoparib when the laboratory abnormality resolves to grade ⩽2(baseline grade for creatinine increases) at a 1 dose level reduction per Table 4. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved grade 3 toxicity lasting longer than 4 weeks or for grade 4 toxicity lasting longer than 1 week. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the medical monitor. Talazoparib must be discontinued if a grade 4 AE recurs after talazoparib resumes.
Grade ≥3 abnormal liver tests	If baseline Grade 1 AST or ALT, temporary hold if elevation >5 × ULN (ALT or AST ⩾3 × ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia [⩾500 eosinophils/µL]) until resolves to grade ⩽1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4. If baseline Grade 2 ALT or AST, temporary hold if elevation >8 × ULN until resolves to grade ⩽1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4. If baseline Grade 1 bilirubin, temporary hold if elevation >3 × ULN until resolves to grade ⩽1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4. If baseline Grade 2 bilirubin, temporary hold if elevation > 5 × ULN until resolves to grade ⩽1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4.

Table 5. Dose Modification and Management Due to Adverse Reactions

Toxicity	Management of Adverse Events
Nonlaboratory grade ≥3 events	Hold talazoparib as follows: • For clinically significant grade 3 AEs, hold talazoparib until the AEs resolves to grade ⩽1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level per Table 4. • For grade 4 AEs, hold talazoparib until the AE resolves to grade ⩽1 or baseline. Resume talazoparib at a 1 dose level reduction per Table 4. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved grade 3 toxicity lasting longer than 4 weeks or for grade 4 toxicity lasting longer than 1 week. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the medical monitor. Talazoparib must be discontinued if a grade 4 AE recurs after treatment resumes.

6.7. Intervention After the End of the Study

No study intervention will be provided to study participants at the end of the study unless otherwise required by local laws or regulations.

Preparations for study closure will occur at the collection of the final data point for primary and secondary study objectives. During study closure preparations, the sponsor may work with sites to explore options for alternative source of treatment for remaining patients in the maintenance phase.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following

- Objective disease progression.
- Global deterioration of health status;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;

- Study terminated by sponsor; or
- Death.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety follow-up until 28 days after the last dose. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, post treatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of IP will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in

detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study specific procedures. Signing of the informed consent by the participant is the start of the study.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA, except:

- The imaging window for eligibility at screening will be allowed to precede the Period 1 Day 1 visit by 60 days to allow for utilization of standard of care imaging.
- Any historical diagnostic testing may be utilized to document mutations, no diagnostic testing will be performed in this study.
- Participants will be required to maintain a diary to capture daily dosing in real-time, date and time of each dose (or missing doses).
- PK shipment requirements will be documented in a Study Laboratory Manual.

The total blood sampling volume for individual participants in this study is approximately 270 mL for the BE phase (57 days) plus 260 mL for completion of 21 cycles. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Unplanned procedures or visits per investigator's discretion for safety management will be reported on the Unscheduled CRFs.

Every effort should be made to ensure that protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the participant. When a protocol required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

Efficacy will not be evaluated in this study. Participants will be evaluated for disease progression per standard of care and investigators will confirm disease progression has not occurred for the participant's continuation in the study.

8.1.1. Imaging Assessments

Participants will provide consent for use of their imaging data for participation in this study. Standard of care assessments will be utilized for respective tumor diagnosis (but no later than every 6-12 months or as clinically indicated) to monitor for continued benefit on treatment. SOC imaging will be utilized for eligibility and RECIST criteria will not be reported during the study.

8.2. Safety Assessments

Safety assessments will include collection of AEs, SAEs, vital signs, 12-lead ECG and laboratory assessments, including pregnancy tests. AEs and SAEs will be assessed per NCI CTCAE version 5.0.

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Oral temperature, pulse/heart rate, weight, and blood pressure will be assessed. Height will be reported at screening.

Blood pressure and pulse rate measurements will be assessed in supine position during the BE/BA Phases and sitting position during the Maintenance Phase with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be

recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

If a) a post dose QTc interval remains ≥60 msec from the baseline **and** is >470 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically abnormal during participation in the study or within 28 (+7) days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the IP. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving IP), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to followup (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing IP.
- A male participant who is receiving or has discontinued IP exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to IP due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the IP by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the IP by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of IP and up to 7 months for females and up to 4 months for males after the last dose of IP.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly (in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing IP.
- A female is found to be breastfeeding while being exposed or having been exposed to IP (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the IP by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a

CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the IP, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy will not be analyzed in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.9.1. Prompt Reporting of Device Deficiencies to Sponsor

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the IP by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the IP under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Lack of dose reduction as specified by the protocol;
- Continuation of treatment although participant met discontinuation criteria;
- Incorrect IP dose by participant;
- Participant did not take IP for 6 or more days (approximately <80%) within 4 weeks, unless dose was withheld due to an AE;
- Participant did not receive treatment as assigned by IRT;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of talazoparib greater than 1 mg within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose. All overdose events are to be reported per requirements in Section 8.3.10.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory for at least 5 half-lives or 28 calendar days after the overdose of talazoparib (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 21 days (3 weeks) from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL of plasma, will be collected for measurement of plasma concentrations of IP as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples outside of the allowed window specified in PK Sampling Schedule on PK Visits in Section 1.3 will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Each plasma sample will be divided into 2 aliquot(s) (1 each for PK). CCI [redacted]

Genetic analyses will not be performed on these plasma samples.

Samples collected for measurement of talazoparib plasma concentrations will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

[redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Statistical Hypothesis

The alternative hypothesis of BE (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 2 separate one-sided hypotheses:
Ho_A: $\mu_T - \mu_R < \theta_L$
H_{1A}: $\theta_L <= \mu_T - \mu_R$
Ho_B: $\mu_T - \mu_R > \theta_U$
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 $[\theta_L, \theta_U]$ defines the BE range.

The 2 one-sided hypotheses will be tested at the $\alpha = 0.05$ levels of significance for log transformed AUC_{24} and C_{max} by constructing the 90% CI for the ratio between the test and reference geometric means.

9.2. Sample Size Determination

It is estimated that 22 participants will be required to provide 90% power that the 90% CI for the Test/Reference ratio of talazoparib AUC_{24} falls within the 80-125% acceptance interval for bioequivalence. Additionally, with 22 participants, probability that Test/Reference ratio for C_{max} will fall within 80%-125% is estimated to be 86%. These estimates are based on the assumption that the true ratio between Test and Reference treatments for AUC_{24} and C_{max} is 1.07 and 1.1 and also assumes within subject standard deviations of 0.407 and 0.17 for $\log_e$ C_{max} and $\log_e$ AUC_{24} respectively, as obtained from rifampin and itraconazole cohorts from study MDV3800-04.

Participants who withdraw from the study or fail to provide evaluable samples may be replaced at the discretion of the sponsor. Approximately 46 participants will be enrolled into the study to ensure at least 22 evaluable participants for the BE phase and 12 evaluable participants for the food effect evaluation phase. The initial number of 46 participants is estimated based on 52% non-evaluable rate and might be adjusted during enrollment if non-evaluable rate changes. The criteria for PK-evaluability will be described in detail in the SAP.

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.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
PK Concentration	The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration in at least 1 treatment period.
PK Parameter	The PK parameter population is defined as all participants randomized and treated who have meaningful primary PK parameter of AUC_{24} or C_{max} in at least 1 treatment period.
Safety	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.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.4.2. Primary Endpoint(s)

To assess BE, natural log transformed AUC_{24} and C_{max} after multiple dosing on the last day of Period 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 Treatment 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 with high-fat/high-calorie meal) 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]

9.4.3. Secondary Endpoint(s)

The PK parameters AUC_{24}, $AUC_{last,}$ C_{max}, C_{trough}, CL/F, and T_{max} on the last day of Period 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 will be compared to assure steady state is reached.

9.4.3.1. Pharmacokinetic Analyses

Derivation of Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours on the last day of treatment period 1 to 3	Linear/Log trapezoidal method
AUC_{last}[a]	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}) on the last day of treatment period 1 to 3	Linear/Log trapezoidal method
C_{max}	Maximum plasma concentration on the last day of treatment period 1 to 3	Observed directly from data
T_{max}	Time for C_{max} on the last day of treatment period 1 to 3	Observed directly from data as time of first occurrence
C_{trough}[b]	Predose plasma drug concentration	Observed directly from data
CL/F	Apparent clearance after oral dose on the last day of treatment period 1 to 3	Dose/ AUC_{24}

a. Calculated when the last measurable PK sample is not taken at 24 hours postdose.
b. Predose sample from a PK-evaluable participant

9.4.3.2. Safety Analyses

Safety analyses will be performed on the safety population using AE data. AEs will be coded in preferred term and system organ class using the MedDRA and classified by severity using the CTCAE version 5.0. The number and percentage of participants with AEs will be presented by MedDRA system organ class and preferred term, relationship to IP, and severity. 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. Descriptive statistics will be used.

CCI [redacted]

9.5. Interim Analyses

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.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use an independent monitoring committee. Data will be reviewed by the sponsor for new and aggregate AEs/SAEs according to SOPs.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as any individual person, judicial body or other of individuals who are legally authorized under state and federal law to consent to research participation on behalf of a designated person will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 30 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the study monitoring plan and respective monitoring vendor contract.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is

being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Study Manual and/or CRF Guidelines.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose Calcium Sodium Potassium Magnesium Chloride Total CO_2 (bicarbonate) AST, ALT[d] Total bilirubin Alkaline phosphatase Uric acid Albumin[d] Phosphorus or phosphate Total protein Direct/Indirect Bilirubin	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Pregnancy test (β-hCG)[c] At screening only: • Coagulation (INR PT, aPTT) or as clinically indicated • FSH[b]

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential with sensitivity of at least 25 IU/mL.
d. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, INR international normalized ratio, alkaline phosphatase.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patients exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None

Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

AE reporting should use concise medical terminology (verbatim) as well as collect the grade on the CRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 listed in the Cancer Therapy Evaluation Program.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event

3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an

assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 4 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 7 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- CCI [redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as Torsades de Pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic at specific location(s) and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient could be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per exclusion criteria 4 (active infection requiring therapy) and exclusion 16 (positive CoVID-19 viral test).

10.8.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.8.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.8.3. Alternative Facilities for Safety Assessments

10.8.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Blood draw for hematology and blood chemistry
- Urine sample collection
- Pregnancy test

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. Study participants should be instructed to collect their laboratory test results and bring them to the next in-clinic visit. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.8.3.2. Imaging

Not Applicable

10.8.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Talazoparib may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for talazoparib. Pfizer does not permit the shipment of talazoparib by mail. The tracking record of shipments and the chain of custody of talazoparib must be kept in the participant's source documents/medical records.

The following is recommended for the administration of talazoparib for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, talazoparib should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in Section 6.5 for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.8.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical exam
- Blood pressure, heart rate, temperature, and weight assessments
- Blood draw for hematology and blood chemistry
- Urine sample collection
- Pregnancy test
- Contraception check
- IP compliance check, accountability, and dispensation
- Adverse event monitoring
- Concomitant medication monitoring

10.8.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.9. Appendix 9: List of Long Half-Life Drugs with No Potential for Drug Interaction with Talazoparib

The following treatments with half-lives greater than 6 days and no potential for DDI with talazoparib will require at least a 30-day washout period prior to randomization: bevacizumab, fulvestrant, ipilumab, nivolumab, pembrolizumab, ramucirumab, and trastuzumab. For drugs with long half-lives (>6 days) not included in the list above, consult with the sponsor regarding DDI potential.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{24}	AUC from time 0 to 24 hours
AUC_{inf}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to last quantifiable concentration
AV	atrioventricular
BA	bioavailability
BCRP	breast cancer resistance protein
BE	bioequivalence
β-hCG	β-human chorionic gonadotropin
BID	twice daily
bpm	beats per minute
BRAF	B-Raf proto-oncogene
BRCA	BReast CAncer gene
BUN	blood urea nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CLCR	creatine clearance
CL/F	apparent clearance of drug from plasma
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
CoVID-19	coronavirus disease of 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Term
C_{trough}	steady-state predose plasma concentration
D	day
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDiary	electronic diary
EGFR	epidermal growth factor receptor
EOS	end of study
EOT	end of treatment
ER	exposure-response
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
F1	bioavailability
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
gBRCAm	germline BRCA-mutated
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methyl cellulose
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log

Abbreviation	Term
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWR	interactive Web-based response
LFT	liver function test
$\log_e$	base-e logarithm
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond
MX1	myxovirus resistance 1
n	number of participants
N/A	not applicable
NDA	New Drug Application
NIMP	noninvestigational medicinal product
NSCLC	non-small cell lung cancer
PARP	poly ADP-ribose polymerase
PARPi	PARP inhibitor
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	taken by mouth
PT	prothrombin time
PUD	peptic ulcer disease
P#D#	Period # Day #
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumor
ROS1	c-ros oncogene 1
RTRT	reference-test-reference-test
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus
SCR	serum creatinine
SMCC	succimidyl-4-N-maleimidomethyl cyclohexane-1-carboxylate
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	single-reference safety document
SToD	study team on demand

Abbreviation	Term
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal half life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma concentration
TRTR	test-reference-test-reference
ULN	upper limit of normal
US	United States
USPI	United States package insert
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cell
WOCBP	woman of childbearing potential

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